

FUNCTIONAL AND CLINICAL RELEVANCE OF OSCILLATORY ACTIVITY WITHIN CORTICO- BASAL-GANGLIA CIRCUITS IN PARKINSON'S DISEASE



Ashwini Oswal

Doctoral thesis

Nuffield Department of Clinical Neuroscience

Oxford University & Brasenose College

i. Declaration

I, Ashwini Oswal, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed:

A handwritten signature in black ink, appearing to read 'Ashwini Oswal', with a stylized, cursive script.

Date: 22nd May 2015

Word count: 46,321 excluding figures, tables, references and appendix

ii. Contents

i. Declaration	2
ii. Contents	3
iii. List of figures	11
iv. List of tables	15
v. Acknowledgements	16
vi. Abbreviations	17
vii. Publications resulting from work related to this thesis	19
viii. Abstract	20
Chapter 1: Introduction	21
1.1 Clinical characterisation of Parkinson's disease	21
1.2 Epidemiology of Parkinson's disease	21
1.3 Genetic factors	22
1.4 Motor symptoms of Parkinson's disease	22
1.5 Non-motor symptoms	23
1.6 Medical treatments for Parkinson's disease	23
1.7 Deep Brain Stimulation and Parkinson's disease	24
1.8 Pathophysiology of Parkinson's disease	26
1.9 Cortico-basal ganglia networks and the pathophysiology of Parkinson's disease	26
1.10 Oscillations in motor control: insights from basal ganglia and cortical recordings	29
1.11 Beta oscillations: a pathophysiological hallmark of Parkinson's disease?	31

1.12 Beta oscillations are synchronized between the cortex and basal ganglia in Parkinson's disease	34
1.13 Task-related reactivity of Beta activity in Parkinson's disease.....	36
1.14 Is Beta an epiphenomenon or causally important in Parkinsonism?	37
1.15 Computational insights into the generation and propagation of beta rhythms in Parkinson's disease	38
1.16 The Gamma frequency band: a prokinetic signal?	38
1.17 Low frequency (theta/alpha) rhythms	40
1.18 Oscillations and Cognitive features of Parkinson's disease	40
1.19 Oscillations and Tremor in Parkinson's disease	42
1.20 Cross frequency interactions	43
1.21 Concluding remarks on synchronised neural activity and the pathophysiology of Parkinson's disease	44
1.22 Aims of this thesis	45
Chapter 2: Methods and Materials.....	46
2.1 Patients and Surgical Procedure	46
2.2 Electrophysiological Data Acquisition	47
2.2.1 STN LFP and Electromyography recordings	47
2.2.2 Magnetoencephalography	48
2.3 Data pre-processing	49
2.4 Spectral analysis and functional connectivity measurement.....	51
2.5 Source level analysis of MEG data by beamforming	54

2.6 Statistical Parametric Mapping and statistical analysis of electrophysiological data	56
Chapter 3: Beta reactivity, prospective facilitation of executive processing and its dependence on dopaminergic therapy in Parkinson's disease.....	
	59
3.1 Introduction	59
3.2 Methods.....	60
3.2.1 Paradigm	61
3.2.2 Recordings.....	64
3.2.3 Spectral Analysis	64
3.2.4 Statistics	66
3.3 Results.....	67
3.4 Discussion	74
Chapter 4: Cognitive factors modulate activity within the human subthalamic nucleus during voluntary movement in Parkinson's disease.	
	78
4.1 Introduction	78
4.2 Methods.....	79
4.2.1 Paradigm	80
4.2.2 Recordings.....	84
4.2.3 Spectral Analysis	84
4.2.4 Statistics	86
4.3 Results.....	89
4.3.1 Behavioural results.....	89
4.3.2 STN LFPs	90

4.4 Discussion	98
Chapter 5: Movement related dynamics of subthalamo-cortical alpha connectivity in Parkinson's disease.	102
5.1 Introduction	102
5.2 Methods.....	104
5.2.1 Experimental paradigm.....	104
5.2.2 LFP-MEG recordings.....	106
5.2.3 Characterisation of individual subject cortical-STN coherence.....	107
5.2.4 Identification of group and individual coherence peaks.....	109
5.2.5 Source activity extraction.....	109
5.2.6 Pre-processing of virtual electrode and LFP data	110
5.2.7 Artefact suppression	110
5.2.8 Excluding data with high frequencies in the evoked response	111
5.2.9 Spectral analysis.....	112
5.2.10 Statistical analysis of time-frequency data	113
5.2.11 Additional statistical analyses	114
5.3 Results.....	115
5.3.1 Topography of STN-cortical alpha coherence during movement and pre-movement	115
5.3.2 Cortical Source Localisation	116
5.3.3 Responses in Cortical sites and STN induced by voluntary movement.....	120
5.3.4 Reactivity Patterns of STN–alpha source coherence	124
5.3.5 Correlation with Clinical Variables	126

5.3.6 Behavioural Data	128
5.4 Discussion	129
Chapter 6: Optimising beamformer region of interest analysis.....	134
6.1 Introduction	134
6.2 Methods.....	135
6.2.1 Spatial dimensionality reduction (ROI projection)	135
6.2.2 Bayesian PCA (bPCA)	138
6.2.3 Beamforming with combined ROI projection and bPCA	139
6.2.4 Validation with Simulations	140
6.2.5 Simulation 1	140
6.2.6 Simulation 2	141
6.2.7 Assessment of method on real data from a single patient with externalised DBS electrode	143
6.3 Results.....	145
6.3.1 Spatial Dimensionality reduction	145
6.3.2 Simulation 1	146
6.3.3 Simulation 2	148
6.3.4 Patient data	154
6.4 Discussion	156
Chapter 7: DBS modulates synchrony within spatially and spectrally distinct resting state networks in PD.....	159
7.1 Introduction	159

7.2 Methods.....	160
7.2.1 Patient and surgical details	160
7.2.2 Electrophysiological recordings: simultaneous MEG and LFP recordings during DBS	163
7.2.3 Experimental Protocol.....	164
7.2.4 Data analysis	164
7.2.5 Data pre-processing and sensor level analysis.....	165
7.2.6 Analysis of local subthalamic nucleus synchrony.....	166
7.2.7 Determining the spatial and spectral profile of coherence changes induced by DBS.....	167
7.2.8 Directionality of STN-cortical coupling.....	170
7.2.9 Correlation with clinical features.....	170
7.3 Results.....	171
7.3.1 DBS effects on local power: DBS specifically suppresses 11-14 Hz activity within the STN.....	171
7.3.2 DBS effects on local power: change in STN LFP 11-14 Hz activity correlates with DBS efficacy	173
7.3.3 Defining resting state networks in PD and handling DBS related artefacts	173
7.3.4 DBS suppresses coupling between STN and a mesial motor beta band network in PD....	175
7.3.5 Ratio of low and high beta band coupling differs between the STN-mesial premotor and STN-M1 networks	177
7.3.6 Phase differences differ between low and high beta band networks linking motor cortex and STN	179
7.3.7 DBS effects on resting state networks: lack of correlation with DBS efficacy.....	182
7.4 Discussion	182

7.4.1 Study limitations	184
7.4.2 DBS influences spatially, functionally and spectrally distinct cortico-subthalamic nucleus networks	185
7.4.3 DBS influences local activity in the STN	188
7.4.4 Conclusions and clinical implications	188
Chapter 8: General discussion	190
8.1 Overview of thesis aims	190
8.2 Motor and non-motor roles of STN oscillatory activities within the beta and gamma frequency bands	192
8.3 The role of STN–cortical networks in the Parkinsonian motor phenotype	195
8.4 Studying synchrony within STN–cortical networks during DBS	196
8.5 How does DBS work in Parkinson’s disease?	197
8.6 Possible implications for future DBS technologies.....	199
8.7 Limitations of the present work and areas for future study	199
Appendix A - Analysis of simultaneous MEG and intracranial LFP recordings during DBS: a protocol and experimental validation	202
A.1 Introduction	202
A.2 Methods.....	204
A.2.1 Simultaneous MEG and LFP recordings	204
A.2.2 Experimental protocol - phantom	206
A.2.3 Patient experiment	208
A.2.4 Simultaneous stimulation and recording from the STN.....	209

A.2.5 Experimental Protocol – patient recordings	210
A.2.6 Electrophysiological Recordings	211
A.2.7 Offline data analysis.....	212
A.2.8 Determining head location	212
A.2.9 Fusion of MEG and LFP data	215
A.2.10 Removal of MEG jumps	216
A.2.11 Trial definition.....	218
A.2.12 Sensor level analysis	218
A.2.13 Source space analysis	219
A.2.14 Nonparametric statistical testing of coherence/power differences.....	221
A.3 Results	222
A.3.1 Stimulation related artefacts	222
A.3.2 Phantom results.....	230
A.3.3 Single subject results	232
A.4 Discussion	233
A.4.1 Implanted vs. externalised patients.....	234
A.4.2 Monopolar vs. bipolar stimulation	235
A.4.3 Analyses of coherence vs. other features.....	236
A.4.4 Factors affecting the recovery of coherence in the presence of DBS.....	237
A.4.5 Summary and conclusions	239
References	240

iii. List of figures

Figure 1.1 A diagram illustrating the hardware components for Deep Brain Stimulation.....	25
Figure 1.2 The cortico-basal ganglia motor loop and its neurotransmitter modulations.....	29
Figure 1.3 STN power spectra observed ON and OFF dopaminergic medication in a cohort of PD patients.	33
Figure 1.4 Resting state networks in Parkinson’s disease.....	35
Figure 3.1 Schematic of two trials during the standard motor task.	63
Figure 3.2 Cue locked spectra OFF medication.....	68
Figure 3.3 Cue locked spectra ON medication.....	69
Figure 3.4 Imperative cue locked STN beta reactivity for the motor task.	71
Figure 3.5 Imperative cue locked STN beta reactivity for the counting task.	72
Figure 3.6 Imperative cue locked STN beta reactivity for selected electrode contacts.....	73
Figure 4.1 Schematic of a typical trial.	81
Figure 4.2 Mean plots of simulated data for all subjects.....	88
Figure 4.3 Behavioural data and EMG analysis.	90
Figure 4.4 Cue locked spectra for the four different reward and trial complexity conditions.....	91
Figure 4.5 Cue locked beta band time series for the four different reward and trial complexity conditions.	92
Figure 4.6 Cue locked gamma band time series for the four different reward and trial complexity conditions. Mean time series of the percentage change in gamma power (60-90 Hz) aligned to the onset of the warning cue (A), the imperative cue (B) and movement onset (C) for the four different reward and trial complexity conditions. Movement related gamma power synchronisation is greater ON medication than OFF medication. Movement related gamma power increases are augmented in high complexity trials (C).	92
Figure 4.7 Statistical analysis of spectra locked to the onset of the warning cue.	93
Figure 4.8 Statistical analysis of spectra locked to movement onset.	94

Figure 4.9 Lower limb data.	96
Figure 5.1 A schematic of the motor tasks.	105
Figure 5.2 Mean across subjects of the normalised DICS beamformer images.....	115
Figure 5.3 Peaks of STN–cortical alpha coherence.	116
Figure 5.4 Time frequency images of power for the STN and cortical source locations OFF medication.	121
Figure 5.5 Time frequency images of power for the STN and cortical source locations ON medication.	121
Figure 5.6 Time series of alpha power for the STN and cortical source locations.	122
Figure 5.7 Bar plots of the main effects for power and coherence.	124
Figure 5.8 Coherence spectra aligned to movement onset.	125
Figure 5.9 Time series of alpha band STN–cortical coherence.	126
Figure 5.10 Correlation of alpha coherence change with clinical improvement.	127
Figure 5.11 Histograms of reaction time data.	128
Figure 5.12 Reciprocal alpha and gamma band STN-cortical coherence changes during movement.	130
Figure 6.1 The Region of Interest projection approach.	146
Figure 6.2 The results of simulation 1.....	147
Figure 6.3 Simulation 2.	149
Figure 6.4 The results of simulation 2.....	150
Figure 6.5 Results of simulation 2.	152
Figure 6.6 Comparison of source reconstruction approaches.	153
Figure 6.7 Spatial specificity of source reconstruction approaches.....	154
Figure 6.8 Patient data.....	155
Figure 7.1 Changes at STN level.	172
Figure 7.2 STN-MEG coherence topography is preserved despite artefact rejection.....	175

Figure 7.3 Effect of 130 Hz DBS on STN-MEG coherence.....	176
Figure 7.4 Differences between STN-MEG coherence in low and high beta bands.....	179
Figure 7.5 Results of Granger causality analysis.	181
Figure 7.6 Estimated conduction delays.	182
Figure 7.7 Schematic of DBS effects on STN-cortical networks	184
Figure A.1 Schematic showing our set up for a patient recording within MEG.	205
Figure A.2 Schematic showing the phantom recording setup within MEG.	208
Figure A.3 Handling of MEG jump artefacts.....	217
Figure A.4 MEG ringing artefacts.	224
Figure A.5 Power spectra of MEG sensor level artefacts during monopolar DBS.....	225
Figure A.6 Power spectra of MEG sensor level artefacts during bipolar DBS.	226
Figure A.7 The origin of low frequency artefacts during monopolar DBS.	228
Figure A.8 Source space analysis for the phantom experiment.....	231
Figure A.9 Single patient source space analysis.....	233

iv. List of tables

Table 4-1 Clinical characteristics of the patients recorded.....	80
Table 4-2 Number of correctly performed trials recorded for each patient.....	83
Table 4-3 Summary of the statistical results for both behavioural and spectral data.	98
Table 5-1 Table showing the selected contacts for each subject.....	120
Table 7-1 Clinical characteristics of patients.....	162

v. Acknowledgements

I am deeply indebted to my two supervisors Peter Brown and Vladimir Litvak, who have provided exceptional guidance, support, friendship and mentorship. They have both taught and helped me more than I could possibly put into words here. I couldn't have asked for a better pair of D.Phil supervisors and I very much hope that I will continue to stay in close touch with both of them in the future.

I feel very humbled to have been able to work with patients whose determination, courage and selflessness in the face of an incurable disease serve as an inspiration. Translational research aims to improve the human state and I hope that this D.Phil. provides me with a foundation for strongly contributing towards this goal.

I must also thank Karl Friston, Rafal Bogacz, Will Penny, Guillaume Flandin and Gareth Barnes for very kindly taking the time to help with many of my technical questions. Additionally I also thank my colleagues and friends from the Brown lab (Simon Little, Anam Anzak, Arpan Mehta, Ashwani Jha, Hayriye Cagnan, Huiling Tan, Alek Pogosyan, JS Brittain), and from the FIL (Bernadette Van Wijk, Peter Zeidman, Giles Story, Sukhbinder Kumar).

This thesis has involved close collaboration with the Functional Neurosurgery team at UCL, especially Tom Foltynie, Patricia Limousin, Ludvic Zrinzo and Marwan Hariz. I am grateful for their combined help, encouragement and support. Additionally, it has also been a pleasure to work with David Bradbury, Al Reid, Spencer Neal and Letty Manyande. Without their collective help and expertise MEG recordings at UCL would not have been possible.

Finally, I must thank my parents and my brother for their incessant support, help and love.

vi. Abbreviations

ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BPCA	Bayesian Principal Component Analysis
COMT	Catechol-O-Methyl transferase
CT	Computerised Tomography
DBS	Deep Brain Stimulation
DFT	Discrete Fourier transform
DICS	Dynamic Imaging of Coherent Sources
EcOG	Electrocorticography
EEG	Electroencephalogram
ERD/ERS	Event related desynchronisation/synchronisation
FFT	Fast Fourier Transform
GABA	Gamma-Aminobutyric acid
GLM	General Linear Model
GPI	Globus pallidus interna
GPe	Globus pallidus externa
LCMV	Linearly Constrained Minimum Variance
LDE	Levodopa equivalent
LFP	Local Field Potential
MAO	Monoamine oxidase
M1	Primary Motor Cortex
MEG	Magnetoencephalography
MPTP	1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine
MRI	Magnetic Resonance Imaging
MVAR	Multivariate Autoregressive Model
PD	Parkinson's disease
Pre-SMA	Pre-supplementary motor area
ROI	Region of Interest
SMA	Supplementary motor area
SNc	Substantia nigra pars compacta
SNr	Substantia nigra pars reticulata

Str	Striatum
SQUID	Superconducting Quantum Interference Device
STG	Superior Temporal Gyrus
STN	Subthalamic Nucleus
SVD	Singular Value Decomposition
UPDRS	Unified Parkinson's Disease Rating Scale
VIM	Ventral Intermediate Nucleus

vii. Publications resulting from work related to this thesis

1. Oswal A, Litvak V, Sauleau P, Brown P. Beta reactivity, prospective facilitation of executive processing, and its dependence on dopaminergic therapy in Parkinson's disease. *J Neurosci*. 2012;32(29):9909–16. (Chapter 3)
2. Oswal A, Litvak V, Brücke C, Huebl J, Schneider G-H, Kühn AA, Brown P. Cognitive factors modulate activity within the human subthalamic nucleus during voluntary movement in Parkinson's disease. *J Neurosci*. 2013;33(40):15815–26. (Chapter 4)
3. Oswal A, Brown P, Litvak V. Movement related dynamics of subthalamo-cortical alpha connectivity in Parkinson's disease. *Neuroimage*. 2013;70:132–42. (Chapter 5)
4. Oswal A, Brown P, Litvak V. Synchronized neural oscillations and the pathophysiology of Parkinson's disease. *Curr Opin Neurol*. 2013;26(6):662–70.
5. Oswal A, Litvak V, Brown P, Woolrich M, Barnes G. Optimising beamformer regions of interest analysis. *Neuroimage*. 2014;102 Pt 2:945–54. (Chapter 6)
6. Oswal A, Jha A, Neal S, Reid A, Bradbury D, Limousin P, Foltynie T, Zrinzo L, Brown P, Litvak V. Analysis of simultaneous MEG and intracranial LFP recordings during Deep Brain Stimulation: a protocol and experimental validation. In submission. (Appendix A)
7. Oswal A, Litvak V, Beudel M, Hariz M, Limousin P, Zrinzo L, Foltynie T, Brown P. Deep Brain Stimulation modulates synchrony within spatially and spectrally distinct resting state networks in Parkinson's disease. In preparation. (Chapter 7)

viii. Abstract

Over the past 20 years there have been significant advances in our understanding of how synchronised neural oscillations relate to cognitive and motor processes both in health and in neurological disease. Oscillations can be considered from the point of view of being the observations of the latent dynamical properties of interacting populations of neurones. With this in mind it becomes evident that their study may inform about underlying functional architectures and principles governing motor and cognitive control.

Cortico-basal-ganglia circuits are canonical feedback loops between cortical and sub-cortical structures, with well-defined anatomy which makes them ideal for the study of oscillatory phenomena. Moreover, these circuits are known to play crucial roles in motor and cognitive processes such that impairments of their normative function may lead to neurological disease states. In this thesis I focus on insights about oscillatory function from cortical-basal ganglia recordings in Parkinson's disease.

I will present evidence from studies showing that the roles of beta (15-30 Hz) and gamma (60–90 Hz) oscillatory activities in motor control are intricately linked to task specific cognitive-motor demands. Furthermore, the timing of activities within these frequency bands relative to movement reveals how distinct spectral phenomena may relate to distinct aspects of cognitive and motor processing. An intricately related aim of this thesis is to begin to establish how the preferred frequencies of interaction and the topographies of long range oscillatory networks within cortico-basal-ganglia loops relate to specific clinical symptoms. In this regard, I will present data revealing the modulation of cortico-basal ganglia coupling by movement, and Parkinson's disease therapies such as levodopa and Deep Brain Stimulation (DBS). Novel methodological developments that facilitate such insights are presented. Finally I discuss how these insights contribute to existing understanding of the pathophysiology of Parkinson's disease, in addition to suggesting novel future therapeutic strategies for DBS.

Chapter 1: Introduction

1.1 Clinical characterisation of Parkinson's disease

Parkinson's disease (PD) is a common neurodegenerative disorder, whose clinical characteristics were first described through the careful observations of Dr James Parkinson in 1817 (Parkinson, 1817). PD is as a heterogeneous clinical entity, the diagnosis of which is based on the presence of the following: 1) A reduction in the speed and amplitude of repeated alternating movements (bradykinesia) 2) Tremor that is typically present at rest at a frequency of 4-6 Hz and 3) Stiffness of passive movements at a joint (rigidity). Perhaps the most influential and widely adopted diagnostic guidelines for PD were formulated by Gibb and colleagues as the Queen Square Brain Bank Criteria (Gibb and Lees, 1988).

1.2 Epidemiology of Parkinson's disease

PD is a very common neurological disorder and has a general population prevalence of 0.3% in industrialised countries (de Lau and Breteler, 2006). The prevalence of PD increases with age to approximately 1% for those in their 60s to 3% for those in their 80s or above (Tanner, 1992).

Incidence and prevalence rates have been relatively stable over time and men are more consistently affected than women with a male to female preponderance of around 1.5 (Twelves et al., 2003; Wooten et al., 2004).

There are numerous studies investigating environmental and lifestyle risk factors contributing to PD, but there are few robust associations. The evidence for a protective effect of coffee and smoking is relatively strong (Wirdefeldt et al., 2011). Conversely, PD risk is increased by exposure to pesticides and herbicides (Pezzoli and Cereda, 2013). MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine) which has a molecular structure that is similar to the herbicide paraquat, can also cause a Parkinsonian syndrome (Ballard et al., 1985).

1.3 Genetic factors

Perhaps some of the most compelling evidence for a genetic contribution to the pathogenesis of PD comes from twin studies of young onset PD (Tanner et al., 1999). While a number of single gene disorders have been identified which may make up between 5-10% of all cases of PD, the polygenic determinants of PD remain more poorly understood (Lesage and Brice, 2009). Of the single gene disorders, mutations in the gene encoding GBA (glucocerebrosidase) are amongst the most common (Beavan and Schapira, 2013). While it is likely that PD is the result of a complex interaction between genetics and environmental factors, developments in understanding the genetic underpinnings of complex diseases are likely to both guide diagnosis and to inform therapeutic advances.

1.4 Motor symptoms of Parkinson's disease

Although PD is characterised by a triad of bradykinesia, rigidity and tremor, other motor features may also point to the diagnosis (Hughes et al., 1992; Lees et al., 2009). For example subtle changes such as reduced arm swing when walking or a reduced facial expression may be present. Other gait abnormalities commonly found in PD include postural instability and gait freezing which in the latter stage of the disease leads to falls. Patients may also develop slurred or festinant speech and sometimes mastication and swallowing may be affected.

The severity of the motor symptoms of PD, which are predominantly unilateral at onset, can be assessed using part III of the Unified Parkinson's Disease Rating Scale (UPDRS)(Goetz et al., 2008). Although the median time interval between diagnosis of the disease and death is 15 years, it is evident that patients exhibit a large degree of heterogeneity in disease progression (Lees et al., 2009). In this regard, it is interesting to note that patients with tremor dominant PD have the slowest rates of progression while those with postural instability progress more quickly (Zetuský et al., 1985).

1.5 Non-motor symptoms

Although PD is classically considered to be a motor disorder, non-motor symptoms constitute an important part of the disease burden (Chaudhuri et al., 2006; Chaudhuri and Schapira, 2009). Importantly, non-motor symptoms, particularly hyposmia and fatigue may also predate the emergence of motor features by many years, giving the opportunity to trial disease modifying therapies in this critical prodromal period (Ponsen et al., 2004).

Among the commonest non-motor symptoms are those related to autonomic dysfunction, such as constipation, erectile dysfunction, postural hypotension and urinary urgency (Chaudhuri et al., 2006; Lees et al., 2009). These symptoms may be treated with appropriate pharmacological therapies. Another important non-motor manifestation is rapid eye movement (REM) sleep behaviour disorder (Gagnon et al., 2002). In this condition, the sufferer acts out their dreams often with vocalisations and movements during sleep. Other neuropsychiatric manifestations of PD include depression and also cognitive impairment (Burn, 2002; Evans et al., 2011). Depression in PD is often multifactorial and may be the result of both the motor disability and neurotransmitter imbalances. Cognitive impairment in PD is both common and progressive. Up to 62% of patients may display mild cognitive impairment at diagnosis and 5 years after diagnosis it is estimated that 10% of patients go on to develop PD dementia (Williams-Gray et al., 2007). PD dementia is characterised by fluctuating levels of alertness, visuospatial difficulties and visual hallucinations.

1.6 Medical treatments for Parkinson's disease

There is currently no cure for Parkinson's disease, but there are many available preparations to manage the motor (Lees et al., 2009; Fox et al., 2011) and also the non-motor symptoms. Given that a hallmark of PD is the loss of dopaminergic neurones, it comes as no surprise that the mainstay of treatment is dopamine replacement therapy, usually with oral tablets. The dopamine prodrug Levodopa is able to cross the blood-brain barrier and is broken down into active

dopamine by decarboxylation. In order to reduce side effects such as nausea which are associated with the peripheral effects of dopamine, levodopa is often combined with a peripheral dopa-decarboxylase-inhibitor such as carbidopa or benserazide. By blocking the peripheral conversion of levodopa to dopamine, these agents also increase drug delivery to the CNS.

Side effects of levodopamine include light headedness, hypomania and daytime somnolence. Furthermore, chronic use is known to predispose to periods of excessive choreiform movements known as dyskinesias and also to periods of excessive and reduced movements which are known as motor fluctuations (Evans et al., 2011). Other more recently introduced therapies include non-ergot derived dopamine receptor agonists such as ropinirole. These agents have been associated with a lower risk of dyskinesias compared to levodopa (Rascol et al., 2000), but they may also increase the risk of impulse control disorders. Such behaviours can be highly significant and range from pathological gambling and punting to compulsive sexual behaviour, compulsive shopping and binge eating (Djamshidian et al., 2011). A different class of drugs, the monoamine oxidase inhibitors (MAO-I), increase dopamine levels by inhibiting dopamine breakdown. The most commonly used MAO-I is rasagiline, which may be used as a monotherapy in early mild disease or in combination with levodopa and dopamine receptor agonists. Additionally, peripheral dopamine degradation may be inhibited by using (COMT) inhibitors such as entacapone. These agents increase the central bioavailability of levodopa and hence prolong its action. Over time, as disease progression ensues, the majority of patients end up on a combination of drugs that must be carefully managed to ensure an optimal balance between motor improvement and drug related side effects (Lees et al., 2009).

1.7 Deep Brain Stimulation and Parkinson's disease

Deep brain stimulation is a very effective surgical therapy for PD which became established following the demonstration that electrical stimulation of the basal ganglia could markedly

improve motor symptoms (Benabid et al., 1987; Limousin et al., 1995). DBS is currently performed when PD is in its relatively advanced stages in order to increase overall on time and to reduce the frequency of dyskinesias and also medication requirements. The surgical procedure involves permanently implanting multicontact electrodes bilaterally within the basal ganglia and subsequently connecting these subcutaneously to a stimulator in the chest wall (Foltynie and Hariz, 2010) (See Figure 1.1). The STN is often the preferred target nucleus for DBS in PD. The long term efficacy of DBS of this site in reducing motor Parkinsonian symptoms has been extensively documented (Rodriguez-Oroz et al., 2005; Deuschl et al., 2006; Witjas et al., 2007; Weaver et al., 2009; Fasano et al., 2010; Follett et al., 2010). The typical improvement in motor scores assessed using the UPDRS III is around 50% (Krack et al., 2003). Post-operative doses of levodopa are reduced by around 50% (Benabid et al., 2009) and there is a reduction in levodopa induced dyskinesias of around 60% (Krack et al., 2003). Furthermore, several reports have demonstrated an improvement in quality of life following DBS surgery (Weaver et al., 2009; Williams et al., 2010).

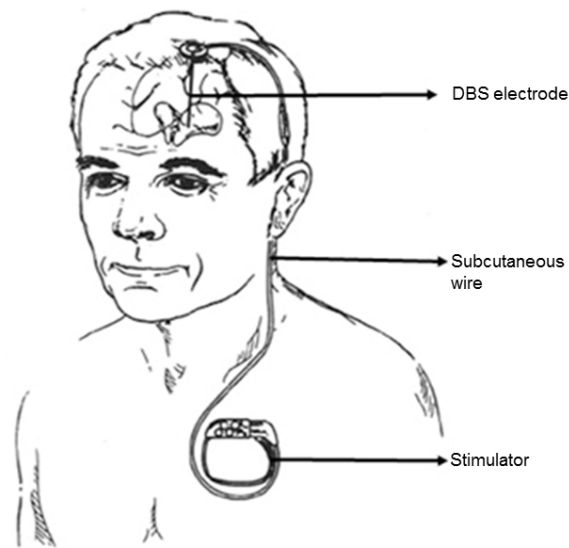


Figure 1.1 A diagram illustrating the hardware components for Deep Brain Stimulation. A multi-contact electrode is implanted into a target nucleus (typically the STN in Parkinson's disease) and is connected to a stimulator which is implanted in the chest wall via a subcutaneous wire. Adapted from <http://www.ucdenver.edu/academics/colleges/medicalschoo/departments/Neurosurgery/patientcare/multi-disciplinaryprograms/Pages/DeepBrainStimulation.aspx>

When considering the case for DBS in an individual patient, the beneficial effects must be weighed against the potential risks and side effects. Surgical adverse event rates are highly variable and include death (0%-4.4%), intracranial haemorrhage (0%-10%), stroke (0%-2%), and infection (0%-15%) (Bronstein et al., 2011). There are also a number of side effects associated with stimulation itself including dysarthria, weight gain, paraesthesia, depression and eyelid opening apraxia. Other significant side effects of DBS include neuro-psychiatric sequelae (Weaver et al., 2009) such as cognitive dysfunction and an increased risk of suicide.

1.8 Pathophysiology of Parkinson's disease

At a cellular level, the hallmark of idiopathic PD is the loss of dopaminergic neurones in the pars compacta of the substantia nigra (Hassler, 1938; Damier et al., 1999). Cell loss may also be found in other regions such as the locus coeruleus, dorsal nucleus of the vagus, raphe nuclei, nucleus basalis of Meynert and the pedunculopontine nucleus. Accompanying the loss of dopaminergic neurones is the accumulation of intracellular cytoplasmic inclusion Lewy bodies. Lewy bodies have a complex constituency comprising alpha-synuclein and ubiquitin and disease progression is proposed to be associated with a spread of Lewy body pathology rostrally up the brainstem to the mesocortex and the neocortex (Wakabayashi et al., 2007). It is becoming evident that the molecular biochemistry underpinning PD is complex and probably involves abnormalities within a spectrum of pathways including protein folding and clearance, mitochondrial function and the ubiquitin-proteasome system (Moore et al., 2005).

1.9 Cortico-basal ganglia networks and the pathophysiology of Parkinson's disease

A question that naturally arises is how the pathophysiological changes thus far described lead to a spectrum of motor and non-motor symptoms that characterise PD? This may in part be addressed by considering the multiple projections of dopaminergic cells onto cortico-basal circuits. In this section, we will briefly review the anatomy and physiological roles of these circuits before discussing their significance to PD.

The basal ganglia are a network of anatomically distinct but functionally interconnected subcortical nuclei. They receive inputs from wide areas within the cerebral cortex and return outputs back to the cerebral cortex via the thalamus, hence forming a cortico-basal ganglia loop. They also project output to the brainstem, via the substantia nigra pars reticulata (SNr) (see Figure 1.2). The most studied cortico-basal ganglia loop is the motor loop (Albin et al., 1989). Cortical motor projections converge on the striatum from which striatal projection neurons innervate the globus pallidus externa (GPe) and interna (GPi), forming the classical indirect and direct pathways, respectively. The subthalamic nucleus (STN), the sole excitatory (glutamatergic) nucleus of the basal ganglia network, also receives direct cortical afferents through a cortico-subthalamic projection, which forms the hyperdirect pathway (Mathai and Smith, 2011). In primates cortical afferents arise predominantly from the primary motor and premotor cortices (Parent and Hazrati, 1995a, 1995b; Nambu, 2008).

An early and also very successful conceptualisation was that, the direct pathway leads to the disinhibition of thalamic neurons and hence cortical excitation, which has a prokinetic effect, favouring movement. In contrast the indirect and hyperdirect pathways lead to the inhibition of cortical neurons and antikinetic effects, biasing against movement. It had been suggested that the reciprocal balance in activities of the direct and hyperdirect/indirect pathways plays a key role in selecting specific desired motor programs and inhibiting undesired ones (Nambu, 2008). In terms of linking this firing rate based model to the pathophysiology of the Parkinsonian state, it was proposed that dopamine depletion favours the activity of the indirect pathway leading to antikinetic effects (Albin et al., 1989; DeLong, 1990). This imbalance was thought to be effectively ameliorated by administration of the dopamine precursor levodopa. Although this firing rate model is a very useful conceptualisation, it is now widely believed to be an oversimplification for a number of reasons. Firstly, anatomical evidence suggests an incomplete segregation in the outputs of the direct and indirect pathways, making the previously accepted anatomical dichotomy between the direct and indirect streams less plausible. Secondly, the simple rate

model does not predict the clinical improvements in movement disorders that are observed following functional neurosurgery in the form of lesioning or Deep Brain Stimulation (DBS) of the globus pallidus and the thalamus (Marsden and Obeso, 1994). Recent physiological studies in primates and in Parkinsonian patients undergoing functional neurosurgery have pointed to a more complex picture of basal ganglia function that implicates not only the firing rates, but also the firing patterns of basal ganglia neurones. For example, recordings in MPTP treated monkeys demonstrated that STN and pallidal firing patterns display oscillatory and bursting behaviour (Bergman et al., 1994). Similar findings have also been observed in Parkinsonian patients undergoing functional neurosurgery for the insertion of DBS electrodes (Levy et al., 2002c). In the next section I review evidence highlighting that the study of synchronised oscillatory activity across cortico-basal-ganglia circuits may finesse our understanding of cognitive and motor functions both in health and in the Parkinsonian diseased state.

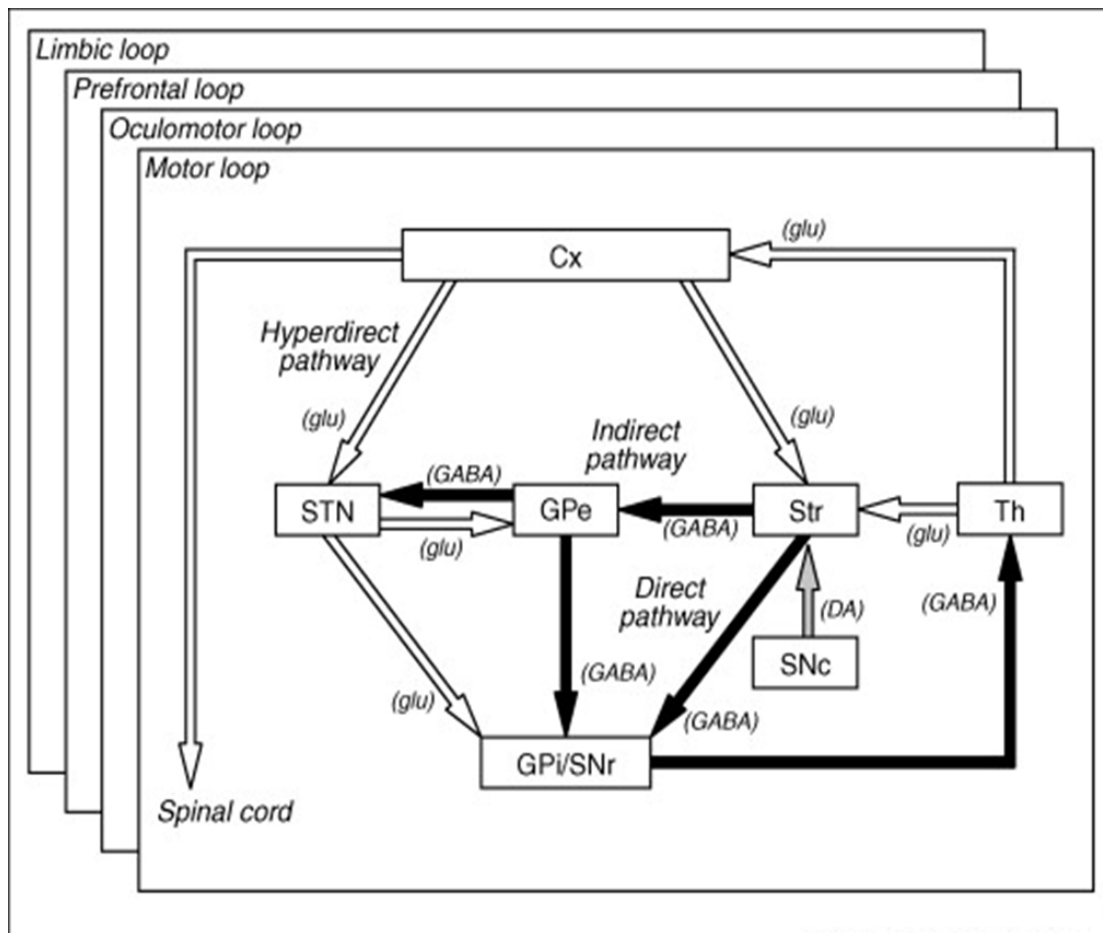


Figure 1.2 The cortico-basal ganglia motor loop and its neurotransmitter modulations. A hyperdirect pathway exists between Cx-STN-GPi/SNr. The direct (Cx-Str-GPi/SNr) and indirect pathways (Cx-Str-GPe-STN-GPi/SNr) are also shown. Open arrows represent excitatory glutaminergic projections whilst closed arrows represent inhibitory GABAergic projections. The grey arrow represents dopaminergic inputs. Cx – cortex; GPe – external segment of the globus pallidus; GPi – internal segment of the globus pallidus; SNc – substantia nigra pars compacta; SNr – substantia nigra pars reticulata; STN – subthalamic nucleus; Str – striatum; Th – thalamus. Reproduced with permission (Nambu, 2008).

1.10 Oscillations in motor control: insights from basal ganglia and cortical recordings

The first description of cortical oscillatory modulations associated with movement demonstrated 20 Hz oscillations close to the central sulcus that desynchronized upon active and passive movements (Jasper and Andrews, 1938). It has subsequently been shown that physiological cortical oscillatory changes in multiple frequency bands, which reflect the degree and extent of synchronization of activity in a local population of neurons, are modulated by the anticipation, execution and termination of voluntary movements (Pfurtscheller et al., 1993; Neuper and

Pfurtscheller, 1996; Pfurtscheller and Lopes da Silva, 1999; Alegre et al., 2005; Foffani et al., 2005).

Both beta (15-30 Hz) and lower frequency alpha rhythms (8-13 Hz) demonstrate event-related-desynchronisation (ERD) prior to movement, with sustained suppression during movement execution (Pfurtscheller and Lopes da Silva, 1999; Alegre et al., 2005). Furthermore beta band activity also displays event-related synchronisation (ERS) following the termination of movement (Neuper and Pfurtscheller, 1996). Activity at higher frequencies in the gamma band (40–90 Hz) in contrast to low frequencies displays ERS prior to movement execution (Salenius et al., 1996). This pattern of reactivity is repeated in the basal ganglia in patients with Parkinson's disease raising two important questions. First, to what extent are the oscillations detected in Parkinson's disease physiological or pathological? Second, what is the relationship of such activity between cortical motor sites and the basal ganglia?

Most of our understanding about oscillatory activity in the basal ganglia in humans comes from patients undergoing functional neurosurgery for the insertion of electrodes for DBS in target nuclei, although there is increasing complementary evidence from animal models of Parkinson's disease. The most common neurosurgical targets for Parkinson's disease are the STN and GPi (Ponce and Lozano, 2010), although others like the thalamus and the pedunculopontine nucleus (PPN) are also targeted for specific indications (Fasano et al., 2012). Here we will focus largely on insights provided by STN recordings.

Recordings from DBS patients offer a unique insight into the functional properties of sub-cortical activity. Recordings in patients can be made intra-operatively from the microelectrodes used to aid functional localisation of surgical targets. Microelectrodes afford recording of single neuronal units, the background firing of multiple units, and of the local field potential (LFP). Alternatively LFP recordings can be made post-operatively, with fewer time constraints, directly from the DBS electrode.

1.11 Beta oscillations: a pathophysiological hallmark of Parkinson's disease?

Several studies have demonstrated that a hallmark of dopamine depletion in the Parkinsonian state is elevated beta band (13-35 Hz) synchronisation in motor areas of the basal ganglia (Hammond et al., 2007) (Figure 1.3). Prominent beta band activity has been recorded from LFPs of the STN, GPi and striatum in Parkinsonian patients (Brown et al., 2001; Williams et al., 2002; Sochurkova and Rektor, 2003; Kühn et al., 2004). These oscillations tend to be maximal in the dorsolateral motor territories of the STN (Levy et al., 2002a, 2002b; Zaidel et al., 2010). Although it is not entirely clear how LFP activity relates to neural spike firing, the locking of neurons to LFP activity over a wide range of frequencies provides support for its use as a measure of the pattern of underlying neuronal synchronization (Moran et al., 2008). LFPs themselves probably result from a complex interaction of cellular and synaptic mechanisms (Logothetis et al., 2001) with the major influence being slow subthreshold post-synaptic potentials (Eccles, 1951).

Beta band activity has often been subdivided into upper (20-35 Hz) and lower (13-20 Hz) bands (de Solages et al., 2010). LFP power tends to dominate in the lower band and is more markedly suppressed by dopaminergic agents such as apomorphine and the dopamine prodrug levodopa (Priori et al., 2004; Marceglia et al., 2006; López-Azcárate et al., 2010; Litvak et al., 2011a) (Figure 1.3). This has fuelled the idea that beta activity is pathologically exaggerated in PD by the dopaminergic deficiency that is core to this disease.

So if beta activity is pathologically exaggerated in PD what is the evidence that this relates to certain phenotypic features? At cortical level the evidence is conflicting. MEG recordings have shown that local beta power over cortical motor areas is increased at rest in PD patients compared to healthy controls and that its movement related suppression is markedly attenuated (Pollok et al., 2012). Importantly however, numerous other studies have failed to demonstrate any significant modulation of cortical beta power by either levodopa (Silberstein et al., 2005; Hirschmann et al., 2011; George et al., 2013) or by DBS (Silberstein et al., 2005; Weiss et al.,

2015). One study has even suggested that levodopa therapy may increase measures of local cortical beta band synchrony (Stoffers et al., 2008). It is important to point out the distinction between measures of local cortical synchrony such as oscillatory power and measures of long range cortico-cortical interactions such as coherence. In this regard it has been proposed that treatments such as levodopa and DBS may modulate long range cortico-cortico synchrony rather than influencing local cortical power (Silberstein et al., 2005; Herz et al., 2014; Weiss et al., 2015).

At the level of the STN spontaneous fluctuations in beta activity have been shown to correlate with clinical state (Chen et al., 2010a; Little et al., 2012). In these studies spontaneous fluctuations have been measured using the coefficient of variation or other measures of complexity which take into account the variance of noisy timeseries measurements and hence may produce more consistent correlations with clinical state than are observed using STN power levels. Fluctuations could arise through variation in the strength, density and spatial extent of phase synchronisation. The latter can be inferred from the phase consistency of beta across DBS electrode contacts (Pogosyan et al., 2010), which also correlates with clinical state. Evidence that beta band oscillations contribute to motor impairment in PD also comes from several reports of levodopa-induced suppressions in LFP beta power and of the incidence of neurons oscillating over this frequency range correlating with treatment induced improvements in bradykinesia and rigidity (Kühn et al., 2006b, 2009; Ray et al., 2008). Interestingly, treatment related suppressions of beta activity have not been shown to correlate with tremor scores. The possibility of a mechanistic role for elevated beta activity in parkinsonism would be strengthened by evidence that beta suppression might occur during DBS as well as following treatment with levodopa. Traditionally it had been thought that DBS mimics the effect of lesioning and exerts a suppressive effect on STN output in keeping with the classical rate model of the disease (Bergman et al., 1990). This idea has been challenged however by two observations; firstly, an increase in SNr activity and, secondly, an increase in GPi activity during high frequency stimulation of the STN, both of which would not be predicted by the classical model of the disease (Hashimoto et al.,

2003; Maurice et al., 2003; Nambu, 2008). The major barrier to understanding how beta band oscillations in the STN are modulated by DBS has been the presence of stimulation induced electrical artefacts which are several orders of magnitude larger than spontaneous LFP fluctuations (Rossi et al., 2007). The development of special amplifiers which suppress DBS artefacts has made it possible to directly demonstrate that DBS suppresses beta band activity in the STN (Eusebio et al., 2011).

The story outlined thus far highlights the importance of exaggerated beta oscillatory synchrony locally in the basal ganglia and cortex in the clinical phenotype of Parkinson's disease, particularly with respect to two of the three cardinal features of the condition -bradykinesia and rigidity.

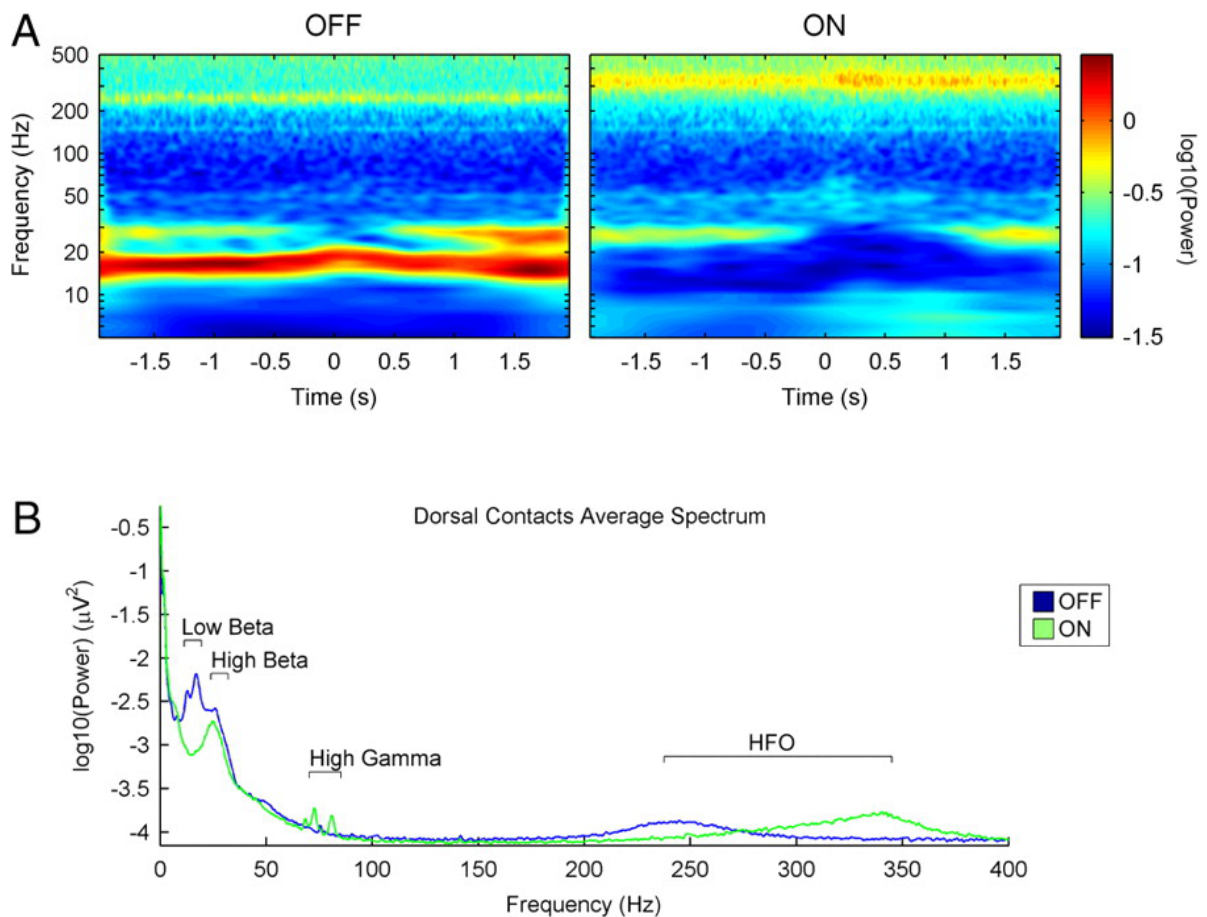


Figure 1.3 STN power spectra observed ON and OFF dopaminergic medication in a cohort of PD patients. **A)** Time-frequency plots showing time evolving spectra centred at the onset of self-initiated wrist movements ($t=0$ s). Beta activity desynchronises prior to and during movement, particularly ON medication. This is accompanied by a concurrent increase in gamma band activity. **B)** The resting spectrum shows a reduction in low, but not high frequency beta power ON medication. There are also

peaks in the theta/alpha, gamma and high-frequency, HFO (250-350 Hz) bands. Reproduced with permission (López-Azcárate et al., 2010).

1.12 Beta oscillations are synchronized between the cortex and basal ganglia in Parkinson's disease

There is also evidence to suggest that excessive synchronization of beta band activity not only locally, but between cortical areas and the basal ganglia, is an important pathological process in PD (Williams et al., 2002; Fogelson et al., 2006; Gradinaru et al., 2009; Hirschmann et al., 2011; Litvak et al., 2011a). Measurements of synchronization between STN and cortical sites in PD patients with DBS electrodes have involved the simultaneous recording of STN LFPs and cortical recordings with either electroencephalography (EEG) or magnetoencephalography (MEG). MEG may offer a number of advantages over EEG measurements including enhanced spatial resolution and the fact that magnetic fields, unlike electric fields, are not distorted by the presence of burr holes (Litvak et al., 2010, 2011a). Resting recordings with MEG have repeatedly confirmed the existence of two spatially and spectrally distinct cortico-STN networks. A beta band network exists between the STN and motor/premotor cortical areas whilst a diffuse alpha band network, the potential roles of which will be later discussed, exists between the STN and temporo-parietal as well as brainstem areas (Hirschmann et al., 2011; Litvak et al., 2011a)(Figure 1.4). A gamma band network between the STN and motor/premotor cortical areas develops or intensifies around the time of movement (Litvak et al., 2012).

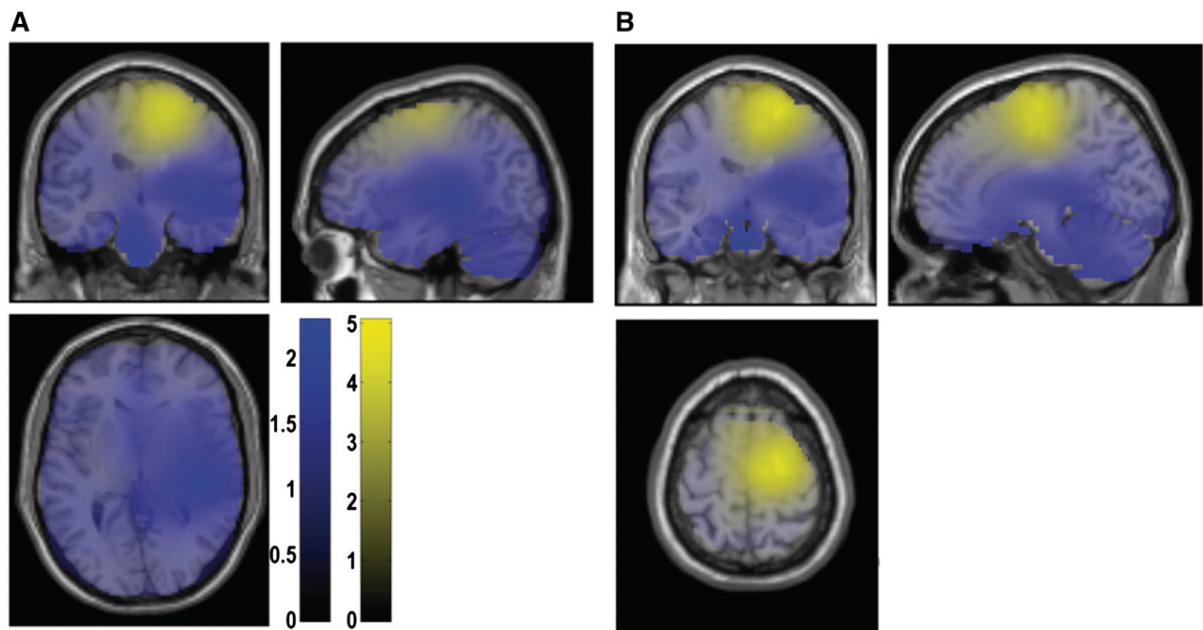


Figure 1.4 Resting state networks in Parkinson's disease. Images showing coherence between the STN and cortical regions in the alpha (blue) and beta (yellow) bands are superimposed onto a T_1 -weighted canonical MRI. Coronal, sagittal and axial sections are displayed, oriented to the image local maxima in the temporo-parietal region (A, alpha, centred at global alpha peak) and the premotor/supplementary motor area region (B, beta, centred at global beta peak). The colour scale is coherence normalized to individual image global values (arbitrary units). A value greater than 1 unit means that the activity in that voxel is consistently greater than the mean across the image. Reproduced with permission (Litvak et al., 2011a).

Using Granger causality based estimates of directionality of coupling between sites, it has been possible to demonstrate that although beta band coupling is bidirectional, it is asymmetric such that cortical beta oscillations are the most likely driver of increased beta band activity in the Parkinsonian basal ganglia (Litvak et al., 2011a). Hence a pathophysiological picture emerges whereby cortical beta activity drives subcortical beta band activity, leading to increased synchronization between and within these sites. This rather simplistic view is complicated by the observation that cortical driving at rest is primarily seen in the upper beta band (Hirschmann et al., 2011; Litvak et al., 2011a), whereas it is the lower beta band in the STN that is most exaggerated and best suppressed following the administration of levodopa in PD (Priori et al., 2004; Marceglia et al., 2006; López-Azcárate et al., 2010; Litvak et al., 2011a). Furthermore, levodopa has not been shown to reduce cortico-STN coherence in the upper beta frequency band

at rest and during self-paced movements (Litvak et al., 2011a, 2012). One possible explanation for these paradoxes stems from the existence of non-linear interactions between STN activities in the upper and lower beta frequency bands, which are severely attenuated by dopamine (Marceglia et al., 2006). Thus maybe in the dopamine depleted state high cortical beta activity is transformed during its relay to subcortical structures into lower frequency activity. Experimental work in this thesis will further explore this question by addressing how synchrony in STN-cortical beta band networks is influenced by DBS.

1.13 Task-related reactivity of Beta activity in Parkinson's disease

Thus far we have provided a picture whereby tonic levels of beta activity in the basal ganglia, and possibly in the cortex, are elevated in PD, and relate to bradykinesia and rigidity. What we have not yet considered is task or event related reactivity in beta synchrony in the Parkinsonian state. A defining feature of beta oscillations at both cortical and subcortical sites is their reactivity upon voluntary movement. Movement preparation is associated with a beta ERD which is further exaggerated by the initiation of movement. Following the termination of movement beta power rebounds (ERS) before normalising. Such changes in beta activity are often bilateral, although they tend to be more pronounced in the hemisphere contralateral to movement (Alegre et al., 2005).

The functional significance of task-related changes in beta activity in patients with Parkinson's disease may depend on when these occur with respect to movement and, in particular, whether they are perimovement or anticipatory. The timing of perimovement beta desynchronisation correlates with reaction times within and across patients (Kühn et al., 2004; Williams et al., 2005). In contrast, phasic increases in beta activity are observed during successful inhibition of pre-potent responses that are observed for example in successful stop trials in Go/NoGo tasks (Kühn et al., 2004). This has led to speculation that beta activity may dynamically antagonise motor processing (Gilbertson et al., 2005; Engel and Fries, 2010), in line with views regarding the

function of tonically elevated beta. Thus beta is phasically reduced when movement is necessary and increased when pre-potent responses have to be suppressed. Changes in the coupling between motor cortex and STN are likely to have similar functional relevance. Beta band coherence is reduced at the time of self-paced movements, with dopamine enhancing this reduction (Cassidy et al., 2002). The study of anticipatory beta reactivity that is temporally divorced from motor processing, but driven by environmental cues will be discussed in further detail in latter parts of this thesis.

1.14 Is Beta an epiphenomenon or causally important in Parkinsonism?

The evidence mentioned thus far implicating beta oscillations in the pathophysiology of the Parkinsonian state is largely correlative. Although it is possible that beta oscillations could be an epiphenomenon of other neural processes underscoring movement, there are a few lines of evidence that would support a causal rather than an epiphenomenal role. Firstly, it has been demonstrated that cortical stimulation at beta frequencies slows voluntary movements and force generation in healthy subjects (Pogosyan et al., 2009; Joundi et al., 2012). Secondly, DBS experiments in which chronically implanted patients are stimulated at low frequencies rather than at high frequencies reveal that stimulation at frequencies between 5-25 Hz exacerbates bradykinesia (Timmermann et al., 2004; Chen et al., 2007; Eusebio et al., 2008). The scale of these effects has been rather disappointing in humans, but in optogenetic rodent models it has been demonstrated that low frequency, 20 Hz stimulation of STN afferent projections markedly worsens Parkinsonian symptoms (Gradinaru et al., 2009). Still, the quantitative importance of beta synchrony in terms of its contributions to bradykinesia and rigidity in patients remains to be fully established.

1.15 Computational insights into the generation and propagation of beta rhythms in Parkinson's disease

Recent computational modelling studies have shed light on the potential mechanisms through which dopamine depletion may lead to exaggerated beta band synchrony in the cortico-basal ganglia circuit (Moran et al., 2011; Marreiros et al., 2012). Dopamine depletion results in increased connectivity between cortex and STN, GPe and STN and STN and GPi. Strengthening connections in any one of these pathways, as well as the pathway from STN to GPe, strongly promotes beta activity. These findings are in line with a model whereby cortical activity is required to maintain the STN-GPe circuit in a resonant state, which in turn promotes the generation and propagation of beta oscillations throughout the cortico-basal ganglia circuit. This is in keeping with numerous other studies highlighting strong interactions between GPe and STN as an important factor in promoting the emergence of beta band oscillatory activity (Albin et al., 1989; Holgado et al., 2010; Cruz et al., 2011; Kumar et al., 2011; Fan et al., 2012).

1.16 The Gamma frequency band: a prokinetic signal?

Several studies have demonstrated gamma oscillations in the spectra of LFPs recorded in the GPi, STN and thalamus of subjects at rest (Williams et al., 2002; Cassidy et al., 2002; Alegre et al., 2005; Alonso-Frech et al., 2006; Devos et al., 2006; Fogelson et al., 2006; Pogosyan et al., 2006; Trottenberg et al., 2006; Androulidakis et al., 2007; Kempf et al., 2009; López-Azcárate et al., 2010). The activity has been termed finely tuned gamma (FTG) as it is sharply tuned to a narrow frequency band within the 60-90 Hz range. It is not limited to patients with Parkinson's disease, nor a consistent feature in such patients (Jenkinson et al., 2012). It is contralaterally enhanced during voluntary movement, so that the direction of change is opposite to that of activity in the beta band. Akin to the beta rhythm, however, subcortical FTG is coherent with motor/frontal cortical activity, but is enhanced by therapy with the dopamine prodrug levodopa (Brown et al., 2001; Cassidy et al., 2002; Williams et al., 2002; Lalo et al., 2008; Litvak et al., 2012).

FTG oscillations have been linked to arousal through demonstrations that they are increased following startling stimuli and during REM sleep, which is associated with cortical arousal (Kempf et al., 2009). In contrast, FTG is absent during states of reduced arousal and during non-REM sleep (Brown et al., 2001; Kempf et al., 2009). Based on these findings and on the above studies highlighting the motoric role of the FTG it has been suggested that the role of oscillations in this frequency band may be to contribute to the vigour or effort of a motor response, which partly relates to the level of phasic arousal. Impairment of motor vigour may be an important feature of the dopamine depleted Parkinsonian state (Jenkinson et al., 2012).

Patients with Parkinson's disease also demonstrate broad band gamma synchronization perimovement, even in the absence of FTG in the resting spectrum (Alegre et al., 2005; Litvak et al., 2012). It is therefore likely that although FTG can contribute to this broad band reactivity, this is not the only factor. Whether broad band gamma reactivity also helps encode motor effort or vigour, rather than biomechanical movement parameters like force, remains unclear. Studies that demonstrate a correlation between both drug related increases in STN gamma activity and STN-cortical gamma-band coherence and motor improvement do not really address this point (Litvak et al., 2012). Similarly studies that show gamma amplitude around movement correlating with the speed and scale of voluntary movements cannot disambiguate vigour from force (Anzak et al., 2012; Brücke et al., 2012; Tan et al., 2013). Cortical stimulation at gamma frequencies in healthy subjects does only modestly increase the rate of development of grip force (Joundi et al., 2012), but this to some extent conflicts with more recent work highlighting that the gamma band may encode motor effort rather than force (Tan et al., 2015). One of the questions I aim to address is whether cognitive factors that are intricately associated with motor preparation - such as knowledge of both the effort required to perform an action or the rewards associated with performing that action – may be encoded in the oscillatory activity of the basal-ganglia.

Finally there is also a much higher frequency ERS upon movement extending up to 600 Hz in the STN (Litvak et al., 2012). So far it is unclear however whether this activity is the product of multiple, dynamic, phase-coupled neuronal clusters spanning this broad frequency range, or reflects the brief and asynchronous burst of activity hypothesized to be an LFP correlate of population firing (Manning et al., 2009; Miller et al., 2009; Ray and Maunsell, 2010).

1.17 Low frequency (theta/alpha) rhythms

A peak in the alpha band is often noted in LFP spectra from the STN in PD, but it does not appear to be substantially modulated by dopamine. Theta/alpha power in the STN is increased during cued movements (Klostermann et al., 2007; Anzak et al., 2012; Alegre et al., 2013), but its response in self-paced movements is less consistent (Singh et al., 2011; Oswal et al., 2013a). In addition, in PD, increased levels of theta and alpha STN power correlate with improved motor performance; specifically power in these frequency bands correlates with force measures during the onset, maintenance and release of maximal grip, and with the latency to onset of grip and its release (Anzak et al., 2012; Tan et al., 2013). These associations raise the possibility that STN activity in the theta/alpha band might subserve a non-specific function related to movement, such as attention.

This is also in keeping with views about coherent activity at similar frequencies between the STN, parieto-temporal cortex and the brainstem of patients with PD (Hirschmann et al., 2011; Litvak et al., 2011a). Nevertheless an empirical demonstration of a putative role for the STN-cortico-brainstem alpha band network in orienting attention is awaited. A key aim of this thesis will be to determine whether the STN-cortico-brainstem alpha band network relates to clinical motor impairments that are observed in PD.

1.18 Oscillations and Cognitive features of Parkinson's disease

As alluded to earlier, it has become increasingly evident that cognitive impairments in patients with PD may also be associated with changes in oscillatory activity in the cortex and in non-motor

regions of the STN. A general phenomenon in PD is the slowing of background oscillatory activity in cortical EEG and MEG, manifest as a diffuse increase in theta and alpha band power (Stoffers et al., 2007; Stam, 2010). However, in PD dementia, this slowing becomes even more marked so that there is an increase in the power of delta rhythms at the expense of a relative reduction in alpha power (Bosboom et al., 2006). Reversal of oscillatory slowing in PD dementia by acetylcholine esterase inhibitors highlights that the spectral changes may be the result of cholinergic neuron loss (Bosboom et al., 2009). Whilst the functional consequences or associations of such oscillatory changes remain to be elucidated, their demonstration in other primarily cognitive disease states such as Alzheimer's disease, suggests an important relationship with cognitive processing.

At the level of the basal ganglia, theta activity in the STN has been shown to be sensitive to conflict in decision making (Cavanagh et al., 2011; Fumagalli et al., 2011) and has accordingly been reported to be particularly elevated in PD patients with impulse control disorders (Rodriguez-Oroz et al., 2011). Similarly, STN activity in the alpha band is suppressed by emotional stimuli, with the degree of suppression correlating with individual valence ratings and the affective state of the patient. It has therefore been suggested that STN alpha band reactivity to emotional stimuli may be an important marker of depressive symptoms in PD (Kühn et al., 2005a; Brücke et al., 2007; Huebl et al., 2011).

Finally, gamma activity in the STN has also been implicated in cognitive processing. It is increased during the performance of paced random number generation and verbal fluency tests. These gamma changes correlate with a measure of randomness which indexes success in switching from automatic counting to a more controlled random generation of numbers (Anzak et al., 2013) and with the ability to switch between sub-categories in verbal fluency tasks (Anzak et al., 2011). Together these studies provide support for STN gamma activity in executive processes such as suppression of habitual or pre-potent responses and switching from automatic to controlled

processing in cognitive tasks. Therefore it is plausible that dopamine dependent impairments of gamma band activity and reactivity in PD may in part be responsible for some cognitive features, such as cognitive inflexibility.

1.19 Oscillations and Tremor in Parkinson's disease

Tremor is the only one of the three cardinal features of PD that itself has a directly measurable oscillatory nature. Tremor dominant types of PD have traditionally been considered distinct to bradykinesia-rigidity dominant subtypes (Jankovic et al., 1990; Rivlin-Etzion et al., 2006) and it is of little surprise therefore that dopamine depletion in the striatum and beta band activity has not been shown to correlate with the severity of PD tremor (Raethjen et al., 2000). A key difficulty in understanding the neural basis of tremor has been the fact that tremor often displays marked variability both over time and across the body, such that the tremor activity of different limbs in a PD patient is almost never coherent (Raethjen et al., 2000; Ben-Pazi et al., 2001). These observations suggest that multiple oscillators, rather than a single oscillator, may drive peripheral tremor.

