The Dysregulation of Synchronized Brain Oscillations in Parkinson’s Disease

TIMOTHY WEST

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Abstract:

This thesis concerns the properties and emergence of pathologically synchronized brain networks in Parkinson’s disease (PD), a neurodegenerative disorder of the motor system. Excessive oscillatory power in the beta frequencies (14-30 Hz), measured from recordings of activity in the subthalamic nucleus (STN) in the basal ganglia, has been repeatedly linked to the motor impairment associated with PD. However, it is not yet known: (i) how this aberrant rhythmicity is generated; and (ii) how this activity may impair propagation of normal activity across the network. This work makes novel analyses of electrophysiological recordings from both patients with PD, as well as rodent models of the neuropathology. In patients, we use both local field potential (LFP) and magnetoencephalography recordings that were made following surgery for deep brain stimulation. In animal models, we investigate multisite LFP recordings from across the networks formed by the cortex and basal ganglia of animals with a pharmacological lesion designed to mimic the generation of dopamine neurons associated with the disease. The nature of altered local and long-distance synchronization is investigated using a combination of tools from signal analysis, dynamical systems theory, and computational modelling. I specifically address: 1) how altered synaptic connectivity arising due to dopamine depletion may lead to the emergence of pathologically rhythmic activity in the beta frequencies; 2) the determination of the time resolved dynamics of beta oscillations and their relationship to cortical input; 3) the plausibility of a hypothesis of a dynamical shift in PD of brain networks towards more stable states. I find evidence that the beta rhythm is pathologically synchronized across the STN and neighbouring structures of the basal ganglia, and that the propagation of normal rhythmic activity is impaired by dopamine depletion.

Impact Statement:

This thesis comprises a significant contribution to the field that spans interests from basic to applied research. The foundations of this work are based in clinical research from patients with Parkinson’s disease (PD) and all research was done with the explicit aim of providing an increased knowledge of the pathology suitable for usage in the development of novel strategies for therapeutic intervention and to better inform clinicians. Specifically, the findings of this work are of high relevance to the development of closed-loop deep brain stimulation, an incipient technology that has a large potential to improve existing and future clinical interventions, not only in PD but a number of other brain disorders such as epilepsy, migraine, dystonia, obsessive compulsive disorder, to name but a few.

In addition, this thesis makes a number of methodological advances that will be of broader value to the research community and biotechnology. Specifically, we provide a detailed validation of a novel signal analysis tool to determine directional interactions in neural signals. Further, we introduce a novel optimization strategy for inference of neural connectivity. These tools have potential usage in the development of brain computer interfaces, as well as more basic neurophysiological research.

Overall, this thesis builds upon our knowledge of the importance of pathological brain rhythms in disease and identifies a number of key biomarkers that may provide targets for clinical intervention. This impact will be enhanced by the publication of the material within this thesis in peer reviewed research over the next year, with relevance for industry and clinical research within five years following.

I, Timothy West confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.
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3 Abbreviations

6-OHDA - 6-hydroxydopamine
ABC – Approximate Bayesian Computation
BG – Basal Ganglia
(d)FC – (Directed) functional connectivity
DBS – Deep brain stimulation
DCM – Dynamic causal modelling
DFA (-PS) – Detrended fluctuation analysis (- for phase synchrony)
ECoG – Electrocorticography
EEG - Electroencephalography
EMG – electromyography
EOG – Electrooculography
GPe/i – Internal/external segment of the globus pallidus
L-DOPA – Levodopa
LFP - Local field potential
MEG – Magnetoencephalography
MSN – Medium sized spiny neurons
MVAR – Multivariate autoregressive
(np)GC – (Non-parametric) Granger causality
NPD – Non-parametric directionality
PD – Parkinson’s disease
PLV – Phase locking value
PPC – Pairwise phase consistency
SEM – Standard error of the mean
SNC – Substantia nigra pars compacta
SNpr – Substantia nigra pars reticulata
STN – Subthalamic nucleus
STR – Striatum
UPDRS – Unified Parkinson’s Disease Rating Scale
(W)PLI – (Weighted) phase lag index
LRTC – Long-range temporal correlations
Part A:
Introduction and Background
Part A: Introduction and Background

1 Overview

The study of neuroscience is underwritten by the idea that macroscopic behaviours such as movement, decision making, and perception are the consequence of the collective action of billions of unseen microscopic states in the brain. One of its fundamental tenets, therefore, is to understand the ordering of these elements, and their activities in time and space (Anderson 1972; Chialvo 2010; Bassett and Gazzaniga 2011). In medicine, the principle of homeostasis is a founding principle that describes the self-organizing processes that act to co-ordinate tissues into organs and permit the body to function in the face of rapid environmental change. It is the breakdown of homeostasis that is manifest as disease. This concept is no less true in the brain, where a disintegration of the normally exquisite spatiotemporal patterning of neural activity results in a pathological abridgment of the brain’s functional repertoire.

In this thesis I will demonstrate how these ideas can frame the pathophysiology of Parkinson’s disease (PD). We take tools from signal analysis to identify changes in the patterning of neurophysiological signals, and then use dynamical systems theory (DST) to yield mechanistic insights into the systems that govern them. In this introduction I will first review the literature pertaining to the known electrophysiology of PD and how this is thought to relate to motor function. As this thesis approaches these topics from a clinical perspective, we focus primarily on recordings of mesoscale brain activity, the predominant form of recordings made in humans, and so maximize the potential for these ideas to translate to solutions for patients. Secondly, I will introduce several approaches from DST that will aid in the understanding of how changes in neural circuits can lead to the emergence of large-scale pathological activity observed in patients.

2 Neural Oscillations, Synchrony in the Motor System and Parkinson’s Disease

2.1 The Role of Rhythmic Activity in the Brain

Brain rhythms have been recorded since the dawn of the 20th century (Millett 2001; Niedermeyer and da Silva 2005) yet neural oscillations have been treated with scepticism and thought to be of limited relevance to brain function (Sejnowski and Paulsen 2006; Lopes da Silva 2013). Oscillations are ubiquitous across nature and produced by the simplest of systems. However, within this ubiquity lies the idea that the brain, as shaped by natural selection, has seized upon the intrinsic utility of time keeping and memory imbued by cyclic activity. Periodicity implies predictability (Schaffer et al. 1993), an axiom that all organisms have seized upon: from microbes, to plants, and to animals, that all entrain their behaviours to the cycles of light and dark, and hot and cool, that are provided by the orbits and rotations of the earth (Johnson et al. 1996; Ouyang et al. 1998; Kondo and Ishiura 1999). In neural systems, oscillatory activity is found in even the most primordial of circuits (Schütt et al. 1999) and synchronization between them found to provide the basis for vital behaviours of life such as the
olfactory systems of insects and the sexual behaviour of fireflies (Strogatz and Stewart 1993; Strogatz 2004). The work of Helmholtz (Helmholtz and Ellis, 1875) first hinted upon perception by resonance in the sensory organs, an idea that was found to hold true across many parts of nervous system, from the cochlear membrane (Nobili et al. 1998) up to the auditory (Lakatos et al. 2005), visual (Herrmann 2001), and olfactory (Freeman and Skarda 1985) cortices.

Oscillating neuronal activity occurs across a range of scales in the brain: within single neurons that exhibit rhythmic changes in the subthreshold potentials of active dendrites (Alonso and Llinás 1989), to periodic firing of action potentials, such as that found in hippocampal neurons (Isokawa-Akesson et al. 1987). Further up the scale is the synchronized ensemble activity of large populations of neurons which give rise to the mesoscale brain oscillations that are detectable in the electrical or magnetic fields measured in the electroencephalogram (EEG), magnetoencephalogram (MEG), or local field potential (LFP). These mesoscale fields arise from the collective, synchronous, dendritic depolarizations of large numbers of neurons and their subsequent axonal currents, this ‘local’ synchronization can be measured as changes in the spectral power of the measured signals and are what we refer to in this thesis as an oscillation. At a higher level, the interaction of spatially distinct populations can lead to the exhibition of ‘long-range’ synchrony of neural activity by which the synaptic connectivity between rhythmically active populations promotes coherent patterns of firing. These phenomena can be measured at the mesoscale through the analysis of the degree to which correlations are present in the time courses of the ensembles’ activities. We refer to these phenomena as either synchronization and/or coherence.

The origins of oscillatory ensemble activity in the brain (a problem with which this thesis is concerned) must arise from the existence of synaptic coupling that can facilitate the collective firing of a population of neurons. Generally, this can occur in several ways: a) a common periodic drive to non-rhythmically firing neurons (master-slave); b) common inputs that may entrain oscillating neurons; c) recurrent circuits of tonically active neurons (mutual-entrainment). Master-slave relations often involve slow rhythms (< 1 Hz) that engage large populations of neurons, for instance the delta rhythm during sleep (Amzica and Steriade 1995). An example of (b) is the modulation of neurons firing in the neocortex by the hippocampal theta (4-8 Hz) rhythm (Sirota et al. 2008). Mutual entrainment (c) can occur at a number of levels, from local generated rhythms arising from interaction between inhibitory interneurons and pyramidal cells in layers of the cortex (Lytton and Sejnowski 1991; Buzsáki and Draguhn 2004; Buzsáki 2006; Tiesinga and Sejnowski 2009), long cortico-thalamic loops (Steriade et al. 1990, 1993), and even longer loops in the motor system such as skeletal muscle/afferent loops (Conway et al. 1995), or vestibular motor loops (Ito 1972). For a fuller discussion of the range of mechanisms that may generate rhythmic neural activity see Gollo et al. (2014).

The periodic ensemble firing of neural activity provides an alternative to the once predominant ‘rate coding’ hypothesis of information encoding in the brain and replaces spike rates with spike timing.
(Engel et al. 1992; Lisman and Jensen 2013). If in the framework of rate coding, the firing of an individual neuron can be thought to signify a single computational proposition, then in terms of temporal coding the proposition is related rather to when or how often the neuron fires (Wilson 2015). Synchronization of rhythmic activity has been tendered as a solution to the ‘binding problem’ by which diverse sensory information may be integrated into a coherent representation by the synchronization of ‘binding’ of neural activities (Eckhorn et al. 1988; Gray et al. 1989; Singer 1999; Engel and Singer 2001). Through synchronization of spatially disparate brain regions, multisensory representations may be bound together by the phase of an oscillation (for a review, see Salinas and Sejnowski 2001). Thus, the synchronization of spatially distinct representations would then allow for the formation of a global, compound percept.

Mechanistically, the ‘communication through coherence’ hypothesis postulates that inter-areal spike coherence may facilitate the optimal transfer of information between neural ensembles, as neurons are most sensitive to input at certain phases of the receiving population’s mean field activity (Fries 2005, 2015). Precise timing of arriving spikes could also act as a selection mechanism, by which one timing is chosen over that of the other, providing a way by which oscillatory inputs may compete (Womelsdorf et al. 2007; Bosman et al. 2012). Importantly, spiking activity of individual neurons has been demonstrated to synchronize to periodic LFP across a number of systems (O’Keefe and Recce 1993; Murthy and Fetz 1996; Baker et al. 1997).

At a larger scale, it has been proposed that synchronized activity facilitates long distance brain communication over diversely functioning networks of the cortex (Varela et al. 2001). Meehan and Bressler (2012) propose that the active cortex is divided into transiently synchronized ‘neurocognitive networks’ that work to integrate information over functionally related areas. In the past 30 years there has been success in establishing the relationship between oscillations and particular brain functions such as memory, movement, and attention (for comprehensive reviews see: Buzsáki 2006; Schnitzler and Gross 2005; Wang et al. 2010). These efforts have resulted in a dominant view of brain oscillations such that activity in a certain frequency can be associated with a particular part of cognition. However, activity in one band can be correlated with more than one function and finding commonalities between results from many different experiments poses a current challenge to the field (Engel et al. 2001; Friston et al. 2015).

2.2 Oscillations in the Motor System

2.2.1 Temporal Organization of Motor Behaviour

The motor system’s requirement to provide high fidelity timing, gain control, and long-distance communication make it an ideal system in which to investigate the temporal coding of activity. Synchronization occurs at many levels across the motor system: between pairs of motor units (Farmer et al. 1993); muscles (Kilner et al. 1999); cortico-spinal interactions (Conway et al. 1995; Salenius et
al. 1997; Halliday et al. 1998); as well as a number of cortico-cortical interactions (for review see van Wijk, Beek, and Daffertshofer 2012). Synchrony in the motor system has been suggested to provide fine-tuning of sensorimotor signalling and facilitate long distance sensorimotor binding (Singer 1994; Farmer 1998); as well as provide control of the segregation and integration of actions (Hommel 2004). Temporal binding in the motor system may act to coordinate and engage distinct motor programmes into so called “cortical assemblies” (Wickens et al. 1994) that may be dictated by the network structure of the musculoskeletal system itself (Kerkman et al. 2018).

2.2.2 Functional Roles for Beta Oscillations in the Motor System

Due to its importance in the pathophysiology of disease, rhythmic activity in the beta range (14-30 Hz) is the principal focus of this thesis. Beta activity is self-sustaining and found in the resting state brain, a property that has led to it being proposed to act as an idling rhythm (Pfurtscheller et al. 1996). More recent work refines this hypothesis, and proposes that beta may signify the degree of cortical inhibition (Engel and Fries 2010). Specifically, it is thought that beta synchrony signals the system’s ‘status quo’ and thus its disruption is a signature of the transient reorganization of motor networks (Farmer, 2004? Brown 2007; Engel and Fries 2010).

At the initiation and maintenance of movement, beta rhythms exhibit a strong desynchronization in the motor cortex (Pfurtscheller and Lopes da Silva 1999). At the onset of movement, beta rhythms are replaced predominantly by gamma rhythms (40 - 120 Hz; Pfurtscheller et al. 1993) and following termination of movement there is a resynchronization of beta rhythms (post-movement beta synchronization: PMBS). Work by Pogosyan et al. (2009) supports a causal role for beta oscillations in movement suppression by demonstrating that subjects who have had their motor cortex entrained at beta rhythms using transcranial alternating current stimulation, display impaired execution of voluntary movement. Modulation of oscillatory power has been found to encode a number of parameters in the motor cortex such as movement force (Mima et al. 1999) and effort (Tan et al. 2015). Specifically, Tan et al. (2014, 2016) has demonstrated that PMBS is correlated with movement error signals that is consistent with model of confidence in the face of sensory uncertainty. In this scheme post movement beta synchronization is thought to index the precision of sensory feedback such that when error is high, there is a reduction in PMBS. Importantly, both cortical and subthalamic neurons have been demonstrated to fire coherently to oscillations in the field potential (Timmermann and Florin 2012; Little and Brown 2014).

Outside of the brain, cortical beta rhythms have been demonstrated to be synchronous with neural activity in the spinal cord and muscles, a feature most prominent during weak tonic muscle contraction. So called corticospinal coherence is suppressed during voluntary movement (Conway et al. 1995; Baker et al. 1997; Salenius et al. 1997; Halliday et al. 1998) but enhanced with moderate increases in force of isometric contractions (Chakarov et al. 2009). Again during voluntary
Part A: Introduction and Background

movement, the coherent frequencies shift to gamma band activity (Brown et al. 1998; Mima et al. 1999).

Beta is also present in subcortical structures. Recent work has demonstrated that beta activity in the basal ganglia (BG), is coherent with a wide range of cortical regions during movement, and this activity decreases following movement termination (Litvak et al. 2012; Hirschmann et al. 2013). Computational modelling of the cortico-BG circuits has demonstrated that the BG are well placed to play important functional roles in models of action selection (Bogacz and Gurney 2007; Herz et al. 2016). Understanding how beta rhythms are coordinated across networks formed by the motor cortex and BG is a current area of research interest (Jurkiewicz et al. 2006; Litvak et al. 2012). Specifically, mapping the synchronization and strength of neural oscillations to indices of behavioural performance is likely to be an important approach to understanding functional roles for subcortical beta rhythms (Friston et al. 2012b).

2.3 Oscillations in Parkinson’s Disease

2.3.1 Parkinson’s as a Neural Dysrhythmia

Excessive or altered oscillatory activity has been observed in diseases as diverse as epilepsy, schizophrenia, depression, and tremor (Uhlhaas and Singer 2006; Hammond et al. 2007). In this thesis we focus upon PD as its principal symptoms are arguably predominantly expressed as impairment of the motor system, a relatively well understood network. Motor behaviour also provides a more direct way by which to assess the expression of changes within the brain in contrast to pathologies such as depression where symptoms are largely affective and internalized. Specifically, PD is characterised by the expression of motor symptoms such as slowness of movement (bradykinesia), rigidity (akinesia), tremor, speech deficits, and gait impairment. However, recent work has also identified the significance of a range of cognitive symptoms that are only just starting to be investigated (Baggio et al, 2015; Aarsland et al, 2017).

The pathophysiological mechanisms underlying the expression of PD are largely unknown although the degeneration of dopaminergic neurones in the substantia-nigra pars compacta (SNpc) of the BG is thought to be the primary cause of pathogenesis (Kalia and Lang 2015). The canonical model of PD, predominant since its inception in 1990, is that of BG processing of cortical commands via separate but parallel cortico-BG pathways (Albin et al. 1989; Alexander and Crutcher 1990). In this rate coding model, the direct and indirect pathways act in antagonism to either respectively promote or suppress motor commands. Interpretation of PD in terms of rate coding proposes that impairment arises from an over-active indirect pathway that in turn drives the BG towards an akinetic state. Recent findings suggest that this perspective is overly simplistic and more recent functional models emphasize the importance of the timing of neural activity in the network (Frank 2006; Hammond et al. 2007; Oswal et al. 2013; Herz et al. 2018).
In patients, as well as animal models of PD, it has been demonstrated that within the basal-ganglia (specifically in the subthalamic nucleus; STN) there is an excessive local synchronization at beta frequencies (as indicated by spectral power) that is diminished by treatment with levodopa (L-DOPA) (Brown et al. 2001; Levy 2002; Priori et al. 2004; Sharott et al. 2005; Kühn et al. 2006; Hammond et al. 2007) and also by high frequency deep brain stimulation (DBS; Kühn et al. 2008; Bronte-Stewart et al. 2009; Whitmer et al. 2012). The amplitude of these oscillations is demonstrably correlated with motor symptoms (specifically, the bradykinetic aspects of impairment) and the degree of reduction of STN beta is predictive of patients’ clinical response to L-DOPA (Kühn et al. 2006, 2008; Ray et al. 2008).

Resting state activity in the human motor cortex appears largely unaffected in PD (Brown 2007) and reported changes are often small or inconsistent across the literature (Hirschmann et al. 2011; Litvak et al. 2011; Vardy et al. 2011). Unlike in the STN, studies with EEG and MEG have not demonstrated any consistent change in cortical beta power in response to treatment, with some studies reporting a decrease (Stoffers et al. 2007; Whitmer et al. 2012), an increase (Melgari et al. 2014), or no change (Litvak et al. 2011). In much of the non-invasively recorded data, a clear beta peak is not distinguishable in power spectra. Results from electrocorticography (ECoG) also fail to show any changes in the raw power but instead show that treatment may act to reduce phase-amplitude coupling between beta phase and the amplitude of broadband activity (de Hemptinne et al. 2015). Cortical activity, however, more clearly modulated by movement: as movement related beta desynchronization is delayed and lower in amplitude in patients when compared to controls, a consistent finding across the literature (Wang et al. 1999; Magnani et al. 2002; Devos et al. 2003). Furthermore, the STN shows strong, resting state, long-distance synchronization (coherence) with both the supplementary motor area (SMA) and the superior temporal gyrus (STG) in the high beta band (20-30 Hz) and alpha band (8-13 Hz) respectively (Litvak et al. 2011).

2.3.2 Impairment by Pathological Beta Oscillations

The intimate relationship between beta oscillations and motor impairment has emerged from a prolonged research effort to establish a causal role between aberrant beta synchrony and the expression of motor impairment in PD (for a review, see Oswal, Brown, and Litvak 2013). This has led to a recasting of PD in terms of neural dysrhythmia. Excessive synchronization of neural population in the BG has been proposed to lead to impairment via ‘jamming open’ (Cagnan et al. 2015) or a ‘radical restriction of the information encoding capacity’ of the BG network (Hanslmayr et al. 2012). In addition to correlative evidence between the power of beta oscillations and motor impairment, work has shown that experimental entrainment of beta rhythms in either the cortex using transcranial stimulation (Pogosyan et al. 2009) or STN using low frequency DBS (Chen et al. 2007; Timmermann and Florin 2012) can both act to promote bradykinetic/rigid symptoms.
Part A: Introduction and Background

Recent work has moved from static analysis of time-averaged spectral power towards analysis of subcortical beta oscillations as a dynamic, time-evolving process. Discrete ‘beta burst’ events have recently been described and found to have both relevance to clinical impairment, as well as be responsive to clinical intervention with dopamine replacement therapy and DBS (Cagnan et al. 2015; Feingold et al. 2015; Tinkhauser et al. 2017). Looking at the time evolution of pathological activity is likely to give further insight into how beta is related to computation in the healthy network and therefore how excessive beta activity might results in the motor impairments associated with PD. For instance, recent work has shown that the ability to modulate STN beta burst activity in a task dependent manner can predict subjects’ motor performance yielding further evidence for the functional importance of transient beta events in motor system processing (Torrecillos et al. 2018).

2.3.3 Modulation of Beta Rhythms by Subthalamic Deep Brain Stimulation

High frequency DBS targeted to the STN or internal segment of the GP (GPI) is a widely employed treatment for PD. STN is a primary target, although GPI DBS is widely used as intervention for dystonia. The mechanism by which DBS acts to reduce the severity of motor symptoms is not well understood. Electrophysiological studies have demonstrated that stimulation acts to attenuate the amplitude of beta oscillations in a way that corresponds to motor symptom improvement (Wingeier et al. 2006; Eusebio et al. 2011; Whitmer et al. 2012). Importantly, it has been demonstrated that the attenuation of beta is sensitive to the frequency of stimulation and phase of the input (Tass 2002) the mechanism of which has been explored in simulations (Holt and Netoff 2014; Holt et al. 2016).

The increasing evidence that beta is implicated in the motor impairments has led to the development of stimulation strategies that aim to directly interrupt beta oscillations. ‘Closed-loop’ stimulation acts to reduce side-effects as well as power consumption of DBS therapy by providing responsive stimulation that is targeted in time to break up ongoing beta activity. This strategy was first demonstrated to be effective in primate models of PD where it was shown that beta bursts in the STN may be disrupted by high frequency DBS and in a way that provides symptom alleviation that is superior to conventional tonic stimulation (Rosin et al. 2011). Work to implement closed loop DBS in patients is gaining traction (Cagnan et al. 2014; Holt et al. 2016) and has been shown to be effective in ameliorating motor symptoms. Improvements in the technology are likely to require a better understanding of how pathological activity emerges as this will lead to more efficient strategies by which to disrupt it.
3 Neuroanatomy of the Basal Ganglia Network and the Emergence of Pathological Beta Rhythms

3.1 Network Dynamics

3.1.1 The Rate Model

An enduring model of the striatal-nigral system is encapsulated in the ‘disinhibition hypothesis’ (Deniau and Chevalier 1985; Chevalier and Deniau 1990) which informed the canonical view of BG physiology (Alexander et al. 1986; Alexander and Crutcher 1990). A schematic of the canonical model of the cortico-basal-ganglia network is given in figure 1 and is largely based on the anatomical work of Smith et al. (1998). The canonical model of BG functional neuroanatomy is predominantly centred around GABAergic inhibition of the thalamus via pallidal projections. Normally tonic activity in the globus pallidus (GP) and substantia nigra pars reticulata (SNpr) generates an inhibitory background by which the thalamus is suppressed. This leads to a tonic suppression of pro-kinetic thalamo-cortical motor loops. Only via the action of striatal inhibition upon the GP and SNpr may this inhibitory drive be removed. According to the model, this mechanism facilitates precise gating of thalamocortical loops to either inhibit or facilitate movement (Alexander and Crutcher 1990).

Figure 1 – Schematic of the networks formed by the cortico-basal ganglia neurons. The anatomical pathways of the cortico-basal-ganglia network are well understood and form the basis of Albin’s classic rate coding model. In this schematic individual nuclei are given by the boxes and names indicated by the acronyms. Excitatory (glutamatergic) and inhibitory (GABAergic) projections are given by the arrow and ball ended lines respectively. Dopaminergic modulation via projections from the substantia nigra par compacta (SNc) to striatal neurons either via D1 or D2 receptors are indicated by the blue lines. D1 receptors have predominantly excitatory effects on the direct pathway whilst D2 have an inhibitory effect upon the indirect pathway.
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This model was built upon by Albin et al. (1989) who proposed the existence of two parallel streams that act antagonistically to inhibit or disinhibit the thalamus. Activity in the direct pathway acts through the striatum (STR) to ‘directly’ inhibit the internal segment of the GP (GPi), resulting in an inhibition of the output nuclei in the GPi. This in turn decreases tonic pallidal inhibition to effectively disinhibit the thalamus. The indirect pathway (STR → GPe → STN → GPi) acts oppositely. Striatal activation inhibits tonic activity in GPe, in turn disinhibiting glutamatergic neurons in the STN which increases firing of the GPi with the summed effect of increasing tonic inhibition of the thalamus. The antagonistic action of the two routes results in activity in ‘direct’ and ‘indirect’ pathway to be thought of as respectively either pro- or anti-kinetic. However, this model lacks a number of more recently described pathways such as the ‘hyper-direct’ pathway (cortex → STN; Nambu et al. 2002), and pallidal striatal projections (Mallet et al. 2012; Abdi et al. 2015; Hegeman et al. 2016), the functional importance of which is only starting to be investigated (Neumann et al. 2018).

3.1.2 The Role of Dopamine on the Striatum

The substantia nigra pars compacta (SNc) comprises a population of dopaminergic neurons which predominantly act to modulate the activity of medium sized spiny neurons (MSNs) in the STR. MSNs express predominantly either D1 or D2 receptors in roughly equal proportions. D1 neurons form the ‘direct’ pathway projecting directly to the GPi. D2 receptors are found on neurons projecting ‘indirectly’ to the output nuclei via the GPe. The action of dopamine upon the two receptor subtypes is antagonistic: in the case of D1 it is excitatory, whilst in D2 it is inhibitory (Gerfen and Wilson 1996). From these observations it has commonly been understood that dopamine promotes movement by biasing the striatal output in favour of activation of the prokinetic ‘direct’ pathways. In PD, the degeneration of dopaminergic neurons in the SNc acts to reduce drive to direct pathway. Instead, the presence of tonically active neurons bias the routing of signals in the BG via the indirect pathway that acts to yield a net inhibition of the thalamus that subsequently restricts relay of motor commands back to cortex (Gerfen et al. 1990). This work has formed the classical view of how dopamine acts to modulate the striatal projection neurons yet recent work suggests that the D1/D2 segregation of direct/indirect pathways is likely an oversimplification (Kupchik et al. 2015).

3.1.3 Neurodynamics and Autonomous Neural Oscillators

The canonical model of the BG is built upon the principles of rate coding of activity, and its construction hinges upon a balance of excitation and inhibition between antagonistic direct and indirect pathways to selectively inhibit the thalamic outputs to cortex under the influence of dopamine. Despite this, examination of the neurophysiology of neurons in the BG has demonstrated the existence rhythmically firing neurons that spike without input. Intrinsically firing neurons in the GP fire tonically but irregularly when receiving synaptic input in vivo. However, when synaptic input is blocked there is a shift towards firing rhythmically (Kita et al. 2004) in a way that is similar to that observed in slices (Mercer et al. 2007). Autonomous firing of neurons in the GP, SNpc and STN arise from very similar
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ionic currents. Namely, a persistent sodium current that is activated much lower than the threshold potential (Do and Bean 2003). This depolarizing sodium current ensures that the cell begins to depolarize immediately following an action potential with a rate that increases as it outcompetes the opposing potassium current.

Bursting of pallidal and subthalamic neurons occurs near the tremor frequency (7-10 Hz) and in PD leads to cells synchronizing at around twice that frequency (Nini et al. 1995). Corresponding LFPs also show a related change with an increase in beta power in the Parkinsonian state (Dostrovsky and Bergman 2004; Brown 2007). If it is the patterning of neural activity and not specifically the rate that determines the flow of information, then a whole new class of models may be formed that have a much better ability to answer questions such as how DBS acts, as well as the link between oscillatory activity and motor impairment. In this thesis we will explicitly examine a number of potential models for the propagation of rhythmic activity across the network.

3.1.4 Basal Ganglia Resonance

It has been hypothesized that elements of the basal-ganglia show a disposition to resonate at beta frequencies, a property that is thought to allow for the amplification of weak motor command signals via a process of stochastic resonance (Chakravarthy 2013). At optimal noise levels, a motor command can induce an oscillation in the resonant circuit. Incoming signals to be integrated may compete via their phase alignment with the ongoing resonance, with highly synchronized inputs matching the phase of the ongoing oscillation adding to the building resonance. This mechanism may provide a mechanism of temporal integration over which the role of the BG as a decision maker could be readily imagined.

As introduced previously, several studies have investigated the resonant properties of the BG experimentally (Eusebio et al. 2009; Cagnan et al. 2015). These studies have aimed to examine whether the BG-cortical circuit acts to resonate in the low beta range and whether dopaminergic input acts to damp this oscillation. Experiments measuring the cortical evoked potentials (cEPs) in response to stimulation suggest that the cortical motor network has a natural frequency at 20 Hz, although it is not clear whether this arises from a local circuit within cortex, or via its interaction with various structures in the subcortex. Eusebio and colleagues fitted simple damped oscillator models to cEPs and demonstrated that dopamine restoration acts to increase damping of oscillatory activity suggesting that dopaminergic modulation acts to limit the extent of resonating activity in these circuits.

How dopamine acts to damp oscillations is unclear. One potential mechanism involves modulating voltage gated conductances within neurons of the striatum (for a review see: Nicola, Surmeier, & Malenka, 2000) that in turn determines the frequency response of a population of neurons. A mechanism of active decorrelation has also been proposed as a way by which the network can suppress runaway oscillatory activity in which tonic input from cells firing outside of the STN and GPi loop, act to continuously reset spike timings to desynchronize the nuclei’s activities. (Wilson 2013). Alternatively,
it is possible that dopamine reduces the strength of re-entrant connections in the BG-thalamo-cortical loop to prevent runaway feedback excitation (Montgomery and Gale 2008; McIntyre and Hahn 2010).

Investigation into the phase dynamics between neural ensembles in both the BG and cortex has provided a finer grained view from which to observe the dynamics of synchrony between interacting populations. Cagnan, Duff, and Brown (2015) have provided evidence for a mechanism of ‘communication by resonance’ between the globus pallidus externus (GPe) and the subthalamic nucleus (STN) by which amplitude envelopes exhibit ramp like increases over periods of extended phase alignment. Crucially, the authors demonstrated periods of resonance were extended in the case of recordings from patients that were OFF L-DOPA treatment. These findings would support the notion that dopamine acts to promote homeostatic mechanisms that prevent runaway synchronization in structures such as the STN.

3.1.5 Pathological Beta Rhythms from Long Distance Connectivity

Connectionist hypotheses concerning the emergence of pathological beta rhythms posit that the generating mechanisms of the oscillation arise from due significant changes in synaptic connectivity that result from the dopamine depletion associated with PD (for a review see Holgado et al. 2010). These hypotheses include the dopamine-dependent modulation of recurrent loops within the network, either between the reciprocally-coupled network of neurons of the STN and the GPe (Plenz and Kital 1999; Bevan et al. 2002; Terman et al. 2002; Holgado et al. 2010; Liu et al. 2017); or of a longer loop involving feedback from BG output nuclei to the cortex via thalamo-cortical tracts (Leblois et al. 2006; Pavlides et al. 2012, 2015). Alternatively, it has been proposed that dopamine depletion disrupts mechanisms which regulate the gain of cortical afferents to the BG and somehow disrupt striatal outflow (Brown 2007; Hammond et al. 2007). The STR has also been implicated in the generation of pathological beta rhythms, either through alterations to its internal dynamics (McCarthy et al. 2011; Damodaran et al. 2015); or via increased striatal inhibition of targets in the GPe that act to promote beta synchrony (Gillies and Willshaw 2004; Kumar et al. 2011). In this thesis we will examine these hypotheses in detail and test their plausibility given a number of experimental observations.

4 Brain Connectivity and Dynamical Views of Neuropathology

4.1 Motivating a Non-Linear Approach to Studying Brain Connectivity

It has become a truism that the brain is a nonlinear, complex, adaptive system and thus there is a strong motivation to cast neuroscientific problems in terms of non-linear dynamical systems theory (DST; Kelso 1995; Gelder 1998). Reasoning for a DST approach follows from the observations that:

1. The brain is massively parallel, and computation is distributed across a network of neural assemblies that interact with many degrees of freedom (Alexander et al. 1986; Wickens et al. 1994).
2. The atoms of the computation in the brain, neurons, are highly non-linear devices showing complex input-output behaviours (London and Häusser 2005).

3. Brain circuitry is highly recurrent, and feedback between neural populations is predominant (Douglas and Martin 2007; Edelman and Gally 2013).

4. There is a high degree of asymmetry in brain networks arising from heterogeneous delays and connection strengths (Ermentrout 1998; Sporns et al. 2005).

5. The brain is plastic, exhibiting morphological changes across multiple spatial and temporal scales (Abraham and Bear 1996; Yuste and Bonhoeffer 2001).

All of these properties give rise to what can formally be described as a high dimensional, hierarchical, recurrent, asymmetrical, and adaptive non-linear dynamical system. This complexity underlies the shortcomings of approaches that have attempted to treat the brain as a digital computer (Churchland and Sejnowski 1992). Despite a relatively quiescent past decade, DST approaches to the brain are seeing a resurgence as developments in technology have made it possible to make high quality, high density recordings in the behaving brain, and provided the computing power by which to analyse and simulate neural activity.

Much of the work from the past 20 years has focused on the application of nonlinear methods to neural time-series analysis to mixed degrees of success (for a comprehensive review, see Stam 2005). Broadly speaking, these methods tend to involve metrics that aim to quantify properties of the supposed underlying dynamical system, estimating things such as its degrees of freedom, entropy, and stability. The limited success of many of these techniques in neuroscience arguably stems from the fact that application of non-linear techniques to large macroscale recordings such as the EEG has typically forgone consideration of the known systematic spatially compartmentalized organization of the brain.

The cortex is divided into many densely interconnected cortical columns that are thought to be modular with respect to their specific functions (Kandel et al. 2000). Breakspear (2004) argues that it may be more pertinent to investigate nonlinear structure in the interactions between neural subsystems rather than the output of those systems independently.

Thus, here we focus our attention on dynamics of neuronal assemblies interacting through the process of synchronization. The coupling of autonomous dynamical systems can facilitate the emergence of synchronous activity between them (Strogatz 2000; Pikovsky et al. 2003), even in the cases when their dynamics are individually chaotic (Pecora et al. 1997). This synchrony can take several different modes such as: complete synchronization; phase synchronization (Rosenblum et al. 1997); anticipated and lag synchronization (Sänger et al. 2012); and generalized synchronization (Pikovsky et al. 2003).

4.2 Dynamical Models of Brain Activity

As outlined in the previous section of this introduction, synchronization of neural ensembles is thought to be of great importance to the function of the brain. Understanding how synchrony arises, how it is
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shaped by the anatomical connectivity of the brain, the dynamics of the oscillators themselves, and how these dynamics malfunction in disease are all questions that we will investigate in the main body of this thesis. To do so we must first understand some basic formulations of dynamical systems as coupled ordinary differential equations (ODEs) and how their dynamics might be characterised in terms of their stability.

Mesoscopic models of brain activity, such as that of a single cortical column, are often abstracted by assuming that the collective activity of a large number of homogeneous neurons can be collapsed to a low dimensional dynamical system via the ‘mean-field’ approximation (Deco et al. 2008) to form a neural mass (Haskell et al. 2001; Marreiros et al. 2009). Periodic activity such as that observed in the visual alpha response, or epileptic seizures have typically been modelled by the reciprocal coupling of excitatory and inhibitory neural masses (Wilson and Cowan 1972; Lopes da Silva et al. 1974; Freeman 1992; Jansen and Rit 1995; David and Friston 2003). In the methods section of this thesis, we will return specifically to the Jansen-Rit model to illustrate how large-scale neural networks may be cast in terms of low dimensional, coupled systems of differential equations.

4.3 An Introduction to Dynamical Stability
4.3.1 Basins of Attraction and Local Stability

In dynamical systems theory a fixed point is a point in state space where the derivatives of the system are equal to zero i.e. there is no time evolution of the system beyond the equilibrium. A time evolving autonomous dynamical system can be expressed as a system of differential equations:

\[
\frac{dx}{dt} = f(x)
\]

And thus, the equilibrium point of the system may be found by solving:

\[
f(x^*) = 0
\]

such that at \( x^* \) the rate of change of the system is equal to zero. The stability of the fixed point describes the dynamics of the system following a small perturbation. A fixed point is stable if the effects of a perturbation dissipate, and after some time, the system returns to the same equilibria. An unstable fixed point will show divergence and the effect of a perturbation will grow larger as time progresses.

For didactic purposes, it is useful to abstract a high dimensional dynamical system described by \( f(x) \) as a low dimensional energy ‘landscape’, \( U(x) \), such that the locations of the unstable and stable fixed points determine the ridges and troughs. System dynamics can be abstracted as the highly damped movement of a ball along the contours of the landscape such that once the fixed point is reached, there is no more motion. In figure 2, examples of two example systems are illustrated.
Figure 2 - Energy landscape $U(x)$ of a bistable system far and near the critical value for bifurcation. The state of a the system at time $t_1$ and $t_2$ is given by the green circles. The system’s equilibrium points are indicated by the orange arrows, 1 and 3 are stable, whilst 2 is unstable. The system is perturbed from equilibrium 3 at time $t_1$, and its state following relaxation is given at $t_2$. The system given in panel (A) is close to a phase transition, the basin of attraction is shallow, and the rate of relaxation is slow. We see that the time taken to return to equilibrium in this case is slowed. In contrast, the system represented by the landscape in (B) is far from the critical transition, the basins of attraction are deeper and relaxation rates faster. These differences in relaxation rates give rise to the phenomenon of ‘critical slowing’ such that ‘memory’ of perturbations in critical systems are extended in time. We note that whilst in both (A) and (B) the equilibrium points remain at the same location in phase space, yet their stabilities are radically different, as is the energy required to transition from one state to another. Figure adapted from Tagliazucchi et al. (2016).

In panel A of figure 2, the landscape of a system close to the critical transition is shown. There is a smooth landscape with two stable fixed points (locations 1 and 3) that lie at the bottoms of shallow basins of attraction and are separated by an unstable node (location 2). If we perturb the system from equilibrium at time $t_0$, to give a new state at $t_1$, we see that its rate of relaxation back to equilibrium is determined by the local curvature of the landscape. The low energy of ridges relative to the basins gives rise to a high susceptibility of the system to a swap between equilibria because of input or endogenous stochastic fluctuations. A system in this state can be said to be close to criticality.

In B, an example of an energy landscape of a system that is far from criticality is given. The basin of attraction is much steeper and as such the rate of return following a perturbation is faster (more positive) than in A. As such the influence of the fluctuation vanishes much faster than the system given in B. It may also be seen that the energy required to transition between basins of attraction is much higher, and the susceptibility to transitioning between states is low.

In these diagrams it is easy to visualise the process of critical slowing by which the time taken for a system to recover from a small perturbation (relative to the energy required to escape the attractor basin) is larger in the near critical state. Perturbing the ball from equilibrium in A result in a much slower rate of relaxation back to the fixed point than in B. Note that in both cases the stable equilibrium remains the same yet changes to the parameterisation of the system alter trajectories in phase space. In this case the system at equilibrium is not changed yet the relative susceptibility to random fluctuations is entirely different. Critical slowing has been found to be a statistical hallmark of
systems approaching a critical transition and has been found to exist in a number of real-world systems such as eutrophic collapse, climate change, and neuron bursting (Dakos et al. 2008; Wang et al. 2012; Meisel et al. 2015).

4.3.2 Lyapunov Stability
The local stability of a dynamical system may be quantified through the calculation of the system’s Lyapunov spectrum (Holmes and Shea-Brown 2006). The rate of convergence or divergence of a system’s trajectories from an equilibrium in response to a small perturbation (such that it remains within the neighbourhood of the attractor in which the linearization remains valid) is given by the Lyapunov exponent. The spectrum of exponents is given by the eigenvalues of the Jacobian matrix (a matrix of the partial derivatives with respect to each of the state variables of the system) of the linearized system at the fixed point. These may be thought as classifying the generalized trajectories of the coupled system. If the system at the fixed point is perturbed by some small amount \( \delta \), then following some time \( t \) the distance from the original state is given by:

\[
d = \delta e^{\lambda t}
\]

The exponent \( \lambda \) is the Lyapunov exponent and quantifies the exponential convergence or divergence (dependent upon the sign) following a perturbation. Positive Lyapunov exponents imply divergence such that the impact of small fluctuations will grow exponentially as time passes. Conversely, negative exponents describe the exponential damping of fluctuations as the system returns to a fixed point. If we compare the systems of the B vs A in figure 2, we would expect that the Lyapunov exponents local to fixed point at location 3 would be much smaller (more negative) in B than in A. The overall stability of the system is dictated by the principal Lyapunov exponent, such that as soon as the largest coefficient becomes positive, then the system will become asymptotically unstable.

The model shown in figure 2 is an example of a system that undergoes a so called ‘pitchfork bifurcation’ in which there is transition from fixed point stability (1 stable fixed point) to a bistable system separate by an unstable node. If we continue to change from A, then the fixed points at locations 1 and 3, will lose their stability. Thus the proximity of the system to the bifurcation can be approximated by observing the Lyapunov exponents as they become less negative.

4.4 Statistics of Critical Transitions

4.4.1 Introduction to Critical Behaviour in the Brain
A set of dynamical regimes exist for which an equilibrium that has a close to zero-valued principal Lyapunov exponent is itself an attractor state. This quasi-equilibrium exists in a system that acts to hold itself close to an unstable critical point via a process of self-organized criticality and has been proposed as an organizing principle of several theoretical and real world dynamical systems (Bak et al. 1987; Bak 1997). Moreover, this mechanism has been proposed to operate in the brain (Beggs 2008; Chialvo 2010;
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Friston et al. 2012a; Hesse and Gross 2014; Massobrio et al. 2015). The emergence of adaptive brain states have been proposed to arise from self-organised criticality (SOC; Hesse and Gross 2014) by which recursive interaction between so-called order parameters (macroscopic properties of the system) and control parameters (structural determinants of the system) drive the global dynamics to lie on or near the critical point of a continuous (second order) phase transition. The exact mechanism by which this is thought to arise in the brain varies from model to model yet most depend on adaptive, activity dependent synaptic plasticity (e.g. Tetzlaff et al. 2010) and the ability for the global state of the system to be detectable at the local level of the adaptive units. Furthermore, robustness of SOC states has been shown to increase with system size (Rubinov et al. 2011). Irrespective of exactly how SOC may arise in the brain, the operation of complex systems at the edge of stability has been shown to facilitate optimal information transfer (Barnett et al. 2013); maximize dynamic range and adaptability (Kinouchi and Copelli 2006; Shew et al. 2009; Hesse and Gross 2014); and facilitate optimal information encoding (Shew et al. 2011).

4.4.2 Critical Slowing-Down, Long Tailed Autocorrelation, and Switching

Critical phenomena have typically been studied in statistical physics in the context of phase transitions. At a phase transition, a system is poised at the border between two qualitatively different states (e.g. liquid and gaseous phases). The qualitative states that arise at the macroscale arise because of the underlying microscopic interactions between the system’s constituent elements. These interactions leave their signatures in the statistics of the macroscale activity.

Systems operating close to critical transition are widely studied outside of neuroscience as they are interesting as potential predictors for large scale upheavals in ecology, climate science, geology, and economics (Scheffer et al. 2009). Indicators such as ‘critical slowing-down’; extended signal autocorrelation; and ‘flickering’ have all been detected in models poised at the edge of criticality, as well as in experimentally measured time-series (Chisholm and Filotas 2009; Aburn et al. 2012; Wang et al. 2012; Meisel et al. 2015). These hallmarks of critically poised systems have also been proposed to be applicable in the brain (Linkenkaer-Hansen et al. 2001; Kelso 2010). Within the brain, the search for statistical indicators of bifurcations has involved extensive modelling work (Friston 1997; Freyer et al. 2011; Aburn et al. 2012; Poil et al. 2012); as well as empirical studies in cell cultures (Beggs and Plenz 2003; Tetzlaff et al. 2010), animals (Shew et al. 2009; Hahn and McIntyre 2010) and humans (Kitzbichler et al. 2009; Berthouze et al. 2010; Meisel et al. 2012; Botcharova et al. 2014).
Extended temporal autocorrelations are a direct consequence of critical slowing down that occur as the principal Lyapunov exponent approaches zero (Sornette 2006; van Nes and Scheffer 2007). As the gradient of the system’s trajectories approach zero at the limit of the critical point, the return time to equilibrium becomes infinitely long. Thus, a randomly perturbed system poised close criticality will exhibit temporal correlations that persist long into its past. At a point approaching criticality, linearization of the system from the fixed-point ceases to be appropriate as higher order terms begin to dominate. At this point, we see a transition from exponential to power law decay of fluctuations indicative of long-term correlations in response to perturbation. In the literature these are termed long-range temporal correlations (LRTCs) and several studies report their existence in recordings from the brain (Linkenkaer-Hansen et al. 2001). Looking for critical transitions is less straightforward in empirical data. Most approaches in the brain have utilized estimation of the exponent of a power-law decay in the autocorrelation length of amplitude fluctuations (Linkenkaer-Hansen et al. 2001; Hardstone et al. 2012; Nikulin et al. 2012) as well as phase interactions (Kitzbichler et al. 2009; Botcharova et al. 2014) in search of markers of SOC (Bak and Paczuski 1995). Power-laws are a necessary but not sufficient indicator of SOC, leading to criticism of some of the stronger claims made in the literature (Touboul and Dejesthe 2010; Beggs and Timme 2012; Dehghani et al. 2012; Farmer 2015). We will return to the tools available for analysis of LRTCs in the methods section of this thesis.

5 Synchronization

Throughout this thesis I will investigate the dynamics of coupled neural systems either through direct analysis of recordings or through simulation of biophysical models of them. Much of the collective synchronization of neural activity can be treated in terms of weakly coupled oscillator theory (Strogatz 2004), of which we will go through some of its basic principles here.
5.1.1 Phase Synchronization of Weakly Coupled Oscillators

A dynamical system with a periodic, self-sustained oscillation can be represented by a stable limit cycle in its phase space (the space incorporating all possible states of a system). A limit cycle is defined as a periodic solution to a system of equations such that \(x(t) = x(t + T_0)\), where \(T_0\) is the period the cycle. The phase \(\phi\) defines the position along the limit cycle, with its rate of change equal to the frequency:

\[
\frac{d\phi}{dt} = \frac{2\pi}{T_0} = \omega_0
\]

If two such oscillators are weakly coupled, then the evolution of their phases may be given by:

\[
\frac{d\phi_1}{dt} = \omega_1 + \epsilon Q(\phi_1, \phi_2)
\]

\[
\frac{d\phi_2}{dt} = \omega_2 + \epsilon Q(\phi_1, \phi_2)
\]

where some coupling function \(Q\) depends on the shape of the limit cycle and is scaled by the coupling force \(\epsilon\). In the simplest case of a limit cycle on the unit circle, the coupling function may be given by \(Q(\phi_1, \phi_2) = \sin(\phi_2 - \phi_1)\). The phase locking condition in \(m:n\) frequency synchrony (Rosenblum et al. 1996; Pikovsky et al. 2003) is given by:

\[
|m\phi_1(t) - n\phi_2(t) + \delta| < \text{constant}
\]

where the phase difference is locked to some rational ratio of the two natural frequencies of the coupled oscillators. Furthermore, oscillators may be synchronized with some constant phase shift \(\delta\). In the case that \(\delta = 0\); the phases coincide exactly, and the oscillators are phase locked with zero offset. When the coupling function \(Q\) is dependent on the phase difference \(\Delta\phi = \phi_1 - \phi_2\) then synchronization will only occur when the frequency mismatch (detuning) \(\Delta\omega = \omega_1 - \omega_2\) is sufficiently small. Dependent on the amount of detuning, the size of \(\delta\) of will increase with larger \(\Delta\omega\).

5.1.2 Nonlinear Synchronization of Coupled Dynamical Systems

Synchronization is generalizable to coupling of dynamical systems beyond that of the simple phase models outlined in the previous section. Consider a generalized dynamical system:

\[
\frac{dx(t)}{dt} = f_\alpha(x(t))
\]

such that the state space vector \(x(t) = \{x_1(t), ..., x_n(t)\}\) describes the values of a system’s \(n\) dependent variables whose evolution is described by some function \(f\) parameterised by the set \(\alpha\). In the simplest case of dynamical coupling, there is a unidirectional influence between a driver (D) and response (R) systems (Pecora et al. 1997). Assuming that coupling is independent of the local dynamics we can write:
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\[
\begin{align*}
\frac{dx^D(t)}{dt} &= f_a(x^D(t)) \\
\frac{dx^R(t)}{dt} &= g_b(x^R(t) + h(x^R(t), x^D(t)))
\end{align*}
\]

Where the driver and response systems \(f_a\) and \(g_b\) (respectively) are unidirectionally coupled by the coupling function \(h\). In a simple example, diffusive coupling function is used:

\[
h(x^R, x^D) = c \cdot (x^R - x^D)
\]

In the case that the systems have identical dynamics i.e. \(f_a(x) = g_b(x)\), then when the coupling constant \(c\) is driven past some critical threshold \(c_k\), the two systems will synchronize identically. That is, following some transient, \(x^R(t) \rightarrow x^D(t)\). An example of a dynamical system modelling the unidirectional coupling of the activity of two neurons is shown in figure 4A. The driver and response neurons are individually modelled by 3-states: \(V^{D/R}, W^{D/R}\) and \(Z^{D/R}\) and the trajectories of a signal neuron through its 3D phase space are shown in panel 4B. The plots in panels C and D show the space

Figure 4 – Dynamical Synchronization of Coupled Wilson Cowan Neurons. (A) Time series of the dynamics of the three state variables from one of the neurons- \(V\) the mean pyramidal membrane potential, \(W\) the mean inhibitory cell potential, and \(Z\) the mean proportion of open potassium channels. (B) Three dimensional representation of the total phase space. The long-time evolution of the dynamical system gives rise to observation of the system’s attractor. (C and D) Example of driver-response coupling of Wilson Cowan columns. With very low coupling constant (panel C; \(c \approx 0\)), the time series are unsynchronized, and the orbits fill the space \(V^R \times V^D\). In the case of suprathreshold coupling (panel D; \(c > c_k\)), following an initial transient the orbits converge and occupy the diagonal subspace termed the synchronization manifold. Asymptotically, the model neurons are identically synchronized. Figure adapted from Breakspear, (2004).
\( V^R \times V^D \) between two strengths of coupling constant \( c \). In panel 4C, the coupling is weak, and the orbits fill the space. In 4D, where the value of the coupling constant \( c \) exceeds the critical value, the activities become synchronized and converge to the diagonal subspace of \( V^R \times V^D \). This subspace is what is referred to as the synchronization manifold. At the asymptotic limit of the coupling constant the neurons become *identically* synchronized. In this setting the *synchronization manifold* (the subspace in which the two systems display synchronization; depicted in figure 4D) will be the diagonal through the full state space.

