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Subcortical-Cortical Network Dynamics in the Human Brain

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Subcortical-Cortical Network Dynamics in the Human Brain

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Biomedical Engineering

by

Mahsa Malekmohammadi

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ABSTRACT OF THE DISSERTATION

Subcortical-Cortical Network Dynamics

in the Human Brain

By

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Doctor of Philosophy in Biomedical Engineering

University of California, Los Angeles, 2015

Professor Nader Pouratian, Co-Chair

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The cerebral cortex is connected to various subcortical structures such as the thalamus and the basal ganglia (BG). The diffuse yet specific patterns of structural connectivity of the thalamus with the cortex suggest thalamocortical connectivity could play an important role in addressing the binding problem. Previous research has established the presence of BG oscillations and their link to functional and pathological connectivity states to the cortical structures. Considering the topographically organized connections between thalamus, BG and the cortex it has been proposed that disruptions to normal oscillatory activity within the cortico-BG-thalamocortical circuits may partly account for the pathophysiology of Parkinson's disease (PD) . Using simultaneous invasive recordings of cortical and thalamic electrophysiological activity in two awake and spontaneously behaving human subjects, we provide direct evidence of thalamic

regulation of cortical activity through a mechanism of phase-amplitude coupling (PAC). Specifically, we show that cortical PAC between the θ phase and β amplitude is spatially dependent on and time variant with the magnitude of thalamocortical θ coherence. Moreover, using causality analysis and MR diffusion tractrography, we provide evidence that thalamic θ activity drives cortical θ oscillations and PAC across structures via structurally constrained pathways..In PD, pathologic oscillatory activity, particularly in the β band, is present in BG and motor cortex. The role of these β oscillations in modulating activity at a network level have not been thoroughly characterized. Using simultaneously recorded cortical and pallidal local field potentials in 20 patients with PD undergoing deep brain stimulation surgery, we confirm increased β activity and β-γ PAC in motor cortical areas. The cortical β band is highly coherent with β activity in the motor region of the GPi where local β-γ and β-(200-300Hz) PAC and cross-site pallido-cortical PAC were observed. Contralateral movement significantly decreased pallido-cortical coherence and PAC as well as local cortical PAC, but did not completely eliminate this coupling, possibly manifesting a deficiency in the diseased BG to disentrain the motor network during action. These results shed light on the dynamic nature of pallidocortical coupling, suggesting β oscillations reverberate through the motor network and modulate activity at a network level.

The dissertation of Mahsa Malekmohammadi is approved.

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Acknowledgments

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PBLICATIONS AND PRESENTATIONS

M. Malekmohammadi*, C. Tsiokos*, N. Au Yong, X. Hu, N. Pouratian, Phase-to-amplitude cross frequency coupling in the Globus Pallidus Internus and motor cortex of patients with Parkinson's disease. (manuscript under prepration, * authors contributed equally to this work)

M. Malekmohammadi, N. Au Yong, N. Pouratian, Power changes in motor cortex and globus pallidus internus with induction of anesthesia in patients with Parkinson's disease. (manuscript under preparation)

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N. Au Yong, M. Malekmohammadi, N. Pouratian, Interhemispheric Comparison of Globus Pallidus Interna and Cortical Local Field Potentials During Movement and Rest. Congress of Neurosurgical Surgeons (CNS) Annual meeting, Boston, MA, October 18-22, 2014.

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M. Malekmohammadi, J. W. Elias, N. Pouratian, "Thalamocortical coupling is spatially specific and structurally constrained", 19th Annual Meeting of the Organization for Human Brain Mapping, June 16-20, 2013, Seattle, WA, USA.

M. Malekmohammadi, S. Asgari, P. Vespa, X. Hu and N. Pouratian, "Dynamic phase amplitude Coupling between ICP and EEG in traumatic brain injured patients", 80th annual scientific meeting of the American association of neurological surgeons, April 14-18, 2012, Miami, Florida, USA.

1. Introduction

1.1. Human Brain Connectivity

Mapping the structural and active functional properties of brain networks is a key goal of basic and clinical neuroscience and medicine.

The novelty and importance of this transformative research was emphasized by the U.S. National Institute of Health in their 2010 announcement for the Human Connectome Project:

> *Understanding neural connectivity in model organisms has made possible an integrated understanding of the interplay of genes, molecules, cells, neural systems, and behavior. Such understanding, in turn, provides the basis for detailed models from which hypotheses about brain function in health and illness can be generated. Without connectivity data, this kind of understanding is not possible for human brain function and dysfunction. Knowledge of human brain connectivity will transform human neuroscience by providing not only a qualitatively novel class of data, but also by providing the basic framework necessary to synthesize diverse data and, ultimately, elucidate how our brains work in health, illness, youth, and old age (2009).*

Importantly, elucidating brain connectivity can lend insight into how the brain functions. Brain connectivity can be investigated in 2 manners (Sakkalis 2011) :

1.1.1. Structural connectivity

For the sake of simplicity, structural connectivity may be considered as fiber pathways tracking over extended regions of the brain, which are in accordance with general anatomical knowledge (Koch, Norris et al. 2002). By searching for structural connectivity we focus on identifying anatomical links between distinct brain regions. In other words, we investigate how these brain structures (regions) are physically connected to each other via direct/indirect fiber pathways containing axonal connections.

The primary noninvasive tool for this analysis is MRI based diffusion weighted imaging (DWI), including both Diffusion Tractography Imaging (DTI) and Diffusion Spectrum Imaging (DSI). DTI works by estimating the diffusion process of water molecules (both the rate of the diffusion and its directionality) in each voxel and reconstructing fiber pathways based on the directionality information. A 3D modeling technique called tractography is then used to represent neural tracts using this data (Hagmann, Jonasson et al. 2006). These methodologies can be used to examine structural connectivity and convey information concerning the white matter fiber tracts.

1.1.2. Functional connectivity

Functional connectivity is defined as the temporal correlation (in terms of statistically significant dependence between distant brain regions) between the activity of different neural ensembles (Fingelkurts, Fingelkurts et al. 2005). In functional connectivity we primarily investigate symmetrical correlations in activity between two (or more) brain regions during either rest or a behavioral task.

Many neurophysiologic signals can be used to assess functional connectivity, including signals derived from single unit and local field potential (LFP) recordings, electroenchaphalography (EEG), magnetoencephalography (MEG), and Functional Magnetic Resonance Imaging (fMRI). Functional connectivity analysis can be done using a variety of methods including pairwise correlation analysis in fMRI activity or Cross Frequency Analysis of electrophyiological signals (EEG, ECoG).

1.1.3. Effective connectivity

As opposed to functional connectivity which simply identify non-directional relationships between different areas of the brain, Effective Connectivity analyses seek to identify asymmetric or causal dependencies between brain regions and can be used as a tool to investigate which brain region is causally influencing other regions during a stage of information processing (Horwitz 2003). The term "information flow" is often used to describe directionally specific effective connectivity. More explicitly, effective connectivity refers to the influence that one neural system exerts over another, either at a synaptic or population level (Friston 2011). Aertsen and Preisl proposed that "effective connectivity should be understood as the experiment and time-dependent, simplest possible circuit diagram that would replicate the observed timing relationships between the recorded neurons.'' This speaks to two important points: effective connectivity is dynamic (activity-dependent), and depends on a model of interactions or coupling (Aertsen and Preissl 1991). The key aspect of effective connectivity analysis is that it ultimately rests on model comparison or optimization. This contrasts with analysis of functional connectivity, which is essentially descriptive in nature.

Modern research on building a human 'connectome' (complete map of human brain connectivity) has typically focused on structural connectivity using MRI and diffusion weighted imaging (DWI) and/or on functional connectivity using fMRI (Delorme, Mullen et al. 2011). However, the brain is a highly dynamic system, with networks constantly adapting and responding to environmental influences so as to best suit the needs of the individual. Therefore a complete description of the human connectome requires accurate mapping and modeling of transient directed information flow or causal dynamics within distributed anatomical networks.

Some of popular methods of effective connectivity analysis include:

Dynamic causal modeling (DCM) (Kiebel, Garrido et al. 2008), structural equation modeling (Schlosser, Wagner et al. 2006), transfer entropy and Granger-Causal method which all can be applied to fMRI and/or electrophysiological data (EEG, ECoG, MEG) (Vicente, Wibral et al. 2011). Some of these techniques (such as DCM) require assuming a special model for the system, however time-series causality measures such as transfer entropy are generally model-free. These methods have different effectiveness. Nonlinear methods such as transfer entropy has poorer performance relative to Granger-Causality method in the presence of noise and since these methods are usually bivariate which in case of presence of inter-relation between signal channels might produce misleading results (Blinowska, Kus et al. 2004; Kus, Kaminski et al. 2004).

1.2. Data and levels of functional connectivity

Different types of data are available to study functional connectivity in human brain. These techniques are divided into two groups of direct (electrophysiological) recordings such as single-unit recordings, EEG, ECoG and MEG and indirect (hemodynamic) measures of electrophysiological activity which are based on assumption of neurovascular coupling. Hemodynamic methods include positron emission tomography (PET) and Blood oxygen level dependent (BOLD) fMRI, (Shibasaki 2008). Different methods have different advantages. For example, MEG measures brain activity with high temporal resolution but has limited ability to localize that activity. fMRI has greater spatial resolution, but lower temporal resolution.

At the neuron level, Gerstein, Perkel, Aertsen and their collaborators established the analysis of electrophysiological data (Gerstein and Perkel 1969; Gerstein and Aertsen 1985; Aertsen, Gerstein et al. 1989; Aertsen and Preissl 1991; Aertsen, Erb et al. 1994). These series of work resulted in discovering the Hebbian cell groups in the effort to describe a mechanism for neuronal plasticity (Hebb 1949; Doidge 2007). Moreover, concepts of “functional” and “effective” connectivity appeared for the first time by (Aertsen, Gerstein et al. 1989).

At the macroscopic level, EEG was the first non-invasive method to examine human brain activity. The use of these data to attempt to examine the functional interactivity between different cortical regions has a long history (Barlow and Brazier 1954; Livanov 1979; Gevins, Cutillo et al. 1989) and a variety of techniques have been used, all of which evaluate the cross-correlation of the signals between pairs of scalp electrodes.

Prior to positron emission tomography (PET) and fMRI, the non-tomographic xenon-133 inhalation technique was used to image functional brain activity in humans, and correlations between pairs of surface detectors were evaluated (Prohovnik, Hakansson et al. 1980). Once PET studies of glucose metabolism began to be performed, several groups used region of interest methods to examine interregional correlations (Clark, Kessler et al. 1984; Horwitz, Duara et al. 1984; Metter, Riege et al. 1984; Bartlett, Brown et al. 1987). In the mid-late 1980s, studies of cognitive function began to be performed with PET, in which regional cerebral blood flow (rCBF) was measured and analyses soon were undertaken to assess functional connectivity either using regions of interest (Horwitz, Grady et al. 1992), or a voxel-based approach (Zeki, Watson et al. 1991; Friston, Frith et al. 1993; Horwitz, McIntosh et al. 1995). Later, as fMRI became an established functional brain imaging tool, a number of studies of interregional functional interactivity using fMRI data acquired from humans at rest (Biswal, Yetkin et al. 1995; Lowe, Mock et al. 1998), or while performing particular tasks (Buchel and Friston 1997; Pfurtscheller and Andrew 1999; Bullmore, Horwitz et al. 2000; Bokde, Tagamets et al. 2001; Hampson, Peterson et al. 2002; Mechelli, Penny et al. 2002). Although different investigators used different terminology to indicate the distinction between the correlated activities of PET/fMRI data and the strengths of the linkages in a causal model, the community eventually converged on Friston's use of the terms functional and effective connectivity to designate these two notions.

1.2.1. Electrophysiology

Direct electrophysiological methods involve recording of electrical currents or magnetic fields resulting from activity of single units or population of neurons.

Single-unit recordings measure electrical response from a single neuron using a microelectrode recording system. Recordings are both intracellular and extracellular. This method, although highly invasive, allows for exquisite spatial and temporal resolution recordings from brain electrophysiological activity. An example study reported by (Boraud, Bezard et al. 2002) in which they used single-unit recordings to explain the structural organization of the basal ganglia in patients with Parkinson's disease.

Electroencephalography (EEG) refers to the recording of brain electrical activity from the surface of scalp. Brain EEG signals mostly originate from cerebral cortex. Because of presence of skull in the pathway of electrical activity measured by EEG, signal-to-noise ratio (SNR) is relatively low in EEG recordings.

Magnetoencephalography (MEG) is a method of recording magnetic fields produced by electrical currents resulting from brain neuronal activity, using very sensitive magnetometers. Although EEG and MEG signals originate from the same neurophysiological processes, there are important differences. Magnetic fields are less distorted than electric fields by the skull and scalp, which results in a better spatial resolution of the MEG. Whereas scalp EEG is sensitive to both tangential and radial components of a current source in a spherical volume conductor, MEG detects only its tangential components. EEG is, therefore, sensitive to activity in more brain areas, but activity that is visible in MEG can also be localized with more accuracy.

Electrocorticography (ECoG) is the practice of using electrodes placed directly on the exposed surface of the brain to record electrical activity from the cerebral cortex. Unlike EEG which is completely invasive, ECoG requires direct exposure of surface of brain. ECoG may be performed either in the operating room during surgery (intraoperative ECoG) or outside of surgery (extraoperative ECoG), in patients who have leads implanted for the medical indication of monitoring for epilpesy. It is currently considered to be the "gold standard" for defining epileptogenic zones in clinical practice and provides an accessible means by which to measure local field potentials (LFPs) in human brain. The power of using ECoG to map brain activity was first described and advocated by Dr. Nathan Crone in 1998 who noticed that the topography of γ band maps was consistent with traditional (and fMRI) maps of eloquent cortices (Crone, Miglioretti et al. 1998). Given the unique spatial and temporal profile of the various LFP frequency bands, it is likely that each represents distinct underlying electrophysiological processes. In humans, regular oscillations have largely been observed in the form of local field potentials (LFPs) recorded through ECoG or deep brain stimulation (DBS) leads implanted for diagnostic or therapeutic purposes, respectively.

1.2.2. Hemodynamic data

Hemodynamic methods can measure localized changes in cerebral blood flow related to neural activity.

PET can detect active brain areas either hemodynamically or metabolically through glucose intake. The areas that are activated by increased blood flow and/or increased glucose intake are visualized in increased signal in the PET image (Shibasaki 2008). This

method indirectly measures the flow of blood to different parts of the brain which is believed to be correlated to brain activity. PET works by measuring emissions from radioactively labeled metabolically active molecules injected into the bloodstream. These data are then computer-processed to generate multi-dimensional images of the distribution of the activity throughout the brain. PET scans were superior to all other metabolic imaging methods in terms of resolution and speed of completion. The biggest drawback of PET scanning is that because the radioactivity decays rapidly, it is limited to monitoring short tasks (Otte and Halsband 2006).

Blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) detects perfusion-related changes by measuring small changes in magnetic susceptibility due to shifts in the relative abundance of deoxygenated hemoglobin (Barbier, Lamalle et al. 2001). The BOLD signal is considered to be temporally integrated (unable to differentiate between responses separated by milliseconds) but relatively spatially segregated. Instead of directly measuring neural activity, BOLD fMRI maps the brain by detecting perfusion-dependent signals that are "coupled" to neuronal activity. Although studies have described close spatial coupling of neuronal activity and perfusion-related mapping signals (Kim, Ronen et al. 2004), several reports have reported exceptions to this assumption. For example, perfusion-related signals can be influenced by recent activity, activation frequency, simultaneous activation of adjacent cortices, and attentional state (Hanslmayr, Volberg et al. 2011; Scheeringa, Fries et al. 2011) Uncertainty also persists with respect to the statistical determination of the spatial extent of activation, which is at least in part attributable to an incomplete understanding of the electrophysiologic and anatomic basis of these signals.