MEG studies have allowed characterization of the brain regions coherent with Parkinsonian resting tremor, hence revealing functional tremor networks. These studies demonstrate the presence of strong EMG coupling with contralateral primary motor cortex (M1) and also coupling between M1 and other premotor, supplementary motor and somatosensory areas as well diencephalic and cerebellar sites (Timmermann et al., 2003).

In patients with PD tremor oscillatory peaks at tremor frequency and tremor harmonics exist within the STN, GPi and thalamus (Lenz et al., 1988; Bergman et al., 1994; Marsden et al., 2000; Brown et al., 2001; Levy et al., 2001) in addition to coherence between these sites and EMG activity (Reck et al., 2009; Pedrosa et al., 2012). Recent work has shown that both in the STN and in the ventral intermediate nucleus (VIM), distinct spatially segregated tremor clusters may relate

to tremor activity in specific muscle groups, pointing to multiple tremor-related sub loops within subcortical structures (Reck et al., 2009; Pedrosa et al., 2012).

In keeping with the finding of prominent thalamic tremor related oscillations in the VIM, is the finding that DBS of this site is successful in the treatment of both Parkinsonian and essential tremor (Koller et al., 2000; Rehnckrona et al., 2003; Barbe et al., 2011). Furthermore, in accord with electrophysiological studies of VIM connectivity, tractography has demonstrated that regions of the VIM adjacent to the most effective contacts for DBS have extensive connectivity with motor cortical and subcortical areas including the cerebellum and brainstem (Klein et al., 2012). Taken together, the above evidence highlights the possible existence of tremor oscillator(s) within basal ganglia-thalamo-cortical circuits. This assertion has gained theoretical support from computational models showing that both dopamine depletion and altered connectivity between nodes of the basal ganglia-thalamo-cortical circuit may lead to tremor like spiking activity (Dovzhenok and Rubchinsky, 2012).

1.20 Cross frequency interactions

We have largely focused on local synchronization and linear measures of synchronization, measured through coherence, of activity across the cortico-basal ganglia circuit. Several lines of evidence however point to the fact that activity in a particular frequency band may either influence activity in other frequency bands or interact with other frequency bands to influence behaviour. Such interactions may be either linear or non-linear (Chen et al., 2010b).

Studies adopting a multivariate approach to correlating activities in multiple frequency bands with behavioural performance during maximal grip demonstrate that effects in the alpha and gamma bands best predict behavioural performance while other features are held constant. Thus the relationship hitherto reported between beta activity and bradykinesia-rigidity might be tightly locked with or even secondary to effects at both lower and higher frequencies (Anzak et al., 2012; Tan et al., 2013).

Another striking feature demonstrated in a variety of physiological studies is the ability of the phase of a low frequency signal, typically in the delta, theta or alpha, range to correlate with the amplitude of a higher frequency oscillation, typically in the gamma range (Canolty et al., 2006; Canolty and Knight, 2010). Phase-amplitude coupling is thought to underlie a number of cognitive processes (Mormann et al., 2005; Demiralp et al., 2007; Tort et al., 2009) and has been proposed as a mechanism for motor impairment in PD. STN LFP recordings in PD patients have demonstrated coupling between the phase of beta band oscillations and the amplitude of high frequency oscillations in the off medicated state. This coupling is reduced by dopamine and by movement with movement related modulations correlating negatively with bradykinesia and rigidity scores (López-Azcárate et al., 2010). Furthermore, electrocorticography (ECoG) studies have demonstrated coupling of beta phase in the STN and in the motor cortex with broad band gamma amplitude over the motor cortex in PD. Such exaggerated coupling appears specific to PD, and it is also suppressed by STN DBS (de Hemptinne et al., 2013).

1.21 Concluding remarks on synchronised neural activity and the pathophysiology of Parkinson's disease

Growing evidence suggests that synchronized neural oscillations at discrete frequencies play a key role in neural communication and information processing both locally and within long range brain networks. Furthermore direct evidence of oscillatory activity being causal to behaviour rather than simply being an epiphenomenon of neural processing is beginning to be provided by experiments studying the behavioural consequences of directly manipulating oscillatory activity.

In PD oscillatory activity has been considered as either antikinetic (beta band) or prokinetic (gamma band), with the balance between these contributing to the motor symptoms of bradykinesia and rigidity. However this simplistic distinction neither captures the full functional roles of activity within these frequency bands and their cross frequency relations, nor explains

non-motor Parkinsonian phenotypes. In this thesis I hope to illustrate that the tonic and phasic reactivity of oscillations across multiple frequencies within spatially segregated loops of the basal ganglia-thalamo-cortical may relate to distinct components of clinical impairment. The hope is that an improved understanding of the role of oscillatory activity in contributing to the symptoms of Parkinsonism may translate into the development of novel therapeutic interventions. This is beginning to be realised, as evidenced by proof-of-principle studies demonstrating that, by specifically focusing on oscillatory activity, closed loop DBS and phase cancelling cortical stimulation may control symptoms in PD (Rosin et al., 2011; Brittain et al., 2013).

1.22 Aims of this thesis

In this thesis I will explore some of the functional and pathophysiological roles of oscillatory activity within cortico-basal ganglia circuits in Parkinson's disease. More specifically I aim to:

- 1) Investigate whether STN oscillatory activity within the physiological beta (15-30 Hz) and gamma bands relates purely to motor processing, or whether it may also convey information about task specific cognitive demands such as motor effort or reward (Chapter 3 and Chapter 4).
- 2) Examine how activity within the previously identified STN-temporo-parietal resting alpha network relates to clinical motor impairment (Chapter 5).
- 3) Develop and validate methodological approaches for interrogating the modulation of functional connectivity within cortico-basal-ganglia circuits during DBS (Chapter 6, Chapter 7 and Appendix A).
- 4) Establish the effects of STN DBS on long range oscillatory synchrony within STN-cortical circuits and hereby relate STN-cortical circuits according to their topography and preferred frequency of interaction to specific clinical symptoms.

Chapter 2: Methods and Materials.

2.1 Patients and Surgical Procedure

All patients studied were diagnosed with PD according the Queen Square Brain bank criteria (Gibb and Lees, 1988). Patients gave their informed written consent to participate in the studies, which were approved by the National Hospital for Neurology & Neurosurgery and Institute of Neurology Joint Research Ethics Committee, the Oxfordshire National Research Ethics Committee B and the Ethics Committee of the Charité University Berlin.

The patients underwent surgical implantation of STN electrodes prior to DBS therapy. Prior to surgery, motor impairments of all patients were evaluated using part III of the Unified Parkinson's Disease Rating Scale (UPDRS) (Goetz et al., 2008) after omitting all dopaminergic medication overnight and then following administration of 200mg of levodopa. This motor score includes 14 items which assess axial function, gait, balance, rest tremor, bradykinesia, rigidity and postural tremor (Goetz et al., 2008). The indications for STN surgery were PD with motor fluctuations and/or tremors that were inadequately controlled with medical therapies (Foltynie and Hariz, 2010). The DBS electrode used was always model 3389 (Medtronic, Minneapolis, MN). This has four platinum-iridium cylindrical surfaces of diameter 1.27mm, length 1.5mm, and centre-to-centre separation of 2mm. The contacts were numbered 0 (lowermost, which is intended to lie in the inferior portion of the STN) to 3 (uppermost, which is intended to lie in the superior portion of the STN or just above it).

Surgical targeting of the DBS electrode was based on preoperative stereotactic imaging (which consists of stereotactic MRI). The STN was targeted by examining it on the axial image containing the largest diameter of the ipsilateral red nucleus (Hariz et al., 2003). The centre of the STN was identified in a plane zero to one millimetre behind the anterior border of the ipsilateral red nucleus (Bejjani et al., 2000). Calculations of Cartesian coordinates of the target point were obtained using navigation software and a double oblique trajectory was planned on

reconstructed three-dimensional images to avoid entry into sulci and ventricles (Zrinzo et al., 2009). Correct localisation of the electrode in the STN was confirmed with immediate post-operative imaging (using MRI with a Leksell frame in situ at the National Hospital for Neurology & Neurosurgery or CT fused with the pre-operative MRI at the John Radcliffe Hospital). After implantation, electrodes were connected to an external connection wire kit that could be used to make recordings for five to seven days until a second surgical procedure in which the external extension wire was removed and the intracranial electrodes were connected to a new sterile wire that was tunnelled subcutaneously towards the sub-clavicular area. This new wire was connected to a pulse generator and battery pack for subsequent DBS therapy. Approximately 6 months following the operation, patients returned for follow up clinic appointment in order to have Part III UPDRS motor scores repeated.

2.2 Electrophysiological Data Acquisition

2.2.1 STN LFP and Electromyography recordings

STN LFPs and muscle activity in the form of electromyographic (EMG) signals were collected using amplifier systems. Over different experiments we used a Digitimer D360 amplifier (Digitimer Ltd, Hertfordshire, UK), a BrainAmp MR (Brain Products GmbH, Gilching, Germany), a Biopotential Analyser Diana (Sechenov Institute of Evolutionary Physiology and Biochemistry, St Petersburg, Russia) and the integrated EEG recording system in the MEG scanner (see below). In most of the experiments presented in this thesis, electrophysiological signals were collected in a monopolar fashion referenced to one of the mastoids, prior to conversion to a bipolar montage. In the case of LFP signals, this involved computing the difference between adjacent contacts of each STN electrode, resulting in 3 bipolar contacts per STN representing the potential difference between contacts 0-1, 1-2, and 2-3. In one experiment (Chapter 7), we directly collected bipolar STN LFPs at the input stage of the amplifier. A bipolar montage was preferred to limit the effects of

volume conduction from distant sources and of stimulation, by harnessing the common mode rejection characteristics of the amplifiers.

2.2.2 Magnetoencephalography

MEG is a non-invasive functional neuroimaging technique that relies on recording magnetic fields which are produced by electrical currents that occur naturally in the brain. Magnetic fields are typically recorded using superconducting quantum interference devices (SQUIDS) which are set in a helmet-shaped dewar that overlies the participant's head. All MEG recordings in this thesis were performed in London with a 275 channel CTF system (VSM MedTech Ltd., Vancouver, Canada).

Magnetic activity recorded from the brain is orders of magnitude lower than background activity due to the earth's magnetic field, the movement of nearby ferromagnetic objects (e.g. underground trains) and other forms of electrical activity (e.g. muscle activity and the heart beat). The effect of these external interferences can to some extent be reduced by enclosing the MEG system within a magnetically shielded room. Furthermore, since sources of noise are typically much further away than the brain signal of interest, it is possible to achieve noise suppression by using the gradient between two neighbouring sensors. Noise from distant sources will be the same at both sensors and is therefore suppressed by subtraction. For closer sources (i.e. brain sources), the activity recorded by both sensors will be subtly different however, giving rise to a differential signal. A similar rationale applies to bipolar EEG recordings. The CTF system uses axial gradiometers, whereby each sensor is referenced to another directly above it.

It is useful to briefly review the electrophysiological basis of signals recorded by MEG. MEG and EEG activity represents the summed activity of ionic currents flowing in dendrites during synaptic transmission. Since Maxwell's equations prescribe that any electrical current will produce a magnetic field, it is this field that is measured. The net current can be thought of as an equivalent current dipole – a single point which has a position, orientation and magnitude. To generate a

signal that is detectable, approximately 50,000 simultaneously active neurones are required (Okada, 1983). Furthermore, these cells and their dendrites must have similar orientations such that they each generate magnetic fields which reinforce each other. In this regard, the activity of cortical pyramidal cells is most likely to contribute to measured activity at the sensors.

Although EEG and MEG signals originate from similar underlying neurophysiological processes, there are a number of important differences (Cohen and Cuffin, 1983, 1991). Firstly, magnetic fields are less distorted than electric fields by the skull, the scalp and the presence of surgical burr holes which results in better spatial resolution of MEG compared to EEG (van den Broek et al., 1998; Bénar and Gotman, 2002; Oostenveld and Oostendorp, 2002). Whilst scalp EEG is sensitive to both tangential and radial components of a current source in a spherical volume conductor, MEG detects only the tangential components. Scalp EEG can, therefore, detect activity both in the sulci and at the top of the cortical gyri, whereas MEG is most sensitive to activity originating in sulci. EEG is sensitive to activity in more brain areas, but the activity that is visible in MEG can be localized with more accuracy. Secondly a major limitation of EEG in the context of this thesis is that scalp recording sites are limited in post-operative patients due to the presence of surgical wounds and dressings. In contrast, MEG can be recorded post-operatively with a large number of sensors around the head without direct skin contact (Litvak et al., 2010).

2.3 Data pre-processing

The data were analysed using custom MATLAB (The Mathworks, Inc, Natick, MA) scripts in conjunction with the SPM (<http://www.fil.ion.ucl.ac.uk/spm/>) and Fieldtrip (<http://www.ru.nl/neuroimaging/fieldtrip/>), (Litvak et al., 2011b; Oostenveld et al., 2011) toolboxes. Aspects of data pre-processing that are specific to experiments will be discussed in the relevant chapters. Here we will provide a more general overview of the pre-processing pipeline before discussing frequency transformation and connectivity metrics.

Data were usually acquired at high sampling rates (as high as 2400 Hz). Higher sampling rates increase data storage and computational requirements, but allow for higher frequencies to be examined (the Nyquist frequency limit equals half the sampling rate). In this thesis I will focus on oscillatory activity at frequencies less than 100 Hz, and therefore it is reasonable to downsample the data to 300 Hz. Importantly, if there are strong spectral peaks in the data at frequencies greater than the frequency to which the data is downsampled, these can ‘fold’ or alias into the downsampled spectrum giving rise to artefacts. This will be discussed further in Chapter 7 in the context of harmonics of DBS frequencies.

The acquired data were hardware filtered during acquisition by the MEG and LFP recording systems and also filtered during the pre-processing stage. Filtering the data essentially removes unwanted frequency components. A high-pass filter (> 1 Hz) was used to remove low frequency fluctuations in the signal due to gradual build-up of electrical charge which can saturate the recording equipment. Butterworth notch filters were also used to remove noise from mains interference at 50 Hz.

An additional stage of pre-processing is artefact removal. In our data there are numerous sources of artefacts, which are specific to the experimental procedure and recording equipment. For example, with MEG recordings, significant artefacts were generated from the ferromagnetic extension cables that were used to record LFPs (Litvak et al., 2010, 2011a). Furthermore, DBS during concurrent MEG generated high amplitude artefacts that will be discussed in Chapter 7. These types of artefacts were an order of magnitude larger than physiological artefacts generated from muscle activity, eye movements or the cardiac cycle. Often our spectral and source localisation methods were sufficient to handle such artefacts, but in the case of MEG recordings during DBS, we were faced with large amplitude jumps, which had to be fixed in the time domain prior to any further analysis (see Chapter 7).

2.4 Spectral analysis and functional connectivity measurement

Since the aim of this thesis was to investigate the spectral patterns of STN and cortical activities, we used a number of standard spectral timeseries analysis methods. Data can be transformed from the time domain into the frequency domain using the Fourier Transform. The motivation for the Fourier transform comes from the study of Fourier series. The Fourier series involves decomposing a periodic function $f(t)$ with period T into the sum of sine and cosine waves.

$$f(t) = \frac{a_0}{2} + \sum_{m=1}^{\infty} \left(a_m \cos \frac{m2\pi t}{T} + b_m \sin \frac{m2\pi t}{T} \right)$$

Where the coefficients are computed as:

$$a_0 = \frac{2}{T} \int_{-T/2}^{T/2} f(t) dt$$

$$a_m = \frac{2}{T} \int_{-T/2}^{T/2} f(t) \cos \frac{m2\pi t}{T} dt$$

$$b_m = \frac{2}{T} \int_{-T/2}^{T/2} f(t) \sin \frac{m2\pi t}{T} dt$$

An alternative representation of this can be derived from Euler's formula, $e^{ix} = \cos x + i \sin x$ which after some manipulation yields the complex form of the Fourier series:

$$f(t) = \sum_{k=-\infty}^{\infty} \left(\frac{2}{T} \int_{-T/2}^{T/2} f(t) e^{-ikt \frac{2\pi}{T}} dt \right) e^{ikt \frac{2\pi}{T}}$$

It is possible to extend this definition by examining the result when T tends towards infinity. This yields the standard equation for the Fourier transform:

$$f(\omega) = \int_{-\infty}^{\infty} f(t)e^{-\omega t} dt$$

In practice when performing the Fourier transform on time series of discrete length, we can use an approximation of the Fourier transform, known as the Discrete Fourier transform (DFT). The DFT can be evaluated over multiple frequencies, and each resulting complex output squared (i.e. the complex conjugate calculated) to result in a single value per frequency. This value, termed power, essentially discards the phase information of the initial signal. The distribution of power over different frequencies is a standard way to visualise the spectral properties of a signal and is termed the power spectrum (or autospectrum). An issue that arises with performing the DFT on a non-integer number of cycles of an input signal is time discontinuity, which manifests in the frequency domain as spectral leakage. Since most real life signals are complex, spectral leakage can be a problem. Its effects may be reduced by pre-multiplying the data by a window function (or taper) which suppresses time discontinuities. A very commonly used taper is hanning taper. We will tend to use the multitaper approach which involves obtaining multiple independent spectral estimates by the use of multiple orthogonal tapers (Thomson, 1982; Mitra and Pesaran, 1999). These spectral estimates can then be averaged, in order to yield a robust estimation of the underlying spectrum.

A key aim of this thesis will be to study interactions or connectivity between distant brain areas both at rest and during various experimental manipulations. There are many techniques to quantify the connectivity between two regions, and these can be broadly divided into three groups: 1) anatomical connectivity is based on the study of anatomical connections between brain regions, for example retrograde tracing studies in animals or diffusion tractography in humans 2) functional connectivity is the study of the statistical relationships of signals, and includes metrics such as correlations and coherence (see below) 3) effective connectivity aims to determine directional interactions between brain regions (Friston et al., 2013, 2014). In this thesis

we are concerned with functional connectivity in the form of coherence, but we will also examine effective connectivity in the form of Granger causal interactions.

Coherence is a frequency domain, linear measure of coupling between timeseries from different brain regions (Thatcher et al., 1986; Buzsáki and Draguhn, 2004). Coherence takes a value bounded between 0 and 1 and is the frequency-domain counterpart of a cross-correlation.

Mathematically, coherence is given by the following relationship, where the numerator is the squared modulus of the cross-spectrum and the denominator is the product of the autospectrum of each signal:

$$C = \frac{|f_{xy}|^2}{f_{xx}f_{yy}}$$

Importantly coherent oscillatory is believed to play an important role in communication between different brain regions (Fries, 2005; Schoffelen et al., 2005; Bastos et al., 2015).

Although the presence of coherence implies functional relationships between time series, it does not provide any information about the directionality of coupling. For example, two brain regions A and B may have time series that are coherent at a particular frequency, but this does not provide any information about whether region A drives region B or vice versa. In this thesis we focus on Granger causality based approaches for investigating directed connectivity. The notion of Granger causality was first proposed by Clive Granger in 1969. Granger argued that causality could be measured by determining the ability of the past of one time series to predict future values of another (Granger, 1969). This description can be cast mathematically in the form of a multivariate autoregressive model (MVAR), which in the case of two time series reduces to a bivariate form. In this thesis we will be concerned with bivariate analysis:

$$X(t) = \sum_{j=1}^p A_{11}X(t-j) + \sum_{j=1}^p A_{12}Y(t-j) + E_1(t)$$

$$Y(t) = \sum_{j=1}^p A_{21}X(t-j) + \sum_{j=1}^p A_{22}Y(t-j) + E_2(t)$$

In the above equation, $Y(t)$ and $X(t)$ are two time series and A is a $2 \times 2 \times p$ matrix which contains the coefficients of the model. The coefficients represent the contribution of each lagged observation to the values of $Y(t)$ and $X(t)$. $E_2(t)$ and $E_1(t)$ represent the predictions errors of the model which are assumed to have a Gaussian distribution. Importantly, the term p represents the model order, which can be determined through a number of approaches. Signal Y is said to Granger cause signal X if the coefficients in A_{12} are jointly significantly non-zero. However, it is worth keeping in mind that this may not be the only explanation for non-zero coefficients. For example non-zero coefficients will also result if signal Y drives signal X through another unrecorded structure or indeed if signals X and Y are separately driven by an unrecorded structure. Such limitations can be to some extent alleviated by including more sites or time series into the assessment of causality. Various frequency domain approaches for Granger causality have been proposed, such as the Directed Transfer Function (Kamiński et al., 2001) and Partial Directed Coherence (Baccalá and Sameshima, 2001). Recently, non-parametric approaches for computing Granger causality, which do not rely on fitting an autoregressive process, but involve factorisation of a spectral density matrix have been developed. These approaches have a number of benefits, including the fact that they make fewer assumptions about the data and can also capture more complex spectral features than are possible with low order autoregressive models (Dhamala et al., 2008).

2.5 Source level analysis of MEG data by beamforming

Both EEG and MEG data can be analysed in sensor space. For example, sensors overlying the frontal cortex, may be used to make inferences about frontal cortical activations. Sensor space analysis has somewhat limited localising power however and more recently algorithms have been

developed to more precisely localise the origin of brain activity (known as source space reconstruction). Source space reconstruction aims to project sensor level data onto 3D brain space, which comprises a large number of dipolar sources with fixed locations. Typically the orientations and amplitudes of each dipolar source need to be determined.

Predicting dipolar activity from the EEG/MEG time series is known as inverse modelling. Inverse modelling is typically ill-posed since it requires anatomical, functional or mathematical constraints in order to have a unique or highly probable solution. Prior to computation of the inverse solution, it is necessary to first map the coordinate system in which sensor positions are represented to the coordinate system of a structural MRI (usually in MNI space) using a rigid body transformation. This procedure is known as co-registration. We used landmark based co-registration based on the presence of three fiducial electrodes: at the nasion and the left and right pre-auricular points. Secondly, it is necessary to know how the activity of a dipole at a particular location with a particular orientation maps to the sensors. This step is known as forward modelling and it can be achieved using Maxwell's equations. In our studies we used a single shell forward model (Nolte, 2003).

A number of different methods have been developed to solve the inverse problem over the years. Simple approaches such as dipole fitting aim to minimise the difference between predicted and observed sensor data by optimising dipole parameters such as position, orientation and time courses. Typically the number of dipoles to be fitted is specified a priori however. In this thesis we will use beamforming as our chosen method of source reconstruction, since it has been previously shown to be very effective at suppressing the types of artefact and noise patterns observed in patients undergoing DBS surgery (Litvak et al., 2010). In such patients the predominant source of artefact arises from ferromagnetic cables connecting the DBS electrode to the recording equipment. Beamforming is an adaptive spatial filter based approach for source reconstruction, where a brain location specific filter is generated based on the principle of

minimising the total source power without suppressing the source of interest. Mathematically this can be framed as a minimisation problem for computing the filter:

$$\min_{W(r)} P = W(r)^t C W(r) \text{ Subject to } W(r)^t L(r) = I$$

Here $W(r)$ is an $N \times 3$ matrix representing the spatial filter for brain location r for the x, y and z orientations. N represents the number of sensor channels and C represents the $N \times N$ data covariance matrix. Finally, $L(r)$ is an $N \times 3$ matrix which represents the location specific forward model or leadfield for the x, y and z orientations and I is an identity matrix. The above problem can be solved using constrained optimisation based on the principle of Lagrange multipliers yielding the following equation for each location specific filter:

$$W(r) = C^{-1} L(r) [L(r)^t C^{-1} L(r)]^{-1}$$

In principle it is possible for C to represent either the data covariance (time domain) (Van Veen et al., 1997; Brookes et al., 2008) or cross-spectral density matrix (frequency domain) (Gross et al., 2001). In Chapter 6 we will formulate a modification to the above equation, for instances where we have a strong prior hypothesis about the location of a signal or activation of interest. We show that this modification may provide improvements in source localisation accuracy in certain experimental circumstances.

2.6 Statistical Parametric Mapping and statistical analysis of electrophysiological data

Statistical analysis was performed by using a general linear model (GLM) based approach, implemented in the SPM12 software package (Statistical Parametric Mapping). SPM is a MATLAB toolbox that was designed to make inferences about regionally specific effects in the brain. However, the statistical principles can be used to make inferences about regionally specific effects in any 1, 2 or 3 dimensional space (Kilner and Friston, 2010).

SPM employs a mass univariate approach to the statistical analysis of images, meaning that the observed data at each voxel, pixel or time point (in the case 3D, 2D or 1D images respectively) is

modelled as a linear combination of one or more explanatory variables with additive Gaussian noise. Take for example, a single voxel with 10 experimental conditions and 10 observations for each condition. The activity of that single voxel would take a different value for each experimental condition, yielding a 100 x 1 vector Y . X is a design matrix, with each explanatory variable (or regressor) as a column vector. In this case X would be a 100 x 10 block diagonal matrix. Typically an additional column of ones is added to the design matrix to model a constant intercept. β represents a vector of parameters which optimally fit the model to the data whilst e is a vector of errors containing the mismatch between the observations and the model.

$$Y = X\beta + e$$

It is relatively straightforward to estimate the β parameter using Ordinary Least Squares, assuming that the errors are independent and identically distributed. Unfortunately however this assumption is rarely true, particularly with repeated measures designs or if the data are temporally auto correlated. SPM therefore uses additional methods to handle such non-sphericity of errors (Worsley and Friston, 1995). One approach involves pre-whitening of the data and design matrix using an estimate of the non-sphericity obtained from a procedure known as restricted maximum likelihood (ReML).

In the analysis presented in this thesis, statistical analysis was performed at the group level using a summary statistic based approach, whereby a single image for each experimental condition of interest for each subject was analysed at the between subject level. While SPM includes a hierarchical framework for incorporating both the between subject variance used here and within subject variance (a so called mixed-effects analysis), the results are not greatly improved with this procedure and so it is rarely used in practice (Friston et al., 2005). Once the GLM has been applied to each voxel, pixel or data point, SPM produces an image of the β parameters for each regressor in the design matrix. Statistical testing of hypothesis can then be performed using the β images, after specifying appropriate contrasts. For example, if our design matrix had just three columns

and we wished to test for regions where the effect of the first regressor was significantly larger than the effect of the second, we could define the contrast $c = [1 \ -1 \ 0]$. The null hypothesis to be tested in this case would be that $c\beta = 0$. This can be tested using the t-statistic, which has a probability distribution following the t-distribution and allows a p value to be calculated for comparison to a pre-specified threshold:

$$t = \frac{c\beta}{\sqrt{c(X^tX)^{-1}c^t\sigma^2}}$$

In the above equation σ^2 represents an estimate of the error variance. Images of the t-statistic for each contrast can be generated in SPM for visualisation (Friston et al., 1994). The resulting t images may be thresholded to a certain p-value, such that surviving voxels, pixels or data points are reported as being significantly activated by an experimental manipulation. Such an approach however runs the risk of false positives (Type 1 errors) due to the multiple comparisons problem. Correcting for this requires an estimate, of the number of independent statistical tests being performed. Because of spatial or temporal correlations (or smoothness) that naturally exist in data, the number of independent statistical tests performed is not simply equal to the number of voxels, pixels or data points. Note that assuming the latter would be equivalent to a Bonferroni correction which tends to be over conservative. SPM uses a branch of mathematics called Random Field Theory to calculate a corrected p value based on the smoothness of the data. Having estimated the smoothness, the expected distribution of topological features in the data such as peaks or clusters can be calculated using the Euler characteristic (Worsley et al., 1992). This allows for more accurate thresholds for statistical parametric maps.

Chapter 3: Beta reactivity, prospective facilitation of executive processing and its dependence on dopaminergic therapy in Parkinson's disease.

3.1 Introduction

Synchronised neural oscillations at beta frequencies have been reported in the basal ganglia of patients with PD and models of this disease (Hammond et al., 2007). Their tonic and phasic suppression by dopaminergic medication and salient cues correlates with changes in motor performance (Kühn et al., 2004; Doyle et al., 2005; Williams et al., 2005; Kempf et al., 2007; Kühn et al., 2009; López-Azcárate et al., 2010; Pogosyan et al., 2009; Ray et al., 2008; Zaidel et al., 2010). Such suppression is accompanied by a surge in dynamic interactions between basal ganglia neurons, involving increased neuronal discharge rates and synchronisation at gamma, or higher, frequencies (Alegre et al., 2005; Androulidakis et al., 2008; Amirnovin et al., 2004; Courtemanche et al., 2003; Devos et al., 2006; Foffani et al., 2003; Kane et al., 2009; Kempf et al., 2007; López-Azcárate et al., 2010; Pogosyan et al., 2006; Özkurt et al., 2011). This raises two possibilities. First, beta suppression could be an epiphenomenon of the shift in neuronal patterning that underscores movement. Second, beta suppression might be necessary to permit the dynamic reconfiguration of neural networks. The distinction is important as in one case beta suppression is an emergent epiphenomenon, inseparable from motor processing, whereas in the other it is an active process that prospectively sets the stage for rate coding and spectral interactions at higher frequencies during motor processing.

Although there is some support for the latter suggestion (Kühn et al., 2004), beta suppression in the basal ganglia has never been disassociated from motor processing in experimental situations, and hence its role as an active and prospective control mechanism remains speculative (Jenkinson and Brown, 2011).

The above issue may also relate to another unsettled question. Dopaminergic medication is effective in suppressing tonic levels of beta synchrony in the basal ganglia (Hammond et al., 2007), but what is more contentious is whether it also improves the phasic reactivity of beta synchrony to salient internal and external cues (Doyle et al., 2005; Androulidakis et al., 2008) or not (Devos et al., 2006). Perhaps, the conflation of different phenomena has confounded such studies.

Finally, it has recently been stressed that the above is a restrictively motoric view of beta suppression, and that the latter may represent a generic control process in executive function, be it primarily motor or cognitive in its nature (Engel and Fries, 2010). These considerations lead to the hypothesis that beta suppression in the basal ganglia can be an active process involved in the prospective control of motor or cognitive readiness (Engel & Fries, 2010; Jenkinson & Brown, 2011) and can thus be disassociated from specific motor parameterization and cognitive processing. Further, this prospective control function of beta synchrony is modulated by dopamine. Accordingly, I developed a paradigm that separates warning of the need for a response from the processing of the specific response, and tested this while recording beta activity from the subthalamic nucleus in patients with PD ON and OFF the dopamine prodrug, levodopa.

3.2 Methods

Ten patients (8 male and 2 female) with idiopathic Parkinson's disease who underwent implantation of deep brain stimulation electrodes in the subthalamic nucleus (STN) at four different surgical centres participated in the study. Each was implanted for the treatment of their PD and with the exception of a single patient, all patients were implanted bilaterally. The clinical characteristics of the patients, surgical details, electrode localisation and paradigm have been described in detail in a previous study (Sauleau et al., 2009). All patients gave informed written

consent to participate in the study, which was approved by the local ethics committees of the different surgical centres.

Five patients were implanted at the University Hospital Gasthuisberg, Leuven, Belgium; three patients were implanted at the Oxford Radcliffe Hospital, Oxford, UK; one patient was implanted at King's College Hospital, London, UK; and one patient was implanted at the National Hospital for Neurology and Neurosurgery, London, UK. None of the patients had any surgical complications, postoperative confusion or severe motor impairment that precluded understanding or performance of the test.

3.2.1 Paradigm

I developed a paradigm that separated warning of the need for a response from the processing of the specific response. This was achieved by presenting a warning cue that signalled the need for a motor or cognitive response followed by an imperative cue which specified the precise response required. At the same time temporal expectancy was limited by pseudo-randomization of the inter-cue interval. Our prediction was that salient warning cues would elicit beta suppression, even when the necessary response and its timing were obscure. Subjects were seated comfortably in a chair. The test consisted of three conditions: a 'standard motor' task and a 'control motor' task consisted of performing body movements according to visual cues presented on a laptop computer, while the remaining condition was a non-motor 'counting' task consisting of counting in silence identical cues while at rest. Each trial began with a fixation cross and then presentation of a warning cue. This could be a black circle (50% probability), square (25% probability) or triangle (25% probability), which substituted the fixation cross provided between trials to limit confounding eye movements (Figure 3.1). The warning cue was followed by a schematic of the body (imperative cue) with a single segment highlighted in red (head, trunk, left arm, right arm, left leg or right leg, with equal probabilities). In the standard motor task, patients

were instructed to move the highlighted body segment whenever preceded by a circle (target cue), but to ignore the body schema cue when this was preceded by either a non-target square or triangle (Figure 3.1). This was reversed in the control motor task, in which patients were instructed to move the highlighted body segment whenever preceded by a square or triangle (target cue), but to ignore the body schema cue when a non-target circle preceded this. In the non-motor counting task, the patients were asked to remain at rest and to count silently in their mind how many left arms were highlighted in red after circles (target cues), ignoring non-target squares and triangles. At the end of the task the subjects were asked to report this number. The experiment began with some demonstration trials in which the intended movements were shown to the patient. These movements consisted of single and brief flexion of the neck, flexion of the trunk, left or right wrist extension, and left or right ankle dorsiflexion. Each of the three tasks was repeated twice, the six blocks being presented in a pseudo-randomized order across patients. The task requirements were verbally explained to the subject prior to the start of each block. Blocks of a given task lasted 4 min, and were followed by 1–2 min rest. Each block of a given task consisted of 24 trials, giving a total number of 48 trials per condition. Each trial started with the presentation of a fixation cross at the centre of a portable PC screen, followed 2.4–5.0 s later by the warning cue of fixed duration (0.5 s) and by a 3.5 s duration second cue of a body schema presented at the centre of the screen. This was followed by a blank screen for 1 s, before the next trial began with reappearance of the fixation cross.

Within each block, trials occurred pseudo-randomly, every 9–11 s. The two consecutive cues were presented with a randomized interval between cue onsets (foreperiod before imperative cue) of 1.5–2.5 s. The distribution of this foreperiod was uniform, meaning that the probability of the target cue appearing at any point in the interval was fixed. Moreover, in choosing similar overall probabilities of target and non-target cues I biased the experimental design so that evoked activity related to behavioural relevance would be stressed over that related to novelty. Thus, our experimental design differed from previous P300 and contingent negativity variation (CNV)

paradigms in so far as the response to the warning cue was disambiguated from specific task-related motor or cognitive processing and behavioural relevance emphasized over novelty.

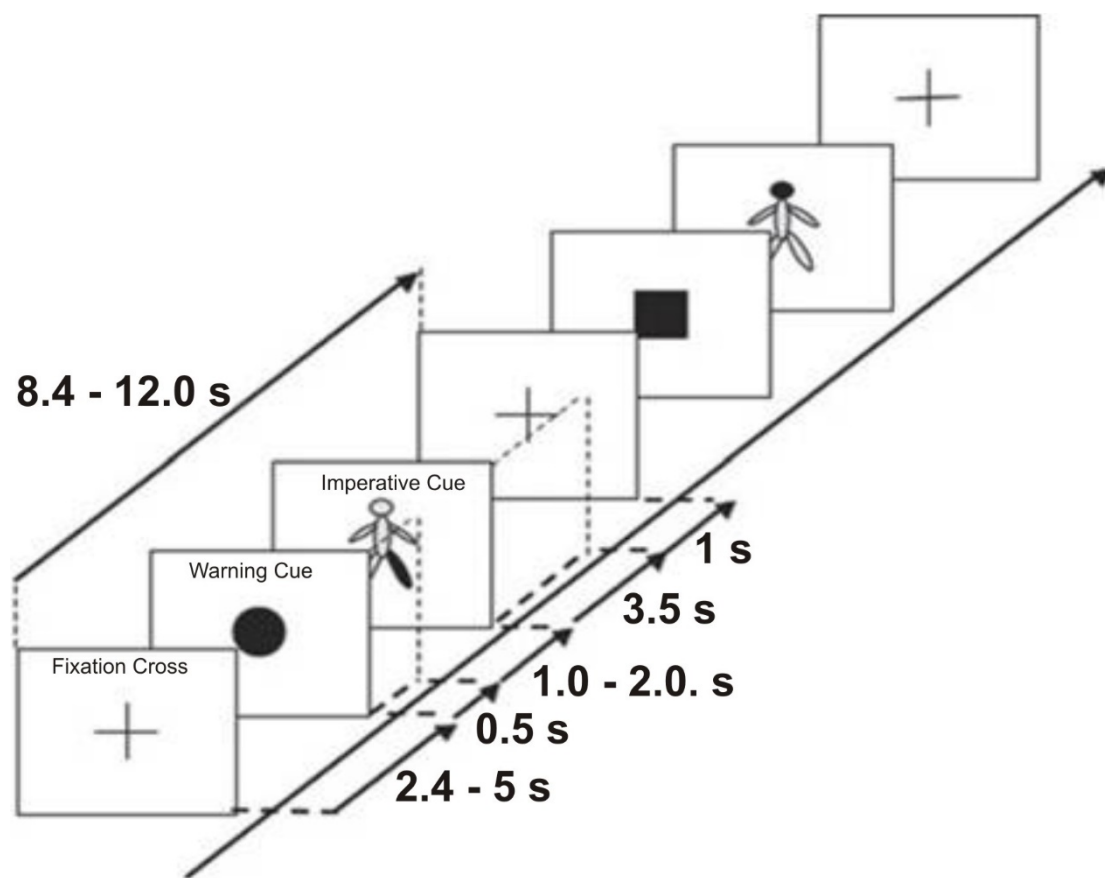


Figure 3.1 Schematic of two trials during the standard motor task.

In this block type patients were instructed to move the highlighted body part indicated in the body schema only when the warning cue was a circle. They were instructed to remain at rest when the body schema was preceded by either a square or a triangle warning cue. The behavioural relevance of the stimuli was reversed in the control motor task. A similar sequence was also used in the counting task.

Patients performed the motor tasks well. There were two types of error. The first related to the warning cue and involved patients subsequently moving when they should not have or failing to move when they should have. On average patients made such errors in 1.2% of trials OFF and ON medication (total number of trials in each drug state was 960 when the two motor tasks were

combined). The second type of error was related to the imperative cue, and involved patients moving the wrong side or body segment. On average patients made such errors in 1.0% of trials OFF and ON medication (total number of trials in each drug state was 960 when the two motor tasks were combined). As I was primarily interested in the evoked response to the warning cue I removed those trials with the first type of error as attention to the warning cue could not be ensured in these instances. This left 44-48 trials in each subject per motor task in each drug state. In the counting task four patients counted wrongly in one block, but correctly in the remaining block OFF medication. ON medication, one patient counted wrongly in one block. Blocks of the counting task were analysed regardless to the presence of errors (48 trials in each subject per drug state).

3.2.2 Recordings

Nine patients were first assessed after overnight withdrawal of antiparkinsonian medication, then 73 ± 18 min after a supra-maximal dose of levodopa (usual morning dose or 200 mg equivalent-levodopa, whichever the higher). One further patient was first recorded ON medication and then OFF medication on two consecutive days.

Local Field Potentials (LFPs) and analogue signals related to the cues were recorded through a Biopotential Analyser Diana (Sechenov Institute of Evolutionary Physiology and Biochemistry, St Petersburg, Russia). LFP activity was recorded monopolarly from the four contacts of each DBS electrode targeting the STN, referenced to linked earlobes, amplified, filtered (0.5–300 Hz) and sampled at a common rate of 1200 Hz.

3.2.3 Spectral Analysis

Signals were exported for off-line processing in Spike 2 V6 software (Cambridge Electronic Design, UK). So as to minimise volume conduction I subtracted the signal from the adjacent but dorsal

electrode contact from each contact to give three bipolar contacts per subthalamic electrode (contacts 01, 12 and 23, in which contact pair 01 was the most caudal). I then removed any DC offset by filtering with a time constant of 1 s. The data were first epoched into trials, excluding trials with errors, and the average signal over all correct trials was removed from each individual trial to generate the induced response. Spectral analysis was carried out for each bipolar electrode pair for all subjects using the multitaper method (Thomson, 1982). The resulting spectra were subsequently averaged. In our main analysis I averaged across all the contact pairs in a given electrode so as to avoid selection bias. However, as beta oscillations are focally generated in the STN (Kühn et al., 2005b; Chen et al., 2006), and not all contacts could be expected to lie in this nucleus, this procedure may under-estimate the scale of effects. Therefore, in a subsidiary analysis, I also averaged data across the best contact pairs from each electrode, so as to have a better idea of the quantitative effects of our experimental factors and so as to facilitate comparison with other studies that have taken this approach. The best contact pair was defined as the contact pair from each electrode showing the greatest beta desynchronisation in the 'response' case (STN 01 x 6, STN 12 x 10 STN 23 x 3).

Spectral analysis was performed for each trial of each of the three conditions, ON and OFF medication for each subject. I separately analysed the spectra locked to the warning cue and to the target imperative cue between specified time periods (shown in individual Figures), in overlapping windows of 400 ms (shifted by 50 ms). The frequency resolution was set to the inverse of the time window (2.5 Hz) for all frequencies. The trial data were averaged (irrespective of the body part highlighted by the imperative cue) for each subject for statistical analysis across the different conditions (6 in total – comprising 3 blocks ON and 3 OFF medication). Percentage change time-frequency responses were obtained by normalizing to the baseline (– 0.8 to – 0 s) before the warning cue.

3.2.4 Statistics

Given that our *a priori* hypothesis specifically involved searching for differences in the beta frequency band (15-30 Hz), I averaged the spectral data over this band by computing a multitaper spectral estimate with central frequency of 22.5 Hz and spatial resolution of 7.5 Hz. This is a more efficient way of estimating beta power than averaging over pre-computed time-frequency images with higher frequency resolution (Mitra and Pesaran, 1999). The averaged beta time series for each condition and electrode were converted into 1D images (Neuroimaging Informatics Technology Initiative format) for statistical analysis in SPM8. Here, I was able to correct for multiple comparisons in time using random field theory (Kilner et al., 2005).

Using this approach I analysed the period between the warning and imperative cues independently for the motor and non-motor tasks using a repeated measures ANOVA for the 10 subjects. I also included subject as a covariate in the design to account for the fact that the time series from the right and left subthalamic nuclei were from the same subject. Additionally I included a side covariate for each subject in order to account for potential differences between recordings from the right and left subthalamic nuclei. For the motor task, the factors were Block (Motor task vs. Control Motor Task), Cue ('response' vs. 'no response') and Dopaminergic state (ON vs. OFF). For the non-motor task, the factors were Cue and Dopaminergic state only. I did not analyse signals after presentation of the imperative cue.

Using this repeated measures design in SPM, I specified t-contrasts to test for times at which significant differences occurred using paired t-tests. Using the t-contrasts in SPM I was able to test for the direction of significance, for example, taking the main effect of cue I could test whether 'response' produced significantly less desynchronisation than 'no response' or *vice versa*. All the reported findings are significant with family-wise error (FWE) correction at the peak level ($p < 0.05$). In addition, I tested the statistical significance of changes in each time series of beta

power relative to baseline by performing serial one sample t-tests in time and correcting for multiple comparisons in SPM8 using random field theory. In the latter case I made our procedure even more conservative by considering only those changes from baseline that were significant over three or more contiguous time points (≥ 150 ms).

In a separate analysis, I performed the same statistics as described above looking for significant differences in the gamma band (60-90 Hz) across conditions for all subjects. Finally, to confirm the focal origin of the LFP beta activity, I defined the contact pair showing the maximum beta power in each electrode as 100% and calculated the mean relative beta power at the remaining contact pairs. The latter were averaged across electrodes, and the mean relative power and its standard error presented.

3.3 Results

Time frequency plots of the induced responses in the 3 different tasks to 'response' and 'no response' warning cues OFF medication are presented in Figure 3.2. To the right hand side of the figure the data are averaged with respect to the appearance of the imperative cue (given as time zero), and presented relative to a baseline period between -3.3 s and -2.5 s. To the left hand side of the figure data are averaged with respect to the onset of the warning cue (given as time zero), and again presented relative to a prestimulus baseline of 0.8 s. In the left hand images the time extends only to 1.5 s after the onset of the warning to prevent contamination from motor responses, which could occur after a minimum foreperiod of 1.5 s. Figure 3.3 shows the corresponding plots ON medication.

Beta desynchronisations were greater following the 'response' than the 'no response' warning cues when ON (Figure 3.3) compared of OFF (Figure 3.2) medication, and in the motor tasks this appeared to be independent of the nature of the 'response' warning target. These effects were also seen in the one subject who was first tested ON medication, *i.e.* in the reverse order to the

other subjects, suggesting that any effects of dopaminergic state were unlikely to have been confounded by the order of task performance.

The effects were confirmed at the group level in an ANOVA with factors target (circle vs. square/triangle), warning cue ('response' vs. 'no response') and medication (ON vs. OFF) in the motor task, where there was no main effect or interaction with target. Accordingly, I amalgamated data from the two motor tasks, in a 2x2 ANOVA with factors warning cue ('response' vs. 'no response') and medication (ON vs. OFF) to test for the main effects and interaction of warning cue and medication.

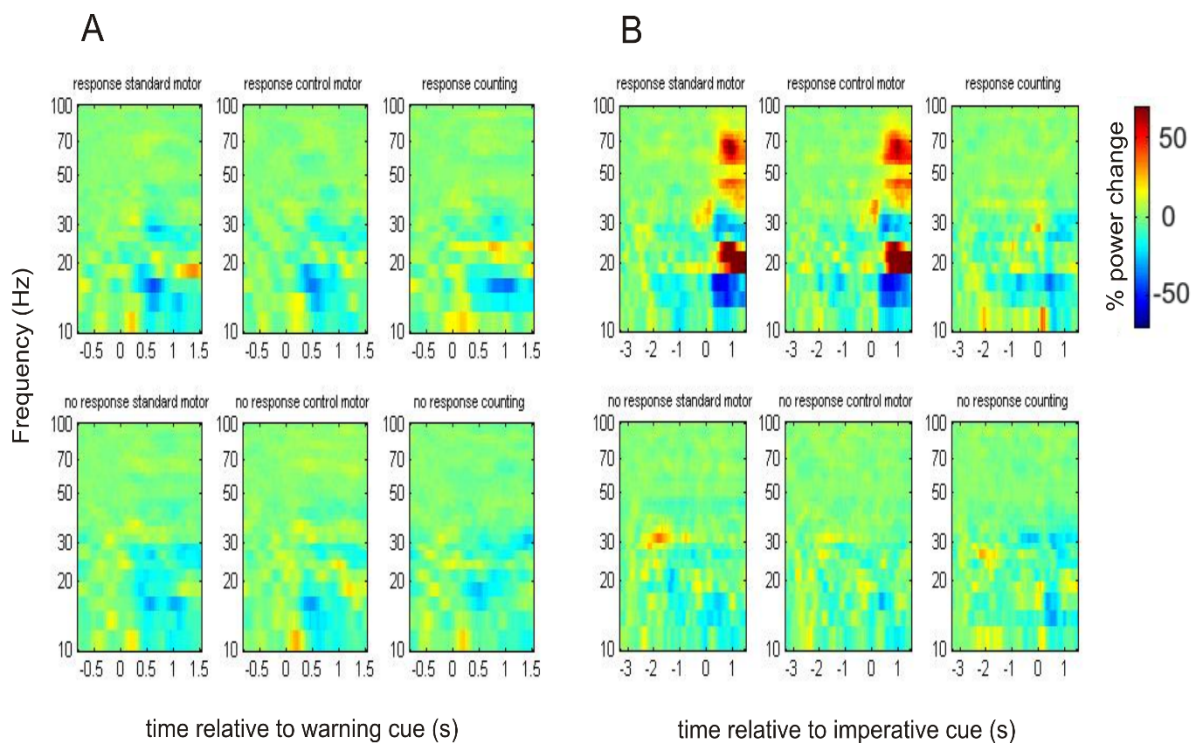


Figure 3.2 Cue locked spectra OFF medication.

Time frequency plots (OFF levodopa), averaged across all subjects, of the induced responses aligned to the onset of the warning (in Panel A) and imperative cues (in Panel B). For the plots aligned to the onset of the warning cue in Panel A, the time window extends to a maximum of 1.5 s, to prevent contamination from any motor responses which could occur after this time period. Power was calculated relative to a 0.8 s period prior to the appearance of the warning cue. Warm colours indicate an increase in power at the respective frequencies, with cooler colours indicating a reduction in power (see colour bar). In each panel, the spectra are plotted for the 'response' and 'no response' conditions of the three different blocks; standard motor (SM), control motor (CM) and the non-motor counting task. The main feature to note in Panel B is that the beta band power appears similar between the response and no response conditions. This was assessed further statistically (see Figures 3.4, 3.5 and results section).

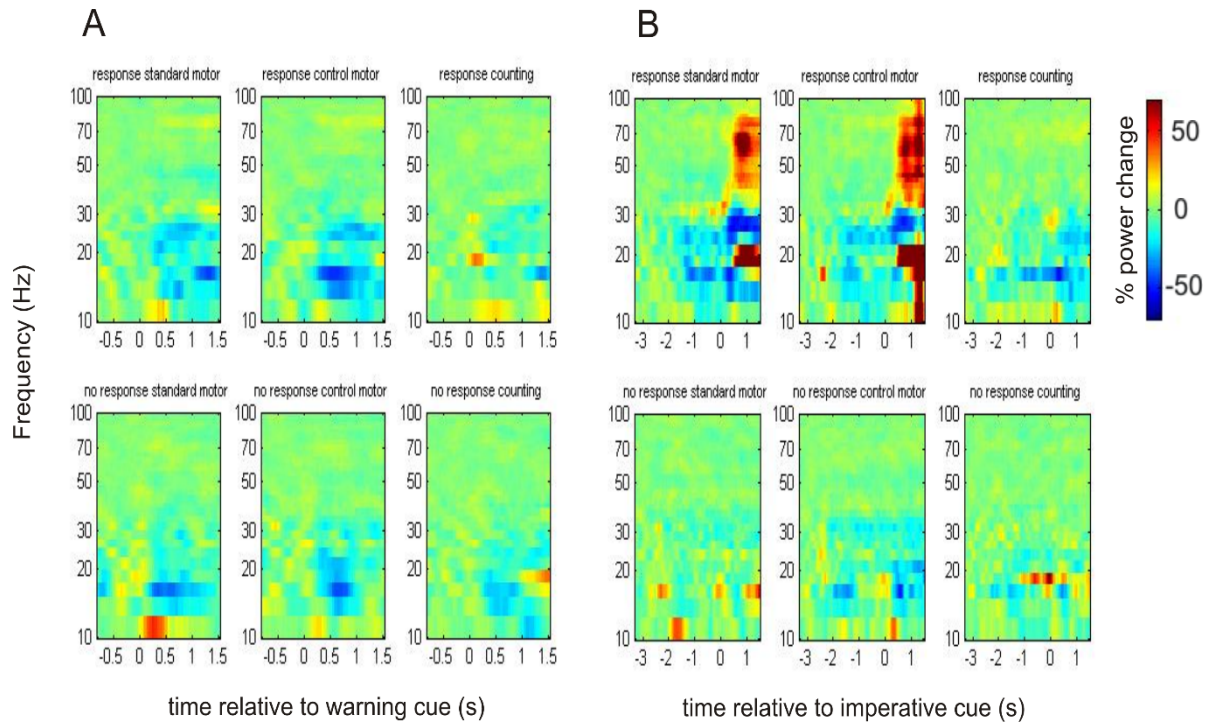


Figure 3.3 Cue locked spectra ON medication.

Time frequency plots as per Figure 3.2, following the administration of levodopa. There is a clearer pattern of beta desynchronisation in the response trials prior to the onset of the imperative cue.

Figure 3.4 (top panel) shows the averaged beta power time series across all subjects in the motor tasks ON and OFF medication aligned to the onset of the imperative cue. On the right hand side of the top panel the times of significance of the main effects of cue and medication and the interaction of cue and medication are indicated (The time points of peak t scores for each main effect and interaction had the following statistics: main effect of cue – t 5.93 df 209 $p < 0.001$, main effect of medication – t 4.17 df 209 $p < 0.001$, cue and medication interaction – t 4.19 df 209 $p < 0.001$). Beta desynchronisation was greater ON medication than OFF medication and greater with 'response' warning cues compared with 'no response' warning cues. There was also an interaction whereby the difference in beta desynchronisation induced by 'response' and 'no response' warning cues ON medication exceeded that OFF medication.

The same analysis is shown for the non-motor counting task in Figure 3.5. Here there was no main effect for medication, but, as with the motor task, there was a main effect of warning cue

and an interaction between medication and cue (the time points of peak t scores for each main effect and interaction had the following statistics: main effect of cue – t 4.97 df 209 $p < 0.001$, cue and medication interaction t 4.23 df 209 $p < 0.001$).

Note that in the 'response' and 'no response' conditions for both tasks ON dopamine there appears to be a gradual beta desynchronisation over the first ~ 1.0 s. This is likely to be an artefact of the variable fore-period. More importantly, the beta desynchronisation is subsequently maintained following the 'response' warning cue but is not maintained following the 'no response' warning cue (Figure 3.4 top and lower panels). Interestingly for the counting task ON medication, there was a statistically significant increase in beta power for the no response condition just prior to the imperative cue (Figure 3.5). There was only a trend towards this effect in the motor task ON medication (Figure 3.4), when this task was considered in isolation. To further explore this specific feature, I contrasted the mean beta power for each electrode in the final 200ms before the imperative cue in 'no response' trials with the mean beta power in the 200ms prior to presentation of the warning 'no response' cue in corresponding trials in a repeated measures ANOVA. I considered period (pre-warning vs pre-imperative), task type (standard motor vs. control motor vs. non-motor counting) and medication (ON vs. OFF) as our main effects, and specifically sought an interaction between period and medication. This was confirmed, so that mean beta power before the imperative cue exceeded that before the corresponding warning cue, but only ON medication ($F(2,216) = 4.54$ $p = 0.0118$). There was also a significant interaction between the three factors period, medication and task type ($F(2,216) = 3.91$, $p = 0.0214$), which arose because the effect of medication on the period before the imperative cue was greatest in the non-motor counting task.

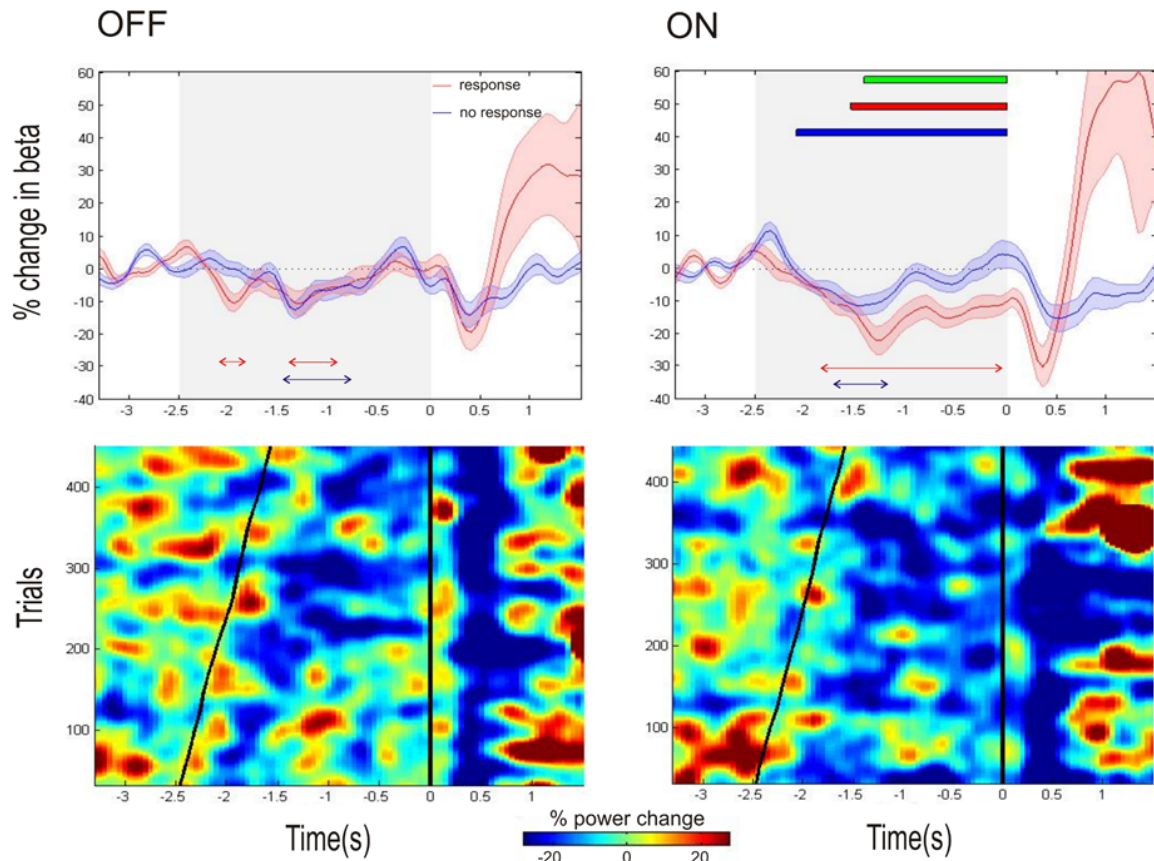


Figure 3.4 Imperative cue locked STN beta reactivity for the motor task.

Upper Panel: Mean time series of the percentage change in beta power (shaded areas indicating the standard error of the mean) relative to a 0.8 s baseline in the motor task for the response and no response conditions. The time series are plotted separately for the OFF and ON medication states, with time zero representing the onset of the imperative cue. The grey shaded area indicates the time between the maximal foreperiod (-2.5 s) and the onset of the imperative cue. Below the time series, the red and blue arrowed lines indicate times at which there was a significant reduction of beta power, occurring consistently over a period of at least 150 ms (FWE corrected, $p < 0.05$) for the response and no response conditions respectively. Also plotted in the figure to the right are the times of: 1) significant main effect of medication (Red solid bar) 2) significant main effect of cue (Blue solid bar) 3) significant interaction between medication and cue (Green solid bar). **Lower Panel:** Here we plot beta power for all the motor response trials of all subjects. Cool colours indicate a reduction in beta power, with warmer colours indicating the opposite (see colour bar). The trials are ordered by foreperiod, with the onset of the warning and imperative cues corresponding to the diagonal and vertical black lines. The noisy individual trial data were smoothed by convolution with a Gaussian prior to plotting. Separate images are plotted for the OFF and ON medication states. There is greater and more prolonged beta desynchronisation ON medication, with maximal desynchronisation occurring after the onset of the warning cue.

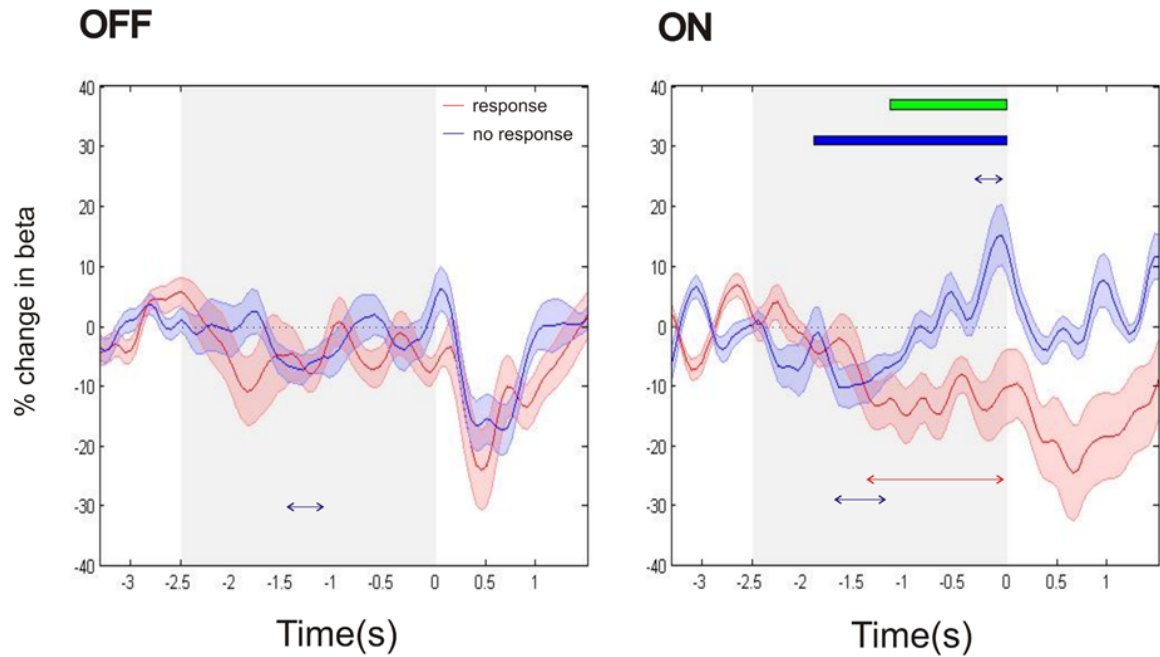


Figure 3.5 Imperative cue locked STN beta reactivity for the counting task. Mean time series of the percentage change in beta power (blue and red shaded regions indicating standard error of the mean) relative to a 0.8 s baseline in the counting task for the response and no response conditions. The time series are plotted separately for the OFF and ON medication states, aligned to the onset of the imperative cue. The grey shaded area indicates the time between the maximal foreperiod (-2.5 s) and the onset of the imperative cue. Above the time series, the blue arrowed line indicates times at which there was a significant increase in beta power, occurring consistently over a period of at least 150 ms (FWE corrected, $p < 0.05$) for the no response condition. Below the time series the red and blue arrowed lines indicate times at which there was a significant reduction in beta power occurring consistently over a period of at least 150 ms (FWE corrected, $p < 0.05$) for the response and no response conditions respectively. Also plotted in the figure to the right are the times of: 1) significant main effect of cue (Blue solid bar) 2) significant interaction between medication and cue (Green solid bar).

In further analysis, I recomputed beta time series, after including only the 'best' contact pair for each electrode. The results are illustrated in Figure 3.6 in which, as before, times of significance of the main effects of cue, medication and their interaction are indicated. The Figure shares the key features of Figures 3.4 and 3.5. In addition, and in line with the interaction between period and medication in the ANOVA performed above, it is now clear that there is a statistically significant increase in beta power for both the motor and counting tasks prior to the onset of the imperative cue in 'no response' trials made ON medication. This was evident even when activity at the best contact pair was considered in isolation for each task.

The foreperiod effects of our experimental factors were frequency selective (Figures 3.2 and 3.3). In a separate analysis of the gamma frequency band, I did not find any significant main effects or interactions for the motor or counting paradigms. Finally, the LFP power in the beta band dropped by a mean of $54.2 \pm 9.9\%$ when the contact pair with the highest baseline beta power was contrasted with the remaining contact pairs of each electrode in the OFF medication state. In 12 out of 19 cases, the contact with the greatest baseline beta power was that with the greatest beta desynchronisation in the ‘response’ case.

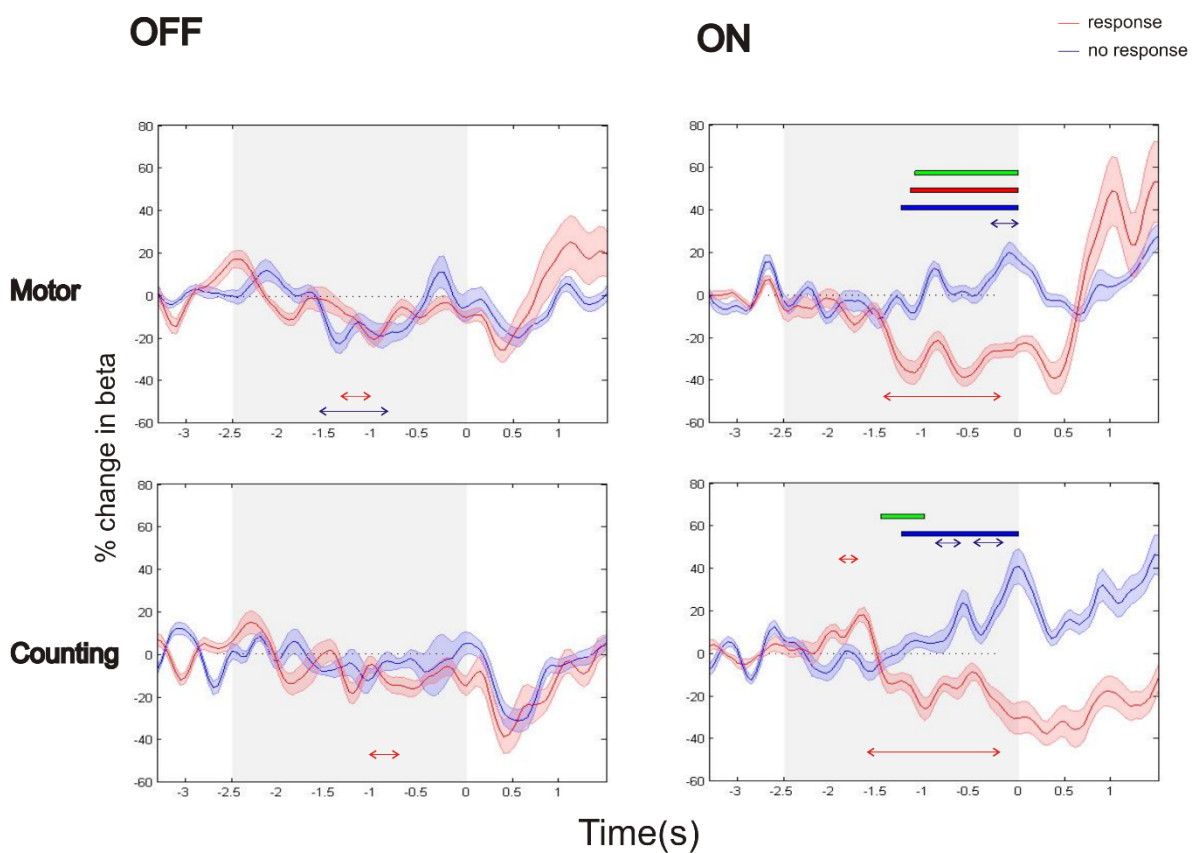


Figure 3.6 Imperative cue locked STN beta reactivity for selected electrode contacts

Beta time series are plotted ON and OFF medication for the best contact pairs across subjects in the motor (upper panel) and counting tasks (lower panel). The grey shaded area indicates the time between the maximal foreperiod (-2.5 s) and the onset of the imperative cue. Above the time series, the blue arrowed lines indicate times at which there was a significant increase in beta power, occurring consistently over a period of at least 150 ms (FWE corrected, $p < 0.05$) for the no response condition. Similarly, below the time series, the red and blue arrowed lines indicate times at which there was a significant reduction of beta power, occurring consistently over a period of at least 150 ms (FWE corrected, $p < 0.05$) for the response and no response conditions respectively. Also plotted in the figure to the right separately for the motor and counting tasks are the times of: 1) significant main effect of medication (Red solid bar) 2) significant main effect of cue (Blue solid bar) 3) significant interaction between medication and cue (Green solid bar).