### 5.1.3 Critical Transitions and Periodic Orbits

The majority of empirical work investigating criticality in the brain so far has sought to identify extended autocorrelations in the amplitude fluctuations of brain activity in the form of LRTCs (Linkenkaer-Hansen et al. 2001; Kello et al. 2010; Hardstone et al. 2012; Nikulin et al. 2012). Signatures of critical transitions have mainly focused upon study in systems where there is a) stochastic forcing; and b) an underlying attractor structure that corresponds to a stable fixed point. Systems that give rise to oscillatory structure such as those that undergo a Hopf bifurcation to give rise to a stable or unstable limit cycle (respectively termed *supercritical* or *subcritical*) are less well studied. Some systems exhibiting oscillatory dynamics have been demonstrated to exhibit critical slowing both analytically and numerically (van Nes and Scheffer 2007; Chisholm and Filotas 2009) such as in the supercritical Hopf bifurcation associated with generalised predator-prey models but also at saddle-node bifurcations in Lotka-Volterra competition models (Chisholm and Filotas 2009). In neurobiology a large class of neural mass models generate oscillations through a transition across a supercritical Hopf bifurcation (Freyer et al. 2011; Aburn et al. 2012). Tuning of these models towards the critical point in the transition to limit cycle behaviour has demonstrated that they exhibit the aforementioned hallmarks of critical transitions, namely long tailed (specifically power law) autocorrelations (Aburn et al. 2012).

When asking if a system will evolve into a synchronized state we must ask whether the manifold itself is attracting or repelling. Typically in DST, the stability of a systems equilibria can be conducted using the notion of Lyapunov stability (Holmes and Shea-Brown 2006). In particular, it is possible to separate Lyapunov exponents into those that are *tangential* to the manifold and describe the evolution of the synchronized dynamics, and those that are *transverse* and describe whether orbits will approach or diverge from the synchronization manifold. If there is at least one positive transverse (also known as *conditional*) exponent then small perturbations away from the manifold will grow, and synchronization will be unstable.

Stability is usually governed by the strength of coupling \( c \). In the case of coupling below the critical value \( (c < c_k) \), stability dictates that the largest transverse Lyapunov exponents is negative: the influence of any perturbations will eventually dissipate. At and above the critical point \( (c > c_k) \) transverse stability is lost as Lyapunov exponents pass zero from below. This transition is known as a
Part A: Introduction and Background

‘blowout’ bifurcation as the system goes from a low dimensional synchronized state to the high dimensional dynamics of the independent systems.

In more biologically realistic systems, there is asymmetry, i.e. \( f \neq g \). This has the effect of ‘pulling’ the synchronization manifold away from the diagonal that occurs in the synchronization of symmetric systems (Kocarev and Parlitz 1996). The manifold is thus given by a smooth mapping between the states of the two interacting systems:

\[
\mathbf{x}^R = \Psi(\mathbf{x}^D)
\]

this mapping provides the foundations of \textit{generalized synchronization} that states that the remapping of \( \mathbf{x}^D \) by \( \Psi \), ensures that “\textit{two close states in the phase space of the response system correspond to two close states in the phase space of the driving system}” (Rulkov et al. 1995). This formulation provides the foundations for several methods which aim to quantify synchrony through projection of a time series back into its phase space. In the methods section of this thesis we will introduce a method for determining extended (power-law) autocorrelations in the time series of phase interactions between neural populations (Detrended fluctuation analysis for phase synchrony Botcharova et al. 2014).

6 Parkinson’s Disease as a Loss of Dynamical (In)stability

Having now introduced some basic principles from dynamical systems and in particular, synchrony in neural systems, we now bring together what we know about the pathophysiology of PD, namely the excessive amplitude of beta oscillations in the subcortex and ask how we can frame pathological activity in terms a shift in the dynamical stability of the system.

As introduced previously, there has been a recent shift in the field of PD electrophysiology to describe the time resolved dynamics of beta activity (Cagnan et al. 2015; Feingold et al. 2015; Tinkhauser et al. 2017). This is in part due to the large interest in developing online, closed-loop stimulation strategies for DBS (Cagnan et al. 2017). As expected from a general hypothesis of aberrant synchronization, these studies have found that the beta oscillations that have been classically identified using time-averaged frequency domain measures, possess fluctuations in their amplitude that can be described as ‘beta bursts’. These arguably discrete events last in the range of 100-700ms, with a duration that is elongated in the pathophysiological state. The extension of beta burst duration would suggest an increased stability of the attractor dynamics that underly the beta state and that the systems resilience to transition away from beta is reduced. Furthermore, other experimental work has analysed the time evolved synchronization between activities in the STN and cortex to demonstrated that its activity is also intermittent (Rubchinsky et al. 2012; Ahn et al. 2015). Modelling of this time-fluctuating synchronization has identified a regime that is best able to reproduce experimental findings when the system is poised between the fully coherent or in-coherent states (Rubchinsky et al. 2012). These findings speak to a literature of self-organized instability in the brain and its failure during disease.
(Friston et al. 2012a; Meisel et al. 2012). As introduced in section 4.4.2, extended autocorrelation of neural signals in the form of LRTCs is expected in systems poised near critical points. Analysis of LFPs from the STN in patients with PD has demonstrated the existence of LRTCs in their amplitude fluctuations (Hohlefeld et al. 2012). This work presented evidence that scaling was decreased following dopamine withdrawal, a finding that would agree with a hypothesis that dopamine acts to poise the system closer to a critical state.

Understanding how dopamine may act to modify the stability of oscillations and long-distance synchronization in the cortico-basal ganglia network is a major aim of this thesis. Specifically, we are interested in how changes in neural connectivity that result from altered plasticity following dopamine withdrawal act to reshape the underlying dynamical system. Thus, we will look at synchronization at the scale of activity within a single nucleus (the STN) and then carry this up to look at how the structures of the basal ganglia are connected under the influence of dopamine. From this initial investigation of the statistical properties of recorded signals we will then use models of the system to ask how the identified changes in connectivity might result in pathological dynamics.
Part A: Introduction and Background
Part B: Hypotheses and Methods
1 Thesis Outline and Hypotheses

1.1 Outline

This thesis concerns the nature of neurophysiological synchronization in the motor system of the brain and its dysregulation in Parkinson’s disease (PD). I am specifically interested in the role of beta synchrony in PD due to numerous findings that demonstrate an intimate link between excessive power of oscillations in the beta band (14-30 Hz) and motor impairment. By analysing the changes in connectivity of the basal-ganglia (BG) that occur during PD and through achieving a better characterization of the dynamics of synchronization across the network, I hope to provide a better insight into the mechanisms that generate pathological activity and motor impairment. This work aims to improve clinical interventions as well as shedding light on the mechanisms that bring about the emergence of pathological oscillations in the brain. My working hypotheses and research questions are summarized in the following:

H I. Pathological beta activity in the STN is diffusively synchronized within the nuclei and across neighbouring structures. This synchronization is altered significantly in PD such that pathological rhythms ‘infect’ connected ensembles to disrupt their normal activity.

H II. Dopamine depletion associated with PD significantly alters the synaptic connectivity of the cortico-BG networks. These changes are manifest in the propagation of rhythmic activity across the network and thus directional functional connectivity should be significantly altered by differences in dopaminergic drive.

H III. Changes to cortical interactions with the BG are not found in the overall degree of synchronization. Instead it is the temporal organization of phase coupling of the STN and cortex, and its relationship to fluctuations in beta oscillations in the BG.

H IV. Strong and persistent oscillatory behaviour such as beta oscillations implies that the underlying dynamics have become more stable. We will propose that these changes should be detectable in statistical hallmarks of stability or proximity to critical transitions.

The relationship between the onset of beta oscillations and PD (Oswal et al. 2013; Brittain and Brown 2014) as well strong evidence for their functional role in the healthy brain (Tan et al. 2014; Palmer et al. 2016) suggest that developing a more sophisticated mechanistic explanation of beta synchrony in the BG, beyond that of the current ‘jamming’ or ‘status quo’ hypotheses will facilitate a better understanding of not only how to better treat disorders of the cortico-BG system but also potential influence of beta rhythms upon motor processing in the system.

In this first part of this section, I will explain the motivation for each hypothesis and outline the methodological approach that I will take to testing them. Then, in the second half of this section, methods that are commonly used throughout this thesis will be explained in more detail. Methods that
are used exclusively within a single project will be described within the methods sections of their respective chapters.

1.1.1 Hypothesis I: Pathological Subcortical Beta Synchronization is Non-Local and Spreads to the Surrounding Network

Beta oscillations in the BG of Parkinson’s disease patients have been demonstrated to be reduced by dopamine (Brown et al. 2001; Priori et al. 2004; Weinberger et al. 2006) as well as through deep brain stimulation (Wingeier et al. 2006; Kühn et al. 2008; Whitmer et al. 2012). Current hypotheses regarding how pathological activity results in motor impairment propose that an overactive subthalamic nucleus (STN) in the BG acts to ‘jam open’ the network. To verify this hypothesis, we will examine the activity recorded from within the STN and quantify the changes that occur to beta power in response to changes in dopamine.

Next, we will test how pathological activity within the STN is related to activity in neighbouring structures. In order to do this will investigate the connectivity between recordings made within the STN and its surrounding networks in the BG. This step requires an analysis of functional connectivity and the changes that occur to it under the influence of dopamine. The analysis of interactions between regions of the brain can be broadly divided into three types of connectivity: structural (axonal projections), functional (statistical dependencies between brain regions), and effective (the causal influence of one region on another) (Friston 2011; Razi and Friston 2016). We focus here on characterising functional and effective connectivity, as these can be estimated directly from neurophysiological recordings.

By measuring first, the functional connectivity (FC) of the system, we are able to determine the existence of correlations between brain regions. These analyses cannot explicitly determine the exact pathways by which they are coupled or any causal relationship between them but can quantify the spectral frequencies at which there is significantly correlated activity and determine how these might change with treatment. In most cases, we look at quantities in the frequency domain (e.g. spectral coherence) that identify statistical dependencies between the amplitudes and/or phases of periodic signals. In PD, it is well reported that there is excessive ‘local’ synchrony in the STN, but it is as yet unclear exactly how spread this activity is across the nuclei and its neighbouring structures. From experimental data we expect to see that either: i) beta is restricted to the STN but blocks propagation of normal activity through it; ii) excessive synchronization between the STN and a small number of other nuclei in some way obstructs normal communication between other parts of the network; or iii) the whole system is strongly and diffusely synchronized indicative of a spread of pathological rhythms. These hypotheses are the primary focus of chapters I and III.
1.1.2 Hypothesis II: Changes in Directional Connectivity Underpin the Emergence of Pathological Beta Activity

Previous work has demonstrated that changes in the organization of synaptic transmission between cortex and BG can result in the emergence of pathological synchrony in both computational models (Holgado et al. 2010; Moran et al. 2011; Marreiros et al. 2013; Pavlides et al. 2015) and experiments (Kumar et al. 2011; McCarthy et al. 2011; Tachibana et al. 2011). Furthermore, L-DOPA, the principle treatment for PD, has been shown to facilitate enhanced neural plasticity, a feature which may help restore normal function but is also implicated in the onset of L-DOPA related dyskinesias (Picconi et al. 2003; Calabresi et al. 2015). Specifically, in line with the original rate model, we expect dopamine withdrawal to lead to an overactivity of the indirect pathway, although how this may express itself in terms of frequency domain features is unknown (Gerfen and Wilson 1996; Zold et al. 2012). We are interested in understanding how the changes in the coupling between neural assemblies that occur following neural degeneration in PD, chiefly the loss of nigrostriatal dopaminergic transmission, are manifest in changes to the dynamical properties of the system as a whole (e.g. the emergence of pathologically stable, rhythmic, synchronized activity).

The network organization of the BG and cortex is founded in the ‘canonical’ model of Albin, Young, & Penney (1989) and the initial interpretation of any results will be made in the context of this model. This model and its derivations (Bolam et al. 2000; Graybiel 2000) are based upon extensive anatomical studies of the axonal transmission between structures of the network. These connections form the scaffolding for a dynamical system that we presume to provide the generating mechanisms of observed neural activities.

Quantifying neural connectivity in experimental data is of great relevance to understanding the passage of information across neural networks. To this end, FC provides a good starting point from which to assess changes in dependencies between recorded signals in disparate regions of the brain. However, it is interesting to ask whether directed transmission of axonal propagated spikes may be determined from analyses of connectivity in field activity. We expect that the large recurrent architecture of the brain (Douglas and Martin 2007; Edelman and Gally 2013) may make the estimation of connectivity between nodes separated by long distances, or a large number of intermediary structures, a challenge. However, the well-studied anatomical connectivity of the BG is a good starting point as the canonical model provides good prior expectations of the patterns of functional connectivity to be found. In actuality, how anatomical connectivity matches with functional connectivity is a standing question in the field and is unlikely to be a straightforward one-to-one mapping (Honey et al. 2009; Deco et al. 2014).

To investigate directed FC (dFC), we will use a combination of approaches which will be discussed later in the methods section. In the introduction we brought forward a number of specific mechanistic hypotheses that have been posited to explain the emergence of pathological activity as a result of
changes in synaptic connectivity. In chapter III, we will examine the plausibility of these mechanisms in light of the patterns of dFC estimated from neural data. In chapter IV we will examine these patterns of connectivity but interpret results through fitting of data to a mechanistic model.

1.1.3 Hypothesis III: Patterning of Interactions between the Cortex and Basal-Ganglia Changes Under the Influence of Dopamine

The motor symptoms associated with PD, such as a difficulty in initiating movements (akinesia), a slowness of movement (bradykinesia), and a paucity of movement (hypokinesia) imply that there is a disconnection between cortical motor commands and their execution. However, a number of studies investigating the long-distance synchronization (coherence) between the cerebral cortex and BG in PD patients have not found definitive evidence of a modulation of cortical-STN functional connectivity by L-DOPA (Hirschmann et al. 2011; Litvak et al. 2011). Instead it has been reported that there is significant coherence in the high beta range (24-30 Hz) that is largely unresponsive to L-DOPA. A recent study has investigated the role of the coupling between the cortex and STN during high amplitude fluctuations in beta power (‘beta bursts’) in the LFP (Tinkhauser et al. 2018). The work reported increased correlation between the beta amplitude profiles in the cortical signals and STN during beta bursting suggesting there was an increased cortico-subthalamic coupling. In chapter V, we will extend this work by investigating the relationship between the relative phase between the structures and the onset of beta fluctuations in the subcortex. Relative phase provides an interesting variable to measure as it has been proposed as an ideal candidate for an ‘order parameter’ in the brain (Bressler and Kelso 2001). Relative phase is a global variable that can signify the coordination between disparate regions of the brain yet remains accessible at a local level. Furthermore the interaction between changes in connectivity and local dynamics is an important question in the field (Cabral et al. 2011; O’Neill et al. 2018). This work will develop a framework to investigate time resolved dynamics to investigate power and phase coupling in unison.

1.1.4 Hypothesis IV: Dopamine Withdrawal Stabilizes the Network and Increases the Propensity of Beta Synchronized States

The functional impairments associated with PD are compatible with a dynamical interpretation of the disease (which we introduced in the previous section of this thesis) in which the brain’s ability to flexibly navigate a set of metastable or multi-stable modes is hindered (Dotov 2014). A failure of self-organized criticality or other dynamical instability has been suggested to underlie the emergence of epileptic seizures, a more generalised hyper-rhythmia than that seen in PD (Meisel et al. 2015), yet a similar mechanism could exist within the cortico-basal-ganglia network. Akinesias, especially in the early stages of PD, are characterised by a difficulty initiating a motor program such as a step, but the movement itself is largely unaffected (Burleigh-Jacobs et al. 1997). This would imply that the locomotor mode (the step) as an attractor state is itself intact yet the manifold on which it is embedded
is significantly altered in PD such that the ability to transition between states is reduced. If we think of the problem in terms of a bi-stable dynamical system (such as that depicted in figure 1 in the introduction) in which there are two attractors- one prokinetic, the other antikinetic- then it can be imagined how changes in the relative curvature of the energy landscape would bias the system’s ability to transition from one to the other. With respect to movement initiation, patients are reported to use a mechanism of ‘sensory-cueing’ by which they use auditory or visual regularities in their environment that can ease the initiation of movement (Grabli et al. 2012). This cueing could result restructuring of the dynamical landscape to effectively decrease the energy required to transition into a prokinetic state. This view is consistent with the proposed role of the BG as a centre of action selection and inhibition (Mink 1996), and specifically a role for the subthalamic nucleus as a dynamical switch for decision making (Frank et al. 2007). In particular the ‘hold your horses’ model of Frank highlights the role of cortical input to BG that acts to increase the effective threshold to permit execution of movement. These kind of dynamical biases (via connectivity) may help better explain the functional anatomy of the network.

From this model of BG synchrony, we would expect that the stability of the synchronization between components in the network would be increased. If it is possible to approximate the changes in synchronization stability when going between treatment and no-treatment or when comparing PD patients and controls, then it may be possible to understand the Parkinsonian state within the framework of a disordered dynamical landscape. Of particular interest is identifying the parameters or connections in the network that most influence the systems propensity to synchronization. Through this, we may identify better ways to which to artificially destabilize the STN in place of the normative physiological mechanisms.

The influence of topology of a network of coupled oscillators upon synchronization is an important question within many applied fields (Wiley et al. 2006; Menck et al. 2013). For example, in the brain it has been demonstrated that the specific wiring patterns of the hippocampus give rise to changes in propensity for different types of epileptic activity. Specifically, increases in the strength of recurrent connections within CA3 reduce the tendency toward seizure activity in favour of increased bursting behaviour (Netoff et al. 2004). In PD, it has been demonstrated experimentally that certain connections in the BG network are required for the generation of beta oscillations (Tachibana et al. 2011). To test these hypotheses, we will take two approaches: a) examine the behaviour of models under perturbation and ask how changes in connectivity modulate their properties, and b) look for statistical markers of ‘criticality’, namely persistent autocorrelation states that may indicate the proximity of the experimental system to the onset of oscillatory activity (through a critical transition). Approach (a) will be the focus of chapter IV and approach (b) will be used in chapters I and IV. In chapter V, we will analyse time evolving beta activity and investigate how cortical phase locking may influence its temporal dynamics as a proxy for a shift in the system’s underlying propensity to be in a synchronized state.
1.1.5 Summary of Research Aims

Taken together, the hypotheses presented here aim to frame PD in terms of a shift in neurodynamic stability of synchronous activity in the brain. In this work we will ask how specific changes in the connectivity between areas of the BG and cortex, inferred from analyses of neurophysiological recordings, have consequences for the large scale dynamics of the system as a whole. If we frame neural synchrony in PD in terms of a pathological stability of brain activity then this will provide a novel view by which to better understand the mechanisms of impairment, pharmacological treatment, and deep brain stimulation (DBS).

2 Experimental Data

The empirical work in this thesis is based upon two sets of data examining the electrophysiology of PD. The first comes directly from patients with idiopathic PD in which LFPs were recorded from the STN along with simultaneous whole head magnetoencephalography (MEG). The second set of data concerns a rodent model of dopamine depletion associated with PD. This data consists of electrocorticography (ECoG) over motor cortex in addition to multisite LFP recordings across several structures of the BG.

2.1 Patients with Parkinson’s Disease

2.1.1 Patient Details and Surgical Implantation of Deep Brain Stimulation Electrodes

The majority of the patient data were taken from a study involving a 17 patient cohort who had all undergone surgery for chronic implantation of DBS electrodes in the STN (see Litvak et al., 2011, 2012). The patients have undergone simultaneous MEG and intracranial recordings. The majority of recordings were performed twice when patients were either ON or OFF their dopaminergic medication. The clinical details of a subset of the cohort, used in chapter I are summarized in table 1. The study was approved by the joint ethics committee of the National Hospital for Neurology and Neurosurgery and the UCL Institute of Neurology, and the patients gave written informed consent before the study onset.

All patients were diagnosed with PD according the Queen Square Brain Bank criteria (Gibb and Lees 1988). The selection criteria, operative procedure and clinical outcomes of DBS therapy have been previously reported (Foltynie et al. 2011). The degree of clinical impairment was assessed prior to surgery (<5 months preoperatively) using part III (motor impairment) of the Unified Parkinson’s Disease Rating Scale (UPDRS) following overnight withdrawal of all dopaminergic medication (OFF) and following administration of their pre-operative dose of levodopa (ON). This gave a wide range of UPDRS scores by which we could correlate signal features with the degree of patients’ motor impairment.
Prior to surgery, the motor impairments of all patients were evaluated using Part III of the Unified Parkinson's Disease Rating Scale (UPDRS) after withdrawal of all dopaminergic medication overnight, and following administration of 200mg of levodopa. The deep brain stimulation electrode used was model 3389 (Medtronic, Minneapolis, MN, USA) with four platinum-iridium cylindrical surfaces of diameter 1.27 mm, length 1.5mm and centre-to-centre separation 2 mm. The contacts were numbered 0 (lowermost, lying just below or in the inferior portion of the subthalamic nucleus) to 3 (uppermost, usually in the superior portion or just above the subthalamic nucleus in the zona incerta). Surgical targeting of the deep brain stimulation electrode was based on stereotactic magnetic resonance images. Fast acquisition T2-weighted 2mm thick contiguous axial slices were acquired with a stereotactic Leksell Frame (Elekta, Sweden). The subthalamic nucleus (especially its medial border; Hariz et al., 2003) was examined on the axial image containing the largest diameter of the ipsilateral red nucleus. The centre of the subthalamic nucleus was identified in a plane 0–1mm behind the anterior border of the ipsilateral red nucleus. Calculations of Cartesian coordinates of the target point were performed on Framelink software (Medtronic). A double oblique trajectory was planned on reconstructed 3D images to avoid entry into sulci and ventricles (Zrinzo et al. 2009). The detailed surgical procedure has been described previously (Foltynie et al., 2010). After implantation, electrodes were connected to an accessory kit, typically both connectors being tunnelled to the left temporoparietal area and externalized through the frontal region. No microelectrode recordings were made. The locations of the electrodes were confirmed with immediate postoperative stereotactic
imaging. Fast spin-echo T2-weighted 2mm thick contiguous axial slices were acquired with the Leksell frame still in situ. One patient was unable to tolerate a postoperative MRI and underwent stereotactic computed tomography scanning instead. Although electrodes were considered to lie within or abutting subthalamic nucleus, we cannot assume that all contacts on each electrode shared this localization; indeed, this would seem highly unlikely given the size and orientation of the nucleus in relation to electrode trajectory.
### Part B: Hypotheses and Methods

#### 2.1.2 Simultaneous subthalamic nucleus local field potential and magnetoencephalogram recordings

Patients underwent simultaneous subthalamic nucleus electrode LFP and 275 channel MEG (CTF/VSM MedTech, Vancouver, Canada) recording between two and six days postoperatively. The data were
sampled at 2400 Hz and stored to disk. For subsequent off-line analysis the data were low-pass filtered at 100 Hz and down-sampled to 300 Hz. Simultaneous to the MEG signal, the LFP, electro-oculographic (EOG) and electromyographic (EMG) signals were recorded using the integrated EEG system and high-pass filtered in hardware (41Hz) to avoid saturation of the amplifiers due to direct current offsets. Four intracranial LFP channels were recorded on each side, referenced to a cephalic reference (forehead for the first two patients, right mastoid for the rest). LFP recordings were converted off-line to a bipolar montage between adjacent contacts (three bipolar channels per side) to limit the effects of volume conduction from distant sources. Electromyography was recorded from right and left first dorsal interosseus muscles with a reference at the muscle tendon. Recordings were made twice, once after omitting all dopaminergic medication overnight and once during the patient’s usual medication regime, in an order counterbalanced across patients. Each recording involved rest blocks and task blocks in a randomized order (Litvak et al. 2010). We focus on data collected during the resting blocks, which lasted 3 min each and were cued visually using MATLAB (The Mathworks Inc, Natick, MA, USA) and a custom script based on the Cogent toolbox http://www.vislab.ucl.ac.uk/cogent). During the rest block, the patient was asked to keep still, relax with their eyes open and focus on a fixation point. A neurologist was present in the magnetically shielded room during the experiment to monitor the patient’s well-being and performance of the task.

Local field potentials and electromyographic (EMG) signals were simultaneously collected using an EEG device integrated in the MEG scanner (CTF/VSM MedTech, Coquitlam, BC, Canada). Bipolar EMG recordings were made from the muscle belly of the first dorsal interosseus of the hand referenced to the tendon. Signals were hardware low-pass filtered (>1Hz) in order to avoid saturation of the amplifier resulting from large DC offsets. In addition, head location data were continuously collected using the Head Position Indicator (HPI) coils placed on the subject’s nasion and the two pre-auricular points. The data were sampled at 2400Hz and stored to disk. The STN electrodes have four contacts at 0,1,2,3 where the zero contact is targeted 2mm below the centre of the STN. LFP recordings were made with reference to a cephalic reference electrode and later converted offline to a bipolar montage giving rise to 3 channels consisting each of a pair of adjacent contacts.

2.2 6-OHDA Rat Model of Parkinson’s Disease

2.2.1 6-Hydroxydopamine Lesions of Dopamine Neurons

Unilateral 6-OHDA lesions were carried out on 200–250 g rats, as described previously (Mallet et al. 2008a, 2008b). Twenty-five minutes before the injection of 6-OHDA, all animals received a bolus of desipramine (25 mg/kg, i.p.; Sigma) to minimize the uptake of 6-OHDA by noradrenergic neurons (Schwarting and Huston 1996a). Anesthesia was induced and maintained with 4% v/v isoflurane (see above). The neurotoxin 6-OHDA (hydrochloride salt; Sigma) was dissolved immediately before use in ice-cold 0.9% w/v NaCl solution containing 0.02% w/v ascorbate to a final concentration of 4 mg/ml.
Part B: Hypotheses and Methods

Then 3 ml of 6-OHDA solution was injected into the region adjacent to the medial substantia nigra (4.5 mm posterior and 1.2 mm lateral of Bregma, and 7.9 mm ventral to the dura. The extent of the dopamine lesion was assessed 14–16 days after 6-OHDA injection by challenge with apomorphine (0.05 mg/kg, s.c.; Sigma) (Schwarting and Huston 1996b). The lesion was considered successful in those animals that made >80 net contraversive rotations in 20 min. Electrophysiological recordings were carried out ipsilateral to 6-OHDA lesions in anesthetized rats 21–42 days after surgery, when pathophysiological changes in the BG are likely to have levelled out near their maxima (Mallet et al. 2008a).

2.2.2 Electrophysiological Recordings

Experimental procedures were carried out on adult male Sprague-Dawley rats (Charles River, Margate, UK) and were conducted in accordance with the Animals (Scientific Procedures) Act, 1986 (UK). Recordings were made in eight dopamine-intact control rats (288–412 g) and nine 6-OHDA-lesioned rats (285–428 g at the time of recording), as described previously (Magill et al. 2006; Mallet et al. 2008a, 2008b; Moran et al. 2011). Briefly, anesthesia was induced with 4% v/v isoflurane (Isoflo, Schering-Plough Ltd., Welwyn Garden City, UK) in O2, and maintained with urethane (1.3 g/kg, i.p.; ethyl carbamate, Sigma, Poole, UK), and supplemental doses of ketamine (30 mg/kg; Ketaset, Willows Francis, Crawley, UK) and xylazine (3 mg/kg; Rompun, Bayer, Germany).

The ECoG was recorded via a 1 mm diameter steel screw juxtaposed to the dura mater above the right frontal cortex (centred at 4.5 mm anterior and 2.0 mm lateral of Bregma, corresponding to the “secondary motor cortex” (M2) of (Paxinos and Watson 2007) or the medial agranular field of the somatic sensorimotor cortex of Donoghue and Wise, (1982); see Figure 1B) and was referenced against another screw implanted in the skull above the ipsilateral cerebellar hemisphere. Raw ECoG was band-pass filtered (0.3–1500 Hz, -3 dB limits) and amplified (2000x; DPA-2FS filter/amplifier: Scientifica Ltd., Harpenden, UK) before acquisition (see below). Extracellular recordings of LFPs in the dorsal striatum (STR), GPe and STN were simultaneously made in each animal using ‘silicon probes’ (NeuroNexus Technologies, Ann Arbor, MI); a first probe captured LFPs in STR and GPe, whereas a second probe captured LFPs in the STN (Figure 1B). Each probe had one vertical array of 16 recording contacts (impedance of 0.9–1.3 MΩ measured at 1000 Hz; area of ~400μm²), and each contact on a given probe was separated by 100 μm. Recording sites in the BG were verified by post hoc histology, as described previously (Magill et al. 2006; Mallet et al. 2008a, 2008b), as well as through comparisons of recorded unit activity with the characteristic discharges of STR, GPe and STN neurons in anesthetized dopamine-intact rats and 6-OHDA-lesioned rats (Magill et al. 2006; Mallet et al. 2008a, 2008b; Abdi et al. 2015; Sharott et al. 2017). The same two probes were used throughout these experiments, but were cleaned after each experiment in a proteolytic enzyme solution to ensure that contact impedances and recording performance were not altered by probe use and re-use (Magill et al. 2006; Sharott et al. 2017).
Monopolar probe signals were recorded using high-impedance unity-gain operational amplifiers (Advanced LinCMOS: Texas Instruments, Dallas, TX) and were referenced against a screw implanted above the contralateral cerebellar hemisphere. After initial amplification, extracellular signals were further amplified (1000x) and low-pass filtered at 6000 Hz using programmable differential amplifiers (Lynx-8: Neuralynx, Tucson, AZ). The ECoG and probe signals were each sampled at 17.9 kHz using a single Power1401 Analog-Digital converter (with integrated ADC16 expansion units) and a PC running Spike2 acquisition and analysis software (Cambridge Electronic Design Ltd., Cambridge, UK). All signals recorded in a given experimental epoch were captured in a single data file. This, together with the use of a fixed/consistent sampling rate and a single acquisition interface, ensured accurate synchronization (temporal alignment) of cortical and BG signals.

Neuronal activity was recorded during episodes of spontaneous ‘cortical activation’, which contain patterns of activity that are similar to those observed during the awake, behaving state (Steriade 2000). Cortical activation was defined according to ECoG activity. Neuronal activity patterns present under this anesthetic regime may only be qualitatively similar to that present in the unanaesthetised brain. However, the urethane-anesthetized animal still serves as a useful model for assessing ensemble dynamics within the BG. Indeed, in 6-OHDA-lesioned animals, exaggerated beta oscillations emerge in cortico-BG circuits during activated brain states thus accurately mimicking the oscillatory activity recorded in awake, un-medicated PD patients.

3 Signal Analysis

3.1 Analysis Software

The majority of the analyses presented in this thesis were performed within MATLAB (The MathWorks, Nantucket, MA) using custom scripts written with a number of toolboxes (for a full list see the appendix 1). Many of the scripts and pipelines for the analyses presented in this thesis are available on GitHub (https://github.com/twestWTCN).

3.2 Preprocessing of LFP Recordings

Neurophysiological recordings are subject to low signal to noise issues especially in the case of external recordings made from outside of the brain. Consequentially, a large part of the recorded signal is non-relevant to brain processes. Artefacts can arise from a diversity of sources such as the electrocardiogram (ECG), head and neck movement, electromyogram (EMG) and oculomotor activity. Most software packages designed for the use of neurophysiological data include implementation for signal preprocessing. Most schemes involve the use of high pass filtering to remove slow baseline drifts and large amplitude deflections from movement; notch filtering to remove line noise occurring at 50/60 Hz; baseline correction; Z-score thresholding to remove segments of signal contaminated by artefact; as
well as more complicated tools such as independent component analysis for the removal of eye blink or ECG artefacts. The preprocessing steps that are required for a study are not universal and are often tailored to the specific requirements of the research’s analysis. In the case of this thesis we give the exact details of signal preprocessing in the methods section of each chapter.

### 3.3 Spectral Analysis

Oscillatory activity as measured in the EEG, MEG or LFP is the result of large-scale synchronization of neural activity that an electromagnetic field that is detectable either as a potential difference between conducting electrodes or as a magnetic flux detectable in a SQUID array. In order to determine the power of oscillatory components in a signal the Fourier transform is used in order to convert signals from the time to the frequency domain.

The power spectrum is given by:

$$S_x(\omega, n) = E[S_x(\omega, n)S_x(\omega, n)^*],$$

where $S$ denotes the complex-valued Fourier spectra, $E$ is the expected value of a function and * indicates the complex conjugate. In order to make comparisons between spectra, normalisation may be achieved by dividing by the total power such that differences in signal gain between subjects may be accounted for.

Thomson’s multi-taper method provides a way to compute spectral estimates but with smoothing in the frequency domain as a result of the multiplication with a set of window functions (Thomson 1982). Multi-taper estimates are made from an average of Fourier transformed short epochs that have been multiplied by a set of orthogonal window functions to yield a frequency smoothing kernel (Prieto et al. 2007).

### 3.4 Functional Connectivity Analysis

#### 3.4.1 Spectral Coherence

The spectral coherence between two signals $X(t, n)$ and $Y(t, n)$ is first determined by estimation of the cross-spectral density, which encapsulates both the mean phase-difference between signals, as well as the correlation of power between $S_x(\omega)$ and $S_y(\omega)$. The cross-spectral density (CSD) is given by:

$$S_{xy}(\omega, n) = E[S_x(\omega, n)S_y(\omega, n)^*]$$

Taking the complex conjugate changes the sign of the imaginary part of $S_y$ such that multiplication of complex conjugates results in a subtraction of the imaginary component. As the imaginary part of the power spectrum is equal to its phase, peaks in the cross spectrum reveal frequencies common to both $x$ and $y$ that are weighted by the degree of phase consistency as well as their amplitudes.
The magnitude squared coherence is the modulus of the CSD normalized by the respective power spectra of its constituents:

$$|R_{xy}(\omega)|^2 = \frac{|S_{xy}(\omega)|^2}{\sqrt{S_{xx}(\omega)S_{yy}(\omega)}}.$$ 

The coherence can be thought of as equivalent to the coefficient of determination $R^2$. It is therefore a real number such that for any given frequency $1$ is equal to maximal correlation between two time series and $0$ indicates an absence of correlation (Halliday et al. 1995). The 95% confidence limits for this measure can be calculated analytically (see Halliday et al. 1995).

### 3.4.2 Phase Synchronization

There is some ambiguity in the coherence measure, in that it yields high values in the presence of correlations in either phase or amplitude. We next look at a set of measures that are designed to measure only correlations in phase. To begin, all of these methods first need an estimate of the instantaneous phases of the signals to be compared. This may be achieved using a number of methods such as Fourier, Hilbert, or wavelet approaches (Le Van Quyen et al. 2001). Arguably the simplest measure of phase synchronization is the phase locking value (PLV; Lachaux et al. 1999; Mormann et al. 2000), a measure of the overall phase consistency. If the relative phase (phase difference) of two signals is stable, then the signals are said to be ‘phase locked’ and are phase synchronized. In the condition of phase synchronization, but in the presence of noise, an estimate of the total phase locking may be estimated from the resultant vector length of the signals relative phase projected onto the unit circle (Lachaux et al. 1999; Mormann et al. 2000):

$$PLV = |\langle e^{i\Delta \phi} \rangle|,$$

with $PLV \gg 0$ indicating that the signals have some degree of phase synchronization. Note that $\langle \cdot \rangle$ indicates the expected value, and $|\cdot|$ is the vector length, $\phi$ is the relative phase, and $i$ is the imaginary unit. When $PLV = 1$, the signals are perfectly phase locked. In finite time PLV can be measured in a signal over a set of $N$ samples:

$$PLV = \left| \frac{1}{N} \sum_{k=0}^{N-1} e^{i\Delta \phi} \right|.$$ 

### 3.4.3 Pairwise Phase Consistency

The PLV is a biased estimator, yielding higher valued estimates than expected for low sample sizes. The PPC is asymptotically equivalent to the population statistic of the squared PLV (Vinck et al. 2010)
Part B: Hypotheses and Methods

Figure 2 – Illustration of the phase lag index (PLI) and weighted phase lag index (WPLI) – Phase differences of two signals are represented as blue lines on the unit circle. In PLI, each non zero phase difference contributes equally to the measure of asymmetry in the distribution. However, small amounts of noise can cause phase lags to turn to leads as they cross the real axis (red line). WPLI negates the effect of such events by weighting the PLI by the magnitude of the imaginary part of the cross spectra (outside rings) such that samples close to the real axis are down weighted. Figure adapted from Vinck et al., (2011).

but does not suffer from sample size bias making it well suited for investigating phase locking within bursts of variable length. For illustration of the general dynamics independent of the beta burst amplitudes we use PPC computed within a sliding window (1 s duration, 99% overlap). The PPC is computed from $N$ samples of the two evolutions of the phases of signals $i$ and $j$:

$$\psi = \frac{2}{N(N-1)} \sum_{j=1}^{N-1} \sum_{k=j+1}^{N} \cos(\phi_i) \cos(\phi_j) + \sin(\phi_i) \sin(\phi_j).$$

The PPC population statistic is equivalent to the squared PLV. For a full derivation and validation of the method please see Vinck et al. (2010).

3.4.4 (Weighted) Phase Lag Index

Coherence, PLV and PPC are all sensitive to spurious effects resulting from volume conduction between the two signals of interest (Bastos and Schoffelen 2016). These are assumed to occur at zero phase lag. In order to overcome this problem, several methods have been developed including analysis of the imaginary part of coherence (Nolte et al. 2004), and the phase lag index (PLI) (Stam et al. 2007). In this thesis we have opted for the weighted phase lag index (WPLI) as it has been demonstrated to be robust to simulated volume conduction effects, robust to noise, and sensitive to a range of relative phase distributions (Vinck et al. 2011). Like coherence WPLI is scaled 0 to 1. Exact details of the WPLI method can be found in Vinck et al. (2011), but we describe the method here briefly. WPLI is a modification of simpler PLI. The PLI effectively quantifies non-zero distribution of phase differences by taking the expected value of the sign of the phase difference:
\[ \Psi \equiv |E\{sgn(\Im \{S_{xy}\})\}|, \]

where \(E\{x\}\) is the expected value, \(sgn\) is the sign function, and \(\Im \{S_{xy}\}\) is the imaginary component of the cross spectrum. This effectively quantifies an index of asymmetry of the distribution of phase differences between two signals. By measuring the contribution of only the non-zero elements of the distribution of phase differences, PLI provides an estimate of functional connectivity that is uncontaminated by zero phase lag interactions that may arise spuriously from field spread. WPLI then adjusts the PLI for bias towards slightly off-zero phase differences, by weighting the phase differences by the magnitude of its corresponding imaginary component of the cross spectrum:

\[ \Phi \equiv \frac{|E\{|\Im \{S_{xy}\}|sgn(\Im \{S_{xy}\})\}|}{E\{|\Im \{X_{xy}\}\}|}. \]

This correction increases the method’s robustness to noise as small deviations from the real axis are weighted far less than those that are perpendicular. This weighting is visualized in figure 2.

### 3.5 Directed Functional Connectivity

#### 3.5.1 An Overview of Directed Functional Connectivity Metrics

There are a number of approaches to determining directed connectivity in the brain. Below we outline a few broad classes of methods:

A. **Time Delayed Correlations** – Basic assumptions of causality often state that the cause precedes the effect in time. Thus by taking the cross-correlation between two signals, a time lagged correlation may imply that the lagged signal is driven. These simple approaches often hit difficulty in oscillatory signals where the periodicity invokes ambiguity with respect to the relationship between leads and lags in time.

B. **Autoregressive Modelling** – Granger introduced the concept of identifying causality in time series by an analysis of the predictive value of a signal’s past to predict the future of another signal, so called Granger Causality (GC). GC methods have typically used autoregressive models to compare signals predictive value via a comparison of the residual variances. See: Granger causality; and multivariate extensions: directed transfer function and partial directed coherence (Pereda et al. 2005).

C. **Informational based measures** – Using tools from information theory provides a more general way of quantifying nonlinear dependencies between signals. Assessing the joint probability distributions between two signals allows for the degree of information that is shared by the two signals. By introducing lags into the computation, it is possible to look for asymmetries in the coupling. These metrics are closely related to GC based tools but allow for non-Gaussian distributions of states. See: transfer entropy (Pereda et al. 2005).
D. **Phase-based approaches** – If one signal leads another consistently in phase then it can be assumed to be driving the other signal. There are issues with causality in this sense as the circularity of phase means that there is ambiguity in what constitutes a lag or a lead (Vakorin et al. 2013). This may be circumvented somewhat by also looking at amplitude fluctuations and how one leads the other. See: phase-slope index (Nolte et al. 2008).

E. **State space** – All of the methods mentioned so far are dependent upon inference of causality from the time domain which may cause difficulty in a number of situations (Sugihara et al. 2012). Instead dependencies in state space can be used. These methods typically depend on state-space projection of time series using delay embedding. Using these trajectories, it is possible to look for non-linear dependencies in the data and again identifying whether a certain signal takes precedence in influencing the trajectory of the coupled signal. Whilst theoretically quite elegant, empirical data are likely to break many of its assumptions See: Asymmetrical measure of bivariate interdependence, convergent-crossover-mapping (Breakspear and Terry 2002; Feldmann and Bhattacharya 2004; Sugihara et al. 2012).

F. **Causal Modelling** – These approaches are closely related to the previous state space methods but instead of backwards projection from time series to states variables, they explicitly define a generative state space model and then use optimization procedures to invert these models on data. These methods can be powerful as way of testing competing hypotheses but their usage for exploratory analyses is limited by the restriction to a finite hypothesis space. See: Dynamic Causal Modelling (David et al. 2006; Daunizeau et al. 2011).

### 3.5.2 Non-Parametric Granger Causality

Granger causality (Granger 1969) is based on the premise that if a signal $X$ causes a signal $Y$, then the past values of $X$ can be used to predict the state of $Y$ beyond that of the information contained in the past of $Y$ alone. This has conventionally been tested in the context of multivariate autoregressive models fit to the data, This usually involves the comparison between the explained variance of $Y$ using a ‘restricted’ model based on the past of $Y$ alone, to that of a ‘full’ model using information from the past of both $X$ and $Y$ (Geweke 1982). Frequency domain extensions of Granger have since been developed (Geweke 1982; Kamiński et al. 2001) and applied widely across the neuroscience domain (e.g. Brovelli et al. 2004).

The requirement to fit multiple MVAR models can cause several difficulties in analysis, namely: i) the requirement of large model orders to capture complex spectral features, ii) computational cost of model inversion, and iii) assumptions as to the correlation structure of the data. In order to avoid the estimation of parametric models, Dhamala et al. (2008) proposed a non-parametric estimator of Granger Causality that can be derived from widely used Fourier or wavelet-based spectral estimation methods which do not suffer from these complications. The method hinges on the derivation of a spectral matrix directly from the spectral transforms of the data (i.e. Fourier or wavelet), rather than from the transfer and noise
covariance matrices specified in an inverted MVAR model. Instead, the spectral matrix itself may be factorized to derive the transfer function and noise covariance matrices of the set of signals (Sayed and Kailath 2001). Via this technique it is possible to decompose the total power spectrum of $X$ between its intrinsic power and the causal contribution from $Y$. For a full derivation and details of its implementation please refer to Dhamala et al. (2008).

3.5.3 Non-Parametric Directionality

Non-parametric directionality provides a model-free estimate of directional correlations within a system through the decomposition of the coherence into components separated by their lags yielding separate instantaneous, forward, and reverse spectra (Halliday 2015). Briefly, this is achieved using pre-whitening of the forward and reverse Fourier transforms. This acts to bring the spectral content of a signal closer to that of white noise. Optimal pre-whitening is achieved using a minimum mean square error scheme to compute the whitening filter. This procedure is equivalent to generating two new random processes which have spectra equal to 1 at all frequencies:

$$S_{xx}^w(\omega) = 1, S_{yy}^w(\omega) = 1.$$ 

The pre-whitening step effectively eliminates the autocorrelation structure of the respective signals but retains bivariate correlations between them. The pre-whitening brings the denominator of the coherence, the product of the autospectra (a normalization factor), to be approximately equal to 1. Thus, the coherence is reduced to the cross spectra:

$$|R_{xy}|^2(\omega) = S_{xy}^w(\omega).$$

As the coherence loses all terms in the denominator it can then be reduced to the time domain via Parseval’s theorem to yield time domain correlation:

$$\rho_{xy}(\tau) = \frac{1}{2\pi} \int_{-\pi}^{+\pi} S_{xy}^w(\omega)e^{i\omega \tau} d\omega.$$ 

This correlation allows for $R_{xy}^2$ to be decomposed into different ranges of lag. We choose to separate into reverse, instantaneous, and forward components:

$$R_{xy}^2 = \int_{\tau<0}^{0} |\rho_{xy}(\tau)|^2 d\tau + \int_{\tau>0}^{0} |\rho_{xy}(\tau)|^2 d\tau.$$ 

These components may be abbreviated to:

$$R_{xy}^2 = R_{xy,-}^2 + R_{xy,0}^2 + R_{xy,+}^2.$$
where component $R_{xy,-}^2$ yields correlations in which $y$ lags $x$, $R_{xy,0}^2$ instantaneous correlations, and $R_{xy,+}^2$ correlations in which $x$ lags $y$. Returning each component back to the frequency domain yield 3 measures that all sum to the original coherence:

$$|R_{xy}(\omega)|^2 = |R'_{xy,-}(\omega)|^2 + |R'_{xy,0}(\omega)|^2 + |R'_{xy,+}(\omega)|^2.$$

Thus, from each component we can estimate spectrally-resolved directional interactions that have been corrected for peaks in the cross-correlations that arise spuriously the signals’ autocorrelations (by using spectral prewhitening). For a full derivation of the NPD method and details of its algorithmic implementation please refer to Halliday et al. (2016).

In addition to bivariate NPD, we used a multivariate extension (Halliday et al. 2016) that allows the directional components of coherence to be conditioned on a third signal. This partialization of NPD is achieved through a partial regression of $x$ and $y$ conditioned on $z$. This analysis decomposes the partial coherence into the same three directional components: forward, reverse, and zero-lag. This analysis can indicate if information in the bivariate interaction shares variance with other parts of the network. For example, the partial correlation between $x$ and $y$ with $z$ as predictor can be used to determine if the flow of information from $x \rightarrow y$ is independent of area $z$, or whether the flow of information is $x \rightarrow z \rightarrow y$, in which case the partial coherence between $x$ and $y$ with $z$ as predictor should be zero. The partial coherence can also be used to investigate if the flow of information is $z \rightarrow x$ and $z \rightarrow y$, or if it is $x \rightarrow y \rightarrow z$ or $z \rightarrow x \rightarrow y$ in which case the partial coherence, and any directional components should be zero.

## 4 Statistics of Critical Transitions

In order for measures of time averaged synchronization (e.g. coherence) to be significant there needs to be consistency over time of the phase and frequency of the two signals. It is possible to characterize phase interactions that are changing across time through an estimate of the long-range temporal correlation (LRTC) of the phase difference time series. Here we describe Detrended Fluctuation Analysis for phase synchrony (DFA-PS; Botcharova et al. 2014). This method estimates the scaling statistics of the instantaneous rate of change of the phase-difference between two signals of interest.

### 4.1.1 Detrended Fluctuation Analysis

A signal is said to have long-range dependencies if non-zero correlations exists between its samples even when separated by long time intervals. In other words, its auto-correlation function has a slow decay. In the case that this decay is assumed to be well approximated by a power law (an assumption that we will return to later in this section), then DFA provides a way of estimating the extent of long-range temporal correlations (LRTCs) present in the signal (Peng et al. 1995; Shao et al. 2012).
Estimation of the power law exponent $\alpha$ directly from the autocorrelation function is usually impractical due to noisy estimates at large lags as well as non-stationarity in the data. Instead DFA estimates the Hurst exponent $H$ which is linearly related to the exponent $\alpha$ by $\alpha = 2 - 2H$.

The DFA estimation is achieved by dividing the signal of interest into a number of equally spaced boxes in which the root mean square deviation of the linearly detrended signal is computed. This process is repeated over a logarithmic range of box scales. The minimum scale at which this may be achieved is determined by the wavelength of the oscillation of interest. In order to obtain a good sample of oscillatory fluctuations we set the minimum box size at 6 times the wavelength of the lower boundary of the bandpass. The maximum is set such that detrended fluctuations are computed for at least 8 subdivisions of the full length signal.

The mean RMS fluctuation for each box size is then plotted against box scale on a double logarithmic plot. If the resulting fluctuation plot is linear then the gradient of its least squares regression is the estimated Hurst exponent $H$ (Peng et al. 1994, 1995). The exponent $H$ characterizes the extent of temporal dependencies in a signal. White noise, i.e., a ‘memoryless’ signal has an exponent $H = 0.5$ in

Figure 3 – Illustration of the calculation of the time derivative of the phase difference time series. (A) The electrophysiological signals are first band-passed at the peak coherent frequency, with a 5 Hz passband. (B) The signals are then Hilbert transformed to yield the instantaneous signal. Taking the angle of the complex series gives the wrapped phase. (C) The phases are unwrapped and then subtracted from one another to yield the instantaneous phase difference. (D) The derivative is approximated by taking the difference between consecutive samples. This signal is then used to estimate the Hurst exponent using DFA. In the series we can see periods of intermittent phase locking that arise from transient periods of synchrony (shaded blue) or desynchrony (shaded orange) between the two signals.
which correlations in time rapidly decay, whilst $H > 0.5$ characterize signals that exhibit ‘memory’ in the form of LRTCs. Increasing exponent size up to a value of 1.0 indicates more persistent temporal correlations and an increasing amount of order in the signal (Hardstone et al. 2012).

4.1.2 DFA for Phase Synchronization

As we are interested in phase dynamics we apply DFA to the derivative of the instantaneous phase difference between two signals as described in Botcharova et al. (2014). The pre-processed continuous signals from sites $x$ and $y$, $D_{x,y}$, are first filtered with a 5 Hz wide passband centred at the frequency with peak coherence $\lambda$ to yield the oscillations $\tilde{D}_{x,y}$ in the frequency band of interest:

$$\tilde{D}_{x,y} = D_{xy}(\lambda).$$

The analytic signal is then computed via the Hilbert transform:

$$A_n e^{i \phi_n} = H[\tilde{D}_{x,y}],$$

and the instantaneous phase is calculated such that:

$$\Delta \phi_{x,y} = \phi_x - \phi_y = \tan^{-1}\{H[\tilde{D}_x] - H[\tilde{D}_y]\}.$$

In order to use DFA, the series $\phi_1 - \phi_2$ must be converted to a bounded process. In order to do this, we take the rate of change (approximate first derivative) of the time series of the phase difference:

$$\Psi = \frac{d(\phi_x - \phi_y)}{dt}.$$

This signal represents the rate of change of phase difference between the two series. When $\Psi$ is at zero the signals are at constant phase relation (Pikovsky et al. 2003). Previous work measuring the DFA of phase synchrony in noisy Kuramoto oscillator models has suggested that the scale free statistics of the rate of change of phase difference are increasingly persistent (as measured by an increasing DFA

<table>
<thead>
<tr>
<th>Linear</th>
<th>$g(x) = ax + b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quadratic</td>
<td>$g(x) = ax^2 + bx + c$</td>
</tr>
<tr>
<td>Cubic</td>
<td>$g(x) = ax^3 + bx^2 + cx + d$</td>
</tr>
<tr>
<td>Quartic</td>
<td>$g(x) = ax^4 + bx^3 + cx^2 + dx + e$</td>
</tr>
<tr>
<td>Quintic</td>
<td>$g(x) = ax^5 + bx^4 + cx^3 + dx^2 + ex + f$</td>
</tr>
<tr>
<td>Square-root</td>
<td>$g(x) = ax^2 + b$</td>
</tr>
<tr>
<td>Cube-root</td>
<td>$g(x) = ax^3 + b$</td>
</tr>
<tr>
<td>Logarithmic</td>
<td>$g(x) = a \log(x) + b$</td>
</tr>
</tbody>
</table>

Table 1 – Family of models for PEB Model Comparison to Assess DFA Fluctuation Plot Linearity
exponent) as the system approaches the phase transition leading to synchronization (Botcharova et al. 2014).