Studies that provide information about spatio-temporal dynamics and electrophysiologic and anatomic basis of BOLD signals are essential to improve our understanding and interpretation of these signals.

fMRI can be employed using two distinct approaches to map the function of the human brain: task-related and resting state. In standard task-activation fMRI, an experimental task of interest is presented alternately with a control task and the BOLD signal during the experimental task is compared to the BOLD signal during the control task (Barbier, Lamalle et al. 2001). Resting-state fMRI approach focuses on spontaneous, rather than task-induced, fluctuations in the blood oxygenation level-dependent (BOLD) signal and identifying correlations of these spontaneous BOLD activations across space and time.

1.3. Directional connectivity

The investigation of brain connectivity can broadly be broken down into two main subcategories:

1.3.1. Cortico-cortical connectivity

The cerebral cortex consists of structurally distinct areas, as defined by location and the cytoarchitecture of the cortex. These cortical areas are interconnected through fiber tracts of the white matters. Each cortical area receives projections from and sends projections to other cortical areas in complex networks via cortico-cortical and callosal axons. The majority of inputs onto cortical neurons arise from other cortical neurons.

1.3.2. Cortico –subcortical connectivity

Oscillatory activity throughout the brain has long been proposed to mediate or facilitate behavioral, perceptual and cognitive functions in humans. The cerebral cortex is connected to various subcortical structures such as the thalamus and the basal ganglia, sending information to them along efferent connections and receiving information from them via afferent connections.

1.3.2.1. Thalamocortical connectivity

Just like a conductor works reciprocally with an orchestra to receive, integrate, and coordinate components, the brain can be hypothesized to require a conductor to coordinate multiple inputs and outputs, cognitive processes, and attentional factors. Most sensory information is routed to the cerebral cortex via the thalamus (Steriade and Llinas 1988). In particular, every sensory system (with the exception of the olfactory system) includes a thalamic nucleus that receives sensory signals and sends them to the associated primary cortical area. The thalamus *is believed* to both process sensory information as well as relay and/or modulate it; each of the primary sensory relay areas in thalamus receives strong "back projections" from the cerebral cortex (Steriade and Llinas 1988). Another major role of the thalamus is devoted to "motor" systems. This has also been and continues to be a subject of interest for investigators. Although historically the thalamus was thought of as a "relay" that simply forwards signals to the cerebral cortex, contemporary research suggests that thalamic function is more selective and modulatory (Zou, Long et al. 2009).

The diffuse yet specific patterns of structural connectivity of the thalamus with the cerebral cortex suggest that thalamocortical connectivity could play an important role in regulating cortical activity. A regulatory role of the thalamus is strongly suggested by the coherence of cortical sleep spindles and alpha activity with thalamocortical interplay activity and intrathalamic feedback (McCormick and Huguenard 1992; Golomb, Wang et al. 1994; Contreras, Destexhe et al. 1996; Bazhenov, Timofeev et al. 1999; Goncalves, de Munck et al. 2006; Liu, de Zwart et al. 2012). In particular, studies using EEG–fMRI and fMRI–fMRI resting state correlation analyses have implicated the pulvinar nucleus of the thalamus in generating and modulating alpha rhythms in the occipital lobe, between which there are extensive reciprocal thalamocortical connections (Goncalves, de Munck et al. 2006; Liu, de Zwart et al. 2012). Other studies (McCormick and Huguenard 1992; Destexhe, McCormick et al. 1993; Golomb, Wang et al. 1994; Contreras, Destexhe et al. 1996; Bazhenov, Timofeev et al. 1999) have utilized theoretical methods to indicate the presence of specific alpha rhythm generators at the thalamic level. The role of the pulvinar in regulating cortical function was further elucidated in a nonhuman primate study (Saalmann, Pinsk et al. 2012) demonstrating that the pulvinar synchronizes activity between interconnected cortical areas according to attentional allocation, suggesting a critical role for the thalamus not only in attentional selection but more generally in regulating information transmission across visual cortices. (Staudigl, Zaehle et al. 2012) investigated thalamocortical communication during human long-term episodic memory retrieval and observed the impact of such thalamocortical communication on local frontal networks is expressed via a modulation of γ power by the thalamic β ($\sim$20–23 Hz) phase. Thalamocortical regulation, however, is not limited to the pulvinar. For example, the

ventrolateral and mediodorsal nuclei of the thalamus are believed to be important components of the frontal cortical-basal ganglia–thalamic circuits mediating motivation and emotional drive, planning, and the expression of goal-directed behaviors (Haber and Calzavara 2009). And in a more recent study (FitzGerald, Valentin et al. 2013) used data from epileptic patients undergoing thalamic deep brain stimulation and reported existence of PAC both within thalamus and prefrontal cortex (PFC) and between them.

Multimodality analyses including both structural and functional data within subjects provide unique opportunities to elucidate the nature of thalamocortical relationships. These analyses, however, hinge on the assumption that structural connectivity analyses, especially that of thalamocortical relationships, are functionally valid. While electrophysiological activity and functional relationships should theoretically correspond well with structural connectivity, complex neuronal interactions may occur via polysynaptic pathways and the strength or robustness of an anatomical connection is not always reflective of its functional significance. This is particularly true when investigating the potential role of one region in modulating or regulating another. Therefore in considering thalamo-cortical connectivity, functional and effective connectivity are as important as structural connectivity. Some studies have previously investigated the structural and functional connectivity of the thalamo-cortical system (Behrens, Johansen-Berg et al. 2003; Behrens, Woolrich et al. 2003; Behrens, Berg et al. 2007; Zhang, Snyder et al. 2008; Klein, Rushworth et al. 2010; Zhang, Snyder et al. 2010; Pouratian, Zheng et al. 2011; Elias, Zheng et al. 2012). In a seminal study using magnetic resonance diffusion tensor imaging (DTI) and probabilistic tractography, Johansen-Berg and colleagues (Behrens, Johansen-Berg et al. 2003) reported

anatomically specific and histologically concordant segmentation of the human thalamus based on each thalamic subregion (or nucleus) having a distinct pattern of cortical connectivity. Subsequent studies (Behrens, Berg et al. 2007) functionally validated this approach, demonstrating that thalamic functional activations during a motor task (detected using functional magnetic resonance imaging) co-localize with the thalamic regions with the highest probability of connectivity with motor and prefrontal cortical areas, respectively. Direct comparisons between structure and function *within subjects* however provide much stronger validation. This opportunity is uniquely afforded by neurosurgical procedures that provide access to invasive local field potential (LFP) recordings from multiple sites within the brain in patients who have also undergone DTI. Using this approach, we (Pouratian, Zheng et al. 2011) showed that probabilistic tractography can be used to segment the thalamus and identify specific thalamic subregions (most likely corresponding to thalamic nuclei (Behrens, Berg et al. 2007)) to be targeted for deep brain stimulation that will result in tremor suppression, suggesting that using this method to segment brain structures is in fact functionally meaningful and reliable across subjects. In a separate study (Elias, Zheng et al. 2012) of patients undergoing intracranial EEG monitoring with intrathalamic depth and subdural cortical strip electrodes, we validated thalamocortical tractography by tracking somatosensory evoked potentials (SSEP) through the thalamus and to the cortex in a manner that was concordant with predictions based on tractography.

Prior to the work described here, no distinct analysis on effective connectivity in thalamo-cortical network has been published. One main reason for this lack of investigation is activity dependent nature of effective connectivity, which requires

specific experimental designs that cannot be captured by the limited temporal resolution of MR imaging techniques.

1.3.2.2. PallidoCortical connectivity

The basal ganglia (BG) is a collection of interconnected subcortical nuclei (including the striatum, globus pallidus, substantia nigra, and subthalamic nucleus (STN) that have inputs and outputs to virtually all areas of the neocortex (Rosin, Nevet et al. 2007). Traditionally thought of only being involved in motor control, BG structures are now considered to be implicated in both expression of goal-directed movement and also emotions or motivation leading to the movement process itself. It has been shown that BG and cortex interact through parallel, segregated circuits (Smith, Raju et al. 2009). Each functional area in the frontal cortex is connected to BG through specific connections (Haber and Calzavara 2009). Cortical inputs enter the BG through the STN and striatum and then sent to substantia nigra and globus pallidus internus (GPi) (DeLong and Wichmann 2010).These specific BG zones are then topographically connected to specific portions of the thalamus which then projects back to the same areas of the cortex from which the circuit initiates (DeLong and Wichmann 2007).

1.4. Parkinson's disease and role of BG

Parkinson's disease (PD), a progressive neurodegenerative disease, is the second most common neurodegenerative disease after Alzheimer's disease (Wirdefeldt, Adami et al. 2011). The principal pathophysiologic mechanism in Parkinson's disease is often described as the loss of dopaminergic neurons with the substantia nigra resulting in loss

of dopamine in the striatum (Wirdefeldt, Adami et al. 2011), accounting, at least in part, for symptomatic motor deficits such as resting tremor, stiffness and slowness in movement (bradykinesia), postural instability and cognitive and emotional impairments and is usually classified as a movement disorder (Jankovic 2008). The Unified Parkinson's Disease Rating Scale [UPDRS] is used to follow the progression of PD (Ramaker, Marinus et al. 2002). Symptoms can be managed through medications (levodopa) or deep brain stimulation of BG nuclei (GPi and STN) or Ventral Intermediate Nucleus (ViM) nucleus of thalamus in advanced stages (Brown 2007; Bronstein, Tagliati et al. 2011). Deep brain stimulation (DBS) is a surgical procedure of implanting a battery-operated medical device (neurostimulator) to deliver high frequency electrical pulses to the targeted areas of BG or thalamus to alleviate debilitating motor symptoms of PD (Apetauerova, Ryan et al. 2006). Despite the long history of DBS (Gildenberg 2005), its direct effect on the physiology of brain cells and neurotransmitters and also exact role of BG in pathophysiology of the disease are still not completely understood (Moro and Lang 2006). DBS electrodes provide the unique opportunity of having access to electrical oscillations in BG. Understanding these oscillations, especially at the network level, may lead to better treatment of movement disorders such as Parkinson's disease (PD).

Although incompletely understood about PD, considering physiological role of BG oscillations in regulating network level activity, it is proposed that irregular oscillatory activity within the cortico-basal ganglia-thalamocortical circuits may account at least in part for the pathophysiology of Parkinson's disease (Brown 2003; Jenkinson and Brown 2011). Loss of dopamine in the BG is associated with a prominent amplification of power in β frequency band (13-35 Hz) throughout the motor system including both the

cortex and the basal ganglia (Mallet, Pogosyan et al. 2008; Cruz, Mallet et al. 2009). These amplified β oscillations are suppressed by movement, medication (levodopa) and DBS (Priori, Foffani et al. 2004; Kuhn, Kupsch et al. 2006; Hammond, Bergman et al. 2007; Eusebio, Thevathasan et al. 2011). A number of studies also reported correlation between degree of local β power suppression and severity of the disease as measured by UPDRS (Little and Brown 2012). Oscillatory activity in γ frequency band within the subthalamo-pallidal-thalamo-cortical circuit was also found to be of functional significance and showed evidence of dynamic modulation both by movement (Foffani, Ardolino et al. 2005) and dopaminergic medication (Brown 2003). Study of single unit recordings (Soares, Kliem et al. 2004) suggest that aberrant LFP synchronization reflects abnormal neuronal bursting activity and firing rate among nearby and distant neuronal populations (Levy, Hutchison et al. 2002).

Studies of cortical activity have also shown that β activity in cortex is correlated with the severity of the disease and reduction in this synchrony with DBS and medication has been found to be correlated with clinical improvement (Silberstein, Pogosyan et al. 2005; de Hemptinne, Ryapolova-Webb et al. 2013). The literature to date has been rich in characterizing the effect of movement or treatment (medication or stimulation) on activity in specific loci within narrow frequency bands. Only few studies have begun to investigate the relationship of signals between nodes within the motor network and more importantly, across frequencies. In addition to the local oscillations in BG or cortex, the work described here aims to establish the role of functional connectivity between these spatially segregated brain areas in the pathophysiology of the disease (Fogelson, Williams et al. 2006; Marreiros, Cagnan et al. 2013).

Besides its pathophysiologic significance, the oscillatory patterns described above may be a biomarker that can be used to study and track disease. Such biomarkers could theoretically be used in development of a DBS system with feedback control.

1.5. Dissertation Goals And Organization

Goal of this dissertation is to discuss two studies to investigate thalamo-cortical network and pallido-cortical network. In both cases simultaneous invasive-recordings from cortex and subcortical structure are used to examine possible mechanisms of regulation. PAC was of particular interest due to the existence of extensive interest and its unique power in explaining non-linear interactions between different frequency rhythms that are claimed to be functional and/or pathological.

This dissertation is divided to 4 chapters including the introduction.

Chapter 2 describes the thalamo-cortical coupling we found in patients with medication-refractory epilepsy who have simultaneous electrophysiological recordings from their thalamus and cerebral cortex. We explored the spatial specificity and time variability of coupling between different frequency bands within and between these structures in an effort to explain functional connectivity in such a network. We also confirmed that these thalamocortical functional relationships are structurally constrained by anatomic pathways.

In Chapter 3 pallidocortical study of 20 patients with Parkinson's disease undergoing deep brain stimulation is investigated. Evidence of pathological functionality of some of

the proposed biomarkers of the PD and their movement-induced modulations are explored and the results are portrayed.

Chapter 4 includes a discussion of the results presented in chapters 2 and 3 as well as suggestions for future works in order to complete the understating of cortico-basal ganglia thalamocortical circuit and specially its involvement in pathophysiology of movement disorders.

2. Thalamic regulation of cortical activity

During past decade more effort has been devoted to explain how oscillations in different frequency bands are interacting with each other mostly through non-linear mechanisms. In particular, the phase of lower frequency oscillations modulate the amplitude of higher frequency rhythms (Canolty, Edwards et al. 2006; Tort, Kramer et al. 2008; Lopez-Azcarate, Tainta et al. 2010). A putative electrophysiological mechanism for subcortico-cortical regulation is cross-frequency coupling (CFC), and more specifically phase-amplitude coupling (PAC), in which the phase of a low frequency rhythm from one signal regulates the power of higher frequency activity (either from the same or another signal). PAC has been described extensively as an inherent property of cortical electrophysiology and is postulated to play a role in regulation of an array of neural networks, including memory and learning, attention, and in sensory and motor processing (Bhattacharya 2001; Fries 2005; Lakatos, Shah et al. 2005). PAC provides a plausible physiological explanation for such subcortico-cortical mechanisms that require dynamic coordination of different frequencies with different spatial properties such as lower frequencies like θ or alpha rhythms (from subcortical region) and higher frequencies like β or γ rhythms (cortical sites) (Canolty and Knight 2010).While many works describe the existence of PAC within a cortical region, the literature has rarely described the spatial specificity of this phenomenon, the time variant nature of these complex relationships, nor the factors that may regulate such variation (Lakatos, Shah et al. 2005; Henriksson, Hyvarinen et al. 2009; Tort, Komorowski et al. 2009; Axmacher, Henseler et al. 2010; Canolty and Knight 2010; Lopez-Azcarate, Tainta et al. 2010; Pienkowski and Eggermont 2010). Specifically, the origin of the phase encoding frequency remains

speculative. Miller and colleagues (Miller, Hermes et al. 2010) provide a comprehensive report of temporal modulation of cortical PAC that is behaviorally-dependent. They identify the thalamus as a putative synchronizing locus that could provide the phase-encoding low frequency rhythms that modulate cortical activity. Given differences in the spatio-temporal profiles of lower and higher frequency electrophysiological rhythms (for example, it has been suggested that lower frequencies like θ modulate activity over large spatial regions and in long temporal windows while higher frequencies modulate activity over small spatial regions and short temporal windows activity) (Canolty and Knight 2010), the possibility of distinct sources for these signals is plausible and in fact probable. Changes in thalamic neuronal activity between tonic (Henning Proske, Jeanmonod et al. 2011) and bursting (Llinas and Jahnsen 1982; McCormick and Huguenard 1992) modes of activity are thought to create electrophysiologic oscillations that spread widely through both intrathalamic and thalamo-cortical connections, creating characteristic thalamocortical rhythms that could modulate cortical activity. Pathological thalamocortical rhythms, or thalamo-cortical dysrhythmia (TCD), have been hypothesized to be central to electrophysiological changes in some functional brain disorders (Llinas, Ribary et al. 1999; Sarnthein, Morel et al. 2005; Sarnthein, Stern et al. 2006; Walton and Llinas 2010). TCD posits that abnormal internally generated low frequency oscillations (mainly in θ range) in the thalamocortical network disrupts the normal state dependent flow between thalamus and cortex resulting in a broad range of functional disorders, including Parkinson's disease, depression, and chronic pain (depending on the thalamocortical network involved) (Llinas, Ribary et al. 1999; Llinas and Steriade 2006; Kane, Hutchison et al. 2009; Jones 2010). Still, direct evidence for a

subcortical source for low frequency rhythms is lacking to date and therefore remains speculatory.