3.4 Discussion

I recorded STN LFPs to warning cues that indicated whether a response would or would not be required in an upcoming motor or cognitive task. To maximally dissociate processing related to the saliency of the warning cue from task specific processing I systematically varied both the timing of the imperative cue after the warning cue and the specific nature of the task to be performed. The core finding was that changes in beta power in the LFP depended on the behavioural relevance of the warning cue. The paradigm ruled out conflation of this with motor related processing, while a control in which the nature of the target and non-target warning cues was reversed confirmed that power changes were not simply related to the sensory processing of the specific form of the target. Warning cues that pointed to the need for a subsequent response were followed by beta power suppression, whereas those that signalled that no response would be necessary were followed by delayed beta power increases that nevertheless preceded the imperative cue. Beta power changes following warning cues signalling the need or not for a subsequent response occurred regardless of whether the necessary response was motor or cognitive, as in the counting task. This provides further evidence that the foreperiod responses were not confounded by motor processing and supports a wider role for beta power modulation in executive function at both subcortical and cortical levels (Engel and Fries, 2010).

This homology between the beta reactivity in the foreperiod of both motor and cognitive tasks extended to a similar dependence on dopamine. Beta reactivity to warning cues was potentiated in the dopamine replenished ON medication state, as evidenced by an interaction between cue and drug in both tasks. The dopamine dependency of beta reactivity in the motor task is consistent with current theories of the nature of oscillatory activity in this frequency band (Jenkinson & Brown, 2011), and there is good evidence that the prevailing level of beta activity in the motor regions of the basal ganglia can be altered by drugs that manipulate dopamine and its receptors, both in patients with PD (Hammond et al., 2007) and those without PD (Kühn et al., 2008a). The dopamine dependency of beta reactivity in the cognitive task is perhaps more

unexpected, but would be in keeping with observations of bradyphrenia and cognitive inflexibility treatable with dopamine in some patients with PD (Rogers et al., 1987; Lees, 1994; Zgaljardic et al., 2003).

What precisely do the foreperiod power changes in the beta band signal? As highlighted above, they depended on the salience of the warning cue, specifically if it predicted or not the possible need for a subsequent response. But they were unlikely to merely relate to saliency as the power differences were more-or-less sustained up to the point of presentation of the imperative cue, and even the no-response cues could be considered to have some behavioural saliency. This makes it more likely that the foreperiod power changes in the beta band relate to anticipation of the motor or cognitive response (and its attendant processing) engendered by the saliency of the cue, rather than cue saliency *per se*. Such an anticipatory process could subserve predictive resourcing of the prospective action and economy of resourcing in the absence of the need for action. This possibility would be in accord with recent theories of the functional role of oscillatory activity in the beta band (Jenkinson & Brown, 2011). The latter posit that beta activity provides a dynamic indicator of the likelihood that a new action will need to be actuated, with the level of beta being inversely proportional to the likelihood that a new action will need to be processed and performed. Alternatively, the sustained beta power changes might relate to working memory processes enlisted by the warning cue. However, the latter seems unlikely as the working memory load of both 'response' and 'no response' warning cues would be similar and yet differential power changes occurred in opposite directions.

The dopamine dependent increase in beta power prior to the imperative cue in 'no response' trials merits further comment. The latter was similar to that reported after nogo imperative cues (Kühn et al., 2004). In the latter case, the beta power increase was interpreted as evidence of an active inhibitory process, consistent with current views that afford the STN a critical role in motor inhibition (Frank et al., 2007; Forstmann et al., 2010; Cavanagh et al., 2011; Ray et al., 2011). By

analogy, the power increase in the current paradigm could relate to the inhibition of a pre-potent response to the imperative cue. However, 'response' and 'no response' trials occurred with equal frequency, and, more importantly, the nature of the response to be inhibited was unknown at this point in time. I would rather view the beta power increase in the same context as the prospective beta power decrease occurring in 'response' trials. Thus, the beta power increase at the end of the foreperiod of 'no response' trials might reflect the predictive withdrawal of resources in the absence of the need for action, which, inevitably, also reduces the likelihood of any erroneous prepotent response.

In summary, the pattern of modulation of STN beta activity reported here is consistent with an active process that prospectively sets the state of readiness for executive processing (be it primarily motor or cognitive), based on the salience of incoming cues. The alternative, that beta suppression could be an epiphenomenon of the shift in neuronal patterning that underscores executive processing seems unlikely as our paradigm dissociated beta power modulation in the foreperiod from any motor related processing. The latter only supervened following the imperative cue, as evidenced by the change in gamma activity at this point, but not before. Even so, the percentage changes in beta power during the foreperiod were of the same order of magnitude as those reported in studies in which task-specific processing has not been excluded from this period (Williams et al., 2003; Kühn et al., 2004; Kühn et al., 2006).

I studied patients so that inferences with regard to normal functioning must be circumspect (Williams et al., 2002). That said, the predictive modulation of basal ganglia beta activity brought on by salient cues tends to parallel the behaviour of beta activity in the cerebral cortex of healthy subjects (Androulidakis et al., 2007; Donner et al., 2009; van Wijk et al., 2009; Tzagarakis et al., 2010; Gould et al., 2011). Other limitations are the presumptive localisation of electrode contacts in the STN (Williams et al., 2002; Fogelson et al., 2006) and the possibility that power changes picked up at the bipolar contacts of the DBS electrode are not really focally generated. Against

the latter, I found a steep gradient in LFP power in the beta band across different bipolar contact pairs consistent with a local generator (Kühn et al., 2004; Kühn et al., 2006), although the strongest argument in favour of the local generation of beta activity in the LFP is the demonstration that the discharge of neurons in the STN tends to be locked to it (Kühn et al., 2005; Levy et al., 2002). A more specific limitation in the current study is that the paradigm was not designed to evaluate whether beta activity was modulated by the temporal expectancy of the imperative cue. This would have helped support the hypothesis that beta modulation prospectively sets the state of readiness for executive processing, but the paradigm did not include a separate training phase where subjects were exposed to multiple trials, allowing them to learn the distribution of foreperiod durations, and I did not give feedback to facilitate learning. Temporal expectancy effects remain an important issue for future investigation.

In conclusion, I have provided evidence that the modulation of beta activity in the STN is not simply an epiphenomenon of the reconfiguration of neural interactions in favour of synchronization at higher frequency during task related processing, but is the consequence of an active process that may prospectively set the state of readiness for executive processing according to the salience of incoming cues. This reactivity in beta band oscillations is impaired when dopamine is deficient.

Chapter 4: Cognitive factors modulate activity within the human subthalamic nucleus during voluntary movement in Parkinson's disease.

4.1 Introduction

Synchronised oscillations in the beta and gamma frequency bands are thought to play a role in motor control in cortico-basal ganglia motor loops (Brown, 2006). STN LFP activity in the beta band is suppressed for several seconds prior to self-paced voluntary movement and following cues salient to forthcoming movement (Williams et al., 2003; Alegre et al., 2005; Androulidakis et al., 2008; Oswal et al., 2012). However, the extent to which such anticipatory changes in beta activity are modulated by contextual factors like reward and by the need to resource more challenging responses remains unclear. Moreover, beta activity in the STN is further suppressed around the time of movement, suggesting that it might not only relate to anticipatory processes but also to the processing of movement (Brown, 2006; Hammond et al., 2007). In addition, reciprocal increases in gamma band synchronisation are seen in the STN during this perimovement period and have likewise been related to the processing of movement (Cassidy et al., 2002; Williams et al., 2002; Alegre et al., 2005; Foffani et al., 2005; Fogelson et al., 2005; Alonso-Frech et al., 2006; Devos et al., 2006; Trottenberg et al., 2006; Androulidakis et al., 2008). Although it is unclear what features are encoded by these reciprocal changes, one possibility is that perimovement spectral changes in the STN, particularly those in the gamma band, encode response force, or, related to this, movement speed (Anzak et al. 2012; Brücke et al. 2012; Brücke et al., 2013; Joundi et al, 2012; Tan et al., 2013a). This would place perimovement spectral changes in the STN at the executive end of processing and disassociate them from any link to the representation of action values thought to be important elsewhere in the basal ganglia (Samejima et al., 2005). Alternatively, they may relate to higher-order phenomena such as the cognitive or motor effort to be exerted in an action that is then organised elsewhere (Mazzoni et al., 2007; Niv and Rivlin-Etzion, 2007; Salamone et al., 2009; Turner and Desmurget, 2010). Again, the extent to

which perimovement spectral changes in the STN are modulated by contextual factors such as potential reward and by task complexity would seem critical information in characterising the functional associations of these oscillations. Specifically, modulation by these contextual factors might help disambiguate whether cognitive demands, and not just force, might be encoded by perimovement spectral changes in the STN.

Here I explore the modulation of both anticipatory and perimovement spectral changes in the STN by potential reward and task complexity, whilst also considering whether dopaminergic state is an important factor in any such modulation. Task complexity was isolated from movement dynamics (which remained similar) through the performance of movements in which the spatial mapping between the cued limb and the limb required to be moved was either compatible or incompatible.

4.2 Methods

Nine patients (7 male and 2 female) with idiopathic Parkinson's disease who underwent implantation of deep brain stimulation electrodes in the subthalamic nucleus (STN) at two surgical centres participated in the study. All procedures were approved by the local ethics committees at the two surgical centres. The clinical characteristics of the patients are shown in Table 4.1. Each was implanted bilaterally for the treatment of their Parkinson's disease.

case	Age & Sex	Disease duration (years)	UPDRS III OFF/ON drug	Daily medication (mg)	Days post-op 1 st recording	Order of Recordings	Test dose levodopa
1	51 M	13	48/32	LDE 900	2	ON 1/OFF 2	200
2	62 M	10	40/15	LDE 400	2	ON 1/OFF 2	100
3	53 M	15	48/18	LDE 1300	2	ON 1/OFF 2	100
4	62 M	9	28/5	LDE 2500	3	OFF 1/ON 2	200
5	56 M	15	31/9	LDE 750	6	ON 1/OFF 2	100
6	53 M	8	16/9	LDE 1100	5	OFF 1/ON 2	100
7	59 F	16	26/9	LDE 1150	3	OFF 1/ON 2; Only ON used	200
8	51 M	19	40/7	LDE 1850	4	OFF 1/ON 2, but unable to perform task OFF	100

						due to severe tremor	
9	49F	10	41/8	LDE 900	4	OFF 1/ON 2 but unable to perform task OFF due to severe tremor	100

Table 4-1 Clinical characteristics of the patients recorded.
LDE = levodopa dose equivalent.

4.2.1 Paradigm

I developed a paradigm that separated the processing of information relating to the warning of the reward or complexity of an upcoming task from the processing of the specific motor response. This was achieved by presenting a warning cue that signalled whether an upcoming stimulus-response pairing was either compatible or incompatible (signalled by a gold or grey arrow, respectively) and also whether correct subsequent motor performance was to be highly or lowly rewarded (signalled by a gold or grey coin; see Figure 4.1). Consequently there were four different types of warning cue, each corresponding to a different trial condition which was presented with equal probability. The warning cue was followed by an imperative cue which comprised a schematic of the body with a single segment highlighted in red (right hand, left hand, right foot or left foot with equal probability). Temporal expectancy of the imperative cue was limited by pseudo-randomisation of the inter cue interval. A fixed reward of 12 Euros or 10 pounds per drug session was given on completion of the whole experiment, although subjects were told at the outset of the experiment that reward depended in an undisclosed manner on performance during the recordings. This subterfuge that reward was not in the end scaled to performance was to avoid discriminating between patients according to disease severity or ability and was agreed by the local ethics committee. Accordingly, patients were not given trial-to-trial feedback on the level of award accrued -although this may have undermined the impact of reward blocks.

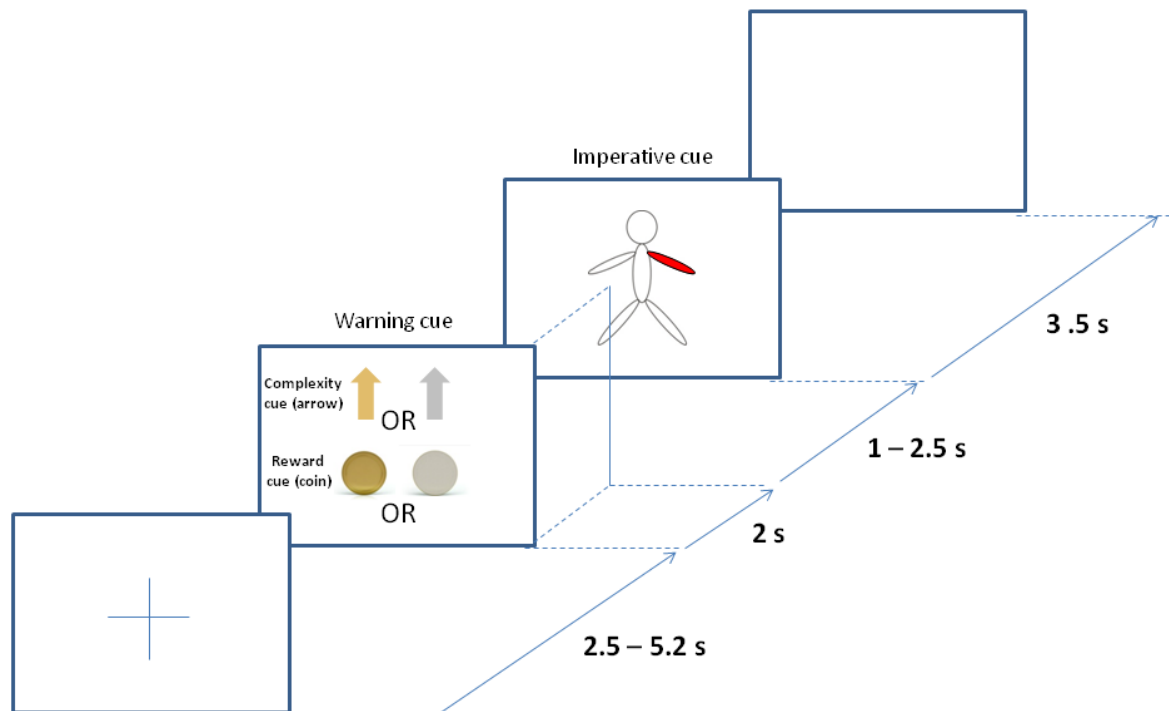


Figure 4.1 Schematic of a typical trial.

A warning cue with an arrow and coin signalled the complexity and reward of an upcoming trial. The presentation of a gold or grey arrow instructed high or low trial complexity whilst the presentation of a gold or grey coin signalled high or low reward, respectively. Patients were instructed to move the highlighted body segment only when the warning cue signalled low trial complexity. In the case of a warning cue signalling high trial complexity, patients were instructed to move the limb diagonally opposite to the limb highlighted in red. For example, in high complexity trials if the left arm was highlighted, the correct response would be to move the right leg.

Crucially the required movement was dependent both on the cued limb and on the information about task complexity in the initial warning cue. In the case of the warning cue indicating an upcoming task of low complexity, imperative stimulus and response were compatible and subjects were instructed to move the cued limb. However in the case of the warning cue indicating an upcoming task of high complexity, subjects were instructed to move the diagonally opposite limb. Thus the subsequent imperative cue and response were incompatible. In this way the correct execution of the two stimulus-response compatibility conditions necessitated direct and indirect visuomotor transformations, respectively. If the required movement was a hand movement, subjects were required to make a button press with the index finger of the corresponding hand, whilst in the case of foot movements, subjects were asked to dorsiflex the

ankle joint. Consequently for each of the two levels of task complexity the final movements of each limb would be similar across the blocks (although the response times might differ). Thus, the cognitive processes required in the low and high complexity trials differed due to their contrasting stimulus-response compatibilities, despite the effect that on average movements did not differ across blocks.

The experiment began with some demonstration trials in which the intended movements were shown to the patient whilst they were seated comfortably in a chair. Subjects were instructed to concentrate on accuracy and speed before the start of the blocks. The experiment was performed in up to four blocks in each medication (ON/OFF) condition (each block containing six trials of each type in pseudo-randomised order). Blocks lasted 4 min, and were followed by 1–2 min rest. Each block consisted of 24 trials. The majority of patients were able to perform all four blocks, however some were only able to perform two or three blocks giving a total number of 12–24 trials per condition. Each trial started with the presentation of a fixation cross at the centre of a portable PC screen (Figure 4.1), followed 2.5–5.2 s later by a warning cue of fixed duration (2 s). The onset of the warning cue was followed by a period of 3 to 4.5 s, before the imperative cue of a body schema which was presented for 3.5 s. This was followed by a blank screen for 1 s, before the next trial began with reappearance of the fixation cross. The fixation cross, warning and imperative cues were centred around the middle of the screen so as to limit confounding eye movements. The total duration of the recordings made ON and OFF medication was about an hour.

Patients were kept under constant visual inspection by the researcher and error trials noted. Error trials consisted of the patient moving the wrong body part. I excluded these trials from subsequent analysis, as I could not be sure of whether the subject had attended to either the warning cue or the imperative cue. The number of trials accepted for each subject and condition

is shown in table 4.2. Furthermore, I deleted blocks of trials with less than a number of trials corresponding to a random choice probability (25%) of moving the 4 body limbs.

Case	ON medication				OFF medication			
	HRLC	LRLC	HRHC	LRHC	HRLC	LRLC	HRHC	LRHC
1	22 (24)	22 (24)	24 (24)	22 (24)	21 (24)	23 (24)	24 (24)	20 (24)
2	20 (24)	23 (24)	20 (24)	19 (24)	14 (24)	19 (24)	18 (24)	18 (24)
3	24 (24)	24 (24)	24 (24)	20 (24)	15 (18)	16 (18)	16 (18)	15 (18)
4	12 (18)	12 (18)	11 (18)	12 (18)	15 (18)	18 (18)	16 (18)	18 (18)
5	24 (24)	20 (24)	24 (24)	24 (24)	10 (18)	8 (18)	8 (18)	6 (18)
6	20 (24)	19 (24)	19 (24)	20 (24)	24 (24)	24 (24)	24 (24)	24 (24)
7	18 (24)	18 (24)	18 (24)	20 (24)	-	-	-	-
8	24 (24)	22 (24)	23 (24)	23 (24)	-	-	-	-
9	8 (12)	8 (12)	12 (12)	3* (12)	-	-	-	-

Table 4-2 Number of correctly performed trials recorded for each patient.

Number of correctly performed trials recorded from each patient in each of the four different conditions ON and OFF levodopa. In brackets the total number of trials recorded from each patient and each condition is provided. HRLC = High Reward and Low Complexity, LRLC = Low Reward and Low Complexity, HRHC = High Reward and High Complexity, LRHC = Low Reward and High Complexity. Starred (*) trials indicate condition that was rejected because the proportion of correctly performed trials ($\leq 25\%$) corresponded to randomly chosen movement.

4.2.2 Recordings

Four patients were first assessed ON medication and then OFF medication on the following day, and the other five were assessed first OFF then ON medication. However, only six of the patients were able to perform/complete the task OFF medication. OFF medication recordings were performed after overnight withdrawal of antiparkinsonian medication (Table 4.1). ON medication recordings were performed one hour after the usual morning dose of antiparkinsonian medication or levodopa 100 mg, whichever was the higher, and were achieved in all subjects.

Surface EMG was recorded from tibialis anterior bilaterally in each patient. Local field potentials (LFPs), EMG and analogue signals related to the cues and button presses were recorded using a D360 amplifier (Digitimer Ltd, Welwyn Garden City, Hertfordshire, UK) in combination with a 1401 A-D converter (Cambridge Electronic Design, Cambridge, UK) and sampled onto a computer using Spike2 V6 software (Cambridge Electronic Design). LFP activity was recorded bipolarly from the four contacts (01, 12 and 23) of each DBS electrode targeting the STN, amplified (50,000x), filtered (1.0–1000 Hz) and sampled at a common rate of 5000 Hz. EMGs were amplified (1000x) and filtered (10-1000 Hz), before being sampled at the above rate.

4.2.3 Spectral Analysis

EMGs were high pass filtered at 10 Hz and the absolute value of the Hilbert transform of the resulting signal was taken (Kilner et al., 2000; Schoffelen et al., 2011), prior to smoothing with a 1 s boxcar function. The resulting signal was standardized by z-transformation and movement onset was defined as the point at which the z-score exceeded 0.5 (see http://fieldtrip.fcdonders.nl/example/detect_the_muscle_activity_in_an_emg_channel_and_use_that_as_trial_definition). This z threshold was used for all subjects and was visually confirmed to correspond to the onset of EMG activity for all trials. The time of onset of movement in the upper limb was determined by the timing of button presses. Data were epoched into trials,

excluding trials with errors. Subsequently, the average LFP signal over all correct trials was removed from the LFP signal of each individual trial to generate the induced response. Spectral analysis was carried out for each bipolar electrode pair for all subjects using the multitaper method (Thomson, 1982). The resulting spectra were averaged across all the contact pairs in a given electrode that had at least one contact in the STN as independently assessed by an experienced neurosurgeon or neurologist specialising in deep brain stimulation who was blinded to the electrophysiological data. Contact classification was performed from peri-operative MRI imaging, as detailed above.

Spectral analysis was performed for each trial of each of the four conditions, ON and OFF medication in each subject. I analysed spectra in overlapping windows of 400 ms, shifted by 50 ms. The frequency resolution was set to the inverse of the time window (2.5 Hz) for up to 25 Hz, then 0.1 times the frequency for 25 to 50 Hz and then to a constant 5 Hz resolution. These settings resulted in a single taper being used for 2.5–30 Hz, 2 tapers for 32.5–42.5 Hz and 3 tapers for 45 Hz and above. The resulting time–frequency images had no discontinuities thanks to the continuous frequency resolution function.

The trial power data were first normalised to a baseline (–0.8 to 0 s) before the warning cue to obtain percentage changes, prior to averaging using robust averaging (irrespective of the body part highlighted by the imperative cue). This was performed for each subject across the different conditions (a maximum of 8 in total, as documented in Table 4.2, and drawn from up to 4 blocks of trials ON and up to 4 blocks OFF medication). The benefits of robust averaging for increasing the signal-to-noise ratio in data with low trial numbers have been previously demonstrated (Litvak et al., 2012; Oswal et al., 2013a). In essence, robust averaging is a special case of the robust general linear model (Wager et al., 2005). The idea is that for each time frequency bin, the distribution of values over trials is considered and outliers are down-weighted when computing the average, thereby affording improved immunity to high power artefacts.

4.2.4 Statistics

I first compared response times of subjects in the eight conditions. For statistical analysis I analysed reciprocal response times, since they are known to have an approximate normal distribution, hence facilitating parametric statistical testing procedures (Carpenter and Williams, 1995). Reciprocal response times were then averaged for each condition in each subject. I was not interested in response time differences between hand and leg movements, in part because our recording techniques would have obfuscated such a difference, but principally because this factor was balanced across all blocks. Accordingly I averaged across movement types and performed a 2 x 2 x 2 repeated measures ANOVA, with factors as described below. Error rates for the different conditions were also analysed in the same way. For the behavioural analysis an F statistic corresponding to a p value of less than 0.05 was taken as a threshold for significance.

To make inferences about the spectral responses and effects of task and drug I used Statistical Parametric Mapping (as implemented in SPM8). This treats the time frequency matrices as images and allows the identification of regions of time frequency space showing significant effects over subjects, while controlling for the implicit multiple comparisons using random field theory (Kilner et al., 2005).

The results of time-frequency analysis were exported to Neuroimaging Informatics Technology Initiative (NIFTI) format and smoothed with a Gaussian smoothing kernel with Full Width Half Maximum (FWHM) of 5 Hz by 500 ms for frequencies 0-100 Hz. All the reported findings are significant with FWE correction at the cluster level ($p < 0.01$ corrected, cluster forming threshold $p < 0.01$ uncorrected). Significant features of the mean responses were determined by subjecting mean power images across conditions to a single-sample t-test across subjects. Prior to testing for the effect of experimental conditions I confirmed that there was no main effect of laterality of movement (IPSILATERAL vs. CONTRALATERAL) on induced STN spectra using a paired t-test. To

test for the effects of experimental conditions I performed repeated measures ANOVA treating the experiment as a 2 x 2 x 2 factorial design with the factors 'Reward' (HIGH vs. LOW), 'task complexity' (HIGH vs. LOW) and 'Drug' (ON MEDICATION vs. OFF MEDICATION). Using this repeated measures design in SPM, which allows for unbalanced designs (e.g. more ON than OFF medication recordings, see Penny and Friston, 2003), I specified t-contrasts to test for times at which significant differences occurred using paired t-tests. Using the t-contrasts in SPM I was able to test for the direction of significance, for example, taking the main effect of drug I could test whether being OFF medication produced significantly less desynchronisation than being on medication or *vice versa*.

I independently analysed the spectra aligned to the onset of the warning cue, the imperative cue and movement onset. In addition to modelling subject-specific dependencies in the recordings from the two hemispheres, I included the side as an additional categorical variable for each subject in order to account for potential differences between recordings from the right and left subthalamic nuclei.

As I was primarily interested in interpreting the significance of premovement spectral changes an important consideration in our analysis was determining the temporal resolution of the spectral changes observed. Specifically, uncertainty in temporal estimates could be introduced by both the windowing of spectral estimation and by subsequent smoothing prior to statistical analysis. In order to further characterize the magnitude of temporal smoothing, I generated simulated data for spectral estimation, smoothing and statistical analysis. Data from each subject were band pass filtered in the beta (15-35 Hz) and gamma (60-90 Hz) bands and normalized by z-transformation. A step increase in gamma amplitude of 40% and a step decrease in beta amplitude of 40% were introduced at a known time, lasting for 0.5s. The resulting time series were summed and added to Gaussian random white noise to create a simulated LFP for each subject prior to spectral

estimation and smoothing using the parameters described above. Statistical analysis was performed by subjecting the simulated data across all subjects to a one sample t-test and testing for positive and negative effects. These simulations suggested that spectral changes in the gamma band might be shifted to the left by about 150ms through windowing for spectral estimation and subsequent smoothing and by less than this in the beta band (Figure 4.2).

Analysis of the EMG amplitude time series centered to movement onset (see spectral analysis for details of thresholding procedure) was also performed using the SPM pipeline with cluster level correction as described above in order to ensure that the muscle activations and their temporal profiles were similar for simple and complex movements. In this case however, given that the amplitudes are vectors, the images had only a time dimension.

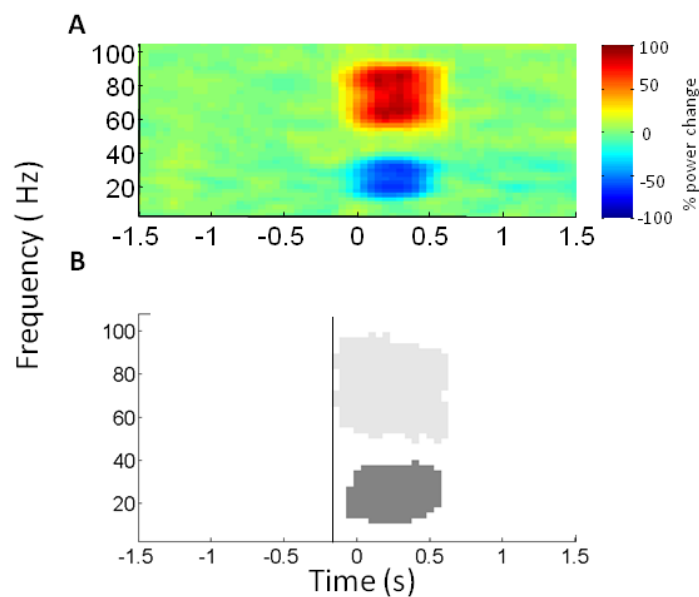


Figure 4.2 Mean plots of simulated data for all subjects.

A step increase and decrease in gamma and beta amplitudes of 40% respectively was simulated at 0 s lasting for 0.5 s. The resulting spectra were added to Gaussian random white noise. Power was determined relative to a 0.8 s baseline between -1.4 s and -0.6 s. Each subject's image was smoothed with a 5 Hz x 500ms Gaussian kernel, before averaging. Panel A shows spectra of the resulting time series averaged across all subjects. Panel B shows significant positive (light grey) and negative (dark grey) clusters of the mean responses in the gamma and beta bands, respectively. The vertical line at -150 ms indicates that statistical changes in the gamma band can be seen as early as this despite the fact that power modulations were only introduced at 0 s.

4.3 Results

4.3.1 Behavioural results

Bar charts of response latencies, averaged across subjects for the four different conditions OFF and ON levodopa are shown in Figure 4.3A. Repeated measures ANOVA revealed a main effect of medication, such that response times were faster ON medication than OFF medication.

Furthermore, there was a main effect of task complexity, with response times slower in low compared to high task complexity trials. There was also an interaction between task complexity and medication, such that the shortening of response times in low task complexity trials was more marked ON medication than OFF medication (please see table 4.3 for details of statistics) . Importantly there was no main effect of reward, or interaction of reward with any of the other factors. As it has been previously reported that STN neuronal activity may be preferentially modulated when switching from automatic to controlled movements (Isoda and Hikosaka, 2008) I investigated this in a further one way ANOVA. Here I tested whether for high task complexity trials there was an effect of task complexity in the preceding trial (HIGH PRECEDING COMPLEXITY vs. LOW PRECEDING COMPLEXITY). Our ANOVA did not reveal significant effects ($F(1,8) = 3.4$, $p = 0.10$).

Of course, reward and task complexity could potentially influence muscle responses as well as response latencies. I was able to explore this further in the lower limbs where movements were recorded with EMG (rather than button press). Here, a separate repeated measures ANOVA of the Hilbert filtered amplitudes of high pass filtered (10 Hz) EMG traces with factors medication, task complexity and reward revealed no main effects or interactions (table 4.3). Lower limb EMG profiles averaged across both medication states in all subjects are shown separately for the core comparison of low versus high task complexity trials in Figure 4.3B.

Analysis of error rates revealed no significant main effects or interactions of medication, reward or task complexity (table 4.3). The mean error rate across subjects was 16.2% with a corresponding standard error of 2.1%.

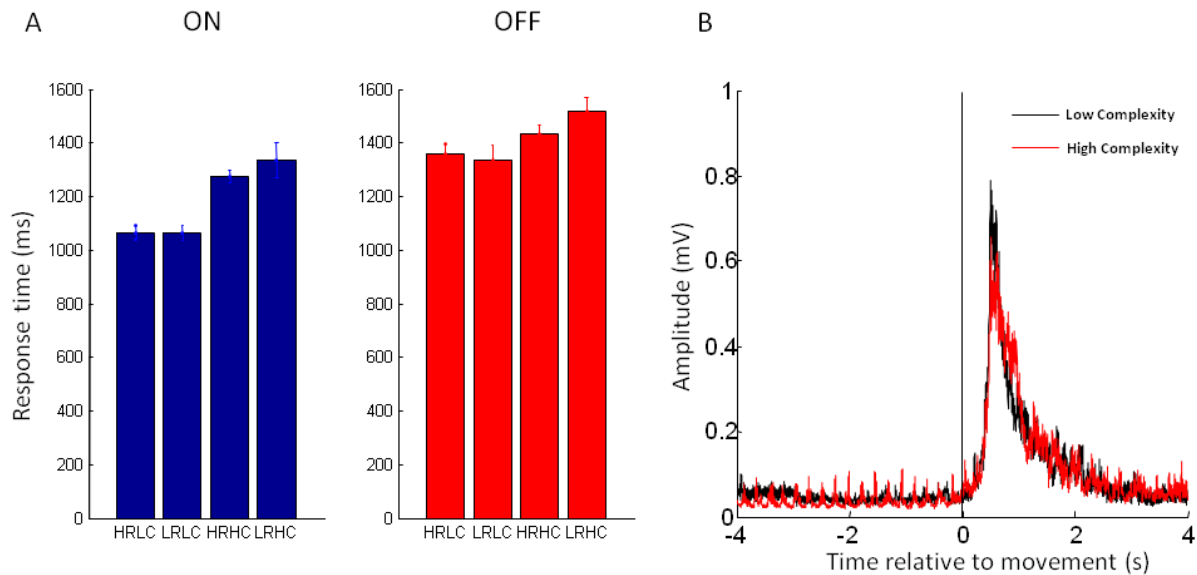


Figure 4.3 Behavioural data and EMG analysis.

(A) Bar charts of response latencies averaged across upper and lower limbs and subjects for the four different conditions ON and OFF levodopa ($\pm$ standard error). HRLC = High Reward and Low Complexity, LRLC = Low Reward and Low Complexity, HRHC = High Reward and High Complexity, LRHC = Low Reward and High Complexity. **(B)** Hilbert amplitudes of high pass filtered (10 Hz) tibialis anterior EMG averaged across both medication states in all subjects shown separately for the core comparison of complex versus non-complex trials. Time zero is onset of EMG. Note contamination of rest period with rest tremor.

4.3.2 STN LFPs

In Figure 4.4 I display spectra averaged across the limbs for the eight different conditions aligned to the onset of the warning cue (Figure 4.4A), the imperative cue (Figure 4.4B) and to movement onset (Figure 4.4C). Common to the plots is a characteristic beta band (13-30 Hz) desynchronisation and a gamma band synchronisation (60-90 Hz) associated with movement. Movement is followed by an increase in beta power. The correspondingly aligned beta and gamma band time series were separately extracted for visualisation in Figures 4.5 and 4.6, respectively.

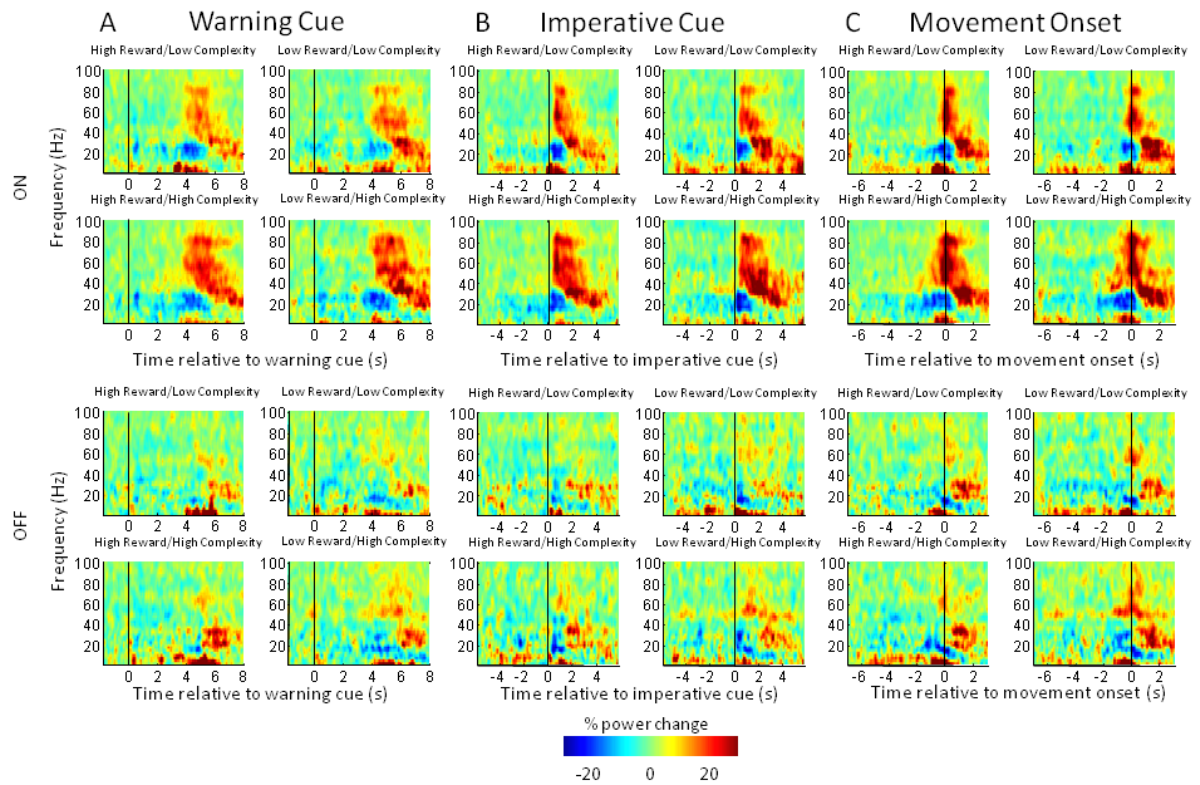


Figure 4.4 Cue locked spectra for the four different reward and trial complexity conditions. Time-Frequency plots averaged across upper and lower limbs and all subjects, of the induced responses aligned to the onset of the warning cue (A), the imperative cue (B) and movement onset (C) for the four different reward and trial complexity conditions. Induced responses ON and OFF levodopa are shown in the upper and lower halves of panels A-C respectively. Power was computed relative to a 0.8 s period before the appearance of the warning cue (see methods) for all conditions. The main features to note are discussed in the results section.

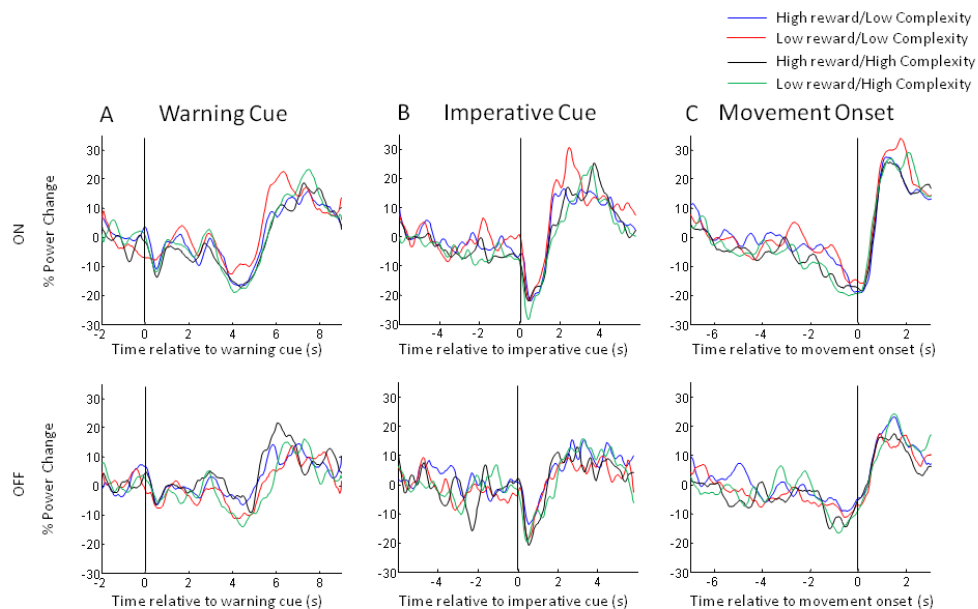


Figure 4.5 Cue locked beta band time series for the four different reward and trial complexity conditions. Mean time series of the percentage change in beta power (15-30 Hz) aligned to the onset of the warning cue (A), the imperative cue (B) and movement onset (C) for the four different reward and trial complexity conditions. The time series have been smoothed with a 10 point moving average and are plotted separately for the ON and OFF medication states in the upper and lower panels, respectively. Note that movement related beta desynchronisation is greater ON medication than OFF medication and there is a trial complexity dependence of this effect such that high complexity trials result in greater premovement desynchronisation than low complexity ones (C).

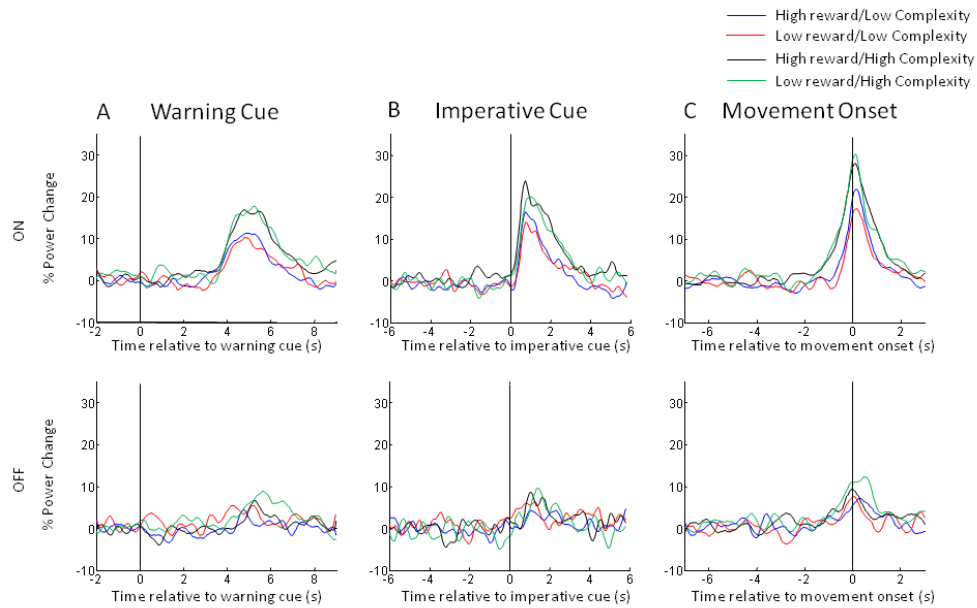


Figure 4.6 Cue locked gamma band time series for the four different reward and trial complexity conditions. Mean time series of the percentage change in gamma power (60-90 Hz) aligned to the onset of the warning cue (A), the imperative cue (B) and movement onset (C) for the four different reward and trial complexity conditions. Movement related gamma power synchronisation is greater ON medication than OFF medication. Movement related gamma power increases are augmented in high complexity trials (C).

Figures 4.7 and 4.8 show time-frequency clusters of significant statistical effects separately for data aligned to the warning cue and movement onset, respectively. In each figure the top panel displays clusters where there was a positive effect (*i.e.* a power increase) of the tested main effect or interaction and the bottom panel shows clusters where there was a negative effect (*i.e.* a power decrease) of the tested main effect or interaction. Corresponding statistical values are provided in table 4.3. In figure 4.7A, the mean effect across all conditions reveals an early event related synchronisation in low frequencies (<10 Hz) around the time of presentation of the

warning cue. In addition, episodically significant beta band suppression is evident from 0.5 s and covers the period up to and beyond presentation of the imperative cue. There are also late mean effects, main effects of medication and task complexity and an interaction between medication and task complexity starting at around 4s and predominantly involving the beta and gamma frequency bands (Figure 4.7A-D). From this figure alone it is impossible to disambiguate whether delayed effects relate to presentation of the imperative cue and preparation of the motor response or whether they reflect differences in re-afference following motor onset. Time-frequency clusters of significant statistical effects for data aligned to imperative cue presentation demonstrated that these late effects followed imperative cue onset, but still did not clarify whether they preceded the motor response (data not shown).

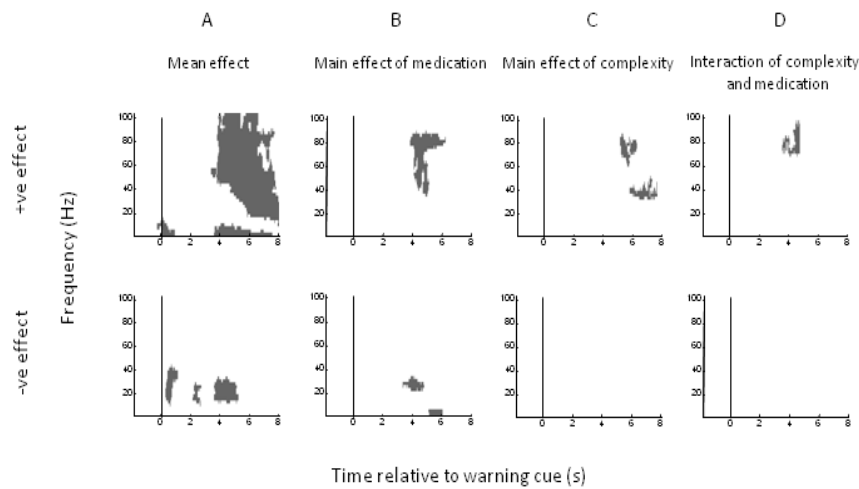


Figure 4.7 Statistical analysis of spectra locked to the onset of the warning cue. Plots of significant positive (upper panel) and negative (lower panel) clusters ($p < 0.01$ cluster level FWE correction) aligned to warning cue onset. T-contrasts correspond to: A) the mean overall effect across all conditions, B) the main effect of medication, C) the main effect of trial complexity and D) the interaction between trial complexity and medication. Reward and interactions with reward were not significant at the cluster level.

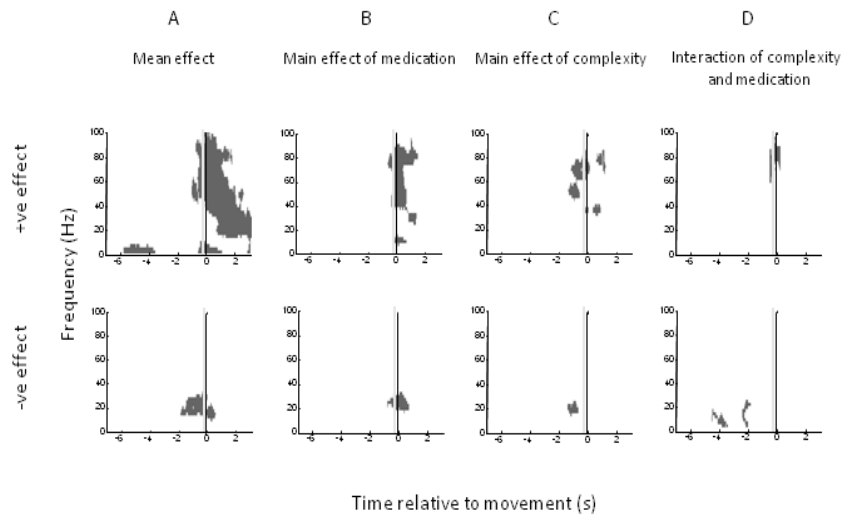


Figure 4.8 Statistical analysis of spectra locked to movement onset.

Plots of significant positive (upper panel) and negative (lower panel) clusters ($p < 0.01$ cluster level FWE correction) for subject images aligned to movement onset. T-contrasts correspond to: A) the mean overall effect across all conditions, B) the main effect of medication, C) the main effect of trial complexity and D) the interaction between trial complexity and medication. Reward and interactions with reward were not significant at the cluster level. The vertical grey line in each plot indicates minus 300 ms, -a conservative estimate of the uncertainty in the timing of movement onset and spectral change.

Realignment to movement onset, however, was more informative (Figure 4.8). Mean effects show an increase in gamma and low frequency (<10 Hz) power and a concomitant reduction in beta power starting prior to movement (Figure 4.8A). Moreover the gamma power is particularly increased with increased task complexity, starting just prior to movement, whilst the beta power is particularly decreased with increased task complexity prior to movement (Figure 4.8C).

Dopamine has an additional effect of supporting the reciprocal gamma and beta power changes in the peri-movement period (Figure 4.8B). Finally there are interactions between medication and task complexity in the gamma band and in the alpha/low beta bands around movement onset and prior to movement onset, respectively (Figure 4.8D). In the case of the significant negative effect shown in Figure 4.8D, it was not clear looking at the spectra (Figure 4.4C) if this was solely the result of there being greater alpha/low beta desynchronisation in the high task complexity trials ON medication. I confirmed that this was the case by specifying t contrasts to compare each of four task complexity and medication conditions and showing that only the high task complexity /ON medication condition was significantly different to any of the others. There

was no main effect of reward, nor was there an interaction of reward with any other factor, in line with the behavioural data. Furthermore, as for the behavioural data, an ANOVA for high complexity trials with preceding trial complexity as a factor revealed no significant effects (minimum cluster level FWE corrected $p = 0.19$, peak t statistic = 4.51). Additionally there was no significant effect of movement laterality on induced spectra (minimum cluster level FWE corrected $p = 0.12$, peak t statistic = 4.03).

The vertical grey lines in figure 4.8 at -300 ms provide a conservative estimate of the uncertainty in the timing of movement onset and spectral change. Simulations suggested that spectral changes in the gamma band might be shifted to the left by about 150 ms through windowing for spectral estimation and subsequent smoothing (and by less than this in the beta band; Figure 4.2). To this I allowed for a further 150 ms leftward shift to accommodate the upper limb records where movement onset was determined from the instant of button depression rather than from EMG. Despite these allowances, mean effects, the main effects of complexity and the alpha/low beta band interaction between complexity and medication still precede movement onset (Figure 4.8). Thus these changes could not be ascribed to differences in afferent feedback once movement had started. Moreover, broadly similar gamma changes were evident before and during movement when only spectra accompanying lower limb movements were considered (Figure 4.9). In the latter case EMG was more likely to capture the very onset of the motor response and also confirmed that there was no difference in the EMG amplitude of the response between low and high task complexity trials (Figure 4.3B). Spectra accompanying lower limb movements only captured a main effect of task complexity in the form of a reduction in beta activity about 5s before movement onset (Figure 4.9D). This was rather different to the task complexity effect in the beta band evident in spectra compiled from upper and lower limb trials (see Figure 4.8C lower panel), and may reflect the lower number of trials when only the lower limb was considered.

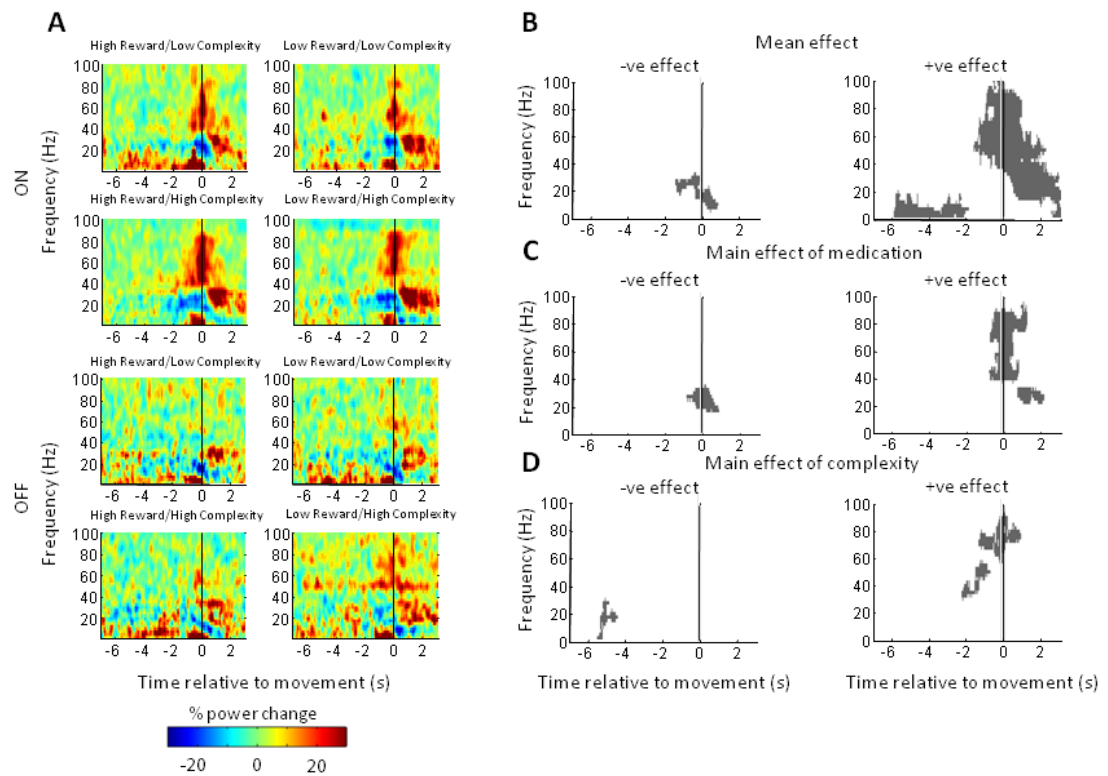


Figure 4.9 Lower limb data.

(A) Time-Frequency plots averaged across lower limbs and all subjects, of the induced responses aligned to the onset of movement for the four different reward and trial complexity conditions. Induced responses ON and OFF levodopa are shown in the upper and lower halves of panels. Power was computed relative to a 0.8 s period before the appearance of the warning cue. **(B - D)** - Plots of significant positive (right panel) and negative (left panel) clusters ($p < 0.01$ cluster level FWE correction) for lower limb subject images aligned to movement onset. T-contrasts correspond to the mean effect **(B)**, the main effect of medication **(C)** and the main effect of trial complexity **(D)**. The interaction between trial complexity and medication, reward and interactions with reward were not significant at the cluster level. The vertical grey lines are shown in each plot as per Figure 4.8, but this time at minus 150 ms to depict the uncertainty in the timing of spectral change.

	Reaction Times	Error Rates	Imperative Cue aligned spectra	Warning Cue aligned spectra	EMG profile aligned to movement onset
			T(92)	T(92)	T(92)
	F(1,52)	F(1,51)	Cluster forming T threshold = 2.37	Cluster forming T threshold = 2.36	Cluster forming T threshold = 2.36

Mean Effect	-	-	P < 0.01, T = 7.66	p < 0.01, T = 11.8	P < 0.01, T = 11.89
			P < 0.01, T = 6.28	P < 0.01, T = 8.87	*
Main Effect Medication	F = 5.97, p = 0.02	F = 0.98, p = 0.33	P < 0.01, T = 4.29	P < 0.01, T = 6.01	*
			P < 0.01, T = 5.83	P < 0.01, T = 5.73	*
Main Effect Complexity	F = 7.36, p < 0.01	F = 0.06, p = 0.80	P < 0.01, T = 5.23	P < 0.01, T = 5.05	*
			P < 0.01, T = 4.68	P = 0.05, T = 4.44	*
Main Effect Reward	F = 0.11, p = 0.75	F = 0.01, p = 0.92	P = 0.32, T = 4.49	P = 0.62, T = 3.38	*
			P = 0.40, T = 4.25	P = 0.12, T = 3.65	*
Interaction Complexity x Medication	F = 5.97, p < 0.01	F = 0.11, p = 0.74	P < 0.01, T = 4.62	P = 0.02, T = 4.98	*
			P = 0.02, T = 4.58	P = 0.34, T = 3.24	*
Interaction Complexity x Reward	F = 0.21, p = 0.65	F = 0.42, p = 0.52	P = 0.07, T = 5.09	P = 0.19, T = 4.16	P = 0.07, T = 2.70
			P = 0.09, T = 3.86	P = 0.27, T = 4.01	*
Interaction Medication x Reward	F = 0.25, p = 0.62	F = 0.19, p = 0.66	P = 0.20, T = 3.78	P = 0.97, T = 3.61	*
			P = 0.27, T = 3.50	P = 0.32, T = 4.23	*

Interaction	F = 0.02,	F = 0.28,	P = 0.56, T = 3.21	P = 0.44, T = 3.38	*
Medication x Reward x Complexity	p = 0.89	p = 0.60	P = 0.32, T = 4.09	P = 0.52, T = 3.49	*

Table 4-3 Summary of the statistical results for both behavioural and spectral data.

In the case of spectral and EMG data the cluster with the lowest FWE corrected p value is reported, along with the peak t value within the cluster. The statistics for each spectral test are shown in a lower and upper row, representing t contrasts testing for significant positive and negative changes in power respectively (see methods). In the case of EMG responses, (*) indicates the absence of any t values exceeding the initial uncorrected cluster forming threshold.

4.4 Discussion

I recorded STN LFPs to warning cues that indicated the reward and task complexity associated with an upcoming motor task. I used a paradigm where subjects were informed about these features prior to being told about the specific response that had to be performed. For reasons to be discussed later reward level had no behavioural effect in the current paradigm, so I will focus discussion on the effects of task complexity which did impact on response time. In this regard, our core findings can be divided in two. As previously reported (Oswal et al., 2012), there is a task-related suppression of STN beta power when the parameters of the movement cannot be prepared in anticipation. Here I show that this effect was not modulated by prior warning of the forthcoming task complexity. This is consistent with current theories positing a specific role for beta desynchronisation in signalling the likelihood of an upcoming action (Tzagarakis et al., 2010; Jenkinson and Brown, 2011), but suggests that this type of pre-movement beta band response does not substantially change with anticipated task demands.

In contrast, task complexity did impact on processing in the STN, as evidenced by the LFP, once movement selection and preparation were possible. Critically, the effect of task complexity on LFP spectra started before movement onset. In addition, movements were, on average, the same

in low and high task complexity trials, except for response time which was corrected for by realignment of LFP data to movement onset in the relevant analysis (Figure 4.8). These two observations suggest that differences in programming of motor dynamics and peripheral reafference are unlikely to explain the task complexity effects.

The contrasting of the two tasks does however expose several different processes of interest. First, the character of the warning cue changed between blocks from a direct cue, instructing a forthcoming simple stimulus-response mapping, to a symbolic cue that provided abstract information about the need for stimulus-response remapping. However, differences in processing entailed by direct and symbolic cues would have been expected to follow these warning cues, as previously demonstrated (Yamagata et al., 2009), and yet at this point there was no effect of task complexity on the LFP nor interaction between task complexity and medication. Second, the symbolic cue might demand a proactive behavioural switching in which more automatic stimulus-response associations have to be replaced by a more controlled behaviour necessary to accomplish the stimulus-response remapping. Direct recordings of neuronal activity in the STN of healthy monkeys demonstrate a clear change in discharge rates peaking just prior to response onset when controlled behaviour is necessary (Isoda and Hikosaka, 2008). Although changes in STN LFP and neuronal firing rate should not be considered synonymous, the switch to a more controlled processing could account for the reciprocal effects in the beta and gamma bands that became evident just prior to movement due to the task complexity effect.

Thus the complexity related effects may be due to the need for more controlled behaviour entailed by active stimulus-response remapping. The STNs role in controlled processing is often seen as the inhibition of competing alternatives, which in this case would be the inhibition of automatic stimulus-response associations. Yet, in LFP terms inhibitory processes in the STN, such as captured in the Go/NoGo or Stroop paradigms, involve relative increases in beta activity rather than the task complexity induced exaggeration of beta suppression seen here (Kuhn et al, 2004;

Brittain et al., 2012). This raises the possibility that the LFP changes in the current study may relate to another feature of controlled behaviour, its draw on limited, in the present context, cognitive capacity (Weingartner et al, 1984). The extent to which limited capacity is taxed can be defined as the effort made in the task, and defined in this way, effort transcends cognitive and motor domains (Lewis, 1964; Botvinick et al., 2009). Thus, it may be relevant that similar exaggerations of beta suppression and gamma synchronisation in the STN are seen when explicitly motor demands are increased (Brucke et al, 2012; Tan et al, 2013b). This leads to speculation that the degree of reciprocal beta-gamma changes in the STN may scale with the cognitive and motor effort expended in the task. Recent models of motor control recognize the need for a general mechanism to regulate the effort expended during a task according to task demands and cost/benefit contingencies (Guigon et al. 2007; Todorov and Jordan 2002). This function has been associated with the basal ganglia, where it is considered to rely on dopaminergic input (Mazzoni et al. 2007; Niv and Rivlin-Etzion, 2007), in line with the interaction between dopaminergic therapy and task complexity in the current study. Although the LFP changes I describe by no means prove a role for the STN in the coding of effort, they serve to demonstrate that changes in oscillatory dynamics in the STN cannot simply be accounted for in terms of the selection and parameterisation of motor variables such as force; in our paradigm the movements made did not differ, but the resources needed to achieve them did.

Task complexity increased both gamma synchronisation and beta desynchronisation before and during the movement. Crucially these reciprocal effects were supported by dopamine, in keeping with the known effects of this neurotransmitter in promoting effortful behaviours (Kurniawan et al., 2011). Previous work has demonstrated that gamma activity in the basal ganglia correlates with force or velocity, but has failed to dissociate these from effort (Anzak et al., 2012; Brücke et al., 2012; Joundi et al., 2012; Tan et al., 2013). One study explicitly contrasted simple, synchronous and complex, sequential finger movements and found no change in peri-movement

gamma activity in the STN (Litvak et al., 2012), although it could be argued that the demands of the complex task were less than in the current paradigm.

The modulation of the depth of beta band desynchronisation by task complexity once motor parameterisation was possible (i.e. after the imperative cue) is also interesting. Most previous studies that have reported a relatively fixed depth of beta desynchronization regardless of force or movement speed (Anzak et al., 2012; Brücke et al., 2012; Joundi et al., 2012), leading to the suggestion that beta desynchronisation may act in a binary fashion to gate movement (Kühn et al., 2004; Kempf et al., 2007; Brücke et al., 2012). The present results suggest that perimovement beta desynchronisation, unlike premovement anticipatory processes in the beta band, may not be fixed but may also be modulated in tasks requiring more cognitive effort. Another recent study has suggested that the same may be true of STN beta with respect to motor effort (Tan et al., 2013b).

Our study does have several limitations. The most conspicuous was the absence of a behavioural effect of reward on response times in light of previous studies demonstrating decreased reaction times with more rewarding stimuli (Kurniawan et al., 2013). Likewise error rates were no different for highly compared to lowly rewarded stimuli. Consequently it is hard to be certain that the subjects made use of information pertaining to reward in the warning cue, perhaps through lack of reinforcement of behavioural salience in the form of post-trial reward or feedback in the current paradigm. Nevertheless, our findings are similar to those in a functional MRI study of healthy subjects in which striatal activity anticipated effort but not reward, despite, albeit limited, reward related behavioural changes (Kurniawan et al., 2013). Whilst previous work has demonstrated cortical beta desynchronisation in parallel with reward anticipation, the magnitude of the reward was correlated with reaction time hence confounding reward and motor processing (Doñamayor et al., 2012).

In summary, I have provided evidence for two patterns of reactivity in the STN LFP in the beta band, one that is anticipatory, and has previously been linked to the likelihood of an upcoming action (Jenkinson and Brown, 2011), and one that is peri-movement in timing and is partially modulated by task complexity as determined by the need for more controlled behaviour and active stimulus-response remapping. The latter is complemented by a task complexity modulated reciprocal reactivity in the gamma band. Crucially, the effects of task complexity in increasing peri-movement beta band desynchronisation and gamma synchronisation are potentiated by levodopa, evidenced by the bidirectional interaction between medication and task complexity. Thus the ability to perform effortful actions may be impaired in hypodopaminergic states such as untreated Parkinson's disease (Mazzoni et al., 2007).

Chapter 5: Movement related dynamics of subthalamo-cortical alpha connectivity in Parkinson's disease.

5.1 Introduction

It is now widely believed that exaggerated beta band (13-30 Hz) activity in the cortico-basal ganglia circuit is an important pathophysiological abnormality in Parkinson's disease contributing particularly to bradykinesia (Uhlhaas and Singer, 2006; Hammond et al., 2007; Eusebio et al., 2009; Weinberger et al., 2009). However, important interactions occur in other frequency bands, and much less is known about how these may contribute to both normal movement and to the pathophysiology of Parkinson's disease.

Advances in neurophysiological methodology have facilitated the simultaneous recording of magnetoencephalographic (MEG) activity from the cortical surface and local field potential activity (LFP) from the basal ganglia, thus enabling the characterisation of resting patterns of

connectivity between the two levels and the investigation of how this may be modulated by movement and the dopamine prodrug, levodopa (Litvak et al., 2010, 2011a, 2012; Hirschmann et al., 2011). This approach affords valuable insights into the complex oscillatory patterns of neuronal activity seen in Parkinson's disease.

Previous work has demonstrated the existence of two spatially and spectrally distinct networks at rest in Parkinsonian patients (Hirschmann et al., 2011; Litvak et al., 2012; Litvak et al., 2011a). A temporoparietal-brainstem network was coherent with the region of the subthalamic nucleus (STN) in the alpha (7-13 Hz) band, whilst a predominantly frontal network was coherent in the beta (15-35 Hz) band. It has been hypothesised that the beta network determines motor state whilst the alpha network may play a role in attentional processing (Hirschmann et al., 2011; Litvak et al., 2011a).