4.1.3 Assessing Fluctuation Plot Linearity

As stated previously, for DFA to yield an interpretable exponent, the assumption that fluctuation scaling is well approximated by a power law must hold true. In the analyses presented in this thesis we remove exponents associated with non-linear DFA plots via a model comparison approach inspired by that previously reported in Botcharova, Farmer & Berthouze (2013). This method compares a range of potential underlying models in order fit to the fluctuation plot and discriminates between them using an estimate of the log model evidence (the free-energy approximation) using a defined level of stringency. This method makes use of the parametric empirical Bayes (PEB) estimator included in the SPM analysis package (Friston et al. 2002; Penny et al. 2011). The free energy approximates the lower bound of the log model evidence and consists of an accuracy and complexity term:

\[ \log p(y|m) = \text{Accuracy}(m) - \text{Complexity}(m). \]

Model fits are compared using an approximation of the Bayes factor \( K \) for comparison of models \( i \) and \( j \):

\[ K_{ij} = \frac{p(y|m = i)}{p(y|m = j)}. \]

We make an approximation to \( K \) by taking the difference of the free energies between the model set outlined in table 1. For more details of the model comparison formulation, see Penny et al. (2010). The best fitting model is assumed to be linear and only rejected when \( -2 \log(K) > 4 \), yielding ‘positive’ evidence in favour of an alternative model over the linear model. It is important to emphasize that in contrast to the previously described methods, fluctuation plots are only rejected if there is strong evidence in favour of an alternative model over the linear model. In this method the level of stringency is defined by the aforementioned criterion and set to match levels of evidence agreed in the established literature (Kass and Raftery 1995).

4.1.4 Permutation Statistics for Significance of DFA Exponents

In order to determine whether the observed exponents for phase ordering are significantly different from those arising from random fluctuations we computed a permutation statistic. For each set of exponents (all frequency bands, ON and OFF L-DOPA, inter- and intra-nuclear) we computed a null-distribution, shuffling the time derivative of the phase difference time series and computing a set of 1000 DFA-PS exponents. This technique preserves the spectral power in the signal but randomizes the temporal structure of the phase difference. P-values were then estimated using:
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\[ P = \frac{b + 1}{m + 1} \]

where \( b \) is the number of DFA-PS exponents computed from the randomized series that exceed the mean exponent observed in the actual data, and \( m \) is the number of permutations used (\( m = 1000 \)) (Smyth et al. 2010). A p-value was determined with the null hypothesis that the mean of the observed exponents was not sufficiently different from that of those computed from a series with uncorrelated phase dynamics.

4.1.5 Construct Validation in Kuramoto Phase Oscillator Models

When DFA is applied to amplitude envelopes, as is predominant in its application to neural data, an increase in the exponent is hypothesised to be a signature of an increase in proximity to a second order phase transition (Hardstone et al. 2012; Poil et al. 2012; Taylor et al. 2013). DFA-PS was developed as an adaptation of the original methods proposed to estimate the proximity of an empirically observed system to a transition to complete phase synchrony. Thus, the method applies DFA to estimate the persistence of a power law decay of the autocorrelation in the derivative of the phase difference between signals.

**Figure 4 – Validation of DFA-PS in a network of coupled Kuramoto oscillators (n=200) with variable coupling strengths.** Results are shown for the average over 1000 simulations with random initial conditions. The effective mean field coupling strength is given by the cyan line; the order parameter R given by the blue line with error bars; the average DFA-PS exponent in pink; and the proportion of validated exponents given by the purple bars. It may be seen that at (A) there is weak coupling, (B) there is the transition to synchronization; and (C) oscillators are fully synchronized. Notably we see that the DFA-PS exponents peak at the onset to synchronization at (B) and that following this, there is a collapse in scaling of the phase interactions as noted by the low proportion of validated exponents. Figure adapted from Botcharova et al. (2014).
The authors validated the ability of DFA-PS to identify a system’s proximity to a critical transition to phase synchronisation by using the Kuramoto model (Botcharova et al. 2014). The Kuramoto model describes the evolution of a large number of coupled phase oscillators in which the onset to synchronization can be observed via the tuning of a coupling constant that determines the strength of the oscillators’ interactions (for an introduction see: Strogatz 2000; Acebrón et al. 2005).

The original authors applied DFA-PS to the phase time series from pairs of oscillators in a large (N=200) system. By adjusting the global coupling parameter $K$ they measured several variables from the phase evolution of the constituent oscillators: the order parameter $R$; the average DFA-PS exponent; the proportion of valid exponents (as measured using the ML-DFA technique by Botcharova et al., 2013); and the “effective mean-field coupling strength” $\Delta Kr$ (Kitzbichler et al. 2009). The key findings are presented in figure 4, and are discussed below.

The coupling space can be divided into three regions indicated by the red circles: A) not synchronized, B) transition to synchrony, and C) complete phase synchrony. At A, coupling is weak, and the resulting order parameter is low indicating little to no phase consistency across the population. The DFA-PS exponents are ~100% valid and are close to 0.5 such that any phase interaction between oscillator pairs is dominated by uncorrelated noise. At C, there is high coupling constant $K$ thus phase coherency is high as indicated by the high value of $R$. We see that the validity of the DFA-PS exponents has collapsed as the fluctuations in phase interactions take on a characteristic scale that is proportional to the frequency of the mean field. Most interesting is region B, where oscillators are transitioning into synchronization. We can see that $R$ as well as $\Delta Kr$ rise sharply, indicating that at this point oscillators begin to rapidly cohere to the mean field. Notably, the DFA-PS exponents rise prior to this transition indicating an increased degree of LRTC's present in the phase interactions between oscillators. The validity of exponents decreases as pairs of oscillators enter full synchronization and no longer exhibit fluctuations.

A similar figure was derived for another oscillator model that used a neurobiologically inspired network topology (Cabral et al. 2011). Interestingly, validity of exponents fell much quicker than in the globally coupled model, yet the exponents that were valid showed a much larger increase (to a maximum exponent of ~0.9). This occurred as the population showed a tendency to separate into heterogenous ‘islands’ of synchronized activity, with transitions occurring within a localized subnetwork of the full brain network. The authors used these empirical results to suggest that the measure provides a proxy for the measuring the proximity of a system to the onset of phase synchronization. In application to neurophysiological data, it is described to measure the system’s predisposition toward synchrony.
4.2 Computational Modelling

4.2.1 Neural Mass Models

Modelling mesoscale brain dynamics such as those measured in the EEG has a long history (Wilson and Cowan 1972; Lopes da Silva et al. 1974; Freeman 1987, 1992; Jansen and Rit 1995; Wendling et al. 2000; David and Friston 2003); for a review see Deco et al. (2008). Models can be split into two broad classes: convolution and conductance based. The former makes an approximation to activity of neural populations through parameterisation of a set of basic functions by which the mean response of a population of homogenous neurons can be approximated. The more detailed conductance models followed on from the work of Hodgkin and Huxley (HH; 1952), utilizing reduced models of the HH single neurons and then approximating activity of large neural populations through the Fokker Planck formalism (for review see Moran, Pinotsis, and Friston 2013). In this section we will focus upon convolution models as these are a good starting point from which to build models as they have the simplest formulation and are computationally inexpensive to evaluate.

4.2.2 Convolution Modelling

The ‘lumped parameter’ model of Lopes da Silva et al. (1974) was the starting point from which convolution neural mass models were based. A neural population was split into two processes. The first process is an input process that transforms average pulse densities that are incoming to the neurons dendrites into post synaptic potentials (PSPs) that can be either excitatory or inhibitory. This transformation is modelled using the convolution $\nu = h * m$ of presynaptic input $m(t)$ with a synaptic kernel $h$. The kernel is given by:

$$h(t) = \begin{cases} \frac{Ht}{\tau} e^{-\alpha t}, & t \geq 0 \\ 0, & t < 0, \end{cases}$$

where $H$ is the maximal synaptic amplitude, and $\tau$ is a synaptic time constant representing the reciprocal of the sum of time constants concerning passive membrane capacitance and dendritic delays.

The second process is an output transformation approximates the spike density that is sent in response to the change in average membrane potential of the population. This transform is described by a sigmoid function:

$$S(\nu) = \frac{2e_0}{1 + e^{r(v_0 - \nu)}}$$

where $e_0$ is the maximum average firing rate of the population, $v_0$ the half maximal PSP, and $r$ the steepness of the sigmoid transition region. The convolution in the input block can be written in the form of a second-order ODE:
\[ \ddot{y}(t) = \frac{H}{\tau} z(t) - \frac{2}{\tau} \dot{y}(t) - \frac{1}{\tau^2} y(t) \]

This may be rewritten as a pair of first-order ODEs:
\[
\begin{align*}
\dot{y}_0(t) &= y_1(t) \\
\dot{y}_1(t) &= \frac{H}{\tau} z(t) - \frac{2}{\tau} y_1(t) - \frac{1}{\tau^2} y_0(t),
\end{align*}
\]

where \( y \) is equal to the membrane voltage and \( z \) is the incoming spike density. For compactness, in further equations we neglect the time dependencies of variables. If we combine the sigmoidal transfer function with the synaptic convolution then we can formulate a model in which we replace \( z \) with a conversion of the incoming populations’ membrane depolarization into spike densities, add a weighting constant \( C \) to modify the strength of synaptic inputs, and add random input \( \rho \) to simulate endogenous noise. Then the former equation becomes:
\[
\begin{align*}
\dot{y}_0 &= y_1 \\
\dot{y}_1 &= \frac{H}{\tau} [S(C \cdot y_w) + p] - \frac{2}{\tau} y_1 - \frac{1}{\tau^2} y_0,
\end{align*}
\]

where \( S(\cdot) \) is the sigmoid function, \( C \) is a coupling constant, \( y_w \) is the membrane potential of the coupled population and \( p \) is a random innovation. Altogether, this gives the equations of motion for a single neural population receiving intrinsic stochastic drive plus extrinsic drive from coupled populations. Most existing convolution models are descendent of this formulation and are distinguished by their specification of the transfer function and the coupling of sub-populations into a heterogeneous neural mass. Jansen and Rit derived a model of cortical alpha generators via the coupling of three neural populations: 2 excitatory and 1 inhibitory:
\[
\begin{align*}
\dot{y}_0 &= y_3 \\
\dot{y}_3 &= \frac{H_e}{\tau_e} [S(y_1 - y_2)] - \frac{2}{\tau_e} y_3 - \frac{1}{\tau_e^2} y_0 \\
\dot{y}_1 &= y_4 \\
\dot{y}_4 &= \frac{H_e}{\tau_e} [C_2 \cdot S(C_1 \cdot y_0) + p] - \frac{2}{\tau_e} y_4 - \frac{1}{\tau_e^2} y_1 \\
\dot{y}_2 &= y_5 \\
\dot{y}_5 &= \frac{H_i}{\tau_i} [C_4 \cdot S(C_3 \cdot y_0)] - \frac{2}{\tau_i} y_5 - \frac{1}{\tau_i^2} y_2.
\end{align*}
\]

The total output of the model is the difference in the excitatory and inhibitory populations \( y = y_1 - y_2 \) which is the membrane potential of the main neural population \( (y_0) \). This is equivalent to the postsynaptic potentials in the superficial dendrites of pyramidal cells in the cortex that sum to generate the majority of the measurable EEG.
Part B: Hypotheses and Methods

Grimbert and Faugeras (2006) conducted a bifurcation analysis of the Jansen-Rit model to determine how the different qualitative signals arose as a function of a stable input to the column whilst restricting parameters to the set defined in their original paper. They computed the equilibria of the set of equations and then determined their linearized stability. They demonstrated the existence of a super-critical Hopf bifurcation in this model by which the system goes from a fixed point to a stable limit cycle under the control of the total spiking input ($z$).

4.3 Coupling of Multiple Columns

Once the formulation of a single column is derived then it is possible to couple multiple columns together by incorporating an extrinsic coupling constant that adds synaptic inputs from coupled columns. Usually only one population in the model acts as the receiving layer and all input goes through it. Connectivity between columns is assumed to be exclusively excitatory to excitatory. Thus the receiver excitatory population in the model becomes:

$$
\dot{y}_0^i = y_1^i,
\dot{y}_1^i = \frac{H_e}{\tau_e} \left[ C \cdot S(x) + p + \sum_{j=1, j \neq i}^{N} K_{ij} y_0^j \right] - \frac{2}{\tau_e} y_0^i - \frac{1}{\tau_e} y_1^i,
$$

where population $i$ is coupled to $N$ populations superscripted by $j$. The total input to the layer is given by the summed activity of all inputs each multiplied by a coupling constant $K_{ij}$. Wendling et al. (2000) demonstrated that the organization and coupling of Jansen-Rit type neural masses give rise to qualitative changes in the resulting signals such that they could tune a model of 3 coupled columns to produce epileptiform-like signals by adjusting the strength of the coupling gain $K$.

5 Statistics for Inference

5.1 Permutation Cluster Statistics

In order to make statistical comparisons of power, connectivity and directionality spectra between lesioned and control recordings we used cluster based permutation testing (Maris and Oostenveld 2007) which avoids introducing bias through the prior specification of frequency bands. Briefly, the method computes multiple independent t-statistics for each sample (channel-frequency pair) between the two experimental conditions (lesion and control). We assume that in regions of the spectra where there is a true physiological difference in the distributions of a metric of interest (i.e. power, iCOH, NPD) there will be a high value of the t-statistic in several adjacent frequency bins and this group of neighbouring bins is called ‘a cluster’.
The purpose of the cluster-based permutation test is to find clusters which are ‘heavier’ (i.e. have a greater sum of t-statistic values in the cluster) than could be expected under the null hypothesis. Candidate clusters to be tested are identified by setting a threshold on the t-statistic. Importantly, this cluster-forming threshold does not affect the false alarm rate of the test, only the sensitivity to large clusters with smaller t-values as opposed to small clusters with large t-values. The statistical significance of candidate clusters is then tested by approximating the reference distribution using a large number of permutations where the condition labels are randomly reassigned and the whole procedure of cluster identification is repeated. The clusters in the original data are then compared to the top tail of the reference distribution according to the pre-defined statistical threshold (typically, 5%). The permutation testing requires no assumption of normality and affords a correction for the multiple comparison problem by controlling the family-wise error rate. For full details of the method, see Maris (2012).

The cluster-forming threshold was $p < 0.05$ and the permutation test threshold was set at $p < 0.025$ (as it is a two-sided test). The number of permutations was set to 5000 which tends a lowest possible P-value equal to 0.0004. Cluster statistics were computed using the ‘ft_freqstatistics’ routine in the Fieldtrip toolbox. For testing of the effect of conditioning upon the NPD estimate, statistics are computed identically as described above, but treating the conditioned and unconditioned spectra as the two experimental conditions of interest. As each animal contained multiple recordings per subcortical site we averaged the spectra from these recordings into a subject mean. Group level plots indicate the group mean in bold ±1 standard error of the mean (S.E.M.).

6 Chapter Abstracts

6.1 Chapter I: Dopaminergic Modulation of Local and Long-Range Synchronization in the Subthalamic Network of Patients with Parkinson’s Disease

In this chapter I investigate the modulation of neuronal interactions occurring in the subthalamic nucleus (STN) in patients with Parkinson’s disease (PD) to address hypotheses H I and IV. Through analysis of local field potentials (LFPs) taken from the STN we hope to determine changes in the patterning of activity in the STN that arises following dopamine depletion. I first use spectral power in attempt to reproduce the well reported findings that beta band activity is suppressed by L-DOPA administration. Secondly, I will investigate the FC within the STN by estimate FC between electrodes implanted at different sites along the axis of the STN. Due to the close spatial proximity, we compare methods of FC that are corrected for volume conduction effects. In order to investigate whether beta activity is diffuse, I also look at the bilateral coupling between STNs, again using FC. Finally, in order to test H
IV. I use DFA-PS on the signals recorded within and between the STN in order to examine the extent to which LRTCs, a signature of critically poised synchrony, are present in the phase interactions between signals.

6.2 Chapter II: Non-Parametric Directionality Metric for Continuous Neural Recordings- A Validation Study

In this chapter we calibrate and validate a method that will be used throughout the remainder of the thesis. Non-parametric directionality (NPD) is a recently described method for estimation of directed functional connectivity (dFC). The method has been introduced and validated using point process data, but no work to date has verified its usage in continuous signals such as the LFP. In this chapter I use simple multivariate autoregressive model (MVAR) to simulate correlated neural signals that we can use to test the efficacy of the NPD in recovering known directional coupling. I use a simple modelling approach to test NPDs ability to recover directed coupling in the face of several confounds typically encountered in empirical data. Namely, we examine the effects of NPD under varying a) signal-to-noise ratios, b) instantaneous mixing of signals, c) common drive, d) parallel and convergent signal routing, and e) heterogeneous delays. Furthermore, I make a comparison of the method with non-parametric Granger causality (npGC), a popular method for model free estimation of dFC. Finally, we test the two metrics in a biophysically realistic network based on the cortico-BG system and compare their respective performance.

6.3 Chapter III: Propagation of Beta/Gamma Rhythms in the Cortico-Basal Ganglia Circuits of the Parkinsonian Rat

Much of the motor impairment associated with Parkinson’s disease is thought to arise from pathological activity in the networks formed by the basal ganglia (BG) and motor cortex. To evaluate several connectionist hypotheses proposed to explain the emergence of pathological oscillations in Parkinsonism, we investigated changes to the directed connectivity in BG networks following dopamine depletion. We recorded local field potentials (LFPs) in the cortex and BG of rats rendered Parkinsonian by injection of 6-hydroxydopamine (6-OHDA) and in dopamine-intact controls. We performed systematic analyses of the networks using a novel tool for estimation of directed interactions (Non-Parametric Directionality, NPD). We used a ‘conditioned’ version of the NPD analysis which reveals the dependence of the correlation between two signals upon a third reference signal. This work aims to establish the extent to which beta activity is present across the BG outside of the STN (H I), and determine how changes in coupling following dopamine depletion may lead to the emergence of pathological beta (H II).
6.4 Chapter IV: Inferring the Mechanisms of Pathological Rhythms in the Cortico-Basal Ganglia Network

Aberrant beta band (14-30 Hz) oscillations and inter-areal synchronization is associated with debilitating motor symptoms associated with Parkinson’s disease. Multiple hypotheses exist concerning the mechanistic origins of pathological beta dynamics (H II). In this section I use a models of neural ensemble activity (i.e. local field potentials) with parameters optimized to match the statistical features (i.e. power and functional connectivity) of data recorded experimentally from the dopamine depleted cortico-basal ganglia system in Parkinsonian rats. Using these optimized models, we explore how the onset of pathological beta synchrony (and resulting oscillations) is modulated through parameterization of connectivity between nuclei and how connectivity determines the systems proximity to a critical transition at the onset of pathological beta oscillations (H IV).

6.5 Chapter V: Cortico-Subthalamic Phase Coupling and Modulation of Beta Bursting in Parkinson’s Disease

High amplitude oscillations in the 14-24 Hz frequencies (low beta) of signals recorded from the subthalamic nucleus (STN) are reliable biomarkers of Parkinsonism and are suppressed with dopamine replacement therapy. However, studies investigating the interaction of the STN with cortex have found that the majority of synchronization occurs in the high beta range (24-34 Hz) and time averaged measures (i.e. coherence) are robust to changes in dopamine levels. In this chapter I investigate whether dopamine instead of changing the overall degree of synchronization acts to re-pattern phase interactions between the two structures. I use a novel method to analyse the statistics of time evolving phase synchronization and investigate its interaction with local power changes (H III).
Part B: Hypotheses and Methods
Part C:

Chapters
Chapter I:
Dopaminergic Modulation of Local and Long-Range Synchronization in the Subthalamic Network of Patients with Parkinson’s Disease
1 Introduction

Synchronized activity in the brain facilitates long distance communication and sensory integration (Buzsáki & Draguhn, 2004; Fries, 2015; Salinas & Sejnowski, 2001). It has been proposed that synchronization in the brain is delicately poised at a transition between completely ordered and disordered interactions (Botcharova, Farmer, & Berthouze, 2014; Kitzbichler, Smith, Christensen, & Bullmore, 2009), a feature that may arise more generally from brain dynamics that are self-organized at the edge of stability (Beggs, 2008; Chialvo, 2010; Shew, Yang, Petermann, Roy, & Plenz, 2009). The dynamics that arise at this transition are hypothesized to facilitate optimal information transfer (Barnett, Lizier, Harré, Seth, & Bossomaier, 2013), maximize dynamic range and adaptability (Kinouchi & Copelli, 2006; Shew et al., 2009) as well as increase the network’s capacity for information storage (Shew, Yang, Yu, Roy, & Plenz, 2011). In the case of pathological states such as epilepsy or tremor, strong neural synchrony that is resistant to external perturbation impairs network function (Hammond, Bergman, & Brown, 2007; Hirschmann et al., 2013; McAuley, 2000; Schnitzler & Gross, 2005; Uhlhaas & Singer, 2006). This suggests that strong stability of synchronous interactions is indicative of pathophysiological states in the brain.

In the motor network of healthy human subjects there are weak beta band oscillations that favor maintenance of steady muscle contraction. These are readily suppressed during movement and also during movement observation (Baker, Kilner, Pinches, & Lemon, 1999; Conway et al., 1995; Farmer, Bremner, Halliday, Rosenberg, & Stephens, 1993). Increased beta band (15-35 Hz) oscillations in the local field potential (LFP) recorded from the basal ganglia during functional neurosurgery (deep brain stimulation - DBS) have been reliably observed to be a hallmark of dopaminergic depletion and akinesia in Parkinson’s Disease (Brown et al., 2001; Hammond et al., 2007; Kühn, Kupsch, Schneider, & Brown, 2006; Weinberger et al., 2006).

The finding of excessive beta oscillations in PD imply a shift from metastability to stability that occurs in the onset of disease (Dotov, 2014). It has been suggested that these dynamics produce a reduction in the information encoding space available to the subcortical motor network that result in the akinetic symptoms of PD (Brittain & Brown, 2014; Hanslmayr, Staudigl, & Fellner, 2012). The mechanisms that generate beta oscillations in subcortical networks are unknown although several models have been suggested that involve either increased cortical drive to a subcortical resonator or a change in cortical feedback (Pavlides, Hogan, & Bogacz, 2015). More complete descriptions of network dynamics will help to discriminate between these potential models.

In this paper, we characterize neural dynamics of local field potentials recorded from different electrode contacts within bilateral subthalamic nuclei (STN) in Parkinson’s patients undergoing deep brain stimulation surgery. As the recording electrode contacts are not entirely enclosed within STN we
describe our results in terms of signals originating from the region surrounding the STN which we abbreviate STNr. The recordings were done in two medication states: when patients were ON and OFF Levodopa (L-DOPA). We analyze local STNr power estimates along with measures of functional connectivity within and between the two STNrs.

For excessive oscillations to affect information processing in a way that influences the capacity for normal movement they should have detectable correlates in measures of network synchrony. Network synchrony may be quantified through linear measures of the correlation between neurophysiological time series (coherence based) as well as non-linear measures (such as Detrended Fluctuation Analysis for Phase Synchrony; DFA-PS) that characterize the dynamics of interactions within and between brain structures. We use standard coherence (Halliday et al., 1995) as well as weighted phase lag index (WPLI) (Vinck, Oostenveld, van Wingerden, Battaglia, & Pennartz, 2011) to control for zero phase lag volume conduction.

In addition to the above approach, we utilize a recently developed measure that characterizes the temporal ordering of phase dynamics between weakly coupled signals using DFA-PS (Botcharova et al., 2014)). Autocorrelation length of fluctuations has been proposed as a possible statistical tool to approximate a system’s proximity to a super-critical Hopf bifurcation (Aburn, Holmes, Roberts, Boonstra, & Breakspear, 2012). Scale free autocorrelation statistics for amplitude envelopes in the STN have previously been reported and scaling was reported to increase following dopamine depletion (Hohlefeld et al., 2012). Using DFA-PS it is possible to detect changes in the scaling statistics of phase interactions which previous modelling work has suggested act as a proxy measurement of a system’s propensity to enter into synchronized states (Botcharova et al., 2014; Kitzbichler et al., 2009). We aim to assess whether this non-linear measure can characterise changes that may occur in the neuronal dynamics of the basal ganglia of patients with PD.

We further assess the changes in the physiological measures for basal ganglia dynamics that occur with administration of L-DOPA in the resting state. We study correlations between changes in the physiological parameters and the severity of motor impairment with respect to Parkinsonian bradykinesia and rigidity. In particular, we are interested in whether the application of non-linear measures of synchronization (DFA-PS) provides additional information that allows better characterization of patients’ clinical state over that of more conventionally used signal processing methods such as power and coherence.

2 Methods and Materials

2.1 Experimental Setup
2.1.1 Patient Details and Surgical Implantation of DBS Electrodes

The majority of the data were taken from a study involving a 17 patient cohort who had all undergone surgery for chronic implantation of deep brain stimulation (DBS) electrodes in the STN (see Litvak et al., 2011, (2012)). The patients have undergone simultaneous magnetoencephalography (MEG) and intracranial recordings, but here we focus on intracranial data only. For full details of the experiment and surgery please see the relevant section of the methods part of this thesis.

2.1.2 Experimental Paradigm

Two recordings were obtained for each patient. One recording was performed after overnight withdrawal from dopaminergic medication, termed the OFF state. The other recording was obtained in the ON state in which the patient had taken their usual dose of medication (>200 mg of levodopa) several hours before the experiment. The ON and OFF recordings were done on different days and the order was counterbalanced across patients.

Data presented here were taken from an experiment in which recordings were made from patients sitting comfortably upright in a state of wakeful rest with their hands on the chair armrests. Subjects were visually cued using MATLAB (The MathWorks, Inc., Natick, Massachusetts) and the Cogent (http://www.vislab.ucl.ac.uk/cogent.php) toolbox and instructed to remain motionless with their eyes open and focused on a fixation cross. The recordings were made for approximately 3 minutes in the presence of a neurologist who monitored task performance and patient’s wellbeing. None of the patients developed tremor during the recordings; their dominant symptoms were bradykinesia and rigidity. EMG was inspected for each patient in the rest period to identify any large/regular movements occurring during the recording. None were found and so a motor rest state was confirmed.

2.2 Signal Analysis

2.2.1 Analysis Software

All offline pre-processing, analysis and basic statistics were made using a combination of proprietary MATLAB scripts as well as functions from SPM (http://www.fil.ion.ucl.ac.uk/spm/) and Fieldtrip (http://www.ru.nl/neuroimaging/fieldtrip/) toolboxes. Regression analyses and mixed modelling were computed using IBM’s SPSS software (SPSS Statistics V 22.0, IBM Corp., Armonk, NY).

2.2.2 Pre-processing of LFP Recordings

Prior to analysis, we inspected the raw LFP recordings in order to identify irregularities and artefacts in the recordings. One patient was removed from the study due to data loss in the left STN channels resulting from amplifier saturation preventing further analysis. All other recordings were deemed valid...
for further pre-processing and analysis giving a total number of 12 patients included in the rest of the analyses.

Application of DFA requires continuous data and for these analyses we opted for a conservative scheme of pre-processing where we aimed (if possible) to rectify artefacts rather than remove them entirely.

Large amplitude jumps in the recordings that spanned multiple channels of a trial were obvious from visual inspection. These jumps originate from transient discharges in the amplifier that could not be entirely resolved at the hardware level. In order to correct for this artefact, we applied a threshold detection method such that when the amplitude exceeded 3 standard deviations the corresponding region of recording was removed. Resulting gaps in the time series were infrequent and transient (5-15 occurrences per recording, 1-20 samples in the original acquisition and equivalent to less than a millisecond). The missing data were then replaced through linear interpolation from the 5 preceding samples.

We then treated the LFP recordings as follows:

I. The mean of the series was subtracted from the signal to bring all trials to a zero baseline.

II. Boundary artefacts (arising from subject movement or instrumentation initialization) were removed following visual identification of their properties in the time series: they were typically 2-10 s in duration and seen as very high amplitude slow fluctuations in the signal. In order to avoid introducing differing lags between channels within a single trial, the signals were truncated at identical points such that all recordings were initialized at the same point in time (+5/-5 s from the start and end points.)

III. The data were down-sampled from the hardware’s native sampling rate of 2400 Hz to 200 Hz.

IV. All recordings were high-pass FIR filtered (passband at >4 Hz) to remove DC and slow baseline fluctuations.

Following pre-processing, signals had mean duration of 162.5±6.7 s. For examples of the outcomes from pre-processing see figure 1.

For all analyses that did not require continuous data (i.e. spectral analysis) we took further steps to reject artefacts by epoching the data into 2 second segments and then using Fieldtrip’s artefact rejection routines (Z-score thresholding) to remove sections of data.

2.2.3 HPI Pre-processing

In order to quantify subject movement during the recording, MEG head position indicator (HPI) data was collected simultaneously to LFP recordings. HPI data were treated in the same way as the artefact-rejected LFP data. Signals were down sampled and large jump artefacts in signal were removed via Z score threshold followed by linear interpolation between gaps. The validity of HPI localization was
verified by examining the pairwise distances between the fiducial coils which should remain constant through each trial (Oswal et al., 2015). All the data were found to be valid for this group of subjects.

2.2.4 Signal Analysis

Spectral estimates were made using Thomson’s multi-taper method (Thomson, 1982) implemented in Fieldtrip. We computed functional connectivity analyses using spectral coherence as well as the weighted phase lag index (WPLI) in order to mitigate against volume conduction effects. For linear measures of coherence to be significant there needs to be consistency over time of the phase and frequency of the two signals. It is possible to characterize phase interactions that are changing across time through an estimate of the long-range temporal correlation of the phase difference time series. Here we utilize Detrended Fluctuation Analysis for phase synchrony (DFA-PS) (Botcharova et al., 2014). DFA plots were validated for linearity using the parametric empirical Bayes technique detailed in the methods section of this thesis.

In order to determine whether the observed exponents for phase ordering were significantly different from those arising from random fluctuations we computed a permutation statistic. For each set of exponents (all frequency bands, ON and OFF L-DOPA, inter- and intra-nuclear) we computed a null-distribution, shuffling the time derivative of the phase difference time series and computing a set of 1000 DFA-PS exponents. This technique preserves the spectral power in the signal but randomizes the temporal structure of the phase difference. P-values were then estimated using:

\[ P = \frac{b + 1}{m + 1} \]

where \( b \) is the number of DFA-PS exponents computed from the randomized series that exceed the mean exponent observed in the actual data, and \( m \) is the number of permutations used (\( m = 1000 \)) (Phipson & Smyth, 2010). A P-value was determined with the null hypothesis that the mean of the observed exponents was not sufficiently different from that of those computed from a series with uncorrelated phase dynamics.

2.3 Subdivision of STN channels

In order to avoid introducing selective bias to our results we avoided the presumption that the channel with highest beta power is closest to STN, as has been done in previous studies. Since part of our analysis is concerned with functional connectivity, we did not wish to reduce the potential dimensions for cross channel coherences nor make assumptions regarding the exact positioning of contacts. Channels were created from a bipolar montage of contacts as shown in figure 1A in the methods section of this thesis.
Channel pairings were divided into two groups: pairs of channels on the same electrode are presumed to be "intra-nuclear"—that is within the region of one STN. Pairings of channels between left and right STN electrodes are termed "inter-nuclear." Altogether there are 6 possible intra-nuclear combinations (3 for each nucleus left and right) and 9 left-right inter-nuclear combinations. When computing summary statistics for bivariate analyses (i.e. coherence) results were reported as an average metric for all pairs in the group. For intra-nuclear pairs the group was split into two averages for pairs originating from either the left or the right STNr. Inter-nuclear results are reported as one average of all 9 pairs. In some cases univariate metrics (power) were entered into regressions alongside the bivariate measure, when this was done the average power of the two channels in each pair was considered.

### 2.4 Statistical Testing

#### 2.4.1 Removing Outliers

In order to correct for outliers in the signal features (power in band, coherence, WPLI and PS-DFA exponents) we opted to use a threshold set using the median absolute deviation (MAD) which is more

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**Figure 1** — **Example procedure for LFP pre-processing.** Example signals are taken from the bipolar STN R01 channel for a single subject. (A) Raw LFP contains artefacts such as high amplitude transients (amplifier jumps), very low frequency baseline drifts, non-zero DC, and boundary artefacts at the extremities of the time series. (B) The pre-processed signal has been truncated, high pass filtered, and large transients removed with missing data replaced via interpolation. The resulting spectra is in (C). (D, E & F) Same as above but for the ON drug experiment). This data is used as it is for PS-DFA and cross correlation analyses. Spectral analyses are computed on epoched data in which bad trials are removed via Z-score thresholding.
robust to the influence of outliers than the more conventionally used standard deviation (Huber, 2004).

For a univariate series \( x_1, x_2, ..., x_n \), the MAD is given by the median of the absolute residuals of the data from its median:

\[
MAD = M(|x_i - M(x_i)|)
\]

where \( x_i \) is the vector of data, and \( M \) is the median of the series. MAD is a consistent estimator of the standard deviation:

\[
\hat{\sigma} = b \cdot MAD
\]

where \( b \) is a constant scale factor that is dependent upon the distribution and is set at \( b = 1.483 \) which assumes data is normally distributed (see section 2.4.2). A decision criterion is then defined by setting a range from the median value using a set number of MADs:

\[
M(x_i) - \theta \cdot b \cdot MAD < X_i < M(x_i) + \theta \cdot b \cdot MAD
\]

where the acceptance range is the median plus or minus a multiplier of the MAD \( (\theta) \). In this case \( \theta \) was set to 2.5 which is set to give a conservative removal of outliers as recommended in (Leys, Ley, Klein, Bernard, & Licata, 2013). When dealing with ON/OFF paired data outliers were removed independently for each set of features.

### 2.4.2 Reporting of Statistics

Unless otherwise stated all tests of the data were computed with the outliers removed by the MAD procedure described in previous section and remaining sample size reported in the tables. When testing for significant differences between signal features in ON and OFF states, the samples were first tested for normality using a Shapiro-Wilk test. For the samples that were normally distributed a paired Student’s t-test was used, otherwise a non-parametric Kruskal-Wallis test was used to compare means. Tests were conducted only for pairs of data in which no outliers had been removed. Degrees of freedom for tests (denoted \( d.f. \)) are reported in brackets marking the test used as well as the 95% confidence interval for the difference in means. Correlations between features were computed using the non-parametric Spearman’s rank-order test and correlation \( r \) coefficients are reported along with their corresponding P-values. When correlations were deemed significant then linear least squares regressions were computed and their corresponding \( R^2 \) reported.

### 2.4.3 Confidence Intervals

Confidence intervals for power spectra and coherence spectra were computed using the analytic expressions given in (Halliday et al., 1995). Confidence limits for cross correlations are computed as in (Hanson & Yang, 2008) and are given by:
\[ c_{1-a} = \sqrt{2} \cdot Erf^{-1}(\alpha) \frac{\sigma_{xy}}{\sqrt{n_t}} \]

where the pooled variance is:

\[ \sigma_{xy} = \sqrt{\frac{N - 1}{N^2} \text{var}(x)\text{var}(y)} \]

where \( N \) is the number of samples in the signals of interest; \( n_t \) is the number of lags included in the test; and \( \text{Erf}^{-1} \) is the inverse complementary error function for a given significance level \( \alpha \). All confidence intervals are given to level of \( P = .05 \).

2.4.4 OFF Drug UPDRS Correlation with Signal Features

Clinical estimates of Parkinsonian bradykinesia and rigidity severity in the ON and OFF state were obtained by summing items 3.3 to 3.7 of the original UPDRS including assessment of arm and leg rigidity; finger tapping; hand and arm movements; and toe tapping (Fahn, Jenner, Marsden, & Teychenne, 1987). We performed pairwise correlation and regression analysis for each LFP measure (power, coherence WPLI and DFA-PS) with the clinical scores. In the case of bivariate measures, lateralized (intra-nuclear) pairings were correlated with contralateral hemi-body scores (scores from assessment of only one side of the body) and for inter-nuclear pairs we used the average score of both left and right assessments. We also correlated measures with clinical improvement as determined by correlating the ON-OFF difference in the clinical scores and the physiological measure of interest.

Results for power, coherence and WPLI when correlated with the clinical scores are shown in table 5 where the Spearman correlation coefficient is shown alongside the coefficient of determination \( (R^2) \) for the corresponding linear regression. The p-value from the correlation is shown as well as the degrees of freedom.

In order to account for nesting of results within subjects we employed a hierarchical mixed design general linear model (GLMM) which incorporated random intercepts for the predictor variables to account for inter-subject variability. The details of this are outlined in section 2.4.5 and full results from models incorporating different covariate sets are shown in table 7.

2.4.5 Mixed Modelling

In order to determine significance of variables as predictors for UPDRS in the presence of covariates we employed regression modelling in SPSS. From this modelling we aimed to identify the unique contribution of a predictor to the explained variance of the response variable. As experimental design resulted in a nested data structure we opted for a hierarchical model which incorporated group level fixed effects in which the effect is treated as a set quantity deviating around a mean; as well as random effects in which inter-subject variability is accounted for with a random intercept for each subject.
This mixed modelling approach is adopted in order to control for dependencies of effects within and between subjects (Friston, Stephan, Lund, Morcom, & Kiebel, 2005).

Our model utilized a general linear model in which fixed effects such as power, coherence and DFA exponents were used as predictors. This was achieved in SPSS syntax using the *mixed* procedure which designs a mixed general linear model (GLMM) in which errors were estimated via maximum likelihood.

In the report, we give P-values for fixed effects as well as the estimated explained variance for each model. The estimated explained variance, $\Omega^2$ is given by:

$$\Omega^2 = 1 - \frac{\text{var}(r_i \text{MIXED})}{\text{var}(r_i \text{RANDOM})}$$

where $\Omega^2$ is a value between 1 and 0 representing the fraction of explained variance; $\text{var}$ indicates variance; $r_i$ is the residual error for either the *MIXED* model with both random and fixed effects or the *RANDOM* model that has random effects only (Xu, 2003).

### Table 1 – Table of results for group level spectral analysis and comparison of ON/OFF drug effects.

Mean and standard deviations of band power and peak frequency in the alpha, low beta and high beta ranges are shown as averages across all channels. P-values are reported for paired t-test in which the significance of the differences in mean values ON and OFF drugs are tested ($P>.05; P>.01$). *†* indicates cases where non-parametric statistics were used due to non-normality in the sample.
3 Results

3.1 Spectral Analysis

3.1.1 Dopaminergic Modulation of Band Power and Frequency

Results of spectral analysis can be seen in figure 2 and table 1. Visual inspection of the spectra as well as analysis of peak frequencies confirms the suitability of the selected bands of interest (alpha-theta: 5-12 Hz, low beta: 13-20 Hz, and high beta: 21-30 Hz). Individual patient’s spectra had varying profiles with some showing more pronounced alpha-theta or beta band peaks. In pooled spectra there were three peaks at frequencies 7.24±1.55, 16.03±2.30 and 25.84±2.56 Hz (see figure 2A) were apparent. The spectral peaks fall in the middle of pre-defined bands suggesting that peaks were not split when segregating bands to compute total power. No significant shifts in frequency were determined for any of the three bands when comparing recordings ON and OFF drug (see table 1 for results of testing).

Analysis of the relative power in bands showed a significant change in average power following medication (figure 2B and table 1) for alpha-theta and low beta but not for high beta. Low beta band power is increased in patients following withdrawal of L-DOPA with a difference in mean (normalized) power between ON and OFF states of -0.17±0.28 (paired t-test(23), P<.05) which is in good agreement with previously published findings (Hammond et al., 2007; Priori et al., 2004; Weinberger et al., 2006). There was no significant ON vs OFF modulation in the high beta band.

![Grand Mean Power Spectra](image1)

**Figure 2 – Pooled power spectra for all subjects either ON or OFF levodopa.** The group level spectra for all 12 subjects and for all channels. The dashed line indicates the 95% analytic confidence limit. Clear modulations can be seen for ON drug in the alpha range 5-12 Hz; and OFF drug exaggeration of the low beta band at 13-20 Hz. There is also significant power in the high beta band 21-30 although L-dopa modulation is less prominent.
At approximately 8 Hz there is a clear peak in both the subject and group level power spectra. Activity at this frequency band will be termed alpha-theta although previous studies looking at similar frequency ranges have used terms such as slow oscillatory activity (Alonso-Frech et al., 2006) or sub-beta (Kato et al., 2015). Similar to previous studies we have found that alpha-theta power is raised in the ON drug state. We demonstrate a significant increase of 0.106±0.26 in mean normalized alpha-theta power for all channels when pooled (paired t-test(23), P<.05).

3.1.2 Correlation of Bandpower with OFF state UPDRS and changes in UPDRS associated with L-DOPA treatment

Low beta band power is positively correlated with clinical scores in the OFF state (r(19) = .662, OFF, see figure 3B) and when entered into a GLMM it was able to account for a third of the UPDRS variance (P=0.001, Ω²=.343). In order to determine if this effect was related to clinical improvement with L-DOPA treatment we correlated the ON minus OFF beta power change with the ON minus OFF difference in UPDRS where we found a significant linear effect (r(20) = .560, ON-OFF, see figure 3D). In a GLMM this accounted for 39% of the variance (P=0.002, Ω²=.386). This result suggests that larger ON state reductions in beta power are correlated with a larger decrease in clinical symptom severity.

There is an opposite effect for power in the alpha-theta band which correlates negatively with OFF drug UPDRS (r(22) = -.609, OFF), suggesting that increased alpha-theta power is associated with less severe
ON/OFF L-DOPA Comparison of AUC Coherence

<table>
<thead>
<tr>
<th></th>
<th>ON</th>
<th>OFF</th>
<th>ON-OFF</th>
<th>d.f.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>Intra</td>
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<td>0.922</td>
<td>2.635</td>
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</tr>
<tr>
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<td>0.240</td>
<td>1.047</td>
<td>0.228</td>
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<td>Low Beta</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra</td>
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<td>2.927</td>
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<td>-0.762</td>
</tr>
<tr>
<td>Inter</td>
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<td>0.187</td>
<td>0.712</td>
<td>0.222</td>
<td>-0.056</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra</td>
<td>3.079</td>
<td>1.205</td>
<td>3.495</td>
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<tr>
<td>Inter</td>
<td>0.846</td>
<td>0.242</td>
<td>0.784</td>
<td>0.221</td>
<td>0.061</td>
</tr>
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</table>

ON/OFF L-DOPA Comparison of AUC WPLI

<table>
<thead>
<tr>
<th></th>
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<th>OFF</th>
<th>ON-OFF</th>
<th>d.f.</th>
<th>P-value</th>
</tr>
</thead>
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<tr>
<td>Alpha</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>Intra</td>
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<td>1.199</td>
<td>2.219</td>
<td>1.375</td>
<td>-0.548</td>
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<tr>
<td>Inter</td>
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<td>0.440</td>
<td>0.736</td>
<td>0.440</td>
<td>-0.074</td>
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<tr>
<td>Low Beta</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra</td>
<td>1.935</td>
<td>1.593</td>
<td>3.151</td>
<td>1.924</td>
<td>-1.215</td>
</tr>
<tr>
<td>Inter</td>
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<td>0.146</td>
<td>0.340</td>
<td>0.154</td>
<td>-0.061</td>
</tr>
<tr>
<td>High Beta</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra</td>
<td>1.746</td>
<td>1.528</td>
<td>3.137</td>
<td>2.089</td>
<td>-1.390</td>
</tr>
<tr>
<td>Inter</td>
<td>0.480</td>
<td>0.303</td>
<td>0.523</td>
<td>0.379</td>
<td>-0.043</td>
</tr>
</tbody>
</table>

Table 2–Table of results for group level coherence analysis and comparison of ON/OFF drug effects. Mean and standard deviations of the integrated coherence and WPLI coherence in the alpha, low beta and high beta ranges are shown for intra-/inter- nuclear and all pairs of contacts. Outlier have been removed. Results from paired t-test to examine the significance of drug related modulation in the mean value of coherence are shown in the final column (P<.05; P<.01).†indicates cases where non-parametric statistics were used due to non-normality in the sample.

clinical disease states (see figure 3A). When entered into the mixed model we found that alpha power could account for a similar degree of explained variance (P=0.002, Ω² = .331). We found no significant correlation for alpha-theta power with drug-induced clinical improvement.

In order to assess the predictive power of both alpha-theta and low beta power together we entered them into a multiple regression. However, neither alpha-theta nor low beta power were identified as significant predictors of OFF state UPDRS (see table 6) when entered together. This effect arises due to collinearity between the two regressors that significantly inflates error estimation. Because there is a strong negative correlation between alpha and low beta band it is not possible to determine which the strongest predictor is.

3.2 Analysis of Functional Connectivity
3.2.1 Dopaminergic Modulation of Coherence

In order to determine if treatment with dopaminergic medication alters functional connectivity within STNr (intra-nuclear) or bilaterally between STNr (inter-nuclear) we measured the coherence between channels. The pooled coherence spectra are shown (figure 4 A-C, top row) with summary statistics reported in table 3. In the pooled intra-nuclear coherence spectra there are peaks at ~8 Hz; ~16 Hz; and another at ~28 Hz. These peaks could be clearly observed in coherence estimates from individual subjects. Statistics for differences in the mean values of coherence are reported as an area under the
curve measure (AUC, termed here integrated coherence). Comparisons between ON and OFF conditions suggest that the effect is significant within the low beta band with intra-nuclear coherence exhibiting a decrease of -0.76±0.57 (paired t-test (21) P<.01, intra-) when the patient is ON drugs,

![Figure 3](image)

Figure 3 – Correlations of band power with UPDRS for bradykinesia/rigidity scores. (A-C) Scatter plot of band power for alpha, low beta and high beta bands with OFF state UPDRS. Correlations were first determined to be significant using Spearman’s test and in the case of significance a linear regression was plot. The corresponding R^2\ is reported alongside. Low alpha power was associated with less severe motor symptoms whilst for low beta the opposite was true. No relationship was found for high beta band. (D) Correlation of ON-OFF low beta band power with ON-OFF UPDRS. The positive correlation was found to be significant and the subsequent linear regression is shown. The relationship suggests that larger reductions in low beta power when ON drug are associated with a greater therapeutic reduction in motor symptoms when ON compared to OFF.
suggesting that L-DOPA reduces beta frequency intra-nuclear synchronization. There was also a comparable yet weaker effect in the high beta band ($-0.416 \pm 0.564$, paired t-test (22) $P<.05$).

For interhemispheric functional connectivity, overall coherence is lower when compared to that observed for within STNr recordings (see figure 4A & B) but it remained above the 95% confidence interval in the range 4-40 Hz. There is a well-defined peak coherence in the alpha-theta band with a maximum coherence at ~0.25. No statistically significant dopaminergic modulation of bilateral functional connectivity was observed (see table 2).

3.1.2 Dopaminergic Modulation of Weighted Phase Lag Index (WPLI)

In order to correct for potential volume conduction effects on the coherence measure we used the WPLI estimate of functional connectivity which is robust to zero phase-lag correlations (Vinck et al., 2011).
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The results of the pooled WPLI are qualitatively similar to those of standard coherence (see figure 4 D-F, bottom row). WPLI statistics are shown in table 2 and summarized in the boxplots in figure 4. For intra-nuclear pairs we observed that the overall coherence is reduced when comparing WPLI to standard coherence (compare figure 4A and D). The modulation effect of L-DOPA on low beta band connectivity was more evident when analysis was conducted with WPLI yielding an ON-OFF difference of -1.22±0.67 (paired t-test (23) P<.05, intra); from this we conclude that standard coherence and WPLI indicate that L-DOPA reduces beta frequency synchronization within the STNr in Parkinson’s patients.

For bilateral inter nuclear STNr connectivity, correction for zero lag interactions heavily attenuated coherences at frequencies >15 Hz to levels to below or close to the significance threshold (see figure 4E). The alpha-theta band interaction observed when using coherence remained in the WPLI although was also attenuated. The overall reduction in coherence would suggest that zero-lag interactions are present in the inter-hemispheric connectivity between STNr. These effects cannot be explained on the grounds of removal of volume conduction and they may reflect the fact that coherence is detecting a zero lag common input to left and right STNr which has been removed by the WPLI method. No
statistically significant modulatory effect of L-DOPA was observed for left STNr to right STNr connectivity as measured with WPLI (see table 2).

<table>
<thead>
<tr>
<th></th>
<th>ON</th>
<th>OFF</th>
<th>Comparison</th>
<th>Total Rejection Rate</th>
</tr>
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<tbody>
<tr>
<td><strong>Alpha</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intra</strong></td>
<td>0.548</td>
<td>0.548</td>
<td>0.001</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>Inter</strong></td>
<td>0.548</td>
<td>0.536</td>
<td>0.001</td>
<td>0.012</td>
</tr>
<tr>
<td><strong>Low Beta</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intra</strong></td>
<td>0.577</td>
<td>0.575</td>
<td>0.001</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Inter</strong></td>
<td>0.549</td>
<td>0.554</td>
<td>0.001</td>
<td>-0.005</td>
</tr>
<tr>
<td><strong>High Beta</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Intra</strong></td>
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<td>0.566</td>
<td>0.003</td>
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<tr>
<td><strong>Inter</strong></td>
<td>0.558</td>
<td>0.557</td>
<td>0.001</td>
<td>0.001</td>
</tr>
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</table>

Table 3 - Table of comparisons of PS-DFA Exponent values for ON or OFF levodopa. Significance for difference in means between ON and OFF was tested using a paired t-test ($P < .05; P < .01$). Exponents are ML-DFA validated and the rejection rate is shown in the 6 right-most columns. Rejection rates are reported either as a subject average or as a rate of the total available exponents from the data.
### Chapter I: Dopaminergic Modulation of STN Synchronization

#### UPDRS Score / Signal Feature Correlations

<table>
<thead>
<tr>
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<th>OFF UPDRS</th>
<th>ON UPDRS</th>
<th>ON-OFF UPDRS DIFFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alpha</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra</td>
<td>-0.609 0.331</td>
<td>-0.117 0.016</td>
<td>0.588 -0.193 0.076 0.388</td>
</tr>
<tr>
<td>Inter</td>
<td>-0.616 0.386</td>
<td>-0.189 0.015</td>
<td>0.557 -0.248 0.100 0.492</td>
</tr>
<tr>
<td><strong>Low Beta</strong></td>
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</tr>
<tr>
<td>Intra</td>
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<td>0.648 0.400</td>
<td>0.002 0.560 0.398 0.007</td>
</tr>
<tr>
<td>Inter</td>
<td>0.688 0.240</td>
<td>0.742 0.585</td>
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<tr>
<td>Intra</td>
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<tr>
<td>Inter</td>
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<td>0.800 0.200 0.003 0.558</td>
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#### Coherence AUC Correlations with Clinical Scores

<table>
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<th>ON-OFF UPDRS DIFFERENCE</th>
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<td></td>
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<td>0.434 0.368 0.100 0.076</td>
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<td>Intra</td>
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<tr>
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</table>

#### WPLI AUC Correlations with Clinical Scores

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<th>ON-OFF UPDRS DIFFERENCE</th>
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<td><strong>Alpha</strong></td>
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<td>Inter</td>
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<td>0.109 0.001</td>
<td>0.278 0.053</td>
<td>0.382 -0.636 0.346 0.030</td>
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</table>

Table 4 - Bivariate correlations of UPDRS with power, coherence and WPLI. Results are shown for ON, OFF, ALL (both ON and OFF) and the DIFFERENCE (ON-OFF) groups of data. The Pearson correlation coefficient (r) is shown alongside the coefficient of determination (RSqr) for the corresponding linear regression. The p-value and the degrees of freedom for the correlations are shown (P > 0.05; P < 0.01).
3.2.2 Correlation of Connectivity Measures with OFF state Motor Symptom Severity

Significant correlations of within nucleus coherence with OFF state UPDRS were found for all three bands although only low beta band interactions survived when removing zero-lag coupling using the WPLI metric (table 4). Intra-nuclear STNr coherence in the low beta band was found to positively correlate with UPDRS ($r(22) = .643$, OFF intra-) suggesting that UPDRS symptom severity increases with increased low beta band coherence. There was also an OFF state UPDRS correlation found for high beta coherence ($r(22) = .460$, OFF intra-) although was not detectable using the WPLI measure and the effect was not independent of power in any of the three bands.