To better elucidate the putative role of PAC as a mechanism of thalamocortical regulation, we analyzed and compared simultaneous cortical and thalamic electrophysiological recordings in two awake and spontaneously behaving human subjects who were undergoing invasive neurophysiological monitoring for medically refractory epilepsy who had had preoperative diffusion tensor imaging. We first extensively characterized cortical PAC to illustrate the time variant nature and spatial specificity of these signals. The time and spatial variance of cortical PAC are compared with simultaneously recorded thalamic LFP power spectra to evaluate the relationship between PAC and thalamocortical coherence of the phase-encoding rhythm. We subsequently used causality analysis and probabilistic tractography analyses to assess the thalamocortical flow of phase encoding rhythms and the structurally constraints on this flow of information.

2.1. Signals and recording

We studied two subjects with intractable epilepsy who underwent invasive monitoring to identify epileptogenic foci. Subdural ECoG strips, each containing four to eight 6 mm diameter contacts with 10 mm spacing (AD-Tech, Racine, WI), were implanted through standard frontal and parietal burr holes, per clinical protocol. After obtaining informed consent from the study participants, depth electrodes were stereotactically implanted subacutely in the thalamus based on a research protocol approved by the University of Virginia Institutional Review Board originally intended to

understand the role of thalamus in seizure propagation (Bertram, Mangan et al. 2001). Each depth electrode consisted of tubing (1.1 mm outer diameter) with 10 cylindrical platinum contacts of 2.3 mm length with an interelectrode distance of 5 mm (AD-Tech). All recordings were done with 200 Hz sampling rate with patients spontaneously behaving (based on simultaneous video recordings). One hour epochs of data were sampled from each subject. Data were extracted from seizure free periods (based on expert neurologist interpretation). Episodes with noise contamination were identified by visual inspection of their power spectra, and periods during which the power spectra had abnormally high values were spliced out of the data. To minimize effects of volume conduction, the data were used in a bipolar montage, with the time courses from adjacent electrodes subtracted from one another.

2.2. Methods

2.2.1. Power spectral analysis

Before further processing 60 Hz line noise was removed from the data and all following steps were done using a moving window of 10 seconds length and 50% overlap. To estimate the power spectral density of both cortical and thalamic signals, we used the multi-taper method implemented in Chronux (Bokil, Andrews et al. 2010). To circumvent the limitations of conventional Fourier analysis in estimation of power spectra (which introduces undesirable bias in its estimate in the setting of noise), the multi-taper method uses mutually orthogonal tapers (which are multiplied element-wise by signals) providing multiple independent estimates of spectra (called tapered spectra). The final spectrum is obtained by averaging these tapered spectra.

2.2.2. Phase Amplitude Coupling

PAC we estimated using Tort's relative entropy method (Tort, Komorowski et al. 2010), which we refer to as Modulation Index (MI). Given signals $X_{raw,1}(t)$ and $X_{raw,2}(t)$ containing phase and amplitude components of interest, respectively, we used wavelet transform (Morlet packet with width 7) to extract the instantaneous phase and amplitude signals respectively, providing $\varphi_{\mathrm{ph}}(\mathrm{t})$ and $A_{amp}(t)$. $\varphi_{\mathrm{ph}}(t)$ phases are then binned and the mean of amplitude ($A_{\mathrm{amp}}(t)$) over each bin is calculated and normalized and referred to as $P(j)$ (for $j = 1,2,\dots,N$ where N is number of bins). P has the characteristics of a probability density function and can be referred to as an "amplitude distribution" when plotted as a function of the phase bins. When there is strong coupling/modulation between phase and amplitude signals this distribution deviates from the uniform distribution. Therefore we define modulation index (MI) to be the distance between uniform distribution and. P. Mathematical formulation for MI would be as follow:

$$D(P,U) = \left(\sum_{j=1}^{N} P(j) \log\left(\frac{P(j)}{U(j)}\right) \right)$$

Where U is the uniform distribution defined over the same phase bins. $D(P,U)$ is the KL distance between P and uniform distribution. Because

$$D(P,U) = \ log(N) + \left(\sum_{j=1}^{N} P(j) \log\big(P(j)\big) \right)$$

Based on the definition of Shannon entropy we can define $H(P)$ to be:

$$H(P) = -\left(\sum_{j=1}^{N} P(j)\log\big(P(j)\big)\right)$$

Therefore $D(P,U)$ can be rewritten as:

$$D(P,U) = \log(N) - H(P)$$

And finally we put:

$$MI = \frac{D(P,U)}{\log(N)} = 1 - \frac{H(P)}{\log(N)}$$

Because $H(U) = \log(N)$, when there is no coupling and P is in fact a uniform distribution, $H(P)$ would be equal to $\log(N)$ and $MI = 0$.

Where there is stronger coupling $H(P)$ becomes smaller than $\log(N)$ and MI increases. We calculated MI using frequencies ranging 1-70 Hz in 1 Hz steps for the phase-encoding signals and 2 Hz steps for amplitude (power) signal.

2.2.3. Surrogate data analysis

A surrogate data analysis using a shuffling procedure was used to evaluate the significance of derived MI values. For each signal pair ($\varphi_{\mathrm{ph}}(t)$, $A_{\mathrm{amp}}(t)$), we generated 100 temporally shuffled versions of amplitude signals and calculated MI values for each. We then compared the true MI relative to the 100 surrogate MI values and obtained a Z-score. Only MI values with corresponding Z-scores above 1.96 (corresponding to a p-

value < 0.05) were maintained for subsequent consideration. MI values that were non-significant (i.e., Z-value less than 1.96) were not included in MI maps.

2.2.4. Cross coherence analysis

After obtaining power spectra ($S_{\mathrm{x}}(f)$ and $S_{\mathrm{y}}(f)$) and also cross spectra ($S_{\mathrm{xy}}(f)$ which is a measure of joint power of two signals x and y per unit frequency) using the multi-taper method, we estimated cross coherence $C_{\mathrm{xy}}(f)$ as:

$$C_{\mathrm{xy}}(f) = \frac{|S_{\mathrm{xy}}(f)|}{\sqrt{S_{\mathrm{x}}(f)S_{\mathrm{y}}(f)}}$$

We calculated the coherence for pairs of signals in thalamocortical network and derived cross coherence as a measure of frequency, which describes degree of co-variability between the two signals over different frequency ranges. To find the time-frequency representation of coherence for the same pair of signals we used a moving window approach to find the coherence at each frequency over time. This form of time-frequency representation allows for observing pattern of change in coherence over time.

2.2.5. Granger causality and directed transfer function analysis

Directional transfer function (DTF) is a derivation of Granger causality (GC), which is a data-driven approach to assess the causal relationship (directional causal interaction) between two time series (Kaminski and Blinowska 1991). This method has been widely used in the analysis of both LFP and intracranial recordings (Brovelli, Ding et al. 2004; Chen, Bressler et al. 2006; Bressler, Richter et al. 2007; Wang, Chen et al. 2007; Bollimunta, Chen et al. 2008; Wang, Chen et al. 2008; Gow, Keller et al. 2009;

Tass, Smirnov et al. 2010; Ding, Mo et al. 2011; Zhang, Chen et al. 2012). However, GC limits analysis to two time series. We therefore used the adapted multivariate version of it, the directed transfer function to further characterize thalamocortical functional relationship. Causality was evaluated using eConnectome (Electrophysiological Connectome) (He, Dai et al. 2011) toolbox an open source Matlab software package that has been specially developed to investigate directional interactions between multiple electrophysiologic signals. DTF takes into account all signals simultaneously and makes possible estimation of activity flow in a given direction as a function of frequency. DTF is robust in respect to noise and constant phase disturbances; in particular it discriminates against volume conduction, which propagates with zero phase (Kaminski, Ding et al. 2001). Normalized version of DTF (which has been used here) is calculated as (Kaminski, Ding et al. 2001):

$$DTF^2_{a\to b}(f) = \frac{|H_{ba}(f)|^2}{\sum_{i=1}^{ch} |H_{bi}(f)|^2}$$

In which $H_{ba}(f)$ is the (a, b) element in the MultiVariate AutoRegressive (MVAR) model Matrix for the system of signals and $DTF^2_{a\to b}(f)\mathrm{DTF}^2_{\mathrm{a}\to\mathrm{b}}(\mathrm{f})$ is a number between 0 and 1 producing the ratio between inflow from channel a to channel b to all the inflows to channel b.

2.2.6. Diffusion Tractography probabilistic segmentation

Probabilistic diffusion tractography was used to define patterns of structural connectivity between regions of interest, using methods previously described in detail using FSL tools (FMRIB's Diffusion toolbox (FDT); http://www.fmrib.ox.ac.uk/fsl)

(Johansen-Berg, Behrens et al. 2005). FDT (BEDPOSTX) uses Bayesian techniques to estimate a probability distribution function (PDF) on the principal fiber direction at each voxel, accounting for the possibility of crossing fibers within each voxel. Two fibers modeled per voxel, a multiplicative factor (i.e., weight) of 1 for the prior on the additional modeled fibers, and 1000 iterations before sampling (Behrens et al., 2007). Eddy current correction was used to apply affine registrations to each volume in the diffusion dataset to register it with the initial reference B0 volume prior to performing tractogrpahy. Skull stripping was performed using the brain extraction tool (BET). Using these PDFs and PROBTRACKX, we could then determine the probability of connection between seed voxels (in the desired cortical strip) and the predefined thalamic targets chosen to cover the inter-space between adjacent thalamic contacts (using 5000 samples, a 0.2 curvature threshold, and loopcheck termination). The cortical seed (corresponding to the location of ECoG recordings) was then segmented into distinct regions on a voxel-by-voxel basis based on the thalamic target with which each cortical voxel was most dominantly connected.

2.3. Results

Simultaneously acquired ECoG and thalamic depth recordings of LFP in two awake and spontaneously behaving patients undergoing invasive electrophysiological monitoring for medication-refractory epilepsy were evaluated. Multiple thalamocortical pairs were evaluated in each subject with similar patterns observed for each thalamocortical pair studied. For descriptive and analytic purposes, detailed results are provided for a single thalamocortical pair in one subject. Results of the other subjects are provided in **Figure 6-7.**

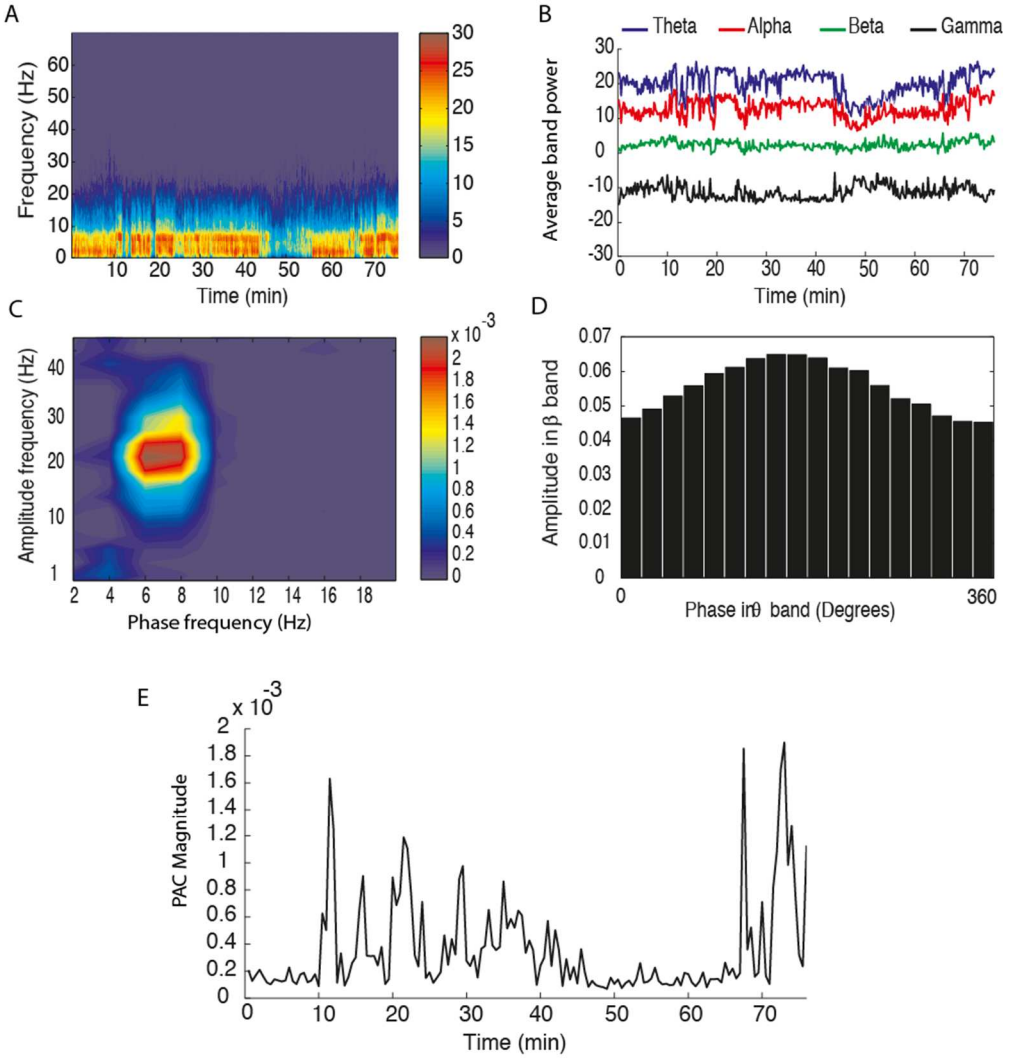

Figure 1 (A) Time Frequency representation of power spectral density for the cortical contact 4 from Fig. 2A. Color bar represents power in dB. (B) Time-dependent variability of distinct frequency bands, demonstrating variability in theta power. (C, D) Assessment of phase-amplitude coupling within cortical contacts consistently revealed significant PAC between the phase of theta frequencies and the amplitude of β rhythms (color bar represents Modulation Index (unit-less)), with peak β amplitudes occurring contemporaneously with theta troughs (E). Theta-β PAC, like theta power, was temporally dynamic, with as much as $3.54 \times 10^{-4} \pm 3.62 \times 10^{-4}$ variability over time.

2.3.1. Temporal Dynamics and Spatial Variability of Cortical Power Spectra and PAC

Cortical ECoG signals demonstrated time-variant spectral power (Figure 1A) with pronounced variability occurring in the θ band (19.92 ± 3.54 dB, Figure 1B). In some contacts (see discussion of spatial variability below), significant PAC between the phase of θ frequencies and the amplitude of β rhythms was noted ($p < 0.05$, Figure 1C and 1D). The phase encoding frequency corresponded to the band containing the most time-dependent variability in power and the peak frequency within this band. At contacts with significant θ-β PAC, the magnitude of the PAC was temporally dynamic ($3.54 \times 10^{-4} \pm 3.62 \times 10^{-4}$, Figure 1E). While PAC was noted in several cortical contacts, it was not uniformly observed across all contacts (Figure 2). In fact, the presence of PAC was related to the presence of a θ peak in the PSD of the ECoG signals at each contact (Figure 2A-C, contacts 3-5).