The modulation of beta band cortico-STN connectivity by movement and levodopa has previously been demonstrated in both Parkinsonian humans and in rodent models of Parkinsonism. These studies would suggest that the beta coherence between the STN and cortex drops before and during movement and during imagination or observation of movement (Cassidy et al., 2002; Sharott et al., 2005; Kühn et al., 2006a; Lalo et al., 2008; Alegre et al., 2010). Recently, using simultaneous recordings of MEG and LFP in the STN it has been shown that the coherence in the gamma frequency (60-90 Hz) band between STN and primary motor cortex (M1) increases with both movement and levodopa therapy. It has also been shown that gamma band coherence is likely to be modulatory rather than related to movement processing, through the demonstration that there are no gamma coherence differences between synchronous and sequential movements. Importantly the change in coherence with medication was found to correlate with the degree of improvement in bradykinesia-rigidity scores (Litvak et al., 2012). In this study of the same patients I specifically aim to characterise how the coherence between the STN and

temporal cortex in the alpha frequency band is modulated by movement and by administration of levodopa. Furthermore, I aim to determine whether coherence changes are primarily modulatory or associated with movement processing by studying sequential and synchronous finger movements. Coherence changes of similar amplitude and duration at movement onset may be expected with modulatory processes such as motor attention or arousal, whilst sustained differences may be predicted during sequential movements in the case of coherence influencing motor processing. A final key aim was to determine whether dopamine induced modulation of alpha coherence was associated with clinical change.

5.2 Methods

This study continues the analysis reported by Litvak et al. (2012) and is based on the same patient cohort. Seventeen patients (age 55 ± 7 years, 6 female, 2 left-handed) were studied. In one patient the surgery was performed only on the right side. All patients were diagnosed with PD according to the Queen Square Brain bank criteria (Gibb and Lees, 1988). In summary, the mean UPDRS part III score OFF medication was 47.6 (standard error 3.8) whilst the mean score ON medication was 13.7 (standard error 1.5).

5.2.1 Experimental paradigm

The experiment was divided into blocks – several minutes of recording. The patients could rest between the blocks. Each block comprised either rest or a movement task. During rest blocks the subjects were instructed to remain still with their eyes open for 3 min (Litvak et al., 2011a). During movement blocks the subjects performed either simultaneous button presses with index, middle and ring finger (SYN) or a sequential button presses with index, ring and then middle finger (SEQ), with either left or right hand (one kind of movement with the same hand within a block). The movements were self-paced. The subjects were instructed to move when they wanted, but not to do it too frequently and take about 15 s between movements without

counting silently (see Figure 5.1). Feedback to the subjects was presented visually, using Matlab (The MathWorks, Inc., Natick, MA) and a custom script based on Cogent (<http://www.vislab.ucl.ac.uk/cogent.php>). This script monitored the movement times and displayed messages on the screen when the inter-movement interval was shorter than 12 s ('slow down') or a movement sequence in the complex condition was incomplete ('sequence incomplete'). These trials were not analysed. When performing correctly the subjects did not get any feedback and the screen just showed a fixation cross. In case of incorrect performance, the script waited to collect another movement so that it ran until 8 correctly performed movements were collected or at most for a total of 7 min. The subjects could usually complete a movement block in 3–4 min. A neurologist was present in the magnetically shielded room during the experiments to monitor the patients and their performance of the task. Up to 18 blocks were performed in each experiment. The order of the conditions was pseudo-randomised separately for blocks 1–9 and blocks 10–18; so that each half would contain one rest block and two movement blocks of each type. In all experiments at least 9 blocks were recorded, but only two patients managed to complete all 18 blocks. A single recording session lasted about 1.5–2.5 h (including preparation).

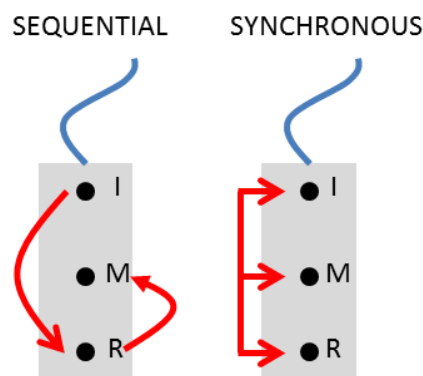


Figure 5.1 A schematic of the motor tasks.
The letters I, M and R indicate the positions of the Index, Middle and Ring fingers on the buttons of the button box. In the sequential motor task, drawn to the left of the figure, patients were instructed to move sequentially in order to depress the buttons. In the synchronised motor task, patients were

instructed to move all three fingers so as to depress the buttons synchronously. The movements were self-paced and performed every 12-15 seconds. The right and left hands were tested separately.

The whole experiment was performed twice: after overnight withdrawal of dopaminergic medication (OFF drug) and after the patients took at least 200 mg of levodopa (ON drug). The order of these drug conditions was counter-balanced over patients. Twelve patients were able to complete both experiments, three were only recorded ON drug and two patients could not tolerate levodopa and were, therefore, only recorded OFF drug.

The two movement patterns differed in several regards, even though the same fingers were used to enact the same key presses. In the SYN task all three fingers simultaneously depressed three keys, whereas in the SEQ task only one finger at a time was used to depress one key. Consequently the conditions differed in their initial parameterization. Nevertheless, the same three keys were eventually depressed in the SEQ task, which therefore went on for longer than synchronous button presses.

5.2.2 LFP-MEG recordings

MEG recordings were obtained with a 275 channel system (CTF/VSM MedTech, Vancouver, Canada). Simultaneously, LFP, electro-oculographic (EOG) and electromyographic (EMG) signals were recorded using an integrated EEG system (amplification $\times 1$, dynamic range ± 125 mV) and high-pass filtered (in hardware) above 1 Hz to avoid saturation of the amplifiers due to DC offsets. All signals were low-pass filtered in hardware below 300 Hz. The data were sampled at 2400 Hz and stored to disk. Four intracranial LFP channels were recorded from each contact, on each side, and referenced to a cephalic reference. LFP recordings were converted off-line to a bipolar montage between adjacent contacts (3 bipolar channels per hemisphere; 01, 12 and 23) to limit the effects of volume conduction from distant sources. EMG data were recorded from right and left first dorsal interosseous muscles with a reference at the muscle tendon. Button presses were also recorded in all subjects.

Head location was monitored using three head position indicator (HPI) coils attached to the subject's nasion and pre-auricular points. For all but the first subject I used continuous head localization and recorded the head locations throughout the experiment. Loss of head tracking occurred intermittently in some patients, possibly due to metal artefacts disrupting the head tracking function of the MEG sensors. During offline processing I compared the instantaneous distances between HPI coils with the distances based on robust average (Holland and Welsch, 1977) of locations across the whole continuous recording. Time frames where discrepancies were detected were discarded and replaced with linear interpolation based on the other time frames. This method works well when the tracking is valid for more than half of the recording, which was the case for all recordings reported here.

5.2.3 Characterisation of individual subject cortical-STN coherence

Selection of STN-LFP channels for the present study was based on the analysis reported in Litvak et al. (2011a). Briefly, for that analysis I computed sensor level coherence between each STN-LFP channel and each MEG channel for each subject during rest over a range of frequencies generating multiple sensor level coherence images. The images for each STN-LFP channel were stacked to produce a 3D image (with two spatial and one frequency dimensions), which was subsequently subjected to statistical comparison with trial-shifted data in SPM8 in order to determine frequency ranges in which there was statistically significant coherence between the STN-LFP channel and MEG channels at rest. For the purposes of the present analysis I selected only those STN contact pairs for each subject with statistically significant coherence with MEG channels in the alpha frequency band (see table 1 for the chosen channels). Importantly for some subjects, different STN channels had significant resting alpha coherence ON and OFF medication. To ensure balanced channel selection for comparing the ON and OFF conditions I selected all channels that were significant in either the ON or OFF condition or significant in both conditions and included them all in subsequent analyses for each medication condition. In this way ON and OFF analyses were of matched STN contact pairs.

Cortical sources coherent with the selected STN-LFP channels in the alpha (7-13 Hz) frequency band were localised using the Dynamic Imaging of Coherent Sources (DICS) beamformer (Gross et al., 2001). The source localisation was performed anew for the present study using data from the movement rather than resting (as in Litvak et al. 2011a) blocks. Given that movements were performed approximately at 12 s intervals I used a temporal window of 8 to 5 s prior to movement across all trials for the purpose of DICS beamformer source localisation. I believed this would provide a good approximation to the resting state since activity in this time window is unlikely to be influenced by the preparation, execution or refference of motor processes. Trials where the LFP data were contaminated by artefacts were rejected prior to DICS analysis (see below for rejection criteria). In subsidiary analysis I also performed beamforming in the time window between 0.5 s before movement to 1.5 s after movement. The purpose of this was to determine if there were any STN-cortical networks in the alpha band that are quiescent at rest and activated by movement.

Lead fields were computed using a single-shell head model (Nolte et al., 2004) based on an inner skull mesh derived by inverse-normalizing a canonical mesh to the subject's individual preoperative MRI image (Mattout et al., 2007). Coregistration between the MRI and magnetoencephelography coordinate systems used three fiducial points: nasion, left and right pre-auricular (see Litvak et al., 2010 for further details). The coherence values were computed on a 3D grid in Montreal Neurological Institute (MNI) space with spacing of 10mm bounded by the inner skull surface. Values at the grid points were then linearly interpolated to produce volumetric images which were furthering smoothed with a 5mm isotropic Gaussian kernel to generate images with 2mm resolution.

5.2.4 Identification of group and individual coherence peaks

To identify the cortical areas consistently coherent with the STN across the group I computed the average of all the individual images that had been generated in the 8 s to 5 s pre-movement period. Importantly, these images had been normalized prior to averaging, by dividing the coherence at each beamformer grid point by the mean of that image. This ensures that each included hemisphere-contact pair contributes equally to the calculation of the average. All images corresponding to left STN contacts were flipped across the mid-sagittal plane to allow comparison of ipsilateral and contralateral sources to the STN regardless of original STN side. The global maximum of the resulting image was defined as the cortical source maximally coherent with the STN across all subjects.

Subsequently, for each subject and each contact we selected from the individual image, the peak closest to this group peak. The individual cortical peaks were then used for time series extraction. This approach represented a compromise between a systematic choice of site and maximisation of coherence. Crucially, in order to ensure immunity from artefact the orientation of the cortical source was defined as the normalised imaginary part of the cross-spectral density vector between the STN-LFP and the three orientations of the cortical source (Nolte et al., 2004; Litvak et al., 2010).

5.2.5 Source activity extraction

Source activity extraction was performed using the Linearly Constrained Maximum Variance (LCMV) beamformer (Van Veen et al., 1997) with DICS beamformer-identified sources and time epochs from -8 to 5 s relative to the button press. Beamformer filters were computed for each trial separately with a trial-specific forward model based on continuous head tracking data. This was done to reduce the confounding effects of head movements and varying numbers of trials across subjects and conditions. I refer the reader to Litvak et al., 2012 for a more detailed discussion of this issue. I used a beamformer regularization of 0.01% of the signal variance

(averaged over channels) as this value was shown to be optimal in our previous studies (Litvak et al. 2010).

5.2.6 Pre-processing of virtual electrode and LFP data

The virtual electrode channels derived from the MEG sometimes contained discontinuous jumps, whose origin could be traced to occasional resets of the SQUID sensor circuitry. These jumps were detected by thresholding the differences between adjacent samples. When a jump was detected the values from 20 samples before to 20 samples after the jump were replaced by the median difference over this segment and the modified difference time series were summed again to produce the original time series with the jump corrected. The corrected data were digitally filtered (1 Hz 5th order high pass, and 4th order notch filters for 50 Hz and all harmonics up to 550 Hz, zero-phase Butterworth in all cases). Finally, prior to spectral analysis, the channel data were standardized by subtracting the mean and dividing by the standard deviation for each channel and trial separately. This ensured all trials contributed equally to estimates of source activity.

5.2.7 Artefact suppression

In our dataset LFP, EMG and EOG data were contaminated by occasional brief electrical discharges due to a grounding problem that could not be completely resolved at the hardware level. Since the occurrence of these spikes was increased around the button press periods it is important to rule out wide-band artefacts as possible reasons for changes in low frequency amplitude or power. The preprocessed LFP and virtual electrode data series were examined for the presence of outliers by thresholding. The thresholds were set such that they could separate the artefacts from the remaining data. These thresholds were 5 standard deviations for the original data and 2 standard deviations for the beamformed source derivative.

This artefact suppression technique was employed at two stages of the present analysis. Firstly prior to DICS beamforming in the period from 8 to 5 s before movement or from 0.5 s before

movement to 1.5 s after movement I removed artefacts from the LFP channels in order to facilitate accurate cross spectral density estimates for beamforming. Secondly in order to preclude contribution of spikes to the button press response, trials with artefacts in the period from 0.2 before movement to 2 s after movement were excluded from the analysis of event related power. The effects of the remaining spikes were suppressed by robust averaging (see Litvak et al. 2012). Trial exclusion was performed separately for beamformed sources and STN channels to minimize data loss. For the analysis of event-related coherence I used all the trials. This was motivated by simulations showing that high-frequency artefacts in only one of the channels had a minor effect on coherence estimates – and were further suppressed by our robust procedure for coherence computation. A more detailed description of the benefits of robust averaging in this particular dataset with artefacts and relatively few trials can be found in Litvak et al. (2012). Essentially the procedure involves computing the distribution of values over trials and down weighting outliers when computing the average. This makes it possible to suppress artefacts restricted to narrow time and frequency ranges without rejecting whole trials.

5.2.8 Excluding data with high frequencies in the evoked response

To further ensure that the phenomena I report are not caused by brief artefacts I computed the averages of both the movement-related LFP and virtual electrode data in the time domain and performed time-frequency analysis of these evoked responses using the same settings as for single trials. Even after exclusion of trials containing artefacts, for some hemispheres I found high-frequency activity around the button press. All of these cases were from the beamformed sources, and not from STN-LFPs. Not all of this activity was clearly artefactual, but since this was a likely explanation I excluded all contact-hemisphere pairs where such activity was found from our analysis of beamformed source power. 15 contact-hemisphere pairs were removed ON medication (from 9 different subjects) and 4 hemisphere contact pairs were excluded OFF medication (for 3 different subjects. Table 5.1 details the data included in the analysis.

5.2.9 Spectral analysis

For efficient spectral estimation from a relatively small number of trials I used multitaper spectral analysis (Thomson, 1982). I estimated the spectra between -8 and 5 s relative to the first button press of each trial, in overlapping windows of 400 ms (shifted by 50 ms). The frequency resolution was set to the inverse of the time window (2.5 Hz) for up to 25 Hz, then 0.1 times the frequency for 25 to 50 Hz and then to a constant 5 Hz resolution. These settings resulted in a single taper being used for 2.5–30 Hz, 2 tapers for 32.5–42.5 Hz and 3 tapers for 45 Hz and above. The resulting time–frequency images had no discontinuities thanks to the continuous frequency resolution function. The time–frequency images were then averaged using robust averaging (Holland and Welsch, 1977; Wager et al., 2005, Litvak et al. 2012) and percentage change time frequency responses were obtained by normalizing to the baseline (8 to 5 s) before button press.

For the purposes of statistical analysis, given our focus on the alpha frequency band (7-13 Hz), I averaged the spectral data over this band by computing a multitaper spectral estimate with central frequency of 10 Hz and frequency resolution of 3 Hz. This is a more efficient way of spectral estimation than averaging over pre-computed time-frequency images with higher frequency resolution (Mittra and Pesaran, 1999). The power time series were then averaged using the robust averaging procedure described above.

Coherence was estimated using a similar spectral estimation procedure except that robust averaging was used during coherence computation and was applied separately to the absolute values of the cross-spectral density and to the power of the two sources (Litvak et al. 2012). In the case of cross-spectra, the weights computed from the absolute values were then applied to the complex cross-spectra when computing the mean coherency over trials. Percent changes in cross-spectral responses were computed as above.

5.2.10 Statistical analysis of time-frequency data

Statistical analysis was performed using Statistical Parametric Mapping (as implemented in SPM8). This treats the time series of alpha power or coherence as images with up to 3 dimensions allowing the identification of time windows showing significant effects over subjects, while controlling for the multiple comparisons using random field theory (Kilner, Kiebel, & Friston, 2005; Litvak et al., 2011b).

The results of time-frequency analysis were exported to Neuroimaging Informatics Technology Initiative (NIfTI) format and smoothed with a Gaussian smoothing kernel with a Full Width Half Maximum (FWHM) of 500 ms. All the reported findings are significant with FWE correction ($p < 0.05$). In the results I also report the peak t statistic with the corresponding p values.

To test for the effects of experimental conditions I constructed a 2x2x2 repeated measures Analysis of Variance (ANOVA) with factors 'Task' (SYN vs. SEQ), 'Drug' (ON vs. OFF) and 'Side' (Ipsilateral vs. Contralateral to the selected STN channel). In this design I included subject and side covariates in order to account for resulting dependencies in the error. Significant features of the mean responses were determined by subjecting mean images across conditions for power and coherence to a single-sample t-test across subjects.

To test for correlation with clinical scores I performed an Analysis of Covariance (ANCOVA) by adding to the ANOVA described above a regressor with contralateral hemibody bradykinesia-rigidity scores. The scores comprised the sum of items 22-26 of the UPDRS part III score. Motor examination was performed pre-operatively, after withdrawal from medication overnight, in a practically defined OFF state (so that patients had their last antiparkinsonian medication 9 -12 hours prior to testing). Motor examination was repeated on the same day one hour after their usual antiparkinsonian treatment, provided the levodopa dose was at least 200 mg. Where this was not the case the patient's standard antiparkinsonian medication was replaced by a single

dose of levodopa 200 mg. Tremor scores were also independently tested as clinical regressors. As mentioned, the UPDRS scores used for clinical correlations were determined pre-operatively. However, this would serve to weaken any correlation between variables. Thus any correlation between the difference in UPDRS ON and OFF medication and the difference in coherence induced by medication may be an under-estimate of the strength of any association.

To test for a main effect of contact pair across subjects I constructed a one way ANOVA with 3 levels, each representing the selected contact pair: 01, 12, and 23. In this design I included subject and side covariates in order to account for resulting dependencies in the error.

5.2.11 Additional statistical analyses

To show that the alpha network during movement had the same topography as during rest I performed a paired t-test of the 3D beamformer images comparing the period from 0.5 s before movement to 1.5 s after movement for all subjects and conditions. To show that the MNI coordinates ON and OFF medication were not significantly different to each other I used the Hotelling's t-squared statistic and its chi-squared approximation.

For the behavioural data, I pooled the timings of all button presses after the first press for all subjects separately for the complex and simple tasks ON and OFF medication. The mean timing was then computed for each of the four conditions for each subject. Subsequently I ran a repeated measures 2x2 ANOVA with factors 'Drug' (ON vs. OFF) and 'Task' (SYN vs. SEQ).

5.3 Results

5.3.1 Topography of STN-cortical alpha coherence during movement and pre-movement

A Paired t-test did not reveal any cortical areas where coherence with the STN was greater in the movement period (0.5 s before movement to 1.5 s after movement) than in the premovement period (8s to 5s prior to movement). See Figure 5.2 for further details.

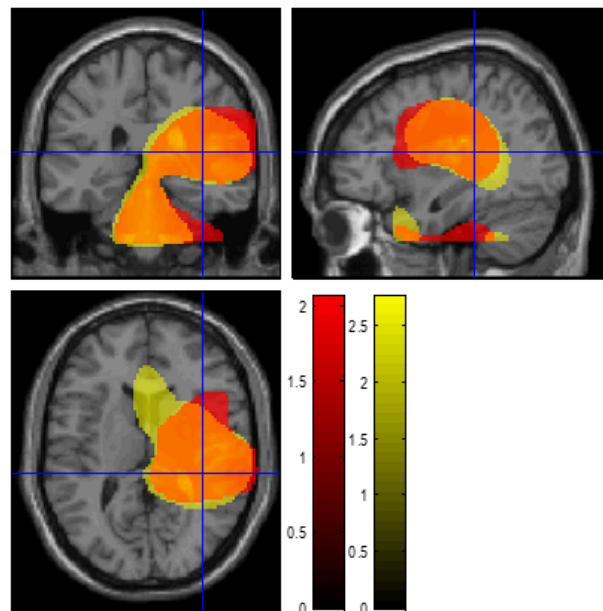


Figure 5.2 Mean across subjects of the normalised DICS beamformer images.

The images have been thresholded such that only voxels with coherence greater than 2 standard deviations above the mean (1 unit) are displayed. Yellow image: the pattern of STN-cortical coherence in the window between 8 s and 5 s prior to movement. Red image: STN-cortical coherence in the window between 0.5s before movement and 1.5s after movement. Both images are superimposed onto a T1 weighted canonical MRI. Coronal, sagittal and axial sections through the image are displayed, oriented to the group peak (shown by the cross hairs) in the window between 8 s and 5 s prior to movement. A paired t-test (see results) failed to reveal any cortical areas where coherence in the red image was greater than that in the yellow image.

5.3.2 Cortical Source Localisation

Cortical source localisation of alpha activity coherent with the STN in the interval of 8s to 5s before movement was performed for the 52 STN contact pairs demonstrating coherence with the temporal cortex in the 17 subjects ON and OFF medication (Figure 5.3). The location of the group peak in MNI co-ordinates was 38 -32 12, corresponding to the right superior temporal gyrus. The mean distance of selected peaks from the group peak in MNI space was 22.2mm (standard error 1.05mm). Furthermore, the mean MNI co-ordinates ON and OFF medication were 42 31 13 and 42 29 16 respectively. The Hotelling's t squared test did not support the hypothesis that the coordinates of sources localised ON medication were significantly different to those localised OFF medication ($\chi^2 = 3.6$, $df = 3$, $p = 0.31$). Individual subject source locations in MNI coordinates and the selected contacts for DICS beamforming are detailed in Table 5.1.

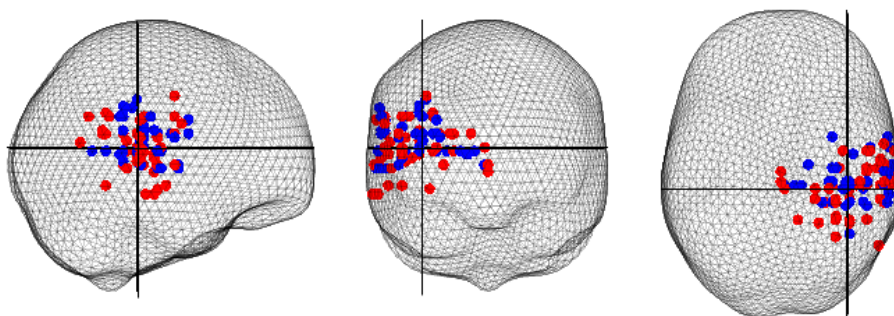


Figure 5.3 Peaks of STN–cortical alpha coherence. Cortical alpha peaks of coherence closest to the group peak (shown by the intersection of the black cross hairs) are plotted for all subjects and contacts both ON and OFF dopaminergic medication (ON, shown in red and OFF shown in blue).

Case	Selected Channel(s)	MNI co-ordinates of source(s)	Rejected channels for analysis of source power/other

			comments
1 OFF	L23* R12* R23*	-24 -40 10 65 -18 0 63 -8 0	
2 ON	L01 R01* R23	-46 -28 30 52 -10 20 60 -18 12	R01,R23
2 OFF	L01* R01 R23*	-38 -28 20 42 -12 20 52 -10 18	
3 ON	L12 L23 R01 R12	-10 -50 20 -22 -52 20 65 -30 28 57 -65 15	L23
3 OFF	L12* L23* R01* R12*	-12 -30 8 -8 -30 10 60 -30 28 50 -28 24	
4 ON	R12	62 -22 6	R12
4 OFF	R12*	52 -8 2	
5 OFF	R12* R23*	60 -20 0 50 -22 6	
6 ON	L01* L12* L23* R12*	-60 -28 10 -56 -20 0 -64 -27 -15 58 -15 -10	
7 ON	L01* L12*	-32 -48 30 -32 -60 30	

	L23*	-32 -50 32	
	R12*	67-22 15	
7 OFF	L01	62 – 40 2	
	L12	-40 -40 36	
	L23*	-36 -32 40	
	R12	38 -42 30	
8 ON	L01*	-58 -30 8	R01, R12, L12
	L12*	-58 -38 0	
	L23*	-44 -30 6	
	R01*	26 -40 2	
	R12	32 -38 10	
	R23*	60 -28 30	
8 OFF	L01	-48 -32 10	
	L12*	-40 -30 10	
	L23	-28 -28 18	
	R01*	30 -40 10	
	R12*	38 -30 10	
	R23*	32 -40 10	
9 ON	L23*	0 -22 -2	
	R23	48 -32 4	
9 OFF	L23	-2 -30 2	
	R23*	16 -18 10	
10 ON	L01*	-20 -32 20	
	L12*	-20 -38 10	
	R01	30 -30 12	
	R23*	40 -32 8	
10 OFF	L01	-40 -58 10	
	L12	-30 -2 28	

	R01*	40 -50 10	
	R23	30 -28 20	
11 ON	L01*	-50 -20 18	L01
	R12	48 -30 18	
	R23*	50 -30 12	
11 OFF	L01	-62 -2 20	L01
	R12*	60 -22 22	
	R23*	62 -24 30	
12 ON	L12*	-50 -50 10	L12
12 OFF	L12*	-40 -40 10	L12
13 ON	L23*	-50 -28 10	R12, R23, L23, R01
	R01*	30 -30 20	
	R12*	28 -32 20	Entire ON recording excluded
	R23*	28 -32 20	
13 OFF	L23*	-64 -20 10	L23, R23
	R01*	38 -30 12	
	R12	32 -20 20	
	R23	30 -20 20	
14 ON	L12	-66 -10 2	L12
	L23*	-50 -22 8	
	R12	36 -10 42	
	R23	40 -38 16	
14 OFF	L12*	-63 -35 35	
	L23	-40 -28 12	
	R12*	48 -40 4	
	R23*	50 -42 8	
15 ON	L01	-40 -52 22	L01
	R01*	34 -20 -12	

15 OFF	L01*	-48 -40 30	
	R01*	40 -40 32	
16 ON	L01*	-40 -50 10	
	L23*	-32 -40 32	
	R01*	50 -10 30	
	R23*	60 -6 26	
17 ON	L12*	-68 -18 -10	

Table 5-1 Table showing the selected contacts for each subject.

Table showing the selected contacts for each subject and whether the subject was recorded ON or OFF medication, or both. In all 12 subjects had both ON and OFF recordings. In the first column of the table * indicates that the channel showed statistically significant resting alpha coherence with the cortex in the corresponding medication state (either ON or OFF medication or both). The second column indicates the MNI location of the selected peak, closest to the group peak for the corresponding channel. Channels rejected for the analysis of event related power due to the presence of high frequency artefact within the corresponding beamformed temporal sources are also listed. Note for subject 13 that the entire ON recording was excluded due to broadband artefacts within the beamformed temporal sources for all selected contacts (see also Litvak et al. 2012).

5.3.3 Responses in Cortical sites and STN induced by voluntary movement

One way ANOVA, revealed no significant effect of the selected contact pair for power spectra from the STN or cortical sites. The peak F statistic for cortical contact pair power was $F_{(2,287)} = 2.8$, with a corresponding value of $p > 0.05$). Similarly for the STN, the results were: $F_{(2,287)} = 2.4$, $p > 0.05$. Figures 5.4 and 5.5 show the power changes induced by button presses at both the beamformer extracted source locations and the STN channels, averaged across all subjects and hemispheres for each of the four different experimental conditions ON and OFF medication. In the STN we see a characteristic event related desynchronisation (ERD) in beta power prior to and during movement, followed by a beta event related synchronisation (ERS). There is also a reduction in alpha activity both prior to and during movement and a broadband gamma ERS associated with movement onset. Activity in the extracted cortical sources is dominated by a beta and alpha power decrease upon movement.

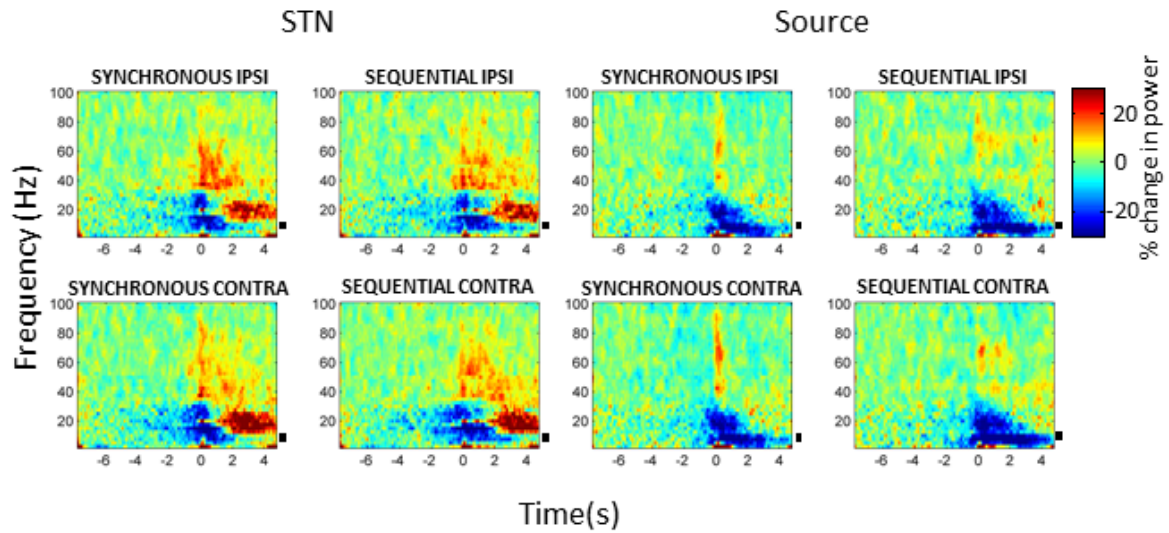


Figure 5.4 Time frequency images of power for the STN and cortical source locations OFF medication. Time frequency images of power, averaged across subjects, for each of the four conditions OFF dopaminergic medication. We used a baseline period from -8 to -5 s prior to movement with power changes reported as percentage change. There is a beta desynchronisation with onset prior to movement and gamma power increase upon movement. The black bars indicate alpha band frequencies between 7-13 Hz.

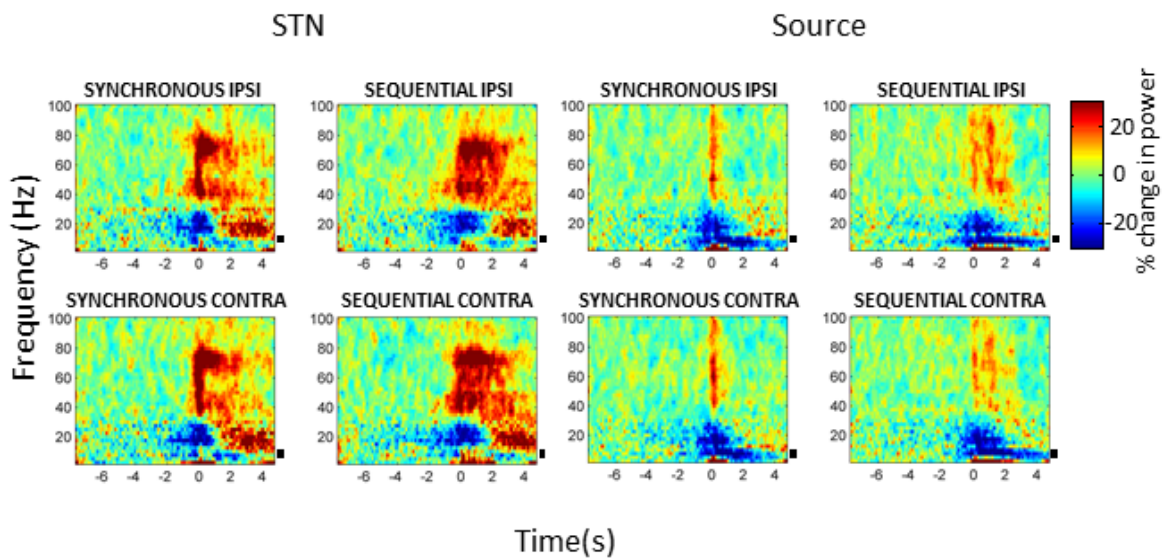


Figure 5.5 Time frequency images of power for the STN and cortical source locations ON medication. As per Figure 5.4, but this time the patients were recorded ON medication.

Since I was explicitly interested in modulations of alpha band power, these time series are plotted for both the STN and cortical sources in Figure 5.6.

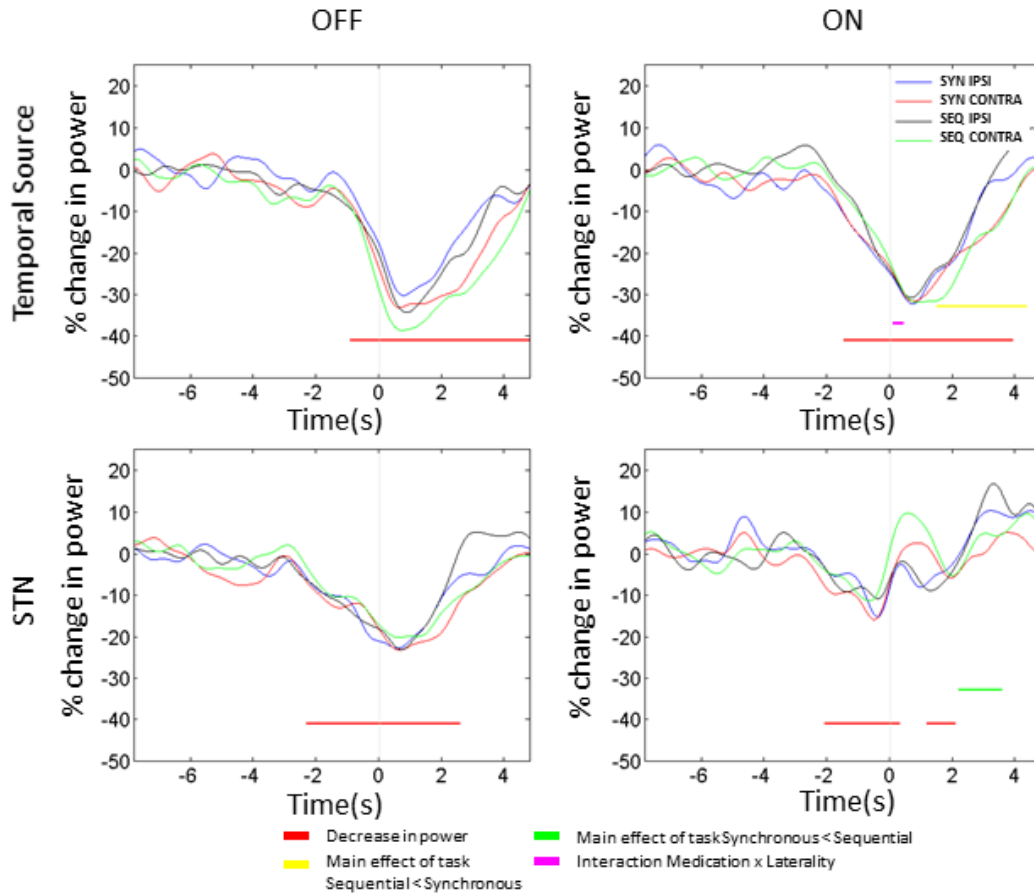


Figure 5.6 Time series of alpha power for the STN and cortical source locations.
Time series of alpha (7-13 Hz) power for all four conditions averaged across subjects for the source and STN both ON and OFF dopaminergic medication. The time series are baseline-corrected from -8 to -5 s prior to movement and the changes are shown as percentage changes from baseline. Time series have been smoothed by a 500 ms FWHM Gaussian kernel. The power changes were subjected to statistical analysis, separately for the STN and source.

In the cortical sources there was a significant ERD in alpha power occurring prior to movement and continuing up to 4 s after movement, both ON and OFF dopaminergic medication (shown by the red lines in Fig 4). The peak t-scores and their corresponding p values are as follows: OFF $t_{282} = 4.2$, $p < 0.01$ and ON $t_{282} = 5.7$, $p < 0.01$). For sake of consistency I display the main effects and interactions in figures 5.6 and 5.9 in the ON plots only. There was also a significant main effect of movement task with sequential movements producing a greater and more prolonged alpha desynchronisation between 1.5 s and 4.3 s after movement onset (shown by the yellow bar in Figure 5.6 – peak $t_{282} = 3.3$, $p < 0.05$; Also see Figure 5.7). The latter may reflect the longer duration of the sequential movements. In addition to this, there was a narrow period of

significant interaction between medication and the laterality of movement, with contralateral movements producing greater alpha desynchronisation than ipsilateral movements predominantly OFF medication (shown by the pink bar in Fig 5.6 – peak t_{282} score 3.4, $p < 0.05$).

For the STN contacts, I observed a significant reduction in alpha power from about 2 s before movement in both the ON and OFF medicated states. OFF medication the peak t_{282} score was 4.6 corresponding to a p value of <0.01 . Similarly ON medication the peak t_{282} score was 3.5, with a corresponding p value of <0.05 . There was significant but delayed main effect of task, shown by the green bar in Figure 5.6, which was opposite in direction to that observed for temporal sources (peak $t_{282} = 3.4$, $p < 0.05$; Also see Figure 5.7). This might reflect a more delayed event-related synchronization following movement in the sequential task. Thus the main effect of task at both cortical and STN levels might reflect the different durations of the tasks, although whether this was more manifest in the timing of the power suppression or power rebound was dependent on level.

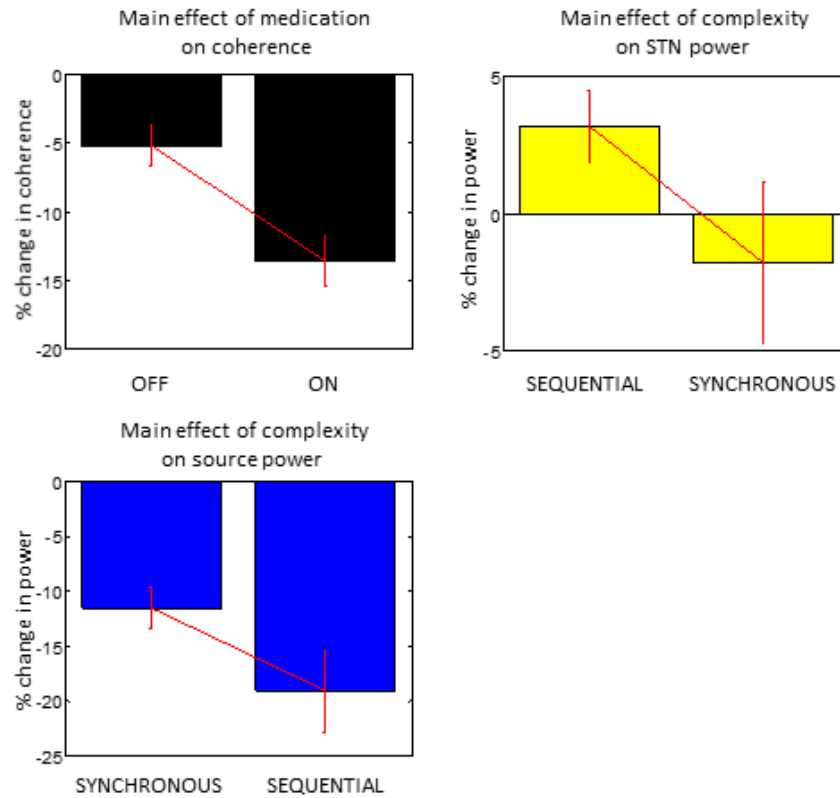


Figure 5.7 Bar plots of the main effects for power and coherence.
The baselined percentage changes in power or coherence corresponding to the main effects averaged over subjects and the entire time window of significance (shown in figures 5.6 and 5.9) are presented with standard errors of the mean.

5.3.4 Reactivity Patterns of STN–alpha source coherence

One way ANOVA, revealed no significant effect of the selected contact pair for coherence spectra (peak $F_{(2,287)} = 1.9$, $p > 0.05$). Figure 5.8 displays the changes in coherence induced by button presses between the beamformer extracted source locations and the STN channels, averaged across all subjects and hemispheres for each of the 4 different experimental conditions ON and OFF medication. Coherence is displayed at frequencies below 25 Hz as statistically significant movement related changes were not seen at higher frequencies.

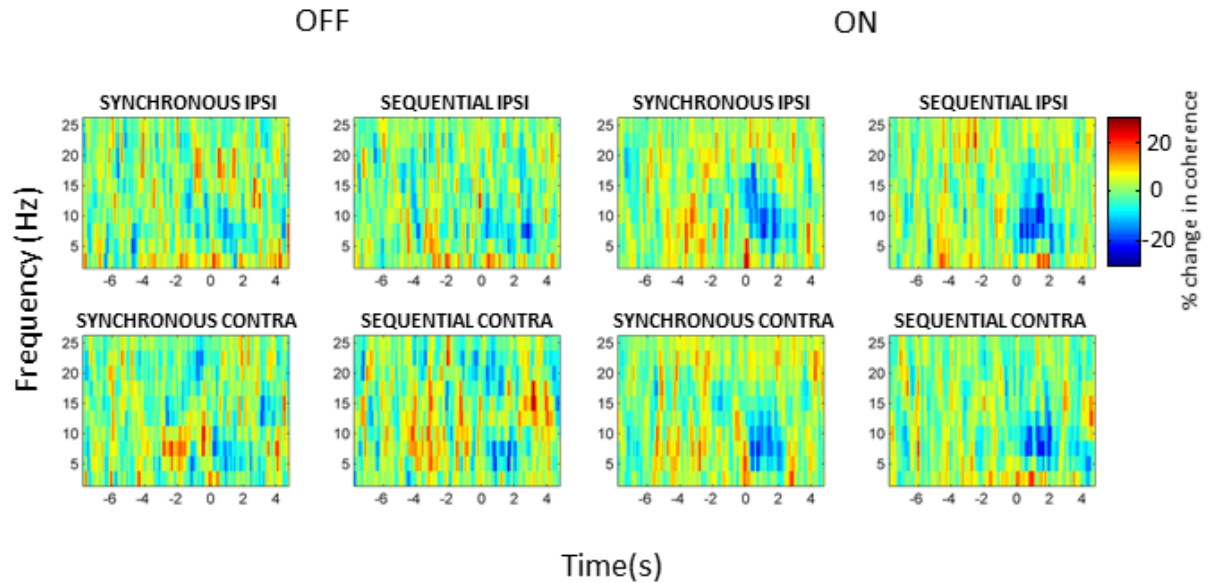


Figure 5.8 Coherence spectra aligned to movement onset.

Time frequency images of coherence, averaged across subjects, for each of the four conditions OFF and ON dopaminergic medication. The coherence spectra have been smoothed by a 2D Gaussian kernel (FWHM of 2.5 Hz and 500 ms). We used a baseline period from -8 to -5 s prior to movement with coherence changes reported as percentage change from this. Movement related changes dominate in the alpha band.

Note that the majority of the change in coherence occurs in the alpha rather than beta frequency bands. The time series of the alpha band coherence between STN and temporal sources is given in the upper panels of figure 5.9. Both ON and OFF medication there was a significant drop in coherence compared to baseline upon movement (red bars in Fig 5.9). The peak t scores and the corresponding p values for these effects were as follows: OFF $t_{282} = 4.1$, $p < 0.01$ and ON $t_{282} = 5.8$, $p < 0.01$. There was an additional main effect of medication in which coherence was significantly less ON than OFF medication after movement (dark grey bar in Fig 5.9, peak $t_{282} = 4.8$, $p < 0.01$; Also see Figure 5.7). Finally, OFF medication there was a narrow time window during which alpha coherence rose prior to movement (peak $t_{282} = 3.2$, $p < 0.05$). For reference, the lower panel in figure 5.9 gives the time series of the alpha band coherence between STN and the primary motor cortex (M1) source (as defined in Litvak et al. 2012). This makes it clear that alpha coherence changes are specific to the temporal cortex. Indeed no significant changes were found when STN-

M1 alpha band coherence was subjected to the same ANOVA as STN-temporal alpha band coherence.

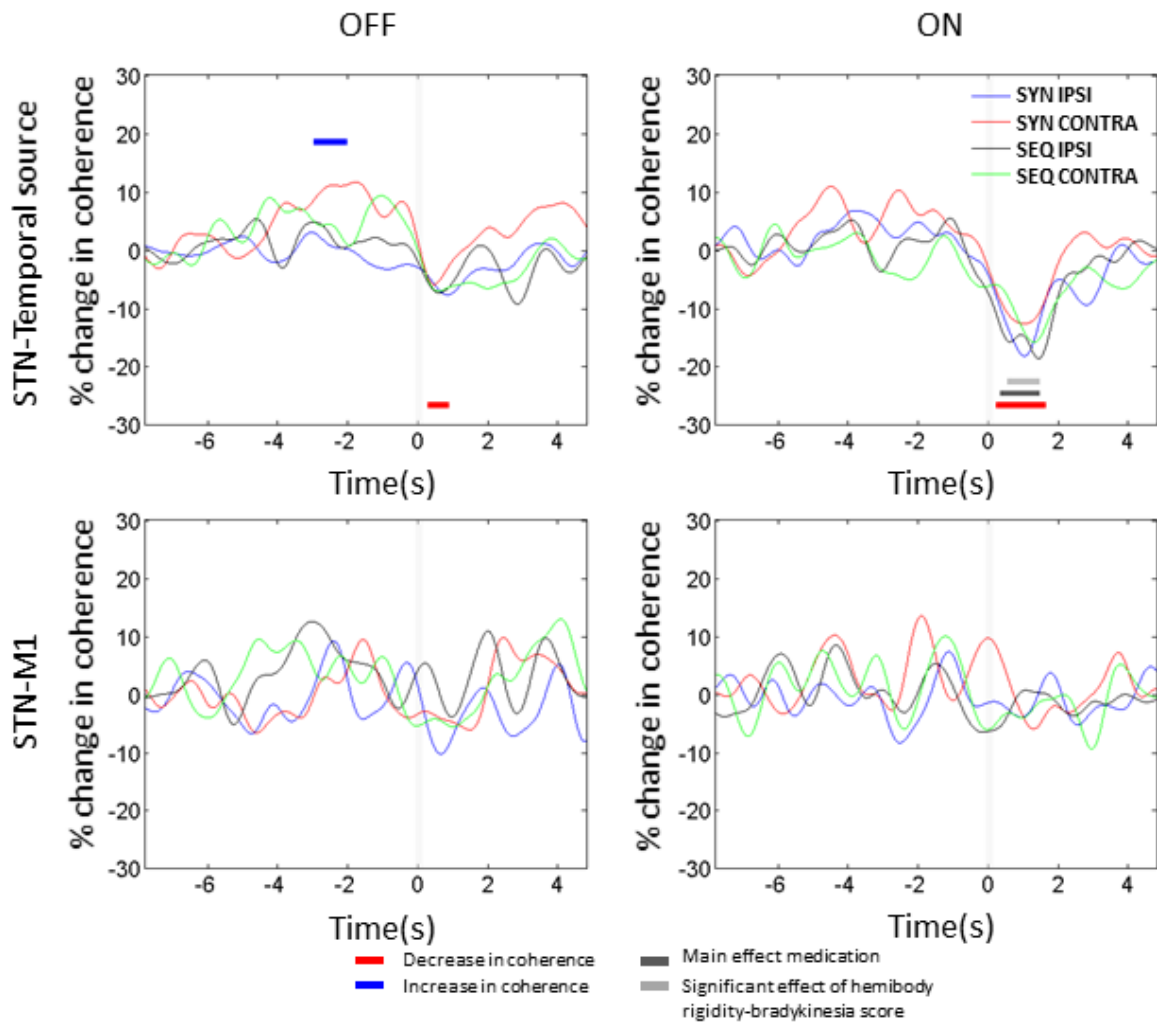


Figure 5.9 Time series of alpha band STN–cortical coherence.

Time series of alpha (7-13 Hz) cortical source-STN coherence averaged across subjects, separately for ON and OFF medication conditions. Changes are shown relative to the baseline from -8 to -5 s prior to movement for all conditions and subjects. Time series have been smoothed by a 500 ms FWHM Gaussian kernel. Upper panel pair: Temporal-STN coherence. Note that the significant main effect of medication, given by the dark grey line, was due to coherence being greater OFF than ON medication. Lower panel pair: M1-STN coherence, where there are no significant changes.

5.3.5 Correlation with Clinical Variables

To assess the possible clinical relevance of the spectral changes described above, I performed an ANCOVA, with the contralateral hemibody bradykinesia-rigidity scores as regressor. No significant correlations were found with either cortical source or STN alpha power. However, significant

clinical correlations with STN-cortical source alpha coherence were identified following the initial button press, whereby bigger movement related drops in alpha coherence with levodopa were associated with bigger improvements in clinical state with levodopa. These were within the time period for which there was a main effect of drug (Grey bar in Figure 5.9). To demonstrate that the correlations with cortical–STN alpha coherence were not driven by outliers I plotted the relations between these effects and clinical improvement for individual hemispheres (Figure 5.10). I also separately correlated hemi-body tremor scores with alpha power and coherence, but found no significant effects. Finally, I considered the question whether the STN-M1 gamma coherence and STN gamma power previously shown to correlate with the same clinical scores explain the same part of the variance as the STN-cortical alpha coherence. Accordingly, I included all three factors in a multiple regression model. Although the model was significant ($F_{(3,16)} = 3.68$, $p = 0.03$, $r^2 = 0.41$), none of the three factors made a significant independent contribution.

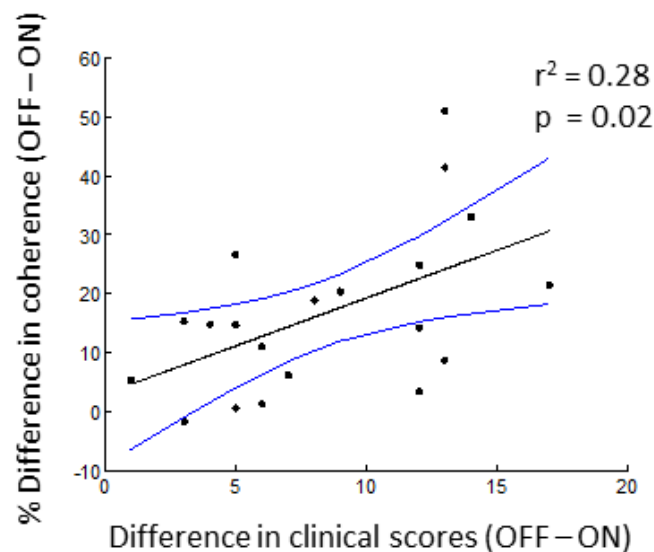


Figure 5.10 Correlation of alpha coherence change with clinical improvement.

Scatter plot of data for 20 hemispheres in 11 subjects (one with only unilateral electrode implantation and one with unilateral STN channel selection based on the selection criteria discussed in the Methods) with paired recordings ON and OFF medication. Difference in hemibody rigidity and bradykinesia scores ON and OFF medication have been plotted against the difference in alpha coherence ON and OFF medication in the interval from 0.5 – 1.45 s after movement onset (averaged across contact pairs, where more than one was coherent with temporal cortical activity). This was the interval over which there was a significant correlation with the hemibody rigidity and bradykinesia score. The r squared value and the corresponding p value of the linear regression ($F = 7.14$, $df = 1,18$) are displayed in addition to confidence intervals for the line of best fit, shown in blue.

5.3.6 Behavioural Data

In figure 5.11 I plot for all trials of all subjects the distributions of the button press timings after the first press (which occurred at time 0s) for the complex and simple tasks ON and OFF medication. The median timings are indicated by the yellow lines. There was a significant main effect of task type with the sequential task resulting in longer intervals between the first and all subsequent button presses ($F(1,13)= 7.8, p = 0.01$). Furthermore there was a significant main effect of medication ($F(1,13)= 5.3, p = 0.04$) and also a significant interaction between task type and medication ($F(1,13)= 4.9, p 0.04$) suggesting that the effect of dopamine on reducing timing intervals was greater in the sequential rather than the synchronous task.

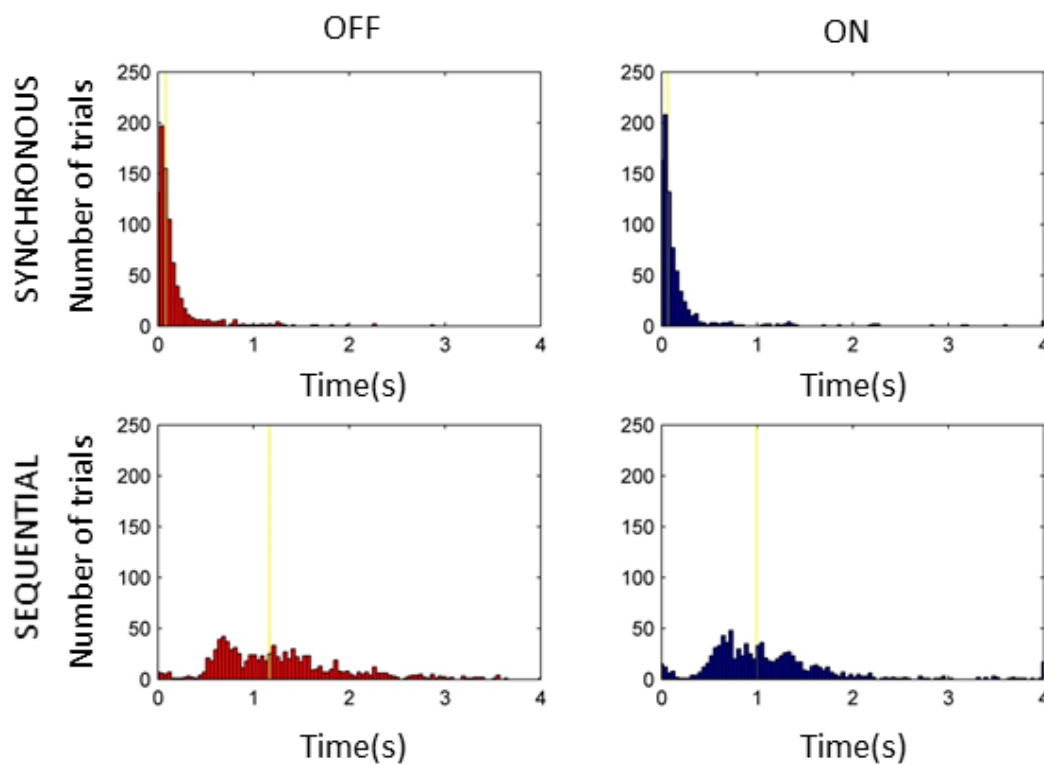


Figure 5.11 Histograms of reaction time data.

Histograms of all button press timings across all subjects, for the sequential and synchronous tasks ON and OFF medication. The initial button press was at 0s. The yellow lines indicate the median timings. The numbers of button presses shown for the four conditions are as follows: 1) synchronous ON – 792 2) synchronous OFF - 830 3) sequential ON – 917 4) sequential OFF – 934.

5.4 Discussion

Previous work using simultaneous MEG and LFP recordings highlighted the existence of a resting alpha band network between the STN and temporal cortical areas which was not modulated by dopaminergic state in patients with Parkinson's disease (Hirschmann et al., 2011; Litvak et al., 2011a). Here I show that the alpha frequency band coherence between temporal cortical areas and the STN is reduced following movement onset and that the degree of suppression in alpha coherence is significantly greater ON than OFF dopaminergic medication. In contrast, alpha power was suppressed up to two seconds before movement and this was unaffected by dopaminergic medication.

The present findings are in several ways the reciprocal of the gamma band coherence between STN and M1 reported in the same patients (Litvak et al., 2012). Alpha band STN-temporal cortex coherence was suppressed with movement, particularly after dopaminergic medication.

Conversely gamma band STN-M1 coherence was increased with movement, particularly after dopaminergic medication. Moreover, the two correlated with clinical state but with opposite polarity. These two correlations, however, were not independent, explaining the same portion of the variance in the change in clinical scores upon treatment. For both, correlations were limited to bradykinesia and rigidity in the contralateral limb. Furthermore, both alpha and gamma coherences were unaffected by the type of movement performed. In other words the increase in gamma and the decrease in alpha were little different in terms of size or duration between sequential or synchronous finger movements. The behavioural data in contrast displayed significant differences in the button press timings between the two movement types.

Furthermore, in keeping with dopamine induced improvements in clinical state, I found that the time intervals between the first and successive button presses were reduced in the ON medicated state. The above observations lead to the tentative suggestion that the two coupled systems are functionally reciprocally related (see Figure 5.12). In other words, around the time of movement our PD patients may have to disengage the STN from its locking to temporal cortex, which is

preferentially at alpha band frequencies, and engage STN locking to M1 in the gamma band.

Dopamine appears necessary for this task-related switch in coupling. Granger causality analysis suggests that coherence is predominantly driven by the temporal lobe in the alpha band (Litvak et al. 2011a) and by the STN in the gamma band (Litvak et al., 2012). The functionality of this relationship, as suggested by a lack of effect of task type, is likely to be modulatory to movement and related to arousal or attention rather than directly to motor processing.

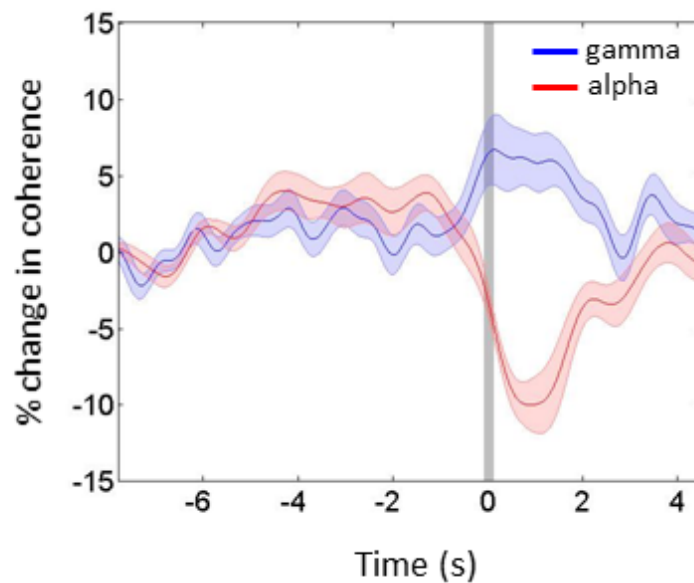


Figure 5.12 Reciprocal alpha and gamma band STN-cortical coherence changes during movement. Here I plot the time courses of coherence in: 1) the gamma band (shown in blue) between STN and beamformer identified primary motor cortex (M1), data taken from Litvak et al. 2012, and 2) the alpha band between STN and temporal cortex. The data are averaged across all subjects and conditions and smoothed with a 500ms FWHM Gaussian kernel. The shaded areas represent standard errors of the mean. Movement is associated with a reduction in alpha band STN-temporal coherence and an increase in STN-M1 gamma band coherence.

The above hypothesis, although speculative, is consistent with the effects of direct stimulation.

Stimulation of the STN at 10 Hz has been reported to increase bradykinesia (Timmermann et al., 2004), whereas stimulation of the STN and M1 at gamma band (60-90 Hz) frequencies facilitates movement (Joundi et al., 2012; Tsang et al., 2012). Treatment with levodopa, which facilitates the above switch in STN connectivity, also improves movement.

The task-related decrease in coupling with temporal cortex identified here is reminiscent of the task-related deactivation of the default mode attention network (Raichle and Snyder, 2007). The parallels are heightened by the association of the latter network with alpha band synchronization (Jann et al., 2009; Knyazev et al., 2011), and by evidence that its task-related deactivation is facilitated by dopamine (Nagano-Saito et al., 2009). These parallels serve to highlight the general role of dopamine in modulating large-scale, interregional networks and their interactions (Walters et al., 2000; Kelly et al., 2009; Gordon et al., 2011; Dang et al., 2012). Task related amplitude and frequency modulations in the beta band have also been demonstrated in the STN and shown to be influenced by dopaminergic state (Foffani et al., 2005).

An alternative explanation for the present findings is that alpha band coherence relates to the presence of rest tremor, to which it is harmonically related. Rest tremor most often disappears with voluntary movement, perhaps accounting for the task-related modulation of alpha coherence. However, coherence with temporal cortex was not a feature of the previously described alpha network coherent in Parkinsonian rest tremor (Timmermann et al., 2004; Pollok et al., 2009). Moreover few patients in this study and in that by Hirschmann et al (2011) had appreciable tremor. Finally, the correlation between treatment-related changes in alpha coherence and corresponding changes in clinical state was limited to bradykinesia-rigidity and not tremor.

Importantly, I found no significant effect of the selected contact pair for power or coherence spectra. Consequently I found no evidence to suggest that the movement related coherence changes observed are limited to a particular region of the STN.

Note that I have been cautious in ascribing function to precise anatomical regions. As previously discussed, there is good evidence that the LFP and MEG cannot be contaminated by one another, but whether the alpha activity in the STN LFP originates within the STN or from a broader brainstem region is unclear (Hirschmann et al., 2011; Litvak et al., 2011a). In the case of MEG, I

have confined ourselves to discussion of cortical regions rather than precise cortical areas, given the spatial noise introduced by metal artefacts and head movements in our patients.

I should also point out that in the present analysis I have found no evidence for the possibility of STN-cortical networks that are quiescent at rest, and become active during movement. Another feature deserving comment is the relationship between the alpha band network in the resting state and the resting beta band coherence between the STN and frontal motor areas. The latter may also show suppression with movement (Cassidy et al., 2002; Lalo et al., 2008), as well as during imagination of movement (Kuhn et al., 2006) and during action observation (Alegre et al., 2010). Although I was unable to confirm a significant suppression of beta band coherence upon movement in the current patient group (Litvak et al., 2012), I did see a negative correlation between levodopa effects on coherence in this band and corresponding changes in bradykinesia and rigidity. Thus the beta band coherence between the STN and frontal motor areas and the alpha band coherence between STN and temporal cortex may both represent networks that have to be disengaged during effective movement. Why there should be two such systems is a question for future work.

It is important to highlight that the processes underpinned by alpha band coherence and local regional alpha band power may be functionally distinct. This is underscored by the different temporal patterns of modulation upon self-paced movement. Thus, although alpha band coherence dropped after the onset of movement, alpha band power local to the STN and temporal cortical source was suppressed up to two seconds before movement onset.

Furthermore, there was no main effect of medication on alpha power, but there was on STN-temporal cortex coherence. Indeed, rather than the greater movement-related drop in coherence seen with levodopa, alpha power in the cortical source contralateral to movement showed greater decreases OFF levodopa. The functional relationships of alpha power at the temporal and subthalamic levels remains unclear, although cortical activity in this frequency band has

previously been related to visuospatial attentional processing, with power typically reducing in anticipation of an upcoming action (Foxe et al., 1998; Thut et al., 2006; Gould et al., 2011; Rohenkohl and Nobre, 2011).

In summary, I have demonstrated a STN-temporal cortex alpha band network that is maximally active at rest and is disengaged with movement. Impaired disengagement of this network with movement may be a significant feature of the hypodopaminergic state in PD and appears to be ameliorated by dopaminergic therapy.

Chapter 6: Optimising beamformer region of interest analysis.

6.1 Introduction

Beamforming is an adaptive spatial filter based method of estimating electrical activity in the human brain based on signals from an M/EEG sensor array. Typically per-location summary statistics of electrical change are used to provide three-dimensional images of brain function. The spatial filter corresponding to a particular brain region is determined based on knowledge of the lead field matrix and from an estimate of the data covariance matrix (Van Veen et al., 1997; Gross et al., 2001; Hillebrand et al., 2005; Brookes et al., 2008). Precise estimation of both the lead fields and the data covariance is therefore essential for accurate beamformer solutions.

This chapter focuses on the accuracy of covariance matrix estimation which, perhaps counterintuitively, is inversely proportional to the number of channels (Brookes et al., 2008). The logic being that one needs more data to make an accurate estimate of the covariance between more channels. In fact it can be shown that doubling the number of M/EEG sensors necessitates that the number of data samples (alternatively the time-bandwidth product) is increased four-fold in order to maintain the same covariance matrix estimation error (see Brookes et al., 2008 for further details). This can become a problem when one is interested in relatively short duration or narrow band phenomena (for example the 0.5-1 s beta rebound, see Pfurtscheller et al., 1999). In this chapter I consider the case in which we do not require whole-brain coverage from the MEG system, but rather have a specific region of interest in mind. This allows us to decrease the effective number of channels and so allows us to make either more accurate estimates or estimates of the same accuracy but with less data.

A well tested channel reduction approach involves projection to a sub-space designed to optimally represent sources within a region of interest (ROI) (see Taulu et al., 2004; Ozkurt et al., 2006; Rodríguez-Rivera et al., 2006 for an overview). Often the ROI may be selected *a priori* based on the experimenter's prior knowledge about areas of task related activity. For example, in

Rodríguez-Rivera et al., 2006, the projection is based on the eigenvectors of the source leadfields within an anatomical ROI, and the number of orthogonal components for the projection must be specified by the user. Importantly, this approach for channel reduction incorporates information from all channels and has been shown to produce more precise source estimates than approaches, involving sub-selecting channels based on either power or location (see Rodríguez-Rivera et al., 2006 for more details).