The effect for low beta remained when measuring connectivity using WPLI ($r(22) = .575$, OFF intra-) and was demonstrated to be a significant predictor when entered into a GLMM ($P<.001$, $\Omega^2 = .41$). In order to determine if this effect was separate to that of low beta power, the two measures were entered as covariates into a multiple regression. It was found that only power was a significant regressor in the model suggesting that any variance explained by WPLI is contained within that explained by power. Thus whilst linear measures of functional low beta band intra-nuclear connectivity related to the severity of the motor OFF state PD, these effects cannot be separated from those of power in the same frequency band. There was no effect found when correlating beta coherence or WPLI change ON minus OFF with clinical improvement following L-DOPA. No significant OFF UPDRS correlations were found for inter-nuclear coherences.

| UPDRS Correlations with Exponents from DFA for Phase Synchrony |
|-----------------|-----------------|-----------------|
| | OFF UPDRS | ON UPDRS | ON-OFF UPDRS |
| | | DIFFERENCE | |
| Alpha | $r$ | RSqr | $p$ | df | $r$ | RSqr | $p$ | df | $r$ | RSqr | $p$ | df |
| Intra | 0.054 | 0.014 | 0.807 | 21 | 0.443 | 0.134 | 0.034 | 21 | 0.081 | 0.013 | 0.713 | 21 |
| Inter | 0.025 | 0.007 | 0.940 | 10 | -0.423 | 0.336 | 0.194 | 9 | 0.517 | 0.305 | 0.089 | 10 |
| Low Beta | | | | | | | | | | | | |
| Intra | 0.043 | 0.040 | 0.854 | 19 | 0.346 | 0.108 | 0.147 | 17 | -0.197 | 0.097 | 0.450 | 15 |
| Inter | 0.725 | 0.471 | 0.008 | 10 | -0.453 | 0.166 | 0.162 | 9 | 0.827 | 0.328 | 0.003 | 9 |
| High Beta | | | | | | | | | | | | |
| Intra | -0.204 | 0.041 | 0.402 | 17 | -0.252 | 0.070 | 0.285 | 18 | -0.279 | 0.052 | 0.295 | 14 |
| Inter | -0.074 | 0.013 | 0.820 | 10 | -0.656 | 0.377 | 0.028 | 9 | 0.355 | 0.109 | 0.286 | 9 |

Table 5 - Bivariate correlations of UPDRS with PS-DFA Exponents. Results are shown for ON, OFF, ALL (both ON and OFF) and the DIFFERENCE (ON-OFF) groups of data. Exponents are ML-DFA validated. The Pearson correlation coefficient ($r$) is shown alongside the coefficient of determination (RSqr) for the corresponding linear regression. The p-value and the degrees of freedom for the correlations are shown ($P>.05; P>.01$).
Chapter I: Dopaminergic Modulation of STN Synchronization

3.3 Measuring Phase Ordering in STN Interactions

3.3.1 Dopaminergic Modulation of DFA-PS Exponents

We applied DFA-PS to the LFP data at frequency bands centered at the peak of the spectral coherence for each respective band. A 2.5 Hz half-band width filter was chosen to allow for changes of the coherent frequency over time, covering the full width of the coherent band, as well as to avoid removing phase dynamics that could be missed with too tight a passband (Boashash, 1992). When reporting exponents, the validation technique (described in the methods) was utilized to identify and remove exponents originating from non-linear DFA plots. Examples of the outcomes of the validation procedure are shown in figure 6.

Results from DFA-PS analysis demonstrate that the majority of fluctuation plots are linear and have non-trivial exponents when compared to exponents from shuffled data (i.e. no correlations present, exponent ≈ 0.5) with P-values for all comparisons below the demonstrating that exponents were significantly different from those determined from purely random phase signals (see table 3 and figure 5A-C). As the majority of fluctuation plots in the alpha and low beta bands were validated as linear, there is evidence for the existence of temporal persistence in the phase relations of the signals of interest indicating long-range temporal correlations (LRTCs), i.e. temporal order within the fluctuation rates of change of phase difference (see Botcharova et al., 2014). Exponents values in the alpha-theta (0.55±0.04, ON, intra-) and low beta (0.58±0.03, ON intra-) bands are in the range that is in agreement with those previously reported in the motor cortex during a movement task (Botcharova, Berthouze, Brookes, Barnes, & Farmer, 2015).
### Table 6 - Mixed GLM Regression Analysis

Results from statistical modelling of UPDRS regression with spectral features such as power in band, coherence and PS-DFA exponents. The bivariate regressions are shown in the first column with the respective p-value of the predictor for UPDRS and the overall $\Omega^2$ (estimated explained variance) for the given model. Models with the addition of a covariate are given in the rest of the table. Models where neither predictor was significant are highlighted in red and are suspected to result from collinearity in the variables.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Bivariate Model</th>
<th>Alpha Power</th>
<th>Low Beta Power</th>
<th>High Beta Power</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$P$</td>
<td>$\Omega^2$</td>
<td>$P$</td>
<td>$\Omega^2$</td>
</tr>
<tr>
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<td>0.493</td>
<td>0.358</td>
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<td>0.358</td>
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<td></td>
<td></td>
</tr>
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<td>0.059</td>
</tr>
<tr>
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<td>0.032</td>
<td>0.450</td>
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</tr>
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<td>Alpha Exponent</td>
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<td></td>
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</tr>
<tr>
<td>Low Beta Exponent</td>
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</tr>
<tr>
<td>High Beta Exponent</td>
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<tr>
<td>Alpha Exponent</td>
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</tr>
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</tr>
<tr>
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</table>

<table>
<thead>
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<th>Alpha Power</th>
<th>Low Beta Power</th>
<th>High Beta Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P$</td>
<td>$\Omega^2$</td>
<td>$P$</td>
<td>$\Omega^2$</td>
</tr>
<tr>
<td>Alpha Power</td>
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<td>0.386</td>
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<tr>
<td>High Beta Power</td>
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<td>Alpha Coherence</td>
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<td>Low Beta Coherence</td>
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<tr>
<td>High Beta Coherence</td>
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<td>Coherence Inter</td>
<td>Alpha Exponent</td>
<td>Low Beta Exponent</td>
<td>High Beta Exponent</td>
</tr>
<tr>
<td>$P$</td>
<td>$\Omega^2$</td>
<td>$P$</td>
<td>$\Omega^2$</td>
</tr>
<tr>
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<td>0.000</td>
</tr>
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<td></td>
</tr>
<tr>
<td>High Beta Exponent</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Chapter I: Dopaminergic Modulation of STN Synchronization

Exponents obtained for LFP phase differences ON and OFF L-DOPA estimated for inter- and intra-nuclear pairings were compared (paired t-test, see figure 5A-C and table 3). There were no significant differences found for mean exponents between ON and OFF drug suggesting that scaling statistics of phase interactions are not modulated by L-DOPA uniformly between patients. In the alpha-theta band most of plots were validated (>86%). The rate of rejection increased for both high and low beta bands where 55%-70% of plots were linear and therefore found to be indicative of long-range dependence.

3.3.2 DFA for Phase Synchrony and OFF drug Clinical State

No significant correlation was found between OFF UPDRS and the exponent values obtained from analysis of STNr intra nuclear DFA-PS. Analysis of OFF state UPDRS with DFA-PS results identified positive correlations for exponent value for inter-nuclear pairs in the low beta frequency band ($r(10) = .725$, OFF inter-). These results demonstrate that increased order in the rate of change of phase differences of bilateral STNr LFP interactions correlates with increasing severity of bradykinetic symptoms in PD. When entered into a GLM we demonstrated that low beta inter-nuclear DFA-PS

Figure 6 - Examples of fluctuation plot validation resulting utilising the PEB-DFA method. Fluctuation plots were fit to a range of models and their respective free energies were computed. For alpha and low beta bands the fluctuation plots are shown alongside the exponent value of the assumed linear fit as well as the log model evidence. An example is shown for each band when ON or OFF L-dopa and a case for which the plot was either accepted or rejected as valid linear. Exponents were rejected in the case that there was strong evidence (BF>6) in favour of an alternative model.
exponents were significant independent predictors of OFF state UPDRS from that explained by differences in low beta power ($P<.05$, $\Omega^2 = .472$). The effect for low beta DFA-PS was not demonstrated to be independent of alpha-theta power as a result of collinearity between the two variables. This correlation was shown to be significant ($r(10) = -.685$, $P<.05$, OFF inter-) and thus it was not possible to determine whether PS-DFA in the alpha-theta band provided added any additional explanation of UPDRS variance over band power alone.

Further analysis investigating the ON-OFF drug associated UPDRS difference demonstrated an effect in the low beta band ($r(9) = .827$, ON-OFF inter-) and this can be seen in the scatter plots in figure 5F. However this effect was not found to be significant when entered into the GLM ($P>.05$, $\Omega^2 = .390$) suggesting that the linear association is driven by extreme values in a small number of patients.

3.4 LFP/HPI Cross Correlation

In order to determine whether UPDRS correlations of power arose from increased movement artefact that may be associated with lower symptom scores we ran a cross-correlations for alpha-theta band passed LFPs with that of the root mean square (RMS) fluctuation of the head movement (HPI) data as measured by the MEG scanner.

From the pooled cross correlation (figure 7) it can be seen that the alpha-theta band envelope does not show significant correlation with the HPI RMS at any lags. This result does not provide evidence for a non-neuronal source of the measured activity in the alpha-theta band.

4 Discussion
4.1 Limitations of the Study

Due to the need for invasive surgery it is not possible to conduct a similar experiment with neurologically healthy subjects. We do not know in healthy subjects what would be normal alpha-theta and beta power levels, coherence, WPLI or PS-DFA. Furthermore, the signal characteristics themselves may be affected by surgery (stun effect), longevity and severity of the disease and chronic medication exposure. To control for this all measures have been performed within the same subject in different conditions-ON or OFF L-DOPA. Symptom severity is measured across subjects and the change in symptom severity with medication is measured within a subject initially and then correlated across subjects.

There is difficulty when comparing localization of recordings across patients. Despite confirmation of electrode targeting with post-operative imaging, variability of individual anatomy in the relatively small structure of the STN makes attributing anatomical location to functionality a challenge. As a consequence the attribution of neurophysiological phenomena to a particular neuroanatomical pathway or network should be viewed with caution.

As previously discussed, measurements of coherence are susceptible to zero-phase volume conduction effects. Whilst we can be confident that volume conduction is not a problem for inter-nuclear interaction, it is likely that volume effects are present within the region within and surrounding STN nuclei due to the close proximity of contacts on the electrode. Studies of volume conduction of LFPs demonstrate that the extent of the effect is complex and dependent on a number of factors such as source density, orientations, and the conducting media. This has led to a wide range of possible distances at which volume conduction may occur, ranging from 0.6 mm upwards to 5 mm (Kajikawa & Schroeder, 2011). The 2 mm contact separation distance for channels within the STN suggests that volume conduction is to be expected.

4.2 Dopamine and Spectral Components of the STNr

4.2.1 STNr Low Beta Power in Parkinson’s Disease

We found that the amplitude of the power in low beta band is positively correlated with UPDRS clinical assessment of the severity of bradykinesia and rigidity symptoms (figure 3B and table 5). These findings suggest that the strength of 13-20 Hz oscillations within the STNr relate to severity of akinetic-rigid symptoms in PD.

We have reproduced the finding that beta power is reduced with treatment with L-DOPA (Hammond et al., 2007; Priori et al., 2004; Weinberger et al., 2006). The effect was found to occur robustly throughout the patient cohort and is evident in a large number of single channel spectra (for an example,
see figure 1C). There is also evidence for the subdivision of beta into high and low bands determined by their responsiveness to dopaminergic therapy such that low beta band is most affected by treatment with L-DOPA (see also Litvak et al., 2011). This effect is clear in the spectra shown in figure 2A, in which two discrete peaks in beta range are seen - the low band is significantly modulated by dopamine, whilst high beta is not significantly changed.

We also note that changes in low beta power ON and OFF L-DOPA correlate with the scale of improvement of clinical symptoms with drug therapy. We show that stronger decreases in low beta power are associated with greater therapeutic benefit of L-DOPA. This effect is similar to that previously reported in Kühn et al., (2006) and strengthens the argument that reduction in beta power within STNr may be a good physiological target for treatments of PD.

4.2.2 STN Alpha-theta power in Parkinson’s disease

In contrast to the findings for power in the low beta range, we report for the first time that the amplitude of alpha-theta power is negatively correlated with bradykinesia/rigidity symptoms. This suggests that increased alpha-theta power is associated with a less Parkinsonian motor state in untreated patients. We further demonstrate that alpha-theta power is increased with dopaminergic therapy.

Alpha power in the STN was first reported by Priori et al., (2004) but these authors did not find it to be affected by L-DOPA. Later Alonso-Frech et al., (2006) reported alpha oscillations the power of which was raised in response to L-DOPA. Furthermore, they reported that the effect was disproportionately represented in patients exhibiting ON drug L-DOPA induced dyskinesias. In the present study we did not find a correlation between head movement and STNr alpha-theta activity. Thus we have no evidence for relation between alpha-theta activity and head movement during the STNr recording in the scanner, although the majority of patients had dyskinesia as one of their predominant symptoms.

The present findings are in agreement with Alonso-Frech et al., (2006) who found no connection between dyskinetic movements and STN alpha activity. This led the previous authors to conclude that alpha increase is not the result of involuntary movement per se but rather the physiological changes that allow dyskinesias to emerge. In future studies it may also be possible to study further the differential effects of alpha increase and beta decrease with improving Parkinsonian state through a more detailed analysis of the other symptoms of Parkinson’s including gait impairment and postural control.

It has been reported that alpha activity correlates strongly with motor effort and to a lesser extent, reactivity in PD (Anzak et al., 2012). Alpha STN activity is also known to be coherent with a wider parietal-temporal network proposed to be tied to attentional functions (Litvak et al., 2011b). Our findings here support the functional importance of alpha-theta band activity in PD.

4.3 Sub-cortical Connectivity within and across STNr
4.3.1 Intra-nuclear Connectivity Increases with Severity of Motor Symptoms

Measurement of spectral coherence within STNr at rest has demonstrated the existence of a positive correlation between OFF state UPDRS and low beta intra-nuclear coherence. This result is maintained with WPLI analysis, thus supporting the hypothesis that measured connectivity is physiological and not the result of field spread. However, the positive relationship between increased UPDRS severity and increase functional connectivity measured with WPLI is statistically dependent on low beta power when regressing for UPDRS. This may be indicative of dispersion of extrinsically generated beta oscillations throughout locally coherent networks within the structures of the STN. This property has been theorized to allow the structure to form a global “switch”-like response to cortical input (Gillies & Willshaw, 2004). It is possible that excess within-STNr coherence may subsequently result in a decreased sensitivity to cortical motor input as the structure is dominated by locally propagating beta oscillations. We found a correlation between increased UPDRS and strength of high beta coupling but again in a mixed regression model this effect was not independent of high beta power. Interestingly previous studies looking at cortical-STN connectivity have suggested that activity in the high beta bands is more likely related to cortical communication (Oswal et al., 2013) although the role of this network in the pathophysiology of PD remains unclear.

4.3.2 Across Hemisphere STN Connectivity

Bilateral connectivity between STNrs is dominated by alpha-theta band coherence that is clearly visible as a peak in the coherence spectrum. This effect remains when correcting for volume conduction with the WPLI method although it is attenuated (figure 4). This functional connectivity was not influenced by L-DOPA. Left-right alpha-theta band functional connectivity did not correlate with the severity of the motor off state.

In contrast to findings of de Solages et al., (2010) we did not find evidence of substantial left-right STN coherence in the beta range. Our results support those of Little et al., (2013) who found most left right STNr coherence in the alpha band. This finding of significant left-right alpha-theta band coherence complements the work of previous authors (de Solages et al., 2010; Hohlefeld et al., 2014; Kato et al., 2015) who found evidence for non-zero lag connectivity when using both standard coherence and the imaginary part of coherence in alpha-theta band. In contrast, we did not find evidence for increased bilateral alpha-theta or beta coherence in response to dopamine nor a relation to motor symptom severity. We suggest that a common drive to the left and right STNr may produce coupling although it is also possible that there is STNr to STNr connection although the actual anatomical connection between nuclei has yet to be elucidated (Little et al., 2013). Future work may be able to yield answers to these questions through the use of measures such as partial coherence to determine the existence of a common source, cortical or sub-cortical.
The reduction of the overall measure of correlation when using WPLI for both inter and intra-nuclear interactions when compared to standard coherence suggests that the contribution of zero-phase effects to the standard coherence is significant. This effect is interesting when considering inter-nuclear interactions as the relatively wide spatial separation of channels across a >26mm wide commissure (Mavridis, Boviatisis, & Anagnostopoulou, 2013) indicates that the effects of volume conduction should be minimal. Zero phase lag interactions are entirely plausible biologically especially in the context of common synaptic input (Gollo et al., 2014; Vicente, Gollo, Mirasso, Fischer, & Pipa, 2008). It is suggested that there exist well-timed broadband cortico-subcortical projections that synchronize STN in both hemispheres via the hyper-direct pathway (Brunenberg et al., 2012). This view is supported by the finding of cortical leading coherence to the STN in the alpha band (Litvak et al., 2011). Our data lend support to the idea that there exists common input to both left and right STNr.

4.4 Persistent Temporal Correlations are present in the Phase Coupled STN

Having identified the significant components of long-range synchrony via coherence as well as localized oscillations via analysis of the power spectrum, we then determined how the temporal structure of pairs of signals’ phase interactions changed with the administration of dopamine and with the expression of clinical symptoms in patients. This is a novel approach to studying synchronization phenomena within the basal ganglia.

Our results demonstrate the existence of LRTCs in the phase dynamics of the coupled STNr for alpha-theta and low beta bands in which non-trivial (>0.5) scaling exponents are measured and the majority of fluctuation plots were deemed to be valid for power law scaling. We demonstrate that low beta band DFA-PS exponent magnitudes for inter-hemispheric pairs positively correlate with symptom severity in the Parkinsonian OFF state. Low beta DFA-PS exponents are predictors of UPDRS independently from low beta power. The scaling statistics of phase dynamics detected by DFA-PS provide a novel way through which to characterize oscillations; one that is distinct from standard measures of power and coherence. These results support the idea that the subcortical network of fluctuating phase interactions is critically poised close to an instability (Aburn et al., 2012).

The findings reported here suggest that the more severe the motor impairment of a patient then the closer the bilateral subthalamic network is to the onset of full phase synchronization (see Botcharova et al, 2014 for model of synchronization onset). In the framework of the critical coupling hypothesis we would suggest that this implies an underlying shift of the STN network towards a supercritical regime from which pathological synchrony can more easily emerge. Such a regime would ultimately reduce the effective transfer entropy via phase, reducing the encoding space available to the network by a recruitment of highly coherent yet informationally redundant neuronal units in the disease state
Previous use of DFA-PS in analyzing changes during movement at the level of the left and right motor cortices show that compared to the resting state, movement is associated with a decrease in exponent value (Botcharova et al., 2015). This would suggest that increased ordering of phase interactions has the effect of being anti-kinetic.

It is interesting to note that whilst changes in linear metrics of bilateral STN functional connectivity (coherence and WPLI) did not correlate with symptom severity, the temporal ordering of phase as measured by DFA-PS did correlate. This would suggest that the bilateral connection is not necessarily important in motor planning but the phase dynamics between them may imply a system that shows increased susceptibility to entrainment by extrinsic drives such as that from the cortex or oscillators in the STN’s local network. This may be indicative of a broader neuro-dynamic shift which increases the resonant properties of the basal ganglia to cortical inputs - a model which has recently been demonstrated to account for the generation of beta oscillations in PD (Pavlides et al., 2015).

Our results demonstrate that in line with theoretical predictions DFA-PS quantifies the propensity of the system to excessive synchronization which in turn relates to clinical impairment. However, in the specific case of pathological oscillations in PD, changes in power, particularly in the low beta band provide a clearer marker of these pathological processes. Given that estimating power is more straightforward than determining the DFA-PS exponent and that it can be done in real time, it does not seem to be the case that computing DFA-PS is a practically useful way of inferring clinical state from STN LFP. However, when recordings from multiple parts of the cortico-basal ganglia circuit are available, DFA-PS might be useful for identifying those connections in the circuit that are susceptible to pathological synchronization. Performing this kind of analysis for cortico-subthalamic connections using MEG data collected from the patients included in the present paper will be the subject of our next study.

4.5 Conclusions

Our study has added further detail to the description of oscillations and synchronous dynamics in the Parkinsonian brain. We report evidence for a counteracting effect of alpha-theta and low beta oscillations and their relation to L-DOPA treatment, which strengthens the idea that beta oscillations act as an akinetic signal. We identified physiological connectivity within STN that may works to propagate beta throughout the structure and would act to effectively block receptivity of the structure to incoming input. This idea is further enhanced by our novel finding that the scaling statistics of inter-nuclear interactions become more ordered in more severe disease states suggesting that the network is pushed closer to the transition to full phase synchronization. These findings may help to explain why oscillations in the STN appear to be so important in determining patients’ motor outcomes and help to
understand the mechanisms by which treatment such as L-DOPA and DBS achieve control of synchronicity.
Chapter I: Dopaminergic Modulation of STN Synchronization

T.O. West (2018): Dysregulation of Synchronized Brain Oscillations in Parkinson’s Disease
Chapter II:
Non-Parametric Directionality Metric for Continuous Neural Recordings: A Validation Study
Chapter II: Non-Parametric Directionality - A Validation Study

1 Introduction

A novel method of estimating directed functional connectivity (dFC) termed Non-Parametric Directionality (NPD) has been described in Halliday (2015) and was recently used to infer directed connectivity between electrophysiological field recordings made in animals (West et al. 2018). Functional connectivity describes the statistical dependencies between brain signals, typically measured as time or frequency domain correlations (Friston 2011; Bastos and Schoffelen 2016). Magnitude squared coherence, equivalent to a frequency domain coefficient of correlation has been widely adopted as the estimator of choice for functional connectivity (Brillinger 1975; Halliday et al. 1995). Undirected measures of functional connectivity are symmetrical, giving no indication of the temporal precedence of correlations, a property posited to underlie causation in time evolving systems (Wiener 1956). dFC aims to estimate statistical asymmetries in the correlated activity of a set of signals, determining the directional influence of one signal over another.

The NPD method provides a model-free metric by which to estimate dFC between recordings of neural activity. NPD works by decomposing the coherence into three temporally independent components separated by the relative lag of the cross-correlations between the signals: 1) forward lagged; 2) reverse lagged; and 3) instantaneously correlated. This may be achieved by eliminating the influence of the autocorrelation structure of the individual signals through a process of spectral pre-whitening which acts to bring the individual signals closer to white-noise but preserves the correlations between them. In the original paper (Halliday 2015) the method was validated using a simple three node network with each node simulated using a conductance model of a spiking neurone in order to generate a series of point processes. The authors demonstrated that NPD was successful in recovering the connectivity from a range of simulated architectures. Furthermore, the method was applied to spike timings recorded from muscle spindle and shown to yield physiologically plausible results of causality. Our recent work has extended the application of NPD to include continuous local field potential (LFP) recordings made from an in vivo preparation of the cortico-basal ganglia system (West et al. 2018).

Estimates of dFC are most frequently computed in the literature using Granger causality or one of its variants (Granger 1969; Geweke 1982; Kamiński et al. 2001; Dhamala et al. 2008a). Granger causality is expressed in terms of the capacity of the information in one signal’s past to predict the future of another signal. This is usually achieved through the implementation of an autoregressive model by which the explained variance of $Y$ is compared between that of a ‘full’ model (i.e. accounting for the past of $X$ and $Y$) and restricted model (i.e. $Y$ only). If a prediction of the future of $Y$ is aided by information from the past of $X$ over that of the past of $Y$ itself, then $X$ is said to be ‘G-causing’ $Y$. In a way similar to NPD, the method requires factorizing out the autoregressive component of the signal (the ‘restricted’ model) to avoid trivial correlations that occur simply due to the periodicity in the signals.
However, the estimation of MVAR parameters, as well as the specification of model order is computationally expensive, and low model orders may not suitably capture the spectral complexity of a signal. An extension to Granger causality, non-parametric Granger causality (npGC), which avoids the requirement for estimation of a transfer function from MVAR model coefficient has been described by Dhamala and colleagues (Dhamala et al. 2008a). In this method transfer functions and noise covariances are estimated through the spectral factorization of Fourier coefficients (Dhamala et al. 2008b). Here, we directly compare npGC with NPD as an estimator of dFC. Both methods share the property of being model free estimates and can be derived from identical spectral transforms made either via Fourier or wavelet techniques.

Estimation of empirical dFC in continuous neural recordings such as the LFP or magneto/electroencephalograms (M/EEG) is complicated by a number of factors: low or asymmetric signal-to-noise ratios (SNR), instantaneous volume conduction, common drive, signal routing via parallel but disjoint paths, and the presence of cyclic paths within a network. All pose potential confounds for the metrics described here. The failure of Granger causality in the presence of large amounts of measurement noise is an established shortcoming of the method (Newbold 1978) which becomes particularly acute in noisy electrophysiological recordings (Nalatore et al. 2007). Instantaneous mixing of the electromagnetic signals generated by distinct sources in the brain has long been known to make estimation of functional connectivity based on signals such as the EEG difficult (Nunez et al. 1997). Common drive is also known to lead to spurious estimates of connectivity as delays in the arrival of the common input can induce lagged correlations between unconnected neurons (Farmer et al. 1993). In the case where the common input is measured, extensions of functional connectivity metrics built upon partial regressions can be used to eliminate spurious connectivity. In the case of NPD, the authors introduced a multivariate extension (Halliday et al. 2016) that can be used to remove influence of common drive through partial regression of a third reference signal.

In this paper we will assess the performance of NPD’s ability to recover the connectomes from a number of simulated architectures and in the face of the aforementioned confounds. Furthermore, we compare the performance of coherence, NPD and npGC in the presence of a number of confounds typically found in neural recordings. We also test the efficacy of using a multivariate extension of NPD, the conditioned (partialized) NPD, as a means of testing for the effects of common drive and its ability to discriminate between parallel signal routing. Finally we will demonstrate the efficacy of NPD at recovering the known neural hierarchies of the striatal-pallidal indirect pathway in the basal ganglia.
2 Methods

2.1 Software for Analysis, Simulations, and Statistics

Data was analysed using a set of proprietary scripts written in MATLAB R2017a (The Mathworks, Nantucket, MA, USA). Nonparametric directionality was implemented using the Neurospec toolbox (http://www.neurospec.org/). MVAR models were implemented using the BSMART toolbox (Cui et al. 2008) implemented in the FieldTrip toolbox (Oostenveld et al. 2011). All scripts for the analyses presented here can be found on Github (URL###). A full list of toolboxes, authors, and links to their source code used can be found in the supplementary materials.

2.2 Functional Connectivity

In this chapter we utilize spectral coherence for estimates of undirected FC, and NPD/npGC for dFC estimates. For their formulation please see the methods section of this thesis.

2.3 Simulations

2.3.1 MVAR Modelling

We utilised a multivariate autoregressive (MVAR) model in order to simulate lagged correlations between simple periodic systems. MVAR models are an extension to 1-dimensional autoregressive models. A \( p \) order MVAR model with \( N \) number of states is given by:

\[
X^n_t = c^n + \sum_{i=1}^{p} \varphi_{ni}^n X^{n}_{t-i} + \epsilon^n_t
\]

where \( \varphi_{ni}^n \) are the autoregressive coefficients for state \( n \) at lag \( i \), \( c^n \) are constants of state \( n \), and \( \epsilon^n_t \) is white noise with zero mean and covariance structure \( R \). The AR model takes a model order \( p \) which determines the number of \( t - p \) previous states of the system that are regressed to form the present state \( X_t \), thus the AR model exhibits short term memory effects. Simple periodic signals may be engineered through setting of alternating coefficients at separate lags. For example, to get a lag two periodicity at state \( n \) we set \( \varphi_{1,2}^n = [1 - 1] \). The matrix of coefficients \( \varphi_p^N \) specifies the terms of a state dependent on itself along the diagonal. In order to introduce correlations between states we introduced non-zero coefficients off of the diagonals. In this way we simulate lagged connectivity by setting positive coefficients between nodes at lags greater than 1. For the parameters of the simulated MVAR models please see appendix I. All simulations were run to yield \( 10^5 \) data samples. We assume a sampling rate of 200 Hz to yield relative timings/frequencies of dynamics.
2.3.2 Observation Modelling

In order to approximate some of the issues that arise in the experimental recording of neural signals, we place an observation model on top of the model of the dynamics:

\[ Y_t = g(X_t, L, \gamma) \]

where the observer function \( g() \) maps from the hidden (dynamical) states \( X_t \) onto the observed states \( Y_t \). The function utilizes a leadfield matrix \( L \) which acts to instantaneously mix signals:

\[ Y_t = (1 - \lambda)X_tL + \lambda\gamma \]

where there is a constraint on \( L \):

\[ \sum_{j=1}^{n} L_{ij} = [1 \ 1 \ 1] \]

There is also the addition of observation (as opposed to state) noise \( \gamma \) which is i.i.d, zero mean, unit variance white noise. The observer model simulates modulation of the signal-to-noise ratio (SNR) through the factor \( \lambda \), where \( \lambda = 1 \) is completely observation noise. Finally, the output \( Y_t \) is constrained to unit variance via Z-normalization. This formalization allows for the simulation of both the modulation of observer gain through \( \lambda \), as well as the instantaneous mixing of signals through the mixing matrix \( L \).

3 Results

3.1 Effects of Lagged Dependencies and Common Drive

We first demonstrate the efficacy of the metrics at recovering simple hierarchical architectures. To this end we present results from a simple 3-node, 3rd order MVAR model with no signal mixing and zero observation noise. The MVAR model is imbued with periodic dynamics that are identical at each node and are driven by noise with fixed covariance structure. Non-zero matrix coefficients are all fixed at 0.5 and the full MVAR parameters can be seen in table 1 of the supplementary information. We design the MVAR model (figure 1A) such that all edges originate at node 1 and correlations are lagged such that input arriving at node 3 lags that at node 2. This introduces a confound as dFC estimates dependent upon temporal lag should determine spurious causality between 2 and 3 as it appears 2 is driving 3 although they just share a common drive. An example time series of the process is shown in figure 1B and the resulting analyses of the functional connectivity are shown in figure 1C.

This model generates rhythmic activity at ~60 Hz as shown by the peaked autospectra for each node. Functional connectivity as measured using standard coherence shows significant connectivity between

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all nodes, albeit reduced for the connection between 2 and 3. We next estimate directed connectivity using NPD. NPD shows that all connections are in the forward direction for \(1 \rightarrow 2\) and \(1 \rightarrow 3\). As the full coherence is equal to the sum of the directional components, the overlap of the forward NPD (spectra in the upper diagonal of the figure) with the coherence shows that the vast majority of the standard coherence is attributable to that occur in the forward NPD. The lag of node 3 with respect to 2 leads to a spurious estimate of coupling from \(2 \rightarrow 3\). We also applied npGC to the simulated data which recovers the designed connectivity in its entirety and without the spurious coupling observed with NPD.

### 3.2 Effects of Low Signal-to-Noise Ratios

Recordings of local field activity in the brain are made in the presence of both endogenous neural background activity as well as observer noise originating from recording equipment and the external environment. In figure 2 we simulate the effects of signal-to-noise ratio (SNR) upon estimates of FC. We used additive Gaussian noise in the observation model to set respectively SNRs of \(1:0\), \(2:1\), and \(3:2\). Following addition of noise we clamped each process to have unit variance. All functional connectivity metrics were resistant to medium degree of additive noise but all FC estimates were heavily attenuated
for the lowest SNR tested. When looking across a range of SNRs (figure 5A) we found both NPD and Granger approached 0 as SNR approached 1:1. Responses were sigmoidal for all three metrics measured with half maximum suppression at around 50% of signal loss. Non-linear least-squares fitting yielded parameter estimates of the logistic decays for each FC metric (midpoint $x_0$; and steepness $\kappa$): coherence $x_0 = 0.70, \kappa = -3.66$; NPD $x_0 = 0.69, \kappa = -3.77$ and npGC $x_0 = 0.53, \kappa = -3.21$. From these estimates and the curves in in figure 5A, it is clear that coherence and NPD effectively share the same response profile to SNR, whilst npGC is slightly more sensitive to noise with estimates starting to curtail at higher SNRs ($\kappa_{npGC} < \kappa_{NPD}$).
Asymmetries in the SNR of different signals are known to distort the estimation of dFC using metrics such as Granger causality (Bastos and Schoffelen 2016). We next tested whether this was true for NPD. We simplified the model to use just 2 nodes, reciprocally connected with the same lag. We then modified the SNR of the first node (X₁) via the same process used for the previous set of simulations. The results of the simulations are shown in figures 3 and 5B. Our simulations confirmed that npGC is biased by differences in SNR between signals showing that even at modest asymmetries (1:2) the weaker signal is estimated to be driven by the stronger i.e. X₂→ X₁. NPD does not suffer from this confound and maintains symmetrical estimation of coupling for all conditions tested. When we look across a large range of asymmetries the response of each metric is apparent (figure 5B). npGC spuriously identifies directed coupling, with the bias strongest around 1:2 SNR. At higher SNRs the coupling is diminished and the symmetrical estimate return as npGC approaches 0 for both directions. In contrast, NPD does not indicate strong directionality, instead the response becomes more variable as the noise increases, and then approaches 0 at high SNR.
3.3 Effects of Instantaneous Signal Mixing

Neurophysiologically recorded signals such as LFPs are subject to instantaneous mixing of the underlying dipole currents as a result of field spread effects. This is well known to pose issues for estimates of functional connectivity (Nolte et al. 2004; Srinivasan et al. 2007; Kajikawa and Schroeder 2011). We next simulated these effects by multiplication of the simulated MVAR process with a linear mixing matrix and we investigated the influence of mixing coefficients upon estimates of dFC. We used an identical model to that in the first part of the previous section (3.2; 3 state, 3rd order) but with a linear observer model to model signal mixing at 0, 25%, and 50% shared variance. The results of the analysis are shown in figure 4.

Figure 4 – Analysis of the effects of instantaneous mixing upon estimates of functional connectivity. The confounding effects of volume conduction were simulated using zero-lag linear mixing of signals generated with a 3 node, 3rd order MVAR model (identical to that in figure 1). We simulate no mixing with \( \lambda = 0 \), 25% mixing \( \lambda = 0.4 \), and 50% mixing \( \lambda = 0.8 \). We approximate the degree to which zero-lag coherence is present in the data by using the instantaneous component of the NPD (blue). DFC is estimated using the lagged components of the NPD (green) and non-parametric Granger (npGC) (red).
We demonstrate the confounding effect of instantaneous mixing by first estimating the degree to which it may influence the zero-lag component of the NPD. We find that the zero-lag NPD is raised by mixing particularly at frequencies outside of the periodic component of the signal. This is due to the fact that the “delayed transmission” simulated using non-zero, off diagonal, 2nd and 3rd order coefficients of the model results in lagged correlations only at the periodic frequencies. Mixed noise outside these bands readily overcomes the power of the noise independent to each node causing zero lag correlations to predominate.

When using NPD to estimate dFC we found that it performs as expected up to a moderate degree of signal mixing (25% shared variance), albeit with a reduction in magnitude. With a larger degree of signal spread the spurious connectivity between nodes 2/3 is increasingly asymmetric with the reverse component emerging at 50% signal spread. npGC performs better and recovers only the connections embedded in the model even at the highest degree of signal mixing tested. Unexpectedly the Granger signal increases with the degree of signal mixing. At the highest degree of mixing tested there is an emergence of spurious causality across all connections with about the same degree to that found with NPD. When testing across a wider range of signal mixing (figure 4B) we show that NPD tails off with greater mixing with a similar profile to that seen when decreasing SNR. Interestingly npGC peaks at a certain degree of mixing and then plateaus to a fixed value even with high amounts of signal spread.

3.4 Neurophysiologically Plausible Networks with Recurrent, Parallel paths, and Heterogeneous Delays

In the next section we ask how the presence of cyclic and parallel paths, as well as heterogeneous transmission delays within a network affect estimates of dFC. We again use the MAR model but introduce an architecture similar to that studied in West et al. (2018) where we considered the directed connectivity of the cortico-subthalamic networks. The network architecture is shown in the schematic in figure 6A and the full MAR model parameters are contained in table 1 of the supplementary information. Briefly, we introduce a ‘high beta’ oscillation in motor cortex node (M2), and a slower “low beta” oscillation in STN. Signals are relayed via two passive nodes equivalent to the striatum (STR) and internal segment of the globus pallidus (GPi). There are two parallel pathways modelled: the “indirect” stream from \( M2 \rightarrow STR \rightarrow STN \); and the ‘hyperdirect’ path from \( M2 \rightarrow STN \). There is also recurrent feedback of the system (via thalamocortical relays) modelled from GPi \( \rightarrow M2 \). We used two sets of cross-node coefficients (\( \alpha \)) and set \( \alpha_1 > \alpha_2 \). Similarly, we used two delay values (\( \delta \)) that were set such that \( \delta_1 > \delta_2 \). We set connections in the hyperdirect pathway to be strong and fast, and weak and slow in the indirect.

dFC analysis of the model output is presented in figure 6B. It can be seen that both NPD and npGC do well at recovering the hierarchical propagation of activity along the indirect and hyperdirect streams.
Figure 5 – Investigating the effects of signal-to-noise ratios (SNR), SNR asymmetries, and instantaneous linear mixing upon functional connectivity metrics: coherence (blue), lagged non-parametric directionality (NPD; green), and non-parametric Granger causality (npGC; red). (A) The effect of SNR was tested in the range from 1:0 to 1:2. All metrics were found to have a sigmoidal response, with half-maximal suppression around SNR = 0.5. (B) The effect of asymmetric SNR was tested by addition of noise to node 1 in the range 1:0 to 1:2 whilst coupling strengths were held fixed. npGC incorrectly identifies asymmetrical coupling for a wide range of SNRs. NPD performs better, with differences in directionality remaining close to zero across the range examined. (C) The effect of instantaneous signal mixing was examined across a range of mixing coefficients (λ). Coherence is shown to increase as zero-lag correlations increase. npGC increases to a maximum at around 15% signal mixing. The lagged NPD shrinks to zero as instantaneous component of coherence dominates.

(top row, 2nd and 3rd columns) as there is a clear passage of the high beta activity. When propagation of the signal converges on a node with different oscillatory dynamics such as at STN, where an intrinsically generated 18 Hz oscillation is mixed with input in the 35 Hz range, the estimates of dFC are weakened. npGC does particularly badly in this case. For instance at the connection STR → STN, where estimates have poor spectral resolution and show an attenuated estimate in the band at which the connectivity is actually occurring. The lagged NPD recovers the connectivity as it is parameterized, with a clear peak in the 25-40 Hz range. However, NPD estimates a direct feedback from STN → STR which is not in the model. This occurs as a result of the feedback loop resulting from (GPi → M2), which propagates the high beta oscillation back through the system leading to a spurious estimation of directionality due to lagged common correlation. When looking at the feedback connection (GPi → M2) using npGC, there is a significant, but flat estimate of causality. In contrast NPD preserves the frequency content of the propagation showing both high and low beta signals.

We next demonstrate the ability of the conditioned NPD to distinguish propagation between parallel routes, as per the indirect and hyperdirect pathways. We choose to partialize the NPD estimate on the signal at STR as this is the entry for the indirect pathway. These estimates are shown in yellow in the figure and show a clear divergence with M2 → STN showing a strong attenuation in the high beta, indicating there is a significant proportion of the signal propagating through STR. Conditioning also attenuates the feedback GPi → M2. This finding would suggest that at least part of the directed coherence arises through activity resonating through the network. This implies that the conditioning can
provide an insight not only into direct connectivity but also the circular propagation of activity in recurrent networks.

3.5 Confounds for conditioned directed connectivity arising from incomplete measurement of signals.

The finding that conditioning of the dFC can affect estimation of correlations arising from both direct and reciprocal connectivity is both a potential benefit and problem: in the case where the system architecture is confidently known, and the conditioned signal \( Z \) is not expected to separate the path between nodes \( X \) and \( Y \), any attenuation when partializing can be assumed to arise in information propagated forward in the network. On the other hand, this finding can also be explained by conventional hierarchical routing (i.e. \( X \to Z \to Y \)) but with incompletely observed signals that would result in only partial attenuation. In the next set of simulations, we ask whether there are any differences in how the measures of dFC behave in the face of incomplete signal observation.
For this set of simulations, we use a 3 node, 3rd order MVAR model, with all nodes generating identical autonomous dynamics and identical cross-node coefficients at equal model lags. We test 3 models to compare 3 types of signal propagation: a) hierarchical (i.e. $X \rightarrow Z \rightarrow Y$), b) feedforward (i.e. $X \rightarrow Y \rightarrow Z$); or c) recurrent (i.e. $X \rightarrow Y \rightarrow Z \rightarrow X$). We simulate incomplete observation of $Z$ by modifying the SNR as in section 3.1.2: ‘Effects of Low Signal-to-Noise Ratios’. The model architectures and results of simulations are shown in figure 7. We demonstrate that in simple hierarchical networks the NPD conditioned on signal $Z$ (NPDxZ) behaves as expected: the estimate of connectivity $X \rightarrow Y$ is attenuated as it is directed via $Z$. With increasing SNR of the observation of $Z$ we show that the conditioning has...
less effect and converges to the estimate yielded by the unconditioned NPD. NPD and npGC remain constant at all SNRs tested.

We next looked at a feedforward network, where $X$ propagates directly to $Y$ but is then fed on to $Z$. Because some of the information passed $X \rightarrow Y$ is contained in $Z$, we expect conditioning to attenuate the direct connection. Again, we find that NPDxZ behaves as expected, although the attenuation is less complete than when $Z$ mediated the connection entirely. Again increasing SNR of the observation of $Z$ decreases the attenuating effect of the conditioned variant.

For the 3rd simulation we investigated the combination of recurrent loops in the network and incomplete signal observation- two features likely to occur in real recordings from neural systems. We find that with complete signal observation (i.e. SNR = 0) the metrics behave similarly to the feedforward model. A notable difference is the increased NPD of $X \rightarrow Y$, as correlations are reinforced by signals resonating across the circuit. As we decreased the SNR of the observation of $Z$ we find a similar effect on npGC as the findings of simulating asymmetric SNR (section 3.2). We find that the npGC estimate of $X \rightarrow Y$ wrongly increases as the observation noise of $Z$ goes up. NPDxZ behaves in a similar way as before, showing attenuation of the estimate at low noise, but converging back to the unconditioned NPD as the signal is sampled less completely.

4 Discussion

The results presented in this paper further validate NPD as a method for estimation of dFC. We have first provided a construct validation of NPD for estimation of the directed interactions between simulated signals. Secondly, we assessed the performance of the metric in the presence of several confounding factors that are likely to arise in experimental recordings from neurophysiological networks, namely: volume conduction, common drive, heterogeneous transmission delays, poor recording SNR, asymmetric SNR, parallel signal paths, and recurrent connectivity. Thirdly, we provide a direct comparison of NPD with a popularly used estimate of dFC – npGC. Finally, we show that the additional information gained from using a conditioned variant of NPD allows for some of the confounding influence of common drive, or complex signal routing, to be negated. The extent to which this is true is dependent upon the spatial extent and gain of the recordings available.

We argue, from the results presented in this paper, that NPD provides a superior estimate of dFC in comparison to npGC. This claim is made on the ground that the npGC estimate is readily confounded by a number of the previously listed factors and fails to recover the spectral fidelity of connectivity in a biologically realistic network architecture.
4.1 A Summary of Effects of Signal Confounds

4.1.1 Effects of A/symmetric Signal-to-Noise Ratios

Functional connectivity estimates are subject to limits of inference implied by the SNR of the available recordings. We demonstrate (figure 5A) that both coherence, NPD, and npGC are degraded by poor SNR with similar logistic decay profiles. However, npGC shows a stronger sensitivity to noise, with estimates degraded more readily than NPD. These findings demonstrate that both methods require a reasonable SNR in order for estimates to be valid but are immune to the occurrence of false-positive errors as a result of significant symmetric SNR degradation.

A number of authors have noted that Granger causality is biased by the existence of asymmetric SNRs (Haufe et al. 2013; Bastos and Schoffelen 2016). Our simulations reinforce this view and demonstrate that npGC is biased to estimate the strongest signal as the driving node (section 3.1.2; figure 5B). This is an important problem as all neurophysiological signals comprise some unknown mixture of the signal of interest and background noise on a source by source basis. As a result, it can rarely be assumed that the SNRs of two signals are balanced. This is particularly important when looking at directed connectivity between signals recorded from two different modalities (e.g. MEG and electromyography) where the estimate will be biased in favour of the higher gain recording (to lead). This has led some authors to suggest the usage of time-reversed data as surrogate comparison for dFC methods (Haufe et al. 2013) because if a true causal effect is present then time reversal should flip the sign of the directionality. Our simulations demonstrate that estimates made using NPD are not subject to this confound and forgo the need for such a surrogate. NPD is still affected by decreased SNR (both asymmetric and symmetric) but shows no bias, as all directional estimates decrease uniformly as the SNR goes down.

4.1.2 Effects of Simulated Volume Conduction through Signal Mixing

Volume conduction effects are ubiquitous across electromagnetic signals of the type measured by MEG/EEG (Nunez et al. 1997; van den Broek et al. 1998) and the LFP (Kajikawa and Schroeder 2011). Instantaneous mixing of independently generated neural activities acts to confound estimates of undirected (Nolte et al. 2004; Srinivasan et al. 2007; Stam et al. 2007) and directed (Brunner et al. 2016; Van de Steen et al. 2016; Kaminski and Blinowska 2017) functional connectivity. In this paper we investigate the extent to which NPD and npGC are also affected by this issue (section 3.3). Our results suggest that npGC can overestimate coupling in the face of instantaneous mixing (figure 5C), due to the increased amount of shared variance that can be explained by one signal from another. By contrast we show that NPD is relatively robust to signal mixing showing low attenuation at 25% mixing. At very high degrees of mixing (>50%), the zero-lag component of the NPD dominates and the lagged NPD values approach zero.
Levels of volume conduction in the real brain diverge with distance but EEG electrodes 5 cm apart will typically show $R^2$ values around 50% shared variance (Nunez et al. 1997) thus sensor level analyses are likely to fall short at distances much closer. Instead, some authors have suggested that functional connectivity analyses are better suited to source localized signals due to the reduced extent of signal leakage (Schoffelen and Gross 2009). This is likely to hold true for the application of NPD analysis to whole brain recordings. Furthermore, NPD provides a degree of estimation of the zero-lag component of coherence thus it is possible to estimate the extent to which coupling is influenced by instantaneous effects. This is beneficial over corrected methods such as imaginary coherence or phase locking index (Nolte et al. 2004; Vinck et al. 2011) which discard this information from instantaneous coupling.

4.1.3 Effects of Common Drive

Common input to two parallel neural populations has long been known to be a confounding factor when estimating functional connectivity (Aertsen et al. 1989; Farmer et al. 1993; Horwitz 2003). The limitations of finite sampling over the brain means that no FC metric is immune to this problem as there always remains the potential for an unmeasured common input to the recorded populations from which an FC estimate is made. Our simulations demonstrate this effect (figure 1) and show a fundamental difference between the NPD and npGC estimates- that is, when the common drive signal is factored into the estimate of npGC it is able to avoid the spurious estimation of connectivity between units with a common drive. This is because the npGC is a multivariate estimate that accounts for the covariance between all signals measured. On the other hand, NPD in its simplest form is measured in a pairwise manner and cannot account for the action of a tertiary signal on the naïve estimate. However, we demonstrate that this issue can be remedied using the conditioned NPD from which the influence of a common drive may be factored (partialized) out, eliminating spurious connectivity between the driven nodes. Whilst this is a solution when the common drive is observed, there still remains the potential confound of an unobserved common signal, to which NPD and nPGC are equally susceptible. These issues can be addressed by model based estimators of effective connectivity which allow for the inference of hidden unobserved states in a causal network (Friston 2011).

4.1.4 Application to Real-World Networks

Ultimately, the utility of methodological developments in estimation of dFC must be measured in their ability to recover the actual patterns of correlated activity in real-world neural networks. These networks are subject to all of the confounds discussed in the previous sections and are complicated by complex network topologies. Networks in the neo-cortex and subcortex are highly re-entrant, containing large number of recurrent connections (Felleman and Van Essen 1991; Douglas and Martin 2007; Edelman and Gally 2013; Markov et al. 2013). The presence of multiple, convergent, parallel paths and cyclic loops all present issues to the assumptions that dFC metrics are built upon, chiefly that temporal precedence implies causality.
This assumption has been weakened somewhat by multiple observations in both simulation and experiment that demonstrate particular (but not necessarily rare) situations in which these metrics may be confounded. Most crucially is the presence of a heterogeneous mix of connection strengths and delays, properties that models suggest imbue the brain with the ability for spontaneous fluctuations in correlated activity such as that observed in the resting state (Ghosh et al. 2008; Deco et al. 2009). We attempted to capture some of this complexity in the MVAR models by introducing differences in the correlation order and coefficients between nodes setup to have an architecture resembling that of the cortico-basal-ganglia network. This network is under scrutiny due to its role in the pathophysiology of several movement disorders (Moran et al. 2011; Tachibana et al. 2011; Marreiros et al. 2013; West et al. 2018). A fuller investigation of the effects of non-linear transmission, and dynamics require validation of these metrics in nonlinear models of neural systems.

We show that a popular metric of dFC, npGC, does not perform well in biologically realistic scenarios. In section 3.4 we show that npGC estimates are readily confounded by i) the convergence of two asynchronous pathways upon a node; and ii) the existence of recurrent connectivity such as that modelled by the return of the basal ganglia to the cortex. We demonstrate that even in the cases where npGC does detect actual connectivity, it loses spectral resolution. Furthermore, we demonstrate that the combination of NPD and conditioned NPD provided a superior method by which to infer real-world connectivity and demonstrate that the partialization of the dFC estimate provides a method by which to distinguish signal propagation via distinct parallel paths.

### 4.1.5 Effects of Limited Signal Observation

The argument that conditioned metrics of dFC such as conditioned NPD show an increased ability to make inference of the causal structure of real-world neural networks hinges upon the assumption that a recorded signal truly captures the complete dynamics of the underlying population through which the signal is routed. In our final set of simulations (section we provided an analysis of how the incomplete observation of signals acts to confound the estimates of dFC under several hypotheses of signal propagation: A) hierarchical, B) feedforward, and C) recurrent connectivity (3.1.5; figure 7). In the case of the simplest architecture (in A), the metrics behave as expected – the less that the signal used to condition captures the underlying dynamics, then the less that the conditioning is able to inform the dFC estimation. In the case of complete signal capture (SNR = 0) the partialization completely attenuates the direct connection in A. In B, the effect of feedforward propagation results in conditioning acting to attenuate the estimate, albeit weakly. In C we show that the re-entrant connection acts to increase the overall coherence due to circuit resonance, and that conditioning acts to bring the NPD estimate closer to that of B (where the re-entrant connection is missing). Unexpectedly, the estimation of npGC is confounded by incomplete observation of the node facilitating feedback, acting to increase the estimation of a directed connection in the feedforward direction. This is likely under the same mechanism of asymmetric SNR discussed previously.
4.2 Extensions and Final Conclusions

We present validation of a novel metric for the assessment of dFC in continuous neural recordings such as that measured in methods commonly used for human neuroimaging. We argue, in the face of common issues posed by recordings in these modalities and the systems that they aim to measure, NPD and its conditioned variant, provide a superior method of estimation over that of npGC, a popular method of dFC estimation. The NPD measure (conditioned and unconditioned) has been recently demonstrated to provide insights into the patterns of propagation of rhythmic neural activity in animal electrophysiology data (West et al. 2018) and the results presented here support its methodological foundations. We suggest that the method is broadly suitable for a range of neuroimaging methodologies, and being impervious to the confounding effects of SNR asymmetry could be successfully applied to multi-modal recordings.

The validation provided here is not extensive, there are a wider range of dFC metrics to which we have not made comparison, and it is possible that other metrics perform better than npGC (for an extensive comparison of many metrics, not including NPD, see Wang et al. 2014). The Granger causality based methods have become a staple of the dFC toolbox and form the statistical foundation for a number of methods since including the directed transfer function and transfer entropy. An adaption of directed transfer function aimed at better estimating direct connectivity (i.e. $X \rightarrow Y$) (Korzeniewska et al. 2003) may perform better in the simulations presented here. NPD shows comparable results to a GC based measure but shows more reliable recovery of complex network topologies and dynamics. NPD is inexpensive to compute, makes limited assumptions of the properties of the data, and is conceptually simple to formulate. It eschews the computationally expensive estimation of model parameters required for estimates such as parametric Granger causality, and directed transfer function, or iterative binning procedures for information-based metrics such as transfer entropy.