2.3.2. Temporally Dynamic and Spatially Specific Thalamocortical PAC

To elucidate relationships between thalamocortical activity and cortical electrophysiological dynamics, we initially evaluated thalamocortical coherence as a measure of thalamocortical functional connectivity between the cortical contacts showing or being adjacent to those with strong PAC and simultaneously recorded LFP from throughout the thalamus. Indeed, inspection of the data suggested cortical contacts demonstrating θ peaks (Figure 2B) and intracortical PAC (Figure 2C, contacts 3-5) seemed to demonstrate increased thalamocortical θ coherence with certain thalamic contacts, suggesting a link between thalamic and cortical θ activity.

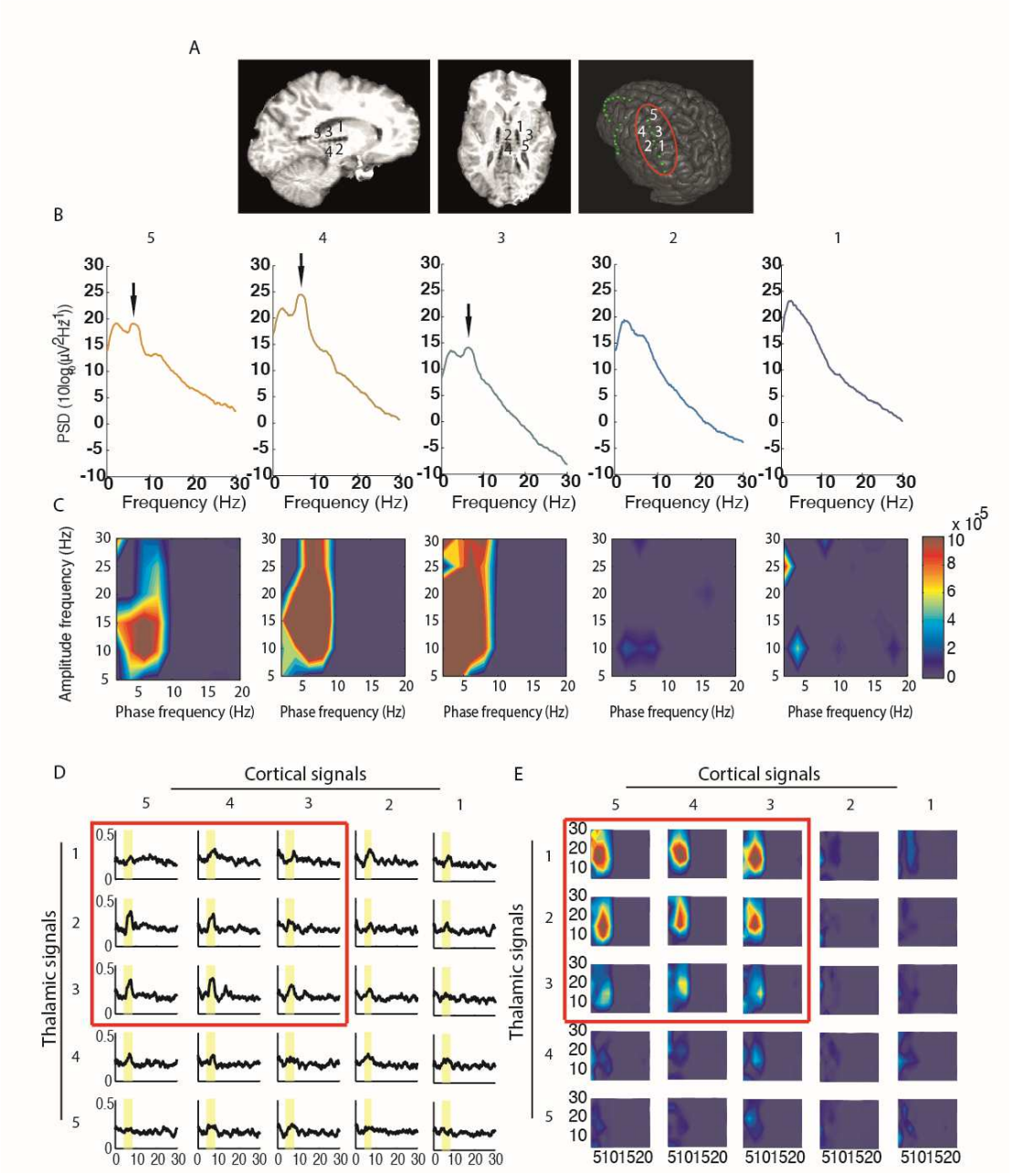

Figure 2 (A) From left to right: electrode placement for thalamic and cortical contacts (B) Power Spectral density for cortical contacts placed according to panel A. (presence of theta peak is indicated by the downward arrow) (C) Intracortical PAC within same cortical contacts as in panel B in which theta-β PAC is observed in cortical signals with theta peak in their power spectral density (as in panel B). (D) coherence between thalamic (columns) and cortical (rows) pairs. (E) PAC between phase of thalamic signals and amplitude of cortical signals. Note the peak of coherence in theta frequency range between thalamic signals and cortical signals with significant theta-β PAC (red box) (using the same scale as panel (C) for PAC)

The relationship between thalamocortical θ coherence and cortical θ power and intracortical PAC is analyzed more quantitatively in subsequent analyses (see next paragraph and Figure 3). Furthermore, thalamocortical pairs demonstrating significant *thalamocortical* PAC (Figure 2E, red box), in which the phase of the θ frequency band from thalamic signals modulates the amplitude of the β band activity recorded from cortical contacts were also found to have strong θ band coherence (corresponding to the same contacts in which we observed intracortical PAC previously described in Figures 1 and 2C). To quantify this correspondence we measured the correlation between thalamocortical θ coherence and thalamocortical PAC over the thalamocortical signal pairs and found $R^2 = 0.4544$ with P-value = 2.2x10-4.

Like cortical θ power and PAC (Figure 1B and 1E), the spatially specific and concordant thalamocortical θ coherence and θ-β PAC were temporally dynamic (Figure 3A and 3E) and significantly correlated in time with one another (Figure 3C, with $R^2 = 0.4138$ and P-Value = 3.9989×10^{-19}). Thalamocortical θ coherence was also highly correlated with cortical θ power (Figures 3A, 3B, 3D, $R^2 = 0.3379$, P-Value = 4.0898×10^{-15}), which itself was highly correlated with intracortical θ-β PAC (Figure 3D and 3H, with $R^2 = 0.4988$ and P-Value = 2.8901×10^{-24}). Finally, thalamocortical and intracortical θ-β PAC were likewise highly correlated (Figure 3G, with $R^2 = 0.3209$ and P-Value = 8.4968×10^{-14}).

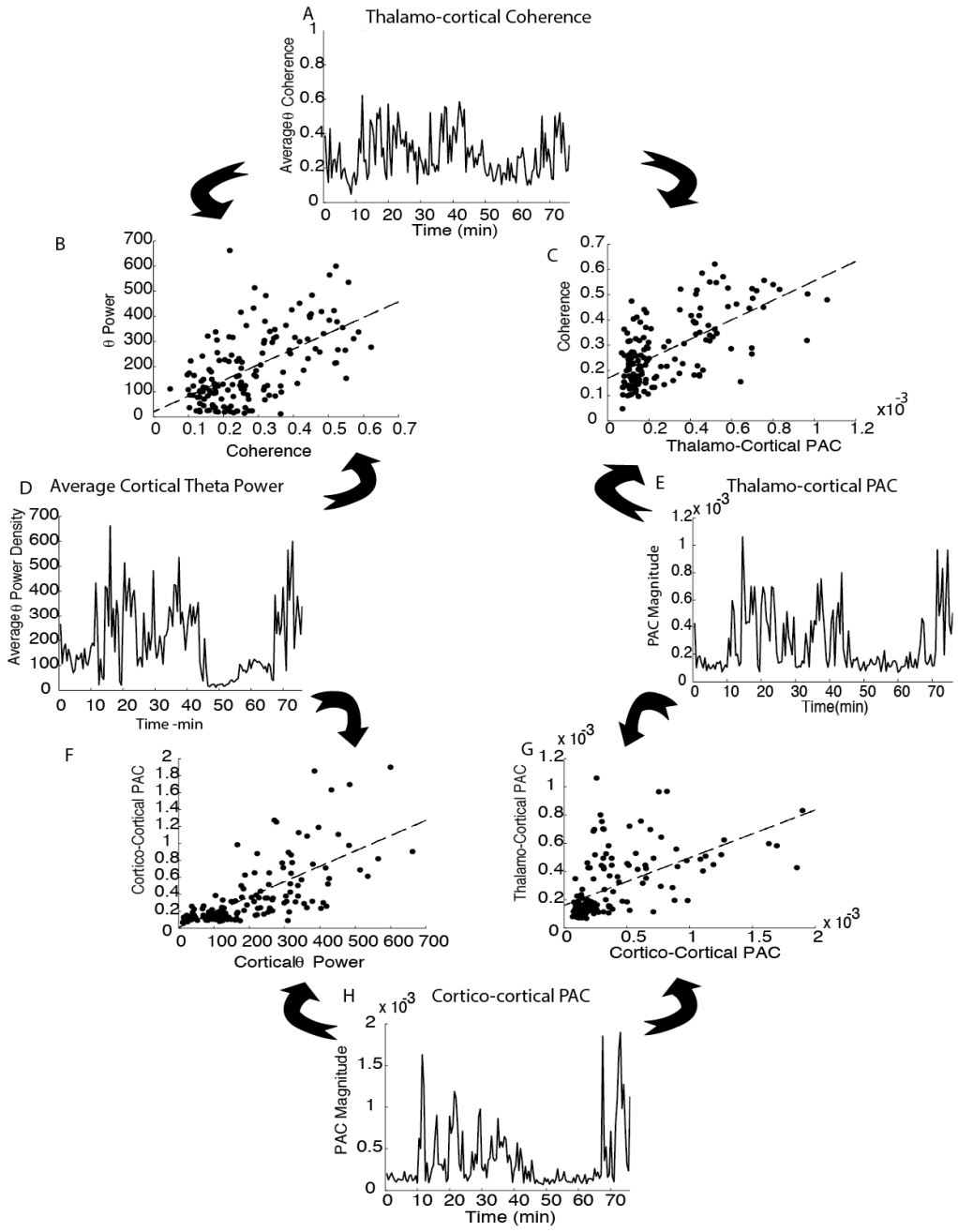

Figure 3 (A) Average theta band thalamo-cortical coherence over time. (B) Scatter plot between average theta coherence and average cortical theta power (R2 = 0.3379, P-Value = 4.0898×10-15). (C) Scatter plot between thalamo-cortical theta coherence and thalamo-cortical PAC (R2 = 0.4138, P-Value = 3.9989×10-19). (D) Average cortical theta power over time. (E) Average Thalamo-cortical PAC over time. (F) Scatter plot between average cortical theta power and cortico-cortical PAC (R2 = 0.4988, P-Value = 2.8901×10-24). (G) Scatter plot between thalamo-cortical and cortico-cortical PAC (R2 = 0.4138, P-Value = 8.4986×10-14). (H) Average cortico-cortical PAC over time

2.3.3. Θ Rhythms Flow from Thalamus to Cortex

We used causality to evaluate which area is driving (causing) activity in the other one, with a particular focus on the phase encoding θ band in order to understand if in fact thalamic signals are driving cortical PAC patterns. Causality analysis between thalamic and cortical contacts found to have high θ flow during a 1 minute period of high PAC demonstrated temporally dynamic patterns as illustrated in Figure 4A-F with cortico-cortical, thalamo-thalamic, and thalamo-cortical influences but little to no cortico-thalamic flow of signals in the θ band. On average (Figure 4G), while there is flow of θ signals within thalamus and within cortex, the direction of flow of θ signals between thalamic and cortical signals is from the thalamus to the cortex.

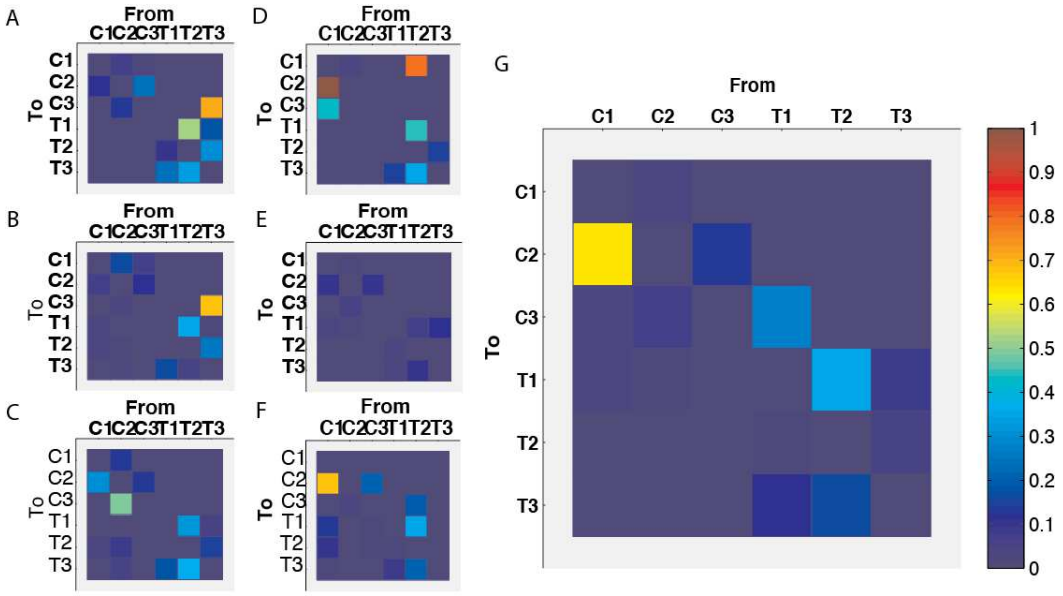

Figure 4(A-F) Average theta DTF for thalamocortical grid every 10 seconds during a 1 minute period of high PAC (C indicates cortical and T indicates thalamic). G) Average theta DTF of panels A-F, demonstrating flow of theta signals within thalamic and within cortical contacts, but only from thalamus to cortex.

2.3.4. Thalamocortical Dynamics are Constrained by Structural Connectivity

The variability of θ power across cortical contacts (Figure 2A) as well as the variability of coherence and PAC across thalamocortical pairs (Figure 3A and 3B) suggest a spatial specificity to the observed variance. Further analyses were therefore done to elucidate the potential contributions of structural connectivity to the observed thalamocortical functional phenomena.

In order to confirm the tight relationship between functional and structural thalamocortical connectivity, we performed probabilistic tractography to determine the relative strength of connectivity between cortical and thalamic recording sites (Figure 4). The strongest probabilistic structural connectivity was identified between the thalamic and ECoG contacts displaying thalamocortical coherence and PAC (Figure 4). Specifically, using the entire ECoG strip as a seed mask, we found that the part of ECoG strip that is most strongly structurally connected to the thalamic contacts of interest (defined as the thalamic contacts that demonstrated thalamocortical coherence and PAC [see Figure 2], as indicated by the target mask as in panels A and B,) corresponds to the three cortical contacts demonstrating the time-variant thalamocortical θ coherence and thalamocortical θ-β PAC detailed in Figures 2 and 3. We calculated the average number of probabilistic tractography "hits" within spherical masks around cortical LFP contacts seeded from thalamic contacts indicated in Fig 5-A and used this as a measure of strength of connectivity to those thalamic contacts. Fig 5-F shows that the strength of thalamocortical connectivity between the thalamic contacts of interest and each cortical contact strongly correlated with average thalamocortical θ-β PAC ($R^2 = 0.9166$, $p=0.01$).