Given a reduced set of sensors (or linear sensor combinations) there remains however the question of whether there is sufficient data to make a reliable covariance matrix estimate. Recent work has shown how using Bayesian PCA one can make an estimate of the latent dimensionality (effective useful number of channels) (Woolrich et al., 2011). Projecting the data into this space and hence ending up with a reduced covariance matrix based on fewer channels is equivalent to optimally regularizing (or diagonally loading) the full covariance matrix.

In this chapter I propose a two-step procedure that unifies the approaches described above. Firstly, an ROI projection is used to reduce the effective number of channel components a-priori. This step is only based on the forward model. Secondly, Bayesian PCA is applied to further refine the dimensionality estimate based on covariance of the ROI-projected data. As both steps have the effect of reducing the effective number of channels the covariance estimate becomes more robust for the same amount of data.

I proceed by outlining and demonstrating the use of ROI projection and bPCA separately. And then go on to show how the combination of these steps improves the accuracy and resolution of beamforming estimates.

6.2 Methods

6.2.1 Spatial dimensionality reduction (ROI projection)

Details of this method can be found in Rodríguez-Rivera et al., 2006. In what follows however I will provide a brief overview of the general principles.

I formulate sensor level MEG activity, x , measured at N channels and T time points as follows:

$$6.1) \quad x = \sum_{l=1}^L H(\theta_l) m(\theta_l) + q$$

$H(\theta_l)$ is an $N \times 3$ lead field matrix representing the scaling of the projection of a unit amplitude dipole at location θ_l , to N channels, in the x , y and z directions respectively. Additionally $m(\theta_l)$ represents a $3 \times T$ matrix of time courses in the x , y and z directions (in this chapter I will use the MNI coordinate system) for a dipole located at θ_l , where $l = 1 \dots L$. Activity is summed over all sources before adding isotropic gaussian white noise, q to the sensors.

The goal is to find a transformation, U_r that minimises the error between the representation of the activity of sources, selected from a ROI, in the original data and in the projected data.

Assuming that U_r is an $N \times M$ matrix with orthonormal columns, where $M < N$, the projected data takes the form.

$$6.2) \quad x_r = U_r^t x$$

The $N \times T$ matrix x has been transformed to an $M \times T$ matrix, x_r corresponding to a reduction in the number of channels from N to M . Rodriguez-Rivera et al., 2006 show that U_r can be computed from the singular value decomposition of the following symmetric matrix:

$$6.3) \quad U S U^t = \sum_{r=1}^R H(\theta_r) H(\theta_r)^t$$

Accordingly, U_r is set to the M columns of U corresponding to the M largest eigenvalues of B (the eigenvalues may be determined from the diagonal of S). This last formulation simply reduces to the approach for dimensionality reduction used in Friston et al., 2008 (in which case the ROI was defined by the space of lead fields on the cortical surface). In addition to dimensionality reduction of the data, a new leadfield set is computed for each brain location θ_l (see equation 6.10). The above formulation can be applied when no prior information is available about the

dipole moment, or when the dipole moment is known a priori e.g. in the case of surface constrained orientations. As an example of this if I consider a source with known orientation along the x-axis, the projection matrix U_r would be computed only from the first column of $H(\theta_r)$.

An important issue with this approach is selecting the dimensionality M . This dimensionality determines the trade-off between the accuracy of the representation of the ROI and the spatial resolution of the resulting projection. In other words, increasing M leads to a more accurate representation of sources in the ROI, but this comes at the cost of also representing sources outside the ROI. Further insights into this trade off can be gained by considering the mean squared error of the linear transformation, which is represented as the sum of the $N-M$ smallest eigenvalues (given by the diagonal elements in S in equation 6.3), normalised by the sum of all eigenvalues.

$$6.4) \quad e(M)^2 = \frac{\sum_{i=M}^N \lambda_i}{\sum_{i=1}^N \lambda_i}$$

Lower values of this error are obtained by minimising the difference between N and M and are associated with more accurate representations of sources in the ROI. A local measure of the ability of the transformation, U_r to represent sources is gained by considering the ratio of the projected source and the original source energies at each spatial location, which mathematically corresponds to the following.

$$6.5) \quad F_M(\theta_l) = \frac{\text{tr}(U_r^t H(\theta_l) H(\theta_l)^t U_r)}{\text{tr}(H(\theta_l) H(\theta_l)^t)}$$

An ideal value for $F_M(\theta_l)$ is 1 for sources within the ROI and 0 for sources outside the ROI. From this it is evident that increasing M will increase the values of the numerator term for sources within and also outside the ROI (see Figure 6.1). Additionally it is also evident that this term will depend on both the size of the ROI and on the sampling resolution of the leadfields within the ROI.

6.2.2 Bayesian PCA (bPCA)

The underlying principle of bayesian PCA is to estimate the true dimensionality of the data based on a generative model and appropriately selected priors. Within the context of beamforming, this estimated dimensionality is then used to act as a surrogate for finding the optimal amount of regularisation required to estimate the data covariance matrix. Expressed more formally, the generative model for bPCA is as follows:

$$6.6) \quad x = Gv + q$$

Here the temporally demeaned data with dimensions $N \times T$ (see equation 6.2) is represented by x . G is of dimensions $N \times P$, where P corresponds to the principal component sensor maps. Finally, v is a $P \times T$ matrix of Gaussian latent (or hidden) variables which when multiplied by the principal component sensor maps with additive zero mean isotropic white noise, $q \sim N(0, \sigma^2 I)$, result in the projected data. Woolrich et al, 2011 use a Variational Bayes (VB) approach (Bishop, 1999) based on Automatic Relevance Determination (ARD) hyperparameter thresholding in order to estimate the optimal number of components P , and hence the dimensionality of the data. An alternative approach based on Bayesian Model Selection (BMS) (Minka, 2008) has been shown to be both more accurate and also more computationally efficient, by virtue of avoiding an iterative VB updating routine. This is the approach I use in the present analysis.

The BMS approach involves computing the evidence for differing latent dimensionality models (or values of P from equation 6.6) of the data. The model with the greatest evidence is then used to infer the true data dimensionality. In essence, a Gaussian likelihood function of the data given the PCA parameters is defined. Combining this likelihood with the required priors gives a complex integral for the model evidence that is efficiently and accurately approximated, using either Laplace's method or the Bayesian Information Criterion (BIC). In practice, the Laplace approximation tends to be more accurate and is for that reason used in the present chapter. A detailed mathematical description and derivation of the BMS method can be found in Minka,

2008, and a MATLAB implementation of the code is provided in the SPM12 distribution (see `spm_pca_order.m`).

In practice an SVD of the channel data x (or ROI projected data, see equation 6.12) is performed yielding:

$$6.7) \quad U_x S_x V_x^t = x$$

The bPCA approach selects the number of columns, P of U_x , which are subsequently used to project the data to a lower dimensional subspace. Letting U_p now represent the first P columns of U_x the final projected data is represented by x_p and has dimensionality $P \times T$.

$$6.8) \quad x_p = U_p^t x$$

6.2.3 Beamforming with combined ROI projection and bPCA

In this chapter, depending on the approach used, the data for beamforming x_b and leadfields for each brain location $H_b(\theta_l)$ take different forms and accordingly have different dimensions.

In the case of beamforming data without bPCA and the ROI projection:

$$6.9) \quad x_b = x \text{ and } H_b(\theta_l) = H(\theta_l)$$

Here x_b is an $N \times T$ matrix whilst $H_b(\theta_l)$ has dimensions $N \times 3$. Similarly, in the case of just performing an ROI projection without bPCA, the data and leadfields take the following form where x_b and $H_b(\theta_l)$ have dimensions $M \times T$ and $M \times 3$ respectively ($M < N$, compare with equation 6.2):

$$6.10) \quad x_b = x_r = U_r^t x \text{ and } H_b(\theta_l) = U_r^t H(\theta_l)$$

When bPCA alone is performed the dimensions of x_b and $H_b(\theta_l)$ are $P \times T$ and $P \times 3$:

$$6.11) \quad x_b = x_p = U_p^t x \text{ and } H_b(\theta_l) = U_p^t H(\theta_l)$$

Finally, when the ROI projection is performed prior to bPCA, assuming that U_p is now calculated for x_r rather than x as per equation 6.7:

$$6.12) \quad x_b = U_p^t U_r^t x \text{ and } H_b(\theta_l) = U_p^t U_r^t H(\theta_l)$$

Here the dimensions of x_b and $H_b(\theta_l)$ are $L \times T$ and $L \times 3$, where L is less than M , N and P .

Linearly Constrained Minimal Variance (LCMV) beamforming (Van Veen et al., 1997) is a commonly used method of source estimation where the goal is to define a spatial filter, $W(\theta_l)$ that when applied to the data, x_b gives an estimate of the source time course, $\hat{m}(\theta_l)$ (in the x, y and z directions) at a particular spatial location θ_l :

$$6.13) \quad \hat{m}(\theta_l) = W(\theta_l) x_b$$

$W(\theta_l)$ depends only on the data covariance matrix, C and the leadfield as follows:

$$6.14) \quad W(\theta_l) = (H_b^t(\theta_l) C^{-1} H_b(\theta_l))^{-1} H_b^t(\theta_l) C^{-1}$$

Where $C = \frac{1}{T-1} \sum_{t=1}^T (x_b(t) - \bar{x}_b)(x_b(t) - \bar{x}_b)^t$

In this chapter the covariance matrix C is estimated without additional regularisation.

6.2.4 Validation with Simulations

Leadfields were computed for a 275 channel MEG system (CTF/VSM MedTech) using a single shell head model (Nolte et al., 2004), based on an inner skull mesh derived by inverse normalising a canonical mesh to a single subject's MRI scan (Mattout et al., 2007).

6.2.5 Simulation 1

The aim of this simulation was to illustrate the complementary dimension reduction performance of ROI projection and the bPCA algorithm. I generated simulated data for 2 source

configurations: 1) a 3 source simulation, with sources located at 10mm spaced intervals (MNI co-ordinates 40 -30 50, 40 -20 50, and 40 -10 50 respectively) and 2) a 27 source simulation with sources located at 10mm spaced intervals on a cubic grid, centred on MNI co-ordinates 40 -20 50. In each case, the orientations of the sources were selected randomly and each source had a Gaussian white noise time course. To maintain generality I did not explicitly fix the dipole moment to exist in the tangential plane and so these analyses should be regarded as conservative, with effective source moment less than or equal to that specified.

Ten seconds of MEG data were generated in total. Gaussian white noise was added to the simulated data such that the ratio of the RMS (root mean squared) amplitude of the signal to that of the noise was 5. Following the generation of simulated data a region of interest projection was performed, with the region of interest comprising all simulated sources. Crucially, I varied the number of components taken from the ROI, and applied a secondary bPCA step in order to determine the dimensionality of the resulting projected data (see Figure 6.2 and methods).

6.2.6 Simulation 2

The aim of this simulation was to compare source localisation metrics in a realistic setting for three approaches of dimensionality reduction: 1) bPCA 2) the ROI projection and 3) a combination of the bPCA and the ROI projection. Background brain activity was represented by 75 randomly oriented sources, with independent Gaussian white noise time courses positioned on a 30mm spaced grid within the brain as shown in red, in Figure 6.3. An additional source with a sinusoidal 20 Hz time course (the source of interest), shown in blue in Figure 6.3 was positioned at the right primary motor cortex (M1, MNI co-ordinates 40 -20 50), to mimic motor cortical activity that might occur naturally during a movement task. This source was oriented along the tangential y direction (in MNI space). Gaussian white noise was added to the sensor signals such that the channel level signal-to-noise ratio (which I denote cSNR) - defined as the ratio of RMS

amplitude of the signal originating within the brain to the RMS amplitude of the noise at MEG channels - was 5.

Ten trials of data of varying lengths were simulated, whilst also altering the ratio of the RMS amplitudes of the source of interest and the noisy sources. This allowed us to explore the effects of altering the source level signal-to-noise ratio (which I denote sSNR, in order to avoid confusion with cSNR) and also the time window for covariance matrix estimation. In order to make the simulation as realistic as possible, two experimental conditions were simulated, with half the trials belonging to each condition. The noisy brain sources were continuously active in both conditions, but the source of interest was active only in one of the conditions and it was inactive in the other. The conditions were thus labelled source 'on' and 'off' respectively, allowing us to also generate a t-statistic of the contrast between the two conditions. Ten realisations of simulated data were computed in order to determine standard errors.

Following the generation of simulated data, the data dimensionality was reduced using one of the three approaches described above. The ROI was a 1cm^3 cubic region surrounding the M1 source with 5mm spatial sampling, yielding 27 leadfields. No additional regularisation was applied to the resulting data covariance matrices. LCMV beamforming was then used to reconstruct source power in the 10-40 Hz band for each trial of the two experimental conditions on a 5mm grid in MNI space, bounded by the inner skull surface. For each grid point a two-sample t-test was then performed, contrasting the source 'on' and source 'off' conditions in order to yield a single t statistic. I compared the absolute value, localisation error in mm and spatial extent or FWHM (full width at half maximum) of the peak, closest to the source of interest, in the volumetric t statistic image between the different reduction methods. In order to ensure accurate localisation of the peak beamformer estimates were also made on a finer 1mm grid extending 5mm around the ideal peak location. . The FWHM was used as a measure of spatial resolution. It was calculated by fitting a Gaussian to the t-statistic profile computed at 1mm intervals away from the peak along

the y axis, and setting $FWHM = 2\sqrt{\ln 2}\sigma_{FWHM}$, where σ_{FWHM} represents the standard deviation of the fit Gaussian. Finally, source timeseries were extracted at the location of the peak t statistic for the trials belonging to the source 'on' condition. The coefficient of determination (R^2) was then computed between the simulated source of interest timeseries and the mean reconstructed timeseries across trials. I also computed the ratio of the mean RMS amplitude of the reconstructed source across trials to that of the simulated source. This provides insight into the degree with which simulated source power is recovered with the different methods.

Finally, I performed an additional simulation in order to gain additional insight into the spatial specificity of the three different approaches for the set up described above. The ROI was shifted in 5mm intervals along a line in the x direction in MNI space towards the opposite hemisphere. The size of the ROI was 1cm^3 from which 27 lead field components were taken. I looked at the value of the peak t-statistic within each shifted ROI for three different conditions: 1) The ROI projection alone, 2) The ROI projection in addition to bPCA and 3) bPCA alone (in this case I was looking at different sections of a single beamformer image). As I expected the ROI techniques to excel for small amounts of data I explored two different trial lengths of 700 ms and 7000 ms whilst keeping the sSNR fixed at 0.

6.2.7 Assessment of method on real data from a single patient with externalised DBS electrode

I demonstrate the application of dimensionality reduction methods on 180 seconds of resting data, epoched into 3 second long trials, collected from a Parkinsonian patient with bilateral therapeutic Deep Brain Stimulation (DBS) electrodes in the subthalamic nucleus (STN). The electrodes were externalised in the days following initial insertion facilitating simultaneous resting MEG and local field potential (LFP) recordings from the STN.

As was previously shown (Litvak et al., 2010) the percutaneous ferromagnetic wires implanted under the patient's skin produce high-amplitude artefacts in the MEG signal. The topographies

associated with these artefacts occupy the leading eigenvectors of the data. Consequently, application of the bPCA algorithm is unlikely to offer immunity to the large artefacts encountered.

I show that projecting the data to a subspace spanned by the leadfields of an ROI prior to using bPCA provides better artefact suppression and hence greater statistical sensitivity.

I compared t images of beta band (15-30 Hz) coherence between the STN and whole brain for bPCA and the ROI projection followed by bPCA. Based on prior knowledge about increased beta band coupling between STN and Primary Motor Cortex in Parkinson's disease (Hirschmann et al., 2011; Litvak et al., 2011a) the ROI was chosen to be an 8cm^3 cubic volume centred on the left primary motor cortex (M1). I used a slightly larger ROI in the case of patient analysis in order to account for uncertainties in the location of M1 due to head movements. Head movements may be more pronounced in Parkinsonian patients relative to healthy controls due to tremor or dystonia. I found that maximal head displacement was 1.64 cm and thus increased the edges of the cubic ROI from 1 to 2 cm. Leadfields were sampled at 10mm intervals within the cubic ROI in order to construct the projection and 27 components were selected. In keeping with previous studies I used the Dynamic Imaging of Coherent Sources (DICS, Gross et al. 2001) beamforming approach to determine cortical sources coherent with a single bipolar left sided STN contact in the beta frequency band. This approach allowed us to generate volumetric images showing coherence between the STN and cortical regions. Although in previous studies I performed group level analysis of coherence images, in the present analysis I wished to determine the statistical significance of a single subject's resting STN-cortical coherence. I consequently generated 10 DICS images by randomly selecting trials of the epoched data with replacement (bootstrapped images) and a further 10 DICS images (bootstrapped and shuffled images) where the coherence was computed after shuffling the STN data with respect to the channels. The shuffling served to destroy any physiological patterns of coherence, whilst any coherence induced by artefacts would be similar in the shuffled and bootstrapped images. A two-sample t test was subsequently performed in order to determine the spatial locations at which coherence in the bootstrapped

images exceeded that in the shuffled images. This approach is similar to previously employed bootstrap approaches for single subject analysis in electrophysiology (Maris, 2012). Statistical analysis were performed in SPM12, and all reported findings are significant with family wise error correction at the peak level ($p < 0.05$).

6.3 Results

6.3.1 Spatial Dimensionality reduction

Figure 6.1 displays features of the ROI projection method for a 1cm^3 cubic ROI centred at MNI coordinates 40 -20 50 mm. Specifically I highlight here the trade-off between the error of the representation of sources in the ROI and spatial selectivity of the ROI – as a function of the number of principal components taken from the ROI. The mean squared error of the ROI shown in upper panel of Figure 6.1 was calculated as per equation 6.4, whilst the spatial filtering properties of the ROI were calculated as per equation 6.5 for grid points spaced at 5mm intervals within the brain. This figure replicates the results shown in Rodriguez-Rivera et al., 2006. Note that as the number of components increases, the squared error of the representation of all sources in the ROI decreases, but the effective size of the ROI grows.

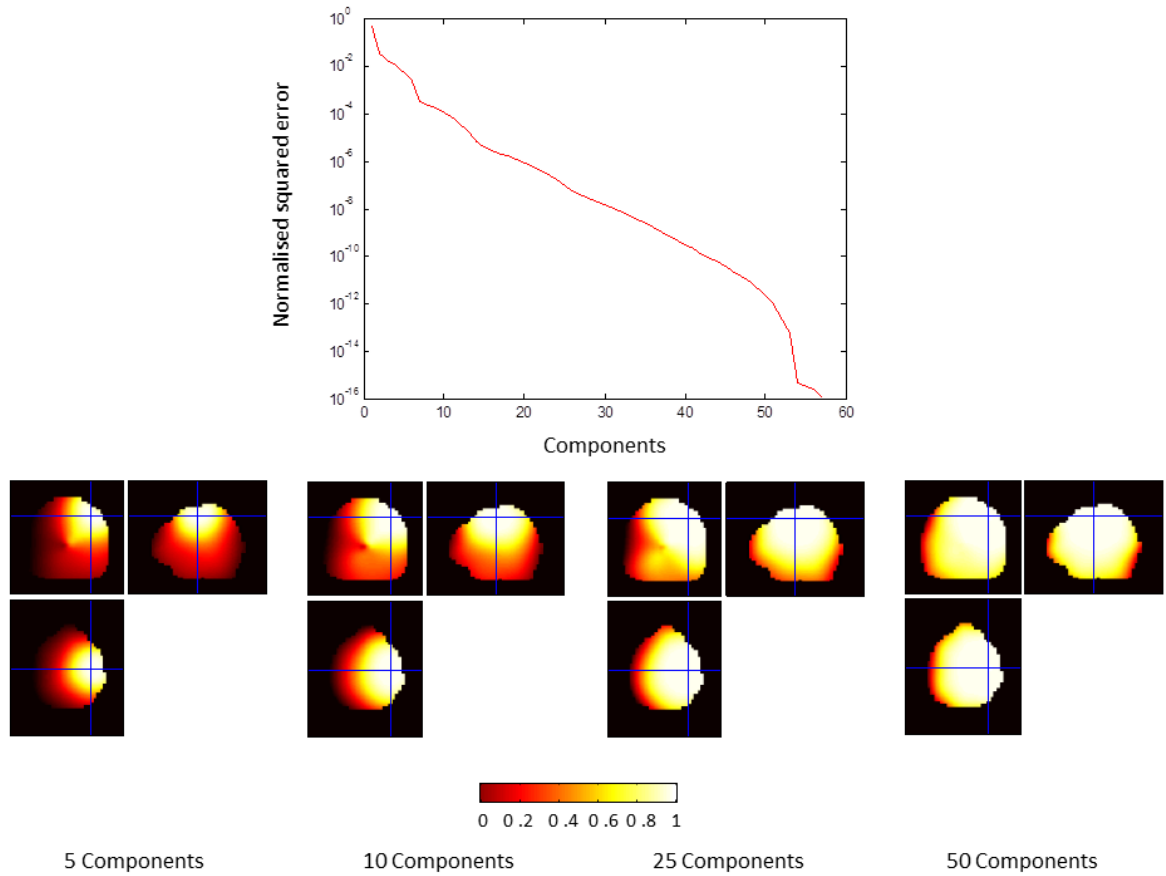


Figure 6.1 The Region of Interest projection approach.

Features of the Region of Interest (ROI) projection method are displayed for a 1cm^3 cubic ROI centred at MNI co-ordinates 40 -20 50 mm (the intersection of the cross-hairs). Source leadfields were computed at 5mm intervals along the faces of the cubic ROI, giving a total of 27 leadfields from the ROI. The top panel displays how the normalised squared error varies with the number of principal components selected from the ROI (see Equation 6.5 and also methods). In the bottom panel of the figure, filtering functions, F_M representing the relative source energies in the projected and original data are computed for each 5mm spaced grid point bounded by inner skull surface. The resulting data were linearly interpolated to create 2mm resolution images (see methods). The colourbar indicates the value of the filtering function, which is expressed as a ratio and therefore has no units. Filtering functions are displayed for different numbers of components selected from the ROI. It is evident that a trade-off exists between accuracy of the representation of the ROI and the spatial resolution of the resulting projection.

6.3.2 Simulation 1

The results of simulation 1 are shown in Figure 6.2. It is important to note in this case that the ROI comprised all active brain sources – either 3 sources or 27 in this case. In both cases, as per the findings of Woolrich et al., 2011, bPCA selects a dimensionality equivalent to the number of sources. Consequently if the number of components selected from the ROI projection is equal to the number of brain sources the resulting projection of the data is equivalent to the projection

yielded by the bPCA approach. Here I specifically wanted to ask whether the addition of bPCA to the ROI projection algorithm would allow us to recover the true dimensionality of the data in the case that more components were selected from the ROI than the number of active brain sources. Figure 6.2 shows that for both the 3 and 27 source simulations (shown by the red circles and blue squares) that the combination of the ROI projection and the bPCA method accurately recovers the true data dimensionality. For example, in the 3 source simulation, taking 3 or more components from the ROI projection and then applying bPCA consistently yields a dimensionality of between 3 and 4. Similarly in the 27 source simulation, taking more than 27 components from the ROI and then applying bPCA consistently yields a dimensionality of between 27 and 28. In both cases, the errors are well within the accuracy of the bPCA algorithm I used (Minka, 2008 for further details). Note in these figures I have also established the behaviour of applying bPCA to the ROI projection when fewer components are taken from the ROI than the number of active brain sources. In this case, applying bPCA does not produce any additional decrement in the estimated dimensionality.

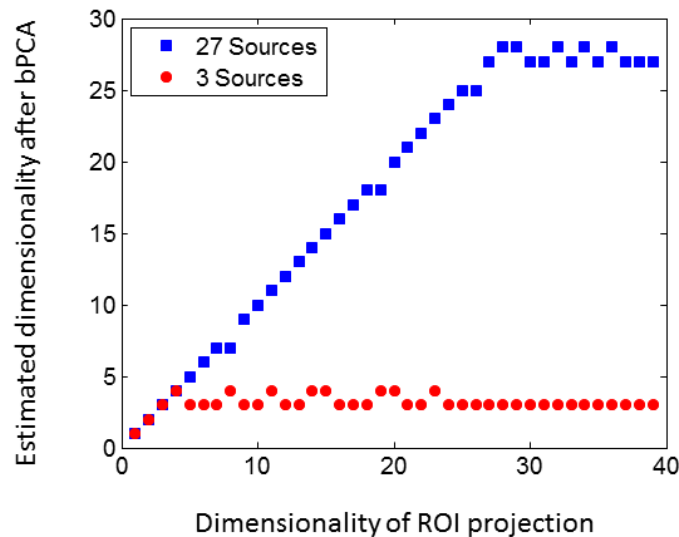


Figure 6.2 The results of simulation 1.

3 and 27 sources were simulated as described in the methods and differing numbers of components were taken for the ROI projection (shown on the x axis) where the ROI comprised all sources. The dimensionality of the resulting projected data was consequently equal to the number of selected components. The y-axis highlights the dimensionality subsequently estimated after performing bPCA. The results for the 3 and 27 source simulations are shown by the red circles and blue squares respectively. Importantly, the use of bPCA following the ROI projection, results in accurate estimation of the number of sources in a ROI.

6.3.3 Simulation 2

I have demonstrated in simulation 1 that the combination of the ROI projection and bPCA can accurately recover the dimensionality of an ROI. The goal of simulation 2 was to compare bPCA with the ROI projection for a realistic scenario and to determine whether the use of the ROI projection prior to bPCA could prove beneficial in terms of suppressing brain activity outside of the ROI.

Figure 6.3 illustrates the position of noisy brain sources (shown in red) and a source of interest (shown in blue) that a 1 cm³ ROI was constructed around. Figure 6.4 shows how source localisation measures specifically for the source of interest vary for bPCA, the ROI projection and the ROI projection plus bPCA as a function of the SNR of the source of interest compared to the noisy brain sources. In all cases a fixed trial length of 1000 ms was used. In addition to showing the improvement in source estimation with increasing SNR for all three approaches, this figure highlights that across a range of SNRs (and particularly at low SNRs) the ROI projection performs better than bPCA (as bPCA has no prior information on the source of interest). More specifically, peak t values are increased and their full width half maxima are reduced. Furthermore, the absolute error in source localisation is reduced and the R² correlation coefficient between the simulated and reconstructed source of interest time course is increased. The increase in the R² is most notable at low SNR levels. The estimation of the true source amplitude is also improved.

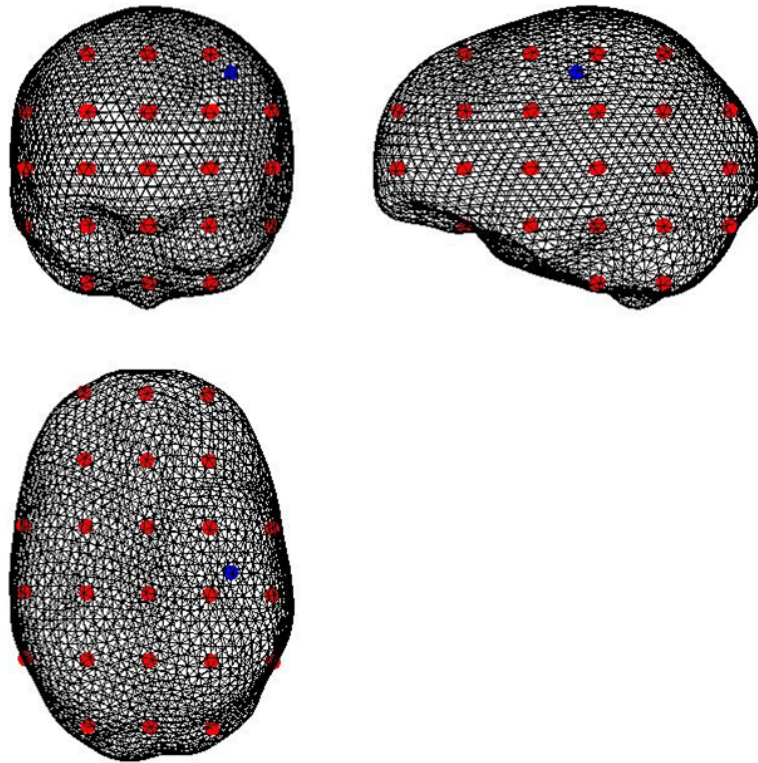


Figure 6.3 Simulation 2.

Here we display an illustration of the set-up of the second simulation. As per the first simulation a 20 Hz sinusoidal source shown in red, was simulated at MNI co-ordinates 40 -20 50. 75 additional noisy sources shown in blue with Gaussian white noise time courses were positioned on 30mm spaced grid points within the brain (see methods for further details). Coronal, sagittal and axial sections through the image are shown. Comparisons of the three reconstruction methods for this simulation are shown in subsequent figures.

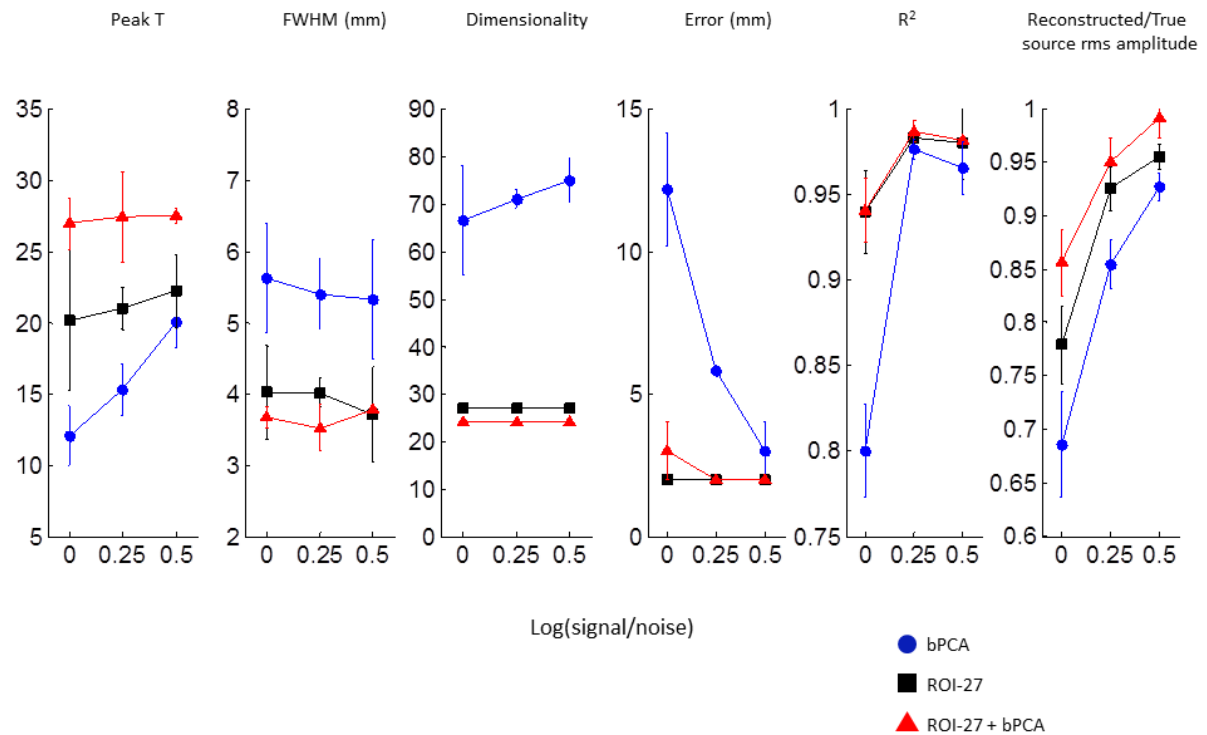


Figure 6.4 The results of simulation 2.

Bayesian PCA (bPCA) is compared with an ROI projection with 27 components (ROI-27) and combination of the two approaches (ROI-27+bPCA) for the set up described in the methods and shown in Figure 6.3. The three approaches are compared for different SNRs of the source of interest in terms of: 1) The peak t value closest to the source of interest 2) The associated FWHM 3) The R^2 correlation coefficient between the simulated and reconstructed source of interest timeseries for the 'on' condition 4) The source localisation error and 5) The ratio of the reconstructed to the simulated rms amplitude of the source of interest for the 'on' condition. The final data dimensionality is also displayed for each approach. The error bars represent standard errors for the 10 realisations of simulated data.

Interestingly, combining the ROI projection with bPCA produces some improvements over the ROI method alone – namely a greater peak t statistic, improved estimation of source amplitude and a reduction in the FWHM. The absolute localisation error and the R^2 correlation coefficient were not markedly improved by the addition of bPCA to the ROI approach. The estimate of data dimensionality from the three algorithms is also shown in the figure for comparison. As per Woolrich et al., 2011 bPCA adapts the estimated data dimensionality for a given sSNR and time window for covariance matrix estimation. The dimensionality estimate for both the ROI

projection and the ROI projection plus bPCA approaches is however more stable across the range of trial lengths and sSNR levels.

I next explored the effect of altering the time window for covariance matrix estimation. The results for a fixed log sSNR of 0 (equal amplitude of signal and noise sources) are shown in Figure 6.5. Ten trials of varying lengths were simulated as described in the methods. Once again we see that the ROI projection produces benefits over bPCA in terms of source localisation metrics across a range of trial lengths. This finding is in keeping with the concept that reducing the data dimensionality in order to represent an ROI reduces the number of samples of data required to accurately estimate the covariance matrix for beamforming. Furthermore, as before adding bPCA to the ROI projection produced improvements in the peak t statistic, source amplitude estimates, and the FWHM relative to the ROI projection alone. Additionally the R^2 correlation coefficient was also improved by combining the ROI projection with bPCA at moderate trial lengths.

These data highlight that significant improvements in source estimation can be produced by dimensionality reduction designed to optimally represent sources in an ROI. In figure 6.6, example t images of the three reconstruction approaches for a trial length of 1000 ms and a log SNR of 0 superimposed on a canonical T1-weighted MRI are displayed. This figure displays a spherical volume of 30mm radius surrounding the source of interest and again shows that enhanced and more focal t statistics can be produced by the ROI projection and its combination with bPCA.

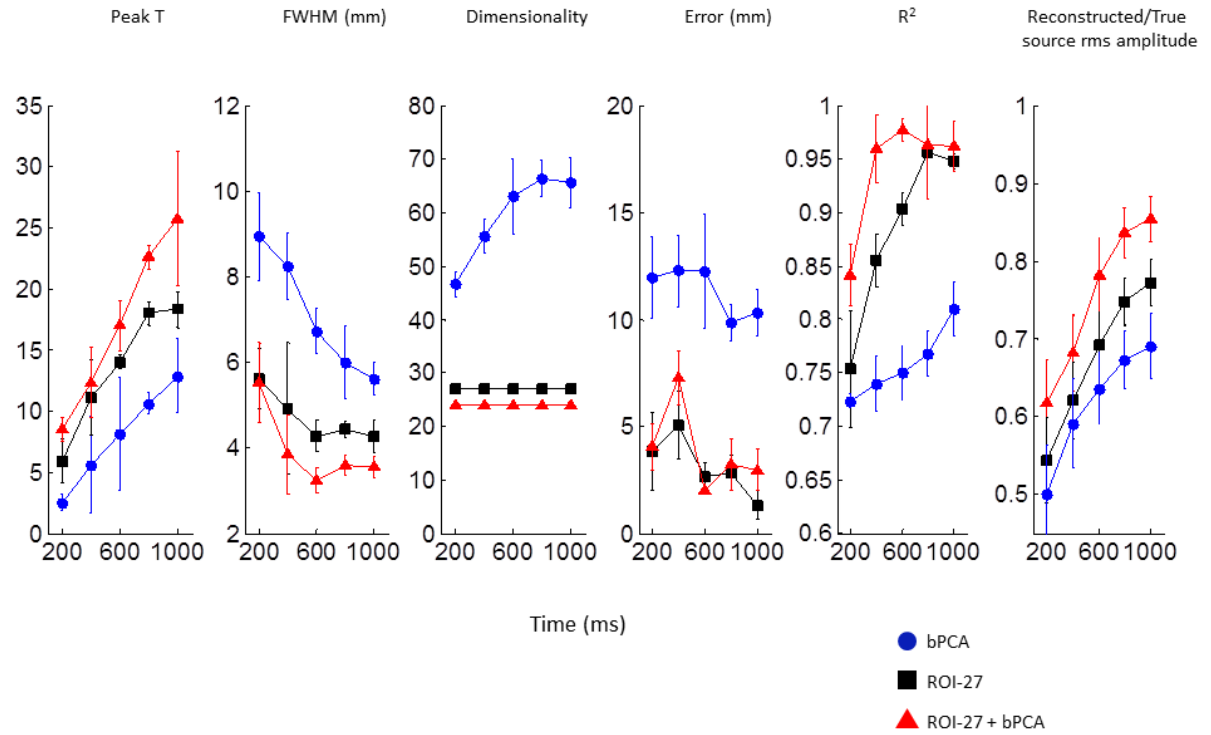


Figure 6.5 Results of simulation 2.

Bayesian PCA (bPCA) is compared with a ROI projection with 27 components (ROI-27) and combination of the two approaches (ROI-27+bPCA) for the set up described in the methods and shown in Figure 6.3. This time however, the trial length for covariance matrix estimation is varied for a fixed SNR level of 0. As per figure 6.4, the three source localisation approaches are compared in terms of the peak t statistic, the FWHM, the R^2 correlation coefficient, the source localisation error and the extent to which the true source rms amplitude is recovered. Final data dimensionalities are once again displayed and the error bars represent standard errors for the 10 realisations of simulated data.

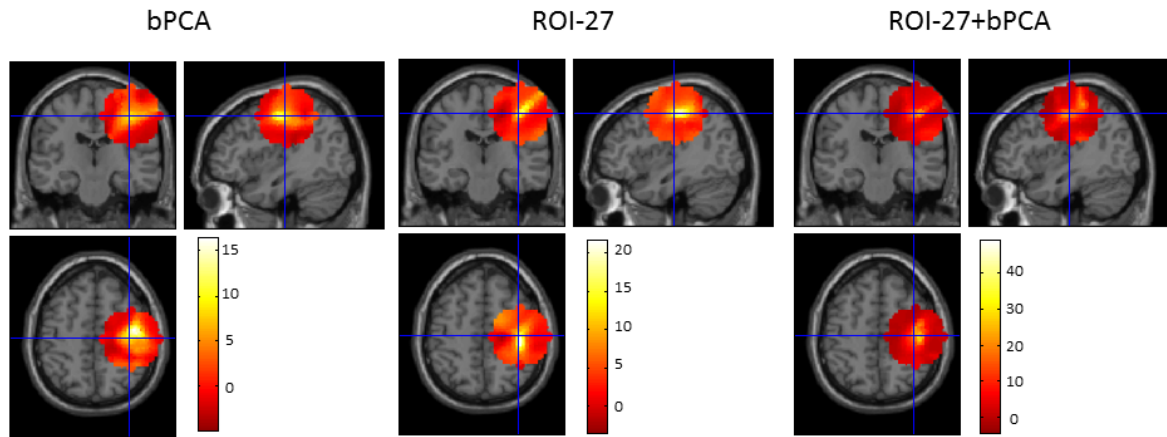


Figure 6.6 Comparison of source reconstruction approaches.

T-images contrasting the source 'on' and source 'off' conditions, superimposed on a canonical T1-weighted MRI, for a 30mm spherical volume surrounding the source of interest (at MNI coordinates 40 - 20 50) are displayed. Coronal, sagittal and axial sections through the images are shown with the crosshairs centred on the source of interest. Colour bars are shown separately for each image. Combining the ROI projection with bPCA results in the highest t values in the vicinity of the source of interest.

Figure 6.7 highlights the spatial specificity of the three different reconstruction approaches for long and short time windows for covariance matrix estimation. The top panel shows spatial filtering functions (as per Figure 6.1) centred on MNI co-ordinates 40 -20 50, 0 -20 50 and -40 -20 50 for illustration. The bottom panel displays the profile of the peak t statistic within each 5mm shifted ROI. The results are displayed for two different trial lengths for each of the three different reconstruction approaches. For large amounts of data (7000 ms) the covariance matrix estimate is precise and ROI manipulations do little to enhance beamformer performance (compare ROI and ROI+bPCA to bPCA-a single optimally regularised beamformer); indeed although there is a slight increase in the peak t-statistic at the source itself, the spatial specificity (the fall off with distance) degrades marginally due to fewer effective channels. For small amounts of data however (700 ms) the ROI based approaches make maximal use of the data available and considerably improve on the single beamformer image (bPCA) with ROI+bPCA performing at the level of an optimally regularized beamformer with ten times the data.

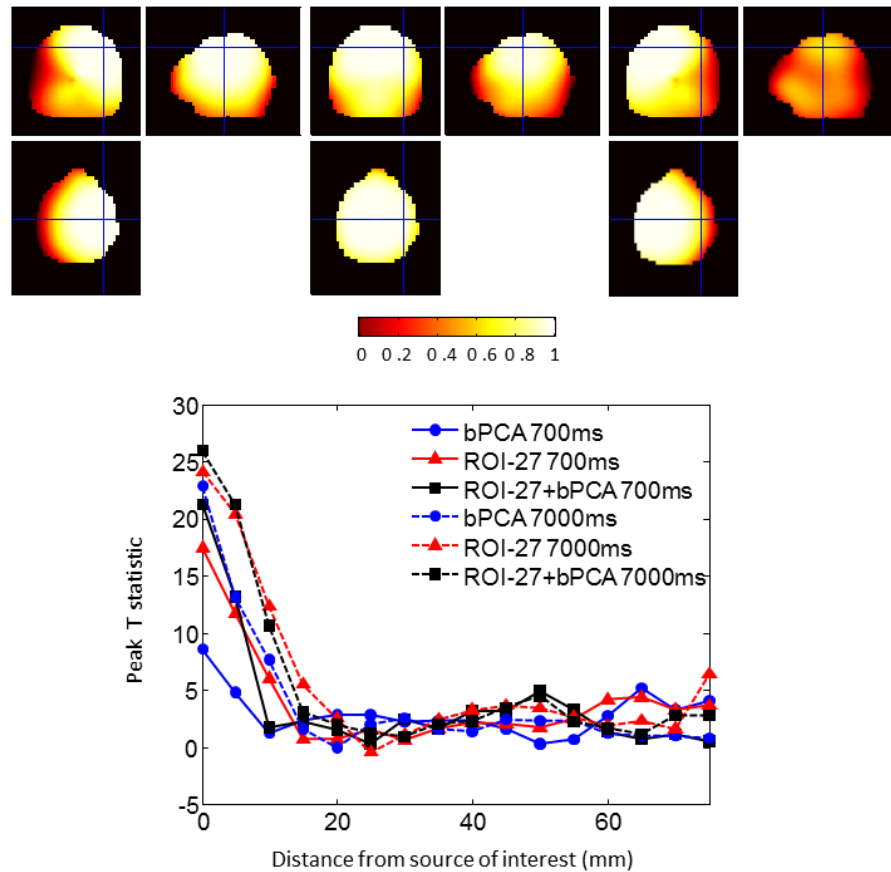


Figure 6.7 Spatial specificity of source reconstruction approaches.

In the upper panel, three spatial filtering profiles are displayed, as per figure 6.1, for a 1cm^3 ROI with 27 components centred on the following MNI co-ordinates: -40 -20 50, 0 -20 50, 40 -20 50. The cross-hairs are centred on the source of interest located at 40 -20 50. The colourbar indicates the value of the filtering function, which is expressed as a ratio and therefore has no units. The bottom half of the figure shows the value of the peak t statistic within a 1cm^3 ROI, as the ROI is shifted distances (in the x direction) from the source of interest. The results are displayed for two different trial lengths, for: 1) the ROI projection with 27 components (ROI-27), 2) bPCA (i.e. just a single optimally regularized beamformer) and 3) the ROI projection followed by bPCA (ROI-27 + bPCA). Note that the main differences between the three approaches are for the small amount of data (solid lines); in this case the ROI+bPCA (solid squares) performs as well as a beamformer with ten times the amount of data (dotted circles).

6.3.4 Patient data

Figure 6.8 highlights the results of the analysis on patient data. In the upper panels I display t statistic images of coherence between the left STN and whole brain areas for bPCA and the ROI projection followed by bPCA with 27 components selected from the ROI. In the case of bPCA, the crosshairs are located at the peak closest to M1, at MNI coordinates -36 -16 58. In this case, bPCA selected a data dimensionality of 141. Importantly, no voxels survived family wise error

correction at the peak level ($p < 0.05$). Combining the ROI projection with bPCA produced more focal images and also resulted in a greater peak T statistic as indicated by the colour bars in panel 6.8B. Furthermore, voxels surviving statistical comparison at the peak level and are indicated in the lower half of panel B. The crosshairs in panel B are located at the peak closest to M1 at MNI coordinates -30 -8 60.

The patient data provide empirical evidence that combining the ROI projection with bPCA can provide increased statistical sensitivity in the presence of large artefacts and a low data SNR.

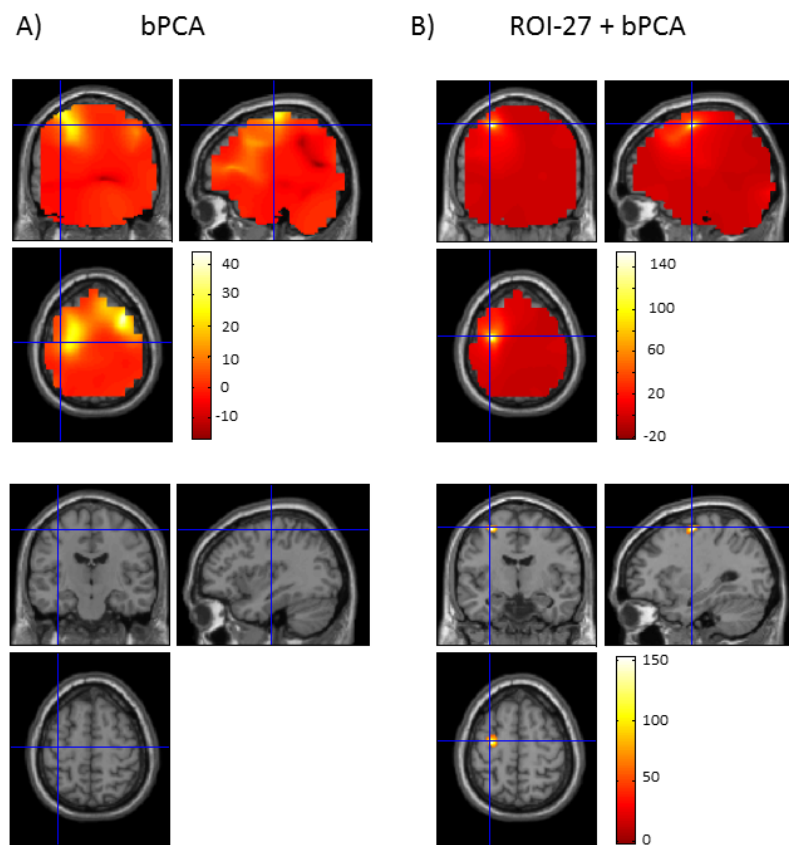


Figure 6.8 Patient data.

The results of analysis of patient data are displayed. The upper halves of panels A and B display t images of coherence between the left STN and cortical areas, computed using bPCA and the ROI projection (with 27 components) combined with bPCA. The ROI was selected as a cubic volume surrounding M1 (see methods for more details). T images are superimposed on a canonical T1-weighted MRI. Combining the ROI projection with bPCA results in more focal t images and a greater peak T statistic (indicated by the colour bars). In the case of bPCA, no voxels survived FWE correction at the peak level ($p < 0.05$) as shown by the lack of highlighted voxels in the lower half of panel A. When the ROI projection was combined bPCA however, 120 voxels survived FWE correction at the peak level, indicated in the lower half of panel B. The cross hairs in panels A and B are centred as described in the methods.

6.4 Discussion

In this chapter I have presented a framework for ROI analysis using beamformers. The choice of an anatomical ROI prior to source estimation has a number of benefits. In addition to excluding uninteresting variance or noise from other regions the brain (or environment), it reduces the effective signal space (decreasing the effective number of channels) thereby improving the estimation of the data covariance. This translates in practice to better artefact immunity and more accurate source reconstruction as quantified by lower FWHM and higher accuracy of the reconstructed time-series.

Importantly, the use of Bayesian PCA to estimate dimensionality removes any arbitrary regularisation stage and can in principle accurately select the number of components from an ROI (Figure 6.2). Additionally, projection of the data to an orthogonal subspace prior to bPCA is desirable, since bPCA subsequently selects orthogonal components in the data.

I think these methods will have specific application in the analysis of non-stationary MEG data where time is short and spatial hypotheses are well defined. For example, recent work (Woolrich et al., 2013; Baker et al., 2014; Brookes et al., 2014) has shown that resting state dynamics display distinct spatio-temporal modes such that different sections of the sensori-motor cortex coordinate within different time-windows. The pre-selection of this ROI (e.g. sensori-motor cortex) a-priori would mean that a more robust characterisation of such modes would be possible within relatively short time windows. I also note that there is no reason why the ROI needs to be spatially contiguous - the leadfields of a number of spatially distinct ROIs could be combined (see equation 6.3) in order to yield a single linear transformation that effectively encompasses multiple regions of interest.

Although our results are encouraging I stress a number of practical issues. The question of how many leadfield components to select from the ROI is one that needs to be answered by the experimenter, but it can be appropriately selected based on the kinds of filter response profiles

generated in Figure 6.1 whilst bearing in mind that the selected number will limit the maximal number of orthogonal modes in the data (i.e. an upper limit for bPCA, see Figure 6.3).

Additionally the size of the ROI needs to be specified, but this can be based on a prior hypothesis about the spatial extent of task related activations – for example one may want to sample the entire visual cortex in the case of visual paradigms. There are a number of ways in which this method could be comprised. The most obvious perhaps is that the selection of an ROI where no signal exists could lead to erroneous inference. On similar note, I have not explicitly examined the effect of correlated sources and how these would interact (if one were slightly outside the ROI but not completely suppressed).

It is also important to note that bPCA relies on a generative model of the data that assumes data samples to be independent and drawn from a Gaussian distribution. Such a model not guaranteed to be appropriate for realistic experimental data, and in these cases directly estimating the data distribution via kernel density based approaches may provide more accurate solutions (see Mohseni et al., 2013 for detailed discussion). Another issue is that the signal to noise gain by using the subspace methods may push the beamformer resolution beyond the grid resolution (Barnes et al., 2004) causing signal peaks to apparently disappear (as they become under sampled). It may therefore be necessary to reduce grid spacing in certain circumstances.

Finally, as shown in figure 6.7, these methods provide a way of balancing the spatial specificity of the beamformer image with the amount of data available. For large stationary data sets with no artefacts one would expect very precise covariance matrices and correspondingly high spatial resolution of optimally regularized beamformer images which would hardly benefit from the ROI projections described here. In cases where the amount of stationary data is small, or in cases where artefacts (or correlated sources) exist in another region of the source space, then I expect these methods to be of considerable benefit. For example, figure 6.7 shows that one can achieve the same spatial specificity with ten times less data using the methods I describe. I believe that

these methods may also be of benefit in certain clinical studies or in studies with children where participants are unable to sit still for long periods of time and hence scanning durations are necessarily limited.

Chapter 7: DBS modulates synchrony within spatially and spectrally distinct resting state networks in PD.

7.1 Introduction

Chronic high frequency deep brain stimulation (DBS) of the STN has become an established and effective means of managing the symptoms of Parkinson's disease (Limousin et al., 1995; Benabid et al., 2009), yet the precise mechanisms through which it exerts therapeutic action remain poorly understood.

It has previously been possible to demonstrate the suppression of beta activity locally within the STN during concurrent high frequency DBS using special amplifiers designed to suppress DBS related artefacts (Rossi et al., 2008; Eusebio et al., 2011; Whitmer et al., 2012). Despite advances in our understanding of DBS effects locally within the STN, it is evident from recent work combining either simultaneous EEG or MEG and intracranial LFP recordings that long range oscillatory synchronisation between the STN and cortical regions (Williams et al., 2002; Fogelson et al., 2006; Hirschmann et al., 2011; Litvak et al., 2011a), and between the two STNs (Hohlefeld et al., 2013; Little et al., 2013b), may also be of physiological and pathological relevance in Parkinson's disease. Two resting state spectrally and spatially distinct STN-cortical resting networks have been identified in Parkinson's disease with cortical activity driving STN activity in both cases. The STN is coupled to temporo-parietal areas at alpha band (7-12 Hz) frequencies and to motor/premotor regions at beta band (13-30 Hz) frequencies.

To date no studies have reported what happens to long-range STN–cortical synchronisation during concurrent DBS. Here I investigate how DBS influences the synchronisation of oscillatory neural activity both locally within the STN and between the STN and cortical regions, and between STNs. I hypothesised that the therapeutic efficacy of DBS relates to both the suppression of local STN beta activity and inter-areal beta band synchronisation between STN and motor cortical regions which drive STN beta activity.

In order to test this hypothesis, I studied 15 Parkinsonian patients undergoing functional neurosurgery for the insertion of STN electrodes. I performed simultaneous MEG and intracranial LFP recordings at rest and during clinically effective DBS. Although MEG offers a number of advantages over EEG in this patient group (Litvak et al., 2010), a major challenge of MEG recordings in the presence of the ferromagnetic extension cables from the DBS electrodes and also high amplitude DBS signals is the existence of artefacts. In Appendix A I have characterised the detailed nature of both these types of artefacts and have developed and validated analytical methods to accurately recover coherence topographies despite their existence.

7.2 Methods

7.2.1 Patient and surgical details

15 patients (mean age 61 years old; 13 male) who underwent bilateral implantation of STN DBS electrodes were recruited (see Table 7.1 for further clinical details). Patients were diagnosed with Parkinson's disease according to the Queen Square Brain Bank criteria (Gibb and Lees, 1988). All patients, except case 10, displayed improvements in motor UPDRS part III motor scores during chronic DBS. Details of localisations of the individual DBS electrode contacts that were used for stimulation and LFP recording are provided in Table 7.1. Recordings were approved by the National Research Ethics Service Committee South Central – Oxford B, and the patients gave written informed consent prior to participation.

Case	Age and Gender	Disease Duration (years)	Pre-operative Medication (mg)	Unified Parkinson's Disease Rating scale UPDRS III Stimulation OFF/ON (off medication)							Anatomical location of contacts 0 to 2 on right (R) and left (L) sides
1	67F	15	LDE 1120	OFF	32	6	10	0	0	8	R0 – inside L0 – inside
				ON	26	9	10	0	0	3	R1 – inside L1 – inside
											R2 – inside L2 – inside
2	67M	7	LDE 2840	OFF	43	12	14	0	10	7	R0 – inside L0 – caudal
				ON	19	7	6	0	0	3	R1 – inside L1 – inside
											R2 – inside L2 – inside
3	67M	8	LDE 200	OFF	21	5	6	0	0	6	R0 – inside L0 – inside
				ON	17	4	6	0	0	6	R1 – inside L1 – inside
											R2 – inside L2 – inside
4	67F	22	LDE 1430	OFF	55	11	13	4	4	10	R0 – medial L0 – inside
				ON	19	4	8	0	1	4	R1 – medial L1 – inside
											R2 – medial L2 – border
5	65M	14	LDE 960	OFF	28	3	6	3	3	8	R0 – rostral L0 – inside
				ON	11	0	1	2	0	4	R1 – medial L1 – inside
											R2 – medial L2 – inside
6	43M	9	LDE 1400	OFF	63	17	19	3	2	12	R0 – inside L0 – inside
				ON	30	4	13	11	0	1	R1 – inside L1 – inside
											R2 – inside L2 – inside
7	61M	8	LDE 400	OFF	56	11	11	6	4	12	R0 – rostral L0 – caudal
				ON	27	5	6	6	6	2	R1 – inside L1 – border
											R2 – medial L2 – inside
8	62M	14	LDE 1640	OFF	39	8	17	3	2	5	R0 – caudal L0 – caudal

				ON	31	8	12	1	2	5	R1 – border L1 – inside R2 – inside L2 – inside
9	60M	8	LDE 456	OFF	46	12	11	6	3	8	R0 – border L0 – inside
				ON	23	4	11	2	1	4	R1 – inside L1 – inside R2 – inside L2 – inside
10	70M	10	LDE 900	OFF	34	8	10	2	2	7	R0 – border L0 – caudal
				ON	34	6	11	2	3	8	R1 – border L1 – inside R2 – inside L2 – border
11	41M	6	LDE 1020	OFF	50	14	15	2	2	10	R0 – caudal L0 – inside
				ON	48	14	18	0	1	11	R1 – border L1 – inside R2 – inside L2 – inside
12	58M	12	LDE 1200	OFF	38	13	10	0	0	9	R0 – border L0 – inside
				ON	13	6	3	1	0	0	R1 – inside L1 – inside R2 – inside L2 – inside
13	68M	12	LDE 1370	OFF	52	8	14	4	5	12	R0 – caudal L0 – inside
				ON	34	7	4	2	2	9	R1 – border L1 – inside R2 – inside L2 – inside
14	60M	12	LDE 1300	OFF	33	7	8	7	2	4	R0 – inside L0 – inside
				ON	22	3	4	6	1	4	R1 – inside L1 – inside R2 – inside L2 – inside
15	59M	13	LDE 1900	OFF	48	8	10	5	7	9	R0 – inside L0 – inside
				OFF	27	5	8	1	3	8	R1 – inside L1 – inside R2 – inside L2 – inside

Table 7-1 Clinical characteristics of patients.

LDE - levodopa dose equivalent. The total UPDRS III motor score and its subscores are presented for the two experimental conditions, no DBS and 130 Hz DBS, which are denoted OFF and ON respectively. A-R denotes the akinesia and rigidity subscore

7.2.2 Electrophysiological recordings: simultaneous MEG and LFP recordings during DBS

MEG data were sampled at 2400 Hz and stored to disk for subsequent offline analyses. LFP activity recorded from both STN electrodes was collected at the same time as MEG using a battery-powered and mains optically isolated BrainAmp system (Brain Products GmbH, Gilching, Germany). Three bipolar channels (0-1, 1-2, 2-3) were recorded from each electrode, so that 0-2 and 1-3 could be derived by the off-line addition of signals from channels 0-1 and 1-2, or 1-2 and 2-3, respectively. LFP recordings were high pass filtered at 1 Hz in the hardware so as to avoid amplifier saturation due to large DC offsets. The data were sampled at 2500 Hz, which was the closest available sampling rate to the one used in MEG. LFPs were recorded onto a laptop that was optically isolated from the BrainAmp hardware. In order to fuse the MEG and LFP data with minimal timing distortions we used a synchronisation signal, measured separately on the two systems (see Appendix A).

In order to permit STN LFP recordings during concurrent stimulation of this nucleus, we used a purpose built stimulation-record amplifier (Rossi et al., 2007; Eusebio et al., 2011; Little et al., 2013a). This allows for monopolar DBS to be administered between either contact 1 or 2 (cathode) of the DBS electrode and an external anodal electrode applied to the patient's chest wall. By recording bipolar LFP between either contacts 0 and 2 (in the case of contact 1 being the cathode) or between contacts 1 and 3 (in the case of contact 2 being the cathode) of the DBS electrode we were able to exploit the common mode rejection properties of the amplifier. In all our patients, contact pair 0-2 was the one with the greatest resting beta activity and I therefore stimulated between contact 1 and the anode. The stimulation-record amplifier was used in combination with an external DBS stimulator (type 3628, Medtronic Inc., Minneapolis, MN) connected to the intracranial electrode. Right and left STNs were separately stimulated and

recorded, whilst the contralateral unstimulated STN was also recorded using the BrainAmp system.

7.2.3 Experimental Protocol

Recordings were performed after overnight withdrawal from dopaminergic medication. The patients were requested to keep their eyes open and to stay still during recordings. The experiment started with a 3 min resting block during which data were collected directly via BrainAmp without the stimulation-record amplifier. The stimulation-record amplifier and external stimulator were then added to the setup and two additional recording runs were performed. Two stimulation conditions were tested independently for the right and left STNs: 0 Hz (no DBS), and 130 Hz monopolar DBS. Each recording run lasted 7 minutes and included both conditions, each selected in a random order and lasting 3 minutes, separated by a 1 minute interval for washout of the effect of the first condition. The right STN was stimulated in the first recording run, whilst the left STN was stimulated in the second recording run.

Monopolar DBS, with a stimulation pulse width of 60 μ s and an amplitude of 3V (corresponding to stimulation parameters that are commonly used clinically) was administered by myself. These same settings were used in all patients. At the onset of DBS, the stimulation voltage was increased slowly, in increments of 0.5V, whilst checking for clinical improvement and for the presence of any stimulation related side effects. Prior to experimentation, clinical assessment of patients confirmed an improvement in part III motor UPDRS scores following DBS.

7.2.4 Data analysis

Only electrodes in which at least one of the recording pair of contacts (0-2) was located within the STN was used for analysis. This led to the exclusion of data from three electrodes. Data from a further three electrodes were excluded as the associated MEG signal contained significant artefacts, affecting greater than 150 channels during the 130 Hz DBS condition (see below). This left 24 subthalamic nuclei for further analysis.

7.2.5 Data pre-processing and sensor level analysis

In Appendix A, I have described our approach for obtaining an accurate estimate of head location for each recording run, based on both an initial measurement of head position and continuous tracking of HPI coils. In practice we found that both the initial measurement and parts of the continuous head tracking could be disrupted by the presence of ferromagnetic wires and the DBS pulses – therefore our approach had to be robust to such interferences. The full details of our approach are defined in Appendix A, but the overall idea is based on the fact that if head position is accurately tracked, the pairwise distances between the HPI coils should stay constant both within a recording run and between recording runs in the same scanning session. Time points where head tracking was lost within a recording run could then be identified and corrected by interpolation, such that the average of the resulting interpolated values would yield a robust estimate of head position. Head and sensor locations were always visually inspected for each subject and compared across runs to make sure that there were no gross outliers or misregistrations.

The raw data files from the CTF-MEG and BrainVision systems were converted to SPM MATLAB-based format. The LFP data were interpolated to 2400 Hz, matching the sampling rate of the MEG data. MEG and LFP recordings were then aligned using the synchronisation signal and combined (see Appendix A).

Visual inspection of the individual MEG channel data obtained during monopolar DBS at 130 Hz revealed high amplitude jumps in some of the channels that lasted only a few samples (Appendix A). Prior to further analysis, we rejected channels where the number of jumps exceeded 0.025% of the number of samples - where we defined a jump as an absolute difference in the magnetic field between adjacent samples of greater than 10^5 fT (femto Tesla). This procedure removed channels that were worst affected by jumps. These channels were removed for the DBS and no DBS conditions for each subject in order to ensure that the data were comparable. In separate

analysis we ensured that beamformer localisation of source activity was not significantly influenced by our channel rejection procedure (see Results).

In the remaining channels with jumps, we repaired the jumps, using an interpolation-based approach. Following the detection of a jump, a fixed segment of data (120 ms) either side of the jump was examined and DBS stimulation pulse peaks within it were identified. The data between DBS pulse peaks greater than two pulses away from the jump on either side were averaged to produce a signal for interpolating the region contaminated with the jump. The contaminated region of data was defined as the segment of data between two DBS pulse peaks of the jump on either side. Finally, the mean of the post-jump data segment was adjusted to correspond to that of the pre-jump data, ensuring smooth fixing of the jump (see Appendix A for further details). Following jump correction, the data were downsampled to 300 Hz and high pass filtered above 1 Hz prior. Margins of 20 s were then removed from the beginning and the end of the no DBS and 130 Hz DBS runs.

7.2.6 Analysis of local subthalamic nucleus synchrony

Power spectra of the stimulated STN and the STN contralateral to the stimulated side were computed using the multitaper spectral estimation with a frequency resolution and taper smoothing frequency of 2.5 Hz (Mitra and Pesaran, 1999). Power spectra were normalised, in order to make them comparable across subjects, by dividing each value by the mean power in the no DBS condition. Coherence between STNs was also computed using the same approach and parameters. In order to test for the effects of DBS on coherence or power, the spectral time series were converted to 1D images and smoothed with a 2.5 Hz Gaussian kernel to ensure conformance to the assumptions of random field theory. The images were then subjected to a paired t-test in SPM in order to determine regions in frequency space where DBS associated spectral changes were significant.

In addition to modelling subject specific dependencies in the recordings from the two hemispheres we included side as an additional categorical variable for each subject to account for potential differences between the recordings from the right and left STNs. All analyses were corrected for multiple comparisons using random field theory and reported findings are significant with FWE correction at the cluster level ($p < 0.05$ corrected, cluster forming threshold $p < 0.01$ uncorrected).

7.2.7 Determining the spatial and spectral profile of coherence changes induced by DBS

Brain areas coherent with the STN LFP were localised using DICS beamforming (Gross et al., 2001) as described in our previous publications (Litvak et al., 2010, 2012; Oswal et al., 2013a, 2014). Beamforming rests on a linear projection of sensor data using a spatial filter that is computed from the leadfield of a location of interest and either the data covariance or the cross-spectral density matrix (Van Veen et al., 1997; Gross et al., 2001). Leadfields were computed using a single shell head model (Nolte, 2003). The model was generated in SPM based on the patient's pre-operative structural MRI and fiducial-based co-registration was performed as described in Litvak et al., 2010. A beamformer regularisation of 0.01% was used as per Litvak et al., 2010.