Overall, NPD provides a simple and compact statistical description of directed dependencies between signals, it is readily interpretable providing the basis for testable hypotheses of effective connectivity in real neural systems.
## 5 Supplementary Information

### 5.1 Table of MVAR Coefficients

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<th>Simulating Common Drive, Signal-to-noise, instantaneous mixing (figure 1, 2, 4, 5)</th>
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### Simulating Incomplete Signals for Conditioning: Feedforward (figure 7B, E)

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### Simulating Incomplete Signals for Conditioning: Feedforward (figure 7C, F)

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Chapter II: Non-Parametric Directionality - A Validation Study

T.O. West (2018): Dysregulation of Synchronized Brain Oscillations in Parkinson’s Disease
Chapter III:
Propagation of Beta/Gamma Rhythms in the Cortico-Basal Ganglia Circuits of the Parkinsonian Rat
1 Introduction

The basal ganglia (BG) are host to a small but important cluster of dopaminergic neurons that act to modulate the activity of a large re-entrant network that comprises the cortico-basal ganglia-thalamo-cortical circuit (DeLong and Wichmann 2010; Lanciego et al. 2012). Investigation of the structure of this network (Smith et al. 1998; Bolam et al. 2000) has led to what has become a canonical view of the circuit (depicted in Figure 1A) and has formed the basis from which a number of process theories of BG function have arisen (for a review, see Schroll and Hamker, 2013).

Recent theory concerning the organisation of brain networks and communication within them via synchronized oscillations (Varela et al. 2001; Fries 2005, 2015; Bressler and Menon 2010; Thut et al. 2012) has emphasised the importance of understanding the dynamics of these networks beyond that afforded by studying structural connectivity alone (Deco et al. 2008, 2012). Neural oscillations and their synchronization have been measured across multiple spatial scales of brain activity, from single neuronal discharges up to the level of mesoscale neural ensembles such as those measured in the local field potential (LFP) or electrocorticogram (ECoG). Moreover, dysregulations of oscillations and inter-areal synchrony have been reported in brain disorders such as Parkinson’s disease (PD), schizophrenia, and epilepsy, leading to the hypothesis that the oscillations themselves bear a causal role in the behavioral impairments associated with these pathologies (Schnitzler and Gross 2005; Uhlhaas and Singer 2006; Hammond et al. 2007).

Excessive beta oscillations (14-30 Hz) in the BG associated with dopamine depletion have been observed reliably in untreated patients with PD (Levy et al. 2000; Brown et al. 2001; Weinberger et al. 2006; Hammond et al. 2007). Beta rhythms are attenuated by treatments such as dopamine replacement therapy (Kühn et al. 2006; Weinberger et al. 2006; West et al. 2016; Beudel et al. 2017; Levy 2002) and deep brain stimulation (DBS) (Ray et al. 2008; Eusebio et al. 2011; Whitmer et al. 2012) in a way that correlates with the degree of improvement of akinetic/rigid motor symptoms. This has strengthened the argument that the pathological beta rhythms are directly related to the functional impairment seen in patients (Hanslmayr et al. 2012; Brittain and Brown 2014). Furthermore, gamma activity in the motor system has been hypothesized to be prokinetic (Schoffelen et al. 2005). In PD, the spectral power of multiunit recordings from STN at 40-90 Hz have been demonstrated to be negatively correlated with bradykinetic symptoms in patients (Sharott et al. 2014).

The pathological oscillations observed in mesoscale electrophysiological signals are a direct consequence of changes to the underlying networks of neuronal ensembles that generate them. This understanding has led to the re-classification of multiple neurological diseases such as PD or Tourette’s as ‘circuit disorders’ (DeLong and Wichmann 2010). Knowledge of how dopamine depletion results in changes to the network, and the subsequent emergence of pathological synchrony is likely to lead to a better understanding of the causes of impairment and its treatments (Shen et al. 2008; Schroll et al. 2013).
2014). Thus, improving insight into how changes network organization leads to the emergence of pathological dynamics is an important line of enquiry (Wichmann and DeLong 1999; Dostrovsky and Bergman 2004; Holgado et al. 2010)

Previous work aiming to understand the origins of the pathological beta rhythm has involved systematic lesioning of the BG network (Ni et al. 2000; Tachibana et al. 2011), computational modelling (Holgado et al. 2010; Moran et al. 2011; Marreiros et al. 2013; Nevado-Holgado et al. 2014; Pavlides et al. 2015; Lienard et al. 2017), and techniques from signal analysis (Sharott et al. 2005a; Mallet et al. 2008a, 2008b; Litvak et al. 2011a). In this paper, we take the latter approach and, through analysis of neural recordings, aim to infer the changes in neural transmission that occur in cortico-BG circuits following chronic dopamine depletion.

Connectivity between parts of the brain can be inferred from the statistical dependencies that arise due to neural transmission: we refer to this as functional connectivity as per Friston (2011). Previous studies have aimed to describe ‘effective’ connectivity (i.e. causal interactions) within this network and have employed the dynamic causal modeling (DCM) framework in order to do so. To date, two such studies have utilised the inversion of biophysical models upon cross spectral densities from recordings in either anaesthetised 6-OHDA lesioned rats (Moran et al. 2011), or awake DBS patients (Marreiros et al. 2013). Both found evidence for the strengthening of the cortico-subthalamic connection (termed the ‘hyper-direct’ pathway (Nambu et al. 2002)) in the dopamine-depleted state.

From this work amongst others, several hypotheses have arisen concerning the emergence of pathological beta rhythms as a result of the dopamine depletion associated with PD (for a review see Holgado et al. 2010). These include the dopamine-dependent modulation of recurrent loops within the network, either between the reciprocally-coupled network of neurons of the subthalamic nucleus (STN) and the external globus pallidus (GPe) (Plenz and Kital 1999; Bevan et al. 2002; Terman et al. 2002; Holgado et al. 2010; Liu et al. 2017); or of a longer loop involving feedback from BG output nuclei to the cortex via thalamo-cortical tracts (Leblois et al. 2006; Pavlides et al. 2012, 2015). Alternatively, it has been proposed that dopamine depletion disrupts mechanisms which regulate the gain of cortical afferents to the BG and somehow disrupt striatal outflow (Brown 2007; Hammond et al. 2007). The striatum (STR) itself has also been implicated in the generation of pathological beta rhythms, either through alterations to its internal dynamics (McCarthy et al. 2011; Damodaran et al. 2015); or via increased striatal inhibition of targets in the GPe that act to promote beta synchrony (Gillies and Willshaw 2004; Kumar et al. 2011a).

Here, using a recently described non-parametric (model-free) signal analysis technique (Halliday et al., 2015), we study the effects of dopamine depletion upon neural connectivity in the network formed by elements of the BG and motor cortex in 6-OHDA-lesioned and dopamine-intact control rats. We employ this method as a measure of directed functional connectivity (hereon shortened to directed
connectivity). It is a model-free estimate that makes no assumptions as to the causes of the data (for discussion see Bastos and Schoffelen 2016), only that temporal precedence implies a driving neuronal influence (please see later sections for discussion). Furthermore, we use a a multivariate extension of the framework (Halliday et al. 2016) in order to determine whether the interaction between two areas shares correlation with activity recorded at a third structure in the network. This approach provides insight into frequency-specific directional connectivity and the degree to which transmission between two coupled regions are autonomous of another reference region. By recording LFPs and ECoG in 6-OHDA–lesioned animals and dopamine-intact controls we aim to identify changes to connectivity that occur as a result of the loss of dopamine from these circuits. Our findings are interpreted within the context of the canonical circuit (Figure 1A), as well as other existing models of basal ganglia.
connectivity, and several hypotheses concerning the generation and propagation neural rhythms in the network.

2 Methods

2.1 Experimental Data

In this chapter we use multisite electrophysiological recordings made in a 6-OHDA rodent model of dopamine depletion. Signals include ECoG recorded from M2 (a homologue of SMA in humans) as
well as LFPs from the STN, GPe and STR. For full experimental details please see the methods section of this thesis.

2.2 Analyses of Neurophysiological Signals

In this chapter we use estimates of spectral power, imaginary part of coherence and non-parametric directionality (NPD). All methods are described in full in the methods section of this thesis.

2.3 Statistics and Visualization

This study employs statistical testing using cluster-based permutation testing outlined in the methods section of this thesis.

The cluster-forming threshold was $p<0.05$ and the permutation test threshold was set at $p<0.025$ (as it is a two-sided test). The number of permutations was set to 5000 which tenders a lowest possible $P$-value equal to 0.0004. Cluster statistics were computed using the ‘ft_freqstatistics’ routine in the Fieldtrip toolbox. For testing of the effect of conditioning upon the NPD estimate, statistics are computed identically as described above, but treating the conditioned and unconditioned spectra as the two experimental conditions of interest. As each animal contained multiple recordings per subcortical site we averaged the spectra from these recordings into a subject mean. Group level plots indicate the group mean in bold ±1 standard error of the mean (S.E.M.).

3 Results

3.1 Spectral Power

Examples of spectra computed from LFP and ECoG signals recorded in individual animals can be seen in figure 2 (B and D). All the 6-OHDA-lesioned rats demonstrated a clear peak in the spectra in the range 18-22 Hz (encompassing low beta/lower end of high beta frequencies) for LFP recordings across all subcortical recording sites as well as for the sensorimotor ECoGs. In some animals, cortical beta was weaker than that observed subcortically. None of the LFP data from control animals contained beta peaks in the spectra although some (4 of 8) showed a wide, low amplitude peak around 20-40 Hz that was clearly above the 1/f background and most prominent in the recordings at M2 (an example of which is seen in figure 2B). Analysis of the group averaged spectra (figure 3) shows that the beta peak is significantly increased in the dopamine-depleted animals. Cluster-based permutation testing demonstrated significant differences in group level spectra between control and lesion conditions with clusters showing increases in power associated with dopamine depletion in the M2 (16-23 Hz, $P=0.001$), STR (18-21 Hz, $P=0.011$), STN (16-21 Hz, $P=0.012$), and GPe (17-22 Hz, $P=0.008$). No differences between lesioned and control animals were found for frequencies >22 Hz in any structures.
3.2 Functional Connectivity: Imaginary Coherence (iCOH)

Initial analyses of connectivity of the recorded LFPs using magnitude squared coherence showed large magnitude (>0.9) wideband (0 - 60Hz) coherences that were indicative of a large field spread effect (data not shown). This was most apparent in subcortical-subcortical analyses but was also detected for cortical-subcortical pairings. To estimate coherence avoiding contamination by volume conduction we opted to calculate non-zero phase lag correlations using the imaginary part of coherence (iCOH) (see figure 4).

We found that activity in the low beta range (14-20 Hz) associated with 6-OHDA dopamine depletion is spread diffusely across the network with all inter-regional comparisons showing a significant beta peak in the iCOH spectrum. Notably, the strongest coherence in the low beta band involved STN, with STN/STR and STN/GPe pairs both showing coefficients greater than 0.2. Within region connectivity (i.e. STN contact 1 to contact 2) was found to be present in this frequency range for only recordings.
within STN or GPe, where there is a clear beta peak. No within region connectivity was found in the STR where the iCOH spectra were flat.

Analysis of statistical differences using the cluster based permutation testing between control and lesioned animals showed significant increases of iCOH in the beta band in the lesioned animals and for 5/10 LFP pairs tested: STN/STR (14-21 Hz, \(P=0.006\)), STN/STN (19-25 Hz, \(P=0.014\)), GPe/STR (14-16 Hz, \(P= 0.010\)), GPe/STN (14-21 Hz, \(P=0.006\)), and GPe/GPe (19-23 Hz, \(P=0.004\)). Notably, no pairs involving M2 showed significant modulation of beta-band activity following dopamine depletion when tested using cluster statistics. Taken generally, these results are indicative of widespread, non-zero lag, low beta-band connectivity across the entire cortico-BG network that is increased in the dopamine-depleted rats.
In the control rats, connectivity in the beta range was reduced relative to the dopamine depleted rats. Instead, there was wide-band iCOH in the high beta/low gamma bands, ranging from 20 Hz to 50 Hz in most cases but up to 70 Hz for the STN/M2 interactions. The majority of gamma band interactions where iCOH was high (> 0.2) were found in connections involving the STN. Additionally, iCOH in these bands is evident between GPe/M2 and GPe/STR although this was weaker (at around ~0.1) than connections analysed with pairs involving the STN. iCOH in these bands is present in both the lesioned and control animals and does not show a strong modulation by dopamine as evidenced by the lack of significant clusters in the permutation tests for these bands. The iCOH analyses present evidence for strong non-zero coherences at these frequencies even when spectral power at these frequencies is small.

It must be noted that there exists a separation between analyses of rhythmicity and correlation of rhythmic activity that are complimentary properties of the signals.

### 3.3 Non-parametric Directionality (NPD)

We next investigated directed connectivity between recorded regions. The results of the analysis using the NPD measure are presented in figure 5. The iCOH and the sum of the non-instantaneous parts (forward and backward) of the NPD are similar, and both methods revealed similar patterns of connectivity (data not shown). Analysis of the instantaneous (zero-lag) NPD in isolation demonstrated the existence of high amplitude, wide-band interactions that were similar to those found with magnitude squared coherence (data not shown), and are likely due to zero-phase field spread of activity between recordings. Analyses of directional interactions of the LFPs and ECoG hereon will use the forward and backward components of the NPD to discern directional connectivity between LFPs recorded from each brain structure. Investigation of individual animals’ functional connectivity revealed that for the majority of animals the NPD spectra (and subsequently partialized spectra) were well represented to that indicated by the group average.

We observed that directional interactions of low beta-band activity in the dopamine depleted animals predominate in the direction leading from M2 and that they descend the hierarchy of the BG. Interestingly we noted a significant difference in the cortical-subthalamic beta band interaction between lesioned and control animals only in the feedback connection STN → M2 (16-18 Hz, P=0.020), which would suggest that STN feedback to M2 is strengthened in the dopamine depleted state. In the case of the STN/GPe circuit, and unlike iCOH, the non-instantaneous components of NPD do not show 6-OHDA related increases in beta coupling in either direction for the lesioned rats. Rather, NPD suggests a directional asymmetry in activity in the high beta/gamma band with forward connections from GPe → STN connection stronger than in the reverse direction (cluster statistics testing differences between forward and backward spectra in the 6-OHDA recordings: 4-43 Hz, P<0.001). Notably, we see a feedback in the STN → STR that is most prominent in the lesion condition, a feature that will be relevant with respect to results discussed later.
The pattern of activity in the high beta/gamma range between cortical and subcortical regions appeared to be principally cortically leading with the coefficient of the interactions in the 20-40 Hz range being up to 2/3 larger in the dopamine-intact control rats (top row of figure 5). Cluster-based permutation analysis showed a significant increase in the high/gamma M2 → GPe NPD in the control vs the lesion condition (25-30 Hz, P=0.020). High beta/gamma connections from subcortical structures feeding back to M2, are weaker than the cortically leading connections, but are still present for striatal and globus pallidus feedback to M2 (first column, row 2 and 4, figure 5). Again, there was a clear peak in the high beta NPD from STN→ STR in the lesioned animals, although a dependence on dopamine was not seen to be significant when testing with cluster statistics. The finding of a large NPD interaction from STN to STR is consistent with previous findings and suggests a role for this pathway in the propagation of beta/gamma rhythms in the motor cortex.
to STR does not accord with the canonical circuit (Figure 1A) but may instead imply feedback to striatum via subcortical thalamo-striatal loops that will be discussed in a later section of this paper.

3.4 Inferring Routing of Brain Rhythms: Partialized Non-Parametric Directionality

We repeated the NPD analysis as before but this time by systematically partialising out (conditioning) the contribution made by LFPs/ECoG recorded from each brain structure to the bivariate analyses presented in the previous section of the results. We again employed cluster statistics to determine significant differences between the non-conditioned NPD spectra and its conditioned variant shown in this section of the results.

3.4.1 Conditioning the NPD using Local Field Potentials Recorded from the STN

We first conducted a partialisation (conditioning) of the NPD estimate using LFPs recorded from within the STN (figure 6). Conditioning with signals from the STN does not remove beta connectivity between the remaining structures in the network although it does weaken the majority of comparisons in the control (6 of 6 comparisons, red bars) but not the lesion (2 of 6 comparisons, blue bars) animals (see figure 6, red and blue bars respectively). Cluster statistics indicate that the following NPDs for the control experiments were significantly reduced by conditioning with the STN signal: M2 → STR (14-33 Hz, P<0.001), M2 → GPe (14-33 Hz, P<0.001; 37-49 Hz, P=0.008), STR → GPe (10-49 Hz, P<0.001), GPe → STR (18-49 Hz, P<0.001) as well as feedback connections (returning to cortex): STR → M2 (14-27 Hz, P<0.001), GPe → M2 (18-49 Hz, P<0.001). Furthermore, conditioning the NPD with the signal from STN does not disrupt the 6-OHDA associated increases of M2 input to either the STR (14-21 Hz, P<0.001) or GPe (14-21 Hz, P<0.001) (black bars). We also found in the dopamine-depleted state that there was increased (relative to the controls) feedback to M2 from both GPe (16-20 Hz, P=0.016) and STR (16-20 Hz, P=0.006).
Notably we observed some separation in the effects of the conditioning between the control and lesion experiments. In the control animals conditioning the NPD on LFPs recorded at STN acted to reduce activity in a wide band (~12-40 Hz) for the forward connections (propagating down the indirect pathway; i.e. M2 → STR, M2 → GPe, and STR → GPe), whilst the return connections (STR → M2, and GPe → M2) were only affected by conditioning at a tighter band corresponding to low beta. This would suggest that in the healthy animal signals returning to cortex via STN occur at low beta frequencies. Lesioned animals only showed reductions at higher frequencies (~24-45 Hz, high beta/low gamma) and only between GPe and STR. We observed that conditioning of the NPD with the STN
signal acted to significantly reduce interactions between STR and GPe in both the forward (STR → GPe, 23-49 Hz, P<0.001) and reverse (GPe → STR, 27-49 Hz, P=0.001) directions (red bars).

3.4.2 Conditioning the NPD using Local Field Potentials Recorded from GPe

Next, we performed the NPD analysis of recorded signals but this time conditioning the interactions with LFPs recorded from within the GPe (figure 7). We found that the conditioning had the effect of reducing NPD estimates in 6 out of 6 possible connections in the controls and 3 out of 6 in the 6-OHDA-lesioned rats. Most notably we found that the conditioning significantly attenuated (when compared to the unconditioned NPD) the low beta band interaction in the M2 → STR connection for both recordings.
made in control (red bar, 14-39 Hz, P<0.001) and lesioned (blue bar, 14-21 Hz, P<0.001) animals implying that signals propagating through STR are highly correlated with that also measured at GPe.

Secondly, we found a reduction of interactions between STR → STN across a wide range of frequencies, again for both control (red bar, 6-49 Hz, P<0.001) and lesioned (blue bar, 4-49 Hz, P<0.001) recordings suggesting signal routing is strongly mediated by GPe in accordance with the canonical indirect pathway. Interestingly we found that although beta NPD in the M2 → STN connection was attenuated by conditioning in the control recordings; for the 6-OHDA recordings, the prominent low beta peak in the NPD remained and no significant effect of conditioning was observed. Similarly, the STN → M2 feedback also retained a sharp beta peak that remained significantly increased in recordings corresponding to the 6-OHDA lesion experiments (black bar, 14-20 Hz, P=0.002).

Figure 8 - Non-parametric directionality conditioned on the STR local field potential - Spectra for each animal are shown by thin lines corresponding to either 6-OHDA lesioned (blue) or control (red). The group averages for either the 6-OHDA dopamine depleted or control animals are shown by bold lines in red or blue respectively. Shading shows the mean ±1 S.E.M. Cluster-based permutation statistics were applied to test the effect of the lesion. Significant clusters are indicated by the black line above the spectra and corresponding P-value. The effect of conditioning with the STR LFP was also tested using cluster permutation statistics. Frequencies where NPD was significantly attenuated by the conditioning are indicated by the red and blue bars (and corresponding P-values) for the control and lesion recordings respectively.
Additionally, we found that when conditioning the STR→ M2 NPD estimate with the GPe signal there was an increased strength of interaction in the 6-OHDA treated animals (black bar, 16-21 Hz, P<0.001).

In the high beta/gamma band we found that conditioning with GPe had a large effect in attenuating the NPD in the forward connections (from M2 descending the indirect pathway) in the control animals: M2 → STR (14-39 Hz, P<0.001), M2 → STN (16-49 Hz, P<0.001), and STR → STN (6-49 Hz, P<0.001) (red bars). In the lesion animals only, 2 of the 6 comparisons made with NPD were significantly attenuated in the 20-50 Hz range: STR → STN (4-49 Hz, P<0.001) and STN → STR (31-45 Hz, P=0.004) (blue bars). This would imply that in control animals, high beta/gamma band interactions in both directions between STN and STR are transmitted via (and linearly mixed with) a signal at GPe.

### 3.4.3 Conditioning the NPD using Local Field Potentials Recorded from the STR

A third set of analyses used the local field potentials recorded at the STR to condition the NPD estimates (figure 8). We found that this had the effect of destroying large parts of the descending interactions (connections from M2 descending the hierarchy of the indirect pathway) in the control animals, namely for M2 → GPe (16-37 Hz, P<0.001) and M2 → STN (16-37 Hz, P<0.001) (red bars). In the lesion recordings, the effect of conditioning split into two ways: 1) Interactions between the STN/GPe were significantly reduced across a very wide band ranging from low-beta to gamma frequencies in both the STN → GPe (8-49 Hz, P<0.001) and GPe → STN (6-49 Hz, P<0.001) coupling (blue bars) and 2) That interactions in the “hyper-direct” M2 → STN connection were not attenuated, although note that the M2 → GPe (likely routed at least in part via the indirect pathway) was suppressed by conditioning with the striatal signal (18-24 Hz, P=0.001, blue bar). This peak is also seen in the feedback connection from STN → M2 where the significant 6-OHDA associated increase in beta feedback reported in previously analysis was found to remain (18-20 Hz, P=0.010, black bar).

Similar to the NPD estimates conditioned with signals recorded at GPe, we found that conditioning with LFPs recorded at STR acted to largely remove the high beta/gamma interactions. In the M2 → GPe connection in control animals we found that high beta/gamma activity was attenuated by STR conditioning (16-37 Hz, P<0.001); furthermore, we observed that 6-OHDA was associated with a significant suppression of activity in this band (27-37 Hz, P<0.001; 41-45 Hz, P=0.004). Additionally, we found that feedback in the high beta/gamma range (for control recordings) from GPe → M2 was significantly attenuated by conditioning with the signal recorded at STR (14-41 Hz, P<0.001, red bar). Furthermore, this connection from GPe → M2, was significantly strengthened in the 6-OHDA animals (35-41 Hz, P=0.002, black bar).

### 3.4.4 Conditioning NPD Using Field Potentials Recorded from M2

The final analyses utilized ECoG signals recorded from the M2 to condition the BG NPD estimates (results in figure 9). We found that the NPD estimates conditioned on M2 were generally flattened and
lacked distinct peaks at either low beta or high beta/gamma frequencies that were seen typically in the other analyses. Altogether 5 of 6 NPD spectra had no distinct spectral peaks. When testing for significant attenuation of NPD following conditioning we found that only control recordings were significantly attenuated (4 of 6 connections, red bars), with high beta gamma peaks most clearly lost in the STR→STN and STN→GPe interactions. The loss of features found in the unconditioned NPD (such as beta or gamma peaks) were equivalent for both the control and 6-OHDA recordings.

When testing for the effects of 6-OHDA, we found that the STN→STR connection was significantly altered. We observed a broad peak from 20-40 Hz in the lesion recordings that was not attenuated by

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Figure 9 - Non-parametric directionality conditioned on the M2 electrocorticogram - Spectra for each animal are shown by thin lines corresponding to either 6-OHDA lesioned (blue) or control (red). The group averages for either the 6-OHDA dopamine depleted or control animals are shown by bold lines in red or blue respectively. Shading shows the mean ±1 S.E.M. Cluster-based permutation statistics were applied to test the effect of the lesion. Significant clusters are indicated by the black line above the spectra and corresponding P-value. The effect of conditioning with the M2 ECoG was also tested using cluster permutation statistics. Frequencies where NPD was significantly attenuated by the conditioning are indicated by the red and blue bars (and corresponding P-values) for the control and lesion recordings respectively.
M2 conditioning and demonstrated a significant increase in strength associated with dopamine depletion (21-27 Hz, \(P=0.007\), black bar).

3.5 Summary of Connectivity Analyses

Using recordings made in control and lesioned rats, we identified functional connectivity between cortical and BG sites that involved either low beta or high beta/gamma oscillations. Broadly speaking, we found that gamma connectivity is sensitive to the conditioning of structures upstream of the STN, particularly GPe and STR, which removes gamma band oscillations from the spectra. In contrast, beta connectivity was found to be robust to partializing using LFPs of any single BG structure. Cortico-subthalamic connectivity in the beta range was unaffected by partialising of GPe or STR, suggesting that M2/STN low beta connectivity is not routed via the indirect pathway. In the next section, we will outline several putative models of oscillatory dynamics and present evidence from our analyses that either support or weaken the plausibility of each model.

4 Discussion

4.1 Hypotheses and evaluation of evidence for signal propagation in the network

We have undertaken a systematic analysis of a dataset involving multisite ECoG/LFP recordings of the cortico-basal ganglia circuit that contains data from a set of dopamine-intact control rats and another set of rats with chronic dopamine depletion induced by a unilateral injection of 6-OHDA. We will next discuss evidence for competing theories of the propagation of oscillatory activity across the Parkinsonian cortico-basal ganglia circuit. We emphasise that our results are indicative of the transmission of rhythmic activity in the circuit and cannot directly access the mechanisms that generate these rhythms. However, as we will argue, results describing the patterns of synchronized activity across the network and the changes that occur to them following dopamine depletion proffer an important insight into how pathological rhythms differentially engage functional networks.

4.1.1 Mechanisms of the Flow of Beta Rhythms in the Basal Ganglia Circuit

Here we will evaluate the evidence provided by the analyses reported here in light of a number of proposed theories concerning the generation and propagation of beta-band activity in the network and the changes that occur during dopamine depletion that lead to its amplification. This work is summarised in table 1.
### Hypotheses for propagation of low beta rhythms

<table>
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<tr>
<th>Mechanism</th>
<th>Long-loop resonance</th>
<th>STN/GPe Resonance Pair</th>
<th>Aberrant (cortico-) striatal output</th>
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<tr>
<td>Pathological beta arises from induction of a loop formed by feedback between cortex and BG</td>
<td>Pathological beta arises from increased coupling of STN/GPe resonance pair.</td>
<td>Pathological beta results from changed internal dynamics of STR and/or its outputs to the indirect pathway.</td>
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**Evidence for:**
- Significant beta band STN/M2 NPD in both the forward and reverse directions.
- The low beta STN → M2 feedback coherence is significantly increased in the lesioned animals.
- STN/M2 NPD is undiminished by conditioning with GPe or STR.
- iCOH of the STN→GPe suggests coupling increases in 6-OHDA experiments.
- The STN→GPe NPD is not attenuated by conditioning with the M2 ECoG.

**Evidence against:**
- Conditioning the NPD with signals from the STN or M2 does not remove beta band NPD between STR and GPe, upstream of the STN.
- No test to determine routing of return signal from STN to cortex.
- There is a strong asymmetry in between the forward and backwards STN→GPe NPDs, suggesting pallidal drive is dominant.
- The STN→GPe NPDs are strongly attenuated by conditioning with the STR signal.
- Conditioning NPDs with the STN signal has little effect on coupling upstream in the indirect pathway.

- STN→GPe NPDs are strongly attenuated by conditioning with STR signals.
- Conditioning of the STR→GPe NPD with the M2 ECoG is only effective in the control animals.
- Conditioning of the STR→GPe NPD with the STN LFPs is only effective in the control animals.

- Unclear whether lack of effect of conditioning is due to change in the STR output or due to change to STN signal such as that occurring due to increased hyperdirect input described in hypothesis 1.

Table 1— Summary of hypotheses of the impact of dopamine depletion on the propagation of beta rhythms in the cortico-basal ganglia circuit.
4.1.1.1 Hypothesis 1: Dopamine depletion in the basal ganglia induces increased beta resonance in the cortical/STN “long-loop”.

Previous authors have suggested that pathological beta rhythms are generated from the strengthening of a long cortical feedback loop that returns from basal ganglia output nuclei via the thalamus. Strengthened coupling is proposed to facilitate pathological resonance at beta frequencies (Brown 2007; van Albada and Robinson 2009; Dovzhenok and Rubchinsky 2012; Pavlides et al. 2015). The first step towards verifying the plausibility of this hypothesis involves determining whether there is indeed functional connectivity between STN and M2 in the beta band, and whether this occurs independently of the cortico-striatal inputs to the indirect pathway.

Analysis of the iCOH for the M2/STN pairing suggests that functional connectivity in the beta band is significantly strengthened in the lesioned animals compared to controls (figure 4). Analysis with NPD demonstrates that there is a beta peak in the directed coherence in the low beta range in the forward M2 → STN connection for both the control and 6-OHDA animals. Furthermore, in the lesioned animals, the feedback connection (STN → M2) is significantly strengthened over that measured in the controls. Neither the hyper-direct M2 → STN connection, nor the subthalamo-cortical feedback (STN → M2) is diminished by either conditioning with signals from the GPe or STR in the lesioned animals (figure 7 and figure 8). This suggests a reciprocal pathway between STN and M2 that is routed independently of STR or GPe, most likely feeding back directly via the BG output nuclei. In contrast, in control rats, NPD of the feedback connections at beta frequencies are significantly decreased by conditioning with the STR signal in the forward (M2 → STN), and backward (STN → M2) directions, suggesting that in the dopamine-intact anaesthetised state, beta band activity is routed via STR, whilst the hyper-direct pathway is relatively quiescent. These findings support the idea that the dopamine-depleted state is associated with a strengthening of the hyper-direct pathway and subthalamo-cortical feedbacks.

Notably, this pathway is not active in isolation but coexists with beta propagation occurring along striatal indirect pathway projections. Most notably, it was found that conditioning of the NPD with LFPs recorded from the STN (figure 6) does not act to remove the 6-OHDA lesion associated beta NPD in the structures ‘upstream’ of the STN (i.e. the STR and GPe). NPD in the low beta range is significant in both directions along parts of the network involving either M2, STR or GPe. We find that striatal-subthalamic interactions are strongly modulated by the GPe signal, a finding in line with propagation down the canonical indirect pathway. Future work to validate the long-loop hypothesis would involve the conditioning of the STN → M2 NPD using signals recorded from BG output nuclei (either internal globus pallidus (GPi /EPN in rat) and/or SNr) or their major targets in the thalamus. If these signals were available, then it would be possible better determine the routing of the cortical return of BG beta activity from the STN.
4.1.1.2 Hypothesis 2: Pathological beta is generated from strengthening of the reciprocally coupled STN/GPe circuit.

A separate hypothesis concerning the generation of pathological beta rhythms in the basal ganglia considers the reciprocally coupled STN/GPe circuit from which increased coupling associated with the loss of dopamine induces a pathological beta resonance that spreads across the rest of the network (Plenz and Kital 1999; Bevan et al. 2002; Holgado et al. 2010; Tachibana et al. 2011).

We note that conditioning the NPD with the M2 signal does not remove the strong STN → GPe directed connectivity, but it does attenuate the GPe → STN (figure 9). This indicates that activity feeding back onto GPe from STN has a sufficiently unique temporal content so as not be partialized out by the cortical ECoG, suggesting that pathological beta activity could be generated by some resonance phenomenon arising from the tight, reciprocal coupling of STN and GPe. However, a number of the analyses presented here suggest that pathological beta does not originate from an autonomous STN/GPe resonator. These can be summarised as follows: 1) Comparison of forward and backward NPD for STN/GPe interactions shows strong asymmetry, with the GPe → STN connection predominating; 2) conditioning of the NPD using the LFPs recorded at the STR significantly reduces the strength of both GPe → STN and STN → GPe NPDs in a way that appears to be irrespective to dopaminergic state (figure 8), suggesting that beta activity in these structures results from beta oscillations propagating through striatum; 3) conditioning the NPD with LFPs recorded at the STN (figure 6) does not act to remove the upstream 6-OHDA associated beta NPD between STR or GPe (although it does significantly weaken beta NPD in the control animals); 4) GPe conditioned NPD analysis does not impair pathological M2/STN beta interactions (figure 7), suggesting that the beta found at STN can be, at least in part, generated independently of a signal found at GPe. The evidence given in point (1) may arise from the very tight coupling of the STN/GPe pair, if full phase synchronization is occurring then the phase alignment between the two nuclei may mislead the NPD to determine the phase leading population to be the drive, when in actuality there is strong reciprocal coupling. The evidence in (2) and (3) points towards a mechanism of striatal modulation of the STN/GPe circuit, perhaps via a pallidal-striatal feedback mechanism such as that described by (Corbit et al. 2016). Taken together we argue these findings provide evidence against pathological beta synchronization in the network arising from dissemination of an autonomously generated rhythm in a STN/GPe “resonator”.

4.1.1.3 Hypothesis 3: Beta arises through aberrant striatal activity and facilitation of downstream hyper-synchrony.

It has been proposed that aberrant striatal activity is involved in the emergence of pathological beta rhythms in the BG arises due to changes to local dynamics within striatum (McCarthy et al. 2011; Damodaran et al. 2015; Sharott et al. 2017); and/or a modification of striatal influence on the STN/GPe sub-circuit (Terman et al. 2002; Kumar et al. 2011b; Sharott et al. 2017). From iCOH analysis of signals
recorded within striatum we do not find any local non-zero phase interactions (unlike that which we find at STN). This finding would suggest that striatal-striatal transmission is sparse, or phase aligned. Our results show that NPD measured at both the STN and GPe are significantly weakened by conditioning with STR signals (figure 8) implying that striatal beta band activity propagates down the indirect pathway. This would be in line with the recent demonstration that the firing of indirect pathway spiny projection neurons is aberrantly (and selectively) entrained to exaggerated beta oscillations in lesioned rats (Sharott et al. 2017).

The weakening of NPD interactions from STR → GPe and GPe→ STN when conditioning with M2 ECoG (figure 9), and only for the dopamine intact controls, may suggest that dopamine depletion results in increased autonomy of the striatal (and indirect pathway) beta rhythm from beta at M2. In support of this hypothesis, we also demonstrate that conditioning of the STR → GPe NPD with the STN signal is only effective (within the low beta range) in the control condition. This again demonstrates that 6-OHDA lesioning results in a striatal signal that retains information independent from that found at STN, providing evidence that it is likely the change of striatal output that occurs following dopamine depletion. There is however some ambiguity as to whether the separation of the striatal signal from that at the STN occurs due to changes to striatal dynamics or instead a change of direct input to the STN such as from a strengthened hyperdirect input as discussed in hypothesis 1.

4.1.2 Hypotheses of the Origins/Routing of High Beta/Gamma Oscillations

The presence of high beta/gamma oscillations in the subcortical network has been noted by a number of authors (Brown et al. 2002; Humphries et al. 2006; Berke 2009; Sharott et al. 2009; van der Meer et al. 2010; Nicolás et al. 2011) but our understanding of the functional propagation of high beta/gamma oscillations through the network is limited. An evaluation of the evidence we present in this paper is summarised in table 2. We report gamma activity in the LFPs as well as connectivity in the range 30-60 Hz which is in good agreement with that previously reported in anaesthetised rats (Magill et al. 2004; Sharott et al. 2005b, 2009). Gamma activity in the awake and moving rat has also been reported, albeit at slightly higher frequencies (Brown et al. 2002; Brazhnik et al. 2012; Delaville et al. 2014).
### Hypotheses for propagation of high beta/gamma rhythms

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Hyper-direct inflow</th>
<th>Cortico-striatal gamma input</th>
<th>Subcortical generator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evidence for:</strong></td>
<td>High beta/gamma enters the subcortical network via the hyper-direct M2→STN connection.</td>
<td>Cortical-gamma enters the BG via the striatum and is passed down the indirect pathway.</td>
<td>High beta/gamma arises from subcortical interactions and/or local dynamics within BG nuclei</td>
</tr>
<tr>
<td>• iCOH shows that M2 ↔ STR interaction is much weaker than the M2 ↔ STN.</td>
<td>• Conditioning subcortical NPDs with ECoG attenuates a large number of connections.</td>
<td>• Conditioning of NPDs using signals from STR or GPe reduces strength of interactions.</td>
<td></td>
</tr>
<tr>
<td>• Conditioning subcortical NPDs with ECoG attenuates a large number of connections.</td>
<td>• Conditioning of the M2 → STN NPD with STR or GPe attenuates interactions in the control condition suggesting signal is passed via striatal-pallidal projections.</td>
<td>• Conditioning of STN→STR NPD with ECoG does not act to remove subthalamo-striatal feedback suggesting existence of subcortical feedback.</td>
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<tr>
<td><strong>Evidence against:</strong></td>
<td>Conditioning of the M2→STN NPD with STR or GPe signals attenuates interactions in the control conditions.</td>
<td>Conditioning of STN→STR NPD with ECoG does not act to remove subthalamo-striatal feedback suggesting existence of subcortical feedback.</td>
<td>No evidence for within STR interaction from iCOH.</td>
</tr>
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</table>

Table 2– Summary of hypotheses for the propagation of high beta/gamma rhythms in the cortico-basal ganglia circuit.
4.1.2.1 Hypothesis 4: High beta/gamma enters the subcortical network via the hyper-direct M2 $\rightarrow$ STN connection.

Results from analyses which used iCOH to investigate non-zero lag correlations between BG structures and the cortex suggested that gamma interactions are routed in a way that bypasses STR as a gamma peak is absent in the M2 (figure 4). This effect is most clear in the control recordings but also to a lesser extent in the 6-OHDA experiments. The hyper-direct pathway is the other principal source of cortical input to the BG, therefore the marked weakness of gamma interaction in the M2/STR when compared to the M2/STN iCOH spectra may imply that the hyper-direct pathway is responsible for gamma input to the network.

However, whilst there is a large peak in the high-beta/low-gamma band NPD for the M2 $\rightarrow$ STN interaction (figure 5), if we examine the same connection but conditioned on LFPs either recorded at STR (figure 7) or GPe (figure 8) we see that the conditioning significantly reduces NPD in the control animals (M2 $\rightarrow$ STN conditioned on STR and M2 $\rightarrow$ STN conditioned on GPe), suggesting any directed coherence between M2 and STN in these animals is routed via striatal-pallidal connections. Furthermore, if we condition the NPD with LFPs recorded at the STN (figure 6), we see that gamma interactions remain in the upstream components (M2 $\rightarrow$ STR, M2 $\rightarrow$ GPe) again suggesting striatal-pallidal connectivity is vital in the propagation of gamma rhythms. When taken together, these data do not supply strong evidence that the source of high beta/gamma input in the network is transferred by a hyper-direct cortico-subthalamic route.

4.1.2.2 Hypothesis 5: Gamma enters the network via cortico-striatal inputs and reaches STN via the indirect pathway in a dopamine dependent manner.

An alternative to high beta/gamma oscillations entering via hyper-direct STN input is that they are channelled via the cortico-striatal indirect pathway. The clearest results of the NPD analysis in the high beta/gamma band can be seen to be for the forward NPDs originating from M2 and passing on to the subcortical regions (figure 5). Connections M2 $\rightarrow$ STR, M2 $\rightarrow$ GPe, and M2 $\rightarrow$ STN all show high values of NPD in this frequency band (> 0.15) suggesting that most of the gamma is directed from the cortex. Furthermore, conditioning the NPD with either LFPs recorded at the STR (figure 8) or GPe LFPs (figure 7) acts to remove gamma interactions both upstream and downstream of the STR (with respect to the indirect pathway). Subsequently, conditioning of the NPD with STN (figure 6) is less effective at attenuating gamma band interactions than when using signals higher in the indirect pathway, suggesting that the gamma descends the hierarchy, from either a cortical or striatal source. Notably, we observed that STN conditioned NPD did not act to attenuate feedback connections from GPe or STR back to the M2. This would suggest routing of gamma to the M2 in a way that occurs independently of STN.
In attempt to elucidate the source of the gamma activity we conditioned the NPD on the cortical ECoG (figure 9). We find that gamma connectivity in the control recordings and in dopamine depletion states acts to significantly reduce NPD coefficients for the GPe → STN and STR → STN connections, yet the feedback connection STN → STR is unaffected. This connection in the control animals shows a peak from 18-42 Hz which is significantly larger than in the lesioned animals. This is in agreement with the hypothesis that gamma rhythms are pro-kinetic; this idea is also supported by patients’ data (Sharott et al. 2014). Furthermore, these findings suggest that gamma activity is directed to upstream components of the indirect pathway in a way independent of M2, perhaps mediated via a subcortical feedback loop.

4.1.2.3 Hypothesis 6: High beta/gamma is generated locally within the basal ganglia network either at STR, STN or GPe

The finding that conditioning the NPD with cortical ECoG does not entirely abolish gamma connectivity within the BG suggests a possible subcortical high beta/gamma generator, or alternatively a source in the cortex that has not been measured in our experiments. Work by Kondabolu et al. (2016) has demonstrated that the optogenetic activation of striatal cholinergic interneurons is sufficient to generate gamma rhythms locally, although not in a way clearly separable from low frequency beta. However, when applying iCOH to signals recorded within STR we find no evidence for local interactions in the high beta/gamma band. Simulations of the BG spiking network by Humphries et al. (2006) suggest that upper-gamma band (40-80 Hz) activity can arise as a result of coupling between the STN and GPe. When we conditioned the NPD with LFPs recorded from either the GPe (figure 7) or STR (figure 8), we found that interactions in the high beta/gamma frequency ranges were abolished in the majority of other subcortical interactions. This would imply that these GPe and STR structures are necessary for the propagation of high beta/gamma interactions in the both the control and 6-OHDA lesion animals. This in combination with the evidence provided for hypothesis 5 suggests that high beta/gamma can originate at either STR or GPe and then propagate to downstream structures. Backward gamma interactions from GPe to STR are apparent in the NPD conditioned on either M2 or STN, suggesting the STR signal is the result of local propagation of a gamma signal from GPe. From the canonical circuit perspective it is not clear how gamma passes upstream from GPe. However, a substantial proportion of GPe neurons that innervate the striatum have been shown to exist, with one GPe cell type (arkypallidal neurons) projecting exclusively to striatum (Mallet et al. 2012; Abdi et al. 2015; Hegeman et al. 2016). This same pathway has been proposed by Corbit et al. (2016) to promote synchronization in the low beta range but the same arguments are likely to apply to high beta/low gamma frequencies.
Chapter III: Propagation of Beta/Gamma Rhythms

4.2 Summary of Findings

In this paper, we have investigated the propagation of oscillatory activity through connected regions of the cortico-basal ganglia network. We have applied a novel model-free method of partialized directed connectivity to achieve a systematic deconstruction of the propagation of rhythmic activity between regions of the network inferred from the LFPs and ECoGs recorded at multiple sites within that network. Using the 6-OHDA-lesioned rat model of Parkinsonism, we demonstrate marked differences in the patterns functional connectivity that result as a consequence of dopamine depletion in the BG.

We find widespread beta synchronization of LFPs across the network that is strongly associated with chronic dopamine depletion. With regards to functional beta connectivity in the network we find evidence for:

1. An increased cortical entrainment of the basal ganglia following dopamine depletion.
2. Significant beta-band connectivity between structures interacting with the STN that is independent of activity upstream in the indirect pathway (at STR and GPe). This is likely to originate from the ‘hyperdirect’ cortico-subthalamic input.
3. Increase in feedback of BG structures to M2 after dopamine depletion, proffering evidence in favour of a hypothesis of dopamine-dependent modulation of the long re-entrant cortico-BG-thalamo-cortical loop.
4. Activity dynamics of the STN/GPe sub circuit that are partly dependent upon output from striatum.
5. A feedback from STN to STR that is independent of M2 and significantly strengthened after dopamine depletion, suggesting a strengthening of recurrent subcortical circuits.

Furthermore, we provide evidence for the existence of high beta/gamma synchrony within the network, with evidence that dopamine depletion acts to weaken these rhythms. We summarise our findings with respect to high beta/gamma band interactions in the following:

1. Gamma propagates down the indirect pathway from STR to GPe to STN. This activity is likely to be generated at the level of the cerebral cortex.
2. Evidence of gamma activity found at STN that is independent of M2 and evidence for a subcortical return of subthalamic outputs back to striatum.
3. Evidence for gamma activity returning to the cortex that is independent of STN, perhaps indicating propagation through the direct pathway.

4.2.1 Propagation of Low Beta via two Coexisting but Distinct Streams

In the case of low beta oscillations, we find our data most strongly support a hypothesis that in the dopamine-depleted condition, beta propagation in the network is biased to favour low beta synchrony via induction of a long cortico-subthalamic loop that inputs to the BG via the hyper-direct pathway.
Furthermore, we see evidence that the return connection from STN to M2 is significantly stronger in the lesioned animals when compared to dopamine-intact controls. This provides supporting evidence for the notion that pathological beta amplification arises from entrainment of the re-entrant cortical/STN loop (Brittain and Brown 2014). We speculate that strengthening of the hyper-direct input acts to “short-circuit” the network, such that transmission of information along the indirect pathway is compromised. Oswal et al. (2016) have provided evidence that deep brain stimulation in patients acts to selectively suppress activity mediated synchrony between mesial premotor regions and the STN which is proposed to be mediated by the hyper-direct pathway. In the “hold your horses” model of the STN’s role in decision making (Frank 2006; Frank et al. 2007), the hyper-direct pathway is proposed to provide a cortical veto signal which may act to suppress premature action. In the case of PD, over activity of this circuit via increased resonance may act to lock the network into a state that ultimately supresses action and movement. These findings are in agreement with previous research which have found good evidence for bidirectional connectivity between STN and cortex (Lalo et al. 2008; Jávor-Duray et al. 2015).

This hypothesis requires further testing through analysis of the role of the BG output nuclei at GPi or SNr (or their targets in the thalamus) in the propagation of activity. This could be achieved using a functional ‘lesion’ approach like that described in this paper. Furthermore, biophysical modelling of the cortico-subthalamic loop may yield insight as to whether this is a plausible mechanism given the known conduction delays for the connections in the network. Long feedback loops involving cortex have been demonstrated to be capable of generating oscillatory activity (Leblois et al. 2006; Pavlides et al. 2015). Work by Shouno et al. (2017) suggests that the required delay for the return of the beta oscillation from STN to cortex may be too great to support resonance in the low beta band and possibly the engagement of shorter subcortical loops either subcortical-thalamic loops (McHaffie et al. 2005) or activity of recurrent subthalamo-striatal projections (Sato et al. 2000; Koshimizu et al. 2013) may be more suitable candidates for supporting beta oscillations through resonance.

The analysis presented here also suggests that a cortico-subthalamic pathway is not the exclusive pathway for beta rhythms within the network, yet may be necessary for enhancement of the STN feedback to cortex that may induce pathological resonance. We would suggest that both the hyperdirect and indirect routes for beta propagation coexist. These two pathways could originate from and be driven by, distinct populations of cortical projections neurons (namely those of the pyramidal tract and intrateleencephalic projections, respectively) and so are likely to show a degree of independence from one another. The data presented here also suggest a second pathway upstream of STN involving the STR that is most evident in the recordings from control rats. We suggest that both pathways contain signals shared by activity measured in the cortical ECoG: conditioning of the NPD acts to remove beta peaks from the majority of connections that were analysed, leaving just beta coherence at the STR → STN connection. These findings support the hypothesis that dopamine cell loss acts to increase the sensitivity...
of the STR to cortical inflow, disrupting the striatum’s role in gating activity to the remainder of the circuit (Magill et al. 2001; Tseng et al. 2001; Sharott et al. 2017).

Notably, our data do not support the hypothesis of beta generation via an autonomous STN/GPe pacemaker network, as directional coherence between the two is heavily attenuated by conditioning with LFPs recorded upstream in the STR and there is significant asymmetry in the NPD with the globus pallidus drive predominating. In agreement, Moran et al. (2011) found evidence for a weakening of the STN to GPe feedback connection in the dopamine depleted state, conflicting with the STN/GPe resonance hypothesis. It may be the case that tight coupling of the STN and GPe results in a near fixed phase relationship in which there is reciprocal coupling yet from the perspective of phase, the GPe appears to lead.

Estimates of effective connectivity from DCM studies have also suggested that input from cortex to STN is strengthened in the Parkinsonian state (Moran et al. 2011), a finding consistent with the idea that dopamine enforces cortical influence upon the STN/GPe network (Magill et al. 2001; Leblois 2006; Leblois et al. 2006; Holgado et al. 2010). It is possible that in PD, cortical activity subsumes the STR as the primary driver of the STN/GPe sub-circuit, effectively acting to “short-circuit” the system. It has been demonstrated that movement is associated with a decreased cortico-pallidal coherence during movement in humans (van Wijk et al. 2017) suggesting that disengagement of cortical influence via this pathway is pro-kinetic. Thus pathological resonance may arise following dopamine depletion through a compensatory mechanism of increased hyperdirect input following an altered or reduced striatal output (Kumar et al. 2011a; Damodaran et al. 2015). In the healthy system it has been proposed that this works to actively de-correlate spiking activity between the two structures (Wilson 2013). The action of dopamine upon these inputs is likely to lead to the promotion of beta amplifying phase alignments between STN and GPe such as that observed by Cagnan, Duff, & Brown (2015).

### 4.2.2 Dopamine Depletion is Associated with an Increased Subthalamo-Striatal Feedback

Taken together, the analyses presented here speak to the existence of a high beta/low gamma rhythm that is in general reduced by dopamine depletion. Specifically, our results indicate that connectivity in the frequency band 27-34 Hz is attenuated by the 6-OHDA lesion. Experiments investigating LFPs in the motor cortex of moving rats have demonstrated an increase in activity in this band during movement suggesting that activity at these frequencies in M2 and SNr is pro-kinetic (Brazhnik et al. 2012). Our data would suggest that high beta/gamma activity in the normal network is predominantly entrained by the cortex as evidenced by: 1) the unconditioned NPD indicates that gamma is prominently in the forward direction leading from cortex to subcortical sources; and 2) conditioning the NPD on ECoG recorded at M2 acts to diminish the subcortical directional coherence across a wide band for all connections not involving STN. However, evidence by Zold and colleagues has demonstrated that
oscillatory activity >20 Hz in corticostriatal afferents is not effectively transmitted through the striatum (Zold et al. 2012) suggesting that the actual mechanism is likely to be more complicated.

Furthermore, following partialization some interactions involving STN do remain. In particular we provide evidence for a significant strengthening of feedback from STN to STR in the lesioned animals in the high beta/gamma band. We speculate that this signal is facilitated through the strengthening of subcortical loops such as that of the thalamo-striatal pathways (McHaffie et al. 2005). Thalamic afferents make up to at least 25% of input onto spiny projection neurons in the STR (Doig et al. 2010; Smith et al. 2014) but have been far less studied than cortical inputs. Work investigating synaptic remodelling following 6-OHDA depletion in mice has suggested that thalamo-striatal inputs to medium spiny neurons are shifted in favour of the indirect pathway (Parker et al. 2016) perhaps enhancing striatal return of subthalamic activity in a mechanism independent of cortex.

4.3 Segregation of Low Beta and High Beta/Gamma Functional Networks

Our analyses present a clear separation in the patterns of inter-areal synchronization between low beta and high beta/low gamma frequencies. We find pathological low beta correlations to be present across large parts of the network, and resistant to conditioning with signals from connected structures. In contrast, high beta/gamma shows a much more hierarchical organization, descending the indirect pathway and possibly looping back subcortically through subthalamic-striatal feedback. Furthermore, high beta/gamma correlations appear to be weakened by the 6-OHDA lesion.