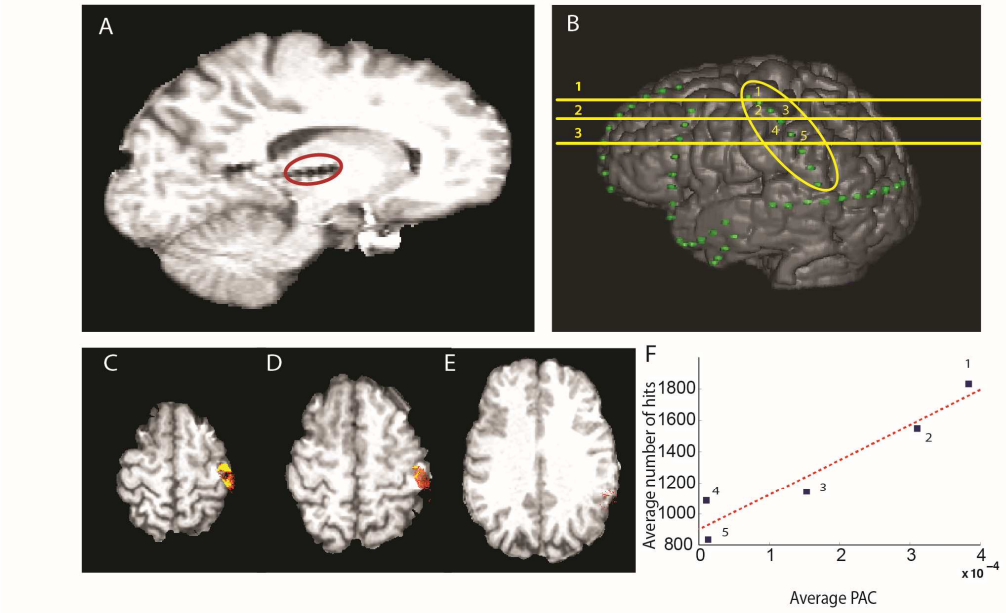

Figure 5 (A-F) Average theta DTF for thalamocortical grid every 10 seconds during a 1 minute period of high PAC (C indicates cortical and T indicates thalamic). G) Average theta DTF of panels A-F, demonstrating flow of theta signals within thalamic and within cortical contacts, but only from thalamus to cortex.

2.3.5. Generalizabilty to other Thalamocortical Pairs in Same and Other Subjects

Identical thalamocortical functional and structural connectivity patterns were observed for other pairs of thalamic and cortical electrodes in this same subject (Figure 6). Likewise, consistent patterns of time variant, spatially specific, and structurally constrained thalamocortical functional coupling and modulation were found in the second subject (Figure 7).

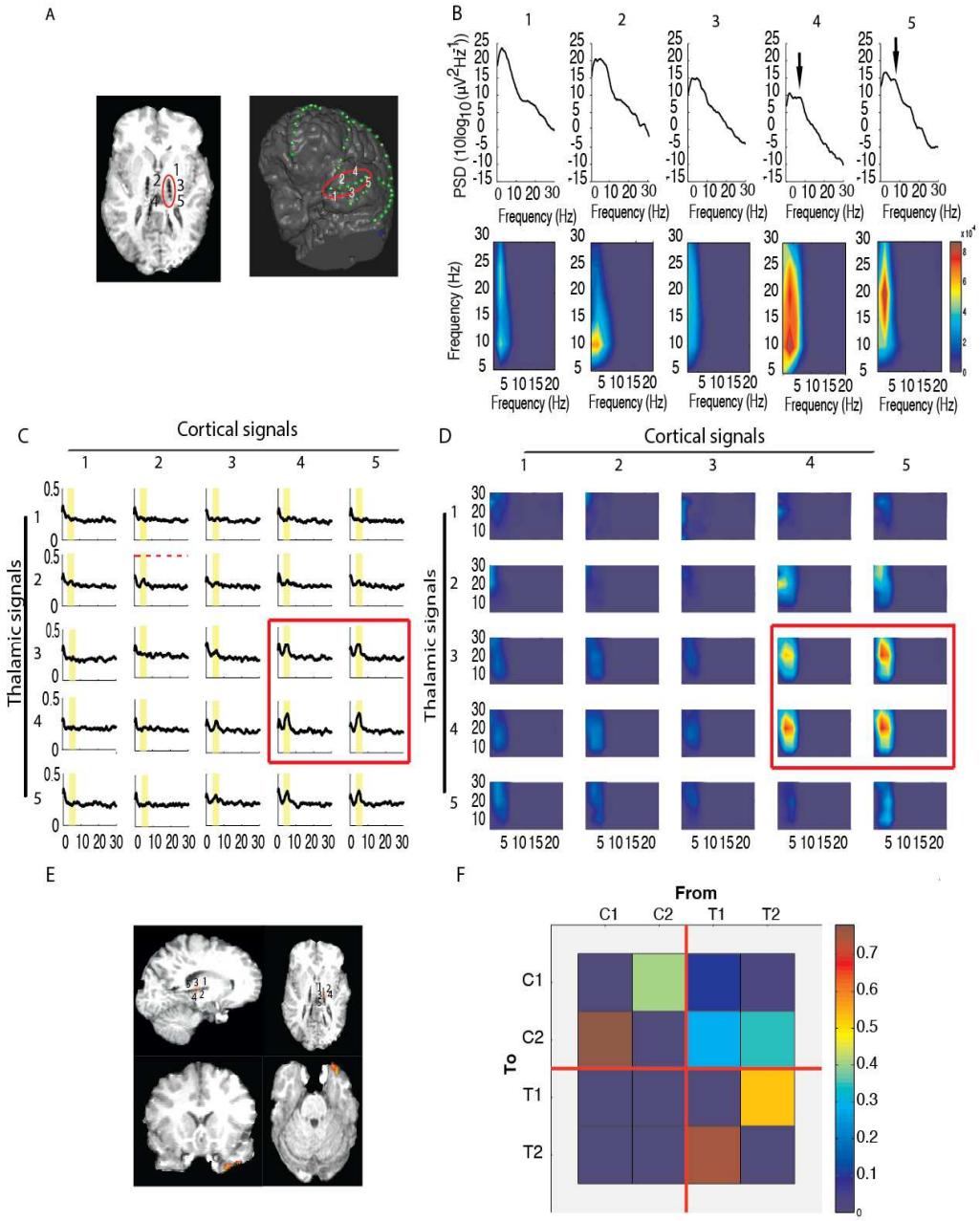

Figure 6 (A) (from left to right) location of thalamic and cortical electrodes B) top row: Power Spectral Denisty for cortical contacts, bottom row: PAC within same cortical contacts as in panel A. C) coherence between thalamic (columns) and cortical (rows) pairs. D) PAC between phase of thalamic signals and amplitude of cortical signals (using the same scale as panel (B) for PAC). E) sagittal and transverse views of probabilistic tractography maps showing the cortical area in the cortical strip most connected to the thalamic target mask F) Average theta DTF for thalamocortical grid Average theta DTF for thalamocortical grid highlighted in panels C and D.

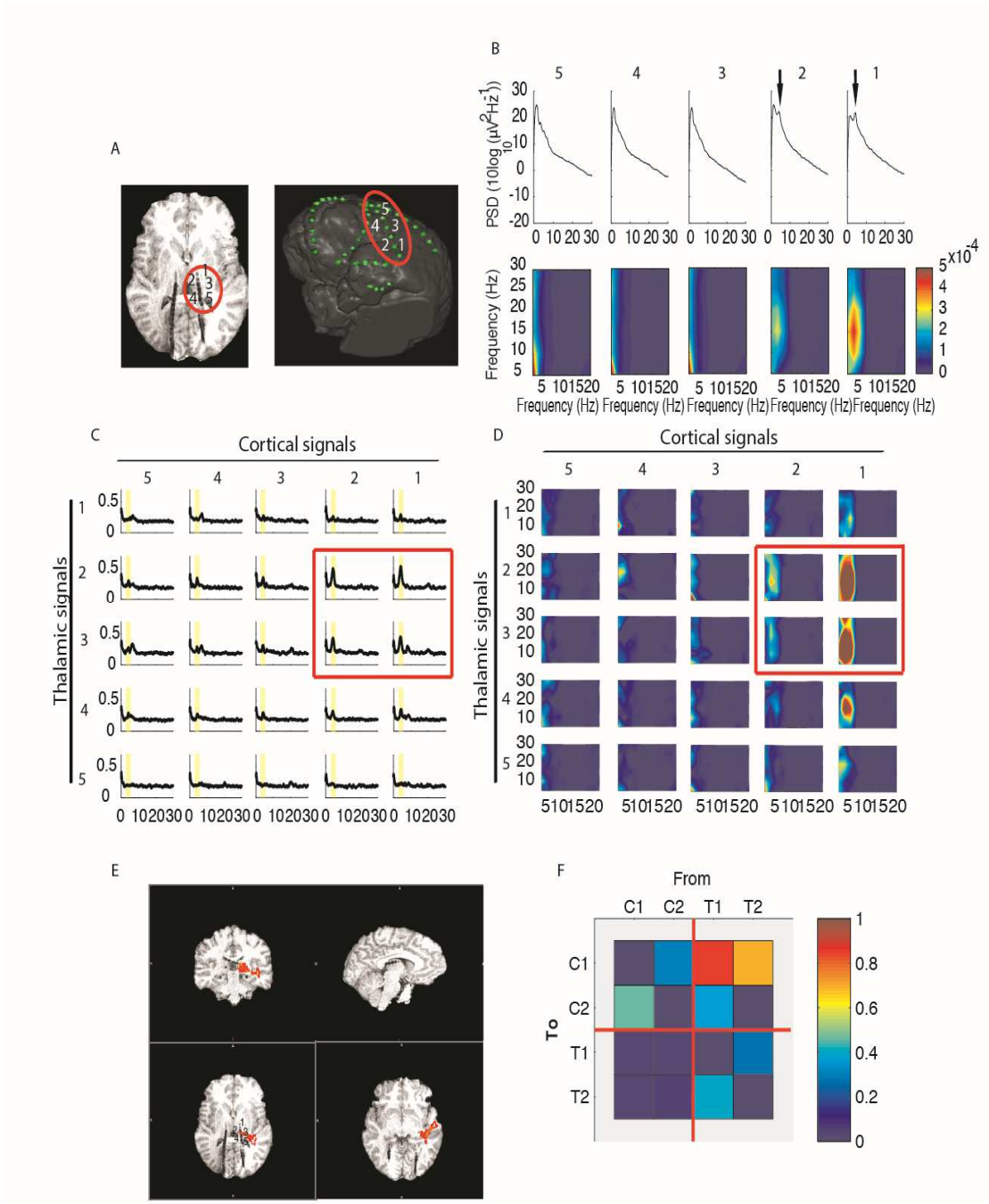

Figure 7 (A) (from left to right) location of thalamic and cortical electrodes B) top row: Power Spectral Denisty for cortical contacts, bottom row: PAC within same cortical contacts as in panel A. C) coherence between thalamic (columns) and cortical (rows) pairs. D) PAC between phase of thalamic signals and amplitude of cortical signals (using the same scale as panel (B) for PAC). E) Results of probabilistic tractography maps showing the cortical area in the cortical strip most connected to the thalamic target mask. F) Average theta DTF for thalamocortical grid Average theta DTF for thalamocortical grid highlighted in panels C and D.

2.4. Disscussion

We sought to use this unique and difficult to acquire dataset of simultaneously recorded ECoG and thalamic LFP recordings in humans to provide new evidence of thalamic modulation of cortical eletrophysiological activity via phase-amplitude coupling. In order to do this, we first highlight the rarely discussed point that cortical PAC is in fact not a universal phenomenon, but a spatially specific and temporally dynamic one. The variable nature of PAC across time and across cortical recording sites and thalamocortical pairs is an essential prerequisite to positing that PAC serves as a dynamic regulatory mechanism of cortical activity. This is consistent with the hypothesized function of PAC in regulation of cortical activity, as it pertains to memory, attention, sensory and motor programming (Bhattacharya 2001; Fries 2005; Lakatos, Shah et al. 2005). While PAC has been recognized as a putative regulation mechanism by which subcortical structures may regulate cortical activity (Tort, Komorowski et al. 2009; Lopez-Azcarate, Tainta et al. 2010; Pienkowski and Eggermont 2010), the etiology and regulation of the phase encoding frequency has remained theoretical. Our analyses provide the first direct electrophysiological evidence of thalamocortical coupling with causality analysis that implicates thalamic contributions to the modulation of spontaneous cortical activity. This study supports the central role of the thalamus, at least in part, in regulating cortical activity and affirms conclusions of other studies based on indirect evidence that thalamus is in fact modulating cortical activity. While the results of the current address the exact purpose or function of PAC, one can hypothesize that PAC could mediate the binding problem, by coordinating activity in distinct cortical areas in order to both integrate information across cortical areas (addressing the combination

problem) as well as to dynamically segregate distinct information processing streams. Studies in nonhuman primates in fact support the potential role of the thalamus in regulating activity across distinct visual cortices, showing that the pulvinar coordinates activity between interconnected cortical areas in an attention-dependent manner (Saalmann, Pinsk et al. 2012). Further task-specific studies in humans are necessary to further characterize the function of PAC.

As would be predicted, thalamic modulation of ongoing spontaneous cortical activity is regulated by structural constraints imposed by direct anatomic connectivity, as defined by MR diffusion connectivity analyses. We did not observe any cases of modulation by second order connections implying the regulatory role of the thalamus is limited to first order connections. This is in fact similar to what Saalmann et al found in nonhuman primates indicating pulvinar synchronizing attentional activity between interconnected cortical regions that are also directly connected to the pulvinar thalamus (Saalmann, Pinsk et al. 2012). The thalamus and its subregions are therefore most likely only regulating and coordinating between cortical regions with which there is direct anatomic connectivity and not exerting a regulatory role via distant synapses. Coordination of distant functional cortices may in fact be mediated by intrathalamic connectivity and interplay.

The coordinated dynamic nature of thalamic and cortical signals and the causality analysis presented are strongly suggestive of a regulatory role of thalamocortical PAC. In these spontaneously behaving subjects, significant time-dependent variability is seen in θ power, β power, thalamocortical θ coherence, intracortical PAC, and thalamocortical PAC. Despite the significant time dependent variability, these measures demonstrate

remarkable co-variance and a consistent relationship, suggesting a uniform process of regulation and modulation. Failure of such coupling may account for pathophysiology of various diseases, as has been suggested by the concept of thalamocortical dysrhythmia in which disruption of the normal flow between thalamus and cortex has been contributed to different functional disorders (Henning Proske, Jeanmonod et al. 2011); (Llinas, Ribary et al. 1999; Llinas and Steriade 2006; Kane, Hutchison et al. 2009; Jones 2010).

While these studies have provided significant insight, there are limitations to the current dataset and analyses. As data was primarily acquired for clinical purposes, sampling frequency was limited to 200 Hz which precludes assessment of coupling of high γ band frequencies, which are an area of increasing interest. With the current insight, future studies should further investigate cortical-subcortical coupling phenomenon using very high sampling rates to better assess high γ (>70Hz) and very high γ (>200Hz) activity. Moreover, as a consequence of using data primarily acquired for clinical purposes, current analyses are done in awake and spontaneous behaving patients with epilepsy, rather than with specific tasks. While this limits the extensibility of the conclusions, it does provide insight into normal brain function in an unconstrained system. Task-based analyses will enable investigators to tease out the components of coupling and better understand causality of thalamocortical relationships in a more controlled setting. Because of the need for invasive recordings, there is no foreseeable way to circumvent recordings in diseases patients; these limitations must always be considered in interpreting the generalizability of the current results.

Nevertheless, having established and provided direct evidence for the first time of thalamocortical regulation in spontaneously behaving humans, future studies must further

elucidate the regulatory role and dynamic nature of thalamocortical PAC. Questions remain as to the precise role of this regulation. Drawing from studies of PAC in Parkinson's disease (PD), it seems that PAC and therefore thalamocortical PAC and modulation is likely inhibitory in nature, with studies suggesting excess PAC in the motor cortex of patients with PD that improves with therapeutic intervention (de Hemptinne, Ryapolova-Webb et al. 2013). Moreover, the role of intrathalamic connectivity in coordinating regulation across remote brain regions remains to be better elucidated.