The source space was defined as a 5mm spaced grid limited to the inner skull compartment. The goal of this particular analysis was to generate a 3D image showing coherence between the STN and all brain regions during the DBS and the no DBS conditions. Given previous studies highlighting the existence of separate alpha (7-12 Hz) and beta (13-30 Hz) band resting STN-cortical networks, I initially restricted our DICS beamformer analysis to these two bands (Hirschmann et al., 2011; Litvak et al., 2011a; Oswal et al., 2013b).

In order to limit the effects of volume conduction we defined the beamformer source orientations as the normalised imaginary part of the cross-spectral density vector between the recorded LFP and the x, y and z orientations of the MEG source (Nolte et al., 2004; Litvak et al., 2010). The resulting coherence values were then linearly interpolated to produce 3D volumetric

images with 2 mm resolution for visualisation. Common spatial filters were used to generate images for the DBS and no DBS conditions. Images were smoothed with an 8 mm isotropic Gaussian kernel to ensure conformance to the assumptions of random field theory prior to statistical analysis in SPM.

For each subject, coherence images were generated for each hemisphere for the two frequency bands in both experimental conditions. Half of the resulting images (all left STN images) were reflected across the median sagittal plane to allow comparison of ipsilateral and contralateral sources to the STN regardless of original STN side. These images were then subjected to a 2×2 factorial ANOVA, with frequency (alpha vs. beta) and stimulation (No DBS vs. 130 Hz DBS) as factors in SPM. Subject and side covariates were also included as described above. I constructed regions of interest (ROI) separately for the alpha and beta networks by performing a two sample t-test of alpha and beta band DICS beamformer images and testing for regions where beta band coupling was significantly greater than alpha band coupling and vice versa. For the definition of these ROIs I used independent data from the 3 minute rest block. All analyses were corrected for multiple comparisons using random field theory and are reported findings are significant with FWE correction at the cluster level ($p < 0.05$ corrected, cluster forming threshold $p < 0.01$ uncorrected).

The direction of the simple main effect of stimulation was estimated by performing one-tailed t-tests. For example for the beta band I could determine brain regions where coherence was significantly decreased by DBS or vice-versa. Similarly t-contrasts could be specified to determine the directionality of any interaction between the two factors. All analyses were corrected for multiple comparisons as explained above. Peak voxels resulting from group-level SPMs of the simple main effects underwent further analysis for coherence and clinical correlations.

First, I performed extraction of the time series (virtual electrode) data for each hemisphere from the location of the peak. I also extracted source time series from the primary motor cortex (M1),

positioned at MNI co-ordinates at 37 -18 53 (right M1) and -37 -18 53 (left M1) (Mayka et al., 2006; Litvak et al., 2012). For source extraction from this ROI I used methods that I presented in Chapter 6. The idea is that in order to minimise the influence of potentially artefactual contributions from outside a predefined ROI, it is possible to project the data to a subspace spanned by the leadfields within an ROI. I used a 1cm cubic ROI centred on the location of the peak, with leadfield sampling at 5mm spaced intervals on the cubic region. The covariance matrix for LCMV beamforming may then be computed after this linear projection step. In this particular analysis I employed a more principled way for determining the optimum amount of regularisation for the data covariance by using bayesian principle component analysis (see Chapter 6). Once again common filters were used for the two experimental conditions, and source orientations were defined as above.

Once individual trial time series were extracted for the different experimental conditions, coherence was computed between the reconstructed source and the reference channel using multitaper spectral estimation with a frequency resolution and taper smoothing frequency of 2.5 Hz (Mitra and Pesaran, 1999). In order to provide additional immunity from artefacts robust averaging was applied to both the cross-spectral density estimates and the auto-spectra across trials prior to computing coherence. Robust averaging is a special case of the robust general linear model (Wager et al., 2005) and involves down weighting the contribution of outlier trials that are contaminated by artefacts. Further details and a validation of robust averaging in a context similar to our present analysis can be found in Litvak et al., 2012 and Oswal et al., 2015.

Cortical power estimates were also determined from source extracted data, using the multitaper approach with robust averaging as described above. Subsequently, the mean power estimates for the alpha and beta bands were compared in the no DBS and 130 Hz DBS conditions using paired t-tests.

7.2.8 Directionality of STN-cortical coupling

To determine the effective directionality of functional coupling between the cortex and the STN I computed a non-parametric variant of spectral Granger causality. In comparison to standard spectral domain Granger causality based approaches, this does not rely on fitting a multivariate autoregressive model and hence makes fewer assumptions about the data (Dhamala et al., 2008). In order to determine the significance of coupling, I compared the Granger estimate of original data to that of surrogate time reversed data using a paired t-test across hemispheres (Haufe et al., 2013). This procedure has been shown to suppress weak asymmetries in the data that are not due to genuine time lagged interactions.

Having established the effective directionality of functional coupling, I estimated the phase delays between the STN and cortical regions. In order to do this I assumed that time delay at each peak frequency where there was coupling was fixed, and hence given by: $\Delta T = \text{abs}(\phi_{\text{cortex}} - \phi_{\text{STN}}) / 2\pi f$ where ΔT represents the time delay between the regions, f indicates the frequency of the signals and $\text{abs}(\phi_{\text{cortex}} - \phi_{\text{STN}})$ represents the magnitude of the phase delay between signals (see Fogelson et al., 2006). Phase differences were estimated from complex cross-spectra after robust averaging (see above). I considered two frequency ranges, 13-21 Hz and 21-30 Hz and regressed phase differences against frequency in order to approximate delays. Only data points for which there was a significant linear relationship between phase and frequency ($p < 0.05$) were included for computation of delays.

7.2.9 Correlation with clinical features

The aim of this analysis was to determine whether changes in motor function induced by DBS correlated with associated electrophysiological changes within STN-cortical circuits. Motor function was assessed through the total UPDRS (Unified Parkinson's Disease Rating Scale) part III score - its constituents comprising, the hemi-body akinesia and rigidity score, the hemi-body

tremor score and truncal akinesia scores. UPDRS III scoring was performed by an experienced neurologist after patients had been withdrawn from their medication overnight and were in an OFF state. In order to assess the effects of DBS, UPDRS III OFF state motor scores were performed immediately prior to surgery and approximately 6 months after the implantation of the IPG (internal pulse generator) with DBS at the same settings as those used in the MEG experiment. The coefficient of determination was used to correlate changes in motor scores with DBS to changes in LFP and MEG signals. For this analysis I only included MEG signals which showed statistically significant modulation by DBS at the group level and all correlations were corrected for multiple comparisons using a Bonferroni correction with an alpha of 0.05.

7.3 Results

7.3.1 DBS effects on local power: DBS specifically suppresses 11-14 Hz activity within the STN

Figure 7.1 shows data averaged from 24 subthalamic electrodes. The upper two panels demonstrate the mean spectral power profiles recorded across bipolar contacts 0-2 of the stimulated STN electrode and of the STN electrode contralateral to the stimulated side during the two experimental conditions. At rest (no DBS condition), there are spectral peaks centred at ~7 Hz, ~15 Hz and ~30 Hz. These approximately correspond to the alpha, low beta and high beta frequency bands, respectively, although these bands have been previously defined according to cortical reactivity and do not precisely match with subcortical spectral reactivities. DBS resulted in a significant suppression of activity in the stimulated STN over 11-14 Hz, which for simplicity we will consider within the low beta frequency band. The 11-14 Hz range is highlighted in the grey in panel a (peak $t_{34} = 2.9$, FWE $p < 0.05$). This effect was lateralised, with no significant change in power in the contralateral, unstimulated STN (panel b, peak $t_{34} = 1.0$, FWE $p > 0.2$).

In contrast to the STN, cortical power in the broad beta band range was not significantly influenced by DBS (For beta coherence peak, peak $t_{34} = 1.3$, FWE $p > 0.1$; for M1 peak $t_{34} = 1.2$, FWE $p > 0.08$) or over any frequency range within this band corrected for multiple comparisons using random field theory ($p < 0.05$ corrected, cluster forming threshold $p < 0.01$ uncorrected). Cortical power was determined from spectral analysis of beamformer extracted time series from the peak location of DBS effects on cortico-STN coupling in the beta band (corresponding to the premotor/supplementary motor areas see below) at MNI co-ordinates 2 –4 64 and also separately from the primary motor cortex (M1).

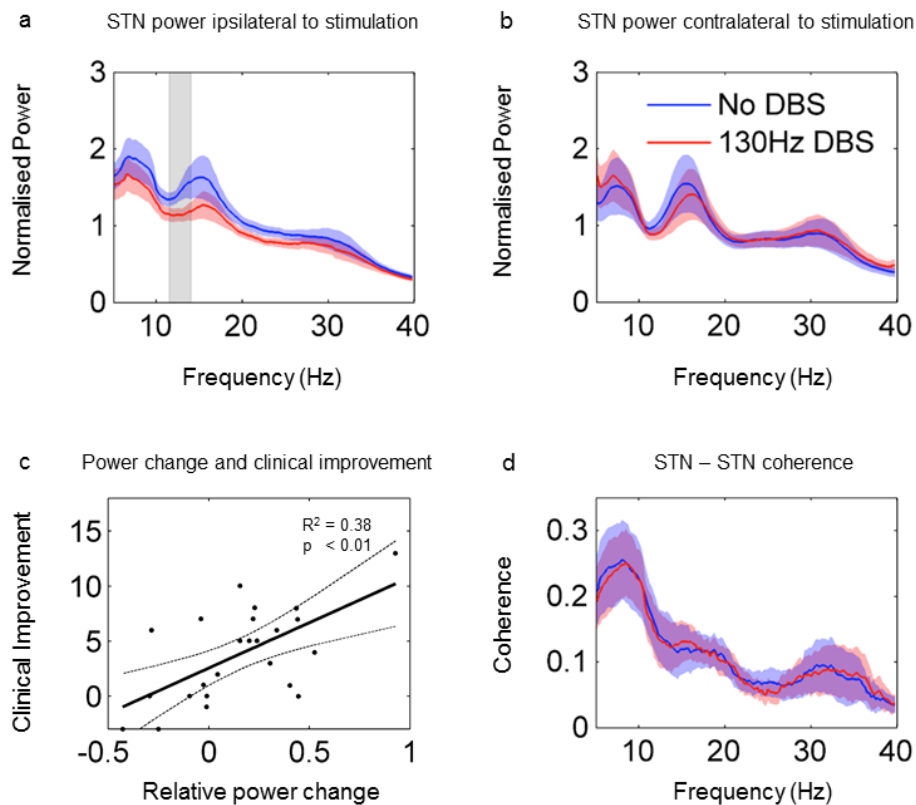


Figure 7.1 Changes at STN level.

(a) Group average normalised power spectra of the stimulated STN during the no DBS and the 130 Hz DBS conditions. The shaded regions represent standard errors of the mean. In the no DBS condition spectral peaks are evident in the alpha (8-12 Hz), low beta (13-20 Hz) and high beta (21-30 Hz) frequency ranges. DBS results in a suppression of power in the frequency range indicated by the grey bar (11–14 Hz). **(b)** Group average spectra of the unstimulated STN contralateral to the stimulated side. There are no significant spectral changes associated with DBS. **(c)** Correlation between DBS related changes in relative power in the 11-14 Hz frequency range across hemispheres and changes in contralateral hemibody akinesia/rigidity scores. A linear regression line is plotted with 95% confidence intervals indicated by the

dotted lines. Clinical improvement (No DBS - 130 Hz DBS contralateral rigidity/akinesia scores) correlated significantly with suppression of 11-14 Hz power (presented as No DBS-130 Hz DBS; $F = 13.6$, $r^2 = 0.38$, $p = 0.0013$). (d) Group average coherence spectra between stimulated and contralateral STNs. Unilateral DBS does not affect coherence between the two STNs.

7.3.2 DBS effects on local power: change in STN LFP 11-14 Hz activity correlates with DBS efficacy

Next I investigated whether clinical improvements in motor scores associated with DBS correlated with DBS associated changes in power in the STN. To optimise my chance of picking up any correlation I averaged power for both experimental conditions over the precise frequency range (11-14 Hz) showing significant power modulation. I found a significant positive correlation between DBS related power suppression in the 11–14 Hz band in the STN and improvements in hemibody akinesia-rigidity scores ($F = 13.6$, $r^2 = 0.38$, $p = 0.0013$).

7.3.3 Defining resting state networks in PD and handling DBS related artefacts

My next goal was to determine the effects of DBS on resting state networks involving the stimulation target, the STN. One of these can be tracked by LFP recordings alone in the form of the coherence between the two STNs. Spectra of the coherence between bipolar contacts 0-2 of the stimulated and contralateral STNs are presented in panel d of Figure 7.1. Peaks in resting coherence (no DBS condition) occur at similar frequencies as peaks in the resting spectral power profiles.

A further two resting state networks can be identified through simultaneous MEG and LFP recordings by characterising STN–cortical coupling in the alpha (7-12 Hz) and beta (13-30 Hz) frequency bands (Hirschmann et al., 2011; Litvak et al., 2011a). First I determined if these same two networks could be identified in the current cohort in the no stimulation condition. Panel b of Figure 7.2 shows mean images of normalised STN-cortical coherence for all included STNs separately for the alpha and broad beta bands. Note that all images for left STNs have been

reflected across the median sagittal plane such that the resulting networks appear on the right hemisphere. The present results match very closely to those previously reported in that two spatially and spectrally segregated STN-cortical networks exist. A broad beta band network exists between the STN and supplementary motor and premotor regions (peak at MNI co-ordinates 48 - 34 18 corresponding to right superior frontal gyrus), while a separate alpha band network exists between STN and temporal areas (peak at MNI co-ordinates 18 -14 68 corresponding to the right superior temporal gyrus).

Prior to exploring how these two networks respond to STN DBS I checked that I could still identify the two networks after rejecting MEG channels that were contaminated with artefacts. In my analysis of the effects of DBS I rejected hemispheres where over 150 channels were contaminated with jumps in the corresponding MEG signal. For the remaining hemispheres, Figure 7.2a shows a 2D topographic plot of all 275 channels, with the interpolated heat map representing the mean proportion of times each channel was rejected in our analysis across subjects. A value of 0 indicates that the channel was never rejected, whilst a value of 1 means that the channel was always rejected. The images for left STNs have been reflected through the midline for display purposes. It is evident that the most frequently rejected channels overlie fronto-temporal regions, where the monopolar stimulation current flows on its path between the implanted stimulated contact and the cutaneous reference.

I then repeated the analysis for the no DBS condition illustrated in Figure 7.2b, but this time excluding all those channels which were rejected due to artefacts in the 130 Hz DBS condition. Figure 7.2c shows the new source reconstructions of the alpha and broad beta networks in the no DBS condition, following channel rejection. The excellent concordance between figures 7.2b and 7.2c highlights that it is possible to accurately recover the resting alpha and beta networks in our patients despite rejecting severely contaminated channels.

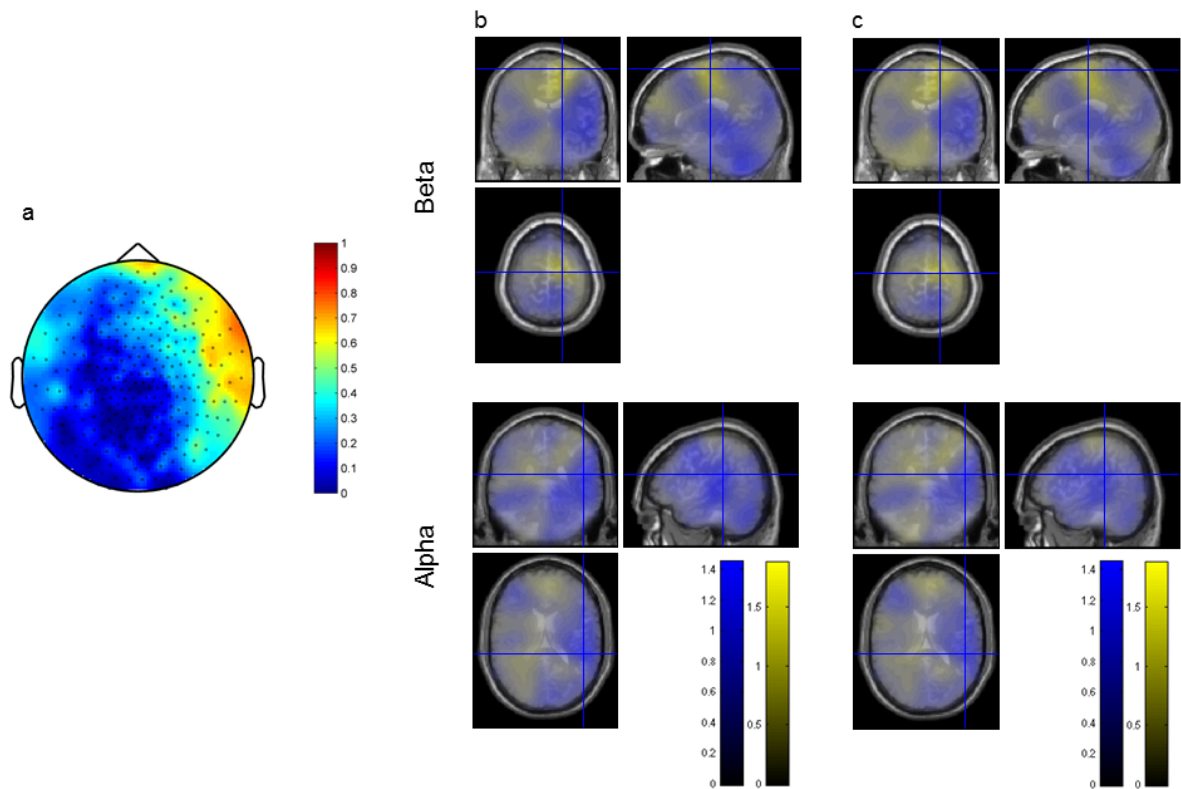


Figure 7.2 STN-MEG coherence topography is preserved despite artefact rejection.

(a) 2D topography plot of all 275 MEG sensors, with the interpolated heat map representing the mean proportion of times each channel was rejected in our analysis across subjects. Value of 0 indicates that the channel was never rejected, whilst a value of 1 means that the channel was always rejected. Channels were rejected due to the presence of large amplitude jump artefacts in the MEG signal (see Methods). Images for left STNs have been reflected through the midline for display purposes. Most frequently rejected channels overlie fronto-temporal regions ipsilateral to the stimulation. (b) Group mean of normalised DICS beamformer images in the no DBS condition with all MEG channels included for source space analysis. (c) Group mean of normalised DICS beamformer images with channels heavily contaminated with jump artefacts rejected prior to source space analysis. In (b) and (c) unthresholded alpha (blue) and beta (yellow) coherence is superimposed onto a T1 weighted canonical MRI. Colour bar represents normalised coherence in arbitrary units. Values greater than 1 indicate that activity in that voxel is consistently greater than the mean across the image. Coronal, sagittal and axial sections through the image are displayed with cross-hairs centred on the image maxima for beta (upper panels) and alpha (lower panels).

7.3.4 DBS suppresses coupling between STN and a mesial motor beta band network in

PD

There was no significant modulation of the coherence between both STNs during DBS (peak $t_{34} = 0.46$, FWE $p > 0.9$). Comparison of subcortico-cortical coherence OFF and ON DBS revealed a

simple main effect of stimulation on coherence in the beta band such that broad beta band coherence was suppressed in relatively focal mesial pre-motor regions, indicated in Figure 7.3a. The coloured region indicates voxels which survived cluster level correction as described in the Methods section. The location of the peak t-statistic (peak $t_{81} = 5.9$, FWE $p < 0.01$) corresponds to MNI co-ordinates 2 -4 64 and the region encompasses mesial pre-motor areas such as the supplementary motor area (SMA), but not the pre-supplementary motor area (pre-SMA). In contrast there was no simple main effect of stimulation on coherence in the alpha band (peak $t_{81} = 3.1$, FWE $p > 0.1$).

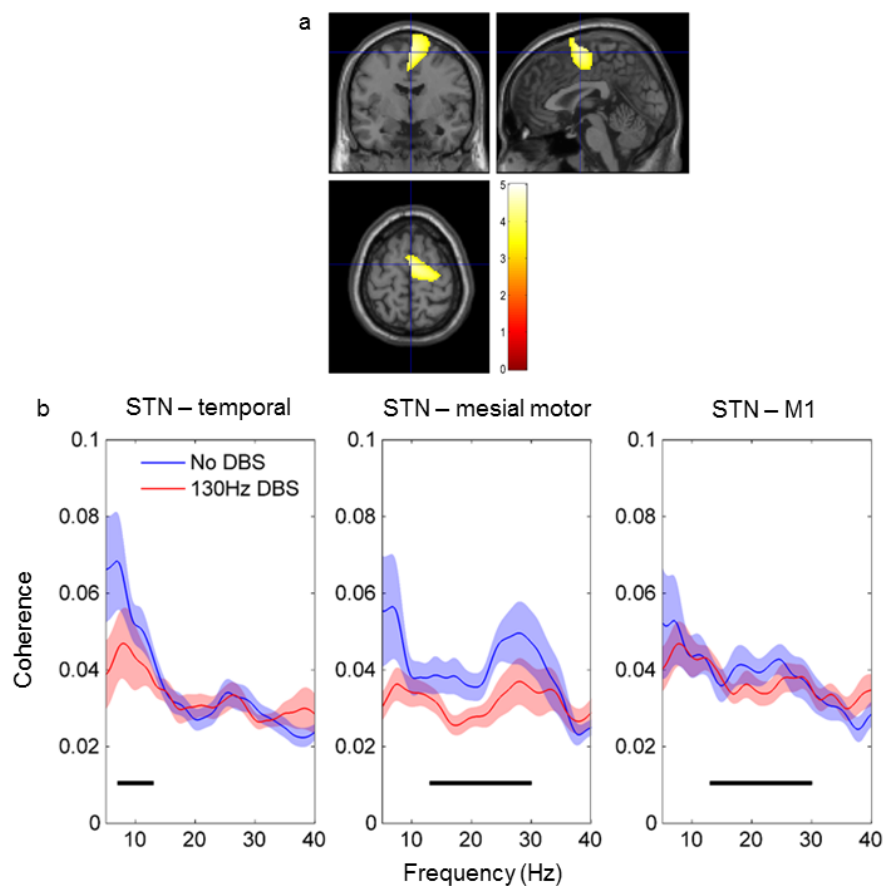


Figure 7.3 Effect of 130 Hz DBS on STN-MEG coherence.

(a) Group thresholded SPM of the simple main effect of DBS on the beta band network. The coloured region indicates areas where DBS significantly suppressed STN-cortical beta band coherence. Values indicated by the colour bar are t statistics. The SPM is superimposed on a T1 weighted canonical MRI with cross-hairs centred on the value of the peak t statistic at MNI co-ordinates 2 – 4 64. For the simple main effect of DBS on the alpha band network, no clusters survived correction for multiple comparisons. **(b) Group mean spectra of coherence computed between the STN and locations of the peak t statistic of simple main effects separately for the alpha and beta networks.** Black bars denote alpha (8-12 Hz) and beta bands (13-30 Hz) in the left and right hand side plots, respectively.

Source extracted coherence spectra are shown in Figure 3b. Source time series were extracted from the primary motor cortex (M1) and from the locations of the peak t-statistic of the simple main effect of stimulation for each frequency band. In the alpha band coherence peaked in the superior temporal gyrus and coherence spectra were similar in the no DBS and the 130 Hz DBS conditions (see left hand side panel of Figure 7.3b). In contrast, in the beta band where coherence peaked in mesial premotor areas of the cortex, DBS resulted in a suppression of coupling between the STN and these regions. Crucially, coupling between STN and primary motor cortex (M1) was not influenced by DBS.

7.3.5 Ratio of low and high beta band coupling differs between the STN-mesial premotor and STN-M1 networks

STN–cortical coherence in the high beta range appeared to dominate over that in the low beta range, but only in the STN-mesial premotor network in the no DBS condition (Figure 7.3b). Given this, I explored whether the topography of STN-cortical coupling in the broad beta band could be topographically further refined in terms of any relative dominance of low or high beta frequencies. Accordingly, I computed DICS beamformer images as before for data from the no DBS condition, but subdivided the beta band into a low (13-20 Hz) and high (21-30 Hz) ranges. A two sample t-test was then used to determine regions within the resting beta network where STN-cortical coupling was greater in the high beta band than in the low beta band and *vice versa*. High beta band coupling was significantly greater than low beta band coupling in posterior mesial pre-motor regions encompassing SMA (see green areas in Figure 4a, peak $t_{83} = 5.7$, $p < 0.01$). However, the reverse contrast, to test for regions where low beta coupling was greater than high beta coupling was not significant (peak $t_{83} = 3.2$, $p > 0.2$). Thus in posterior mesial pre-motor areas, such as SMA, STN-cortical cortical coherence dominated in the high as opposed to the low beta frequency range. Outside of this mesial region, there was no frequency preference of STN-cortical beta band coupling.

The region where resting STN-cortical coupling is greater in the high beta band than in the low beta band largely coincided with that in which beta band STN-cortical coupling was suppressed by DBS. This is highlighted in Figure 7.4b, where the green areas represent the regions where high beta band coherence dominates and the area in red represents regions where DBS suppressed STN-cortical beta band coupling.

An important question arising from the above findings is whether DBS predominantly therefore suppresses high, rather than low, beta STN-cortical coherence. In order to address this, I constructed a 2 x 2 x 2 ANOVA repeated measures with factors band (low vs high beta), cortical topography (mesial vs. remaining motor) and stimulation (no DBS vs. 130 Hz DBS). Mesial motor areas were defined as all voxels incorporated within the region where high beta STN-cortical coupling was greater than low beta STN-cortical coupling (regions shown in green in figures 7.4a and b). The remaining motor region was defined as all of the voxels outside the mesial region, but inside the resting beta band network (shown in yellow in figures 7.4a and b). Coherence values of voxels within these regions were averaged to yield a single value for each level of the ANOVA. As expected there was a main effect of stimulation, with DBS producing significant beta suppression ($F_{1, 184} = 9.82, p < 0.01$), but no main effect of cortical topography ($F_{1, 184} = 0.8, p = 0.37$) or band ($F_{1, 184} = 0.06, p = 0.80$). There were, however, interactions between cortical topography and band ($F_{1, 184} = 3.96, p < 0.05$) and between stimulation and cortical topography ($F_{1, 184} = 10.98, p < 0.01$), - such that high beta band coupling was greater in mesial rather than in remaining motor regions and DBS predominantly reduced beta activity in the mesial areas. Crucially however there was no interaction between stimulation and band ($F_{1, 184} = 2.02, p = 0.16$), nor was there an interaction between all three factors ($F_{1, 184} = 0.98, p = 0.32$). The lack of an interaction between stimulation and band was corroborated by considering the effect of DBS on coherence with 1 Hz resolution. This reinforced that the suppression of coherence by DBS was fairly evenly distributed across the broad beta band (Figure 7.3b).

Taken together my results highlight that STN-cortical coupling is greater in the high than in the low beta band in posterior mesial pre-motor regions and that DBS preferentially suppresses STN-cortical coupling within this region. Crucially however DBS does not preferentially suppress high or low beta band cortico-STN coupling within the mesial pre-motor or remaining motor regions.

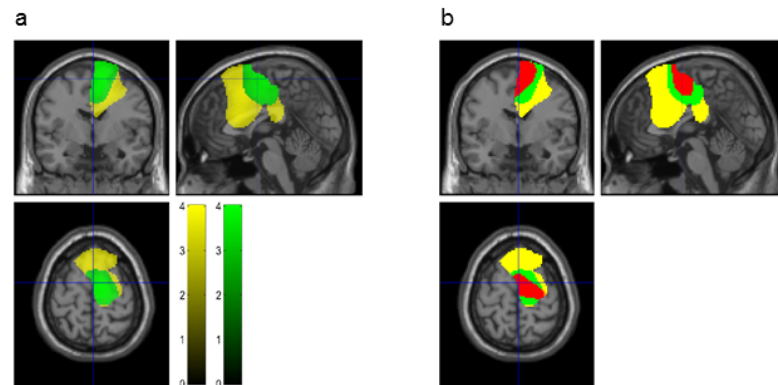


Figure 7.4 Differences between STN-MEG coherence in low and high beta bands.

(a) Thresholded SPMs superimposed onto a T1 weighted canonical MRI with region in yellow representing voxels where STN-cortical coupling was significantly greater in the beta band than in the alpha band in the resting block. Region in green represents voxels within the resting beta network where STN-cortical coupling in the high beta frequency range (21-30 Hz) exceeded coupling within the low beta range (13-20 Hz). Colour bars for the yellow and green images represent t-statistics. **(b)** Resting beta network (yellow), high beta network (green) and cortical region where STN-cortical beta band coupling is suppressed by DBS (red) are all superimposed.

7.3.6 Phase differences differ between low and high beta band networks linking motor cortex and STN

The evidence above suggests that mesial premotor cortex involves more high than low frequency beta coupling, and that DBS of the STN preferentially suppresses coupling with these cortical areas, but without distinguishing between the lower and upper beta band frequency ranges. Next I sought to further characterise couplings in the lower and upper beta band and to test the hypothesis that they might relate to indirect and hyperdirect connectivity with the STN, respectively. First, I confirmed that coupling involved cortical driving of STN, both for the upper and lower beta bands during and without STN DBS. Figure 7.5 plots the mean difference in upper and lower beta band Granger causality between the original and time reversed data, averaged

across hemispheres for the no DBS and 130 Hz DBS conditions. For this analysis I used source time series extracted from the location of peak t-statistic of the simple main effect of DBS in the beta band (at MNI co-ordinates 2 -4 64, corresponding to mesial premotor regions) and from primary motor cortex (M1 at MNI co-ordinates 37 -18 53). The difference in Granger causality was significantly greater than zero in the direction of cortex leading the STN for both the no DBS and the 130 Hz DBS conditions, for both cortical regions and both beta sub-bands. For the STN–mesial network, one sample t test statistics for the low beta sub-band were: $t_{23} = 2.1$, $p = 0.02$ in the no DBS condition, and $t_{23} = 1.9$, $p = 0.03$ in the 130 Hz DBS condition. For the same location and the high beta sub-band one sample t tests were: $t_{23} = 2.6$, $p < 0.01$ in the no DBS condition, and $t_{23} = 2.5$, $p = 0.01$ in the 130 Hz DBS condition. Similarly for the STN-M1 network and the low beta sub-band: $t_{23} = 2.2$, $p = 0.02$ in the no DBS condition, and $t_{23} = 2.1$, $p = 0.02$ in the 130 Hz DBS condition. For the high beta sub-band of the STN-M1 network: $t_{23} = 2$, $p = 0.03$ in the no DBS condition, and $t_{23} = 1.9$, $p = 0.03$ in the 130 Hz DBS condition.

Second, I sought to estimate the net time delays between the cortex and STN. There was a significant linear relationship between phase and frequency allowing net delays to be estimated in 18 out of the 24 hemispheres (Figure 7.6). For the no DBS condition, the mean delays between the location of the peak t-statistic of the simple main effect of DBS in the beta band in the mesial premotor cortex and the STN was 46 ms and 20 ms for the low and high beta frequency ranges, respectively (Figure 7.6). To explore the dependence of delays on the beta sub-band, DBS state and cortical location I constructed a 2 x 2 x 2 ANOVA with factors sub-band (low vs. high beta), DBS (no DBS vs. DBS) and cortical location (mesial premotor vs. M1). There was a main effect of sub-band such that net delays were lower for the high beta sub-band ($F_{1,84} = 16.85$, $p < 0.01$), but no other significant main effects or interactions.

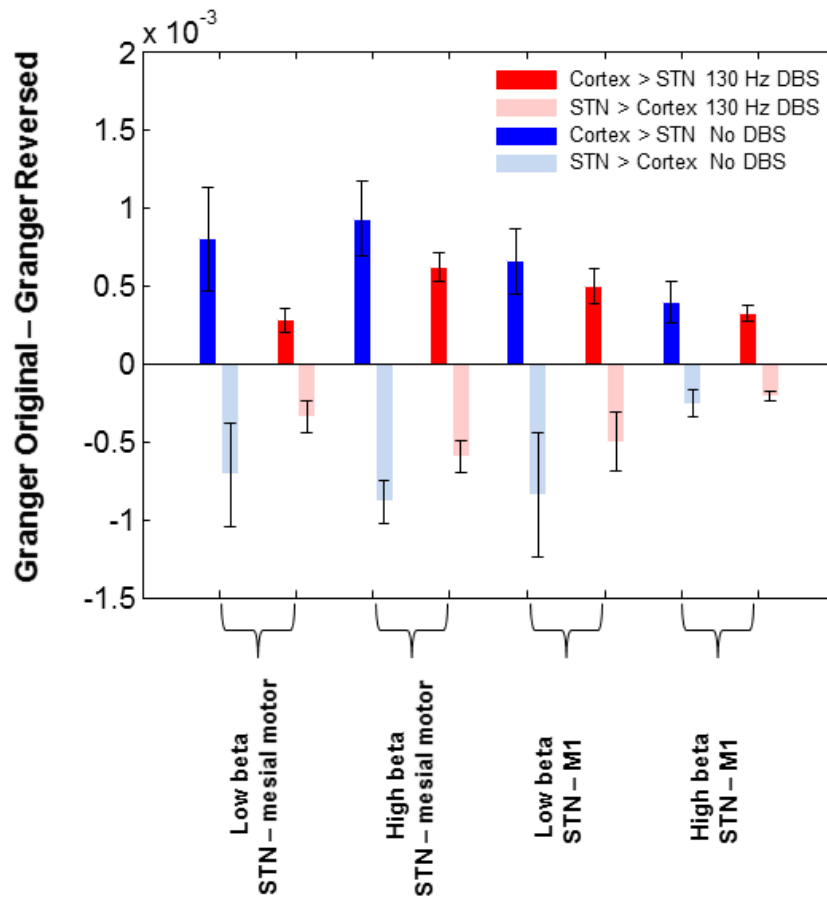


Figure 7.5 Results of Granger causality analysis.

Group mean difference in Granger causality between original and time reversed data in no DBS and 130 Hz DBS conditions for the high and low beta sub-bands. Source time series were extracted from the location of the peak t-statistic of the simple main effect of DBS in the beta band (at MNI co-ordinates 2 -4 64 corresponding to mesial motor regions) and additionally from primary motor cortex (M1). The difference in Granger causality is significantly greater than zero in the direction of cortex leading the STN for both cortical regions in the no DBS and the 130 Hz DBS conditions (see Results). Vertical bars represent standard errors of the mean. In contrast the difference in Granger causality is less than zero in the direction of STN leading the cortex, confirming that cortical activity led that in STN.

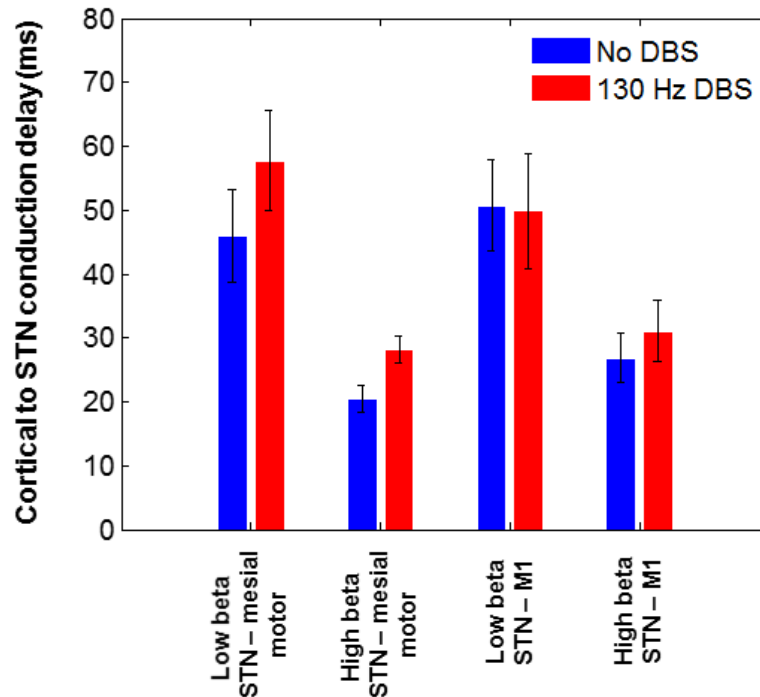


Figure 7.6 Estimated conduction delays.

Group mean conduction delays between cortical regions (M1 and the location of the peak t-statistic for the simple main effect of DBS on the beta network at MNI co-ordinates 2 -4 64) and the STN are shown for the low (13-20 Hz) and high beta (21-30 Hz) sub-bands in both experimental conditions. The vertical bars represent standard errors of the mean. Conduction delays are significantly greater for the low beta frequency range than for the high beta frequency range.

7.3.7 DBS effects on resting state networks: lack of correlation with DBS efficacy

Finally, I investigated whether clinical improvements in motor scores associated with DBS correlated with DBS associated changes in STN-cortical beta band coherence across subjects. I used coherence values averaged over the broad 13-30 Hz beta range and also separately across the 13-21 Hz and 21-30 Hz sub-bands. None of the comparisons yielded significant correlations.

7.4 Discussion

DBS suppressed synchronised neuronal activity within the STN, preferentially at low beta rather than high beta frequencies. Suppression in the low beta band correlated with motor improvement. In contrast, DBS suppressed the coupling of STN to cortical motor regions across the entire beta frequency band, and this did not correlate with clinical improvement. The effect of STN DBS on coupling with cortex was spatially selective and restricted to mesial premotor

cortical areas. The latter were distinguished from more lateral motor cortical areas, including the primary motor cortex, by coupling with STN that was stronger in the high than in the low beta frequency band, whereas these were more evenly balanced over lateral motor cortical areas. Coupling between STN and cortical motor areas consisted of a predominant drive from cortex to STN, but coupling in the higher beta frequency band had a much more rapid effect on STN activity than that in the lower beta frequency band. These observations raise the possibility that cortical connectivity with the STN in the high and low beta bands may reflect coupling mediated predominantly by the hyperdirect and indirect pathways to STN, respectively (Alexander and Crutcher, 1990; DeLong, 1990). Our findings also imply that the hyperdirect connectivity, characterised by activity in the high beta band, dominates in mesial premotor cortical areas. It was the coupling between these latter areas and STN that was most sensitive to DBS (see summary schema in Figure 7.7). Collectively my results are consistent with the hypothesis that the therapeutic effects of STN DBS are mediated predominantly by suppression of low beta activity locally within the STN (Eusebio et al., 2012). In addition, the present results suggest that DBS may reverse the strengthening of the hyperdirect pathway which may be a necessary prerequisite for the development of exaggerated beta activity in the STN (Holgado et al., 2010).

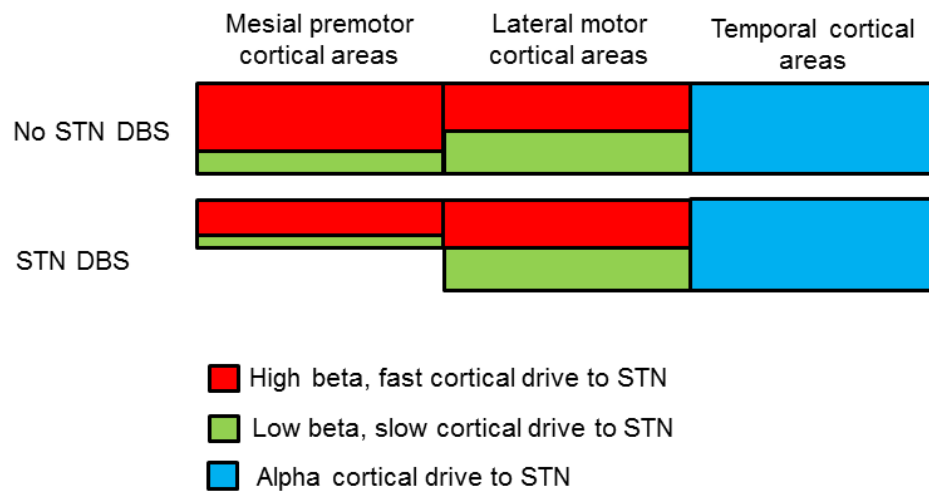


Figure 7.7 Schematic of DBS effects on STN-cortical networks

Mesial premotor areas, including the SMA are preferentially coupled to the STN at rest at high (red) rather than at low (green) beta frequencies. This pattern is not observed for lateral motor areas, including M1, where coupling to the STN is more evenly distributed across beta frequencies. STN DBS acts to suppress driving of the STN by mesial premotor regions in the low and high beta sub-bands. Crucially these effects of DBS are limited to the STN-mesial premotor network and are not observed in the patterns of DBS reactivity of the STN-lateral motor network.

7.4.1 Study limitations

Before considering the functional and clinical significance of my findings it is prudent to highlight the limitations of the study. First, as recordings were made a few days after electrode implantation they are likely to be affected by a post-operative stun effect which has been associated with a reduction in spontaneous beta activity in the STN (Chen et al., 2006). Second, the timings of our experimental conditions were determined by clinical constraints, particularly patient fatigue, in this post-operative period. Specifically, the wash-out period between conditions was only one minute so that effects persisting beyond cessation of stimulation may have tended to obscure differences between stimulation regimens. Likewise, signals were analysed that were recorded as little as 20 s (mean 110 s) after the onset of 130 Hz DBS, thereby likely failing to reflect the full effect of stimulation (Lopiano et al., 2003; Temperli et al., 2003). However, even 20 s of stimulation is sufficient to have some effects on beta activity (Wingeier et al., 2006), and even after 200 s of STN DBS beta power changes have resolved within 30 s of

stimulation offset (Kühn et al., 2008b). Third, I focussed on linear interactions between sites, in the form of coherence, and this will have missed non-linear phenomena such as cross-frequency phase-amplitude coupling (Özkurt et al., 2011; de Hemptinne et al., 2015a).

7.4.2 DBS influences spatially, functionally and spectrally distinct cortico-subthalamic nucleus networks

Previous resting state recordings in PD patients have demonstrated the existence of spatially and spectrally segregated STN-cortical networks. The STN is coupled to motor regions in the beta band, and also to temporal regions in the alpha frequency range. I replicated these findings in this study, and report novel differential influences of DBS on activity within these networks.

Firstly, DBS did not influence coupling between the STN and temporal areas in the alpha band. While this is in keeping with a lack of the effect the dopamine prodrug levodopa on this network at rest, it is worth noting that movement related suppression of STN-temporal alpha band coupling is enhanced by levodopa and that this change correlates with clinical motor impairments (Oswal et al., 2013a). The precise role of the alpha band STN-temporal network remains to be fully elucidated, but it may reflect activity in the anatomical connection between the STN and superior temporal gyrus identified in human tractography studies (Brunenberg et al., 2012).

In contrast, DBS suppressed beta band synchronisation between the STN and cortical motor regions. However, here my results suggested that this STN-cortical motor circuit can be further divided on functional grounds, including reactivity to DBS. Thus STN DBS suppressed beta band synchronisation between the STN and mesial motor regions encompassing the SMA, but had no effect on the coupling between the STN and lateral motor regions that included primary motor cortex. This differential reactivity to DBS was paralleled by spectral differences between these motor sub-circuits. Those mesial areas that uncoupled from the STN during DBS were more strongly coupled to the STN in the high beta than the low beta frequency range. In contrast, motor areas outside of this mesial premotor region exhibited beta band coupling with the STN

that was more balanced between low and high frequencies within the beta band. A similar dominance of STN coherence with mesial cortical areas at higher beta frequencies has also been inferred from EEG studies, although without the spatial resolution possible here (Fogelson et al., 2006). Nevertheless, both mesial and lateral motor regions in the cerebral cortex were Granger causal for activity in the STN in the beta band, an important observation that rules out direct pick-up of cortical activities by our DBS electrodes.

Does this functional division of STN coupling with mesial and lateral motor regions find any correlate in anatomical studies? Tractography studies in both healthy humans and in patients with PD have demonstrated the existence of direct anatomical connectivity between the SMA and the STN consistent with the hyperdirect pathway identified in rodents and non-human primates (Baudrexel et al., 2011; Brunenberg et al., 2012). In line with the proposal that the hyperdirect pathway characterised by activity in the upper beta frequency band might dominate the drive from mesial motor regions to STN a study using MRI tractography to place electrocorticographic electrodes over the origin of the hyperdirect pathway in mesial motor cortical areas confirmed high beta band coherence between these electrodes and STN at rest, although coherence changes were not reported during DBS (Whitmer et al., 2012). Conversely, another recent study placed electrocorticographic electrodes directly over the primary motor cortex and reported peak coherence in the low beta frequency band (de Hemptinne et al., 2015a).

I hypothesise that STN coherence with cortical motor regions in the high and low beta frequency ranges might correspond to activities predominantly driven by the classical hyperdirect and the indirect pathways to the STN, respectively (Alexander and Crutcher, 1990; DeLong, 1990). In line with this, Granger causality was consistent with cortical driving of STN in both sub-bands and the phase delays to STN were much shorter for the high beta than the low beta frequency range. Indeed, the differential net temporal lead of cortex in the two frequency sub-bands compares very favourably with that reported in an independent patient cohort studied with EEG (Fogelson

et al., 2006). The relatively long (20 ms) delay to STN in the high beta band may arise because activities in the hyperdirect and indirect pathways are only relatively and not absolutely spectrally distinct. In this case estimates of the delay in the hyperdirect pathway will be exaggerated by the indirect component overlapping in frequency (Cassidy and Brown, 2003).

Numerous prior studies have proposed excessive hyperdirect pathway activity as an important factor in the motor dysfunction in PD, with some of these providing experimental or modelling evidence that DBS selectively suppresses this increased hyperdirect pathway coupling (Dejean et al., 2008; Tachibana et al., 2011; Gradinaru et al., 2009; Leblois et al., 2006; Baudrexel et al., 2011, 2014; Holgado et al., 2010; Moran et al., 2011; Marreiros et al., 2013; Kang and Lowery, 2013, 2014). The lack of correlation between the weakening of STN coherence with mesial cortical motor areas and clinical improvement upon DBS would be consistent with the view that a strengthened hyperdirect pathway is a pre-requisite for beta activity, in so far as this reflects motor dysfunction, but not sufficient (Holgado et al., 2010; Moran et al., 2011; Marreiros et al., 2012).

Observations in rodents suggest that the effects of DBS on the hyperdirect pathway may be secondary to the antidromic activation of corresponding axons (Dejean et al., 2008; Gradinaru et al., 2009). This is supported in patient studies by recordings of STN DBS evoked cortical potentials of short latency that are able to follow high stimulation frequencies (Ashby et al., 2001; Devergnas and Wichmann, 2011; Walker et al., 2012). These evoked potentials are reported to be maximal in amplitude over mesial cortical areas, despite the presence of more lateral burr holes (Ashby et al., 2001; Walker et al., 2012). In line with this, the present results suggest that the hyperdirect pathway may be disproportionately represented in mesial cortical motor areas. It remains to be determined why DBS in the targeted region of the STN might preferentially affect inputs from these latter areas, but it is possible that they have lower stimulation thresholds due to differences in axon diameter or orientation.

7.4.3 DBS influences local activity in the STN

DBS suppressed STN LFP power in the low beta frequency range, consistent with previous reports (Kühn et al., 2008b; Bronte-Stewart et al., 2009; Eusebio et al., 2011; Whitmer et al., 2012).

Furthermore, the extent of low beta power suppression during DBS correlated with clinical motor improvement. Previously this had only been demonstrated immediately after cessation of DBS (Kühn et al., 2008b). The suppression of low beta power in the STN by DBS is somewhat paradoxical given that the only cortical drive to be weakened by DBS was that from mesial premotor cortical areas which preferentially involved upper beta band activity. This might be taken to argue that the pattern of local oscillatory synchronisation in the STN is determined by more than simply the nature of cortical drives, and allows for subcortical loops that amplify or generate activity in the beta, particularly low beta frequency band in the STN. The reciprocal connectivity between STN and GPe is often cited in this regard (Holgado et al., 2010; Cruz et al., 2011; Moran et al., 2011; Tachibana et al., 2011; Marreiros et al., 2012). These subcortical loops promoting activity in the beta band may then also be weakened by DBS, an action shared by dopaminergic therapy (Kühn et al., 2006b, 2009; Weinberger et al., 2006; Ray et al., 2008; Marreiros et al., 2012).

7.4.4 Conclusions and clinical implications

Experimental and computational modelling studies suggest that an abnormally strengthened hyperdirect pathway between motor cortical areas and the subthalamic nucleus is a pre-requisite for pathological oscillations in basal ganglia circuits in Parkinson's disease. The strength and changes in the strength of such oscillations correlate with the extent of motor impairment and changes in motor impairment in this condition (Kühn et al., 2006, 2009; Weinberger et al., 2006; Ray et al., 2008; Chen et al, 2010; López-Azcárate et al, 2010; Özkurt et al, 2011; Sharott et al, 2014). Studies in rodent models of Parkinsonism have suggested that subthalamic deep brain stimulation, may at least partially act by disrupting the hyperdirect pathway through antidromic activation, thereby removing one of the necessary conditions for pathological oscillations (Li et

al., 2007, 2012; Dejean et al., 2008; Gradinaru et al., 2009; Holgado et al., 2010). Using simultaneous magnetoencephalography and local field potential recordings I demonstrate that the therapeutic effects of DBS in Parkinsonian patients are indeed associated with a selective attenuation of the presumed hyperdirect drive to the STN, and diminished oscillatory activity in this nucleus. The lack of and presence of clinical correlations with these respective effects adds further weight to the notion that a strengthened hyperdirect pathway is a pre-requisite for locally generated or amplified beta activity but that it is the severity of the latter which may determine or index motor impairment (Holgado et al., 2010; Moran et al., 2011; Marreiros et al., 2012).

My findings also reinforce the principle that different functional cortico-subcortical loops passing through the basal ganglia may not only be characterised by their differential cortical topography, but also by their preference for conducting activities in certain frequency ranges (Fogelson et al., 2006; Hirschmann et al., 2011; Litvak et al., 2011a). Thus temporal, lateral motor and mesial motor cortical loops could be distinguished by their relative preference for driving activities in the alpha, low beta and high beta ranges. A critical future challenge then is to define how activities in these different loops may underlie different symptoms. Then stimulation could be further refined and made patient specific by tailoring both its delivery (Bour et al., 2015) and pattern (Cagnan et al., 2013; Little et al., 2013a) according to the nature of the local field potential activities recorded at the stimulation target.

Chapter 8: General discussion

8.1 Overview of thesis aims

In this thesis I aimed to address a number of questions concerning the functional and pathophysiological roles of oscillatory activities within cortico-basal ganglia circuits. In this regard I specifically focussed on insights gained from electrophysiological studies of patients with Parkinson's disease for a number of reasons. Firstly Parkinson's disease is by the far the most common and extensively studied disease process known to influence cortico-basal ganglia circuits and recent therapeutic advances in functional neurosurgery have made it possible to gain highly informative invasive electrophysiological recordings from these circuits. Secondly since dopamine deficiency lies at the core of Parkinson's disease it is possible to study patients ON and OFF their dopaminergic medication and hence make inferences about the roles of oscillatory activities both in disease and in the spectrum between the healthy and diseased state. This approach is based on the premise that the core deficit in Parkinson's disease is partially reversed by exogenous dopamine administration. However a note of caution is that the homology between brain states in treated Parkinson's disease and in health is only likely to be approximate at best. Finally, I believe that the study of Parkinson's disease may provide a foundation for the development of novel therapeutic regimens designed to specifically target aberrant or pathological brain networks. In this regard there have been some very encouraging recent proof of principle studies highlighting improvements in both tremor amplitude and bradykinesia/rigidity through adaptive stimulation regimes (Rosin et al., 2011; Brittain et al., 2013; Little et al., 2013a).

I will now provide a brief overview of the questions I set out to address in the introduction. In Chapters 3 and 4 I aimed to address whether STN oscillatory activity in the physiological beta and gamma frequency ranges relates purely to motor processing or whether it may more generally indicate task specific cognitive demands. Firstly I determined whether such reactivity was present following the presentation of cues that instructed the need for future action, regardless of

whether the action to be performed was a motor task or a cognitive task. Secondly I tested whether two key contextual factors that are intimately related to motor performance - knowledge about task complexity and the potential reward associated with task performance - could influence perimovement beta and gamma oscillatory activities. Crucially I dissociated these contextual factors from motor preparation and parameterisation.

In Chapter 5, I went on to study interactions between the STN and cortical regions in PD during movement. Using simultaneous MEG and intracranial STN LFP recordings, it had previously been established that two resting STN–cortical networks exist in patients with PD (Hirschmann et al., 2011; Litvak et al., 2011a). An alpha band network exists between the STN and temporal regions, while a beta band network exists between the STN and premotor/motor regions. It had been established that movement was associated with a slight suppression of beta band coupling between the STN and motor regions and the emergence of a transient STN–motor gamma band network. Crucially, coupling within the gamma network was strengthened by levodopa with medication related improvements in clinical scores correlating with increases in coupling (Litvak et al., 2012). This finding suggested oscillatory activities within long range STN–motor cortical circuits may have important pathophysiological roles in PD. I wanted to ask whether oscillatory activity within the identified STN–temporal resting alpha band network could also play a role in motor performance in PD. There have been some suggestions that this network and particularly synchronised alpha frequencies might be important in attentional processes and hence may not relate to motor processing, but this remains to be tested (Palva and Palva, 2007; Litvak et al., 2011a; Bauer et al., 2012).

The effects of dopaminergic medication on resting patterns of activity within the STN–cortical alpha and beta band networks had been established in a single previous study (Litvak et al., 2011a). It is interesting to note that despite the fact that dopamine is known to suppress synchronised beta band activity within the STN, it had relatively few effects on STN–cortical

coupling over this frequency range. In fact, Litvak et al 2011 actually observed a somewhat counterintuitive dopamine related increase in coherence between the STN and premotor regions. While there may be a number of reasons for the lack of dopaminergic effects on resting coherence including the stun effect (see limitations), one plausible explanation which cannot be discounted is that the STN–motor beta network relates to normal physiology rather than being pathological. It is very hard to discount this possibility without the opportunity to record from the subthalamic area of healthy subjects or non-Parkinsonian patients, but further insights on this question can be gained from the study of the effects of DBS on these networks. For example if exaggerated STN–motor beta coherence were a pathophysiological process in PD we might expect that DBS would suppress this excessive synchrony, with the degree of synchrony suppression probably correlating with DBS related clinical motor improvements. A second inter-related reason for studying DBS effects on STN–cortical networks is to identify the mechanisms through which DBS exerts therapeutic benefit. Such knowledge has the potential to guide therapeutic advances in DBS technologies (see section 8.5).

In order to study DBS effects on STN–cortical networks I developed and validated appropriate methodological techniques in Chapters 6 and Appendix A. Chapter 7 then presents insights on the effects of DBS on synchronised oscillatory activity within STN–cortical networks.

8.2 Motor and non-motor roles of STN oscillatory activities within the beta and gamma frequency bands

Chapter 3 was the first study in PD to dissociate beta suppression from motor processing. STN LFPs were recorded for warning cues that indicated whether a response would or would not be required in an upcoming motor or cognitive task. To maximally dissociate processing related to the saliency of the warning cue from task specific processing we systematically varied both the timing of the imperative cue after the warning cue and the specific nature of the task to be performed. The core finding was that changes in beta power in the LFP depended on the

behavioural relevance of the warning cue. Warning cues that pointed to the need for a subsequent response were followed by beta power suppression, whereas those that signalled that no response would be necessary were followed by delayed beta power increases. Beta power changes following warning cues signalling the need or not for a subsequent response occurred regardless of whether the necessary response was motor or cognitive. Furthermore, beta reactivity to warning cues was potentiated in the dopamine replenished state for both the motor and the non-motor tasks.

An interesting feature, worthy of further discussion that emerged from this study was a dopamine dependent sustained change in the beta power signal that persisted up to the point of presentation of the imperative cue (see Figure 3.6). The direction of the sustained change, (either a desynchronisation or a hypersynchronisation) depended on the salience of the warning cue, but crucially this was not the only contributory factor since the power change persisted up to the point of imperative cue presentation. This makes it more likely that the power changes in the beta band relate to anticipation of the motor or cognitive response engendered by the saliency of the cue, rather than cue saliency *per se*. Such an anticipatory process could subserve predictive resourcing of the prospective action and economy of resourcing in the absence of the need for action. This possibility would be in accord with recent theories of the functional role of oscillatory activity in the beta band (Jenkinson & Brown, 2011). The latter posit that beta activity provides a dynamic indicator of the likelihood that a new action will need to be actuated, with the level of beta being inversely proportional to the likelihood that a new action will need to be processed and performed. Interestingly in our study we used foreperiods that were randomly selected between 2.4 and 5 seconds. Therefore, one might expect anticipation to gradually build up over this time period (see also Oswal et al., 2007 for a more formal discussion) and for beta power changes to reciprocally reflect this. While our data in Figure 3.6 do support that beta power progressively decreased with increasing foreperiod following warning cues that instructed the

need for future movement, I must point out that I did not explicitly test whether the STN beta signal dynamically tracks probabilities.

In summary Chapter 3 provided evidence that the modulation of beta activity in the STN is not simply an epiphenomenon of the reconfiguration of neural interactions in favour of synchronization at higher frequency during task related processing. Rather, it is the consequence of an active process that may prospectively set the state of readiness for executive processing according to the salience of incoming environmental cues. This reactivity in beta band oscillations is impaired when dopamine is deficient.

In Chapter 3 I predominantly explored anticipatory spectral changes within the STN, while in Chapter 4 I explored both anticipatory and perimovement spectral changes in response to information about two important contextual factors - task complexity and reward. As reported in Chapter 3 there was a task-related suppression of STN beta power when the parameters of the movement could not be prepared in anticipation. Crucially this effect was not modulated by prior warning of the forthcoming task complexity which is in keeping with a role for beta desynchronisation in signalling the likelihood of an upcoming action. Task complexity did impact on processing in the STN, once movement selection and preparation were possible. Task complexity increased both gamma synchronisation and beta desynchronisation before and during the movement leading to speculation that the degree of reciprocal beta-gamma change in the STN may scale with the cognitive and motor effort expended in the task. These reciprocal oscillatory changes were supported by dopamine, which is in keeping with the known effects of this neurotransmitter in promoting effortful behaviours (Kurniawan et al., 2011).

Recent models of motor control recognize the need for a general mechanism to regulate the effort expended during a task according to task demands and cost/benefit contingencies (Guigon et al. 2007; Todorov and Jordan 2002) and this function has been associated with the basal ganglia (Mazzoni et al. 2007; Niv and Rivlin-Etzion, 2007). Although the reciprocal LFP changes I

describe by no means prove a role for the STN in the coding of effort, they are nevertheless suggestive. Furthermore, my work has been followed by more recent demonstrations that STN gamma band activity encodes effort (Tan et al., 2015).

In summary Chapters 3 and 4 provide evidence that oscillatory activity within the STN may subserve different roles depending on its timing relative to environmental cues and movement. Cue locked beta reactivity may subserve an anticipatory role which signals the likelihood that an upcoming action needs to be performed. Pre and peri-movement reciprocal oscillatory activity in contrast may code for effort.

8.3 The role of STN–cortical networks in the Parkinsonian motor phenotype

The study of movement and medication related modulations in synchronised oscillatory activity within STN–cortical circuits offers a powerful insight into the pathophysiological mechanisms underpinning motor impairments in PD. In Chapter 5 I established that the STN uncouples from temporal regions in the alpha band during voluntary movement, and furthermore that this process is at least partially dependent on dopamine. Importantly, dopamine related reductions in STN-temporal alpha band coherence correlated with improvements in motor UPDRS scores, highlighting the potential importance of this network in the pathophysiology of PD.

The present findings are in several ways the reciprocal of the gamma band coherence between STN and M1 reported in the same patients (Litvak et al., 2012). Gamma band STN-M1 coherence was increased with movement, particularly after dopaminergic medication, with increases in coherence correlating with motor improvement. Crucially changes in STN-temporal coupling within the alpha band and STN-M1 coupling in the gamma band explained a similar portion of the variance in the clinical response to treatment. This would imply that the dopamine dependent disengagement of the STN from its locking to temporal cortex at alpha band frequencies, and the engagement of STN locking to motor cortex in the gamma band are two related and partially dependent processes.

Importantly coupling within both of these networks was not influenced by whether a simple or a more complex motor task was being performed leading to the suggestion that the alpha and gamma band networks may play a modulatory role and are related to attention or arousal rather than to motor processing. Note in light of the results of Chapter 4 that we did not observe an increase in STN-M1 gamma band coherence with tasks requiring greater effort, but there may be a number of explanations for this, including that suggestion that local STN gamma band activity could encode features that are distinct to activity that is synchronised between the STN and cortex.

Whilst there is a body of evidence linking alpha oscillations to attentional processes (Clayton et al., 2015) confirmation of a putative role for the STN-temporal alpha band network in orienting attention is awaited. At present I am involved in a study where we are exploring whether STN-temporal alpha band activity may be lateralised or modulated by visual cues instructing spatial attention, for example in the Posner task. If the STN-temporal alpha network does primarily relate to attentional processes, this network may form a neural substrate for explaining how attentional deficits in PD relate to motor impairments. This hypothesis is supported by correlations of attentional deficits in PD with motor impairment such as gait freezing and falls (Yarnall et al., 2011; Tessitore et al., 2012).

8.4 Studying synchrony within STN–cortical networks during DBS

A key goal of this thesis was to develop methods that would allow me to study the effects of DBS on STN-cortical networks. A major challenge in this regard was to handle high amplitude DBS artefacts that occurred both locally in the STN LFP and at the MEG sensor array. In Appendix A I describe the methods that were used to suppress these artefacts and to obtain valid estimates of coherence. Artefacts in the LFP could be well suppressed using a custom built amplifier while artefacts at the MEG sensors were handled using a combination of channel rejection, jump correction and source space analysis with beamformers. Additionally in Chapter 6, I introduced a

modification to the standard beamforming approach, in order to optimally represent sources within a region of interest and hence suppress potential artefactual sources outside this.

8.5 How does DBS work in Parkinson's disease?

Chapter 7 aimed to shed light on the mechanisms through which DBS exerts therapeutic effects. DBS primarily suppressed low beta frequency activity in the STN, with the extent of suppression correlating with clinical motor improvements across subjects. Interestingly, DBS did not influence coupling within the resting STN-temporal alpha band network, which is in keeping with our results from Chapter 5 highlighting that this network is unlikely to play a role in motor processing. In contrast, DBS did suppress broad beta band coupling between the STN and mesial premotor areas such as the SMA. These mesial premotor regions predominantly drive STN activity in the beta band at rest and it was evident from our Granger causality analysis that DBS was reducing the cortical driving of the STN.

A further feature of our findings was that the STN–cortical motor beta circuit could be further subdivided based on spectral preferences and regions that were reactive to DBS. Thus STN DBS suppressed beta band synchronisation between the STN and mesial motor regions encompassing the SMA, but had no effect on the coupling between the STN and lateral motor regions that included primary motor cortex. This differential reactivity to DBS was paralleled by spectral differences between these motor sub-circuits. Those mesial areas that uncoupled from the STN during DBS were more strongly coupled to the STN in the high beta than the low beta frequency range. In contrast, motor areas outside of this mesial premotor region exhibited beta band coupling with the STN that was more balanced between low and high frequencies within the beta band.

It is interesting to ask whether this functional division of STN coupling with mesial and lateral motor regions has any anatomical correlates. Tractography studies in both healthy humans and in patients with PD have demonstrated the existence of direct anatomical connectivity between the

SMA and the STN consistent with the hyperdirect pathway identified in rodents and non-human primates (Baudrexel et al., 2011; Brunenberg et al., 2012). In line with the proposal that the hyperdirect pathway characterised by activity in the upper beta frequency band might dominate the drive from mesial motor regions to STN a study using MRI tractography to place electrocorticographic electrodes over the origin of the hyperdirect pathway in mesial motor cortical areas confirmed high beta band coherence between these electrodes and STN at rest (Whitmer et al., 2012). Conversely, another study placed electrocorticographic electrodes directly over the primary motor cortex and reported peak coherence in the low beta frequency band (de Hemptinne et al., 2015b).

Accordingly, we hypothesise that STN coherence with cortical motor regions in the high and low beta frequency ranges might correspond to activities predominantly driven by the classical hyperdirect and the indirect pathways to the STN, respectively (Alexander and Crutcher, 1990; DeLong, 1990). In line with this, Granger causality was consistent with cortical driving of STN in both sub-bands and the phase delays to STN were much shorter for the high beta than the low beta frequency range (see Chapter 7).

Our results are therefore in keeping with the hypothesis that exaggerated cortical driving of the STN via the hyperdirect pathway (Alexander and Crutcher, 1990; DeLong, 1990) maybe of pathological relevance in PD and that DBS acts to suppress this. These findings are consistent with those of other computational and experimental studies exploring the role of an exaggerated hyperdirect pathway in PD (Dejean et al., 2008; Gradinaru et al., 2009; Holgado et al., 2010; Moran et al., 2011; Marreiros et al., 2012; Kang and Lowery, 2013, 2014). Nevertheless, this rather neat summary is somewhat complicated by two findings: 1) that we did not find a significant correlation between the weakening of STN coherence with mesial motor cortical areas and clinical improvement upon DBS and 2) That low beta frequency band power suppression in the STN by DBS is somewhat paradoxical given that the only cortical drive to be weakened by DBS

was that from mesial premotor cortical areas which preferentially involved upper beta band activity. Taken together these findings point to the fact that although exaggerated hyperdirect pathway activity may be a pre-requisite for beta activity, it is not on its own sufficient (Holgado et al., 2010; Moran et al., 2011; Marreiros et al., 2012), and secondly that the pattern of local oscillatory synchronisation in the STN is determined by more than simply the nature of cortical drives. Subcortical loops, for example between the STN and the GPe, that amplify or generate activity in the beta sub-bands may exist (Holgado et al., 2010; Moran et al., 2011; Marreiros et al., 2012). These subcortical loops may be suppressed by DBS and also by dopamine (Kühn et al., 2006b, 2009; Weinberger et al., 2006; Ray et al., 2008).