Multiple studies investigating the electrophysiology of patients with PD (Priori et al. 2004; López-Azcárate et al. 2010) have found evidence for the functional differentiation between low and high beta frequency activity. Low beta is found to be increased by dopamine depletion and correlates with bradykinetic/rigid symptoms in patients, whereas high beta is less responsive to dopamine changes. Interestingly, dopamine replacement in patients has been shown to decouple high and low beta frequencies when analysing with spectral bicoherence (Marceglia et al. 2006). Cortico-subthalamic coherence is also found at this frequency in patients, although again this is largely unresponsive to dopamine (Litvak et al. 2011b). We also find evidence for high beta coherence between BG and cortex although unlike that found in patients, we find this connectivity to be weakened and shifted to low beta frequencies by 6-OHDA induced dopamine depletion.

In the current paper we have not made analysis of the interaction or co-existence of the two frequency bands described. This is an interesting problem as the beta network is more responsive to dopamine depletion than that at the high beta/gamma frequencies. Future work may utilise tools such as analysis of cross-frequency coupling and time resolved spectral analysis to do so.
4.4 Study Limitations

4.4.1 Incomplete Signals for Conditioning

The use of partial coherence for inferring neural connectivity is not in itself a novel approach (Rosenberg et al. 1998; Eichler et al. 2003; Salvador et al. 2005; Medkour et al. 2009), and the application of the partialized NPD to LFPs recorded in the rat hippocampus has been previously reported (Halliday et al. 2016). However, these analyses assume that the signals used for conditioning completely capture the activity going through the proposed pathway. This however is unlikely to be entirely the case due to the finite sampling of the structures afforded from the use of electrodes. That said the large number of channels used for recordings in the present study ensure that multiple samples are obtained from within each brain structure. In the data presented here, subcortical structures were recorded from between 2-8 different channels which were all used to condition the estimate of directed coherence. It should also be noted that this sampling limitation is likely to apply most to the larger structures that were analysed, namely the motor cortex and striatum, whereas recordings from the smaller sized STN are more likely to capture a larger share of the total activity. This factor must be considered when interpreting conditioning of the NPD with respect to STR signals. It could be the case that M2 → STN connectivity remains in the face of conditioning with the STR LFP as a result of incomplete sampling of neural fields within striatum.

4.4.2 Inference of Connectivity from Non-Spiking Brain Activity

This study is based upon an analysis of mesoscale recordings of brain activity as measured either in the ECoG or the LFP. Transmission of information in the brain is due to axonal propagation of action potentials is not explicitly captured in these signals. LFPs and ECoG comprise a conglomerate of sub- and supra-threshold events that may or may not be tied to spike activity and so direct inference of neurophysiological connectivity *per se* is limited by this. Nonetheless, spike timing has been shown to tightly correlate with negative deflection of the LFP (Destexhe et al. 1999) and increasing evidence that the field itself modulates neural activity is emerging (Qiu et al. 2015; Goldwyn and Rinzel 2016). With respect to the basal ganglia, it has been previously demonstrated by Mallet and colleagues that beta-band activity in the LFPs recorded at STN and GPe of lesioned rats are associated with increased bet-frequency synchronization of action potential firing by neurons in these structures (Mallet et al. 2008a, 2008b) but see also Magill et al. (2004) where coupling of GPe units and slow wave activity in the LFP is relatively weak in dopamine-intact rats. Furthermore, we provide evidence for the existence of temporally lagged correlations between rhythmic local field potentials recorded between distinct regions of the cortico-BG network that imply causation from one signal to another, a phenomenon that would itself not be possible without the transmission of action potentials. Future work will require an investigation to determine whether directional interactions are ascertainable from multiunit activity and how this relates to lagged synchronization of LFPs.
4.4.3 Limits to Inference of Causal Interactions and Mechanisms from Neurophysiological Signals Alone

In this paper, we aim to infer how neural activity propagates across the BG network by investigating the statistical relationships between brain signals. The challenges that this approach face are well documented (Friston 2011; Bastos and Schoffelen 2016). With respect to this study, the benefits that we claim for using a model free, non-parametric approach (namely agnosticism to the underlying generating mechanisms of the data) may in turn limit the degree of inference that can be made. Estimates of directed functional connectivity in this paper follow from the assumptions that temporal precedence is indicative of causation. It is however well documented that zero lag synchronization can emerge from neural circuits with particular (but not unusual) network motifs (Vicente et al. 2008; Viriyopase et al. 2012; Gollo et al. 2014). Additionally, “anticipatory” synchronization in which positive lags arise from a directed input have also been described in theoretical neural dynamics (Ambika and Amritkar 2009; Ghosh and Roy Chowdhury 2010; Matias et al. 2011). The anatomically tightly coupled STN-GPe sub-circuit is a prime candidate for which these phenomena may permit vanishingly small phase lags that make the interactions blind to NPD. Answers to these problems may be given in the future by the fitting of biophysical models to the data presented in this paper. This would provide a well-defined, quantitative description of the potential mechanisms that act to generate the phenomena we have described.

Furthermore, this study makes inference from the sample statistics of the experimental groups and does not make systematic investigation as to the existence of heterogeneity in the functional connectivity of the group. Such work would likely involve cluster analysis of the connectivity in order to ask the interesting question of whether localized dopamine depletion can result in a range of distinct individual patterns of beta/gamma propagation.

Moreover, we must stress that analysis of functional connectivity cannot access directly the mechanisms that generate sustained neural oscillations and their synchronization. This requires direct experimental manipulations of connections in the network such as that by Tachibana et al. (2011). Nonetheless, the biophysical transmission of rhythmic neural activity and the changes that occur to it following a manipulation such as the 6-OHDA induced ablation of dopamine neurons leave behind a signature that is accessible to the tools of functional connectivity. Further, the ability to apply systematic “functional lesions” such as that afforded by the conditioned NPD analysis, only acts to more increase our ability to infer the generative mechanisms of the observed data.

4.5 Conclusion

Overall, we provide a systematic deconstruction of the propagation of pathological rhythms across the Parkinsonian cortico-basal ganglia circuit in vivo. These findings strengthen our understanding of how normal and pathological rhythms propagate across the network. Our work highlights the importance of
considering non-canonical connections in the network, in particular the activity of recurrent subcortical projections that may act to amplify pathological activity within the BG. Future work will aim to understand the exact changes to the network required to generate the patterns of functional connectivity presented here, as well as to investigate the relationship with spiking activity in the network.
Chapter IV:
Inferring the Mechanisms of Pathological Rhythms in the Cortico-Basal Ganglia Network
1 Introduction

It is hypothesised that many high order brain functions are founded on the emergence of the coordination of neural activity across disparate regions of the brain (Varela et al. 2001; Bressler and Menon 2010). This has led to the recasting of many brain pathologies as ‘circuit disorders’ by which the altered strength of long distance synaptic projections is thought to result in the generation and/or spread of pathological activity which disrupts the functioning of the brain as a whole (DeLong and Wichmann 2010; Carrera and Tononi 2014; Fornito et al. 2015). This has led to the widespread application of methods for assessing changes in brain connectivity associated with disease. This problem has been typically approached in terms of either anatomical connectivity – the measurement of the axonal tracts and synaptic projections in the brain, or functional connectivity (FC) – the estimation of the statistical dependencies that arise due to coupling of neural activities (Deco et al. 2011; Friston 2011). Directed FC (dFC) indicates statistics that aim to determine asymmetries in the dependencies between signals (i.e. one signal driving another). Whilst it is possible for an overlap between networks derived anatomically and functionally, extensive computational and experimental analysis has demonstrated the relationship is not a straightforward one-to-one mapping (Honey et al. 2009; Cabral et al. 2014; Ton et al. 2014). Understanding how altered neural plasticity associated with disease is manifest in the statistics recorded with FC remains an outstanding question in understanding the origins of pathological brain activity.

Extensive electrophysiological evidence exists for a relationship between excessive beta band (14-30 Hz) activity and motor impairments observed in Parkinson’s disease (PD) (Brown et al. 2001; Levy 2002; Ray et al. 2008). Connectionist hypotheses of the impairment hypothesise that pathological activity emerges from the loss of dopamine which induces plastic changes in the synaptic projections between nuclei of the basal ganglia and regions of the motor cortex (Bevan et al. 2002; Brittain and Brown 2014). In animal models of PD, it can take days to weeks for pathological activity in the STN and subsequent motor impairment to emerge following the initial lesion (Mallet et al. 2008b). A large body of computational work exists that has established a number of plausible hypotheses concerning the generation of beta rhythms in the cortico-basal ganglia circuit (Terman et al. 2002; Holgado et al. 2010). In previous work, we conducted a systematic analysis of the dFC between signals recorded at multiple sites across the networks formed by the motor cortex and basal ganglia (West et al. 2018). Through synthesis of a wide body of evidence arising from systematic functional lesioning we arrived at a plausible explanation of the findings through a mechanism of ‘short-circuiting’ by which the normal propagation of activity through the basal ganglia is disrupted by the excessive engagement of the hyperdirect pathway, a direct connection from the motor cortex to subthalamic nucleus (STN) (Nambu et al. 2002) and its associated feedback assumed to occur via the thalamus. In this paper we employ
mathematical modelling to ask whether this mechanism is truly capable of generating the data features we have previously observed and reported.

We do so by estimating the parameters of a dynamical state-space model describing the system of interest (the cortico-basal-ganglia network) and then exploring how the model parameters shape the propagation of beta rhythms. In particular, we are interested in the effect of the strength of connectivity between different neural populations upon the emergence of beta rhythms. Furthermore, we ask how well dFC, measured from the signals alone, can predict the known structural connectivity encoded in the model equations. This approach draws inspiration from dynamic causal modelling (Moran et al. 2011; Marreiros et al. 2013; van Wijk et al. 2018) but uses an optimization scheme (Approximate Bayesian Computation; ABC) that avoids the computationally expensive estimation of the likelihood function, and is thus well suited for systems which are expensive to evaluate due to a large state and/or parameter space. The ABC scheme provides a tool for the stochastic inversion of high dimensional models upon generic data features via an iterative sampling method (Toni and Stumpf 2009; Toni et al. 2009; Sunnåker et al. 2013). The use of this optimization approach allows for questions to be asked of inverted models beyond that of their steady state behaviour. Indeed, much of the neurophysiological literature is now focused on transient spontaneous or stochastic dynamics such as ‘beta bursts’ and their relationship to intermittent neural synchrony (Rubchinsky et al. 2012; Cagnan et al. 2015; Feingold et al. 2015; Tinkhauser et al. 2018; van Ede et al. 2018). Finally, the usage of inverted computational models allows for the investigation of the system parameters that determine its phase transitions. In this way we investigate how parameters relate to the onset of rhythmic behaviour, and investigate statistical signatures that may be used in empirical data to estimate a system’s proximity to the transition.

2 Methods

2.1 Approach

We implement a model of the basal-ganglia-cortical network based upon neural mass approximations of neuronal population activity (Lopes da Silva et al. 1974; Jansen and Rit 1995). The model has a similar form to that of previous studies (Moran et al. 2011; Marreiros et al. 2013; van Wijk et al. 2018) which have utilized the dynamic causal modelling (DCM) framework for the inversion of model parameters upon empirical neural data. We take a similar approach but adapt the state equations such that they explicitly incorporate: i) finite time delays, and ii) stochastic input. These additions make the models computationally more expensive to evaluate and thus unsuitable for the current DCM inversion scheme (based upon variational Bayes under Laplacian assumptions of Gaussian posteriors) for resting state activity. This is due to the fact that the DCM scheme makes several approximations to avoid integrating the equations in the time domain. We therefore have adopted an alternative optimization scheme, Approximate Bayesian Computation (ABC; Beaumont et al. 2002; Toni et al. 2009), that
bypasses the estimation of likelihood functions required by other stochastic methods such as Markov Chain Monte-Carlo or Gibbs sampling. We instead use rejection-sampling over a prior density of parameters, and iteratively update the estimate of the posterior as the model converges to yield outputs with increasing resemblance to the data.

We use the ABC scheme to invert the parameters of a proposed generative model (a set of state equations describing mesoscale neuronal dynamics) upon the summary statistics of empirical data (i.e. autospectral density and dFC). We use data from our previously reported study of directed FC in a rat model of PD (West et al. 2018) that was based on data recorded in previous experiments (Magill et al. 2004, 2006). We start from simple models of sub-circuits of the full network and then build up to increasing complex models by using Bayesian model comparison to establish the most plausible patterns of directed functional connectivity. Furthermore, we use these models to explore the relationship between anatomical connectivity encoded in model parameters with the observed functional connectivity. Finally, we investigate how bifurcations in the optimized models are parameterized by connectivity and establish the degree to which statistical tools such as estimation of extended autocorrelation (Scheffer et al. 2009) can be used to estimate the proximity to critical transitions.

2.2 Experimental Data

2.2.1 Experimental Recordings

All data used for the inference of model parameters comes from an original experimental study in rats lesioned with 6-hydroxydopamine (6-OHDA) in order to deplete the dopaminergic system in the substantia nigra. The 6-OHDA lesion is a model of the neuronal degeneration associated with PD in humans. The animals were implanted with two electrodes to measure local field potentials (LFP) from multiple structures in the basal ganglia: dorsal striatum (STR), external segment of the globus pallidus (GPe), and the subthalamic nucleus (STN). Each probe had a vertical array of 16 recording contacts with 100 μm separation. One probe recorded LFPs in STR and GPe, whilst the second measured LFPs from STN. Additionally, a 1 mm diameter cortical screw was implanted over area M2 of the motor cortex, which is the homologue of the Supplementary Motor Area (SMA) in humans (Paxinos and Watson 2007), to record electrocorticographic activity (ECoG). Following recovery from surgery, the animals were recorded under anaesthesia induced with 4% v/v isoflurane in O2 and maintained with urethane (1.3g g/kg, i.p.). A hind-paw pinch was made in order to induce periods of “cortical-activation” (Steriade 2000) as opposed to slow wave sleep.

Recordings were made for ~180s from 17 rats (8 dopamine intact controls and 9 6-OHDA lesioned rats). Monopolar probe signals were recorded using high-impedance unity-gain operational amplifiers (Advanced LinCMOS: Texas Instruments, Dallas, TX) and were referenced against a screw implanted
above the contralateral cerebellar hemisphere. After initial amplification, extracellular signals were further amplified (1000x) and low-pass filtered at 6000 Hz using programmable differential amplifiers (Lynx-8: Neuralynx, Tucson, AZ). The ECoG and probe signals were each sampled at 17.9 kHz using a Power1401 Analog-Digital converter and a PC running Spike2 acquisition and analysis software (Cambridge Electronic Design Ltd., Cambridge, UK). Recording sites in the BG were verified by post hoc histology, as described previously (Magill et al. 2006; Mallet et al. 2008a, 2008b). For full details of the recording setup, experiments, and 6-OHD lesioning see Magill et al. (2006), and Mallet et al. (2008).

2.2.2 Acquisition and Pre-processing

To isolate LFPs and ECoGs, all electrophysiological data were down-sampled from a hardware native 17.9 kHz to 250 Hz using Spike2 acquisition and analysis software (version 4; Cambridge Electronic Design Ltd., Cambridge, UK). Data were then imported from Spike2 into MATLAB where they were analysed using custom scripts utilizing routines from the Neurospec software package (http://www.neurospec.org/). Data were pre-processed as follows: i) truncated to remove 1 second of from either end of the recording; ii) mean subtracted; iii) band-passed filtered 4-100 Hz with a finite impulse response, two-pass (zero-lag) filter designed such that the filter order is rounded to the number of samples for 3 periods of the lowest frequency; iv) split into 1 second epochs; and v) each epoch was subjected to a Z-score threshold criterion such that epochs containing any high amplitude artefacts were removed. Examples of signals following pre-processing are shown alongside a schematic of the network in figure 1.

2.3 Signal Analysis

Power analyses were made using the averaged periodogram method across 1 second epochs and a Hanning taper to reduce the effects of spectral leakage. Frequencies between 49-51 Hz were removed so that there was no contribution from 50 Hz line noise. We opted to remove the 1/f background by first performing a linear regression on the log-log spectra and subtracting the linear component. This ensured that the inversion scheme was focused upon the spectral peaks in the data and not the profile of 1/f background noise.

Estimates of directed connectivity were computed using non-parametric directionality (NPD) (Halliday 2015) as implemented in the Neurospec software package. This analysis combines Minimum Mean Square Error (MMSE) pre-whitening with forward and reverse Fourier transforms to decompose coherence estimates at each frequency into three components: forward, reverse and zero lag. These components are defined according to the corresponding time lags in the cross-correlation function derived from the MMSE pre-whitened cross-spectrum. The advantage of this approach is that it allows decomposition of the signal into distinct forward and reverse components of coherence separate from the zero-lag (or instantaneous) component of coherence which can reflect volume conduction. The
method uses temporal precedence to determine directionality. For example, STN activity lagging M2 activity results in a significant forward component of coherence between M2 and STN (when M2 supplies the reference time series), whereas in the same data set STN activity leading M2 activity results in a significant reverse component of coherence. For a detailed formulation of the method and its validation see Halliday (2015). For comparison between empirical and simulated data we used group averaged recordings from either the control or lesioned animals.

Since autospectral density and NPD are used as summary statistics for inversion of a state space model we simplify the data features to remove noise and reduce them to those components we wish to model. This is achieved by fitting a sum of 1, 2 or 3 Gaussians to the spectra using a maximum likelihood estimator and applying a likelihood ratio test to select the best model. In this way the spectra can be represented as a smooth sum of normal modes with peaks corresponding to the peak in the spectra (i.e. alpha, high or low beta frequencies). This was done to smooth the empirical data features only. Spectra computed from simulated data were allowed to deviate in whatever way model dynamics dictated.

2.4 Model of Population Activity in the Cortico-Basal-Ganglia-Thalamic Network

2.4.1 Formulation of the Cortico-Basal-Ganglia Model

As stated previously, we draw on the architecture of previous models but adapted the equations to incorporate delays and stochastic input. A schematic of the model can be seen in figure 1 and is based on that described in van Wijk et al. (2018). For the cortex we use a model of the motor microcircuit (MMC) (Bhatt et al. 2016) which is treated as one node of the network. The MMC is itself a modification of the canonical microcircuit model (CMC) (Bastos et al. 2012; Pinotsis et al. 2013) which accounts for differences between the cytoarchitecture of the primary motor cortex and that of the visual cortex on which the original CMC models were based (Shipp 2005; Beul and Hilgetag 2015). The model comprises 3 populations of glutamatergic pyramidal populations: superior (SP), medial (MP), and deep (DP). The model also contains a separate inhibitory interneuron population (II) which accounts for lateral inhibitory input (Fino et al. 2013).

For the subcortical sources (i.e. basal ganglia and thalamus), we model the intrinsic dynamics of each of the nuclei with a single neural mass and then link them together with extrinsic long-distance connections. The rodent STR is comprised of 95% GABAergic projection neurons (medium spiny neurons) and 5% morphologically varied interspersed interneurons (Bishop et al. 1982; Gerfen and Wilson 1996). We lump together the activity of these interneurons as a single inhibitory self-connection. The STN is the primary excitatory population within the basal ganglia and studies in rodents show that it consists predominantly of medium sized glutamatergic projection neurons (Kita and Kitai 1987). The pallidus is split into internal/external segments (GPI/GPe). The GPI is the BG’s main output nucleus.
Figure 1 – Schematic of the motor cortex and basal-ganglia-thalamus model of neural ensemble activity. Individual inhibitory GABAergic (blue) or excitatory glutamatergic (red) populations are shown by the circles and triangles. Connections between the populations are indicated by the lines projecting from the respective ensemble. The model is broadly split into the motor cortex microcircuit (MCM; yellow shaded background), and the basal-ganglia nuclei plus thalamus (blue shaded background). The MCM is split into three pyramidal populations: superficial (SP), middle (MP), and deep (DP). All three populations interact with a generic interneuron population (II). Pyramidal populations undergo self-inhibition, accounting for interspersed interneurons local to the layer (e.g. basket cells). In the basal ganglia we model the main excitatory population – subthalamic nucleus (STN), as well as the 3 inhibitory nuclei: internal/external globus pallidus (GPI/GPe), and striatum (STR). The main basal ganglia outputs feedback to cortex via an excitatory thalamic population. Alongside the schematic are example traces from the experimental recordings made in the 6-OHDA lesioned rats.

and consists of tonically firing GABAergic neurons that send inhibitory projections to several parts of the subcortex including ventral thalamus (Smith et al. 1998). Similarly to the STR, for both pallidal nuclei we also included inhibitory self-connections to model the action of local axons collaterals (Kita and Kita 1994; Sato et al. 2000). Each node receives a stochastic input assumed to be either spontaneous background noise or random exogenous inputs not explicitly incorporated into the model.

The anatomical connectivity between structures is based on the main known GABAergic and Glutamatergic projections that have form the standard basal ganglia network (Smith et al. 1998; Bolam et al. 2000) incorporating both the direct (STR → GPI) and indirect (STR → GPe → STN → GPI) pathways. Additionally the model incorporates glutamatergic feedback from STN to GPe which has
been suggested as a potential generator of pathological beta oscillations (Bevan et al. 2002). Furthermore we model the hyperdirect connection M2 → STN (Nambu et al. 2002). Finally, there is a feedback from the basal-ganglia to cortex via projections from the ventrolateral thalamus (motor) to both layer 4 and 5b (Yamawaki et al. 2014) which we model as excitatory connections to MP and DP of the MMC respectively.

2.4.2 Neural Mass Modelling

In order to simulate continuous neural signals through biophysically plausible mechanisms we used a coupled network of convolution neural mass models (Lopes da Silva 1991; Jansen and Rit 1995). A single neural mass approximates the population activity of a large number of homogenous neurons (Moran et al. 2013). These models rest on the assumption that an incoming spike density arriving at the population via synaptic projections can be converted to a post synaptic potential by convolution with a synaptic response kernel to simulate post synaptic depolarization. The system then outputs temporally integrated post synaptic potentials as a spike density with a typically sigmoidal response function. Thus populations may be coupled via intrinsic connectivity to simulate the dynamics within cortical columns, and extrinsic connectivity to simulate inter-areal coupling (Wendling et al. 2000; David and Friston 2003). A single mass of coupled populations is given generally by the form:

\[ \dot{v}_i = x_i \]

\[ \dot{x}_i = \frac{H_i}{\tau_i} \left( u_i + S(v_j) \right) - \frac{2}{\tau_i} x_i - \frac{1}{\tau_i^2} v_i, \]

where the average postsynaptic membrane potential of the \( i \)th population is given by \( v_i \), and is parameterized by a synaptic gain \( H_i \) and a lumped post synaptic time constant \( \tau_i \). The input to the mass is given in brackets and comprises some background noise \( u_i \) and a combined input from the other \( j \) populations. Membrane potentials are converted to spike densities for convolution via the sigmoid operator:

\[ S^i(v) = \frac{1}{1 + e^{-R^i v}}, \]

which is itself parameterised by \( R^i \) which determines the slope of the activation function (a parameter specific to node \( i \)), or the effective variance of the population’s firing thresholds. Masses within columns are intrinsically coupled such that inhibitory and excitatory populations interact such that inhibitory cells have negative connection weights and vice versa for excitatory cells. In order to couple distant columns, inputs to population \( i \) from \( j \) are coupled via a weighted adjacency matrix \( \omega \):

\[ v^i_j = \sum_{j=1}^{J} \omega_{ij} v_j \]
In order to create the full model describing the basal ganglia and motor cortex, masses are coupled with a structure outlined in the schematic in figure 1. We model inhibitory connections by flipping the sign on the adjacency matrix, such that they have a subtractive influence. In total there are 14 state equations that are an adaption of the full model described in van Wijk et al. (2018).

2.4.3 Numerical Integration of Stochastic-Delay Differential Equations

We incorporated finite transmission delays by formulating the state space equations to explicitly depend on the past values of the sending node. This was achieved by modifying the extrinsic connectivity matrices by indexing past values with a matrix $D$ with elements $D_{ij}$ specifying the delay for connection of population $i$ to $j$. Thus, the total external input to node $i$ at time $t$ is:

$$v_i^j(t) = \sum_{j=1}^{l} \omega_{ij} v_j(t - D_{ij}),$$

with the constraint that $D_{ij} > 0$.

The model also incorporates stochastic input $u$ representing background activity. We formulate this input by:

$$u_i = C_i W,$$

where

$$W \sim N(0, \sigma),$$

and $C$ represents a gain factor on the noise scaling the noise for population $i$. The noise $W$ is drawn from a zero-mean normal distribution, with a standard deviation $\sigma$ that is set for the whole model. In the model presented here we introduce stochastic innovations that are independent of the state variable. In this case, the interpretation of the stochastic integral is simplified, and forward Euler with a suitably small step size (less than half of the fastest time constants) has been demonstrated to yield accurate results (Ewald et al. 2004). For the purposes of integration, we rescale the noise by the square-root of the integration step $h$ (as per Hansen et al. 2006):

$$\tilde{u}_i = u_i \sqrt{h}.$$

It is important to note that the naïve application of deterministic integration schemes to stochastic problems has been demonstrated to lead to inaccurate or at worst, spurious, solutions (Ewald et al. 2004). In this work we use a more standard but computationally expensive solver (forward Euler with a small step size) that has previously been demonstrated to yield accurate solutions (Lemaréchal et al. 2018). Furthermore, approximations to absorb delay equations (in order to simplify the integration of the equations) using numerical approximation of the system’s Jacobian (David et al. 2006; Ostwald and
Starke 2016), as is done in dynamic causal modelling, has been demonstrated to be inaccurate in the same types of neural mass models presented here (Lemaréchal et al. 2018). The integration scheme presented here limit the assumptions of the form of the model and provides a simple, accurate method by which to solve the system of stochastic-delay differential equation that specify our model of neural dynamics.

### 2.4.4 Testing Statistics of Critical Transitions

Previous work in the types of neural mass models used here (Jansen-Rit) has demonstrated that they exhibit a super-critical Hopf bifurcation with increasing input $u_i$. Furthermore, this transition from a stable fixed point to a stable limit cycle behaviour may be determined statistically (as opposed to analytically) using the autocorrelation length (Aburn et al. 2012). Autocorrelation length is known to be a statistical hallmark of many types of systems approaching a critical transition (Scheffer et al. 2009) and has become of increasing interest to the neuroscience as evidence to support theories of self-organized criticality (Bak and Paczuski 1995; Linkenkaer-Hansen et al. 2001; Meisel et al. 2012) for local neuronal computation, but also distributed communication via synchronization (Cerf et al. 2004; Botcharova et al. 2014; Bressler and Richter 2015). In this work we investigate whether bifurcations exist, and whether they are detectable by statistical analysis of the time series. We utilize detrended fluctuation analysis (DFA; Peng et al. 1994, 1995) as a tool to estimate long range autocorrelations. DFA provides an approximation to the Hurst exponent $H$, with $H > 0.5$ indicating the existence of long-range temporal correlations. We apply this technique to amplitude envelopes of the band-passed time series data (modulus of the Hilbert transformed signal), as proposed by Linkenkaer-Hansen et al. (2001).

To determine analytically the proximity of the system to a bifurcation, we approximate the Lyapunov stability by numerical estimation of the Jacobian matrix. The Jacobian is estimated via finite difference approximation, taking the state of the system after simulation as a point on the trajectory around a local equilibrium. The eigenvalues of the Jacobian are taken as estimates of the Lyapunov spectra $\lambda$, with the stability of the system determined by the largest exponent $\lambda_1$. Stability is lost when $\lambda_1 > 0$. We thus track the approach to bifurcation in terms of the zero-crossing of $\lambda_1$ and investigate whether the analytic estimation of stability corresponds to those measured statistically as described above.

### 2.5 Approximate Bayesian Computation for Model Estimation

#### 2.5.1 Description of Inversion Scheme

In order to estimate the parameters given the empirical recordings we use a stochastic scheme, similar in formulation to Markov Chain Monte-Carlo (MCMC) approaches but that bypasses the need for the computationally expensive estimation of a model likelihood. Namely, we base the optimisation on approximate Bayesian computation (ABC; Beaumont et al. 2002; see also Sunnåker et al. 2013), an
algorithm described for the inversion of high dimensional non-linear models frequently encountered in many areas of systems biology (Ratmann et al. 2009; Toni and Stumpf 2009; Toni et al. 2009). The approach is formulated for problems where models are complex and data sets are large. We use a rejection sampling approach in order to form a sample of draws from a prior distribution and estimate the posterior via iterative rejection of samples based on some shrinking distance between the sample and the empirical data. The ABC rejection algorithm follows as such:

1. Specify prior distribution of parameters, \( P(\theta) \) of the model \( M \).
2. Randomly sample \( N \) times from the prior to yield samples \( \hat{\theta}_n \).
3. Simulate pseudo-data \( \hat{D}_n \) from \( M(\hat{\theta}_n) \).
4. Compute summary statistic of \( \mu_n \) of pseudo-data \( \hat{D}_n \).
5. Compute distance \( \rho \) of \( \mu_n \) from \( \mu_0 \) (summary statistic of the empirical data).
6. Reject \( \hat{\theta}_n \) if the distance is \( \rho(\mu_n, \mu_0) \geq \epsilon_q \).
7. Approximate the posterior, \( P(\theta|D_0) \), from the distribution of the accepted parameter samples.
8. Iterate for \( q = 1, \ldots, Q \), setting \( P(\theta) = P(\theta|D_0) \), and shrinking the distance threshold \( \epsilon_{q+1} < \epsilon_q \).

We form the prior joint distribution using a multivariate Gaussian with identity covariance which forms the basis for the draw at \( q = 1 \). The model \( M \) is specified by the state equations of the dynamical system \( F \) and observation model \( G \):

\[
M(x, \theta) = G(F(x, \theta^F), \theta^G),
\]

where the superscripted \( \theta^F \) and \( \theta^G \) denote the subset of parameters for the dynamical and observation models (\( F, G \) respectively). The choice of the summary statistic, which acts to compactly represent the (time-series) data, must encode the properties of interest in the real data. Here, we use the auto-spectra and directed functional connectivity matrices (non-zero NPD). We choose to use NPD as it simplifies the observation modelling by directly removing the zero-lag component of coherence, and thus signal mixing is zero. We assess the distance of the data from pseudo-data using the function \( \rho(\mu_1, \mu_2) \) which we set as the normalized root mean squared error (NRMSE), scaled to the (unmatched) variances of the autospectra and NPD. The shrinking distance threshold \( \epsilon \) ensures that the posterior estimates converge upon solutions that most accurately reproduce the summary statistics of the observed data. We set \( \epsilon_q = \frac{1}{q^4} + c \) where \( c \) sets the initial threshold at iteration \( q = 1 \).

Once a sample of parameters has been accepted we then estimate the posterior density \( P(\theta|D_0) \) from them. We make nonparametric estimation of the marginal densities for each parameter using a kernel density estimator (Silverman 2018) for the univariate probability density functions. We then conjoin the marginal densities using a t-copula to give the joint posterior estimate. The copula provides a
mathematically convenient way of creating the joint probability distribution whilst preserving the original marginal distributions. We then do an empirical update such that the posterior now becomes the prior for the next iteration: \( P(\theta) \rightarrow P(\theta, D_0) \).

The determination of the covariance structure acts to reduce the parameter space for optimization by constraining parameters together. We can estimate the rank of the posterior parameter space by taking the eigenvalues of the covariance matrix and normalizing the coefficients by their total sum. Taking a cumulative sum of the ordered coefficients we can then determine the number of modes that can explain 95% of the variance. In this way we measure the effective dimensions of the model to be optimized and expect this to reduce as the model converges.

### 2.5.2 Model Comparison

We make a simple comparison between models (hypotheses) by drawing \( N \) times from the posterior and then computing an exceedance probability to estimate the marginal probability of model \( m \) given data \( D_0 \):

\[
P(m|D_0) \approx \frac{\# \text{samples} > \epsilon^*}{N}
\]

where \( \epsilon^* \) is some threshold on the distance metric \( \rho \) that is suitably small to give an acceptable fit on the data. If \( \epsilon^* \) is held constant and the data is identical between models, then the exceedance probabilities may be compared to yield the model that gives the most accurate fit. Furthermore, when comparing inverted models, we assess both the approximate model evidence \( P(m|D) \) and the divergence of the posterior from the prior using an estimation of the Kullback-Leibler (KL) divergence. We then estimate the KL divergence of the posterior density \( P_2 \) (estimated using the kernel-density estimator) from the prior density \( P_1 \) (assuming it is normally distributed with identity covariance) over \( F \) discretized bins of the density:

\[
D_{KL}(P_1 || P_0) = -\sum_{i=1}^{F} P_0(i) \log \frac{P_0(i)}{P_1(i)}.
\]

This is a simplification of the full multivariate divergence and ignores the dependencies between variables encoded in the posterior covariance. Ultimately, we use the scores provided by the KL divergence as a guide for model comparison when models achieve similar degrees of accuracy. In this case the deciding factor predominantly arises from the form of the prior density such that the model that requires minimal deviation from the prior parameters will be preferred. This stems from the fact that this model specifically will provide the most parsimonious explanation for the data since the majority of the model’s explanatory power is contained in the structure specified by the prior expectations of the experimenter. The implications of this issue will be discussed later in the chapter.
2.6 Testing Groups of Models: Inferring Mechanisms of Beta Generation

This paper investigates the plausibility of several mechanisms proposed to explain the emergence of pathological beta oscillations in the basal ganglia of a model of Parkinson’s disease. To this end a primary aim of this study is to ask what signatures (in terms of the dFC) are hallmarks of certain mechanisms and whether it is possible to distinguish them via their statistical properties alone. To do this we isolate mechanistically relevant sub-circuits of the full model and then selectively optimize parameters on data features relevant to the problem. We will investigate 3 frequently proposed mechanisms of pathological beta oscillation generation and propagation: I) beta is generated from the activity interactions between the reciprocal STN/GPe pairing; II) beta is related to rhythms generated in the motor cortex and their modulation of subcortical activity via the hyperdirect pathway; and III) beta is generated by activity propagating through the indirect pathway via the striatum. In each case we will isolate only the relevant nodes and connections and then use data to infer model parameters. In this chapter we will largely avoid questions relating to the thalamocortical feedback, due in part to the absence of recordings from output nuclei at GPi or thalamus. Extensions of the work presented here might provide insight into how these feedbacks may contribute to the observed signatures of FC.

To test model hypothesis I) we isolate just the STN and GPe with their respective excitatory and inhibitory projections. We fit the sub-model’s parameters to the autospectra only, such that the circuit is optimized to generate beta in both the STN and GPe nodes but without any constraints of FC. We then dissect the circuit looking at the contribution of the excitation and inhibition in isolation.

To test model hypothesis II) we investigate the role of the motor cortex’s hyperdirect projection to the STN. We use the STN/GPe circuit optimized as for I) but introduce a separately optimized M2 node fit to autospectra from control animals. In this way, the cortex is optimized to generate non-pathological activity and we can investigate how its normal activity can enhance pathological oscillations in the basal ganglia.

Finally, we test model hypothesis III) through asking how beta oscillations can be filtered by the striatum and propagate through the indirect pathway. For this model we optimize the intrinsic parameters (time constants and gains) of the M2 to yield beta rhythms, and then fit the rest of the model to the lesioned data leaving all parameters unconstrained.
3 Results

3.1 Model Fitting and Parameter Optimization

We used the ABC framework to optimize parameters of the full MBGT model and sub-models to reproduce the FC observed in real experimental recordings. The results of an example inversion are presented in figure 2 and examples of simulated time series are given in figures 3, 4 and 5. In general, fitted models exhibited rich dynamics including oscillations, inter-areal synchrony, and transient burst like events.

In figure 1A we show examples of the simulated and empirical summary time series analysis (autospectra and NPD) at three points during the optimization. It can be seen that over the course of the optimization process the simulated data converges to the observed. Testing with simpler models (i.e., 3

Figure 2 – Summary of the Fitting Procedure Using Approximate Bayesian Computation – Parameters of neuronal state space models were fit using a Monte Carlo sampling approach. (A) Iteration gradually converges on the summary statistics using autospectra (black) and non-parametric directionality (NPD; red) of the empirical data (-). Individual samples (---) as well as the best fit (---) for that iteration are shown for 3 example steps. (B) Optimization is made with an iterative scheme to resample parameters from samples that are restricted to some shrinking distance metric (normalised root mean squared error; NRMSE). (C) Prior densities are specified (---) so to restrict the model space. Iterative updating with rejection sampling results in a posterior estimate of the marginal densities (•) using a kernel density estimation. Marginals are conjoined using a t-copula with covariance structure (D). This yields an estimate of the joint posterior, a 3-D sample of which is shown in (E). Upon convergence this estimates the posterior means of the n dimensional parameter space.
or fewer nodes) allowed even more accurate fits ranging up to 80% of explained variance. Optimization generally followed a fast initial trajectory in the first 15 iterations and then slowed (figure 2B). As the scheme converged onto a solution, the kernel density estimates of marginal posterior parameters (figure 2C) increased in precision indicating data was informative for the parameter estimation. The estimated joint posterior density (via a t-copula) exhibits a rich covariance structure (figure 2D) indicating learnt relationships between parameters that provide information as to how parameters can be organized to yield physiologically plausible model outputs. Estimation of the rank of the posterior parameter space

Figure 3 – Simulations of STN-GPe subcircuit as a generator of pathological beta (β1, 14-20 Hz) oscillations. The model parameters were chosen from an optimization of the STN/GPe autospectra from dopamine lesioned rats. The figure shows the results from 3 simulations of the STN (red) – GPe (blue) circuit: (A) Reciprocal connectivity between STN and GPe; (B) Excitation from STN to GPe; and (C) GPe inhibiting STN. Examples of simulated traces are shown below the schematics. All traces are time-locked with identical stochastic processes between models. (D) The power spectral density at each node is shown on the diagonal (black), whilst directed functional connectivity is shown using NPD for either STN to GPe (blue) or GPe to STN (red). All three models are shown (STN → GPe ‘-’; STN ↔ GPe ‘-’; STN ← GPe ‘-’). (E) Heatmaps of maximum beta power in the parameter space of model 2 (reciprocal). Blue indicates strong beta power whereas red indicates weak. Isoclines for beta power are overlaid. The black cross (+) indicates the parameters of the data inverted model. The power for GPe (top) and STN (bottom) is shown separately. Maps suggest STN will more readily enter into synchrony, especially when GPe inhibition is low. (F) Same as (E) but instead changing the time constants of the GPe and STN (T_{GPe} and T_{STN} respectively).
indicates that the effective dimensionality is significantly reduced by the covariance estimation. Optimized models show a reduction of 50-70% in their rank (reducing from 71 independent parameters, to 16 independent parameter modes). This contributes to significantly reducing the under determination of the optimization procedure.

3.2 STN/GPe Circuit as an Autonomous Generator of Beta Oscillations

3.2.1 Parametrization for Beta Generation

We next used the optimization procedures to investigate the conditions that produce beta oscillations via reciprocal connections from the STN-GPe circuit. To do this, we used a reduced model comprising only the STN and GPe nodes and we fitted parameters to generate the autospectra observed in the lesioned recordings (containing a high amplitude low beta peak $\beta_1$). In this way we can ask specifically how this circuit can give rise to beta in isolation from inputs from the rest of the system. We optimized the reciprocally connected model, and then removed each connection (from STN or GPe) to examine the two nodes activity in isolation. The results from simulations are shown in figure 3. We demonstrate that given suitable parameterization, the system can generate beta oscillations that are qualitatively similar to those seen in vivo, but that neither node is able to generate beta on its own (figure 3A-C).

Despite being reciprocally coupled, directed FC (measured with NPD) indicates a strong lead from GPe → STN and with an overall broadband connectivity (figure 3D, top-right) as determined by the experimental data. Despite this, inspection of the fitted parameters shows that the excitatory connection is 40% stronger (STN → GPe: 3606 spikes.s$^{-1}$ vs GPe → STN: 2176 spikes.s$^{-1}$) yet the NPD difference is closer to 95%. We next set the individual connections to zero to yield two separate models: a) GPe inhibiting STN and b) STN exciting GPe (figure 3B and C). We find that the directional components (figure 3D, off-diagonal) are asymmetrical such that the directed coherence associated with inhibition is much greater (NPD $> 0.8$) than that with excitation (NPD $< 0.1$). This would suggest that the signature functional connectivity is most largely shaped by the inhibiting population, perhaps because the subtractive influence of one signal on another results in more correlated fluctuations.

We next investigate how the power of the beta oscillation varies across the parameter space of the relative connection strengths (figure 3E). The distributions of power show that the STN will readily enter into a state that gives rise to beta oscillations given either strong GPe inhibition or by reinforcing its own inhibition via increasing input to reciprocally coupled GPe. Beta power in the GPe responds differently and its parameterization (in figure 3E) shows an additional region where it can engage in beta when the input from STN is reduced.

The time constants of the two populations are distinctly separated – the GPe is slower with $\tau_{GPe} = 7\text{ms}$, whereas $\tau_{STN} = 1\text{ms}$, a feature that is apparent in the examples of their autonomous dynamics (figure
Analysis of the beta power at a range of time constants of $\tau_{\text{GPe}}$ and $\tau_{\text{STN}}$ (figure 3F) suggests that for a fixed connectivity (from the inversion) there is actually a broad number of time constant combinations that can lead to the emergence of a large amount of beta. The relationship, however, is strongest when there is a fast/slow split between the STN and GPe. The heatmap in 3F shows that beta can be readily reproduced when the ratio between the excitation and inhibitory time constants are clamped facilitating a corridor of parameter space where the reciprocal excitation-inhibition can give rise to periodic behaviour at beta frequencies.

3.2.2 Examination of Bifurcation Points

We note that both parameter spaces (connectivity and time constants) show rapid transition boundaries. With connection strengths, the border lies at an inverse relationship between inhibition and excitation – with too little of either excitation or inhibition the dynamics settles on a non-oscillatory state, whereas with too much excitation or inhibition the model exponentially diverges or saturates. The map over time constants shows the existence of multiple bifurcation points over which beta oscillations may...

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**Figure 4** – Numerical analysis of stability of the STN/GPe circuit when varying the connection strengths (left column) or time constants (right column) along a transection of parameter space (indicated in figure 3 D and E). The parameters were sampled along the diagonal indicated in figures 3E and F with sample points a, b, c and d aligned to the previous figure. (A and E) Plots of the beta power of the STN and GPe. We also show the DFA $\alpha$ estimates of the Hurst exponent as a measure of the persistence of the autocorrelation sequence of the amplitude envelope (bold), as well as the linearity score (from PEB model comparison), and the signal variance for the simulated STN (B and F) and GPe (C and G). (D and H) Plots of the eigenspectra (4 state variables) computed from the numerical approximation of the Jacobian for each system. The dashed line aids identification of zero-crossings indicative of system bifurcations.
emerge or disappear. We transect the parameter space examined with respect to the connection strengths and time constants (figures 3 E and F) and investigate the evolution of this transition into beta oscillations. This analysis is shown in figure 4.

We demonstrate in figure 4A, that the transition into beta oscillation occurs rapidly between a range of $10^0 - 10^{0.5}$ in terms of the log scale deviation from the prior value of connectivity for STN and GPe. Examination of the Lyapunov spectra (figure 4D) indicates that the largest exponent crosses zero around the same point, indicative of the transition. Following the transition, we see also a divergence of the exponents, indicating a mix of stable and unstable modes. Statistical estimation of the autocorrelation length of the signals (using DFA estimates of the Hurst exponent; 4B and C) does not yield a good indication of the transition. It would be expected that the autocorrelation length would increase with approach to the transition, a feature that is not seen in these simulations. Instead there is an increase in the linearity of the fluctuation plots around the transition. We also see a rise in the amplitude envelope variance prior to transition and then a swift collapse once the system settles into a stable periodic state around $10^1$.

The state transitions with respect to the time constants $\tau_{GPe}$ and $\tau_{STN}$ are more complicated, as indicated by the discontinuous distribution of beta across parameter space indicated in figure 3F, and the transection examined in figure 4E. We show that there are multiple bifurcations across the parameter set examined, with a large onset of beta around $10^{-1} \log$ deviation of the time constants, but then also a second lying between the sample points b and c at $10^0$ and $10^1$. Estimation of the Lyapunov exponents in figure 4H does not indicate a zero crossing at the same points, rather there is a region of instability between $10^0$ and $10^{1.5}$. DFA exponents are better indicators here, showing a definite but small increase in the $\alpha$ estimate from 0.6 to 0.65. Similar to the previous analysis of connectivity induced bifurcations, the linearity of the DFA fluctuation plots is a better indication of the transition points. We also again show that the variance of the amplitude fluctuations rises towards the transition point at $10^1 \log$ time constants, and then collapses as the system passes through. Interestingly, the parameter estimates map the system very close to the main transition to beta oscillations (inferred parameters indicated by crosses in figure 3E and F).

Overall it is clear (with respect to connectivity parameters) that there is a clear transition into beta synchrony that is associated with a destabilization (zero-crossing of principal Lyapunov exponents). However the purported indicator of proximity to the transition (DFA) did not perform as expected, showing no clear change upon approach to the onset of beta. Instead the variance of the amplitude fluctuations shows a better-behaved relationship, increasing prior to onset, and then collapsing before the sharpest increase in beta power. The transition parameterized by population time-constants appears to be much more complex as indicated by the riddled manifold in which beta emerges (figure 3F). The
presence of multiple transitions makes locating the system with respect to a transition more complicated than for the simpler case that occurs when modifying coupling between the populations.

3.3 The Role of the Cortex on Subcortically Generated Beta—Influence via Hyperdirect Input

3.3.1 Parametrization of Motor Cortex and its Projections

We next conducted a set of simulations to investigate how cortical inputs to the STN via the hyperdirect pathway modulate the activity of the STN/GPe sub-circuit. We started with the model structure outlined in section 3.2, but introduced a cortical source modelled using the MMC model. We parametrized the STN/GPe circuit from an optimization upon the 6-OHDA lesioned auto-spectra. We assume this circuit is the generator of pathological beta, and that cortical activity is ‘healthy’. The extent to which these assumptions are valid are not tested in this section, but are introduced to pose a hypothetical model of activity in which beta is generated entirely in the subcortex. Thus, we separately inverted the MMC model on autospectra from the control animals to avoid introducing another source of low beta (14-21 Hz). The results of the simulations are presented in figure 5.

In the first model with an independent cortical source, we demonstrate that the STN/GPe circuit generates beta as before. The unconnected cortical model shows intrinsic slow (<1.5 Hz) and fast (>30 Hz) oscillations. In this first model, directed FC estimated with NPD correctly shows that there is no coupling between M2 and subcortical sources, and the pattern of NPD between STN and GPe remains as previous, with GPe influence on STN predominating.

We now connect the M2 model to the STN simulating the hyperdirect projection (model 2; figure 5B). The example traces of the simulation show that the STN and GPe now contain a higher frequency component. This is apparent when looking at the autospectra where the low beta (14-20 Hz) peak is conjoined with that of high beta (20-35 Hz; figure 5D diagonal). The M2 input also has the effect of suppressing the directed FC from GPe to STN, and the asymmetry flips with STN predominant over GPe. Despite this flip in the apparent direction of the drive, the STN/GPe circuit still oscillates at beta frequencies. Furthermore, the NPD shows a peak as the high beta from the cortex propagates to STN and subsequently GPe. There is some spurious NPD from STN to M2, a confound that may result from the pallidal return of the M2 beta back to STN.
We next look at the effects of a reciprocal feedback from STN → M2, an abstraction that simulates the thalamocortical feedback from the output of the BG. In this case we see that this effectively pushes up the frequency of the dominant $\beta_2$ across all of the connected nodes towards low gamma (>35 Hz) and
makes the two peaks at $\beta_1$ and $\beta_2$ more separate. Directed FC shows that the return connection (STN → M2) is projecting back beta to the M2, an effect that can be seen also in the M2 autospectra where there appears a low beta peak in addition to the intrinsically generated high beta. Feedback connections to M2 from STN or GPe are not greatly apparent. Furthermore, the analysis of parameter maps in figure 5E suggests that contrary to the hypothesis of beta generation via induction of thalamocortical afferents, increased strength of feedback from STN to cortex acts to suppress rather than enhance beta. Increased drive from M2 will, however, maintain beta or may push the system into a metastable region of
parameter space. At sufficiently high connection strengths the model either becomes unstable (exponential divergence) or loses oscillatory dynamics (emergence of stable fixed point).

It is likely the reciprocal connection confuses dFC as the feedback acts to establish a common drive – i.e. both M2 and GPe are driven by STN, thus M2 → GPe appears strengthened. Analysis of this connections in figure 5D shows that this is indeed the case, thus it is likely that the estimates would

Figure 7 – Results of Model Comparison to Test the Roles of Indirect Pathway Serial Transfer in Combination with Hyperdirect Cortical Input. We present results from the comparison of 8 different models containing the motor cortex (M2), striatum (STR), subthalamic nucleus (STN), and external segment of the globus pallidus (GPe). These models are outlined by the ball and stick figures, full model descriptions can be found in the main text, and priors in supplementary information. Following model inversion, we made 1000 draws from the posterior parameter distributions and re-simulated the data computing the summary statistics (power spectra and non-parametric directionality (NPD)). (B) The sample means of the models (coloured lines) are shown alongside the data (black line). (C) Violin plots of the distribution of the normalized mean root square error (NMRSE) of the model samples. (D) The exceedance probability approximation to the model evidence \( P(M|D) \) is computed to compare the probability of the models given the data. Model 4 is the best fitting. (E) The Kullback-Leibler divergence of the posterior from prior is shown for each model. Large values indicate high divergence and overfitting.
likely be enhanced by introducing conditioned metrics of FC that act to elucidate the role of a tertiary reference signal on bivariate coupling (see Halliday et al. 2016).

3.3.2 Comparison of Models Comprising the STN/GPe Interacting with M2

In order to infer the most plausible model given the experimental data, we compared a set of 7 alternative models that had parameters optimized on the experimental data. We compared the results by inspecting the accuracy of the inversion using an exceedance probability approximation to the model evidence with \( N = 1000 \) draws from the joint posterior and \( \epsilon = -0.25 \) (method detailed in section 2.5.2). We also computed the KL divergence (also section 2.5.2) of the posteriors from the priors as a measure of the degree of overfitting. The results of the model comparison are presented in figure 5. We present seven models below (also illustrated in figure 6A):

- **Model (1):** M2 independent of the STN/GPe;
- **Model (2):** M2 excitation to the STN;
- **Model (3):** Reciprocal connections between STN and M2;
- **Model (4):** STN excitation of M2;
- **Model (5):** Same as model 4 but using model 1 STN/GPe posteriors as empirical priors;
- **Model (6):** Same as model 3 but using model 1 STN/GPe posteriors as empirical priors;
- **Model (7):** Same as model 2 but using model 1 STN/GPe posteriors as empirical priors.

As the cortical source is comprised of several heterogeneous subpopulations it may readily yield autonomously generated \( \beta_1 \) and \( \beta_2 \) rhythms. To provide an alternative, we set the last three models to use the posterior estimates of parameters that can generate beta via the STN/GPe circuit in model 1. This is done to bias the models such that they will exhibit subcortically generated beta from the STN/GPe rather than from the cortex.

Altogether we find that the models yield a diversity of fits (figure 6B and C) ranging from poor (\(< -1 \) NMRSE) to a good representation of the empirical data (\(> 0 \) NRMSE). When comparing estimates of the model evidence and KL divergence (figure 6D and E) we find that the worst model is model 3 (reciprocal feedback from STN and M2) which has a 0 probability of exceeding the threshold for accuracy. This model suffered from poor stability as the reciprocal excitation was prone to lead to exponential divergence of states. All models containing the STN \( \rightarrow \) M2 connection (models 3, 4, 5, and 6) performed poorly, which may indicate that if feedback is to be modelled it needs a more complete description with addition of a node for the thalamic relay.

Altogether the best models were model 1 (independent cortex; \( P = 0.92 \)), model 2 (hyperdirect input; \( P = 0.96 \)), and model 7 (hyperdirect input with STN/GPe beta resonance; \( P = 0.99 \)). We found that in the case of model 7 the functional connectivity recreates a high beta/low gamma input to the STN from the M2, a key finding in West et al. (2018). The case for model 7 being the most plausible amongst those
tested is further strengthened by the posterior estimates having the lowest divergence from priors (figure 6E), indicating that less deviation from parameter priors was required for the inversion. This analysis would suggest that the most plausible network involves subcortically generated beta combined with a hyperdirect projection from motor cortex parameterized to yield high beta/gamma oscillations.