3. Network analysis of GPi and motor cortex in patients with Parkinson's disease

Alterations in the functional connectivity between the basal ganglia (BG) and cortex are likely a pathophysiological cornerstone of Parkinson's disease. Phase-amplitude coupling (PAC) plays a pivotal role in information processing throughout the motor network and is considered to be closely related to the pathophysiology. PAC in the motor cortex (M1) is exaggerated in PD patients compared to patients with epilepsy without movement disorder (de Hemptinne, Ryapolova-Webb et al. 2013). Furthermore, treatment (both medication and stimulation) changes this pattern of coupling. For instance subthalamic (STN) stimulation reduces the magnitude of PAC between phase of β and amplitude of γ in motor cortex (M1) (de Hemptinne, Ryapolova-Webb et al. 2013). Likewise, PAC within the STN between the phase of β and amplitude of very high γ frequencies (around 300Hz) is suppressed with dopaminergic medication (Lopez-Azcarate, Tainta et al. 2010).

The goal of this chapter is to characterize presence and activity-related modulation of PAC in the cortical and subcortical (GPi) motor network and how measures of PAC in distinct nodes of this network are inter-related with respect to cross-site coherence. Using simultaneous cortical-subcortical LFP recordings in PD patients undergoing deep brain stimulation (DBS), we demonstrated the time co-variability of cortical-GPi CFC to local spectral power as well as β coherence between GPi and motor cortex. We found PAC to be co-variable with coherence between the motor cortex and GPi, suggesting it may be a key mechanism of information integration across the entire cortico-basal ganglia circuit.

3.1. Subjects and recordings

We obtained deep brain LFP recordings from right GPi and simultaneous right frontoparietal electrocorticographic recordings (Figure 8) during rest and cued movement in 20 subjects (4 female and 16 male with age of 62.42 ± 11.71, Table 1) undergoing awake DBS implantation for Parkinson's disease. All subjects signed an informed consent form approved by the institutional review board (IRB) at the University of California, Los Angeles.

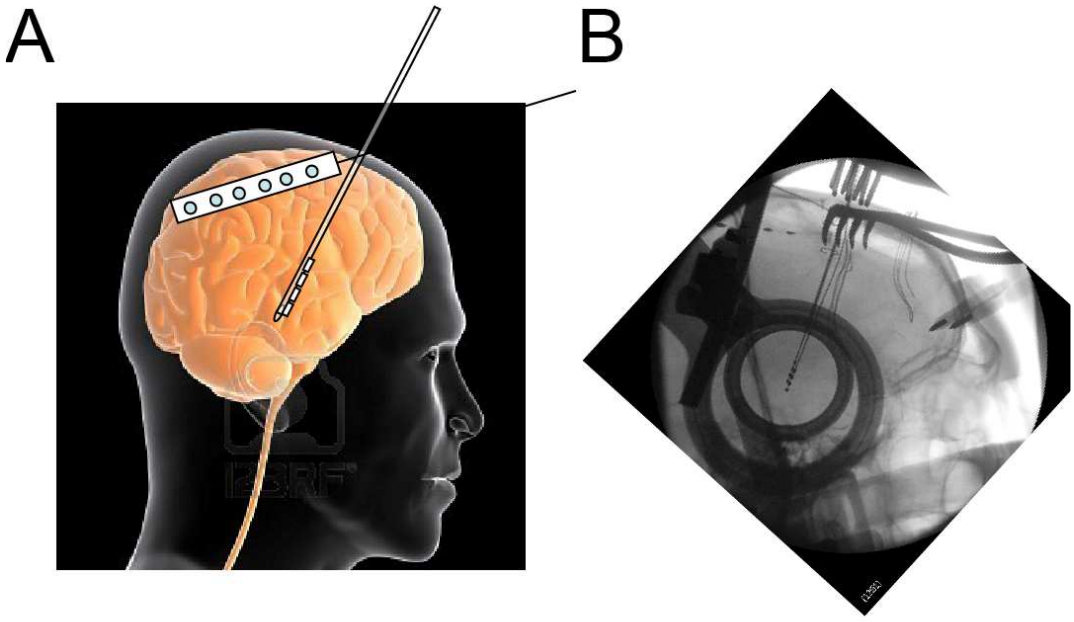

Figure 8 (A) Schematic showing electrode placement during DBS surgery ECoG strip extending frontoparietal through the burr hole and 4-ring DBS lead inserted in the right GPi (B) CT-scan showing the electrodes inserted into the brain

Table 1Subjects' demographic and clinical information

Subject ID	Gender	Age	MDS-UPDRS PIII off	MDS-UPDRS PIII on
S1	M	63	32	11
S2	F	78	35	NA
S4	M	65	NA	18
S5	M	66	35	18
S6	M	64	51	25
S7	F	76	39	22
S8	M	59	30	21
S9	M	72	43	9
S10	M	52	58	3
S11	M	60	21	4
S12	M	70	42	14
S13	M	69	52	14
S14	F	63	52	27
S15	F	69	33	9
S16	M	64	NA	21
S17	M	67	NA	17
S18	M	40	56	42
S19	M	72	46	9
S20	M	63	38	15
S21	M	51	59	40

3.1.1. Intraoperative electrophysiological recordings

For all subjects pallidal local field potentials were recorded from the DBS lead's four ring electrode contacts (DBS0-DBS3) (Medtronic, Model 3387, length 1.5mm, inter-contact distance 1.5mm) at their target coordinates for therapeutic stimulation. Data from additional locations along the last 24mm of the DBS lead trajectory were obtained in a subset, which were included in the analysis of a prior publication (Tsiokos, Hu et al. 2013). Unilateral electrocorticographic (ECoG) recordings were obtained from the right frontoparietal region by advancing a subdural ECoG strip with eight 4 mm platinum contacts with 1 cm inter-contact spacing (ECoG0-ECoG7) posteriorly through the burr hole used for DBS implantation in all but two subjects in whom recordings were not possible due to clinical reasons. Signal acquisition was performed using BCI2000 v2 or v3 connected to an amplifier (g.Tec, g.USBamp 2.0) using a sampling rate of 2400 Hz with a 0.1Hz-1000Hz band-pass filter. A data glove (5DT data glove 5 Ultra) worn by the patient on the left hand contralateral to the ECoG strip provided concurrent recordings at a slower effective sampling rate which was oversampled at 2400 Hz by BCI2000 using stair step interpolation. Ground and reference connections to the scalp were used. In addition, an amplifier potential equalization ECG lead was attached to the patient's left shoulder. A description of how the target coordinates for the GPi lead implantation were obtained is provided elsewhere (Tsiokos, Hu et al. 2013). Briefly, the DBS lead was targeted to the motor region of GPI, corresponding to the ventral posterolateral portion of GPi, usually 2 mm anterior, 19-24 mm lateral, and 4-6 mm inferior to the mid-commissural point (depending on individual patient anatomy). All trajectories were

confirmed clinically with intraoperative microelectrode recordings and intraoperative awake macrostimulation testing of final lead position, but this clinical data was not recorded in a manner that could be used for direct comparison with the current results.

3.1.2. Task and Timing

Deep brain and cortical signals were recorded at the final electrode implant position, during a 6 minute trial of alternating 30 seconds periods of rest and contralateral hand movement. In a subset of patients, as described in a previous publication (Tsiokos, Hu et al. 2013), signals were recorded as the DBS lead was advanced towards target during an 11 minute recording session which included 60 second intervals of rest, contralateral hand movement and transition (during which the lead was advanced). In these subjects, we have data recorded throughout a 24 mm span leading to the final DBS target location providing an opportunity to compare the signals in the target location and locations proximal to it in the trajectory.

3.2. Methods

3.2.1. Time series Preprocessing

Recorded signals were preprocessed to exclude time segments contaminated with artifacts as described previously (Tsiokos, Hu et al. 2013). All time epochs with artifact in any contact were removed prior to analysis. Visual inspection was used to remove segments with abnormal high spectral values or excessive noise harmonics. Bipolar (BIP) and Common Average Referenced (CAR) configurations were used for further analyses. To obtain bipolar signals, we subtracted each electrode time series from its immediate

neighboring electrode signal. CAR signals from ECoG strip and DBS lead were calculated by subtracting the local average across ECoG and DBS leads, respectively.

3.2.2. Spectral analysis

Six seconds, non-overlapping windows were used to calculate power spectral density for all subjects for both rest and movement trials. Prior to further analyses 60 Hz line noise was removed from signals by fitting significant sine waves at the line frequency and its harmonics and removing them from original data. To calculate the power spectra we used multitapering method implemented in Chronux (http://chronux.org/). The average band power for the θ (4 – 8 Hz), α (8-12 Hz), low β (12 – 20 Hz), high β (20 – 35 Hz), low γ (35 – 80 Hz), high γ (80 – 150 Hz), and very high γ (150 – 300 Hz), were calculated for each time window. These values were used to examine the temporal covariabiliy between fluctuations in power and other metrics such as PAC.

3.2.3. Cortical Movement Responsive Sites

For cortical recordings, ECoG signals were analyzed to identify the contacts that showed the greatest movement-related changes in spectral power. High β band power was chosen to determine the movement-responsive-sites (MRSs) because its movement-related change was most consistent across subjects. While both low and high γ band power changes were seen, given the very focal nature of γ band activations (Pfurtscheller, Graimann et al. 2003) and the fact that only a strip of electrodes were used for this analysis, movement-related changes in γ spectral power were not consistently observed across all subjects. For each subject, the MRS was chosen to be the contact with maximal high β band power suppression.

3.2.4. Coherence

We calculated the coherence for pairs of cortical and pallidal signals and derived cross coherence as a function of frequency for the range of frequencies 0 – 300 Hz to describe degree of co-variability between the signal pairs over different frequency ranges. To find the time-frequency representation of coherence for the same pair of signals, we emulated the moving window approach used in the spectral analyses described above, allowing evaluation of patterns of change in coherence over time.

3.2.5. Phase-to-amplitude cross-frequency coupling (PAC)

Phase amplitude coupling was calculated using the modulation index measure previously described (Canolty, Edwards et al. 2006; Tort, Kramer et al. 2008). For the pair of signals being examined, band pass filtering (2 way least square FIR) and Hilbert transform was used to extract instantaneous phase and amplitude time series. Mean values for amplitude time series were binned based on their corresponding phase values from the phase time series (Allocated into 18 bins with equal width).

After normalization (to the sum of mean values for all 18 bins) the mean values could be considered to have the characteristics of a probability density function referred to as "amplitude distribution". When there is strong coupling/modulation between phase and amplitude signals, this distribution deviates from the uniform distribution. Therefore the Kullback_Liebler distance between amplitude distribution and uniform distribution was proposed as a reliable measure of coupling (mathematical derivation is provided in Chapter2).

To account for statistical significance for the MI values extracted an approach of surrogate data analysis has been used (Identical to Chapter 2)

We used 50 surrogates for each phase and amplitude pair to derive a z-score approximation for the PAC in relation to the population of the surrogates. We used the range of frequency components for phase signal between 2-35 Hz in 1 Hz steps with 4 Hz bandwidth, and for amplitude signal between 3 – 300 Hz in 1 Hz steps and 6 Hz bandwidth, usinglarger bandwidth for the amplitude signal to accommodate for the increased spectral leakage of the LFPs in faster oscillations. The computation of PAC over a range of IPS and IAS components yielded a map of z-scores.

3.2.6. Statistical Analysis

All statistical analyses were done in R. Inter-subject analyses were performed to compare different quantities across the group of subjects. Violin plots (A Tukey's box plot with a rotated kernel density plot on each side) capable of adding information of local density estimates to the basic summary statistics (Hintze and Nelson 1998), guided us to use appropriate test to perform statistical comparisons between different variables. Oftentimes deviation of data distribution from normal distribution (skewness) precluded us from using two- sample t-test. For non-normal distributions assumption of independence between mean and variance of the sample data no longer holds and leads to poor performance of the t-test.

Robust method of Yuen-Welch test working by trimming a percentage of the more extreme cases from the population and adjusting the skewness and kurtosis of the

distribution to bring it closer to the normal distributions, has been proposed to account for inadequacy of regular two sample t-test (Wilcox 2012).

To examine the symmetry of coherence and PAC between GPi and morot cortex over time we derived each measure for blocks of rest and movement and rescaled them such that each measure has its maximum value to be equal to 1. We then found the sum of differences between corresponding points in time for each measure and used one-sample student t-test to compare the sum of differences for group of subjects with 0.

3.3. Results

3.3.1. Movement related changes in cortical signals

Calculating power spectral density in cortical signals during rest revealed presence of spectral peak at high β frequencies with mean of 23.79 ± 3.73 Hz across subjects.

Movement related changes in contralateral cortical power spectra were consistently observed across subjects, including a decrease in β power (both low and high) and increase in high γ power (Figure 9A and 9B). While movement related power changes were often seen across multiple contacts, the magnitude of movement modulation varied across the ECoG strip (Figure 10A shows how different cortical contacts show different power modulation by movement for a sample of subjects). The contact with the greatest high β power suppression was designated the movement-responsive sites (MRS) for subsequent analyses.

Movement-related changes in power spectra were more comprehensively evaluated in MRS.

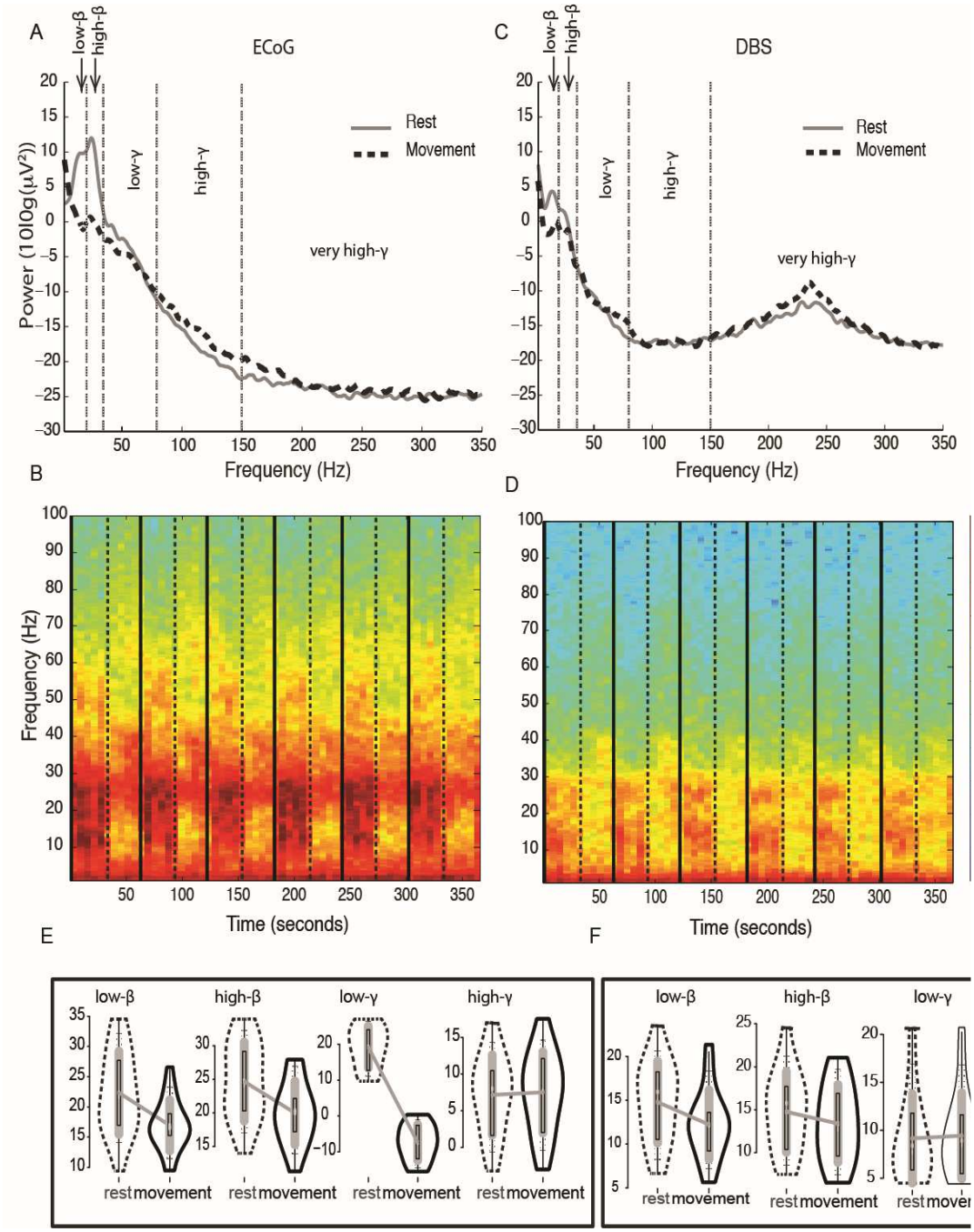

Figure 9 (A) Average power for movement and rest for the signal from a cortical contact (later identified as the MRS) for Subject S1. Dashed vertical lines are used to distinguish different frequency bands of low and high β and low and high γ (B) Time frequency power spectra for the same subject color coded - warmer colors indicate higher power. (C_D) show similar graphs as in (A-B) for the most ventral DBS contact for the same subject. (E) shows violin plots of different frequency bands for the group of subjects in their cortical MRS and how they change with movement. (F) is similar to (E) for pallidal signals in the group of subjects