8.6 Possible implications for future DBS technologies

The results and hypothesis presented in this thesis suggest that therapeutic benefits may be gained for PD by directly targeting hyperdirect pathway driving of STN beta activity. This may be achieved by either invasive or non-invasive cortical stimulation regimes for example, and some studies do suggest that non-invasive cortical stimulation at specific frequencies can enhance or suppress motor performance in healthy subjects (Pogosyan et al., 2009; Joundi et al., 2012). A major challenge of developing this work for therapeutic advances will be to specifically target cortical regions which drive and may lead to STN beta activity.

8.7 Limitations of the present work and areas for future study

I wish to point out a number of limitations of the work presented in this thesis and suggest some areas for future study. Many of the limitations specific to each study have already been presented in the relevant chapters and here I will present a brief overview before discussing some more general methodological issues.

First of all as earlier mentioned we must be careful when drawing conclusions about the physiological roles of oscillatory activities when studying patients with PD, particularly in the immediate post-operative period where local power reactivity is likely to be impaired due to the

so called 'stun' effect (Chen et al., 2006). Nevertheless, since a dopamine deficit lies at the core of the pathophysiology of PD, contrasting oscillatory activities and behaviour when patients are ON and OFF their dopaminergic medication remains a highly useful approach (Williams et al., 2002). Another limitation is the fact that I did not subdivide the STN into its constituent anatomical and functional zones when considering local and inter-areal synchronisation. There is now a body of evidence arguing that the STN may have spatially segregated areas dedicated to motor processing (dorsal areas) and to more cognitive functions in the limbic and associative domains (ventral areas) (Rodriguez-Oroz et al., 2001, 2011; Mallet et al., 2007; Lardeux et al., 2009). Other studies, however, reveal that the STN is not so neatly segregated and that neurons throughout the nucleus may be involved in motor control and cognition (Haynes and Haber, 2013; Eisenstein et al., 2014). The evidence is therefore conflicting, but novel high field imaging techniques combined with tractography do offer the potential to resolve some of these issues. Related to this point is the fact we cannot be sure if the LFPs we are recording with STN macroelectrodes originate from within the nucleus or whether they represent volume conduction from nearby sources. In my experimental chapters I argued that by using bipolar contact pairs I can limit the effects of volume conduction and also that the steep gradient in LFP power across different bipolar contact pairs combined with the fact that discharge of STN neurones tends to be locked to LFP activity are strong arguments in favour of the generation of the local generation of the LFP (Levy et al., 2002b; Kühn et al., 2004, 2005b, 2006b).

Additionally I would like to point out that many of the analyses in this thesis have been of a correlative nature. While correlations are a critical step in establishing relationships, they by no means imply causality. In order to demonstrate causal relationships, the behavioural and clinical consequences of specifically modulating oscillatory activities within the brain networks that I have studied need to be established. Techniques such as transcranial alternating current stimulation offer the possibility to non-invasively stimulate cortical regions, but as yet they are not focal

enough to stimulate specific STN-cortical networks in isolation (Pogosyan et al., 2009; Joundi et al., 2012).

A final methodological limitation with the approaches that I have used in this thesis is the fact that I assume that brain signals are stationary when performing Fourier based spectral analysis over long time windows or when computing covariance matrices for beamformer source localisation estimates. Note that when considering movement related effects in Chapters 3, 4 and 5 I also performed spectral estimation over short time windows in the region of 400 ms, in order to provide increased temporal resolution. Whilst averaging over long segments of data can increase signal to noise ratios, which is particularly beneficial under the conditions we faced with patient MEG recordings (Litvak et al., 2010), we must bear in mind that resting and task related brain activity is not stationary - but rather it exhibits a complex and dynamic repertoire (Deco et al., 2008; Woolrich et al., 2013; Baker et al., 2014). I remain excited and optimistic about the possibility of applying both data driven (Sweeney-Reed and Nasuto, 2007) and model based approaches towards understanding short time scale brain dynamics in health and disease (Baker et al., 2014). In this regard I point out that the methods developed in Chapter 6 offer the possibility to reduce the amount of data required for beamforming and hence may be used in conjunction with the aforementioned model based approaches for investigating short timescale dynamics (Woolrich et al., 2013).

Appendix A - Analysis of simultaneous MEG and intracranial LFP recordings during DBS: a protocol and experimental validation

A.1 Introduction

Each DBS procedure presents a unique opportunity to gain valuable translational insights about electrophysiological brain activity in pathological disease states (Oswal et al., 2013b). Accordingly, DBS electrodes are sometimes externalised post-operatively, to facilitate local field potential recordings from target nuclei. As a result, it has been possible to gain valuable information about the clinical and functional correlates of oscillatory activity within the STN in PD. An additional role of such recordings has been to shed light on the local therapeutic mechanisms of DBS. For example, it has been possible to show that DBS reduces beta band activity within the STN (Rossi et al., 2008; Eusebio et al., 2011), and furthermore that the extent of beta reduction correlates with clinical improvement (Kühn et al., 2006b, 2009; Ray et al., 2008; Chen et al., 2010a). Such insights are being translated into improved clinical therapies, as highlighted by a seminal study of adaptive DBS in the Parkinsonian non-human primate (Rosin et al., 2011), and recent pilot work also suggesting that adaptive DBS, triggered to beta band amplitude, may potentially be better than conventional DBS at ameliorating Parkinsonian symptoms in patients (Little et al., 2013a). Despite these promising early insights, many questions remain yet to be answered about the neuromodulatory effects of DBS on long-range brain networks. Magnetoencephalography (MEG) may provide a powerful approach for imaging brain networks during DBS.

Previous work from using simultaneous MEG and resting intracranial LFP recordings has shown the existence of two spatially and spectrally distinct networks between the STN and cortical regions in PD (Litvak et al., 2010, 2011a; Hirschmann et al., 2011). An alpha band network exists between the STN and temporo-parietal and brainstem regions, whilst a beta band network exists between the STN and motor/premotor regions. Furthermore, the initiation of movement is accompanied by a dopamine dependent reduction in coherence in both of these networks and a

concomitant emergence of gamma band synchrony between the STN and primary motor cortex (Litvak et al., 2012; Oswal et al., 2013a). The identified resting state networks may play an important role in the pathophysiology of PD, highlighted by the fact that dopamine dependent modulations in their activities correlate with dopamine related improvements in clinical scores. Although such correlations by no means imply causation, their presence is highly informative. It is worthwhile noting that even in the absence of DBS, these recordings are severely contaminated by the presence of high amplitude artefacts related to the presence of ferromagnetic extension wires from the DBS electrodes to the recording equipment. However, source space analysis using beamformers enables effective suppression of such artefacts, allowing for valid physiological inferences to be made (Litvak et al., 2010; Oswal et al., 2014). Non-ferromagnetic extension wires have recently been made available, but only to restricted centres (Hirschmann et al., 2011).

Although it has been possible to simultaneously stimulate and record from the STN, and also to record from the STN during concurrent MEG, no methods have as yet been developed to combine these two approaches and allow simultaneous MEG and intracranial LFP recordings during DBS. The utility for such recordings is clear, since they would enable the characterisation of both local effects of DBS and of the effects of DBS on connectivity between target nuclei and distal brain regions. Such information could benefit current understanding of the therapeutic mechanisms of DBS in addition to informing future developments in DBS technologies.

In this Appendix I describe the experimental setup for simultaneous MEG and intracranial LFP recordings during DBS. I also detail the analysis procedure making it possible to recover coherence between the LFP and the MEG in the presence of stimulation, despite artefacts due to ferromagnetic extension wires, and those due to DBS currents that will not be obviated by the use of non-ferromagnetic extension wires. The proposed methods are validated using a dipole phantom and applied to data from a single PD patient with electrodes in the STN.

A.2 Methods

A.2.1 Simultaneous MEG and LFP recordings

All the MEG recordings described in the present results were performed using a CTF 275-channel MEG system (CTF/VSM MedTech, Vancouver, Canada). An important advantage of this system is the high dynamic range of its sensors and their robustness to strong external interferences.

In our previous studies we used the EEG system integrated in CTF-MEG to record the intracranial data (Litvak et al., 2011a, 2012; Oswal et al., 2013a). My rationale for moving away from this approach was that the recording equipment was not isolated from the mains power supply and thus did not comply with newer and more rigorous local safety standards. The approach I use in the present study is to record LFP and other electrophysiological measurements from the patient using a battery-powered and optically isolated BrainAmp system (Brain Products GmbH, Gilching, Germany). The challenge that this approach poses is fusing the EEG and MEG data with minimal timing distortions. For this purpose I propose to use a synchronisation signal recorded on both systems. The optimal type of signal is random white noise because it can only be matched in a unique way.

Any noise generator capable of producing wide-band noise with an appropriate amplitude can be used. My generator was built utilising an 8.2 V Zener diode biased close to its avalanche region. This was achieved using a variable potentiometer, while an oscilloscope was used to ensure the maximum noise was produced. The noise was amplified to 500 mV peak-to-peak range. To control the exact output amplitude a variable resistor on the output was included. Note that connecting the noise generator with cables to both the MEG and the EEG amplifier would create a breach in the optical isolation and defeat its purpose. Fortunately, the BrainAmp system provides a solution by combining two optically isolated amplifiers into one system with synchronous sampling – accordingly one of these amplifiers was used to record the noise signal, whilst the other was used to record physiological activity (see Figure A.1).

Figure A.1 details the experimental set up. I note that it is possible to record the white noise and the physiological signals (LFP, EEG, EOG, EMG) in either a monopolar or a bipolar fashion. For the purposes of my experiment I recorded physiological signals bipolarly (using an 8 channel bipolar ExG BrainAmp amplifier), since the stimulation-record amplifier was designed to give bipolar outputs (see below). The white noise was recorded using a 32 channel monopolar BrainAmp MR plus amplifier. This set up was approved by the MEG safety board of the Wellcome Trust Centre for Neuroimaging, following extensive in-house safety testing.

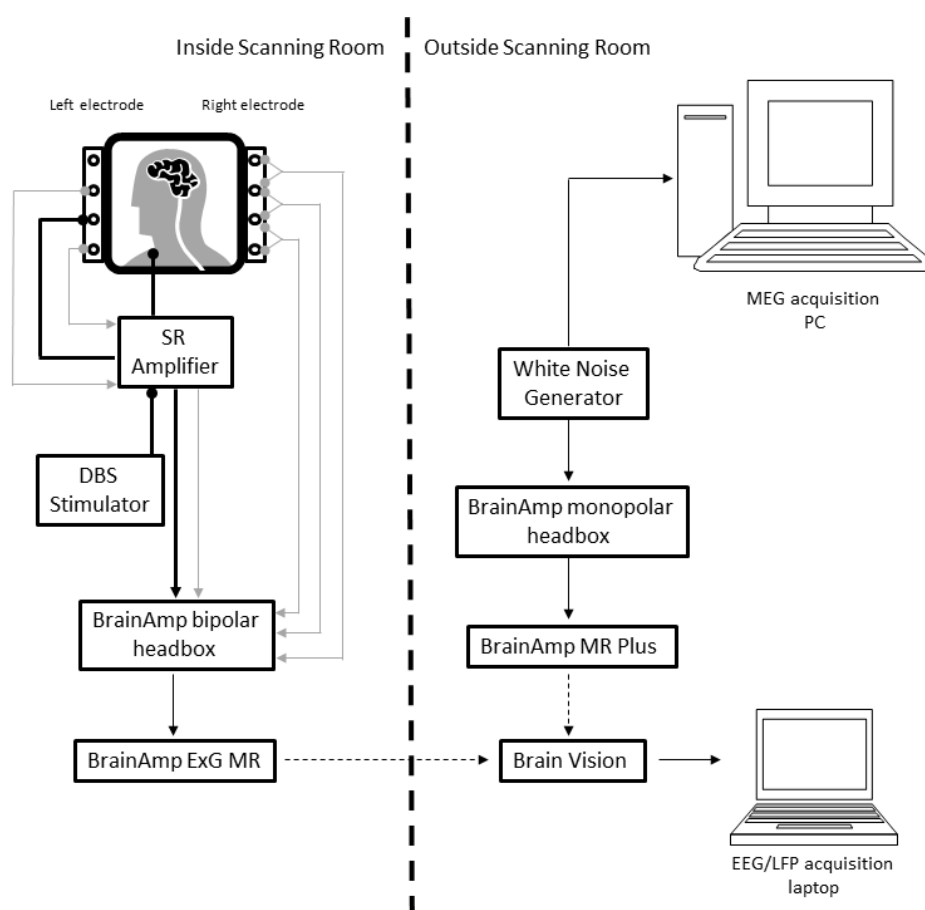


Figure A.1 Schematic showing our set up for a patient recording within MEG.

A bipolar LFP between contacts 0 and 2 of the DBS electrode (see grey lines originating from left electrode) is recorded during concurrent DBS by the stimulation record (SR) amplifier. DBS is given in a monopolar fashion between contact 1 of the DBS electrode and a reference attached to the patient's clavicle (see black lines ending with circles). The SR amplifier outputs the recorded LFP and the stimulation signal (grey arrowed line and black arrowed line) to a bipolar BrainAmp headbox. The latter is also used to record bipolar LFPs from the side not being stimulated (see grey arrowed lines originating from the right electrode). Black dashed arrows depict optic fibre cables, which serve to optically isolate

the patient from a mains power source (see methods section). The timings of signals recorded from the MEG and the LFP acquisition laptop are synchronised through the independent recording of a single white noise source on the two systems (see methods for further details).

A.2.2 Experimental protocol - phantom

To demonstrate that MEG activity coherent with a reference channel can be accurately recovered in the presence of DBS artefacts I performed an experiment with a MEG phantom. I used a CTF current dipole phantom comprising a spherical plastic container, holding saline, in which a dipolar source can be immersed (see schematic of setup in Figure A.2). The dipolar source was driven by a 27 Hz sinusoidal signal, so as to mimic activity within the physiological beta range, and its amplitude was set to 6.7 μ A to create a peak in the power spectrum slightly exceeding the background noise level (see Figure 9.4. The ratio of the RMS amplitude of the 27 Hz peak to that of background noise was 3.3).

In addition to the dipolar source, additional electrodes were immersed in the phantom. This was done via openings at the bottom of the sphere that are usually used to vary the position of the dipole source. The openings were sealed around the electrodes to prevent saline leakage. One of the additional electrodes was a clinical DBS electrode, model 3389 (Medtronic Neurological Division, Minneapolis, MN) with four platinum-iridium cylindrical surfaces (1.27 mm diameter and 1.5 mm length) and a centre-to-centre separation of 2 mm. Contact 0 was the closest to the electrode tip and contact 3 – the farthest. To emulate monopolar stimulation we immersed an additional anodal reference electrode in the phantom. Accordingly, in the present recordings monopolar DBS was administered between contact 1 of the DBS electrode and the anode. Bipolar DBS in contrast is administered between adjacent contacts of the DBS electrode. In my phantom recordings, bipolar stimulation was administered between contacts 0 (cathode) and 1 (anode) of the DBS electrode. Note that in my recordings with the phantom, I tested monopolar and bipolar DBS separately in order to characterise the different kinds of sensor artefacts produced by each

of these stimulation regimes. All analyses of coherence however are presented only during monopolar DBS (see below).

A copy of the sinusoidal input to the current dipole was recorded bipolarly with the BrainAmp amplifier system as would be done with the intracranial LFP. Note that although in the monopolar arrangement I could also record the potential difference between contacts 0 and 2 of the DBS electrode (see below for details), using it as a surrogate LFP would not mimic the patient recording well. This is because the dipole signal would only be picked up by volume conduction in water from a distant source, whereas in the real patient the LFP signal is picked up from neurons surrounding the electrode. Consequently I did not use the stimulation-record amplifier (see below) for my phantom recordings.

Three Head Position Indicator (HPI) coils were attached to the phantom in order to facilitate co-registration between the MEG co-ordinate system and the phantom. The phantom was raised into the MEG helmet and whilst the dipolar source was active, three minute recordings were performed for each of the following experimental conditions: 1) No DBS, 2) Monopolar DBS at 130 Hz 3) Monopolar DBS at 20 Hz 4) Bipolar DBS at 130 Hz 5) Bipolar DBS at 20 Hz.

DBS was administered with a Medtronic external stimulator (type 3628) via a custom built stimulation-record amplifier (see below) with a pulse width of 60 μ s and amplitude of 3V. Our measurements showed that the current flowing through the phantom for these parameters was 6 mA which corresponds to charge of 0.36 μ C/phase and charge density of 6 μ C/cm²*phase. These values are similar to those measured for real DBS in patients (Kuncel and Grill, 2004). The rise time of the pulse was $\sim$ 1 μ s.

Although stimulation at 130 Hz produces the greatest clinical benefit, I also explored the effect of stimulating at 20 Hz as a means of probing beta band resonance within the cortico-subthalamic nucleus network.

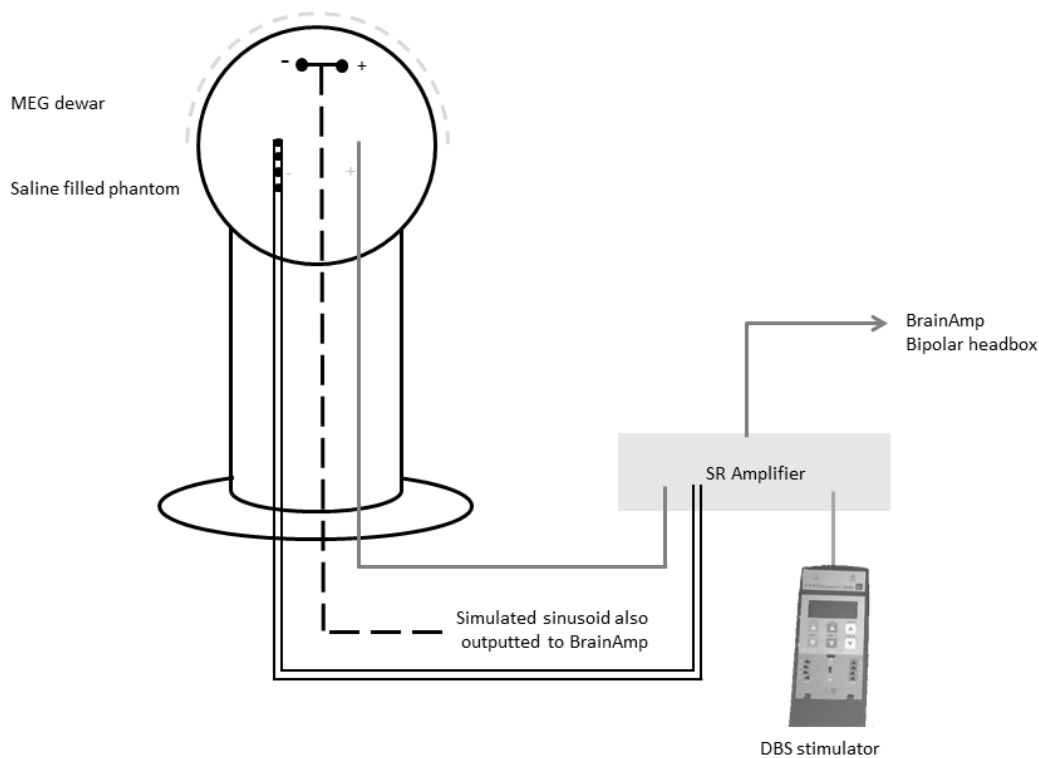


Figure A.2 Schematic showing the phantom recording setup within MEG.

The phantom was filled with saline and positioned in the MEG Dewar. Three electrodes were immersed in the phantom: 1) An electrode which simulated a dipole with a sinusoidal signal at 27 Hz (shown by the dashed black line), 2) A clinical DBS electrode (see methods), one contact of which was used to administer monopolar DBS at clinical settings, and 3) A second electrode for DBS such that monopolar DBS was administered between this electrode and contact 1 of the DBS electrode. In this case, contact 1 of the DBS electrode was the cathode. Note that in this schematic, the dipolar source is shown as being central within the phantom, but its exact location is shown more precisely in Figure 9.7. For the phantom recordings the stimulation-record amplifier (SR amplifier) was used in conjunction with the external stimulator to provide DBS. In patient recordings however, the SR amplifier was also used to record the STN LFP during DBS and to amplify this before outputting it to the BrainAmp device. A copy of the simulated sinusoidal signal was also outputted to BrainAmp.

A.2.3 Patient experiment

I present data from a 43 year old male patient with a nine year history of PD, who underwent implantation of bilateral DBS electrodes in the STN. The recordings were approved by the local

NRES ethics committee (REC No: 11/SC/0522), and the patient gave written informed consent prior to participation. The permanent DBS macroelectrode implanted in the STN was model 3389 as in the phantom experiment (see above). Further details of the operative procedure can be found in (Foltynie and Hariz, 2010; Foltynie et al., 2011). The locations of the electrodes were confirmed following implantation with immediate postoperative fast spin-echo T2-weighted magnetic resonance imaging (MRI) with a Leksell frame still in situ. The patient's preoperative T2-weighted MRI was used to construct a head model (see source space analysis for further details). Electrode extension cables were externalized through the scalp to enable recordings prior to connection to a subcutaneous DBS pacemaker, implanted in a second operative procedure 7 days later.

A.2.4 Simultaneous stimulation and recording from the STN

In this section I detail the approach for simultaneously stimulating the STN and recording the STN LFP during MEG recordings. I used a purpose built stimulation-record amplifier that was a variant of the design used in previous studies not involving MEG (Rossi et al., 2007; Eusebio et al., 2011; Little et al., 2013a). This amplifier was only used in the patient recordings and not for recordings with the phantom.

This design is based on the idea that when stimulating one of the two middle contacts (contact 1 or 2) monopolarly while recording from the two adjacent contacts of the DBS electrode (0 and 2 or 1 and 3, respectively) one can use the common mode rejection property of the front stage differential amplifier to reduce the DBS artefact and line noise. Both these signals are seen similarly by the recording contacts. The stimulation-record amplifier is used in combination with a clinically approved external DBS stimulator (type 3628, Medtronic Inc., Minneapolis, MN) connected to the intracranial electrode via the amplifier circuit.

The amplifier consists of the following components:

1. Front stage amplifier with a gain of x10 (any higher could saturate the amplifier due to DC voltages on the contacts).
2. DC blocking component, to remove any offsets that could cause saturation of the subsequent stages.
3. Low pass filter at 40 Hz to further reduce the line noise and DBS artefacts (when 130 Hz DBS is delivered). This filter is based on a Sallen-Key low pass design with -12db per stage. Two stages were used giving -24db of attenuation for each doubling of frequency after 40 Hz, which is in most cases sufficient to recover the frequencies of interest.
4. In addition to the LFP from the stimulated location the amplifier also generates a copy of the stimulation train which can later be used e.g. for segmenting the data. This is achieved by connecting the stimulator signal to an opto-isolator in parallel with the patient. The stimulator pulse of about 60 μ s is too fast for sampling by the EEG amplifier requiring the use of a 555 timer circuit to stretch the pulse to approximately 2 ms. The pulse is then reduced in amplitude to a few mV.

The amplifier produces two bipolar output signals compatible with the BrainAmp ExG box: LFP and stimulation train copy. Consequently during blocks of recordings with DBS ON, I was able to record both a single bipolar LFP from the side being stimulated, and 3 bipolar LFPs from the contralateral side.

A.2.5 Experimental Protocol – patient recordings

Recordings were performed after overnight withdrawal from dopaminergic medication. The patient was requested to keep his eyes open and to stay still during recordings. I was present inside the magnetically shielded scanner room at all times during the recordings, to monitor the wellbeing of the patient and to administer DBS.

The experiment started with a 4 min resting block during which data were collected directly via BrainAmp without the stim-record amplifier. The stim-record amplifier and external stimulator were then added to the setup and two additional recording runs were performed. Two stimulation conditions were tested independently for the right and left STNs: 0 Hz (no DBS), and 130 Hz monopolar DBS. The right and left STNs were stimulated separately in different recording runs. Each recording run was 7 minutes long and included two conditions, each lasting 3 minutes, separated by a 1 minute interval for washout of the effect of the first condition. Stimulation conditions were assigned to runs in random order. I also tested DBS at 5 Hz and 20 Hz in the same experiment but the data are not presented here.

Monopolar DBS, between contact 1 and an external reference applied to the patient's clavicle was administered by the neurologist. The stimulation pulse width and amplitude were 60 μ s and 3V respectively. At the onset of DBS, the stimulation voltage was increased slowly, in increments of 0.5V, whilst checking for clinical improvement and for the presence of any stimulation related side effects. Prior to experimentation, clinical assessment of the patient confirmed an improvement in motor (Part III) Unified Parkinson's Disease Rating Scale (UPDRS) scores with monopolar DBS at 3V and 130 Hz.

A.2.6 Electrophysiological Recordings

MEG data were sampled at 2400 Hz and stored to disk for subsequent offline analyses. Head location was continuously monitored throughout the experiment. For runs with two active DBS conditions a recording of ~1 min without DBS was added at the beginning to aid extraction of head location (see below).

LFP recordings from both STNs were simultaneously collected using the BrainAmp system. Patient data were collected via the 8-channel bipolar headbox and BrainAmp ExG amplifier, as shown in Figure 9.1. Eight intracranial LFP channels representing contacts 0-3 of each DBS macroelectrode were converted using bridge connectors into a bipolar montage, between

adjacent contacts. This resulted in 3 bipolar channels (0-1, 1-2, 2-3) recorded from each side and an additional channel recording the potential difference between contacts number 0 on the two sides (L0-R0) to enable if necessary converting the data to monopolar recordings referenced to the contralateral side.

After the initial resting recording the right side channels and L0-R0 channel were disconnected and bipolar channels #1 and #2 of the headbox were used for the stimulus train copy and the LFP recording from the stimulation-record amplifier. Channels #3 and #4 were left unused and channels #5-7 recorded from the unstimulated side. Initially this was the left side, but after the first two stimulation runs the connectors were swapped so that left became the stimulated side and right the unstimulated side.

LFP recordings were high pass filtered at 1 Hz in the hardware so as to avoid amplifier saturation due to large DC offsets. The data were sampled at 2500 Hz which was the closest available sampling rate to the one used in MEG. LFPs were recorded onto a laptop that was optically isolated from the BrainAmp hardware. Random noise from the noise generator was recorded simultaneously on the BrainAmp system via the 32-channel monopolar BrainAmp MR Plus amplifier and the MEG via one of the Analogue to Digital Converter (ADC) channels (see Figure A.1).

A.2.7 Offline data analysis

All analyses were performed using custom MATLAB scripts in combination with the SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/software/>)(Litvak et al., 2011b), Data Analysis in Source Space (DAiSS, <http://code.google.com/p/spm-beamforming-toolbox/>) and Fieldtrip (<http://www.ru.nl/neuroimaging/fieldtrip/>) toolboxes (Oostenveld et al., 2011).

A.2.8 Determining head location

In a previous paper (Litvak et al. 2012) a way of dealing with intermittent problems with head tracking was described based on the fact that the measured distances between the HPI coils

should stay constant (up to the measurement precision) when the head location is correctly measured. Here we describe a further development of this idea aimed at maximal usage of head tracking information recorded in the same session. The CTF system records the head location at the beginning of a run and also can be configured to record head location data continuously throughout the run. The initial measurement is controlled by the MEG operator who is shown whether the measurement is valid for all the three fiducials and if not has the possibility to wait further until a valid measurement is obtained. In our experience, obtaining valid initial measurements has been difficult due to the interferences of the ferromagnetic percutaneous wires (Litvak et al., 2010) with MEG sensors. It seems to require stable tracking for a few seconds so often a measurement that seems to be correct is still not accepted by the CTF software due to instabilities. I therefore opted not to wait too long in these cases and started the recording in order to avoid exhausting the patient.

An experiment usually produces a number of separate runs each containing an initial head location measurement (possibly invalid) and continuous head location data for the whole run, part of which might also be invalid. The idea of the analysis described below is to generate the best estimate of the head location in each run even if a large portion of the head location measurements are invalid. The analysis is based on the assumption that for valid head location measurements the pairwise distances between HPI coils will be the same (up to a small measurement error) whereas for invalid measurements they will be highly variable. Our approach had been optimised to work on a large group of recordings without concurrent DBS and was robust enough to work unmodified also with recordings including DBS despite the fact that during stimulation delivery head tracking was clearly disrupted.

We performed two passes on combined head tracking data from all runs. The aim of the first pass was to determine the distances between HPI coils. For this purpose I collected from each run two head location estimates. The first was the initial head location measurement. The second was

extracted from continuous location data by computing pairwise distances between fiducials in cm, rounding to the nearest integer and finding the most common value across time (using 'mode' function in Matlab). Time points for which one of the distances differed from its mode value by more than 1 cm were marked as invalid and interpolated using linear interpolation and extrapolation over the whole run. Corrected head location was then computed as the median over all points, original and interpolated.

I then examined pairwise distances between fiducials for all the collected measurements. In a typical stimulation experiment there would be 5 runs, yielding 10 measurements. Again, 'mode' function was used to find the most common set of distances and measurements with distances differing from the mode by more than 1 cm were marked as invalid. Averaged distances for the valid measurements were used in the second pass over the data. This pass again involved correction and interpolation of the original continuous head tracking traces with the difference being that distances for each time point were compared not to the mode of that same run but to the valid distances computed across all runs in the first pass. The rationale for that was that there might be some cases where tracking was valid only briefly so that the true values were not even most common in a run. Still if those brief moments could be identified one would get a better estimate of head location in that run than by taking it from a different run.

Finally, the original and corrected head locations were examined for the second time across all runs and their validity was determined by comparing distances to their most common values as described above. The average of all the valid locations was then computed. Each run was assigned a head location in the following order of preference. If the location computed from continuous head tracking data was valid, it was used because it best reflected the true head location during the measurement. If not, the initial measurement was used. If both run-specific measurements were not valid, the average over the valid measurements from other runs was used.

In practice, in the absolute majority of cases including the one presented in this report a run-specific head location could be successfully recovered. Head and sensor locations were always visually inspected and compared across runs to make sure that there are no gross outliers and misregistrations.

A.2.9 Fusion of MEG and LFP data

As the first processing step the raw data files from the CTF-MEG and BrainVision systems were converted to SPM MATLAB-based format. The LFP data were downsampled to 2400 Hz, matching the sampling rate of the MEG data. The white noise recordings from the MEG and BrainVision systems were linearly de-trended prior to cross-correlating the two timeseries. If both recordings were valid and the MEG and LFP files were matched correctly a clear peak could be detected in the cross correlation exceeding by far the background cross-correlation values. Our criterion for detecting this peak was that the ratio of the peak value to the median of the absolute values of cross-correlation across all delays was above 25. Based on the location of the peak with respect to the zero lag I determined the offset of the two recordings. This value could be used for the initial rough alignment. By computing local cross-correlations for different parts of the recording I found that this rough alignment would result in a slow drift between the two noise traces which would typically accumulate to 0.7 samples per minute of recording. The reason for this drift could be the fact that the true sampling rates of the two recordings were slightly different. We thus refined the alignment further using the following procedure. Non overlapping one-second segments were defined in the units of samples for the MEG data starting with the first sample. Corresponding segments were then defined for LFP data by adding the offset value determined from global cross-correlation to the MEG segment definition. MEG segments for which there was no LFP counterpart (due to asynchronous start and end of the two recordings) were discarded. Cross-correlations were then computed segment-wise between the MEG and LFP noise copies. For each segment, if a clear peak (exceeding 0.2 for normalised cross-correlation) was found in the lag range of ± 20 samples (± 8.3 ms) the corresponding offset was added to its LFP segment definition,

so that repeating the procedure with corrected LFP segment definition would only yield peaks at zero lag.

The resulting segment definitions for MEG and LFP were then used to epoch the full MEG and LFP data. The epoched datasets were fused and then converted again into a continuous recording (which was straightforward because the segments were consecutive in time). In this new dataset MEG and LFP data were fused and aligned. We chose to perform the fusion as early as possible in the processing pipeline to be able to process our older datasets recorded with the CTF EEG system and the new fused datasets in the same way.

A.2.10 Removal of MEG jumps

Visual inspection of the individual channel data obtained during monopolar DBS revealed high amplitude jumps in some of the channels that lasted only a few samples (see Figure A.3 and Results). The jumps contained power at all frequencies and could not, therefore, be removed by simple filtering. Importantly, however in both stimulation conditions, the majority of channels were not affected by jumps.

Prior to further analysis, I rejected channels where the number of jumps exceeded 0.025% of the number of samples - where we defined a jump as an absolute difference in the magnetic field between adjacent samples of greater than 10^5 fT. This procedure removed channels that were worst affected by jumps. These channels were removed for all experimental conditions to keep them comparable. In the remaining channels with jumps, I repaired the jumps, using an interpolation-based approach (see Figure A.3). Following the detection of a jump, a fixed segment of data (120 ms) either side of the jump was examined and DBS stimulation pulse peaks within it were identified. The data between DBS pulse peaks greater than two pulses away from the jump on either side were averaged to produce a signal for interpolating the region contaminated with the jump. The contaminated region of data was defined as the segment of data between two DBS pulse peaks of the jump on either side. Finally, the mean of the post-jump data segment was

adjusted to correspond to that of the pre-jump data, ensuring smooth fixing of the jump.

Following jump correction, the data were downsampled to 300 Hz and high pass filtered above 1 Hz prior to epoching.

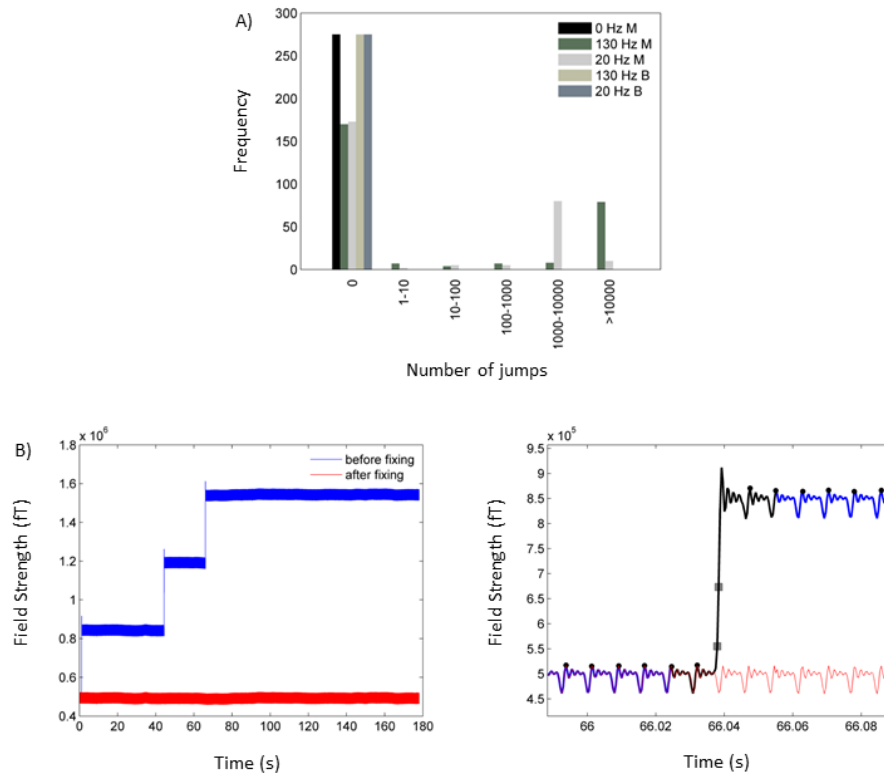


Figure A.3 Handling of MEG jump artefacts.

A: The frequency of the number of jumps in each channel is plotted for the different experimental conditions in the phantom experiment. The stimulation conditions are labelled in the legend by the frequency of stimulation in Hz and either M or B which represent monopolar or bipolar stimulation respectively. Large amplitude jumps were not present during bipolar DBS at 130 Hz or 20 Hz or when DBS was OFF (see black bar), but appeared during monopolar stimulation at both 20 Hz and 130 Hz. **B:** The plot on the left hand side shows the signal recorded by a single MEG channel before (blue) and after (red) fixing of three segments containing jumps, using the interpolation technique described in the methods. The plot on the right hand side shows a segment of data surrounding the third jump. The blue and red lines display the data before and after fixing of the jump. The black line represents the data segment that is interpolated and the grey squares show samples either side of the first jump within the region encompassed by the black line. Interpolation involved averaging data segments between stimulation pulse peaks (shown by the black dots) as described in the methods.

A.2.11 Trial definition

For phantom data each stimulation frequency was recorded in a separate run and the recording was started and stopped with DBS ongoing. Therefore, the fused data were epoched into 4s long trials starting with the recording onset.

For patient data the situation was more complicated with stimulation parameters changing during the recording. I, therefore, used the stimulation train copy generated by the stimulation-record amplifier to segment the recording. Stimulation peaks were detected in the continuous recording and the segments where the stimulation frequency matched one of the two known frequencies for that run (or in the case of 0 Hz where there was no stimulation) were identified. Margins of 20s were then removed from the beginning and the end of the segment to only include a stable stimulation period sufficiently distant from any parameter changes. This period was epoched into 4s segments.

A.2.12 Sensor level analysis

I characterised the time and spectral domain components of DBS artefacts. Spectral analysis of individual channel data was performed by pre-multiplying the data with a hanning taper prior to spectral decomposition using the Fast Fourier Transform. Further details on the artefacts may be found in the results section and in Figures A.4, A.5 and A.6.

We have previously defined methodology for determining the statistical significance of resting coherence between a bipolar contact pair of the STN DBS electrode and all MEG sensors (Litvak et al., 2011a). This approach allows us to define frequency bands for subsequent source space analysis in individual patients. In short, we computed coherence between the STN 0-2 bipole and all MEG channels between 5-45 Hz with 2.5 Hz resolution. Scalp maps of coherence at each frequency were linearly interpolated to produce 2D images. These 2D images were then stacked to produce a single 3D image having 2 spatial dimensions and 1 frequency dimension (Kilner and Friston, 2010). Ten surrogate images were also generated for statistical comparison, using the

same approach, but with the order of the STN-LFP trials shuffled. The original and shuffled images were smoothed with a 10mm x 10mm x 2.5 Hz Gaussian kernel and subjected to a two sample t-test using standard SPM analyses (Kilner et al., 2005; Litvak et al., 2011b). The SPMs were thresholded at $p < 0.01$ (family wise error corrected) to enable the identification of significant regions in frequency and sensor space.

A.2.13 Source space analysis

Sources coherent with the reference channels were localised using DICS beamforming (Gross et al., 2001) as described in our previous publications (Litvak et al., 2010, 2012; Oswal et al., 2013a, 2014). Beamforming rests on a linear projection of sensor data using a spatial filter that is computed from the leadfield of a location of interest and either the data covariance or the cross-spectral density matrix (Van Veen et al., 1997; Gross et al., 2001).

For the phantom lead fields were computed using a single sphere model coregistered to MEG sensors based on HPI coil location measurements. For the patient I used a single shell head model (Nolte, 2003, also called corrected-sphere model in more recent literature). The model was generated in SPM based on the patient's pre-operative structural MRI and fiducial-based co-registration was performed as described in Litvak et al., (2010).

The source space was defined as a 5mm spaced grid limited to the inside of the sphere for the phantom or to the inside of the skull compartment for the patient. For the phantom experiment, DICS beamforming was used to provide estimates of coherence in the 26-28 Hz band between the simulated sinusoidal signal and each point spaced on a 5 mm spaced grid within the phantom. Since the simulated signal that was recorded by the BrainAmp had an unrealistically large coherence with the same signal recorded by MEG, I added random Gaussian noise with fixed RMS amplitude to the recorded simulated sinusoidal signal in order to reduce the coherence to a more physiologically plausible value. No noise was added to the MEG signal, however.

The goal of this particular analysis was to generate a 3D image showing coherence between the simulated sinusoidal signal recorded with the BrainAmp and the spherical volume encompassed by the phantom. This is the kind of analysis that has been typically applied to patient data in our previous studies. A similar approach was also used for the single subject data I present, with a few important differences as discussed below. Firstly for the patient experiment, DICS beamforming was used to provide coherence estimates in the physiological frequency range that was identified as being significant in sensor level analysis. Secondly the reference signal used was the bipolar output of the stimulation-record amplifier, representing the potential difference between contacts 0 and 2 of the inserted left DBS electrode. Thirdly, for source extraction in the patient analyses I defined the beamformer source orientation as the normalised imaginary part of the cross-spectral density vector between the recorded LFP and the x, y and z orientations of the MEG source (Nolte et al., 2004; Litvak et al., 2010). This helps to focus on the cortical signal component coherent with a delay to the subcortical LFP, which might not be the highest amplitude component at each location. In the case of the phantom experiment, however, the simulated dipole signal was the only signal in the system and there was no delay between it and the reference. Therefore, I just used the orientation of maximum power (Gross et al., 2001).

The resulting coherence values were then linearly interpolated to produce 3D volumetric images with 2 mm resolution for visualisation. Importantly, common spatial filters were used to generate images for each of the three different experimental conditions. Common spatial filters were generated from the data covariance matrix computed using all experimental conditions. These filters were then applied separately to the data for each experimental condition in order to allow comparison of experimental conditions. In the case of the phantom experiment, due to the presence of just a single simulated source and absence of movement-related artefacts, a regularisation parameter of 10% was required in order to produce clear coherence peaks for visualisation. In contrast, a lower regularisation of 0.1% (as per Litvak et al., 2010) was used for the patient experiment. Once a single coherence image had been generated for each stimulation

condition in the phantom experiment, the images were averaged in order to select a single peak location for timeseries extraction using LCMV beamforming (Van Veen et al., 1997). Importantly, in the patient experiment I was not interested in generating DICS images for each stimulation condition, but instead wanted to determine how resting STN-cortical coupling is influenced by DBS. Accordingly I generated a DICS image of STN-cortical coherence only in the no DBS condition.

Having identified a location of peak coherence, source timeseries were extracted from this location using LCMV beamforming. Common filters were used for the three different experimental conditions with regularisation parameters as described above for the DICS beamforming stage. Once individual trial timeseries were extracted for the three different experimental conditions, coherence was computed between the reconstructed source and the reference channel using multitaper spectral estimation with a frequency resolution and taper smoothing frequency of 2 Hz (Mitra and Pesaran, 1999). The power spectrum of the reconstructed source could also be computed using the same approach. In the case of patient recordings, the source time series were extracted from the DICS image peak. In order to provide additional immunity from artefacts robust averaging was applied to both the cross-spectral density estimates and the auto-spectra across trials prior to computing coherence. In essence robust averaging is a special case of the robust general linear model (Wager et al., 2005) and involves down weighting the contribution of outlier trials that are contaminated by artefacts. Further details and a validation of robust averaging in a context similar to our present analysis can be found in Litvak et al., 2012.

A.2.14 Nonparametric statistical testing of coherence/power differences

Finally, for the phantom data I performed statistical comparison of the differences in coherence between the three conditions. I used non-parametric permutation testing, whereby individual

trials of the two time series were randomly assigned to one of the three condition labels prior to computing coherence. One thousand such permutations were employed, giving rise to a null distribution of absolute conditions specific coherence differences. In order to control for there being multiple (three) pairwise comparisons (no stimulation vs. 20 Hz, no stimulation vs. 130 Hz and 20 Hz vs 130 Hz) I constructed the null distribution from the maximal absolute coherence difference between the three conditions at each permutation, following the procedure described by Ernst, 2004. Following construction of the null I used a significance level of $\alpha = 0.05$, in order to check for significant differences in coherence between the three experimental conditions. For statistical analyses in the phantom experiment I was only interested in testing for significant differences in coherence between conditions at 27 Hz since this was the frequency of the simulated signal. The same approach was used to test for statistically significant differences in power.

A.3 Results

A.3.1 Stimulation related artefacts

Raw data recorded in the absence of DBS in the patient showed ferromagnetic metal related artefacts that have been previously described by Litvak et al., 2010. These artefacts were absent in the phantom due to absence of movement, breathing, a heart beat and also the fact that ferromagnetic parts in the phantom were not as close to the sensors. Data recorded during stimulation in both the patient and the phantom showed three additional kinds of artefacts specific to DBS: 1) DBS pulses followed by ringing 2) Low frequency artefacts 3) Jump artefacts. The first type of artefact was observed during both bipolar and monopolar DBS, whereas the second and third types of artefact were observed only during monopolar DBS. In the following paragraphs I will describe these artefacts in further detail.

Firstly, each DBS pulse produced a large artefact followed by a ringing response in all channels whose amplitude ranged from hundreds to several thousands of femtoTesla (fT). This ringing

arises from the response of the antialiasing hardware filter in the CTF machinery to a stimulation pulse. In our recordings, with a sampling frequency of 2400 Hz, the antialiasing filter was an 8th order elliptic low-pass filter with a cut off of 600 Hz. This filter resulted in a ringing decay time constant of 4.8 ms. As a result, most of the period between stimulation pulses (7.7 ms) was affected by ringing during both monopolar and bipolar DBS at 130 Hz (see right hand side panel of Figure A.4). In contrast, the period between stimulation pulses at 20 Hz is longer (50 ms) and therefore less affected by ringing (see left hand side panel of Figure A.4). In comparing the upper and lower panels of Figure A.4, it is worthwhile noting that the magnitude of the artefacts induced by monopolar DBS at both stimulation frequencies was an order of magnitude (approximately 30x) greater than that induced by bipolar DBS. Although the antialiasing filter had an undesirable side effect of introducing severe ringing artefacts, it prevented the emergence of spurious peaks in the power spectrum, generated by aliasing of stimulation frequency harmonics above the Nyquist frequency of 1200 Hz.

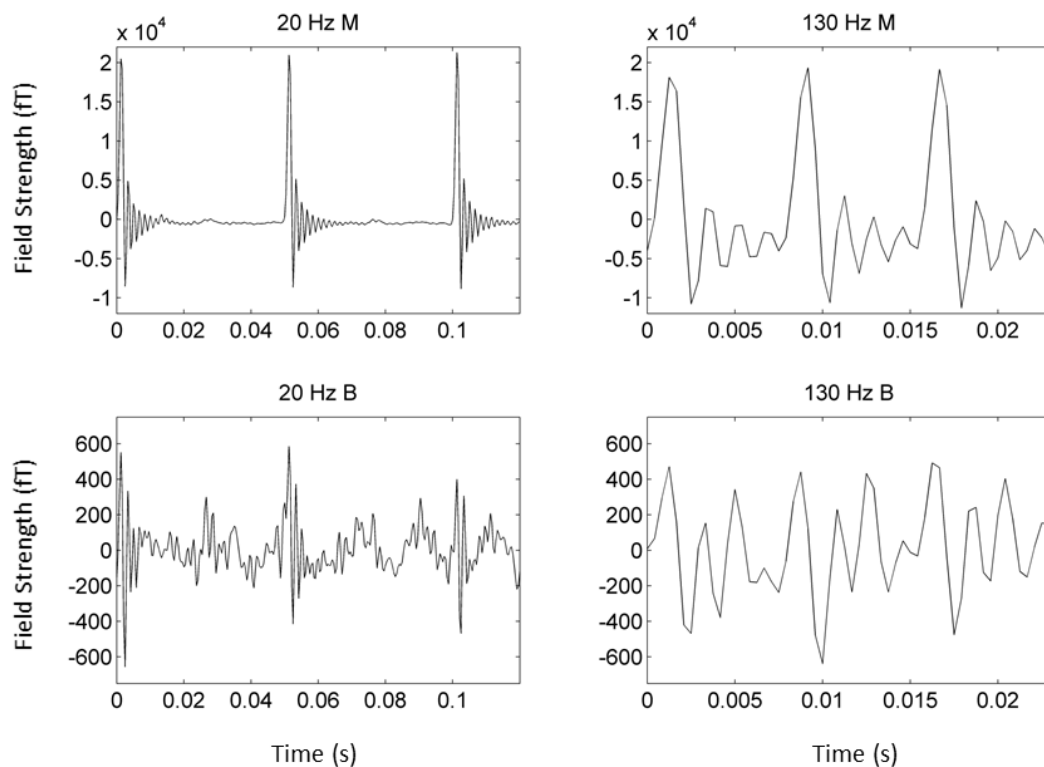


Figure A.4 MEG ringing artefacts.

The ringing artefacts are shown for a single MEG channel following three stimulation pulses for the 20 Hz and 130 Hz monopolar and bipolar stimulation conditions. The artefacts induced by bipolar DBS are an order of magnitude of approximately 25x less than those induced by monopolar DBS. Furthermore, the period between stimulation pulses is longer during 20 Hz DBS than during 130 Hz DBS (50 ms during 20 Hz and 7.7 ms during 130 Hz) and is consequently less influenced by ringing artefacts.

Figure A.5 shows the power spectrum averaged across all MEG channels for the no DBS and monopolar DBS conditions in the phantom experiment. Note that channels with jumps caused by DBS had either been corrected or excluded from all conditions prior to plotting (see below for more details on jump artefacts). For sake of clarity spectra for the bipolar DBS conditions are shown in separate figure, Figure A.6. These spectra show a number of important features. Firstly, a peak at 27 Hz representing the simulated sinusoid is well visualised in all conditions. With no DBS, there are additional peaks at 50 Hz and 100 Hz representing line noise and its first harmonic. In addition two small noise peaks are present at 60 Hz and 120 Hz. These are likely to come from some distant electrical equipment outside the shielded room and are present in all empty room recordings in our MEG system when synthetic gradient noise compensation is turned off. In our study I was not able to use synthetic gradient noise compensation due to the presence of DBS

related artefacts in the reference channels. Secondly, DBS at 20 Hz results in additional high amplitude peaks at 20 Hz and its harmonics (40 Hz, 60 Hz, 80 Hz, 100 Hz, 120 Hz, 140 Hz). Comparing monopolar (black line in Figure A.5) with bipolar (black line in Figure A.6) DBS at 20 Hz, it is evident that the amplitudes of the 20 Hz peak and its harmonics are markedly lower with bipolar DBS. A similar pattern is also observed for monopolar (red line in Figure A.5) and bipolar (red line in Figure A.6) DBS at 130 Hz. A more detailed analysis of the reasons for differences between monopolar and bipolar DBS is reserved for the discussion.

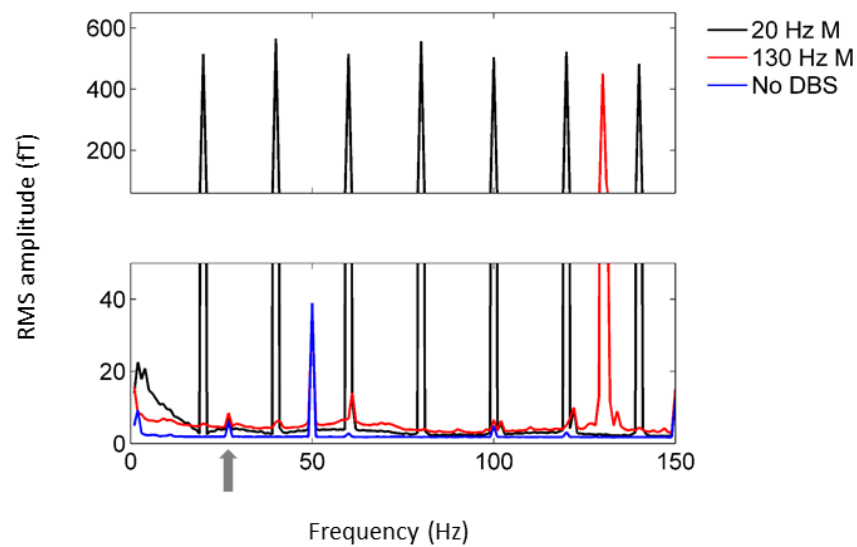


Figure A.5 Power spectra of MEG sensor level artefacts during monopolar DBS. The mean spectra across all MEG channels are shown for the No DBS, 130 Hz monopolar DBS and 20 Hz monopolar DBS conditions in the phantom experiment. Channels with jumps have either been excluded, or corrected using interpolation prior to spectral analysis (see Methods). The spectral peak at 27 Hz (indicated by the grey arrow) represents the simulated sinusoid and is well visualised in all experimental conditions. The large peak at 50 Hz represents power line noise. Monopolar DBS results in a large artefact peak at the stimulation frequency (20 Hz or 130 Hz) and its harmonics. An interesting feature of this plot is that monopolar DBS leads to an increase in background power which is particularly prominent at frequencies less than 20 Hz. The origin of these artefacts is examined in more detail in Figure A.7. Similar spectra are shown for the bipolar DBS conditions in Figure A.6.

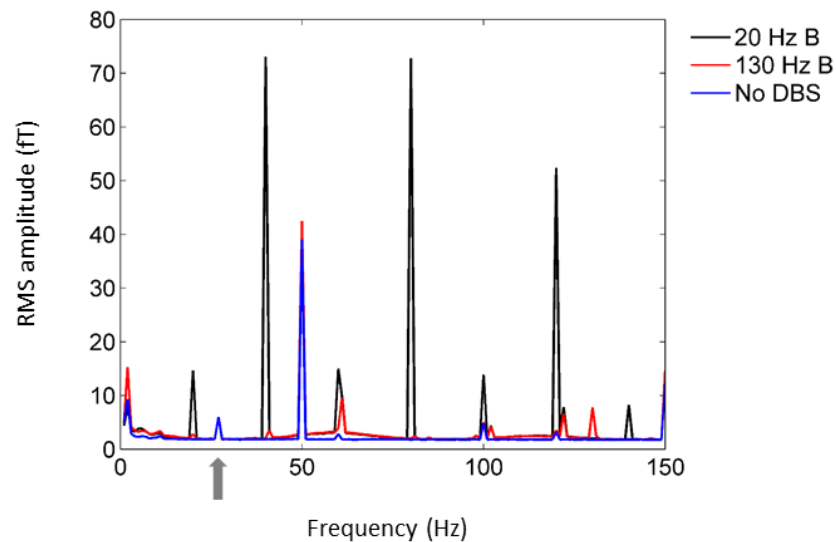


Figure A.6 Power spectra of MEG sensor level artefacts during bipolar DBS.

The mean spectra across all MEG channels are shown for the No DBS, 130 Hz bipolar DBS and 20 Hz bipolar DBS conditions in the phantom experiment. The spectral peak at 27 Hz (indicated by the grey arrow) represents the simulated sinusoid and is well visualised in all experimental conditions. The large peak at 50 Hz represents power line noise. Bipolar DBS results in a large artefact peak at the stimulation frequency (20 Hz or 130 Hz) and its harmonics. Note for the 20 Hz bipolar DBS condition, that the amplitude of even numbered harmonics (at 40 Hz, 80 Hz, and 120 Hz) exceeds that of odd numbered ones (at 60 Hz, 100 Hz and 140 Hz). See results for further discussion of this figure and of the differences in artefacts induced by monopolar and bipolar DBS.

A further interesting feature observed in Figure A.5 with monopolar rather than bipolar DBS is the presence of increased power at frequencies less than 20 Hz. In order to ascertain whether this behaviour was arising from all channels, or just a subset of channels I plotted individual channel spectra for the no-DBS and two monopolar DBS conditions (see upper panel of Figure A.7). Note that the spectra for the two stimulation conditions contain fewer channels, since channels with large numbers of jumps have been rejected (see below). These plots share some of the features of Figure A.5 and also reveal that the low frequency (<20 Hz) artefacts are not restricted to small groups of channels, but are spatially spread out. Additionally, it is evident that the low frequency artefacts affected a greater proportion of channels, and had higher amplitudes in the 20 Hz monopolar DBS condition.

In order to establish the temporal characteristics of the low frequency artefacts, I present data from a single channel and a 0.5 s long recording period with the highest power in frequencies less than 20 Hz. Data are presented in the lower panel of Figure A.7 for the no DBS condition and the two monopolar DBS conditions. The left hand side plots (Panel A) show 0.5 s of data with the same y axis for comparison of the signal amplitudes. The middle plots (Panel B) show only 0.08 s of data and the y axis are varied so that the signal can be visualised in all 3 conditions. The amplitude fluctuations for the no DBS plot in Panel A are barely visible since the amplitude of the signal during monopolar DBS is increased approximately 60x. The plots on the far right are the spectra of the data presented in Panel A. From these plots it is evident that the peak at 2Hz in the no DBS condition is the result of slow DC drifts in the signal. Furthermore, the sub 20 Hz artefacts observed with monopolar DBS are the result of fluctuations in the signal baseline between stimulation pulses (best seen in the bottom left hand plot in the lower panel of figure A.7).

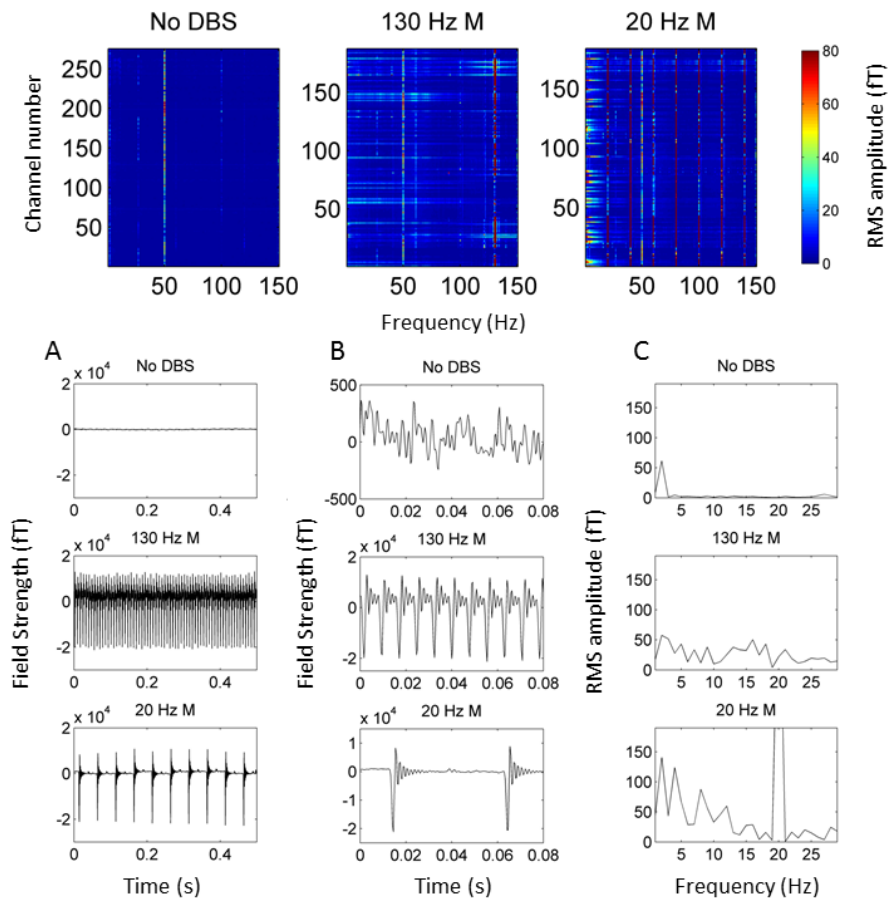


Figure A.7 The origin of low frequency artefacts during monopolar DBS.

In order to gain insight into the origin of low frequency artefacts (<20 Hz) arising in the two monopolar stimulation conditions, we show individual channel spectra in the upper panel of the figure. For reference, the no-DBS condition is compared to 130 Hz monopolar DBS (130 Hz M) and 20 Hz monopolar DBS (20 Hz M). The colour bar represents RMS amplitude in femtoTesla (fT). In addition to the features seen in Figure A.4, it is evident that low frequency (< 20 Hz) artefacts affect a larger proportion of channels in the 20 Hz monopolar condition than in the 130 Hz monopolar condition. In the left most three figures (A) of the lower panel we show 0.5 seconds of data from the single channel with the greatest overall power at frequencies less than 20 Hz in each condition. In order to compare the conditions, the y-axis ranges are identical. The corresponding spectra are shown in the rightmost three figures of the lower panel (C). Finally, the middle three figures of the lower panel (B) show a much shorter segment of the same data (0.08 s) with differing y-axis ranges for visualisation. In the no DBS condition, there is a spectral peak at 2 Hz due to DC slow drifts. During both monopolar DBS conditions, large stimulation pulse artefacts are observed followed by ringing. The low frequency (< 20 Hz) components observed during monopolar DBS are due to fluctuations in the DC baseline between stimulation pulses (see Results).

The third type of artefact I noted was jumps affecting a subset of the channels during monopolar DBS at either 20 Hz or 130 Hz. Jumps comprised abrupt changes in the signal level with a fixed amplitude of $\sim 3.5 \times 10^5$ fT (there are differences between individual channels depending on their calibration), followed by a ringing artefact as described above. This value corresponds to Φ_0 - one quantum of magnetic flux in the CTF SQUID sensors. This indicates that the jumps resulted from

the inability of SQUID electronics to lock to the DBS pulse due to its very fast rise time. Different MEG channels varied in the number of jumps they contained. Figure A.3A is a histogram of the number of channels affected by different numbers of jumps at the different stimulation conditions. Data are shown for the phantom recording, and similar features were present in the patient data. The majority of the 275 channels recorded during monopolar DBS were not contaminated by jumps. Some channels had only a small number of jumps, but there were also channels with a very large number of jumps where the recording over the whole session looked like a staircase. Since channels with a large number of jumps were only a minority and the amount of useful signal potentially recoverable from them by any correction method appeared to be small, I excluded these channels from further analysis (see Methods). For the remaining channels I used an interpolation approach to remove the jumps and preserve the rest of the recording. Figure A.3B shows single channel data, for a channel with 3 jumps at a stimulation frequency of 130 Hz before (blue line) and after (red line) fixing of the jumps using the interpolation-based approach described in Methods. On the right hand side of Panel B I have zoomed into the region surrounding the third jump. Samples either side of the detected jump are indicated by the grey squares and the region affected by the jump, which is interpolated is shown in black. The original data and the fixed data are shown in blue and red respectively.

Although our experiments revealed that bipolar DBS resulted in fewer artefacts than monopolar DBS (see discussion), I was unable to perform simultaneous stimulation and recording of the STN during bipolar DBS as the common mode rejection of our stimulation record amplifier required that the two recording contacts symmetrically sensed the stimulation signal. In the following sections I, therefore, restrict our analysis to the effects of monopolar DBS. I first show using the CTF current dipole phantom that it is possible to accurately recover coherence between a reference channel and an MEG signal in source space, using beamforming, despite the presence of monopolar DBS related artefacts.

A.3.2 Phantom results

Figure A.8A shows DICS beamformer source space images of coherence for the phantom experiment during the no DBS and two monopolar DBS conditions. As discussed in the methods section, coherence was computed in the 26-28 Hz band between the simulated sinusoidal signal with added random noise and each point on a 5 mm grid within the phantom. A clear peak in coherence (shown by the intersection of the cross-hairs), corresponding to the location of the simulated dipole, is observed at each of the different stimulation conditions and the absolute values of coherence are comparable across conditions. Panel B of Figure A.8 shows coherence between the simulated sinusoid with added noise and the time-series extracted from the peak of the DICS images for the three different experimental conditions. At 27 Hz, the frequency of the stimulated sinusoidal signal, coherence values are statistically indistinguishable for the three stimulation conditions. This is highlighted by the fact that the observed differences in coherence between the three conditions at 27 Hz do not fall within the 5% extremes of the constructed null distribution, indicated by the grey dots of Figure A.8B. These results highlight that it is possible to accurately recover simulated coherence in the presence of high amplitude artefacts caused by monopolar DBS. More specifically, coherence values are not statistically different when DBS is off and artefacts are absent to when DBS is on and artefacts are present. It is not surprising that the low frequency artefacts observed at the sensor level during monopolar DBS are not seen in source reconstructed coherence spectra. The reason for this is the presence of consistent phase relationships between the simulated sinusoid and its activity represented at the MEG sensors and the lack of such consistent phase relationships between the simulated sinusoid and DBS related artefacts. In Figure A.8C, I also display a power spectrum of the time-series extracted from the peak of the DICS image for the three different experimental conditions. At 27 Hz, the frequency of the stimulated sinusoidal signal, power values are statistically indistinguishable for the three stimulation conditions - highlighted by the fact that the observed differences in power do not fall within the 5% extremes of the constructed null distribution. Furthermore, an important feature of

this plot is that low frequency power artefacts observed at sensor level (see Figure A.5 and Figure A.7) are quite well suppressed by source space analysis through beamforming.