3.4 Modelling the Combined Propagation of Pathological Rhythms via Interacting Indirect and Hyperdirect Pathways

3.4.1 Model Comparison

We next set up a group of models to test plausible mechanisms concerning the routing of oscillatory activity when including not only hyperdirect input but also the indirect route from cortex to striatum. In the simplest case, the transfer is serial going from cortico-striatal input and descending the hierarchy of the pathway: M2 → STR → GPe → STN. We also examine the role of the STN feedback to GPe, as well as the effect of the hyperdirect input upon the network. In order to do this, we again used a model comparison with eight competing models defined as below and illustrated in figure 7A:

- **Model (1):** Serial propagation via indirect pathway;
- **Model (2):** Serial propagation plus STN feedback to GPe;
- **Model (3):** Serial propagation plus hyperdirect input (M2 → STN);
- **Model (4):** Serial propagation plus hyperdirect and STN feedback to GPe;
- **Model (5):** Same as model 3 but using MMC priors for lesioned M2 autospectra;
- **Model (6):** Same as model 4 but using MMC priors for lesioned M2 autospectra;
- **Model (7):** Same as model 2 but using MMC priors for lesioned M2 autospectra, and lesion STN/GPe autospectra;
- **Model (8):** Same as model 4 but using MMC priors for lesioned M2 autospectra, and lesion STN/GPe autospectra.

Again, we included additional models with prior constraints on intrinsic parameters set from a previous inversion in order to bias models in favour of certain beta generating circuits. In this case we defined models where the cortical source was biased to produce both $\beta_1$ and $\beta_2$ rhythms (models 5 and 6) allowing for the testing of simple propagation of cortically generated rhythms.

As in the previous section we found that the autospectra are generally well fit by all of the models tested (figure 7B). Models were predominantly discernible by their ability to give good approximations to the empirically observed directed functional connectivity (measured using NPD). Overall, we found models 1, 2, 8, and 7 to yield the 4 worst fits to the functional connectivity (figure 7D). None of the models tested were able to reproduce the backwards connections from either GPe or STN → M2. The top 4 models (models 6, 5, 3, and 4 respectively) all required the inclusion of the hyperdirect connection,
whilst the high accuracy yielded by model 5 demonstrates a mechanism that can reproduce the observed data features without induction of the STN → GPe feedback, with a beta oscillation that is generated in the cortex. This model however required a larger deviation from the prior density than those including the subthalamic projection (model 4 and 6) as indicated in figure 7E.

From these data it is clear that that: a) serial propagation alone is not enough to well explain the data; and b) the hyperdirect pathway is required for good fits. The smaller divergence of models 6 compared to 5 suggests that a hyperdirect interaction with the STN/GPe subcircuit is the most parsimonious explanation for the observed data. Comparison of models 8 and 6 suggests that a cortically generated beta is also most likely, and that the inclusion of two beta sources in model 8 in motor cortex and the STN/GPe subcircuit acts to reduce the accuracy of optimized models. This finding may suggest an incompatibility of two mechanisms of beta generation.

4 Discussion

4.1 Discrepancy Between Structural Connectivity and Functional Connectivity

In a previous study we examined the directed functional connectivity of the cortico-basal-ganglia network using NPD (West et al. 2018). This method infers the directedness of correlations between neural signals from their respective lag (whilst correcting for signal autocorrelations). In this chapter, we have identified particular issues through making naïve inferences of structural connectivity from the directed FC alone especially in the cases where there is reciprocity in the network. NPD appears to work well for recovery of hierarchical or serial propagation such as in the models figure 7, implying that inference of anatomical pathways such as the indirect pathway of the basal ganglia may be well estimated. However, we find that introduction of parallel routing via the hyperdirect pathway can confound estimates, yielding spurious connections such as the STR → M2 found for several models.

In many cases the NPD reports reverse directionality when it is structurally (as parameterized in model connectivity) in the forward direction (and vice versa). For example, in figure 6, in which models with purely serial flow are simulated (model 1, 3, and 5) we see reverse NPD (e.g. GPe → STR) where there is none, and even purely hierarchical models can generate data that looks in some part reciprocal. However, the spurious NPD is often low magnitude, and broadband – note the failure to reproduce the feedback of GPe or STN to M2 in any of the models. It is likely the case that conditioned estimates of FC will help clear up some of these false detections that arise due to common drive.

The most significant example of mismatch between structural and functional connectivity is manifest in the simulations of the STN/GPe circuit in isolation (figure 3). In this case, the reciprocal connectivity is designed to give rise to beta oscillations. However, the NPD shows a strong asymmetry despite the
relatively close strengths of the respective connections. In the autonomous case we find that pallidal drive (inhibition) seems to dominate in the NPD. Interestingly, introduction of cortical projections in figure 5, appears to flip this relationship to favour the STN → GPe NPD. The signature broadband asymmetric NPD strongly resembles that reported in West et al. (2018) where we suggested that the asymmetrical FC was evidence against the STN/GPe beta hypothesis. The results presented here suggest that this conclusion is not valid and that the observed spectra are precisely the type that arise when modelling the circuit.

Altogether these findings strengthen the argument for the adoption of model-based estimation of connectivity in approaches such as DCM and related methods such as the one taken here, by demonstrating that the complexities inherent in actual neural transmission are likely to confound most FC metrics. Thus, for a robust interpretation of the statistical signatures manifest in FC metrics it is necessary to propose and test causal models of the observed data, and then make inference of the actual “effective” connectivity through comparison of the models’ respective performances.

### 4.2 Critical Transitions to Beta Rhythms

We are interested in whether it is possible to ascertain the proximity of a system to a critical transition point because a) these states have been shown to facilitate optimal computational properties (Kinouchi and Copelli 2006; Shew et al. 2009); and b) they can be indicative of the propensity for the system to enter into a pathological regime (Park et al. 2011). This is of relevance to PD, as the finding of excessive beta band activity may imply an increased stability of the dynamical states associated with the pathology and lead to the subsequent changes in the properties of transient events such as beta bursts (e.g. Tinkhauser et al. 2017). In figures 3E and F, and figure 4 we investigated the parameterization of the STN/GPe system as it enters into an oscillatory state.

We demonstrated that the transition with respect to the connectivity parameters is abrupt but organized in such a way that it depends upon the ratio of excitatory and inhibitory drives. The stability of the system to perturbation was estimated at the approach to the transition, where we found that there was a zero-crossing of the largest Lyapunov exponent approximately at the onset of beta. We next asked whether it was possible, without access to the state equations, to infer the proximity of the system to the critical point using statistical estimators. Extended persistence of the autocorrelation of a system’s time evolution is well known to be a hallmark of critical behaviour (Scheffer et al. 2009). Previously, Aburn et al. (2012) have shown that a coupled neural mass (such as the type presented here) exhibits a super-critical Hopf bifurcation and that the system shows extended autocorrelation upon its approach. In our simulations, we use DFA (Peng et al. 1995) for amplitude fluctuations (Linkenkaer-Hansen et al. 2001) to estimate the Hurst exponent $H$, a measure of signal persistence. We fail to demonstrate an increase in $H$ at the onset of the transition, but instead show that the fluctuations are better fit by a
power-law on the approach to the transition. The exact reasons for why DFA exponents do not work well in the models presented here is currently unclear.

The relationship between the population time constants of the STN and GPe with respect to the onset of beta rhythms is less straightforward (figure 3F and 2nd column of figure 4). We show that there is an initial onset of synchrony between the populations at a certain threshold, however, following this there are a series of ridges in which the system may be parameterized in and out of beta. It is interesting that the ABC inference of parameters of the system estimated both connection strengths as well as time constants that were situated close to the onset of beta oscillation. This finding is in line with Rubchinsky et al. (2012) in which models that best reproduce empirical dynamics are positioned at the transition between coherent and incoherent states. Interestingly, work from Hohlefeld et al. (2012) has suggested that long-range temporal correlations in the STN are increased in patients with Levodopa and report scaling exponents in a similar range to those measured in the models presented here. This would suggest that the healthy system moves closer towards the critical point as approach from disordered to more ordered interactions. Barnett and colleagues have demonstrated that optimal transfer of information in fact occurs in this region, approaching but not directly at the critical point (Barnett et al. 2013). In future work it would be interesting to investigate whether the estimation of model parameters from dopamine intact animals can also predict a positioning of the system closer to the transition to beta.

4.3 Importance of the STN/GPe Circuit

The extensive modelling of the subcircuit formed by the STN and GPe demonstrates its importance in generating the observed patterns of FC (figure 3). The strong anatomical connectivity of these structures has identified them as a strong candidate for the generation of beta rhythms in the BG (Bevan et al. 2002). In our first simulations presented in figure 3, we demonstrate that the STN/GPe circuit can be parameterized to yield beta oscillations independently of inputs from the rest of the network. We demonstrate that the potential for this network to oscillate arises in a region of parameter space where excitation and inhibition are asymmetric such that one must dominate. This finding has also been found in generators of cortical rhythms via the PING (pyramidal-interneuron-network-gamma) mechanism (Tiesinga and Sejnowski 2009).

Furthermore, we find that there is a complex relationship between the time constants of the two populations and demonstrate multiple points of transition to and from beta activity. From the parameter inversion we suggest that subthalamic excitation is an order of magnitude faster than that of the pallidal inhibition – a situation that is known to favour induction of beta/gamma range activity in neuronal models of rhythmic activity in excitation-inhibition circuits (Brunel and Wang 2003). Furthermore, inversion suggests that in the case of the 6-OHDA lesioned network, subthalamic transmission is the strongest. This finding is well explained by the dopamine dependent pre- and post-synaptic suppression of subthalamic projections via the D2-like and D4-like receptors respectively (Hernández et al. 2006).
When investigating more complete models of the basal ganglia that incorporate the cortex and/or indirect pathway (figure 6 and 7) we demonstrate, using model selection, that including the reciprocal connection from STN to GPe can result in the most accurately fitting models, especially when parameterized to generate $\beta_1$ rhythms. However, models for which $\beta_1$ generating priors are included in both the motor cortex and GPe/STN generally were some of the worst performing models (figure 7; models 7 and 8) suggesting that the two mechanisms may be incompatible. Models that lacked reciprocal connections required the motor cortex to be parameterized to states that can generate $\beta_1$ oscillations. Work from Tachibana et al. (2011) has demonstrated that subcortical $\beta_1$ is abolished when either of the connections between STN/GPe are removed, implying that the activity is not simply a transmission of cortically generated activity.

### 4.4 Role of the Hyperdirect Projection

The hyperdirect pathway from cortex to STN is suggested to have a number of functionally important roles in the network (Nambu et al. 2002; Frank et al. 2007). In chapter III, we suggested that the hyperdirect pathway is overactive in the dopamine depleted state and that subthalamic return to the cortex was also enhanced. Using the same data here, we reiterate the importance of including the hyperdirect connections in models of the observed functional connectivity. Models without this connection generally provide the weakest fits to the data (models 4 and 5 in figure 6; and models 1, 2, and 7 in figure 7). Inspection of model fits suggests that the hyperdirect pathway is important for the injection of cortically generated $\beta_1$ rhythms into the STN. This is in agreement with the findings in West et al. (2018) where we found that partializing the indirect pathway left connectivity between STN and motor cortex in the $\beta_1$ range only.

Investigation of the role of the hyperdirect pathway in shaping STN/GPE generated beta in figure 5E illustrates that an increase in strength of the M2 $\rightarrow$ STN connection can act to desynchronize STN and GPe. This effect is particularly apparent in the inferred system whose parameters are close to the transition to beta. In this state it is easy to envisage how small changes in the firing rate of cortical projections may tip the system in and out of beta synchrony. This finding is in line with recent evidence indicating that both mice and primate models of PD exhibit a diminution in the transmission strength of the hyperdirect pathway (Mathai et al. 2015; Chu et al. 2017) but is discordant with the suggestions of chapter II, and others in the literature that excessive hyperdirect input is pathological (Moran et al. 2011; Pavlides et al. 2015; West et al. 2018). It is likely that the story is more complicated, with abnormal STN/GPe transmission setting up the conditions that facilitate M2/STN synchronization without strengthening input (for example see Baufreton et al. 2005).
4.5 Limitations of the Model and Optimization Scheme

In the models investigated we have not explicitly examined the role of thalamo-cortical feedback or the direct pathway. Recordings from neither the internal segment of the globus pallidus (GPI; the main BG output nuclei) nor the thalamus were made in the experiment presented here and so estimates of the autospectra and FC would need to be inferred from the other observed states. This provides a challenge to the inference of parameters and needs proper validation using simulated data. We have previously shown feedback from the BG to be accentuated during dopamine depletion and it is likely this additional modelling will add additional explanatory power beyond the inferences laid out in this work. Furthermore, additional work should be done in order to infer the changes that occur between the control and lesioned animals. This can be done by modelling the systems as identical but under the influence of a secondary set of “modulatory” parameters that change between experimental conditions, in a way similar to that of van Wijk et al. (2018).

The models presented are typically underdetermined so finding a relevant solution is a challenge for the optimization scheme and subsequent model comparison. This problem is aided by the specification of prior beliefs concerning the parameters, which effectively acts to constrain the solutions to those within a range of parameter space that we believe to be reasonable. Furthermore, we augment the optimization through the estimation of parameter covariances, a factor which we demonstrate to reduce the effective rank of the parameters to be optimized, coalescing them into correlated modes. In the case of disparate models that achieve similar bounds of accuracy, the judgement of plausibility hinges predominantly on the deviation of the models from our prior beliefs (as estimated in the KL divergence). This problem can be rectified, at least in part, by increasing the degree to which the models may be informed by data. Inclusion of alternative data features such as statistics of transient behaviour such as bursting may help in better determination of the relevant solutions.

4.6 Conclusions

Overall, we provide a novel approach to inference of the parameters of neural networks from experimental data that explicitly incorporates delayed transmission and stochasticity. We present results which facilitate the mechanistic interpretation of the extensive FC analyses previously reported in West et al. (2018). Our findings illustrate the discrepancies between structural and functional estimates of connectivity and support the notion that model based methods are necessary for proper inference of system connectivity. This work strengthens the view of the importance of the STN/GPe circuit as a subcortical source of pathological beta oscillations and examines the conditions required for their generation. Moreover, we demonstrate that the hyperdirect connection is necessary for synthesis of the experimentally observed data features but its influence on the STN/GPe circuit is likely to be suppressive of beta.
Chapter IV: Inferring Mechanisms of the Generators of Beta Rhythms

T.O. West (2018): Dysregulation of Synchronized Brain Oscillations in Parkinson’s Disease
Chapter IV: Inferring Mechanisms of the Generators of Beta Rhythms
Chapter V:

Cortico-Subthalamic Phase Coupling and Modulation of Beta Bursting in Parkinson’s Disease
1 Introduction

In the motor system, the synchronization of the activity of pools of motor neurons as well as larger distributed neural ensembles has been demonstrated to be of functional importance to behaviour (Conway et al. 1995; Salenius et al. 1997; Farmer 1998; Baker et al. 1999; van Wijk et al. 2012). However, in Parkinson’s disease (PD), excessive beta band (14-20 Hz) oscillations in the basal ganglia are associated with chronic subcortical dopamine depletion and the resulting motor impairments (Brown et al. 2002; Kühn et al. 2006; Ray et al. 2008; Pogosyan et al. 2009). Multiple hypotheses concerning the origins of pathological beta oscillations posit that plastic changes in the circuits that form the cortico-basal ganglia-thalamic relay are involved. Recent evidence from rodents has supported a mechanism of subthalamic “short-circuiting” whereby increased feedback from the STN to motor cortex engages the network into a state of pathological resonance (West et al. 2017) a mechanism supported by a body of theoretical work (Guo and Rubin 2011; Pavlides et al. 2015).

In patients with PD, it has been previously demonstrated with magnetoencephalography (MEG) that functional connectivity between the motor cortex and STN occurs predominantly in the high beta band (24-34 Hz) with a response to L-DOPA that is largely unclear: either showing weak enhancement (Supplementary Motor Area (SMA); Litvak et al. 2011) or suppression (M1; Hirschmann et al. 2013). A mechanism of increased and pathological cortico-subthalamic resonance in untreated compared to treated PD would suggest: a) an overall increase in coherence between STN and cortex; b) correlated fluctuations of beta amplitude between these regions; c) and an increased directional connectivity from the STN returning to cortex. Moreover, if synchronization between the two regions is a precondition for beta amplification then the relative phase of the two populations sets a globally accessible ‘coordination’ parameter (Tognoli and Kelso 2014) that modulates local amplitude fluctuations. Thus, it should be possible to determine local changes in the ensemble activity of the nuclei as recorded in the oscillatory power of local field potential from the relative phase between STN and cortex.

Spontaneous activity in the brain forms the substrate for everyday cognition. The transient engagement and dissolution of distributed neural networks is thought to facilitate the integration of sensorimotor information (Gray et al. 1989; Roelfsema et al. 1997; Engel and Singer 2001) over widely disparate brain regions (Tononi et al. 1998; Bressler and Kelso 2001; Varela et al. 2001; Deco et al. 2015). Constant reconfiguration of brain networks allows for shifts in and out of states that will promote neural synchrony (Womelsdorf et al. 2007). Specifically, subthalamo-pallidal phase locking has been demonstrated to modulate beta activity, with relative phase of the nuclei setting the conditions for enhancement or suppression of rhythmic activity (Cagnan et al. 2015).

A better understanding of the coordinated activity of the cortex and basal ganglia leading to pathological activity is vital for the potential development of improved strategies for closed loop
stimulation (Little and Brown 2012; Holt et al. 2016; Cagnan et al. 2017). Phasic stimulation via deep brain electrodes has been demonstrated to be effective in disrupting pathological activity (Little et al. 2013; Tinkhauser et al. 2017a).

In this study we investigate the time resolved dynamics of beta activity in the STN. Previous work has demonstrated that beta activity can be segregated into transient “bursts” of activity that are modulated by movement (Feingold et al. 2015), L-DOPA (Tinkhauser et al. 2017b) and deep brain stimulation (DBS; Tinkhauser et al. 2017a). In this work we look specifically at how the properties of beta bursts such as amplitude and duration are related to the phase coupling between the STN and motor cortex. We posit that dopamine depletion results in a reordering of phase interactions between STN and motor cortex that results in a regime in which subcortical beta synchrony is promoted.

2 Methods

2.1 Experimental Data

This chapter uses data taken from a study of Parkinson’s patients (n = 10) who have undergone surgery for DBS. We use simultaneous recorded local field potentials (LFPs) from the STN, and whole head MEG. For full details of the patient cohort, surgery, post-operative localization, and recording procedures, please see part 2.1 of the methods section of this thesis.

2.2 Data Pre-processing, Analysis and Statistics

2.2.1 Software for Data Analysis and Statistics

Data was analysed using a set of proprietary scripts written in MATLAB R2017a (The Mathworks, Nantucket, MA, USA). Analysis and statistics utilized routines from the Fieldtrip software package (Oostenveld et al. 2011; http://www.fieldtriptoolbox.org/) and SPM 12.3 (http://www.fil.ion.ucl.ac.uk/spm/). Nonparametric directionality was implemented using the Neurospec toolbox (http://www.neurospec.org/). Circular statistics were computed using scripts from the CircStat toolbox (Berens 2009; http://bethgelab.org/software/circstat/). All scripts for the analyses presented in this report can be found as a Github repository: https://github.com/twestWTCN/Cortical_Parkinsons_Networks. A full list of toolboxes used can be found in the supplementary information.

2.2.2 Data Preprocessing

Data preprocessing was performed in two passes: first data was treated continuously, and then was epoched for analyses that averaged over windows (e.g. computing a periodogram). Firstly, raw data was read into Fieldtrip from the native CTF recording format. Data was truncated by ~1s at either ends following visual inspection to remove artefacts originating from initial movements and ensure
that head localization and recording gain was stable. Missing data in the recordings was replaced by linear interpolation. Similarly, large jumps in the recordings, occurring due to amplifier switching or transient fluctuations in the recording apparatus, were identified by Z-score thresholding of the rectified signal in order to find jumps exceeding 6 standard deviations, and missing data was interpolated. Data were down sampled (with low-pass filter to avoid aliasing) to a rate of 256 Hz, and then were bandpass filtered (Butterworth, two-pass, filter order optimized) in 4-98 Hz. All data was notch filtered at 50 Hz to remove line noise artefacts. Periodogram estimates were made by averaging over non-overlapping windows each 1.5s in duration.

2.2.3 Localization of Coherent Sources and Construction of Virtual Electrodes

For this study we used regions of interest (ROIs) in the cortex that were found to be functionally connected with the subthalamic nucleus. This was determined by the identification of peaks in the spatial distribution of STN/cortex coherence computed using Dynamic Imaging of Coherent sources (DICS, Gross et al. 2001). These ROIs were originally reported in Litvak et al. (2011) but we briefly outline the process here. DICS is a beamformer method that is based on the linear projection of sensor data to the source level using a spatial filter computed from the lead field of a topological source model. The beamformer solution is constrained upon minimization of the local cross-spectral density and thus requires sensor level data to be transferred into the frequency domain. DICS allows for a coherence value to be computed between a reference signal (in our case the STN LFPs) and each vertex of a 3D model representing potential sources of activity in the brain (Gross et al. 2001). In this paper we focus upon alpha and high beta connectivity, as these have been previously demonstrated by Litvak et al. to be the frequency band in which coherent cortical networks form with the STN during the resting state.

DICS was run for each subject using a single-shell head model (Nolte et al. 2004) that is based on an canonical inner skull mesh that is warped to the subject’s pre-operative MRI. Co-registration between the native MRI coordinates and the CTF system used for MEG localization was achieved by aligning three fiducial points: nasion, left and right pre-auricular points. Regions of interest (ROIs) were identified by taking the peaks of the resulting DICS images. Overall, we used identical ROIs to that reported in Litvak et al. (2011), in supplementary motor area (SMA: 18, -6, 58 MNI). This source was found to be maximally coherent in beta band. ROIs were taken ipsilateral to the STN.

As the DICS beamformer operates in the frequency domain we used an additional linearly constrained minimum variance (LCMV) beamformer (Van Veen and Buckley 1988) to compute a time domain filter for computation of virtual electrodes at the ROI identified with the DICS. The LCMV beamformer was computed with the same forward model but optimized using the cross-covariance matrix rather than the cross-spectral density. The leadfield at each vertex of the source model contains a dipole with orientation along the 3 cardinal axes; we combined these orientations by applying a
singular value decomposition in order to make a linear projection along one vector corresponding to
the dominant dipole orientation. As the ROIs chosen were taken from group averaged images returned
by the DICS we computed virtual electrodes for all vertices falling within a radius of 1.5cm of the
specified ROI for each hemisphere to allow for individual differences in spatial distributions. We then
selected one channel that had the maximum beta power within the radius surrounding the ROI.

Coherences were computed between this signal and each channel of the DBS electrode. We selected
the virtual source and DBS electrode channel pair that had the largest valued peak in the coherence for
the respective frequency band. If no sufficiently strong coherence (< 0.1 units of coherence) within
this band was present in any of the recordings, then no further analysis for this hemisphere was made.
This yields a possible total of 26 signal pairs (from the SMA and STN) per experimental condition per
source (2 signals x 2 hemisphere x 13 subjects x 2 conditions).

2.2.4 Spectral Analysis and Functional Connectivity

All spectral analyses used multitaper estimates as outlined in the methods section of this thesis. We
estimate either undirected or directed time averaged functional connectivity using magnitude squared
coherence or non-parametric directionality. The formulations of both are outlined in the methods
section.

2.2.5 Analysis of Subthalamic Beta Burst and Cortical Phase Locking

In order to examine the time resolved dynamics of pathological beta burst events in the STN and its
relationship to phase locked activity in the cortex we adapted a mixture of approaches that have
previously been adopted to identify transient amplitude dynamics (Tinkhauser et al. 2017b) and its
relationship to phase locking (Cagnan et al. 2015).

Specifically, we make a time resolved decomposition of both the amplitude and phase of the signals
measured at the STN and SMA using complex Morlet wavelets. Wavelets provide a method to make a
narrowband estimate of the analytic signal that has shown to be broadly equivalent to the narrowband
Hilbert transform (Le Van Quyen et al. 2001) but have the useful quality that the bandwidth of the
wavelet scales with the frequency of interest, ensuring optimal time-frequency resolution. In order to
ensure differences in signal power were not affected by recording gain, we normalized the recordings
to zero mean and unit variance prior to the wavelet decomposition. We implemented the wavelets
using the ‘ft_specest_wavelet’ method, using a width of 11 cycles with a cut-off of ±5 stds on the
Gaussian envelope of the wavelets. At 22 Hz this yields a bandwidth of 4 Hz (2 x frequency /
bandwidth).

We compute the amplitude of the wavelet as the modulus, and the phase as the argument. For
amplitude dynamics (beta-bursts) we take the frequency at which there is peak power in STN across
the whole beta range (24-34 Hz). Similarly, for computation of phase dynamics we choose the
frequency at which there is maximal coherence in the beta range. Beta bursts were detected by setting a threshold on the amplitude. In order to select this threshold, we concatenated the data ON and OFF for each hemisphere and then chose the 75th percentile of the amplitude distribution. This threshold is essentially arbitrary but aims to provide an upper estimate of the tails of the amplitude distribution. Previous work has demonstrated that in similar analyses the effects of experimental conditions upon burst properties are relatively robust to changes in the threshold (Tinkhauser et al. 2017a). In this study we also investigate how the effects of L-DOPA may change over differing definitions of the beta bursts. We estimate the length of the bursts as the number of samples for which the amplitude consecutively exceeds the threshold. We define the burst amplitude as the mean amplitude over this series of points. In order to remove small threshold crossings occurring due to noise, we set a minimum burst length of 4 periods of the lower bound of the wavelet bandwidth and remove any bursts below this length.

Within each burst we examine the properties of phase locking between the STN and the source in the SMA that is known a priori to be coherent in the beta range (as determined using DICS). In order to do this, we estimate the relative phase at each time step: $\Delta \phi_{ij} = \phi_i - \phi_j$. In order to determine the degree of phase consistency between the signals we use the pairwise-phase consistency (PPC) which has been demonstrated to be a measure of phase synchronization equivalent to the more commonly used phase locking value (Lachaux et al. 1999; Hurtado et al. 2005). The PLV is a biased estimator, yielding spuriously high estimates for low sample sizes. The PPC is asymptotically equivalent to the population statistic of the squared PLV (Vinck et al. 2010) but does not suffer from sample size bias which makes it well suited for investigating phase locking within bursts of variable length. For illustration of the general dynamics independent of the beta burst amplitudes we use PPC computed within a sliding window (1 s duration, 99% overlap). The PPC is computed from $N$ samples of the two evolutions of the phases of signals $i$ and $j$:

$$\psi = \frac{2}{N(N-1)} \sum_{j=1}^{N-1} \sum_{k=j+1}^{N} \cos(\phi_j) \cos(\phi_i) + \sin(\phi_j) \sin(\phi_i).$$

The PPC population statistic is equivalent to the squared PLV. For a full derivation and validation of the method please see Vinck et al. (2010). We also compute the average relative phase for each burst computed as the circular mean of the relative phases within the window (using the CircStats toolbox). When comparing PPC against burst statistics we report the distribution of within burst phase locking as the percentage difference of the $i^{th}$ burst’s PPC from the sample median:

$$\% \Delta PPC = \frac{\psi - \bar{\psi}}{\bar{\psi}} \times 100.$$ 

In the results we also present distributions of both the absolute amplitude and the percentage change in amplitude of the $i^{th}$ burst from the sample median:
%ΔA = \frac{A_i - \bar{A}}{A} \times 100.

In this way we normalize the amplitudes to remove effects arising from the difference in amplitude alone. When reporting the frequency of bursts we convert bin counts to probabilities (burst.s\(^{-1}\)) by dividing by the total time of the recording (e.g. 6 bursts in 60 s has a frequency of 0.1 burst.s\(^{-1}\)).

### 2.2.6 Data Surrogates

In order to ascertain whether any structure revealed is merely an artefact of the analysis techniques we constructed two sets of surrogates that either a) maintained variance but destroyed temporal structure; or b) maintained amplitude fluctuations but removed any structure in phase. The first and most liberal surrogate was performed by random permutation of the samples of the original time series data. The second, more conservative surrogate, was computed by taking the Fourier transform of the signal and resampling the phase without replacement, maintain amplitude coefficients, and then returning to the time domain using the inverse Fourier transform (Hurtado et al. 2004; Cagnan et al. 2015). These surrogates were computed for each recording and the distributions compared directly. We used the first type of surrogate to establish the significance of statistics quantifying amplitude fluctuations (bursts) as the permutation will destroy any structure in the beta envelopes. We use the second type of surrogate when investigating the relationship between beta bursting and the phase locking between signals. This is because the phase randomization maintains beta burst properties whilst shuffling the phase relationships between signals. We indicate the permutation surrogate (type (a)) as perm\(_{\text{shuff}}\); and the phase randomized surrogate (type (b)) as perm\(_{\phi}\).

### 2.2.7 Statistical Inference from Experimental Manipulations

In order to test for the effect of experimental conditions upon continuous statistics such as power or coherence we used cluster-based permutation testing which avoids introducing bias through the prior specification of frequency bands for testing (Maris and Oostenveld 2007). The method is described in full in the methods chapter of this thesis.

We used a cluster-forming threshold of P < 0.05 and a permutation test threshold at p < 0.025 (as the test is two-sided). The number of permutations was set to 5000 which tenders a lowest possible P-value equal to 0.0004. Cluster statistics were computed using the relevant routines in the Fieldtrip toolbox.

Comparisons between distributions were computed using either two sample t-tests at the subject level or repeated measures ANOVA at the group level. For pairwise comparisons within bins we used paired t-tests, with a significance threshold (P < 0.05) adjusted for multiple comparisons using the Benjamini-Hochberg procedure to control the false discovery rate (FDR). In order to test for correlations between amplitude, duration and length we computed non-parametric statistics for
correlation (Spearman’s rank correlation), and then if significant performed a least square estimate for linear regression (with zero-intercept) and report $R^2$ and regression coefficients.

In order to correlate with clinical scores we take assessment of patients’ motor performance using the total score in the Unified Parkinson's Disease Rating Scale (UPDRS) part III and also separately the sum of the lateralized bradykinesia and rigidity scores, taken contralateral to the STN from which the LFPs were recorded. We computed correlations again using Spearman’s rank correlation. Because of the low number of samples available for inference we also employed a robust regression that negates the influence of outliers using a bisquare weighting of regression errors (Holland and Welsch 1977). In the case that the Spearman correlation yielded a significant test value we then also show the parameters of both the robust and standard linear regressions. Correlations with clinical improvement were also made by taking the difference in scores ON and OFF L-DOPA and performing the same tests for rank correlation.

2.3 General Approach

This work investigates the nature of 1) amplitude fluctuations in beta frequency oscillations recorded from the STN; and 2) their relationship to coupling with activity recorded from the SMA in the cortex. We will take the approach of first summarising activities using the time averaged statistics such as power or coherence, and then subsequently decomposing the constituent signals in the time domain to gain further insight into how the exact patterning and properties of these phenomena change in response to L-DOPA. In the first half of the results we examine amplitude fluctuations in the STN, first by analysing spectral power and then investigation of the bursts’ amplitudes and durations that give rise to the time averaged statistic. In the second, the influence of signal coupling with the SMA is introduced by looking at the time averaged coherence and non-parametric directionality, and subsequent investigation of how the time varying coupling between these structures impacts the previously described amplitude fluctuations.

3 Results

3.1 Analysis of STN Amplitude Changes

3.1.1 Power Spectra

We computed power spectra across the cohort of subjects recorded. Analysis for an example subject as well as the group level results, are shown in figure 1. Examination of the spectra from the MEG beamformed sources at SMA shows a typical 1/f profile. Peaks can be seen in individual spectra (figure 1A) but at the group level there is a weak inflection from background in the beta range (figure 1C). Group averaged spectra are comparable to that found in Litvak et al. (2011). STN power spectra (figure 1B and D) are typical of that presented in previous studies (Brown et al. 2001; Kühn et al.
There is a clear peak in the low beta range (14-21 Hz) that is suppressed by L-DOPA (cluster statistic (-); 12-23 Hz, $P = 0.018$). There is also a peak at high beta (21-30 Hz).

Figure 1 – Spectral analysis of signals recorded at the supplementary motor area (SMA) and subthalamic nucleus (STN) when ON (red) and OFF (blue) L-DOPA for an example subject (top row) and at the group level (bottom row). Subject specific sources were determined as the vertex of the source model with maximum beta frequency power within a 1.5 cm radius of the group level ROI. (A) Power spectra of the MEG signal source localized to the SMA. (B) Power spectra of the local field potentials recorded from DBS electrodes implanted to the STN. (C) Same as (A), but for group level. (D) Same as (B), but for group level. Shaded bounds indicate ±1 S.E.M. Bold bars above spectra indicate regions with significant experimental effect as indicated by t-test cluster statistics.

although this signal is unchanged by L-DOPA. Cluster-statistics also detected a positive increase (following L-DOPA) in high beta/gamma rhythms (cluster statistic (+); 31-48 Hz, $P = 0.001$). This effect may be an artefact of the normalization of spectra as the effect is in the roll-off of the spectra and not of a distinct spectral peak. We next tested for the correlation between the maximum beta power within each hemisphere and the total UPDRS.
3.1.2 Burst Statistics in an Example Subject

We next present results from the analysis of beta bursts as determined by the process detailed in the methods and illustrated figure 2. In figure 2 we show an analysis from an example subject.

Figure 2 – Example of the wavelet analysis and subsequent identification of beta bursting, and transient synchronization in a single subject when OFF (blue; 1st column) and OFF (red; 2nd column) L-DOPA. In order to approximate the band restricted signal, electrophysiological recordings were decomposed using Morlet wavelets with a bandwidth of 8 Hz and equivalent Gaussian window width of 5 cycles of the centre frequency. (A and B) The instantaneous amplitude was then computed by taking the modulus of the Hilbert of the wavelet decomposed signal. The 75% percentile of the data concatenated across conditions (black dashed line) was then used as the threshold for discriminating burst events. (C and D) In order to illustrate the time evolved phase locking for this figure, the bandlimited signal was divided into sliding windows (1s duration, 99% overlap) and the instantaneous phase computed as the argument of the Hilbert transform. We then compute the PPC within each window as a measure of time evolving degree of phase locking (1 equal to full phase consistency). In the actual analyses presented in the results, analyses use time windows determined by suprathreshold burst events (rather than sliding windows), and compute the PPC within these. (E and F) Same as above but zoomed to yield a 10s example of the time evolution of the signals (PPC given by dashed line; beta amplitude by bold line).

In the time evolving beta amplitude (figure 3A). Comparing figure 2A and B, there is a clear difference between OFF and ON L-DOPA with a visibly higher proportion of the beta amplitude.
exceeding threshold (75% percentile) in the OFF recording. In contrast, when looking at the time evolving phase locking (as estimated using the PPC) between STN and SMA the difference between conditions is not clear but shows fluctuations in magnitude as the two brain regions transiently engage and disengage in phase synchronization. When plot together in figures 2E and F, it can be seen that both the STN beta

![Image of Figure 3 - Example analysis of STN beta bursts from a single subject when either ON (red) or OFF (blue) L-DOPA. (A) Histogram of the distribution of burst durations (ms). Bin frequencies are normalized by the recording length to give units of burst.min⁻¹. Statistics above chart indicate outcome from t-test for difference in burst durations ON vs OFF L-DOPA. (B) Same as (A) but for burst amplitude. (C) Scatter plot of the burst amplitudes vs burst duration. Regressions are shown with intercept fixed at the origin. (D) Bar chart of the burst durations binned by their amplitudes. Y-axis values are weighted to account for frequency within each bin. (E) Same as (D) but for burst amplitudes binned by duration. Error bars indicate ±1 S.E.M.](image-url)
amplitude and the STN/SMA phase locking show temporal variation that appears to be correlated (to some degree) in time. We will return to the significance of these fluctuations in phase coupling in the second part of the results.

Figure 4 – Group level analysis of STN beta bursts from all subjects recorded when either ON (red) or OFF (blue) L-DOPA. Surrogates (shuffled) are also shown alongside data (grey). (A) Histogram of the distribution of the log_{10} burst durations (ms). Bin frequencies are normalized by the recording length to give units of burst.min^{-1}. Statistics above chart indicate outcome from t-test of difference in mean burst duration ON and OFF. (B) Same as (A) but for burst amplitudes. (C) Bar chart of the burst durations binned by their amplitudes. Y-axis values are weighted to account for frequency within each bin. (E) Same as (D) but for burst amplitudes binned by duration. Significance bars indicate significant Wilcoxon test ON vs OFF within each bin. P-values are FDR corrected for multiple comparisons. Error bars indicate ±1 S.E.M.
Next, we examine the distributions of the STN beta burst amplitudes and durations. An analysis from an example subject is presented in figure 3. Figure 3A presents the distribution of the burst durations when ON and OFF L-DOPA. Whilst it can be seen that the majority of bursts are short (< 350 ms), bursts recorded following the withdrawal of L-DOPA have an increased probability of being longer in duration. When testing for differences in distributions we found that beta bursts in the OFF state were longer on average by 107ms (figure 3A; Wilcoxon (+); 107 [53 161], P<0.001). Similarly, OFF state bursts also showed a propensity to be higher in amplitude (figure 4B; Wilcoxon (+): 2.9 [1.0 4.7], P<0.001). Subsequently, we investigated the relationship between burst amplitude and duration.

From figure 3C, it is clear that there is a strong relationship between burst length and amplitude, an observation confirmed by correlation analysis (OFF, Spearman’s R = 0.49, P<0.001; ON, Spearman’s R = 0.49, P<0.001). When looking at the burst durations binned by their amplitude (figure 3D) we find that there is a tendency for bursts of matched duration (ON and OFF) to exhibit larger amplitudes when patients were OFF L-DOPA. Similarly, when looking at the durations of bursts binned by their amplitudes we find that on average bursts exhibit larger amplitudes across almost all scales of duration. This is most apparent for bursts >450ms where bursts in the ON condition show some reduction in amplitude, whereas in the OFF they remain of high amplitude. Furthermore, there is a marked occurrence of long duration, high amplitude events that are not seen at all when subjects are

![Figure 5](image-url)
in ON state having self-administered L-DOPA.

3.1.3 Group Level Statistics of Burst Properties

To ascertain whether the results found within single subjects were representative of the entire clinical group, we conducted an analysis of the results of the burst analysis pooled across all the recordings. The results are summarised in figure 4. To determine whether the burst statistics found in the experimental data contained structure that would occur beyond random chance we compare the data against sample matched surrogates that were derived from the original data samples. For the results presented here we use the permutation surrogates (indicated by Surr_perm).

In figure 4A, we present the group level burst durations that have been log transformed. These results show that the distributions of the burst durations are well fit by a log normal distribution, and we report the statistics in log_{10} units. Statistical testing for differences in the distributions of beta burst durations demonstrate that they are: a) longer than expected from the randomized surrogate distribution (OFF-Surr., Wilcoxon (+), 0.19 [0.18 0.21], P<0.001) and that bursts are ~30% longer when patients are OFF L-DOPA (OFF-ON, Wilcoxon (+), 0.11 [0.1 0.12], P < 0.001). Next, we analysed the pooled burst amplitudes (figure 4B) and show that bursts are significantly stronger than the surrogate when OFF (Wilcoxon (+), 0.32 [0.20 0.43], P < 0.001) as well as ON (Wilcoxon (+), 0.20 [0.08 0.33], P = 0.001) L-DOPA. In agreement with the subject level results, there was a significant increase in the burst amplitudes of patients when OFF L-DOPA (Wilcoxon (+), 0.13 [0.11 0.14], P = 0.001).

Next, bursts were binned by their amplitudes and their mean durations computed (figure 4C). By comparing distributions ON and OFF L-DOPA, it can be seen that bursts recorded following dopamine withdrawal show: 1) a significant decrease in duration for low amplitudes, but 2) show an increased propensity for bursts of above average amplitude to be longer than their counterparts in the ON state. Complimentary, when bursts’ mean amplitudes were binned by their durations (figure 4D), results show an increased probability of finding duration bursts and with much higher amplitudes than similarly long bursts recorded in the ON state. The absence of any significant changes between ON and OFF L-DOPA for bursts less than 500ms suggests that it is the long duration bursts that are pathological, as bursts >500ms consistently show significant increases in mean amplitude in the OFF state. This may suggest a deficit in some extinguishing mechanism of burst amplitude following L-DOPA withdrawal.

3.1.4 Relationship Between Burst Amplitude and Duration

Figure 3C presents evidence from a single subject that there is a strong relationship between burst duration and amplitude. We next investigated whether this finding was consistent with a group level analysis. For each recording we performed a non-parametric test of correlation (Spearman’s R) as
well as a least squares linear regression (constrained to zero-intercept). The results of this analysis are presented in figure 5. In figure 5A, we show a scatter plot of all bursts’ amplitudes plot against their durations. Subsequently, we plot the regression of the group averaged coefficients for each experimental condition and surrogate (figure 5A, bold lines). We did not find a significant difference in the linear coefficients between any of the groups. All groups exhibited a regression coefficient of roughly 30 ms.A⁻¹, where A is normalized units of burst amplitude. There is a region where there are large differences between ON and OFF (indicated by the blue shaded circle), specifically for high amplitude, long duration bursts that are predominantly occupied by bursts from the OFF. We see that bursts of similarly long durations are present but are of lower amplitudes.

In figure 5B, we demonstrate that bursts from both ON and OFF recordings followed a strong positive correlation, but that this relationship can be partly reproduced in the time shuffled surrogate. However, the correlation coefficients of the OFF are significantly larger than those computed from its shuffled surrogates (OFF-Surr., Wilcoxon (+), 0.20 [0.07 0.32], P = 0.005). There was a small increase in the correlations OFF versus ON, but the effect was not significant when corrected for multiple comparisons (OFF-ON, Wilcoxon (+), 0.05 [0.00 0.09], P = 0.029).

We observed that whilst there appears to be a linear relationship between burst amplitude and duration, the variance of the duration increases with amplitude, a phenomenon in regression analysis known as heteroscedacity. Several tests exist to determine the existence of heteroscedacity. Here we use White’s test (White 1980) which performs an auxiliary regression on the errors from the principle regression to assess the presence of linearly increasing errors. This statistic is then used to test for differences in coefficients between experimental conditions. The results of the analysis are shown in figure 5C, where it is shown that there are marked differences in the White statistic between conditions indicating a significant shift in the degree to which errors are heteroscedastic. This property is not well reproduced in the shuffled data as indicated by the low test statistic (< 0.1) compared to the actual data. We find that the variance of the OFF distributed bursts increases more strongly with amplitude than for the ON (Wilcoxon (+), 0.12 [0.07 0.17], P < 0.001). The auxiliary regression in the OFF condition is much steeper than in the ON. Examination of the variances of the ON suggests however that the change in variance of the response for ON is nonlinear, as indicated by the abrupt loss of bursts in the region indicated by the blue ellipse.

3.2 Investigating the Influence of Coupling with the SMA

Having analysed in detail the burst statistics of beta activity in the STN, we next introduce the influence of the signal recorded in the SMA. We will first identify the time averaged functional connectivity between the regions, and then using time resolved techniques we will establish the relationship between STN/SMA phase coupling and STN beta burst properties.
3.2.1 Functional Connectivity

Functional connectivity between the STN and SMA was estimated using coherence in order to identify changes that may occur when patients were either ON or OFF L-DOPA (figure 6). In figure 6A and C we show an example of the spectral coherence between STN and SMA in an example subject and at the group level. At both the subject and group levels there is a clear peak in the coherence around 20-30 Hz (high beta). In the pooled group spectra (figure 6B) there is a broadening of the OFF condition coherence to extend to lower frequencies of beta (>14 Hz). However, we found no statistical evidence for modulation of spectral coherence with L-DOPA (cluster statistics; P>0.05). In figure 6C we present analysis of how the coherence relates to clinical impairment. We find there is a significant correlation between the coherence and UPDRS (hemibody scores: Rho = 0.67, P = 0.001; and total scores: Rho = 0.66, P = 0.008). These effects were found to be preserved when outliers were removed using robust correlations. Using partial correlation with beta power we next assessed to what degree the correlations of UPDRS with coherence could be explained by beta power. We found that the correlation was reduced but maintained significance (hemibody scores; Rho_p = 0.56, P = 0.01), with beta power sharing ~18% of the explained UPDRS variance.

3.2.2 Directed Coherence

Coherence is a symmetrical measure, thus in order to determine how directional influences from either the STN or SMA are influenced by L-DOPA, we used NPD to analyse the same data (figure 7). In figure 7A it can be seen that there is a large peak in the cortically leading coherence (SMA → STN) at high beta frequencies similar to those seen in the standard coherence. The cortically leading
coherence is predominant, with only a small peak observable in the reverse direction (STN → SMA). When testing for a difference in coherence following administration of L-DOPA at the group level (figure 7B and E), we find that only the forward component is suppressed (cluster statistic (-): 14-36 Hz, P = 0.019). No significant L-DOPA related modulation of the STN → SMA NPD was found.

We next investigated whether the directed coherence (NPD) could improve prediction of the patient’s clinical state as indicated by their UPDRS. In figure 7C, the magnitude of STN → SMA NPD positively correlates with motor symptom severity (hemibody scores; Spearman’s Rho = 0.65, P = 0.002; and total scores; Spearman’s Rho = 0.65 Rho = 0.60, P = 0.005). In the case of the hemibody scores there is a slightly stronger correlation than that estimates with standard coherence. However, conducting a partial correlation with respect to the undirected coherence demonstrated that there was no significant independent contribution of NPD to the correlation over that of coherence alone (total scores; Partial Rho; Rhoₚ = 0.10, P = 0.678).

![Figure 7](image_url)

**Figure 7** Group level analysis of functional connectivity between signals recorded from STN and SMA in all subjects when either ON (red) and OFF (blue) L-DOPA, and its relation to OFF state motor impairment severity. Motor impairment was assessed using part III of the UPDRS, and hemi-body (lateralized) scores are shown. (A) Magnitude squared coherence between STN and SMA. (B) Forward NPD spectra for directed coherence from SMA to STN. (C) Reverse NPD spectra for directed coherence from STN to SMA. (D) Scatter of peak beta STN/SMA coherence vs OFF hemibody akinesia score. (E) Same as (D) but for SMA to STN NPD. (F) Same as (D) but for STN to SMA NPD. Shaded bounds indicate ±1 S.E.M. Bold bars above spectra indicate regions with significant experimental effect as indicated by t-test cluster statistics. Red lines through scatter plots indicate significant linear regression. Associated Spearman’s R value and associated P-value are shown above. Robust regressions with bisquare weighted errors are also shown (Rₑₒₚ and Pₑₒₚ).
Chapter V: Beta Burst and Cortico-Subthalamic Relative Phase

Figure 8 – Group Level Statistics of Beta Burst Amplitude and their Relationship to STN/SMA Phase Coupling.

Beta burst amplitudes (both absolute, and relative change measures) were binned across degrees of phase coupling and relative phase difference between STN and SMA. Relative phase distributions are recentred per hemisphere to the bin yielding the largest mean value. Surrogate is phase randomized OFF recordings. (A) Percentage change in beta burst amplitude (from median amplitude) versus the percentage difference (from median) phase coupling as estimated using the pairwise phase consistency (PPC). (B) Absolute burst amplitude (a.u.) binned by the relative phase between STN and SMA (degrees). (C) Percentage change in burst amplitude versus relative phase between STN and SMA (degrees). All significance bars indicate significant two-sample t-tests. Only ON and OFF comparisons were tested. P-values are False Discovery Rate corrected. (*) indicates test with P < 0.05 but not surviving FDR correction.
3.2.3 Interaction of STN Beta Burst Dynamics and Time Resolved STN/SMA Phase Coupling

In section 3.2.1 it was demonstrated that there is significant coupling between the STN and the SMA, and in 3.2.2 we provide evidence that the influence of the SMA upon the STN is modulated by dopamine. We next investigate how the time resolved phase coupling between the STN and SMA relates to the properties of STN beta bursting that were described in detail in section 3.1.3. Results from these analyses are shown in figure 8.

First, we investigate how the degree of phase locking relates to the percentage change in burst amplitude. In these analyses, we again use a surrogate but use the phase randomized signal (Surr\_phi), which preserves the amplitude structure of the original signals yet removes structure in the phase relationships between them. We estimate the phase locking within bursts using the PPC (outlined in the methods) computed from the Wavelet phase estimates of the respective signals. In figure 8A the burst amplitudes are binned by the percentage change in their PPC from the sample median (signified in the figures by %Δ) with 0 indicating phase locking at the median. We show that peak burst amplitudes in both conditions occur when phase locking is 30% weaker relative to the sample median, and that burst amplitudes are lowest when the PPC is above average in strength. This is likely related to the findings presented in figure 4D that shows that higher amplitude bursts tend to be longer in duration. Thus, it is likely that longer duration bursts show a decreased degree of phase locking. When comparing between conditions we find that bursts in the OFF recordings show larger amplitudes than expected from the phase randomized surrogate in the range from -85%Δ to 0%Δ within-burst PPC. Most notably we find that compared to the recordings made when patients were ON L-DOPA, burst amplitudes for bins with weak phase coupling are higher in the OFF, testing significant in the two weakest bins of the PPC (%Δ PPC = [-89.57]; Wilcoxon (+), P < 0.010). Furthermore, when looking only at the median bin (0%Δ PPC) we find that burst amplitudes show a larger deviation from the condition average in OFF compared to ON (%Δ PPC = [-89.57]; Wilcoxon (+), P < 0.05 (not corrected)). These results suggest that during the OFF state most high amplitude bursts occur when phase locking with the cortex is low and that beta bursts show less suppression associated with phase locking with the SMA.

Having established the relevance of cortical phase locking to subthalamic beta burst activity, we next ask whether particular phase differences between the STN and SMA shape beta burst amplitudes. In figure 8B and C we show pooled distributions of the burst amplitudes binned by the mean relative phase (between STN and SMA) across the burst. As the peak relative phase changed across recordings, we recentred all distributions to the maximum bin set at 0°. Results show that in the OFF
recordings, amplitudes of bursts found at the centre phase (0°) are roughly double in amplitude of those found in the opposite orientation (~180°). The experimentally derived distributions significantly deviate from the null distribution formed from the phase randomized surrogate. The distribution of Surr\(\phi\) can be broadly described as a uniform distribution with a small peak at the centre- an artefact of the recentring of distributions that leads to a peak even with random data. This finding highlights the importance of construction of appropriate surrogate data and the implications of the synthesis of structured phase distributions from randomized data will be examined in the discussion. In figure 8C, the amplitude is normalized by the median within each conditions and differences ON and OFF become more apparent. Results show that phases precluding the peak of the distribution (at 0°) show an amplification in the OFF compared to ON distributions (OFF-ON, relative phase bin centre -51°, Wilcoxon (+), 1.68 [0.78 2.60], P = 0.001). This finding of amplification in the phases precluding the centre bin may relate to the finding in figure 7B, which suggest that cortically leading signals are strengthened when patients are OFF L-DOPA.

Inspection of the distributions in figure 8 suggest that both the absolute and percentage change in amplitude follow a circular normal (Von Mises) distribution. To test this, we performed a nonlinear
least squares regression of each hemisphere using the percentage change in burst amplitude and relative phase as variables. In figure 9 the group level results from this analysis may be seen. We show that the best fit to the Von Mises is found using the distributions from the phase randomized data that present high $R^2$ greater than 60% explained variance. This occurs because the randomized distributions are uniformly distributed across the relative phase and are readily modelled with a flattened function (asymptotically uniform distribution). In the case of the experimental data we show that the bursts recorded when ON L-DOPA are well modelled by the Von Mises distribution. The distributions OFF L-DOPA exhibit worse fits to the distribution, with coefficients of determination smaller than the surrogate (figure 6B; Wilcoxon (-), -0.21 [-0.38 -0.04], P = 0.014 (uncorrected)). From figure 9A, the OFF distribution appears to have a larger y-axis offset indicating a higher amplitude of burst expected across the relative phase. We also found this to be larger than the surrogate distribution (figure 6B; Wilcoxon (-), 0.42 [-0.07 0.91], P = 0.036 (uncorrected)) but no significant change was found when compared with the ON state recordings (OFF-ON, Wilcoxon (+), 0.51 [-0.03 1.05], P = 0.07). These results suggest an amplification of beta bursts across a larger range of relative phases in the OFF condition, and a overall loss of organization that is better defined when patients are ON L-DOPA.