Across subjects, significant movement-related modulation of high β power was observed at MRS (Yuen's test, $p = 5.18 \times 10^{-4}$), with an average high β suppression of 47.79% with movement at MRS. In contrast, while high β suppression was also observed at non-MRS sites (Yuen's test, $p = 3.48 \times 10^{-3}$), the average high β suppression at these sites was 32% (Figure 10C high β power modulation in MRS was significantly greater than in non MRS with p = 0.0018) . Significant movement-related changes were observed within other frequency bands at MRS as well (Figure 9E), including low β ($p = 1.27 \times 10^{-3}$, low, and high γ ($p = 4.48 \times 10^{-14}$ and p = 0.024 respectively). This contrasts with non-MRS, in which modulation of only low β ($p = 2.43 \times 10^{-4}$) and low γ ($p = 4.84 \times 10^{-3}$) were noted.

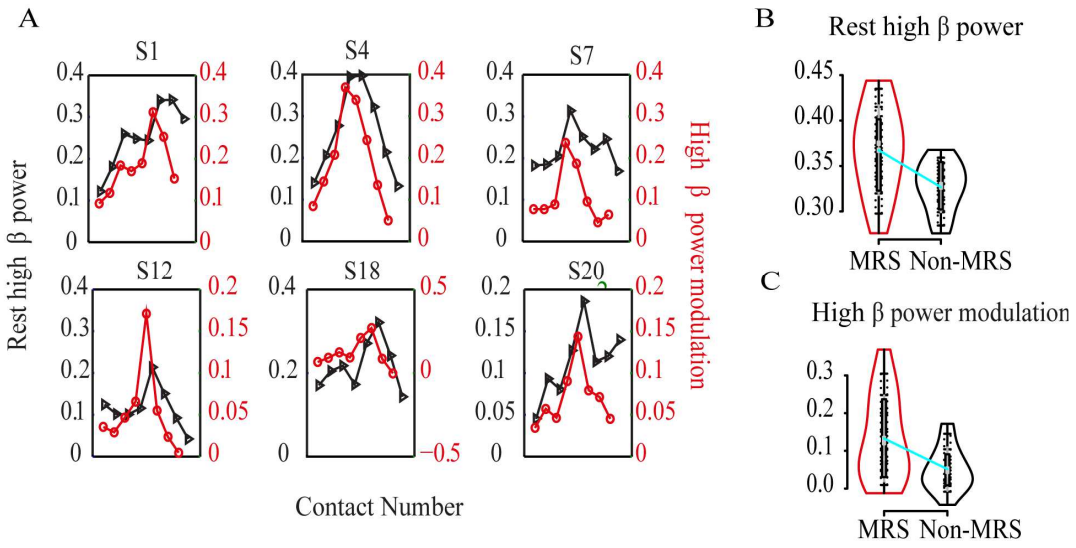

Figure 10 (A) Black curves show how high β power during rest changes between different cortical contacts exhibiting a peak power change near the middle of the strip. Red Curves show similar tracks for high β power modulation induced movement over different cortical contacts (maximal β power suppression was used to identify cortical MRS as explained in the text) (B) Violin plots of baseline (rest) high β power between MRS and non-MRS for the group of subjects (C) Violin plots of high β power modulation caused by movement for MRS and non-MRS for the group of subjects.

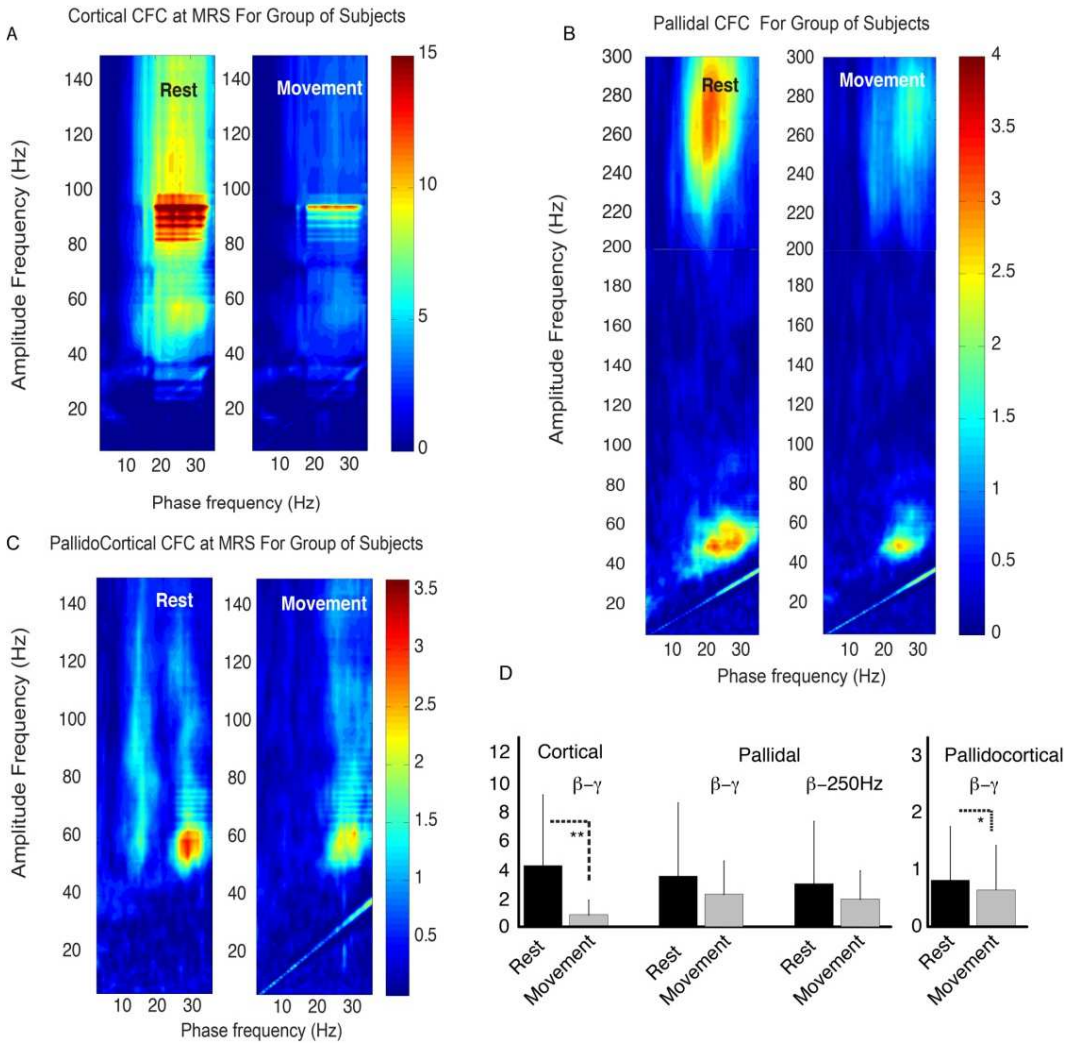

Figure 11 (A) PACFC map (Z-scores) whitin cortical MRS averaged across the group of subjects for rest and movement episodes indicating presence of coupling between phase of high β and amplitude of high γ during rest, which is suppressed by finger movement. (B) PACFC map (Z-scores) within GPi-DBS0 averaged across the group of subjects for rest and movement episodes indicating presence of coupling between phase of high β and amplitude of high γ and also between phase of high β and amplitude of very high γ (250 Hz) during rest, which is suppressed by finger movement. (C) PACFC map (Z-scores) between phase of GPi-DBS0 and amplitude of ECoG-MRS averaged across the group of subjects for rest and movement episodes indicating presence of coupling between phase of high β and amplitude of high γ during rest, which is suppressed by finger movement. (D) shows the group difference between rest and movement PACFC for cortical, pallidal and pallidocortical (from left to right) patterns. ((**) indicates that difference is significant with p-value < 0.01 and (*) shows that the difference is significant with p-value < 0.05)

In addition to characterizing differences in movement related changes in power spectra, we explored whether there are differences in baseline (resting) power spectra between MRS and non-MRS. In particular we found that MRS had greater baseline high β power than non-MRS (paired t-test, $p = 8.08 \times 10^{-5}$) Figure 10B. Further exploration revealed that the magnitude of movement related high β suppression (Measured as absolute suppression normalized to the total power) was related to the high β power at rest (Figure 10A and C). Similar modulation of baseline power spectral characteristics was not seen for other baseline spectral bands. We identified the cortical contact with maximal baseline high β power and confirmed that for all subjects MRS is the same contact with maximal baseline high β power (12 subjects) or its immediate neighbor (8 subjects).

We also identified PAC between the phase of high β and amplitude of high γ bands for all subjects at MRS (Figure 11A). The sites of maximal coupling had either a one-to-one correspondence with MRSs (for 10 subjects), or their immediate neighbors (other 10 subjects). β-γ PAC was significantly greater at MRS as opposed to non-MRS sites (paired t-test, $p = 1.06 \times 10^{-3}$). . At MRS, movement was associated with a significant decrease in the cortical PAC (Figure 11A and 11D Yuen t-test, p-value = 0.0022). We compared movement induced changes in β-γ PAC between MRS and non-MRS cortical signals across subjects and found that movement induced changes in cortical PAC were greatest at MRS in the group of subject (with $p = 7.03 \times 10^{-3}$) Figure 12B. Spatial correlation of PAC with baseline high β Coherence over the cortical contacts (Figure 12A) also were examined and sites of maximal baseline high β coherence were closely matched to the sites of maximal PAC modulation (10 subjects same contacts and 10 subjects their immediate neighbor)

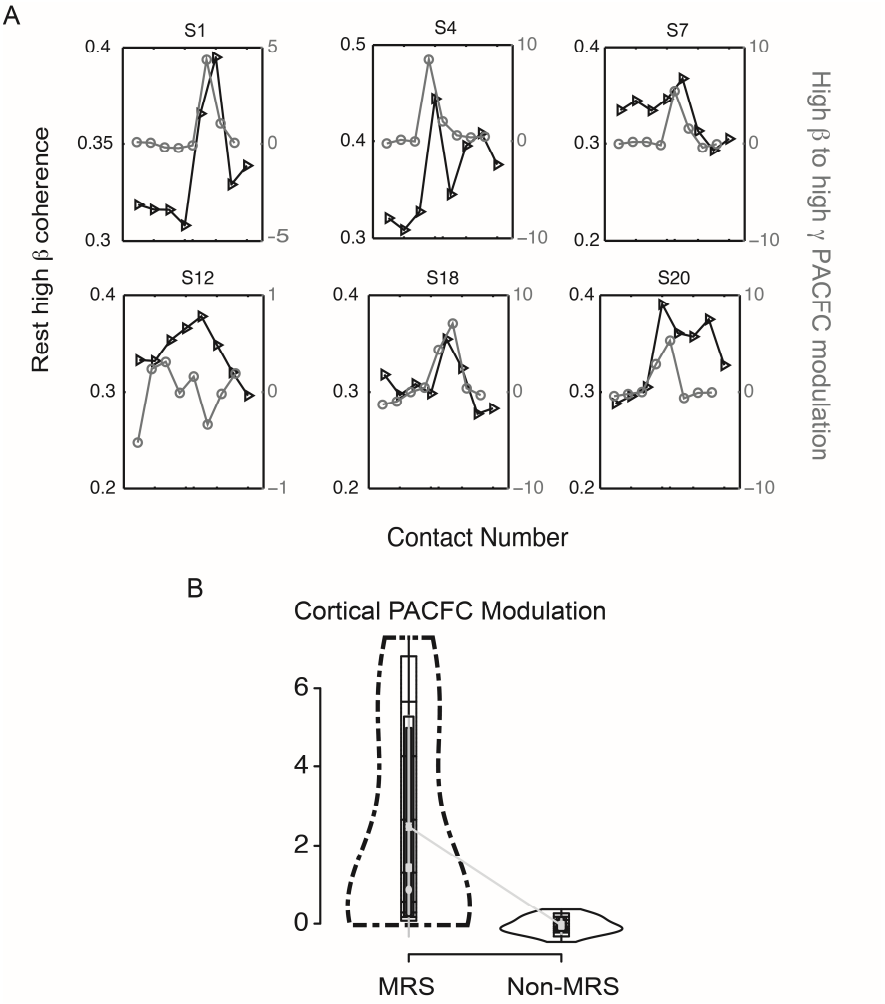

Figure 12 (A) Spatial correspondence between movement induced changes in cortical PACFC (high β to high γ) and average high β coherence between GPi-DBS0 and cortical contacts (ECoG0-ECoG7) for 6 subjects (B) Violin plots of movement induced changes in cortical PACFC between MRS and non-MRS cortical contacts

3.3.2. Movement related changes in pallidal signals

Spectral profiles with the GPi were similar to that seen in the cortex, but with a less prominent β peak and a distinct very high γ peak, centered at 230 Hz, as previously described (Figure 1 C and D, (Tsiokos, Hu et al. 2013)). The mean β peak across all subjects was 23.05±5.17 Hz.

Movement-related changes in spectral power were also observed in pallidal signals. Following a similar pattern to the cortical signals, high β power suppression and γ power increase were observed at the most ventral DBS contact in all subjects (Figure 9C-D). High β power suppression was statistically significant ($p = 0.00139$, paired Yuen t-test) between rest and movement for the group of subjects at this contact (Figure 1F), with a mean suppression of 34.57%. Low β and low γ power also showed significant changes with movement ($p = 0.003$ and $p = 0.04$). While high γ power also seemed to increase with movement, this change was not statistically significant ($p = 0.07$).

We identified PAC within GPi between phase of high β and amplitude of low γ and also between phase of high β and amplitude of 250 Hz in 15 subjects (Figure 11B left panel). On average peak cortical PAC is stronger (higher z-scores peak cortical z-score is 20.52 and peak pallidal z-score is 3.37) when compared to pallidal PAC (Figure 11A-B). Although movement seemed to suppress pallidal PAC (Figure 11B), this did not reach statistical significance ($p = 0.26$, Figure 11D)

3.3.3. Relationship between pallidal and cortical signals

3.3.3.1. High β coherence between GPi and Cortex

During rest coherence between the GPi and MRS was observed in β frequencies (Figure 13A). Average high β coherence was higher between pairs of GPi and MRS cortical signals (17 subjects) or their immediate neighbors (3 subjects) (with average value of 0.38) as compared to pairs of GPi and non-MRS cortical signals (average of 0.22) and $p = 1.857 \times 10^{-3}$ (Figure 14). For the subset of subjects with recordings along the DBS trajectory, the average β coherence increased as the DBS lead approached the final

(target) location in the GPi (Figure 13B). Movement results in a significant decrease in average low/high β coherence, reducing from 0.363 at rest to 0.331 during movement (p=0.003912, Figure 13C). An illustrative example is shown in Figure 13A (same subject as in Figure1) demonstrating modulation of pallidal-cortical coherence as a function of frequency.