4 Discussion

The results presented here build upon an emerging body of work that has examined the complex nature of pathological activity that emerges within the networks formed by the cortex and basal ganglia in disorders such as PD. In this paper we analysed a) the dynamics of beta burst events in LFP recordings made in the STN, and b) investigated how these subcortical bursts are related to phase locking with the cortex. We have first presented time averaged statistics of either power or coherence, and then decomposed these measures into their time resolved counterparts in order to elucidate the temporal patterning that is not otherwise accessible with the original metrics.

4.1.1 Confounds and Limitations

As an overall increase in the average beta power is the principal electrophysiological hallmark of the Parkinsonian local field potential it is difficult to establish the causal relationship between properties of subthalamic beta bursts and subthalamo-cortical coupling. Firstly, the difference in baseline power between experimental conditions creates a confound with regards to signal-to-noise that may impact the signal analysis methods we use in this study. For this reason, we present all results alongside suitable surrogates that act as a null distribution with matched signal properties. The phase randomized surrogate is particularly important in this respect as it provides a benchmark signal which preserves the signal-to-noise of the original signals but removes any structure in the signals’ phase relationships. In this way we are able to distinguish which properties of the observed distributions are...
an artefact of the analyses and which arise as a result of actual physiological differences. For instance, in figure 8B and C, we show that phase randomized surrogates show a non-uniform distribution of amplitude versus relative phase when averaged across a group.

This result occurs because of the pooling of recentred distributions, that although random, will always have some average and thus centring on the average artificially creates a peak at the group level. This finding raises the concern that studies employing recentring of circular data (such as phase) need to pay particular attention to how this is conducted to avoid the construction of what on the surface appears to be a meaningful distribution. For instance, recentring distributions according to the peak phase of one condition over that of another (such as that done in Cagnan et al. 2015) may introduce a bias towards the chosen condition to have a tighter peaked distribution. This is particularly important in human studies where shifts in instrumentation between recording sessions may mean that phase alignment changes with each recording. In this case we would suggest that alignment is done on a condition by condition basis in order to avoid the introduction of bias. However, the particulars of the methods will depend on the exact nature of how phase alignments are expected to change over different experimental conditions and between recordings and so surrogates will also form an important step in validating results.

Furthermore, as beta power change is so marked it is difficult to elucidate the causal relationship between properties such as cortical coupling or burst duration. In particular it is unclear whether exaggerated subcortical beta power results in changes in cortical interactions or whether it is cortical
coupling that acts first. Future work will need to investigate the precise timing of beta bursting by investigating how STN/SMA phase locking may pre-empt beta burst amplification. Studies employing generative modelling to synthesise the types of data features presented here will be better suited to answer these types of questions by providing better defined mechanistic explanations as to how the phenomena described here may come about.

4.1.2 Dopamine Depletion Results in Prolonged and Amplified Beta Bursts

The results presented in section 3.1 indicate that the increase in power typically found with spectral analysis of STN LFPs may arise from the propensity for transient beta bursts to become elongated and increasingly amplified. Maximum burst lengths increased by ~600ms following withdrawal from L-DOPA and long bursts were found to be much higher in amplitude than their counterparts recorded when patients were ON. Similarly, high amplitude bursts became more probable and had durations much greater than expected from bursts of the same amplitude found in the ON condition. We also found that low amplitude bursts, associated with the less symptomatic ON condition, were effectively shortened when patients were OFF suggesting a shift of bursts from short and low amplitude, to long and high amplitude. These results are in good agreement with a similar analysis presented in Tinkhauser et al. (2017b) who also showed increase in burst duration and amplitude, as well as a decrease in short duration bursts in the OFF condition.

Furthermore, in section 3.1.4 the relationship between burst duration and amplitude was analysed in detail. Our results are again in broad agreement with Tinkhauser et al. (2017b) who also showed a strong positive correlation between burst duration and amplitude. Whilst these previous results as well as ours showed that correlation coefficients did not significantly deviate between ON and OFF L-DOPA, our results extend the analysis by establishing the existence of an expanding variance of burst durations with increasing burst amplitude as indicated by a significant increase in the so-called heteroscedasticity of the errors in the OFF condition (figure 5C). These findings reinforce the idea that bursts arising during dopamine withdrawal show a tendency to be longer in duration in the OFF condition than for bursts of the same amplitude recorded when ON. This is illustrated by the shaded regions in figure 5C where we show that whilst high amplitude bursts do occur when patients are ON dopamine, their durations are relatively short when compared with the pathological bursts’ distributions. This may be indicative of the existence of a normal wide range of burst amplitudes in the ‘healthy’ state, yet mechanisms which act to prevent over elongated bursts are deficient in the dopamine withdrawing brain. It may be the case that normal physiological mechanisms that act to terminate runaway spatiotemporal synchronization fail following the loss of dopamine, such that increased amplitude oscillations leads to the over-recruitment of neighbouring neurons. These results may inform strategies for closed loop stimulation by better characterizing the types of bursts associated with pathological states.
4.1.3 Directional Analysis of STN and SMA suggests Cortical Input is Predominant

In section 3.2.2 it was demonstrated that directed coherence is predominantly leading from the SMA to the STN and occurs at the high beta frequencies. This finding is in agreement with previous studies using Granger causality in this patient data (Litvak et al. 2011) as well as 6-OHDA rodent models (Sharott et al. 2005). In the OFF experiments we find evidence for: a) a broadening of this interaction into the low beta range, b) an increased strength of NPD from SMA to STN. This pattern of directed connectivity has not been previously reported in patients, but resembles that seen in West et al. (2018) where dopamine depleted rats showed a shift in coherence between M2 and STN towards the more pathologically associated low beta range. In addition to finding that the SMA → STN NPD is modulated by L-DOPA we find that this directed coherence correlates with the OFF UPDRS scores as well or better than the standard coherence measure. We did not find any evidence however that there was a significant improvement in the predictive value of NPD for UPDRS over that of coherence alone.

The significance of cortical drive to the STN in the emergence of pathological subcortical activity is unclear. However, work presented in chapter IV of this thesis suggests that cortically generated rhythms may be amplified by the resonant properties of the subnetwork formed by the STN and GPe in the BG. Recent work using field recordings from human cortex and STN unit recordings suggests that this could be the case as STN units were demonstrated to show sustained synchronization to premotor beta oscillations although whether this entrainment occurs via ‘hyperdirect’ cortico-subthalamic projection or more ‘indirect’ striatal routes is not clear (Sharott et al. 2018). Thus frequency specific entrainment of resonant networks in the subcortex may provide an ideal explanation for heightened and broadened forward NPD in the pathological state (Weinrich et al. 2017).

These data provide no evidence for a dopamine related modulation of feedback connectivity from the STN to SMA. This absence of a return beta interaction provides evidence against the induction of the thalamocortical “long loop” purported to be important for the emergence of pathological beta rhythms. This is in contrast to evidence from rodents which suggest this pathway is strengthened by dopamine depletion (West et al. 2018). The majority of work that conjectures the importance of the thalamocortical relay in patients is largely based on theoretical modelling (Rubin and Terman 2004; Guo and Rubin 2011; Pavlides et al. 2015) and to date we are not aware of any experimental evidence suggesting the importance of this pathway for the emergence of pathological beta in patients PD. There is more evidence for its engagement in tremor networks (Hua et al. 1998; Helmich et al. 2011; Dovzhenok and Rubchinsky 2012; Cagnan et al. 2014) perhaps explaining the differential effects of clinical interventions targeting the thalamus in PD and tremor (Benabid 2003).
4.1.4 Influence of Cortical Phase Coupling Upon STN Burst Behaviour

This work presents a novel analysis that connects previously described properties of beta burst activity in the STN with phase coupling of the STN and SMA. We demonstrate that a) the largest amplitude bursts OFF L-DOPA are associated with a weaker than average phase locking, and b) burst amplitude is significantly modulated by the specific relative phase between STN and SMA. Previous work looking at long distance coupling of STN activity has identified heightened amplitude bursts are associated with across-hemispheric correlation of STN beta envelopes (Tinkhauser et al. 2017b).

The results presented in this chapter provide evidence of the regulation of STN beta amplitudes via coupling of activity with the SMA. Specifically, we show that pathological bursts with the greatest amplitudes occur when phase coupling is weakest (figure 8A). However, even at average phase coupling bursts are higher than would be expected from either the surrogate or from recordings when ON L-DOPA. Previous work looking at phase coupling between STN and the motor cortex has suggested that OFF state burst activity is associated with a higher degree of coupling yet did not investigate how coupling was distributed across the burst amplitudes (Tinkhauser et al. 2018). Our analyses in section 3.2.2 suggest that coupling overall is increased in the OFF state yet the findings in figure 8 suggest that the mechanism is not a straightforward increase in network coupling resulting in increased amplitude bursts. Instead it may be the case that coupling sets up the network for resonance yet ultimately autonomous burst activity may be associated with pathologically high amplitude bursting. We do not have an explanation at this stage for the paradox of the OFF state being associated with both increased burst amplitude and increased STN-SMA coupling, but those two phenomena being negatively correlated. Resolving this paradox will be the subject of our future work.

Our second set of analyses look at how the relative phase between the STN and SMA relates to beta burst activity. We show that burst amplitudes follow a non-uniform distribution across the range of relative phases, showing a clear preferred phase at which beta is promoted. Specifically, we demonstrate that ON state burst amplitudes are well fit by a circular normal distribution across the relative phase. In the OFF state, this organization becomes less clear and burst amplitudes (distribution offset) is high across all potential relative phases. In the OFF state we show that relative phases preceding the peak (i.e. phase leading) show a significant amplification of beta bursts over that found in the ON state. These findings may support the evidence of increased cortical drive in the OFF state by showing that phase leading beta in the cortex can act to promote beta amplification in the STN. Overall, these analyses are similar in scope to that of Cagnan et al. (2015) who investigated the coupling between the STN and GPe in the BG. The findings of the relative phase between STN and SMA show a different profile in that the former showed good evidence of mutual resonance between the structures. Instead, we suggest that the asymmetry found in figure 8C, is indicative of entrainment by cortex rather than a mutual coupling. This is again in line with the findings of the directed functional connectivity reported in this chapter.
4.1.5 Altered Beta Trajectories as Dynamic Signatures of System Changes

The importance of investigating time resolved brain dynamics should not be understated. It is well understood that time-averaged statistics such as that measured by the power or coherence can be blind to changes in temporal patterning (Hurtado et al. 2005; Fingelkurts and Fingelkurts 2010). The analysis of transient, burst like behaviour in beta activity in the activity of the STN such as that presented here and previously reported yields important insights into: a) the mechanisms that are involved in the emergence of pathological activity, and b) biomarkers that may be useful for disrupting pathological activity using approaches such as phasic closed loop stimulation (Holt et al. 2016; Cagnan et al. 2017).

In figure 9, we illustrate the potential dynamical systems that can generate transient fluctuations in beta power with a range of different properties of their subsequent trajectories. Imagining the evolution of beta rhythms as a traversal across a dynamical landscape we can intuitively understand how endogenous perturbations arising from noise or sensory input can result in different patterning of time evolving beta bursts. Alongside each of the three proposed models we give an example of the time evolution of beta activity and a description of the expected burst properties. Importantly, all models can yield equal amounts of time averaged beta power given sufficiently parameterized inputs. Rather, the models differ in the stability of their equilibria and thus their transients will differ following random perturbation. In model A, there is a stable trough at with an equilibrium at state $x_1$, for which the beta power is low. Under the influence of random perturbation, fluctuations in amplitude are expected decay rapidly yet given significantly strong input can still yield high amplitude, but short beta bursts. In the case of model B, the system is in a metastable state where the system is close to a (pitchfork) bifurcation. In this case, the system under input will dwell for extended periods of time around the emerging equilibrium, a property that will be manifest in the statistics of its dwell durations to yield high amplitude bursts that decay as the system returns to the equilibria. At C, the system has undergone a bifurcation to become bistable and thus given sufficient input, the system will transition between the stable equilibria at $x_1$ and $x_3$. In this case we expect extended dwell distributions and bimodal distributions in the burst amplitudes.

Using the above illustration, we can understand how changes in the dynamical stability of the system arising from L-DOPA challenge can manifest themselves in the properties of the transient dynamics. Given the data presented here we see that burst distributions follow a truncated log normal distribution that extends over about 1.5 orders of magnitude. The distributions of amplitude also yield a similar distribution. These data would conform most closely to model 2. Increases in the distribution of both burst amplitude and duration would suggest that the system moves closer to a state like model 3 when patients are withdrawing from L-DOPA explaining the predominance of high amplitude and long duration beta burst events.
4.1.6 Relevance for Closed-Loop Brain Stimulation for Parkinsonism

In this work we present evidence for a link between long distance neural synchronization and changes in local oscillatory amplitude of beta oscillations in the STN, of which directional connectivity analysis suggest is driven by activity in the cortex. Theoretical work has demonstrated that distributed synchronization goes hand-in-hand with changes in oscillatory amplitude (Tewarie et al. 2018) with a dependency on the endogenous amplitude fluctuations of the nodes on their own (Daffertshofer and van Wijk 2011).

Irrespective of mechanisms, the results presented here suggest the existence of a separation between healthy and pathological activity. For instance, whilst beta burst activity when patients are ON L-DOPA is less than when OFF, we show that there is a distribution of low amplitude burst lasting up to 600ms. Whether these are expression of normative neuronal activity or subdued pathological activity is not clear, though if it is the former then the segregation between distributions may provide an ideal decision threshold at which to apply stimulation in attempt to terminate bursts that are either too long or too large in amplitude. The distribution of burst durations and amplitudes (figure 5A) suggests a region in the space of burst properties (amplitude x duration) that is pathological, namely medium amplitude but elongated bursts. We find that whilst high amplitude bursts in the ON recordings are rare, when they do occur they tend to have far shorter durations than in the OFF. This finding is apparent in difference in the variance of burst durations across the range of amplitudes (figure 5C).

These findings may suggest the loss of endogenous regulatory mechanisms which act to extinguish correlated activity in the healthy state (Wilson 2013), a role that may be replaced by exogenous stimulation. The better characterization of burst properties associated with pathological states may help inform strategies that aim to provide on-line disruption of pathological activity via closed loop stimulation (Little et al. 2013).

The importance of the relative phase of cortical activity with respect to amplifying beta oscillations in the STN may provide potential markers to disrupt activity via brain stimulation. We find that the largest changes in beta amplification in the OFF state are associated with phases preceding the subject’s most common phase alignment and may provide a way of demarcating windows of activity that are most susceptible to disruption via methods such as DBS or cortical stimulation. Non-invasive cortical stimulation has been used in the past but to mixed success (Fregni et al. 2006) highlighting a need for improved understanding as to how cortical activity a) propagates to STN; and b) interacts with pathological beta. The findings presented here would suggest that regions of the cortex that project directly to STN via ‘hyperdirect’ pathway may be best suited as stimulation in these regions are likely to have the largest impact on activity evolving within the STN. Recent developments in tractography may help to make cortical stimulation a more viable prospect (Rodrigues et al. 2018).
4.2 Conclusions

Overall in this chapter we provide a detailed analysis of the electrophysiological activity recorded from the human STN during PD and its relationship to activity in the SMA of the cortex. We demonstrate how static measures of activity such as power and coherence relate to time evolving dynamics, specifically dynamic fluctuations in amplitude of rhythmic activity termed bursts. We reproduce previous findings pertaining to increased propensity of bursts to be elongated following the withdrawal of L-DOPA and show that the relationship between burst duration and amplitude can be used to better determine activity associated with the pathological state. In the second half of this analysis we introduced recordings from the SMA and demonstrated that coupling with the STN is a) significant in the high beta band; and b) predominantly explained by cortical drive to the STN. Furthermore, it is shown that STN beta burst properties are shaped by phase coupling with the cortex, with the highest amplitude bursts occurring during periods of phase desynchronization. Results also show the propensity for high amplitude bursts to be associated with phase alignments that correspond to a phase lead from cortex, a finding that may explain the static measures of directed functional connectivity. Altogether, this work builds upon improved descriptions of transient neural activity in disease and will help inform improved strategies for on-line decoding and disruption of pathological subcortical activity in PD.

5 Supplementary Data

5.1 Supplementary Information- Toolboxes used in Analyses and Plotting

1. ‘Boundedline’, Kelly Kearney: https://github.com/kakearney/boundedline-pkg
9. SPM 12 toolbox, UCL: https://www.fil.ion.ucl.ac.uk/spm/
10. ‘Superbar’, Scott Clowe: https://github.com/scottclowe/superbar
Part D:
Discussion and Conclusions
1 Restatement of Original Hypotheses

We now briefly restate the original hypotheses originally outlined in section II of this thesis:

H I. Pathological beta activity is non-local to the STN and is diffusively spread across much of its local network in the basal ganglia (BG).

H II. Directed connectivity is altered by dopamine depletion. Altered patterns of innervation results in a change to the detectable patterns of propagating rhythmic activity across the networks formed by the cortex and BG.

H III. Dopamine depletion results in altered coupling between the cortex and STN. This is not the result of overall state averaged synchronization but instead due to its patterning in time, and its relation to local amplitude fluctuations.

H IV. Persistent synchronization of rhythmic activity may imply an excessive stability of the underlying dynamical states. This may be detectable in data by measuring a loss of extended autocorrelations in the interactions between neural populations.

We will next summarise the aims and findings of the previous chapters of this thesis and frame them in terms of the hypotheses.

2 Summary of Chapters

2.1 Chapter I: The Parkinsonian Subthalamic Network: Measures of Power, Linear, and Nonlinear Synchronization and their Relationship to L-DOPA Treatment and OFF State Motor Severity

In this work we introduce the electrophysiological properties of the subthalamic nucleus (STN), the main structure associated with the pathological activity associated with Parkinson’s disease and a principal target of deep brain stimulation (DBS). We introduce the application of several key methods from signal processing including power spectral analysis of local field potentials (LFPs) and estimation of the functional connectivity (FC) between them. Moreover, we investigate the application of metrics that are robust to the effect of volume conduction to estimate FC between spatially proximal recordings to examine evidence in favour of H I. Using these tools, we examine the changes that occur in the LFP recordings of Parkinsonian patients following withdrawal from levodopa (L-DOPA). We demonstrate, in support of H I, that the STN exhibits a significant non-zero lag coherence across recordings made from within the same nucleus and that the degree of ‘intranuclear’ coupling is correlated with both beta power as well as scores of patient’s clinical severity. Additionally, we applied a novel metric purported to estimate the proximity of a system to a critical transition at the onset of phase synchronization (DFA-PS: detrended fluctuation analysis for phase-synchrony). We demonstrate that this measure of the bilateral phase interactions between left and right STN is significantly more ordered than when measured in permuted data and that this is correlated with clinical scores of akinesia, suggesting the
proximity of the pathological state closer towards the transition for the most severely impaired patients. This is evidence against H IV, as it suggests a movement of the system closer to the transition rather than away. We will return to this when evaluating the hypotheses in a later section.

2.2 Chapter II: Non-Parametric Directionality Metric for Continuous Neural Recordings: A Validation Study

In this chapter we provided a framework for which we validated a key methodology, non-parametric directionality (NPD), that was used throughout the thesis. We set up a number of simple linear models and then tested the performance of NPD in recovering the parameterized patterns of connectivity. Moreover, we made a direct comparison of the metric with non-parametric Granger causality (npGC), another commonly used estimator of directed functional connectivity (dFC). By incorporating several confounding factors known to exist in empirically derived data, we examined the performance of the metrics under the conditions in which they are likely to be employed experimentally. We found that npGC is readily confounded by asymmetries in the signal-to-noise ratios (SNR) between signals, showing a bias towards the strongest signal being the causal drive. We show that NPD is robust to this effect and does not lead to false-positives even when signal quality is poor. Furthermore, we demonstrate that volume conduction can also bias npGC estimates of dFC whereas NPD estimates will only be attenuated as more of the coherence is attributed to the zero-lag component.

We also show that many of the confounds introduced by complex network structures such as parallel routing and reciprocal coupling can be remedied using conditioned estimates of NPD, which use a 3rd reference signal to infer auxiliary dependencies beyond that made in a simple pair-wise analysis. We do however note the limitation that incomplete observation of nodes can act to distort inferences made using conditioned estimates. From this work, we argue that NPD is well suited for the analysis of dFC in continuous data (to test H II) and is particularly advantageous in cases of multimodal data where large differences in SNR are to be expected.

2.3 Chapter III: Propagation of Beta/Gamma Rhythms in the Cortico-Basal Ganglia Circuits of the Parkinsonian Rat

In this study we applied the NPD metric introduced in chapter II to investigate the changes in dFC of the networks formed by the basal-ganglia and cortex following the loss of dopamine (H II). This is an ideal system from which to study FC as its anatomical connectivity is well understood. We took data recorded in a rodent model of dopamine depletion associated with Parkinsonism and investigated the changes that occur between control animals following the lesion. We used this system to examine the likelihood of several commonly proposed mechanisms for the generation of beta rhythms given empirically estimated patterns of FC. We find evidence for the dopamine dependency of directed connectivity in the low-beta (14-20 Hz) and high-beta/low-gamma (20-40 Hz) range, finding that activity in the latter is most prominent in the dopamine intact controls. Notably, using NPD and its
conditioned variant, we demonstrate that we can recover known anatomical circuits of the system such as the so-called ‘indirect’ pathway. Moreover, we provide novel results that suggest that the over-recruitment of the ‘hyperdirect’ cortico-subthalamic pathway and its feedback to cortex is exhibited following dopamine depletion. We also show that rhythms at high beta/gamma are susceptible to conditioning which indicates a hierarchical organization compared to those at low beta which were robust to conditioning with any one structure. These data provide clear evidence for H II.

2.4 Chapter IV: Inferring the Mechanisms of Pathological Rhythms in the Cortico-Basal Ganglia Network

Having made an extensive analysis of the FC of the cortico-basal ganglia system described in the previous chapter. We next embodied our hypotheses (broadly summarised in H II) regarding the mechanisms of generation of beta activity in a set of computational models. These models have been previously described but we now introduce a novel approach to parameter inference using the patterns of connectivity associated with dopamine depletion described in chapter III. We use Bayesian model comparison to reassess the hypotheses introduced in the previous chapter by comparing different models’ performances in reproducing the connectivity observed in experimental data. Results demonstrate that models incorporating the hyperdirect pathway tend to yield the best explanations for the data. We find that in the best-fitting models, cortically generated high-beta/gamma activity propagates via the striatal indirect pathway. The parallel hyperdirect pathway then introduces lower frequency into the subsystem formed by the subthalamic nucleus (STN) and external segment of the globus pallidus (GPe) that will tend to amplify via resonance to yield high amplitude beta oscillations. These models provide testable hypotheses regarding the circuitry required for the generation and maintenance of pathological activity in the cortico-basal ganglia circuit.

Moreover, we investigate the transition to the onset of oscillatory dynamics (H IV) in the STN/GPe subsystem parameterized by either the strength of connectivity or the time constants of the two populations. We demonstrate the system undergoes a bifurcation with a dependency on the ratio between excitation and inhibition of the reciprocally coupled populations. We examine metrics of autocorrelation that may yield important insight into estimating the proximity of empirically observed systems to transition points and do not find them to be indicative of the proximity to transition in simulated data. Furthermore, we demonstrate that the model inversion achieves best fits to the data when the systems’ parameters place it close to a critical transition. This provides evidence in favour of H IV, but may suggest some problems with estimation of critical statistics in empirical data.

2.5 Chapter V: Cortico-Subthalamic Phase Coupling and Modulation of Beta Bursting in Parkinson’s Disease

Considering the findings from chapters III and IV which established the importance of cortico-subthalamic connectivity in the emergence of pathological beta rhythms associated with Parkinsonism,
we made a novel analysis of data recorded from patients with Parkinson’s disease (PD). To examine H III, we use simultaneously recorded whole head magnetoencephalography (MEG) and local field potentials (LFPs) from the STN of patients who have undergone surgery for deep brain stimulation (DBS). In this analysis, we investigate the transient fluctuations in beta activity (‘bursts’) and their relationship to phase coupling between the STN and motor cortex, specifically the source localized signal from the supplementary motor area (SMA). We provide evidence that demonstrates that amplitude matched beta bursts are elongated following withdrawal of medication (OFF state). Further analysis revealed that OFF state bursts were far less constrained to a linear relationship between amplitude and duration, showing high amplitudes for even short duration events. In contrary, ON state bursts were much more tightly organized, with burst duration more strictly proportional to burst amplitude.

Analysis of directed functional connectivity using NPD demonstrated that coherence was predominantly directed from SMA to STN. This directed coherence was strengthened in the OFF state and showed widening of frequencies extending into low beta following L-DOPA withdrawal (further evidence in favour of HII). However, analysis of the within-burst phase coupling demonstrated that during withdrawal high amplitude bursts are predominant when the phase coupling is weakened. We found that highest amplitude bursts were found to preclude the peak relative phase for coupling. This data provides evidence in favour of H III suggesting that there is change in the relationship between cortical phase coupling and subcortical amplitude of beta following dopamine depletion.

3 Evaluation of Hypotheses

3.1 Hypothesis I: Pathological Subcortical Beta Synchronization is Non-Local and Diffuse Across the Surrounding Network

Since it first reporting, pathological beta in PD has been proposed to be part of a generalized aberrancy of synchronized dynamics in the basal ganglia (Farmer 2002; Hammond et al. 2007) that acts to impede normal passage of information through the network. However, how exactly beta activity spreads across the network is largely unknown. In chapter I, we demonstrated that beta activity is synchronous across distally recorded sites within the same STN, with time lagged phase correlations delayed transmission (chapter I, figure 4C). This finding is in good agreement with Lourens et al. (2013) who demonstrated that single units are synchronized across the human STN. Further, the degree of so called ‘intranuclear’ coherence was shown to be correlated with beta power at the individual electrodes. Whether this relationship is functional or due to differences in SNR is not clear in these data. However, computational modelling has established the importance of intranuclear coherence in determining the stability of emergent oscillatory behaviour to yield ‘pulse’ or ‘switch’ like patterns of beta (Gillies and Willshaw 2004), in addition to evidence of interactions between projection neurons within the STN (Gillies et al. 2002). In chapter III, we again analysed within nuclei coherence, but in LFPs recorded from 6-OHDA
lesioned rats (C III, figure 4, diagonal). These findings confirmed the presence of within nuclei coherence in the STN and GPe but markedly not in the STR. Furthermore, this coherence was present only in the lesioned animals, suggesting it may be functionally implicated in the impairment. This relationship needs to be examined more closely with respect to unit activity in order to establish the coupling between neurons within the STN and its relationship to oscillations in the LFP.

In chapter III, we extended our view by analysing not only the STN, but also activity recorded from surrounding nuclei in the BG and cortex. We demonstrated that following the dopamine depletion lesion, beta activity is diffusely spread across the network. Furthermore, we showed using partialized metrics of dFC that beta could not be localized to one structure. In the data from rats this is true even of the cortex, where there is significant coherence at pathological frequencies. However, when examining MEG data from patients, source localized to SMA (chapter V) we do not find pathological beta in the power spectra (chapter V, figure 2B), and only to a weak degree in the cortico-subthalamic coherence. Instead the majority of coupling occurs in the higher frequency range of beta where pathological changes are not typically observed. We will return to this finding when examining H IV.

3.2 Hypothesis II: Changes in Directional Connectivity Underpins the Emergence of Pathological Beta Activity

Due to its progressive emergence in PD, and delayed expression following dopamine lesioning in animal models, pathological beta activity has been proposed to arise from plastic changes in networks formed by the cortex and BG (Holgado et al. 2010; Tachibana et al. 2011). This synaptic reorganization must leave its signature in the pattern of dFC between networks. We evaluate this hypothesis most directly in chapters III and IV where we characterized the dFC in a rodent model of PD. We show conclusive evidence that dFC is significantly altered following a 6-OHDA lesion and specifically demonstrate that much of the changes involve a shift in inter-areal connectivity to the pathological low beta range. Furthermore, using conditioned estimates of dFC, we employed a method of ‘functional lesioning’ to show that this beta rhythm was impervious to the removal of any one structure in the network, suggesting a diffuse synchronization across the pathological system.

In chapter III, we analysed the estimated pattern of dFC in empirical data and used a process of abduction to assess the plausibility of a number of mechanistic hypotheses concerning the emergence of pathological beta oscillations in the STN. This work suggested a number of features that were significantly altered by lesion induced dopamine depletion: a) increased drive to the STN at low beta frequencies via the hyper-direct pathway; b) marked feedback from BG outputs returning back to the cortex; c) presence of subcortical loops from STN back to STR independent of cortex. We noted from this data that a mechanism of mutual entrainment of the STN and GPe did not seem likely due to the presence of an asymmetric patterning of dFC between the two structures.
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Whilst this data provided clear evidence for a change in dFC with respect to altered dopaminergic drive, due to the observational nature of this study we could not ask whether these changes in connectivity were ultimately responsible for the emergence of pathological beta. This would require an interventional study such as that by Tachibana et al. (2011) who used a pharmacological lesioning approach in attempt to disrupt beta in primate model of PD. However, future work may be done to investigate how variations in the effect of the lesion in the rodents upon changes in dFC may correlate with their overall expression of STN beta power.

In order to more rigorously explore the relationship between estimated dFC and the underlying changes in synaptic connectivity, in chapter III we constructed a set of computational models based upon previous work (Moran et al. 2011; Marreiros et al. 2013; van Wijk et al. 2018) and inverted these models upon the data introduced in chapter IV. This inversion scheme allowed for the explicit comparison of the performance of competing hypotheses (parameterized into models) at explaining the patterns of dFC in the empirical data. These data most strongly support a hypothesis that a strengthened hyperdirect pathway was most likely explanation for the increased beta coherence seen across the subcortical network following the dopamine lesion. Furthermore, modelling of the STN/GPe subcircuit also demonstrated that contrary to our suggestion in chapter III that mutual entrainment was unlikely, a reciprocally coupled network may indeed yield a pattern of asymmetric dFC similar to that observed in the electrophysiological data.

Despite the strong evidence for synaptic reorganization in rodent models of PD, in the patient data the picture is less clear. Unlike in rodents, we only had access to the STN and cortex and so could not investigate dFC within human BG. However, analysis of dFC between the STN and SMA in chapter V, showed limited evidence of a change following withdrawal of L-DOPA from patients. We present some evidence for increased drive to the STN from the SMA when patients were OFF yet no change in feedback was present, although return from STN to SMA was significant in both experimental conditions.

Taken together, it is clear from acute dopamine lesions that there is a large shift in the synaptic organization of the BG and cortex, that seems to move towards pathological beta frequencies. Evidence that beta is not well removed by lesioning any one structure in this network suggests that synaptic changes may act to generate beta at a system level, rather than patterns of dFC reflecting mere dissemination of a locally generated pathological oscillation. Whether the same mechanisms are present in patients is unclear, the limited spatial sampling of data does not allow for the measurement of dFC within the BG, however, similar shifts in cortical drive from SMA to STN to lower frequency beta are aligned with the results from rodents.
3.3 Hypothesis III: The Influence of the Cortex Upon Subthalamic Beta Activity is Modified by the Influence of Dopamine

The repeated finding that long-distance, time-averaged synchronization (coherence) between the STN and cortex is largely unaffected by L-DOPA withdrawal in patients (Hirschmann et al. 2011; Litvak et al. 2011) complicates the hypothesis that supposes excessive subcortical beta oscillations somehow spread to the cortex to disrupt its normal functioning. As an alternative, we propose that the interaction of subcortical activity with cortical coupling is altered following dopamine depletion. We test this hypothesis predominantly in chapter V by examining how the time evolving amplitude fluctuations of pathological beta rhythms are related to phase coupling with the cortex.

Firstly, the results presented in chapters III and IV emphasize the importance of cortical drive in the synthesis of pathological beta activity in the STN and its synchronization with surrounding structures in the BG. As discussed with relevance to H II- the analysis of directional connectivity in Parkinsonian rats demonstrates that cortical drive is significantly altered by dopamine depletion- shifting to lower frequencies and appearing to provide input directly to STN instead of routing via striatum. Modelling work in chapter IV reinforces this view and demonstrated that models lacking the ‘hyper-direct’ connection performed poorly. In chapter V, we analysed directly how time varying fluctuations in beta amplitude (so called ‘bursts’) were shaped by their relationship to activity in the SMA. We demonstrate that beta burst amplitude in the STN is related to the degree of phase coupling with the SMA. Principally we show that beta is amplified in the STN even for low degrees of phase synchronization when patients are OFF L-DOPA treatment, whereas in the ‘healthier’ ON condition, beta bursts are co-occurring with periods of normal phase coupling. Furthermore, it was shown that the relative phase between the STN and SMA acts to modify beta burst amplitudes. Data in chapter IV suggests that dopamine depletion acts to increase the range of relative phase at which beta can be promoted. Specifically, it was found that phases leading from cortex lead to the biggest changes in burst amplitudes when OFF L-DOPA. These data provide strong evidence for H III and suggest an altered relationship between cortical activity and STN beta under the influence of dopamine.

3.4 Hypothesis IV: Dopamine Withdrawal Stabilizes the Network and Increases the Propensity of Beta Synchronized States

In the methods section we outlined our reasoning for casting PD in terms of dynamical stability, namely that the hypothesis that a pathological inflexibility of the motor system is related to excessive local (oscillations) and long-range synchronization can be framed mechanistically in terms of a ‘loss of instability’ a property ultimately results in altered information processing and behavioural impairment. In chapter I, we used a statistical estimator of a system’s proximity to a critical transition to investigate whether fluctuations in the phase coupling between left and right STN were indicative of an increasingly stable mode of synchronization following the withdrawal of L-DOPA in patients with PD. These data
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did not provide any evidence that dopamine depletion results in the restructuring of phase interactions that would be expected had the system moved closer to the critical point (evidence against H IV). However, we did find that long range temporal correlations (LRTCs) in the phase interactions were positively correlated with the degree of motor impairment in patients. Following the work of Botcharova et al. (2014) this would imply that the most severely impaired networks are closer to the critical transition (i.e. critically poised), a finding that is against the reasoning of H IV. We however note several methodological issues that make interpretation of this metric difficult. These will be detailed in a coming section of this discussion.

Irrespective of a lack of evidence for changes following dopamine depletion, we found that in both ON and OFF states there was good evidence for power-law scaling of phase interactions, a precondition for systems found close to a transition point. In chapter V we examined transient fluctuations in both the amplitude of beta activity in the STN as well as phase coupling with the SMA. These analyses demonstrate that both exhibit intermittent dynamics that are typical in systems that are far from equilibrium (Rabinovich and Varona 2011). Beta bursts may be examples of ‘flickering’ behaviour by which the transition across alternative basins of attractions leads to the switching between states (Wang et al. 2012). In this case the finding of elongated dwell times in the beta state may be a signature of increased dynamical stability of the state that gives rise to beta oscillations.

This explanation is supported further by evidence in chapter IV where we show that model systems that are inverted upon the experimental electrophysiological data give rise to the best explanations when they are poised close to the instability where beta oscillations emerge. This finding is found even in the simplest systems (such as the STN/GPe sub-circuit) where in order to simulate time-averaged statistics such as coherence at values that are away from 0 (incoherent) or 1 (completely coherent) then the simplest solution in these models is to converge at parameters that poise the system close to a critical point. In this way, intermittencies that emerge in these states readily give rise to ‘flickering’ beta burst like activity that when averaged in time to compute coherence give values neatly poised at the onset of coherency (i.e. close to 0.5).

None of the results here can provide direct evidence of changes in stability. In order to do this, it will be necessary to 1) experimentally manipulate system parameters to observe system states on the approach to a transition; and 2) systematically perturb the network to observe slowed relaxation and other critical statistics (such as those described in the introduction and methods). Experiments aiming to achieve (1) are likely to utilize significant developments in optogenetics such that they may act to adjust system parameters such as synaptic efficacy in a gradual manner that can allow for the existence of a state transition (e.g. emergence of beta oscillations) to be quantified. The second approach (2) is also readily achievable, both in patients were DBS strategies for dynamic experimentation have begun.
to become possible and also in animals where again optogenetic intervention can be used to specifically probe the perturbation to particular nuclei.

4 Evaluation of Data and Methods

4.1 Experimental Data

A large component of the body of work presented in this thesis concerns a comparison between the pathological electrophysiology recorded from either lesion models of PD or patients themselves. The use of animal models affords access to extensive recordings across multiple sites of the cortico-basal-ganglia network that would otherwise be extremely difficult or impossible to conduct in humans. However, it is important to bear in mind the differences in the nature of the pathologies. In the case of the animal models Parkinsonian type behaviours are induced using an acute neurochemical lesion that will produce its effects within a matter of days. The lesions are well targeted and conducted to be as homogenous across the group of animals as experimentally possible. On the other hand, there are large degrees of uncertainty concerning the nature of individual patients’ pathologies that makes comparison, even within an experimental group, a challenging prospect.

4.1.1 Patients with Parkinson’s Disease

In chapter I we analysed in close detail the mesoscale field activity recorded from the human STN. We illustrated the most marked and reproducible finding in the electrophysiology of PD that is a principle motivation for the studies presented in this thesis- namely the presence of an aberrant low beta (14 20 Hz) oscillation in the STN. This feature is common to both the patients and animal models and an important challenge to this work is elucidating potential mechanisms of its generation and comparing the evidence across the two species. However, the pooled spectra of the individual patients provide a somewhat deceptive view, presenting a far clearer picture of the effects than the one which exists following inspection of individual recordings. In chapter I, we also show spectra from a typical subject where we show that whilst beta is clearly present, its definition as two separable peaks at high and low sub-bands is far from universal. This issue is a more general criticism of the larger patient literature where the focus on presenting group averages of spectral features (without showing the spectra from which these statistics are taken or even presenting sample variance) can lead to misleadingly simple representations, particularly when clinical sample sizes are often very low. This effect is even more important when discussing FC where the increased complexity of the problem introduces an even larger degree of heterogeneity across subjects.

We note that both the profiles and effects of L-DOPA on FC between MEG source localized activity and local field potentials are faced by several difficulties. Firstly, the large size of DBS electrodes with respect to the size of the STN means that sampling over the structure is large and thus differences in the targets of synaptic projections arriving at the STN can explain some of the marked differences in
connectivity from different channels targeted to the same STN. Recent work using anatomical modelling of STN and tractography has used hyperdirect tract density near stimulating contact to predict the functional effects of DBS (Neumann et al. 2018) with future work certain to investigate differences in the FC associated with anatomical differences in recording location.

4.1.2 Rodent Models of Dopamine Lesions

In chapters III and IV we utilized LFP data recorded from the 6-OHDA rat model and compared it with that from un-lesioned control animals. As the recordings were made under anaesthesia we look at recordings occurring during periods of “cortical activation” induced with a hind paw pinch. These periods are characterized by an exit from slow-wave activity to something that appears more akin to the activity during wakeful rest. Nonetheless, the degree to which this state corresponds to actual waking activity is unclear, and it is possible that the engagement of the thalamocortical relay in beta frequencies (a finding that was markedly absent in patient recordings) may be a consequence of changes in thalamic inhibition in sleep like states (McCormick and Bal 1997; Wichmann and DeLong 1999).

Nonetheless, the changes in FC following dopamine cell loss are significant and numerous. The most apparent change across the network is a shift in patterns of connectivity from high frequency beta/gamma (24-40 Hz) towards the lower frequency beta (14-21 Hz). In chapter V we present evidence in the NPD that a similar effect occurs in patients, but rather than a shift in frequency, we see a broadening of the coherence from high beta into low beta. Nonetheless, the effect in the rodent recordings is far more apparent.

4.1.3 Limitations of Resting State Recordings

All the data presented in this thesis were recorded in either a state of rest (for the patients), or in the case of the animals, under urethane anaesthesia. The relatively long recordings of several minutes allow for the observation of spontaneous brain activity in the absence of explicit stimuli or task demands. How this activity is organized and what it can tell us about the state of the underlying neural system is a key question of this thesis. However, this approach only gives insight into the neural mechanisms and tying together resting state activity with cognitive processes is a standing challenge to the field of cognitive neuroscience as a whole (Deco et al. 2011; Raichle 2011). Recent paradigms that involve natural scene viewing such as watching movies, may provide a better understanding how endogenously structured brain activity responds to structured exogenous sensory input (Betti et al. 2013). Ultimately, complete descriptions of how this occurs will require paradigms that can investigate how spontaneous brain activity biases perception or action preparation for intentional behaviour. With respect to the functional importance of beta oscillations this may allow for insights not only into how pathological activity results in motor problems such as freezing and akinesia, but also into how it modulates cognitive processes.
4.2 Analysis Methods

4.2.1 Volume Conduction and Referencing

The origins of extracellular fields such as that measured in the LFP and MEG are numerous and how they are generated across different structures is generally not well understood (Nunez et al. 1997; Pesaran 2009; Buzsáki et al. 2012). In the case of whole-head MEG and electroencephalography, it is well understood that the signals recorded at the scalp are a mixture of signals arising from spatially distributed sources on the order of several centimetres apart (Nunez et al. 1997; van den Broek et al. 1998) and thus FC measures applied to scalp signals are unlikely to be informative. In the case of the data presented in chapter V, we use a single source that is localized to a spatial region of the brain (SMA). In this case there is less concern of mixing although beamforming will still exhibit spatial leakage, albeit heavily reduced compared to scalp signals.

The assumption that the LFP is indeed “local” has also been under scrutiny with reports suggesting volume conduction of signals to LFPs is very local at 150 μm (Katzner et al. 2009) from the origins up to claims of instantaneous propagation of signals from over a centimetre away (Kajikawa and Schroeder 2011). Taken together it appears that the extent of spatial resolution of the LFP is highly dependent on the geometry of the generating currents. This has led to concern that distantly referenced LFPs may not be that spatially restricted (Mitzdorf 1985). In patient data used in chapters I and V we avoided this issue by referencing electrodes into bipolar montages in which subtraction of measured voltages acts to remove common signal components. In the rodent data used in chapters III and IV, the issue was more complicated due to the high density of contacts in which bipolar montages acts to destroy the signal due to common pickup from the same neural pool. Instead we opted to maintain monopolar signals referenced to inert skull near the cerebellum. We found that modular organization in good agreement with the anatomy could be recovered if we used FC metrics robust to zero-lag effects.

4.2.2 Functional Connectivity: Correction for Zero-Lag Correlations

Traditional metrics of functional connectivity such as coherence or the phase locking value will yield spurious estimates in the presence of zero lag field spread effects (Bastos and Schoffelen 2016) such as those described in the previous section. In the methods section of this thesis we justify the usage of methods designed to be robust to these effects for applications in neurophysiological data. In chapter I we examined the connectivity within the individual human STN, a small area of several millimetres. We demonstrate that volume conduction yields broadband correlations with no definitive features in the coherence. However, by application of the weighted phase lag index (WPLI) we are able to better resolve the lagged coherence between signals recorded within the same nuclei.

The benefits of methods such as these was even more apparent when applying imaginary coherence (iCOH) in chapter III to estimate FC between different nuclei of the basal ganglia such as the STN and GPe, where the monopolar montage left a high amount of residual common pickup. Standard coherence
again revealed just a high magnitude broadband roll-off devoid of features. However, iCOH applied to the same data revealed several interesting structures in the FC spectra.

Measures designed to be robust to volume conduction are generally conservative, in that they remove all parts of the correlation that are at (or around in the case of WPLI) zero phase lag. Theoretical as well as experimental evidence suggests that the physiological occurrence of zero-lag correlations is not uncommon (Roelfsema et al. 1997; Vicente et al. 2008; Gollo et al. 2014). In chapter II we introduce a method of dFC (NPD) that acts to separate the standard coherence into 2 directional, and 1 instantaneous component where we show that the zero-lag component is well estimated when simulated by instantaneous mixing of signals.

4.2.3 Directed Functional Connectivity

The estimation of hierarchical interactions in the brain is of importance to a number of areas of study such as elucidating mechanisms of top down predictive processing (Bastos et al. 2012; Bressler and Richter 2015). dFC measures are often subject to the same confounds faced by undirected methods, namely volume conduction, poor and asymmetric SNRs. In chapter II we compare the performance of the recently described NPD with another commonly used metric (npGC) and arguably show that NPD is more accurate in recovering structural connectivity across a wide range of conditions whilst equally being more robust to the effects mentioned previously. In chapter III we demonstrate an application of NPD to estimate functional coupling within an anatomical circuit that is well described (Bolam et al. 2000) and demonstrate that it is able to distinguish a number of functionally important pathways such as the indirect and hyperdirect routes.

However, computational modelling of the dFC patterns presented in chapter III demonstrates that naïve inference of structural connectivity directly from the functional can lead to errors in a number of circumstances. In particular, in chapter III we concluded that “… our data do not support the hypothesis of beta generation via an autonomous STN/GPe pacemaker network, as … there is significant asymmetry in the NPD with drive from the globus pallidus predominating”. When we model this subsystem and fit the parameters to yield patterns of NPD similar to that observed we find that in fact when the circuit is set up to oscillate via reciprocal excitation and inhibition then an asymmetric dFC is expected. This discrepancy between structural and functional connectivity is beginning to be understood (Daffertshofer and van Wijk 2011; Park and Friston 2013; Deco et al. 2014) and our findings amongst others should be a source of caution to studies making inference directly from functional connectivity. Instead, model based approaches that attempt to frame connectivity in terms of mechanisms are better placed to understand the actual propagation of activity within a neural network. In contrast, FC signatures may or may not be generated in a way that allows straightforward mapping from function back to structure.
4.2.4 Causation in Reciprocally Coupled Systems

It is notable that the example of structure/function discrepancy described previously arises from reciprocally coupled networks. In chapter II we demonstrate that even in simple autoregressive models, when reciprocally coupled nodes or circuits form loops, dFC can be readily confounded because of the multiplication of lagged correlations as activity cycles around the network. Reciprocal connectivity can act to undermine some of the tenants of dFC measures, namely that temporal precedence implies causation and that cause and effect are separable (Sugihara et al. 2012). It has been noted across several fields such as ecology that the notion of Granger causation and temporal separation of cause and effect is invalidated by the presence of even weak reciprocal coupling (Yang et al. 2018). The large loop formed by the thalamo-cortical system, on which we focus the attention of chapters IV and V, is just one of many re-entrant circuits in the brain (Wickens et al. 1994; McHaffie et al. 2005; Edelman and Gally 2013). Given such reciprocal coupling it may naively be expected that dFC metrics will yield symmetrical results yet our simulations in chapters II and IV show that this is not necessarily the case.

Dynamical systems approaches to causation are one solution as they eschew the need to investigate temporal ordering of cause and effect and instead estimate the dependency in the state space. Sugihara et al. (2012) propose a method dependent on state-space projection which they term convergent cross mapping (CCM). Whilst CCM and related methods rely on reconstruction of the state space from the time series, other methods such as dynamic causal modelling (e.g. Moran et al. 2009) or that formulated in chapter IV put a Bayesian perspective on top of the state space approach, engendering prior knowledge of the system’s causal structure into a generative model that can then be tested via Bayesian model comparison.

4.2.5 Dynamical Approaches to Systems Neuroscience

Asking simple dynamical questions of neurophysiological systems such as: “How stable is this system to perturbation?”; “How sensitive is this system to a change in its structure?”; and investigations of transient behaviour: “How do states of this system interact?” there is the potential for deeper understanding of how they function and what goes wrong in disease. This approach is taken by much of the “harder” basic neurosciences where vast developments in technology (such as advanced molecular interventions and optogenetics) have facilitated novel protocols to perturb the neural systems with great fidelity. Human neuroscience is catching up, but still the major paradigm involves evoking a particular cognitive demand and then imaging the changes in the brain that occur as a response. In this case, the task or stimuli is assumed to take the place of experimental intervention yet the mapping from stimuli to neuronal activation is poorly understood.

This situation has arisen from a limited number of tools that allow direct perturbation of the brain activity which has predominantly been limited to transcranial magnetic stimulation (TMS) or more recently transcranial direct/alternating current stimulation (tDCS/tACS). In patient populations, clinical
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interventions such as DBS, provide a unique opportunity to perturb systems that would otherwise be inaccessible. Recent evidence has demonstrated that these methods can modify brain rhythms (Eusebio et al. 2011; Helfrich et al. 2014; Vossen et al. 2015; Tinkhauser et al. 2017) and furthermore can affect behaviour (Pogosyan et al. 2009; Herz et al. 2018). Much work is needed to understand how these interventions elicit their effects (Bestmann et al. 2015).

In chapter IV we present a number of dynamical models that have parameters optimized to reproduce the statistics of observed experimental data. The nature of these models provides a number of testable predictions with regards to how the real system will respond to experimental interference. This approach may be a useful one: by first predicting system parameters from steady state behaviour we can then ask how this relates to the system’s response to stimulation or cognitive stimuli. Furthermore, fitted stochastic models like that in chapter IV yield intermittent behaviour such as the beta bursts analysed in chapter V. Future work using these types of approaches can help understand the mechanisms that preclude the observation of pathological activity and inform improved strategies for intervention with technologies such as phasic closed loop DBS (Little et al. 2013; Cagnan et al. 2017).

4.2.6 Criticality in the Brain

As an adjunct to the dynamical systems perspective we discuss in the previous section, we have introduced the notion of ‘criticality’ and related ‘self-organized criticality’ (SOC) and in chapters I and IV investigated the usage of potential statistical markers of critical processes. In chapter I we started with the hypothesis that pathological activity in the basal ganglia in PD is associated with a structural change in the circuit that results in a positioning of the system closer to a critical transition to the onset of beta synchrony. We applied a previously described methodology (DFA-PS; Botcharova et al. 2014) which attempts to access features of extended signal autocorrelation that are known to occur at the approach to a critical transition (Scheffer et al. 2009).

Specifically, DFA-PS looks at fluctuations in phase relationship between signals that has been demonstrated to be a signature of the onset of phase synchronization. We demonstrated in chapter I that bi-lateral phase synchronization between left and right STN showed extended autocorrelation beyond that of randomized data and that the extent of the autocorrelation’s persistence was positively correlated with patient’s symptom severity. However, there are several issues that were found when applying this methodology to empirical data. One has been previously discussed in this section of the thesis and pertains to volume conduction effects. We again note that instantaneous phase correlation between signals is likely to interact with the PS-DFA metric in some as of yet unknown way. Furthermore, validation of the method was originally conducted in phase-models and the influence of simultaneous amplitude fluctuations is again unknown. The nature by which phase is estimated from empirical signals (predominantly via the Hilbert transform) means that phase estimates are meaningless when the amplitude of the signal is very small, thus it is likely that any structure in the time series of the phase
comprises both real fluctuations in the underlying oscillations phase, but also artefact arising from loss of signal (Freeman et al. 2006). Future application of these methods, especially when investigating coupling between EEG/MEG signals, will require correction for these confounds.

Overall, the search for statistical hallmarks of criticality in resting systems can only go so far—whether these statistics give any insight over that of more standard linear measures is yet to be demonstrated. In particular, measures that estimate power-law distributions of neural fluctuations should be explicitly limiting their findings as evidence—these are necessary but not sufficient statistics for systems exhibiting SOC. Studies should also make efforts to explicitly analyse the degree to which these statistics give any gains in information over more standard methods. In chapter I we show that DFA-PS can give increased predictive power of patient’s clinical severity scores, although the gains are relatively small. Nonetheless the complex nature of methods of these type means that they are readily influenced by a range of preprocessing decisions (i.e. filter types, artefact correction) and even recording hardware, thus the strongest evidence should be provided by parallel analyses using alternative methods which measure similar features. Again we reiterate the need for basic computational modelling to establish theoretical explanation of observed results and to produce testable predictions to allow for falsification and verification of experimental results (O’Neill et al. 2018).
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Part E:

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