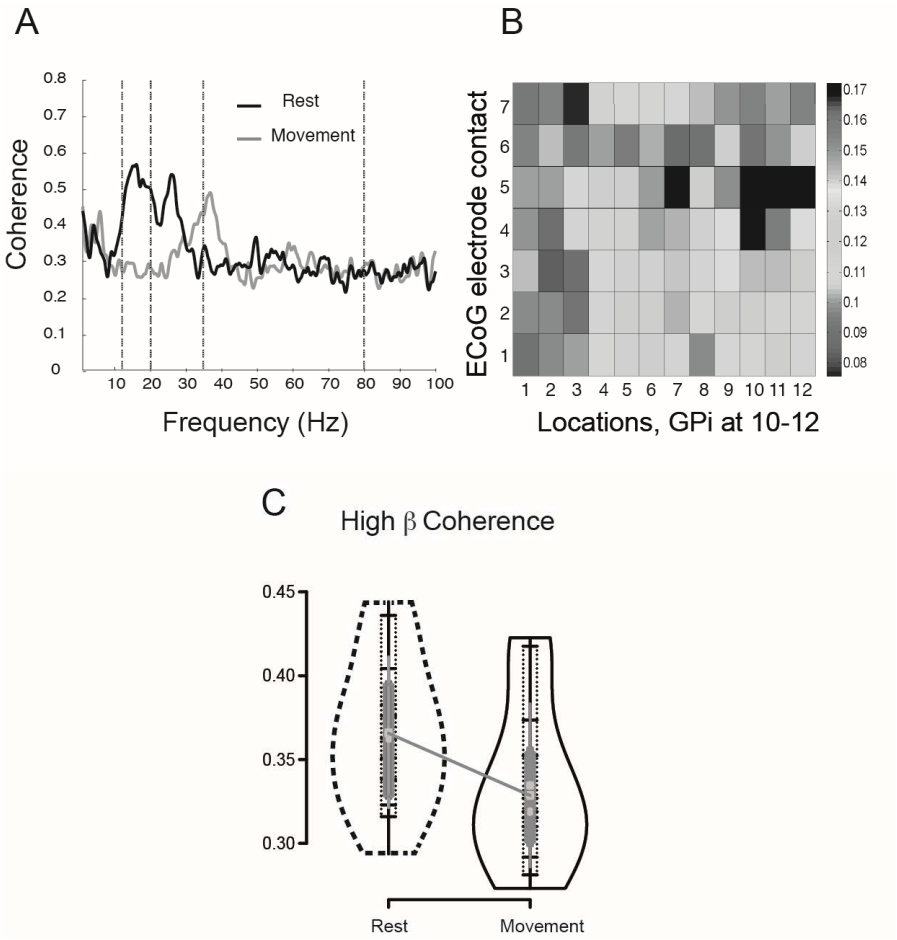

Figure 13 (A) Coherence as a function of freqeucny between DBS0 and cortical MRS for subject S1, which shows suppression in β coherence, caused by movement (B) For S14 β coherence during rest between cortical MRS (ECoG5) and DBS0 increases as lead is advanced toward the target location (C) Violin plots of average high β power change between rest and movement for group of subjects

3.3.3.2. PAC between GPi and MRS cortex

PAC across the GPi and MRS in motor cortex was present between the phase of the GPi β band and the amplitude of the MRS γ band (Figure 11C). Notably, we observed lower z-scores for peak pallidocortical PAC as compared to cortical CFC (with peak z-score of 3.18). Figure 11C shows the average PAC for rest and movement averaged for the group of subjects. Movement causes reduction in pallidocortical PAC and changes were statistically significant across group of subjects ($p = 0.02875$) (Figure 13D).

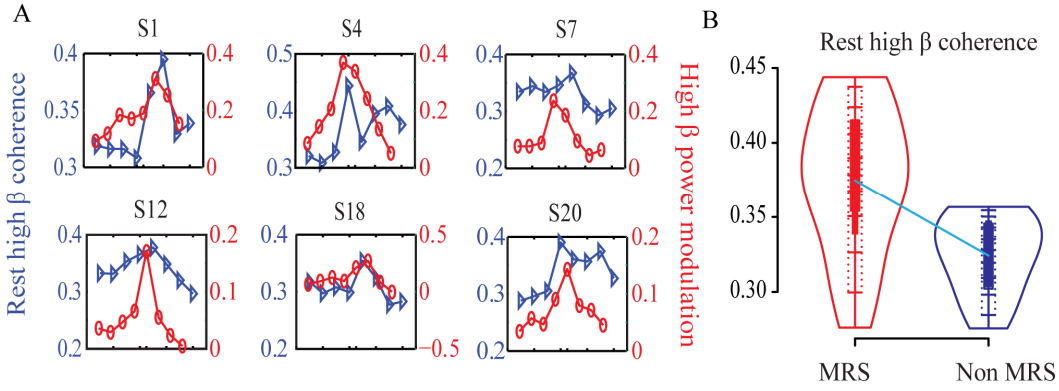

Figure 14 (A) Spatial correspondence between high β coherence during rest and movement induced modulation in high β power for 6 subjects (B) Violin plots of rest high β coherence between MRS and non-MRS cortical contacts

3.3.4. Temporal correlation between PAC and β coherence

Temporal correlations between pallidocortical β coherence, cortical β-γ PAC, and pallidocortical β-γ PAC were examined for the subset of subjects with 6 minutes of recordings at the final DBS position (providing sufficient temporal data for such analyses). The three metrics (coherence, cortical PAC, and pallidocortical PAC) were calculated for consecutive episodes of rest and movement (6 rest episodes and 6

movement episodes resulting in 12 values). Nine subjects (out of 12) showed significant correlation between cortical and pallidocortical PAC (with p-value < 0.05). From those, 6 subjects demonstrate significant correspondence between pallidocortical PAC and pallidocortical high β coherence. In addition, there is significant correlation between cortical PAC and pallidocortical high β coherence in 7 subjects. One subject also showed high correlation between cortical PAC and pallidocortical high β coherence but not a high correlation between cortical and pallidocortical PAC.

In addition to the correlation as explained in the methods we explored symmetry between three measurements. One sample t-test couldn't reject the null hypothesis and lead to presence of symmetry between Cortical PAC and Pallidocortical PAC (with $p = 0.48$) and also between cortical PAC and pallidocortical coherence (with $p = 0.13$). However symmetry between pallidocortical coherence and pallidocortical PAC couldn't be confirmed as the t-test rejects the numm hypothesis of sum of differences between two curves to be differentiable from 0.

3.4. Discussion

Phase amplitude coupling has been observed extensively in different cortical areas of humans and primates, including the human frontal (Schack, Vath et al. 2002) and temporal lobes (Canolty, Edwards et al. 2006), and the human motor cortex in Parkinson's disease (de Hemptinne, Ryapolova-Webb et al. 2013). It has been suggested to serve as a pathophysiologic mechanism for Parkinson's disease (de Hemptinne, Ryapolova-Webb et al. 2013; Yang, Vanegas et al. 2014). While other studies have examined the role of treatment on cortical PAC (including subthalamic nucleus (STN) both stimulation and medications), the effect of movement itself on cortical PAC has not been characterized. Moreover, the relationship of cortical PAC to subcortical signals, in particular those of the basal ganglia has not been extensively characterized. Given the phase encoding frequency in the β band and the preponderance of β throughout the motor network in Parkinson's disease, we propose that understanding the movement modulation of PAC both at the local and network level are key investigations to piece together the complex pathophysiologic network underlying Parkinson's disease.

In this study, we verified the presence of β – γ PAC in patients with Parkinson's disease and demonstrate that these signals are not only modulated by treatment (as reported by others) but that they are also modulated by movement (both locally and across nodes within the motor network). Moreover, we demonstrate a spatially specific and temporally dynamic relationship between subcortical and cortical β signals that are tied to cortical PAC dynamics. Finally, we report previously unreported PAC within the GPi between both β – γ and β – very high γ (250 Hz). Our results complement previous human studies on the STN (Yang, Vanegas et al. 2014).

3.4.1. PAC within the motor cortex

Previous studies have reported increased β activity and PAC in the motor cortex in Parkinson's disease (Cruz, Mallet et al. 2009; Crowell, Ryapolova-Webb et al. 2012; de Hemptinne, Ryapolova-Webb et al. 2013).The relationship between these signals however has not been characterized. Here, we demonstrate spatial correlations between these signals, suggesting a common underlying etiology interrelating these observations. In this study, MRS, which we use to electrophysiologically define motor cortex are characterized by the highest regional β power and β – γ PAC.

3.4.2. PAC within the GPi

The power spectral analysis of LFP signals from GPi showed presence of peaks in the power of the high β band similar to the motor cortex which is involved in local PAC within the GPi. Uniquely, the GPi has a 200-300 Hz component, which is movement-responsive, which we have previously characterized in great detail (Tsiokos, Hu et al. 2013). De Hemptinne, et al. identified PAC within the STN (de Hemptinne, Ryapolova-Webb et al. 2013), which has also been reported by Lopez-Azcarate, et al. (Lopez-Azcarate, Tainta et al. 2010). Notably, in both studies, in the state when patients were off-medication and stimulation, movement had a small effect on coupling. Such observation could underlie an inability of the diseased basal ganglia to suppress PAC. Similar to these other reports, while our results demonstrate qualitative reductions in pallidal PAC with movement, this did not reach statistical significance, suggesting an inability to suppress subcortical PAC may contribute, in part, to the pathophysiological manifestations of PD.

Furthermore, movement was reported to cause an increase in the magnitude of the peak at the 200-300 Hz frequency range (Tsiokos, Hu et al. 2013) in subjects included in the present study, while the current results suppression of PAC between the β band and 200-300 Hz in some subjects. The findings suggest opposing actions for the two frequency bands (high β and 200-300 Hz band)indicating a "pro-kinetic" role for 200-300 Hz and an "anti-kinetic" role for high β band. This finding complements the previous finding in STN suggesting a network-wide effect of the two frequency rhythms(Brown 2003). The failure to complete eliminate PAC with movement might be indicative of Parkinson's disease related dysfunction.

3.4.3. PAC between GPi and motor cortex

In a previous study in epilepsy patients, we illustrated how low frequency thalamic signals can causally modulate cortical signals via thalamocortical PAC. While there are fundamental differences between the connectivity of the thalamus and cortex (single synapse) as opposed to GPi and cortex (two synapses with presumed intervening thalamic processing/integration), exploring the relationship between subcortical and cortical signals may provide insight into the pathophysiologic control mechanisms given the presence of increased β throughout the motor network in PD and the suggestion of PAC as a pathophysiologic mechanism of PD.

In the majority of subjects, pallidocrotical coherence demonstrated significant temporal correlation with cortical β-γ PAC as well as pallidocortical β-γ PAC. A valid concern was due to small sample number (n = 12) affecting the correlation values. However we note that even between random time series observing a correlation of 0.3 or above indicating a

pattern of positive influence between the two time series is highly unusual Overall, these results strongly suggest a *dynamic pathologic network structure* underlying PD based on a coherent β oscillation rather than a disease node within the motor network. This has significant implications for the study of PD pathophysiology, which has traditionally focused on studying and characterizing the pathophysiology of a single area (cortical or subcortical).

4. Conclusions and Future Work

Although the thalamus is believed to regulate and coordinate cortical activity both within and across functional regions, such as motor and visual cortices, direct evidence for such regulation and the mechanism of regulation remains poorly described. Using simultaneous invasive recordings of cortical and thalamic electrophysiological activity in two awake and spontaneously behaving human subjects, we provide direct evidence of thalamic regulation of cortical activity through a mechanism of phase-amplitude coupling (PAC), in which the phase of low frequency oscillations regulates the amplitude of higher frequency oscillations. We hypothesized that cortical PAC is intimately related to thalamocortical functional and structural connectivity. Our results indicate that cortical PAC is spatially specific and time variant and its variance is related to patterns of thalamocortical structural and coherent thalamocortical activity.

Specifically, we show that cortical PAC between the theta phase and beta amplitude is spatially dependent on and time variant with the magnitude of thalamocortical theta coherence. Moreover, using causality analysis and MR diffusion tractrography, we provide evidence that thalamic theta activity drives cortical theta oscillations and PAC across structures and that these thalamocortical relationships are structurally constrained by anatomic pathways. This relationship allows for new evidence of thalamocortical PAC. Given the diffuse connectivity of the thalamus with the cerebral cortex, thalamocortical PAC may play an important role in addressing the binding problem, including both integration and segregation of information within and across cortical areas. In accordance with the diffuse connectivity of the thalamus with the cerebral cortex, the current work provides direct causal evidence that the thalamus exerts regulatory control over ongoing cortical activity, at least in part, through a mechanism of phase-amplitude coupling, in

which low frequency thalamic rhythms, such as theta, directly regulate higher frequency cortical activity in the beta range and possibly beyond, although that remains speculative based on the current data and analysis. Such modulation is spatially specific and structurally constrained, as evidenced by within subject diffusion tractography analysis. These results strongly suggest the thalamus is not a "relay" but that it actively modulates cortical activity in a time variant and structurally constrained manner.

Alterations in the functional connectivity between the basal ganglia (BG) and cortex are likely a pathophysiological cornerstone of Parkinson's disease (PD) (Fogelson et al. 2006; Marreiros et al. 2013), yet non-invasive imaging cannot assess these relationships with sufficient temporal and spatial resolution. Currently our understanding of the corticao-basla ganglia-thalamocortical is still incomplete and present models are not able to cover all aspects of activity in the motor system.

Decades long research efforts have tried to establish the role of hierarchical relationships between normal and aberrant oscillations in the basal ganglia and their link to functional and pathophysiology of movement disorders. Phase-amplitude coupling (PAC), in particular, has been shown to be present both within and between the structures in human subthalamic nucleus (STN) and motor cortices. Given PD is likely a disease related to pathological networks, we hypothesized that cross-regional coupling of β band (13-35 Hz) local field potentials (LFP) may reflect PD associated changes in cortico-basal ganglia functional connectivity. Using simultaneous cortical-subcortical LFP recordings in humans undergoing deep brain stimulation (DBS) implantation, we demonstrated the time co-variability of cortical-GPi CFC to local spectral power as well as β coherence between GPi and motor cortex.

In our study we identified presence of two types of PAC in the human GPi: β – γ and β – very high γ and confirmed that contralateral movement significantly decreases β power both within cortex and GPi and causes decrease in the coupling (coherence and CFC) between the two sites possibly manifesting a deficiency in the diseased BG. These changes are spatially specific and temporally dynamic, suggesting they may be related to dynamic and coherent motor-network-wide β oscillations. Strong CFC might be a pathologic mechanism transcending the local sites, as evidenced by its correlation to coherence and CFC between the GPi and motor cortex.

Exact characterization of PAC and its complete role in the pathophysiology of the Parkinson's disease and the disease severity as measured by standard system of UPDRS still remains to be studied in extensive details. Different patterns of movement and behavioral tasks and their effects on the power and PAC coupling pattern both within and between structures need to be further explored. Considering the mult-synaptic connections in the cortico-basl ganglia-thalamocortical circuit, more nodes of the circuit should be studied simultaneously if possible.

Also due to the limitations of recordings from diseased group and the fact that normal subjects cant udergo such invasive procedures there is a need to compare the results of this study on the group of control subjects such as epilepsy patients or dystonia or essential tremor patients to further expand the role of power and PAC in the pathophysiology of the disease.

The findings then can be incorporated into extensive computational models to account for the differences between basal ganglia nuclei in terms of oscillatory activity.

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