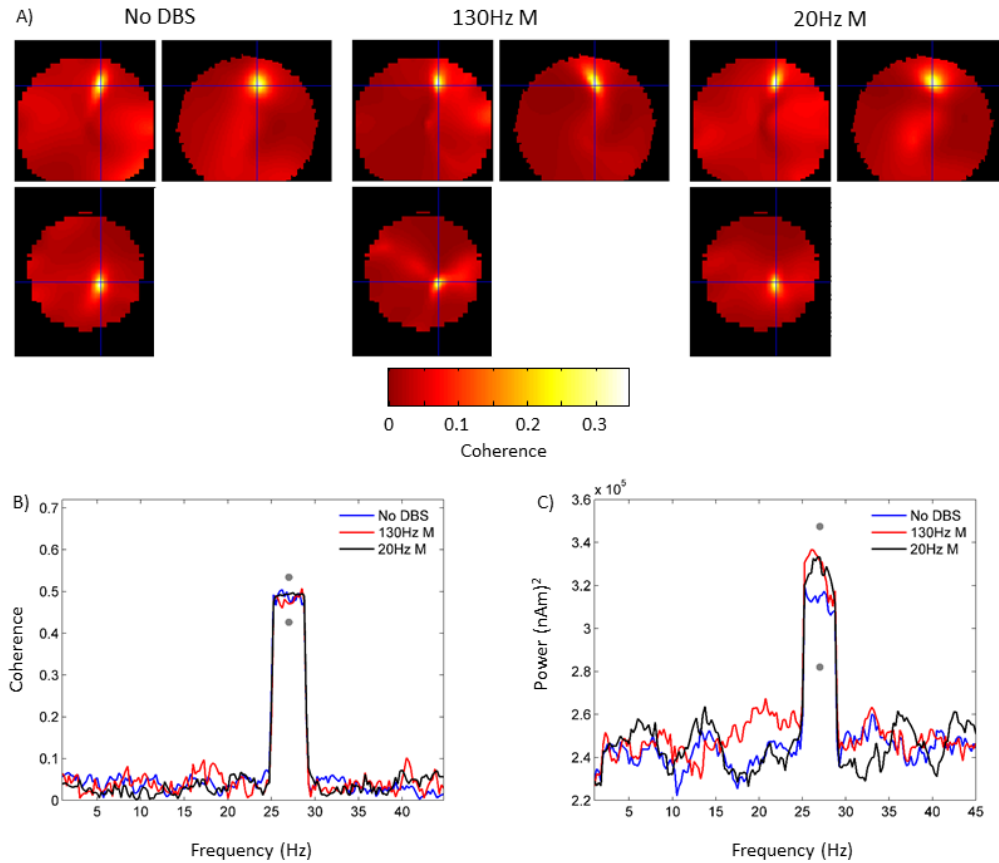


Figure A.8 Source space analysis for the phantom experiment.

Panel A shows DICS beamformer images of coherence between the simulated LFP and a 5mm spaced grid within the phantom. These images were interpolated, as described in Methods, giving final images with 2 mm resolution. Coherence images are shown for the three different experimental conditions: no-DBS, monopolar DBS at 130 Hz and monopolar DBS at 20 Hz. In all cases the coherent source was clearly visualised, and the coherence values (see colour bar) were comparable between the three different stimulation conditions. The intersection of the cross-hairs indicates the location of the peak value of coherence, which was identical across experimental conditions. Panel B shows coherence between the simulated LFP and LCMV beamformer extracted source timeseries from the location of peak coherence indicated by the cross-hairs in Panel A. Coherence is plotted as a function of frequency for the three experimental conditions. The grey dots indicate 95% confidence intervals of the null distribution of condition specific coherence differences at 27 Hz generated by permutation testing (see Methods for further details). For sake of visualisation, this confidence interval has been added to the absolute value of coherence at 27 Hz for the no DBS condition. All of the observed differences in coherence between stimulation conditions lie within this limit, highlighting the absence of statistically significant differences. Panel C shows a power spectrum of the extracted source timeseries with the grey dots representing 95% confidence intervals of the null distribution of condition specific power differences at 27 Hz which have been added to the absolute value of power at 27 Hz for the no DBS condition.

A.3.3 Single subject results

The patient had a good clinical response to DBS, with total OFF medication UPDRS part III motor scores improving from 63 to 30 with the introduction of bilateral STN DBS at 130 Hz. All three types of artefact found in the phantom experiment were present in the patient data.

Furthermore, the numbers of channels affected by jumps was also similar. Single subject data are presented in Figure A.9. Figure A.9A shows a DICS beamformer image of coherence between contacts 0 and 2 of the left STN electrode and cortical regions at rest in the no DBS condition. Coherence was computed over the entire beta band (15–30 Hz) in keeping with our previous studies and also those of others (Hirschmann et al., 2011; Litvak et al., 2011a). The anatomical location of peak resting coherence corresponds to the intersection of the cross hairs at MNI co-ordinates -6 -10 66. This peak was located relatively close to the group peak of beta band coherence identified in our previous studies, at MNI co-ordinates -18 6 58, which corresponding to the location of the supplementary motor/premotor areas (Litvak et al., 2011a). LCMV beamforming was used to extract source timeseries from the peak of the beta band DICS image, for the no DBS and the 130 Hz monopolar DBS conditions. Power spectra of the source timeseries are shown in Figure A.9C (the grey bars represent regions within the beta band). Importantly, as per the results of the phantom experiment (Figure A.8) sensor space low frequency artefacts induced by monopolar DBS are not present following beamformer source extraction. In fact low frequency (<15 Hz) activity is markedly higher in the no DBS condition than in the 130 Hz monopolar DBS condition. This is reassuring since there important differences between the phantom and patient experiments in terms of the potential sources of noise (see discussion).

Coherence computed between contacts 0 and 2 of the left STN electrode and source extracted time series for the no DBS and the 130 Hz DBS conditions is shown in Figure A.9B. In the no DBS condition there is a clear peak in coherence towards the upper end of the beta frequency range, and this appears to be suppressed by DBS. This may be in keeping with the suppression of cortical

power in the high beta range that is observed in Figure A.9C, but I will reserve further statistical analysis and comment of DBS effects on cortico-STN coupling to Chapter 8.

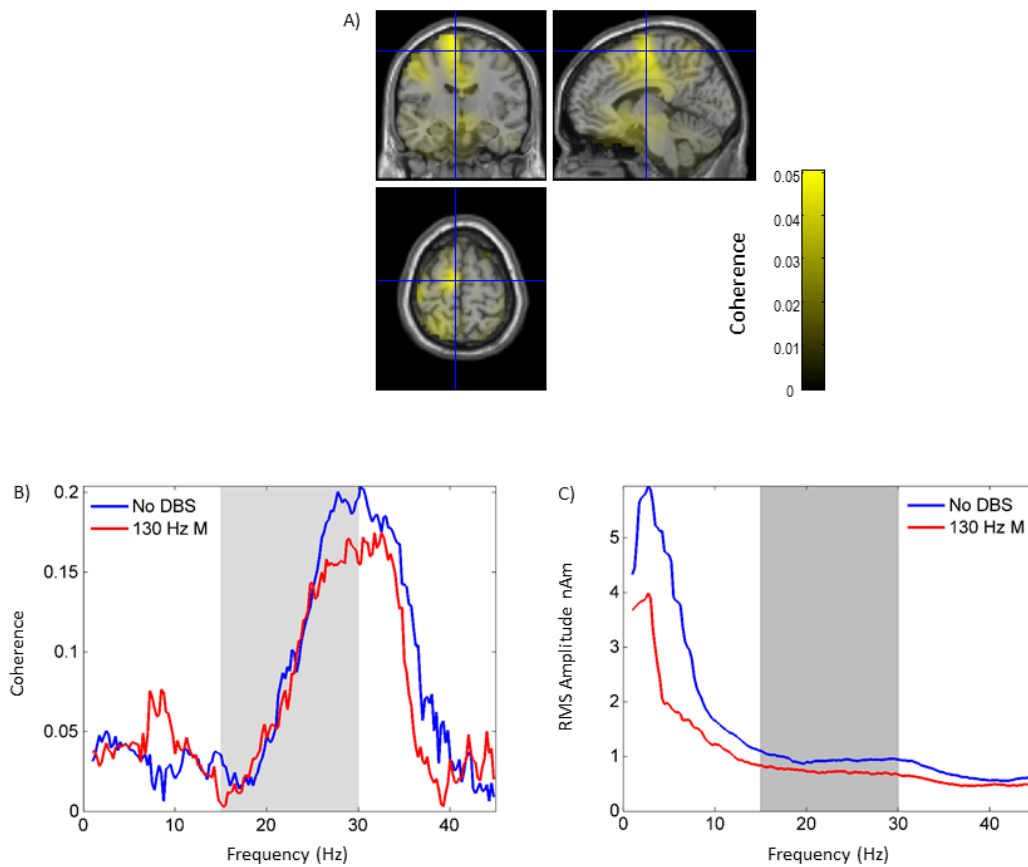


Figure A.9 Single patient source space analysis.

The results of patient data are shown. Panel B shows a DICS beamformer image of coherence in the beta frequency (15-30 Hz) range between the left STN 0-2 bipole and the whole brain. The DICS coherence image is superimposed onto a T1 weighted canonical MRI. Coronal, sagittal and axial sections through the image are displayed. The intersection of the cross-hairs represents the location of peak coherence (MNI co-ordinates -6 -10 66 corresponding to the premotor/supplementary motor areas). Source timeseries are extracted from the location of peak and source RMS amplitudes and STN-cortical source coherence are computed for the no DBS and the 130 Hz DBS conditions. The results are shown in Figures A.9C and A.9B respectively. The grey region indicates the beta frequency range which was used to determine the location of the cortical source.

A.4 Discussion

Recording MEG during DBS is probably one of the most challenging applications of MEG in general. The reason for this is that very weak magnetic field changes induced by synchronised neural activity must be detected in the presence of much stronger fluctuations caused by stimulation currents. DBS in the MEG scanner has been attempted before by several research

groups (Ray et al., 2007, 2009; Mohseni et al., 2010, 2012; Airaksinen et al., 2011, 2012, 2014; Cao et al., 2015a). Ramirez et al., 2011 also used a phantom to study DBS artefacts in MEG. I will now discuss several important issues pertaining to our present study in the context of previous studies combining DBS and MEG recordings.

A.4.1 Implanted vs. externalised patients

In all previous DBS MEG studies, patients were recruited after stimulator implantation and therefore had a stimulator implanted in their chest wall and no externalised wires. The artefacts observed in such patients are different to those I have described. Heart-beat locked artefacts from ferromagnetic wires in the head are likely to be reduced in implanted patients (although I have not done the comparison myself). The reason for this is that a major source of this artefact is the percutaneous externalisation wire that moves with arterial pulses on the scalp (Litvak et al., 2010). This percutaneous wire is removed once the stimulator is implanted and the wire that subsequently connects the DBS electrode to the stimulator is neither ferromagnetic nor as mobile, since it is buried in the subcutaneous tissue.

On the other hand the implanted stimulator in internalised patients is ferromagnetic and hence may give rise to breathing and heart beat related movement artefacts even when it is turned off. When the stimulator is on the currents flowing inside it induce magnetic field changes that affect the MEG sensors for both monopolar and bipolar stimulation. Since the fields generated by the stimulator have spatial patterns clearly distinct from those coming from inside the head, denoising methods making use of spatial topographies such as Signal Space Separation (SSS, Taulu et al., 2004), temporal Signal Space Separation (tSSS, Taulu and Simola, 2006) or S^3P (Ramírez et al., 2011) can remove them effectively.

For our study I recruited patients who underwent DBS surgery in two stages. In the first stage only the intracranial electrodes were implanted and the contacts were externalised for recording using a stainless steel percutaneous extension wire. Only later, a few days after our recording session,

was the stimulator implanted. Thus, our patients did not have a stimulator in the chest but did have ferromagnetic metal parts on the head. It is possible to use non-ferromagnetic titanium wires, which are MEG compatible and induce fewer artefacts, but these have not yet been clinically approved for use in the UK. In any case using titanium wires would not eliminate stimulation-related artefacts which are the focus of this report, but only heart beat and movement-related artefacts that we have previously shown to be effectively suppressed by beamforming (Litvak et al., 2010, 2011a, 2012; Oswal et al., 2013a).

The external stimulator used as part of our setup (see Figure A.1) was inside the magnetically shielded MEG room but much further away from the MEG helmet than an implanted stimulator would be (about 1.5 m). The reason for not placing the stimulation equipment outside the shielded room was to ensure that the clinician administering DBS could observe the patient closely at all times for safety purposes. Although the stimulator and stimulation record amplifier will contribute to the MEG signal when they are turned on, this contribution appears to be negligible in relation to the stimulation artefacts in our data.

A.4.2 Monopolar vs. bipolar stimulation

Stimulation-induced magnetic fields that are recorded by the MEG system as artefacts originate from currents flowing in the loop including the stimulation equipment, the wires and the patient. Total magnetic flux generated by this loop is proportional to the area bounded by the current paths. In the case of bipolar stimulation the current flows to and from the patient through intertwined wires and the only place where it leaves the wires is the stimulation site where it is carried by charged ions between two contacts located just 0.5 mm apart. Although some fraction of the current takes a longer path through the brain tissues according to the distribution of impedances, this fraction appears to be small and only induces weak magnetic flux. The situation is entirely different for monopolar stimulation. In this case the current flows from the stimulated contact in the brain to the reference located on the chest passing through large parts of the head

and the upper body, thereby creating a large loop. This explains the striking differences I observed between the artefacts induced by monopolar and bipolar DBS.

In theory, combining bipolar DBS with MEG and LFP recordings would result in fewer artefacts, but that would require a stimulation-record amplifier with an initial stage that is not saturated by the large potential gradient created by bipolar stimulation and is at the same time sensitive enough to record the LFP signal which is weaker by many orders of magnitude. To the best of our knowledge, a stimulation record amplifier that facilitates bipolar stimulation and recording has not been described. In any case, it is perhaps more clinically relevant to consider the case of monopolar DBS since this is often seen as being more clinically effective in terms of ameliorating Parkinsonian symptoms (Deli et al., 2011).

A.4.3 Analyses of coherence vs. other features

The present study is the first to our knowledge to describe simultaneous MEG and LFP recording during DBS. Previous studies reporting DBS during MEG recordings have focussed on the analyses of changes in power of spontaneous brain oscillations (Airaksinen et al., 2012; Mohseni et al., 2012; Cao et al., 2015b), changes in cortico-muscular coherence (Park et al., 2009; Connolly et al., 2012; Airaksinen et al., 2014) or differences in sensory evoked potentials induced by DBS (Ray et al., 2009; Airaksinen et al., 2011). Of these three types of studies, analyses of cortico-muscular coherence are the most similar to our study as they also focus on coherence between MEG and a reference channel. However, cortico-muscular coherence and cortico-subthalamic nucleus coherence are distinct phenomena that can be differentially modulated by movement and dopaminergic medication (Hirschmann et al., 2013).

Thus the present study is more closely related to the previous studies (Litvak et al., 2010, 2011a, 2012; Hirschmann et al., 2011, 2013a, 2013b; Oswal et al., 2013a) examining cortico-subthalamic nucleus coherence and its modulation by different experimental factors. As modulations by

movement, dopaminergic drugs, severity of the clinical symptoms and tremor have been previously described, studying the effect of DBS is to our mind the next logical step.

A.4.4 Factors affecting the recovery of coherence in the presence of DBS

We have previously demonstrated (Litvak et al., 2010) that cortical signals coherent with the STN can be recovered in the presence of MEG artefacts which exceed the amplitude of physiological MEG signals by several orders of magnitude providing that the MEG system remains in its linear range (e.g. there is no signal clipping). The CTF MEG system is unique in this respect as it possesses a particularly wide dynamic range of up to approximately 7×10^8 fT which exceeds by far even the range of magnetic interferences induced by monopolar DBS.

However, the system is still limited in its ability to track rapidly changing signals. This is because the measurement of magnetic flux with a SQUID involves a feedback loop implemented with electronics that forces a current into the SQUID to keep the flux constant. If the applied field varies too quickly, the electronics loses lock to the signal which results in jumps of fixed amplitude (on our system 3.3×10^5 to 3.8×10^5 fT depending on the channel). The appearance of jumps is also affected by the intrinsic noise of the SQUID. If the external interference and the intrinsic noise are small, no unlocks will occur, while in an intermediate range the jumps will occur occasionally (as in Figure A.3B).

The problem could potentially be mitigated by changing the DBS pulse shape to exclude very high frequencies (or equivalently reduce the pulse rise time). However, the safety and clinical efficacy of such modified pulses has not been demonstrated. Thus I preferred to keep DBS settings close to those used in routine clinical practice and tackle the jump problem by data post-processing. But if there is further interest in combining MEG with monopolar DBS in the future, optimizing both MEG and DBS hardware settings is definitely a promising direction to reduce artefact contamination.

I have dealt with jumps in three different ways: 1) excluding severely affected channels, 2) correcting by interpolation and 3) using robust methods for computing coherence. The vast majority of jumps were contained within the excluded channels.

The second type of artefact I observed were DBS stimulation pulses followed by ringing, the latter being the result of antialiasing filters. The antialiasing filters had a beneficial effect of prevented aliasing artefacts, which have been observed in other DBS MEG studies (Ramírez et al., 2011), but had a side effect of producing ringing, which contaminated most of the interval between pulses in the 130 Hz DBS condition (see Results). One approach for shortening the ringing artefacts would be to use a much higher sampling rate and hence a higher antialiasing filter cut off frequency, since aliasing would only be observed for frequencies greater than the Nyquist frequency (half the sampling rate). Using a higher cut off frequency for the antialiasing filter has the beneficial effect of shortening the time constant of the ringing artefacts, but comes at a computational cost of having to deal with large volumes of data acquired at high sampling rates. The final type of artefact I observed was low frequency artefacts occurring at frequencies less than 20 Hz during monopolar DBS. These could potentially affect coherence in that range and should be taken into account in future data analyses. However, coherences at frequencies above 20 Hz in both phantom and patient did not appear to be affected.

Despite the presence of the observed artefacts I was able to recover simulated coherence in source space using beamforming in the phantom experiment. More specifically, source space coherence values were similar when DBS was OFF and artefacts were absent to when DBS was ON. It is worth mentioning that although we attempted to make the phantom experiment as similar as possible to a patient recording, there are still some differences. For instance, I used a pure sinusoid as the ‘cortical’ signal, and did not incorporate other competing sources. These factors resulted in unrealistically high coherence with the reference channels that I had to artificially reduce by adding random noise to the latter.

Analysis of single patient data also revealed comparable coherence spectra when DBS was ON and OFF. I will however leave a detailed discussion of the effects of DBS on cortico-STN coupling to be the subject of discussion in Chapter 7.

A.4.5 Summary and conclusions

The present study paves the way to using MEG as a means of studying DBS effects on oscillatory connectivity between subcortical stimulation targets and the rest of the brain. I have demonstrated that physiological components of interest can be recovered from MEG data in the presence of DBS artefacts as well as artefacts from ferromagnetic percutaneous wires. Accordingly, the effects of DBS on LFP-MEG coherence can be studied.

References

- Airaksinen K, Butorina A, Pekkonen E, Nurminen J, Taulu S, Ahonen A, Schnitzler A, Mäkelä JP (2012) Somatomotor mu rhythm amplitude correlates with rigidity during deep brain stimulation in Parkinsonian patients. *Clin Neurophysiol* 123:2010–2017.
- Airaksinen K, Mäkelä JP, Nurminen J, Luoma J, Taulu S, Ahonen A, Pekkonen E (2014) Cortico-muscular coherence in advanced Parkinson's disease with deep brain stimulation. *Clin Neurophysiol* S1388-2457.
- Airaksinen K, Mäkelä JP, Taulu S, Ahonen A, Nurminen J, Schnitzler A, Pekkonen E (2011) Effects of DBS on auditory and somatosensory processing in Parkinson's disease. *Hum Brain Mapp* 32:1091–1099.
- Albin RL, Young AB, Penney JB (1989) The functional anatomy of basal ganglia disorders. *Trends Neurosci* 12:366–375.
- Alegre M, Alonso-Frech F, Rodríguez-Oroz MC, Guridi J, Zamarbide I, Valencia M, Manrique M, Obeso JA, Artieda J (2005) Movement-related changes in oscillatory activity in the human subthalamic nucleus: ipsilateral vs. contralateral movements. *Eur J Neurosci* 22:2315–2324.
- Alegre M, Lopez-Azcarate J, Obeso I, Wilkinson L, Rodríguez-Oroz MC, Valencia M, Garcia-Garcia D, Guridi J, Artieda J, Jahanshahi M, Obeso JA (2013) The subthalamic nucleus is involved in successful inhibition in the stop-signal task: a local field potential study in Parkinson's disease. *Exp Neurol* 239:1–12.
- Alegre M, Rodríguez-Oroz MC, Valencia M, Pérez-Alcázar M, Guridi J, Iriarte J, Obeso J a, Artieda J (2010) Changes in subthalamic activity during movement observation in Parkinson's disease: is the mirror system mirrored in the basal ganglia? *Clin Neurophysiol* 121:414–425.
- Alexander GE, Crutcher MD (1990) Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends Neurosci* 13:266–271.
- Alonso-Frech F, Zamarbide I, Alegre M, Rodríguez-Oroz MC, Guridi J, Manrique M, Valencia M, Artieda J, Obeso JA (2006) Slow oscillatory activity and levodopa-induced dyskinesias in Parkinson's disease. *Brain* 129:1748–1757.
- Amirnovin R, Williams ZM, Cosgrove GR, Eskandar EN (2004) Visually guided movements suppress subthalamic oscillations in Parkinson's disease patients. *J Neurosci* 24:11302.
- Androulidakis AG, Brücke C, Kempf F, Kupsch A, Aziz T, Ashkan K, Kühn A a, Brown P (2008) Amplitude modulation of oscillatory activity in the subthalamic nucleus during movement. *Eur J Neurosci* 27:1277–1284.
- Androulidakis AG, Doyle LMF, Yarrow K, Litvak V, Gilbertson TP, Brown P (2007) Anticipatory changes in beta synchrony in the human corticospinal system and associated improvements in task performance. *Eur J Neurosci* 25:3758–3765.

- Anzak A, Gaynor L, Beigi M, Foltynie T, Limousin P, Zrinzo L, Brown P, Jahanshahi M (2013) Subthalamic nucleus gamma oscillations mediate a switch from automatic to controlled processing: a study of random number generation in Parkinson's disease. *Neuroimage* 64:284–289.
- Anzak A, Gaynor L, Beigi M, Limousin P, Hariz M, Zrinzo L, Foltynie T, Brown P, Jahanshahi M (2011) A gamma band specific role of the subthalamic nucleus in switching during verbal fluency tasks in Parkinson's disease. *Exp Neurol* 232:136–142.
- Anzak A, Tan H, Pogosyan A, Foltynie T, Limousin P, Zrinzo L, Hariz M, Ashkan K, Bogdanovic M, Green AL, Aziz T, Brown P (2012) Subthalamic nucleus activity optimizes maximal effort motor responses in Parkinson's disease. *Brain* 135:2766–2778.
- Baccalá LA, Sameshima K (2001) Partial directed coherence: a new concept in neural structure determination. *Biol Cybern* 84:463–474.
- Baker AP, Brookes MJ, Rezek IA, Smith SM, Behrens T, Probert Smith PJ, Woolrich M (2014) Fast transient networks in spontaneous human brain activity. *Elife* 3:e01867.
- Ballard PA, Tetrud JW, Langston JW (1985) Permanent human parkinsonism due to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP): seven cases. *Neurology* 35:949–956.
- Barbe MT, Liebhart L, Runge M, Pauls KAM, Wojtecki L, Schnitzler A, Allert N, Fink GR, Sturm V, Maarouf M, Timmermann L (2011) Deep brain stimulation in the nucleus ventralis intermedius in patients with essential tremor: habituation of tremor suppression. *J Neurol* 258:434–439.
- Barnes GR, Hillebrand A, Fawcett IP, Singh KD (2004) Realistic spatial sampling for MEG beamformer images. *Hum Brain Mapp* 23:120–127.
- Bastos AM, Vezoli J, Fries P (2015) Communication through coherence with inter-areal delays. *Curr Opin Neurobiol* 31:173–180.
- Baudrexel S, Witte T, Seifried C, von Wegner F, Beissner F, Klein JC, Steinmetz H, Deichmann R, Roeper J, Hilker R (2011) Resting state fMRI reveals increased subthalamic nucleus-motor cortex connectivity in Parkinson's disease. *Neuroimage* 55:1728–1738.
- Bauer M, Kluge C, Bach D, Bradbury D, Heinze HJ, Dolan RJ, Driver J (2012) Cholinergic enhancement of visual attention and neural oscillations in the human brain. *Curr Biol* 22:397–402.
- Beavan MS, Schapira AH V (2013) Glucocerebrosidase mutations and the pathogenesis of Parkinson disease. *Ann Med* 45:511–521.
- Bejjani B-P, Dormont D, Pidoux B, Yelnik J, Damier P, Arnulf I, Bonnet A-M, Marsault C, Agid Y, Philippon J, Cornu P (2000) Bilateral subthalamic stimulation for Parkinson's disease by using three-dimensional stereotactic magnetic resonance imaging and electrophysiological guidance. *J Neurosurg* 92:615–625.
- Benabid AL, Chabardes S, Mitrofanis J, Pollak P (2009) Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. *Lancet Neurol* 8:67–81.

- Benabid AL, Pollak P, Louveau A, Henry S, de Rougemont J (1987) Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. *Appl Neurophysiol* 50:344–346.
- Bénar CG, Gotman J (2002) Modeling of post-surgical brain and skull defects in the EEG inverse problem with the boundary element method. *Clin Neurophysiol* 113:48–56.
- Ben-Pazi H, Bergman H, Goldberg JA, Giladi N, Hansel D, Reches A, Simon ES (2001) Synchrony of rest tremor in multiple limbs in parkinson's disease: evidence for multiple oscillators. *J Neural Transm* 108:287–296.
- Bergman H, Wichmann T, DeLong MR (1990) Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. *Science* 249:1436–1438.
- Bergman H, Wichmann T, Karmon B, DeLong MR (1994) The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism. *J Neurophysiol* 72:507–520.
- Bishop C (1999) Variational Principal Components. *Artif Neural Networks*.
- Bosboom JLW, Stoffers D, Stam CJ, Berendse HW, Wolters EC (2009) Cholinergic modulation of MEG resting-state oscillatory activity in Parkinson's disease related dementia. *Clin Neurophysiol* 120:910–915.
- Bosboom JLW, Stoffers D, Stam CJ, van Dijk BW, Verbunt J, Berendse HW, Wolters EC (2006) Resting state oscillatory brain dynamics in Parkinson's disease: an MEG study. *Clin Neurophysiol* 117:2521–2531.
- Bour LJ, Lourens MAJ, Verhagen R, de Bie RMA, van den Munckhof P, Schuurman PR, Contarino MF (2015) Directional Recording of Subthalamic Spectral Power Densities in Parkinson's Disease and the Effect of Steering Deep Brain Stimulation. *Brain Stimul*.
- Brittain J-S, Probert-Smith P, Aziz TZ, Brown P (2013) Tremor Suppression by Rhythmic Transcranial Current Stimulation. *Curr Biol* 23:436–440.
- Bronstein JM et al. (2011) Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues. *Arch Neurol* 68:165.
- Bronte-Stewart H, Barberini C, Koop MM, Hill BC, Henderson JM, Wingeier B (2009) The STN beta-band profile in Parkinson's disease is stationary and shows prolonged attenuation after deep brain stimulation. *Exp Neurol* 215:20–28.
- Brookes MJ, O'Neill GC, Hall EL, Woolrich MW, Baker A, Palazzo-Corner S, Robson SE, Morris PG, Barnes GR (2014) Measuring temporal, spectral and spatial changes in electrophysiological brain network connectivity. *Neuroimage* 91C:282–299.
- Brookes MJ, Vrba J, Robinson SE, Stevenson CM, Peters AM, Barnes GR, Hillebrand A, Morris PG (2008) Optimising experimental design for MEG beamformer imaging. *Neuroimage* 39:1788–1802.
- Brown P (2006) Bad oscillations in Parkinson's disease. *J Neural Transm Suppl*:27–30.

- Brown P, Oliviero A, Mazzone P, Insola A, Tonali P, Di Lazzaro V (2001) Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. *J Neurosci* 21:1033–1038.
- Brücke C, Bock A, Huebl J, Krauss JK, Schönecker T, Schneider G-H, Brown P, Kühn AA (2013) Thalamic gamma oscillations correlate with reaction time in a Go/noGo task in patients with essential tremor. *Neuroimage* 75C:36–45.
- Brücke C, Huebl J, Schönecker T, Neumann W-J, Yarrow K, Kupsch A, Blahak C, Lütjens G, Brown P, Krauss JK, Schneider G-H, Kühn AA (2012) Scaling of movement is related to pallidal γ oscillations in patients with dystonia. *J Neurosci* 32:1008–1019.
- Brücke C, Kupsch A, Schneider G-H, Hariz MI, Nuttin B, Kopp U, Kempf F, Trottenberg T, Doyle L, Chen CC, Yarrow K, Brown P, Kühn AA (2007) The subthalamic region is activated during valence-related emotional processing in patients with Parkinson's disease. *Eur J Neurosci* 26:767–774.
- Brunenberg EJL, Moeskops P, Backes WH, Pollo C, Cammoun L, Vilanova A, Janssen MLF, Visser-Vandewalle VERM, ter Haar Romeny BM, Thiran J-P, Platel B (2012) Structural and resting state functional connectivity of the subthalamic nucleus: identification of motor STN parts and the hyperdirect pathway. *PLoS One* 7:e39061.
- Burn DJ (2002) Beyond the iron mask: towards better recognition and treatment of depression associated with Parkinson's disease. *Mov Disord* 17:445–454.
- Buzsáki G, Draguhn A (2004) Neuronal oscillations in cortical networks. *Science* 304:1926–1929.
- Cagnan H, Brittain J-S, Little S, Foltynie T, Limousin P, Zrinzo L, Hariz M, Joint C, Fitzgerald J, Green AL, Aziz T, Brown P (2013) Phase dependent modulation of tremor amplitude in essential tremor through thalamic stimulation. *Brain* 136:3062–3075.
- Canolty RT, Edwards E, Dalal SS, Soltani M, Nagarajan SS, Kirsch HE, Berger MS, Barbaro NM, Knight RT (2006) High gamma power is phase-locked to theta oscillations in human neocortex. *Science* 313:1626–1628.
- Canolty RT, Knight RT (2010) The functional role of cross-frequency coupling. *Trends Cogn Sci* 14:506–515.
- Cao C, Li D, Jiang T, Ince NF, Zhan S, Zhang J, Sha Z, Sun B (2015a) Resting state cortical oscillations of patients with Parkinson disease and with and without subthalamic deep brain stimulation: a magnetoencephalography study. *J Clin Neurophysiol* 32:109–118.
- Cao C, Li D, Jiang T, Ince NF, Zhan S, Zhang J, Sha Z, Sun B (2015b) Resting state cortical oscillations of PD patients without and with Subthalamic deep brain stimulation, a MEG study. *J Clin Neurophysiol* 32:109–118.
- Carpenter RH, Williams ML (1995) Neural computation of log likelihood in control of saccadic eye movements. *Nature* 377:59–62.
- Cassidy M, Brown P (2003) Spectral phase estimates in the setting of multidirectional coupling. *J Neurosci Methods* 127:95–103.

- Cassidy M, Mazzone P, Oliviero A, Insola A, Tonali P, Di Lazzaro V, Brown P (2002) Movement-related changes in synchronization in the human basal ganglia. *Brain* 125:1235–1246.
- Cavanagh JF, Wiecki T V, Cohen MX, Figueroa CM, Samanta J, Sherman SJ, Frank MJ (2011) Subthalamic nucleus stimulation reverses mediofrontal influence over decision threshold. *Nat Neurosci* 14:1462–1467.
- Chaudhuri KR, Healy DG, Schapira AH V (2006) Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurol* 5:235–245.
- Chaudhuri KR, Schapira AH V (2009) Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *Lancet Neurol* 8:464–474.
- Chen CC, Hsu YT, Chan HL, Chiou SM, Tu PH, Lee ST, Tsai CH, Lu CS, Brown P (2010a) Complexity of subthalamic 13-35 Hz oscillatory activity directly correlates with clinical impairment in patients with Parkinson's disease. *Exp Neurol* 224:234–240.
- Chen C-C, Kilner JM, Friston KJ, Kiebel SJ, Jolly RK, Ward NS (2010b) Nonlinear coupling in the human motor system. *J Neurosci* 30:8393–8399.
- Chen CC, Lin WY, Chan HL, Hsu YT, Tu PH, Lee ST, Chiou SM, Tsai CH, Lu CS, Brown P (2011) Stimulation of the subthalamic region at 20Hz slows the development of grip force in Parkinson's disease. *Exp Neurol* 231:91–96.
- Chen CC, Litvak V, Gilbertson T, Kühn A, Lu CS, Lee ST, Tsai CH, Tisch S, Limousin P, Hariz M, Brown P (2007) Excessive synchronization of basal ganglia neurons at 20 Hz slows movement in Parkinson's disease. *Exp Neurol* 205:214–221.
- Chen CC, Pogosyan A, Zrinzo LU, Tisch S, Limousin P, Ashkan K, Yousry T, Hariz MI, Brown P (2006) Intra-operative recordings of local field potentials can help localize the subthalamic nucleus in Parkinson's disease surgery. *Exp Neurol* 198:214–221.
- Clayton MS, Yeung N, Cohen Kadosh R (2015) The roles of cortical oscillations in sustained attention. *Trends Cogn Sci* 19:188–195.
- Cohen D, Cuffin BN (1983) Demonstration of useful differences between magnetoencephalogram and electroencephalogram. *Electroencephalogr Clin Neurophysiol* 56:38–51.
- Cohen D, Cuffin BN (1991) EEG versus MEG localization accuracy: theory and experiment. *Brain Topogr* 4:95–103.
- Connolly AT, Bajwa JA, Johnson MD (2012) Cortical magnetoencephalography of deep brain stimulation for the treatment of postural tremor. *Brain Stimul* 5:616–624.
- Courtemanche R, Fujii N, Graybiel AM (2003) Synchronous, focally modulated beta-band oscillations characterize local field potential activity in the striatum of awake behaving monkeys. *J Neurosci* 23:11741–11752.
- Cruz A V, Mallet N, Magill PJ, Brown P, Averbeck BB (2011) Effects of dopamine depletion on information flow between the subthalamic nucleus and external globus pallidus. *J Neurophysiol* 106:2012–2023.

- Damier P, Hirsch EC, Agid Y, Graybiel AM (1999) The substantia nigra of the human brain. II. Patterns of loss of dopamine-containing neurons in Parkinson's disease. *Brain* 122 (Pt 8):1437–1448.
- Dang LC, O'Neil JP, Jagust WJ (2012) Dopamine supports coupling of attention-related networks. *J Neurosci* 32:9582–9587.
- De Hemptinne C, Ryapolova-Webb ES, Air EL, Garcia PA, Miller KJ, Ojemann JG, Ostrem JL, Galifianakis NB, Starr PA (2013) Exaggerated phase-amplitude coupling in the primary motor cortex in Parkinson disease. *Proc Natl Acad Sci* 110:4780–4785.
- De Hemptinne C, Swann NC, Ostrem JL, Ryapolova-Webb ES, San Luciano M, Galifianakis NB, Starr PA (2015a) Therapeutic deep brain stimulation reduces cortical phase-amplitude coupling in Parkinson's disease. *Nat Neurosci* 18:779–786.
- De Hemptinne C, Swann NC, Ostrem JL, Ryapolova-Webb ES, San Luciano M, Galifianakis NB, Starr PA (2015b) Therapeutic deep brain stimulation reduces cortical phase-amplitude coupling in Parkinson's disease. *Nat Neurosci* 18:779–786.
- De Lau LML, Breteler MMB (2006) Epidemiology of Parkinson's disease. *Lancet Neurol* 5:525–535.
- De Solages C, Hill BC, Koop MM, Henderson JM, Bronte-Stewart H (2010) Bilateral symmetry and coherence of subthalamic nuclei beta band activity in Parkinson's disease. *Exp Neurol* 221:260–266.
- Deco G, Jirsa VK, Robinson PA, Breakspear M, Friston K (2008) The dynamic brain: from spiking neurons to neural masses and cortical fields. *PLoS Comput Biol* 4:e1000092.
- Dejean C, Gross CE, Bioulac B, Boraud T (2008) Dynamic changes in the cortex-basal ganglia network after dopamine depletion in the rat. *J Neurophysiol* 100:385–396.
- Deli G, Balas I, Nagy F, Balazs E, Janszky J, Komoly S, Kovacs N (2011) Comparison of the efficacy of unipolar and bipolar electrode configuration during subthalamic deep brain stimulation. *Parkinsonism Relat Disord* 17:50–54.
- DeLong MR (1990) Primate models of movement disorders of basal ganglia origin. *Trends Neurosci* 13:281–285.
- Demiralp T, Bayraktaroglu Z, Lenz D, Junge S, Busch NA, Maess B, Ergen M, Herrmann CS (2007) Gamma amplitudes are coupled to theta phase in human EEG during visual perception. *Int J Psychophysiol* 64:24–30.
- Deuschl G et al. (2006) A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med* 355:896–908.
- Devos D, Szurhaj W, Reyns N, Labyt E, Houdayer E, Bourriez JL, Cassim F, Krystkowiak P, Blond S, Destée A, Derambure P, Defebvre L (2006) Predominance of the contralateral movement-related activity in the subthalamo-cortical loop. *Clin Neurophysiol* 117:2315–2327.
- Dhamala M, Rangarajan G, Ding M (2008) Analyzing information flow in brain networks with nonparametric Granger causality. *Neuroimage* 41:354–362.

- Djamshidian A, Auerbach BB, Lees AJ, O'Sullivan SS (2011) Clinical aspects of impulsive compulsive behaviours in Parkinson's disease. *J Neurol Sci* 310:183–188.
- Doñamayor N, Schoenfeld MA, Münte TF (2012) Magneto- and electroencephalographic manifestations of reward anticipation and delivery. *Neuroimage* 62:17–29.
- Dovzhenok A, Rubchinsky LL (2012) On the origin of tremor in Parkinson's disease. *PLoS One* 7:e41598.
- Doyle LMF, Kühn AA, Hariz M, Kupsch A, Schneider G-H, Brown P (2005) Levodopa-induced modulation of subthalamic beta oscillations during self-paced movements in patients with Parkinson's disease. *Eur J Neurosci* 21:1403–1412.
- Eccles J (1951) Interpretation of action potentials evoked in the cerebral cortex. *Electroencephalogr Clin Neurophysiol* 3 3:449–464.
- Eisenstein SA, Koller JM, Black KD, Campbell MC, Lugar HM, Ushe M, Tabbal SD, Karimi M, Hershey T, Perlmutter JS, Black KJ (2014) Functional anatomy of subthalamic nucleus stimulation in Parkinson disease. *Ann Neurol* 76:279–295.
- Engel AK, Fries P (2010) Beta-band oscillations--signalling the status quo? *Curr Opin Neurobiol* 20:156–165.
- Ernst MD (2004) Permutation Methods: A Basis for Exact Inference. *Stat Sci* 19:676–685.
- Eusebio A, Cagnan H, Brown P (2012) Does suppression of oscillatory synchronisation mediate some of the therapeutic effects of DBS in patients with Parkinson's disease? *Front Integr Neurosci* 6:47.
- Eusebio A, Chen CC, Lu CS, Lee ST, Tsai CH, Limousin P, Hariz M, Brown P (2008) Effects of low-frequency stimulation of the subthalamic nucleus on movement in Parkinson's disease. *Exp Neurol* 209:125–130.
- Eusebio A, Pogosyan A, Wang S, Auerbach B, Gaynor LD, Cantiniaux S, Witjas T, Limousin P, Azulay J-P, Brown P (2009) Resonance in subthalamo-cortical circuits in Parkinson's disease. *Brain* 132:2139–2150.
- Eusebio A, Thevathasan W, Doyle Gaynor L, Pogosyan A, Bye E, Foltynie T, Zrinzo L, Ashkan K, Aziz T, Brown P (2011) Deep brain stimulation can suppress pathological synchronisation in parkinsonian patients. *J Neurol Neurosurg Psychiatry* 82:569–573.
- Evans JR, Mason SL, Williams-Gray CH, Foltynie T, Brayne C, Robbins TW, Barker RA (2011) The natural history of treated Parkinson's disease in an incident, community based cohort. *J Neurol Neurosurg Psychiatry* 82:1112–1118.
- Fan KY, Baufreton J, Surmeier DJ, Chan CS, Bevan MD (2012) Proliferation of external globus pallidus-subthalamic nucleus synapses following degeneration of midbrain dopamine neurons. *J Neurosci* 32:13718–13728.
- Fasano A, Daniele A, Albanese A (2012) Treatment of motor and non-motor features of Parkinson's disease with deep brain stimulation. *Lancet Neurol* 11:429–442.

- Fasano A, Romito LM, Daniele A, Piano C, Zinno M, Bentivoglio AR, Albanese A (2010) Motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants. *Brain* 133:2664–2676.
- Foffani G, Bianchi A, Baselli G, Priori A (2005) Movement-related frequency modulation of beta oscillatory activity in the human subthalamic nucleus. *J Physiol* 568:699–711.
- Foffani G, Priori A, Egidio M, Rampini P, Tamma F, Caputo E, Moxon KA, Cerutti S, Barbieri S (2003) 300-Hz subthalamic oscillations in Parkinson's disease. *Brain* 126:2153–2163.
- Fogelson N, Pogosyan A, Kühn AA, Kupsch A, van Bruggen G, Speelman H, Tijssen M, Quartarone A, Insola A, Mazzone P, Di Lazzaro V, Limousin P, Brown P (2005) Reciprocal interactions between oscillatory activities of different frequencies in the subthalamic region of patients with Parkinson's disease. *Eur J Neurosci* 22:257–266.
- Fogelson N, Williams D, Tijssen M, van Bruggen G, Speelman H, Brown P (2006) Different functional loops between cerebral cortex and the subthalamic area in Parkinson's disease. *Cereb cortex* 16:64–75.
- Follett KA et al. (2010) Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med* 362:2077–2091.
- Foltynie T, Hariz MI (2010) Surgical management of Parkinson's disease. *Expert Rev Neurother* 10:903–914.
- Foltynie T, Zrinzo L, Martinez-Torres I, Tripoliti E, Petersen E, Holl E, Aviles-Olmos I, Jahanshahi M, Hariz M, Limousin P (2011) MRI-guided STN DBS in Parkinson's disease without microelectrode recording: efficacy and safety. *J Neurol Neurosurg Psychiatry* 82:358–363.
- Forstmann BU, Anwander A, Schäfer A, Neumann J, Brown S, Wagenmakers E-J, Bogacz R, Turner R (2010) Cortico-striatal connections predict control over speed and accuracy in perceptual decision making. *Proc Natl Acad Sci U S A* 107:15916–15920.
- Fox SH, Katzenschlager R, Lim S-Y, Ravina B, Seppi K, Coelho M, Poewe W, Rascol O, Goetz CG, Sampaio C (2011) The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the motor symptoms of Parkinson's disease. *Mov Disord* 26 Suppl 3:S2–S41.
- Foxe JJ, Simpson G V, Ahlfors SP (1998) Parieto-occipital approximately 10 Hz activity reflects anticipatory state of visual attention mechanisms. *Neuroreport* 9:3929–3933.
- Frank MJ, Samanta J, Moustafa A a, Sherman SJ (2007) Hold your horses: impulsivity, deep brain stimulation, and medication in parkinsonism. *Science* 318:1309–1312.
- Fries P (2005) A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. *Trends Cogn Sci* 9:474–480.
- Friston K, Harrison L, Daunizeau J, Kiebel S, Phillips C, Trujillo-Barreto N, Henson R, Flandin G, Mattout J (2008) Multiple sparse priors for the M/EEG inverse problem. *Neuroimage* 39:1104–1120.

- Friston K, Moran R, Seth AK (2013) Analysing connectivity with Granger causality and dynamic causal modelling. *Curr Opin Neurobiol* 23:172–178.
- Friston KJ, Bastos AM, Oswal A, van Wijk B, Richter C, Litvak V (2014) Granger causality revisited. *Neuroimage* 101:796–808.
- Friston KJ, Holmes AP, Worsley KJ, Poline J-P, Frith CD, Frackowiak RSJ (1994) Statistical parametric maps in functional imaging: A general linear approach. *Hum Brain Mapp* 2:189–210.
- Friston KJ, Stephan KE, Lund TE, Morcom A, Kiebel S (2005) Mixed-effects and fMRI studies. *Neuroimage* 24:244–252.
- Fumagalli M, Giannicola G, Rosa M, Marceglia S, Lucchiari C, Mrakic-Sposta S, Servello D, Pacchetti C, Porta M, Sassi M, Zangaglia R, Franzini A, Albanese A, Romito L, Piacentini S, Zago S, Pravettoni G, Barbieri S, Priori A (2011) Conflict-dependent dynamic of subthalamic nucleus oscillations during moral decisions. *Soc Neurosci* 6:243–256.
- Gagnon JF, Bédard MA, Fantini ML, Petit D, Panisset M, Rompré S, Carrier J, Montplaisir J (2002) REM sleep behavior disorder and REM sleep without atonia in Parkinson's disease. *Neurology* 59:585–589.
- George JS, Strunk J, Mak-McCully R, Houser M, Poizner H, Aron AR (2013) Dopaminergic therapy in Parkinson's disease decreases cortical beta band coherence in the resting state and increases cortical beta band power during executive control. *NeuroImage Clin* 3:261–270.
- Gibb WR, Lees AJ (1988) A comparison of clinical and pathological features of young- and old-onset Parkinson's disease. *Neurology* 38:1402–1406.
- Gilbertson T, Lalo E, Doyle L, Di Lazzaro V, Cioni B, Brown P (2005) Existing motor state is favored at the expense of new movement during 13-35 Hz oscillatory synchrony in the human corticospinal system. *J Neurosci* 25:7771.
- Goetz CG et al. (2008) Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord* 23:2129–2170.
- Gordon EM, Stollstorff M, Devaney JM, Bean S, Vaidya CJ (2011) Effect of Dopamine Transporter Genotype on Intrinsic Functional Connectivity Depends on Cognitive State. *Cereb cortex* In Press.
- Gould IC, Rushworth MF, Nobre AC (2011) Indexing the graded allocation of visuospatial attention using anticipatory alpha oscillations. *J Neurophysiol* 105:1318–1326.
- Gradinaru V, Mogri M, Thompson KR, Henderson JM, Deisseroth K (2009) Optical deconstruction of parkinsonian neural circuitry. *Science* 324:354–359.
- Granger C (1969) Investigating Causal Relations by Econometric Models and Cross-Spectral Methods. *Econometrics* 37:424–438.

- Gross J, Kujala J, Hamalainen M, Timmermann L, Schnitzler A, Salmelin R (2001) Dynamic imaging of coherent sources: Studying neural interactions in the human brain. *Proc Natl Acad Sci U S A* 98:694–699.
- Hammond C, Bergman H, Brown P (2007) Pathological synchronization in Parkinson's disease: networks, models and treatments. *Trends Neurosci* 30:357–364.
- Hariz MI, Krack P, Melvill R, Jorgensen J V, Hamel W, Hirabayashi H, Lenders M, Wesslen N, Tengvar M, Yousry TA (2003) A quick and universal method for stereotactic visualization of the subthalamic nucleus before and after implantation of deep brain stimulation electrodes. *Stereotact Funct Neurosurg* 80:96–101.
- Hashimoto T, Elder CM, Okun MS, Patrick SK, Vitek JL (2003) Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. *J Neurosci* 23:1916–1923.
- Hassler R (1938) Zur Pathologie der Paralysis agitans und des postenzephalitischen Parkinsonismus. *J Psychol Neurol* 48:387–476.
- Haufe S, Nikulin V V, Müller K-R, Nolte G (2013) A critical assessment of connectivity measures for EEG data: a simulation study. *Neuroimage* 64:120–133.
- Haynes WIA, Haber SN (2013) The Organization of Prefrontal-Subthalamic Inputs in Primates Provides an Anatomical Substrate for Both Functional Specificity and Integration: Implications for Basal Ganglia Models and Deep Brain Stimulation. *J Neurosci* 33:4804–4814.
- Herz DM, Siebner HR, Hulme OJ, Florin E, Christensen MS, Timmermann L (2014) Levodopa reinstates connectivity from prefrontal to premotor cortex during externally paced movement in Parkinson's disease. *Neuroimage* 90:15–23.
- Hillebrand A, Singh KD, Holliday IE, Furlong PL, Barnes GR (2005) A new approach to neuroimaging with magnetoencephalography. *Hum Brain Mapp* 25:199–211.
- Hirschmann J, Hartmann CJ, Butz M, Hoogenboom N, Özkurt TE, Elben S, Vesper J, Wojtecki L, Schnitzler A (2013a) A direct relationship between oscillatory subthalamic nucleus-cortex coupling and rest tremor in Parkinson's disease. *Brain* 136:3659–3670.
- Hirschmann J, Özkurt TE, Butz M, Homburger M, Elben S, Hartmann CJ, Vesper J, Wojtecki L, Schnitzler A (2011) Distinct oscillatory STN-cortical loops revealed by simultaneous MEG and local field potential recordings in patients with Parkinson's disease. *Neuroimage* 55:1159–1168.
- Hirschmann J, Özkurt TE, Butz M, Homburger M, Elben S, Hartmann CJ, Vesper J, Wojtecki L, Schnitzler A (2013b) Differential modulation of STN-cortical and cortico-muscular coherence by movement and levodopa in Parkinson's disease. *Neuroimage* 68:203–213.
- Hohlefeld FU, Huchzermeyer C, Huebl J, Schneider G-H, Nolte G, Brücke C, Schönecker T, Kühn AA, Curio G, Nikulin V V (2013) Functional and effective connectivity in subthalamic local field potential recordings of patients with Parkinson's disease. *Neuroscience* 250:320–332.
- Holgado AJN, Terry JR, Bogacz R (2010) Conditions for the generation of beta oscillations in the subthalamic nucleus-globus pallidus network. *J Neurosci* 30:12340–12352.

- Huebl J, Schoenecker T, Siegert S, Brücke C, Schneider G-H, Kupsch A, Yarrow K, Kühn AA (2011) Modulation of subthalamic alpha activity to emotional stimuli correlates with depressive symptoms in Parkinson's disease. *Mov Disord* 26:477–483.
- Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 55:181–184.
- Jankovic J, McDermott M, Carter J, Gauthier S, Goetz C, Golbe L, Huber S, Koller W, Olanow C, Shoulson I (1990) Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. *Neurology* 40:1529–1534.
- Jann K, Dierks T, Boesch C, Kottlow M, Strik W, Koenig T (2009) BOLD correlates of EEG alpha phase-locking and the fMRI default mode network. *Neuroimage* 45:903–916.
- Jasper H, Andrews H (1938) Electroencephalography. III Normal differentiation of occipital and precentral regions in man. *Arch Neurol Psychiatry* 39:96–115.
- Jenkinson N, Brown P (2011) New insights into the relationship between dopamine, beta oscillations and motor function. *Trends Neurosci* 34:611–618.
- Jenkinson N, Kühn AA, Brown P (2012) Gamma oscillations in the human basal ganglia. *Exp Neurol* 245:72–76.
- Joundi RA, Jenkinson N, Brittain J-S, Aziz TZ, Brown P (2012) Driving oscillatory activity in the human cortex enhances motor performance. *Curr Biol* 22:403–407.
- Joundi RA, Jenkinson N, Brittain J-S, Aziz TZ BP (n.d.) Driving oscillatory activity in the human cortex enhances motor performance. Prep.
- Kamiński M, Ding M, Truccolo WA, Bressler SL (2001) Evaluating causal relations in neural systems: granger causality, directed transfer function and statistical assessment of significance. *Biol Cybern* 85:145–157.
- Kane A, Hutchison WD, Hodaie M, Lozano AM, Dostrovsky JO (2009) Dopamine-dependent high-frequency oscillatory activity in thalamus and subthalamic nucleus of patients with Parkinson's disease. *Neuroreport* 20:1549–1553.
- Kang G, Lowery MM (2013) Interaction of Oscillations, and Their Suppression via Deep Brain Stimulation, in a Model of the Cortico-Basal Ganglia Network. *IEEE Trans Neural Syst Rehabil Eng* 21:244–253.
- Kang G, Lowery MM (2014) Effects of antidromic and orthodromic activation of STN afferent axons during DBS in Parkinson's disease: a simulation study. *Front Comput Neurosci* 8:32.
- Kelly C, de Zubicaray G, Di Martino A, Copland DA, Reiss PT, Klein DF, Castellanos FX, Milham MP, McMahon K (2009) L-dopa modulates functional connectivity in striatal cognitive and motor networks: a double-blind placebo-controlled study. *J Neurosci* 29:7364–7378.
- Kempf F, Brücke C, Salih F, Trottenberg T, Kupsch A, Schneider G-H, Doyle Gaynor LMF, Hoffmann K-T, Vesper J, Wöhrle J, Altenmüller D-M, Krauss JK, Mazzone P, Di Lazzaro V, Yelnik J, Kühn

- AA, Brown P (2009) Gamma activity and reactivity in human thalamic local field potentials. *Eur J Neurosci* 29:943–953.
- Kempf F, Kühn AA, Kupsch A, Brücke C, Weise L, Schneider G-H, Brown P (2007) Premovement activities in the subthalamic area of patients with Parkinson's disease and their dependence on task. *Eur J Neurosci* 25:3137–3145.
- Kilner JM, Baker SN, Salenius S, Hari R, Lemon RN (2000) Human cortical muscle coherence is directly related to specific motor parameters. *J Neurosci* 20:8838–8845.
- Kilner JM, Friston KJ (2010) Topological inference for EEG and MEG. *Ann Appl Stat* 4:1272–1290.
- Kilner JM, Kiebel SJ, Friston KJ (2005) Applications of random field theory to electrophysiology. *Neurosci Lett* 374:174–178.
- Klein JC, Barbe MT, Seifried C, Baudrexel S, Runge M, Maarouf M, Gasser T, Hattingen E, Liebig T, Deichmann R, Timmermann L, Weise L, Hilker R (2012) The tremor network targeted by successful VIM deep brain stimulation in humans. *Neurology* 78:787–795.
- Klostermann F, Nikulin V V, Kühn AA, Marzinzik F, Wahl M, Pogosyan A, Kupsch A, Schneider G-H, Brown P, Curio G (2007) Task-related differential dynamics of EEG alpha- and beta-band synchronization in cortico-basal motor structures. *Eur J Neurosci* 25:1604–1615.
- Knyazev GG, Slobodskoj-Plusnin JY, Bocharov A V, Pyrkova L V (2011) The default mode network and EEG α oscillations: an independent component analysis. *Brain Res* 1402:67–79.
- Koller WC, Pahwa PR, Lyons KE, Wilkinson SB (2000) Deep brain stimulation of the Vim nucleus of the thalamus for the treatment of tremor. *Neurology* 55:S29–S33.
- Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, Koudsie A, Limousin PD, Benazzouz A, LeBas JF, Benabid A-L, Pollak P (2003) Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med* 349:1925–1934.
- Kühn AA, Brücke C, Schneider G-H, Trottenberg T, Kivi A, Kupsch A, Capelle HH, Krauss JK, Brown P (2008a) Increased beta activity in dystonia patients after drug-induced dopamine deficiency. *Exp Neurol* 214:140–143.
- Kühn AA, Doyle L, Pogosyan A, Yarrow K, Kupsch A, Schneider G-H, Hariz MI, Trottenberg T, Brown P (2006a) Modulation of beta oscillations in the subthalamic area during motor imagery in Parkinson's disease. *Brain* 129:695–706.
- Kühn AA, Hariz MI, Silberstein P, Tisch S, Kupsch A, Schneider G-H, Limousin-Dowsey P, Yarrow K, Brown P (2005a) Activation of the subthalamic region during emotional processing in Parkinson disease. *Neurology* 65:707–713.
- Kühn AA, Kempf F, Brücke C, Gaynor Doyle L, Martinez-Torres I, Pogosyan A, Trottenberg T, Kupsch A, Schneider G-H, Hariz MI, Vandenberghe W, Nuttin B, Brown P (2008b) High-frequency stimulation of the subthalamic nucleus suppresses oscillatory beta activity in patients with Parkinson's disease in parallel with improvement in motor performance. *J Neurosci* 28:6165–6173.

- Kühn AA, Kupsch A, Schneider G-H, Brown P (2006b) Reduction in subthalamic 8-35 Hz oscillatory activity correlates with clinical improvement in Parkinson's disease. *Eur J Neurosci* 23:1956–1960.
- Kühn AA, Trottenberg T, Kivi A, Kupsch A, Schneider G-H, Brown P (2005b) The relationship between local field potential and neuronal discharge in the subthalamic nucleus of patients with Parkinson's disease. *Exp Neurol* 194:212–220.
- Kühn AA, Tsui A, Aziz T, Ray N, Brücke C, Kupsch A, Schneider G-H, Brown P (2009) Pathological synchronisation in the subthalamic nucleus of patients with Parkinson's disease relates to both bradykinesia and rigidity. *Exp Neurol* 215:380–387.
- Kühn AA, Williams D, Kupsch A, Limousin P, Hariz M, Schneider G-H, Yarrow K, Brown P (2004) Event-related beta desynchronization in human subthalamic nucleus correlates with motor performance. *Brain* 127:735–746.
- Kumar A, Cardanobile S, Rotter S, Aertsen A (2011) The role of inhibition in generating and controlling Parkinson's disease oscillations in the Basal Ganglia. *Front Syst Neurosci* 5:86.
- Kuncel AM, Grill WM (2004) Selection of stimulus parameters for deep brain stimulation. *Clin Neurophysiol* 115:2431–2441.
- Kurniawan IT, Guitart-Masip M, Dayan P, Dolan RJ (2013) Effort and Valuation in the Brain: The Effects of Anticipation and Execution. *J Neurosci* 33:6160–6169.
- Kurniawan IT, Guitart-Masip M, Dolan RJ (2011) Dopamine and effort-based decision making. *Front Neurosci* 5:81.
- Lalo E, Thobois S, Sharott A, Polo G, Mertens P, Pogosyan A, Brown P (2008) Patterns of bidirectional communication between cortex and basal ganglia during movement in patients with Parkinson disease. *J Neurosci* 28:3008–3016.
- Lardeux S, Pernaud R, Palleressompoulle D, Baunez C (2009) Beyond the reward pathway: coding reward magnitude and error in the rat subthalamic nucleus. *J Neurophysiol* 102:2526–2537.
- Lees AJ (1994) The concept of bradyphrenia. *Rev Neurol (Paris)* 150:823–826.
- Lees AJ, Hardy J, Revesz T (2009) Parkinson's disease. *Lancet* 373:2055–2066.
- Lenz FA, Tasker RR, Kwan HC, Schnider S, Kwong R, Murayama Y, Dostrovsky JO, Murphy JT (1988) Single unit analysis of the human ventral thalamic nuclear group: correlation of thalamic "tremor cells" with the 3-6 Hz component of parkinsonian tremor. *J Neurosci* 8:754–764.
- Lesage S, Brice A (2009) Parkinson's disease: from monogenic forms to genetic susceptibility factors. *Hum Mol Genet* 18:R48–R59.
- Levy R, Ashby P, Hutchison WD, Lang AE, Lozano AM, Dostrovsky JO (2002a) Dependence of subthalamic nucleus oscillations on movement and dopamine in Parkinson's disease. *Brain* 125:1196–1209.

- Levy R, Dostrovsky JO, Lang AE, Sime E, Hutchison WD, Lozano AM (2001) Effects of apomorphine on subthalamic nucleus and globus pallidus internus neurons in patients with Parkinson's disease. *J Neurophysiol* 86:249–260.
- Levy R, Hutchinson W, Lozano A, Dostrovsky JO (2002b) Synchronised neuronal discharge in the basal ganglia of parkinsonia patients is limited to oscillatory activity. *J Neurosci* 22:2855–2861.
- Levy R, Hutchison WD, Lozano AM, Dostrovsky JO (2002c) Synchronized Neuronal Discharge in the Basal Ganglia of Parkinsonian Patients Is Limited to Oscillatory Activity. *J Neurosci* 22:2855–2861.
- Li Q, Ke Y, Chan DCW, Qian Z-M, Yung KKL, Ko H, Arbuthnott GW, Yung W-H (2012) Therapeutic deep brain stimulation in Parkinsonian rats directly influences motor cortex. *Neuron* 76:1030–1041.
- Li S, Arbuthnott GW, Jutras MJ, Goldberg JA, Jaeger D (2007) Resonant antidromic cortical circuit activation as a consequence of high-frequency subthalamic deep-brain stimulation. *J Neurophysiol* 98:3525–3537.
- Limousin P, Pollak P, Benazzouz A, Hoffmann D, Le Bas JF, Broussolle E, Perret JE, Benabid AL (1995) Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *Lancet* 345:91–95.
- Little S, Pogosyan A, Kuhn AA, Brown P (2012) β band stability over time correlates with Parkinsonian rigidity and bradykinesia. *Exp Neurol* 236:383–388.
- Little S, Pogosyan A, Neal S, Zavala B, Zrinzo L, Hariz M, Foltynie T, Limousin P, Ashkan K, FitzGerald J, Green AL, Aziz TZ, Brown P (2013a) Adaptive deep brain stimulation in advanced Parkinson disease. *Ann Neurol* 74:449–457.
- Little S, Tan H, Anzak A, Pogosyan A, Kühn A, Brown P (2013b) Bilateral functional connectivity of the basal ganglia in patients with Parkinson's disease and its modulation by dopaminergic treatment. *PLoS One* 8:e82762.
- Litvak V, Eusebio A, Jha A, Oostenveld R, Barnes G, Foltynie T, Limousin P, Zrinzo L, Hariz MI, Friston K, Brown P (2012) Movement-Related Changes in Local and Long-Range Synchronization in Parkinson's Disease Revealed by Simultaneous Magnetoencephalography and Intracranial Recordings. *J Neurosci* 32:10541–10553.
- Litvak V, Eusebio A, Jha A, Oostenveld R, Barnes GR, Penny WD, Zrinzo L, Hariz MI, Limousin P, Friston KJ, Brown P (2010) Optimized beamforming for simultaneous MEG and intracranial local field potential recordings in deep brain stimulation patients. *Neuroimage* 50:1578–1588.
- Litvak V, Jha A, Eusebio A, Oostenveld R, Foltynie T, Limousin P, Zrinzo L, Hariz MI, Friston K, Brown P (2011a) Resting oscillatory cortico-subthalamic connectivity in patients with Parkinson's disease. *Brain* 134:359–374.

- Litvak V, Mattout J, Kiebel S, Phillips C, Henson R, Kilner J, Barnes G, Oostenveld R, Daunizeau J, Flandin G, Penny W, Friston K (2011b) EEG and MEG data analysis in SPM8. *Comput Intell Neurosci* 2011:852961.
- Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A (2001) Neurophysiological investigation of the basis of the fMRI signal. *Nature* 412:150–157.
- López-Azcárate J, Tainta M, Rodríguez-Oroz MC, Valencia M, González R, Guridi J, Iriarte J, Obeso JA, Artieda J, Alegre M (2010) Coupling between beta and high-frequency activity in the human subthalamic nucleus may be a pathophysiological mechanism in Parkinson's disease. *J Neurosci* 30:6667–6677.
- Lopiano L, Torre E, Benedetti F, Bergamasco B, Perozzo P, Pollo A, Rizzone M, Tavella A, Lanotte M (2003) Temporal changes in movement time during the switch of the stimulators in Parkinson's disease patients treated by subthalamic nucleus stimulation. *Eur Neurol* 50:94–99.
- Mallet L, Schüpbach M, N'Diaye K, Remy P, Bardinet E, Czernecki V, Welter M-L, Pelissolo A, Ruberg M, Agid Y, Yelnik J (2007) Stimulation of subterritories of the subthalamic nucleus reveals its role in the integration of the emotional and motor aspects of behavior. *Proc Natl Acad Sci* 104:10661–10666.
- Manning JR, Jacobs J, Fried I, Kahana MJ (2009) Broadband shifts in local field potential power spectra are correlated with single-neuron spiking in humans. *J Neurosci* 29:13613–13620.
- Marceglia S, Foffani G, Bianchi AM, Baselli G, Tamma F, Egidio M, Priori A (2006) Dopamine-dependent non-linear correlation between subthalamic rhythms in Parkinson's disease. *J Physiol* 571:579–591.
- Maris E (2012) Statistical testing in electrophysiological studies. *Psychophysiology* 49:549–565.
- Marreiros AC, Cagnan H, Moran RJ, Friston KJ, Brown P (2012) Basal ganglia-cortical interactions in Parkinsonian patients. *Neuroimage* 66C:301–310.
- Marsden CD, Obeso JA (1994) The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease. *Brain* 117 (Pt 4:877–897.
- Marsden JF, Ashby P, Limousin-Dowsey P, Rothwell JC, Brown P (2000) Coherence between cerebellar thalamus, cortex and muscle in man: cerebellar thalamus interactions. *Brain* 123 (Pt 7:1459–1470.
- Mathai A, Smith Y (2011) The corticostriatal and corticosubthalamic pathways: two entries, one target. So what? *Front Syst Neurosci* 5:64.
- Mattout J, Henson RN, Friston KJ (2007) Canonical source reconstruction for MEG. *Comput Intell Neurosci*:67613.
- Maurice N, Thierry A-M, Glowinski J, Deniau J-M (2003) Spontaneous and evoked activity of substantia nigra pars reticulata neurons during high-frequency stimulation of the subthalamic nucleus. *J Neurosci* 23:9929–9936.

- Mayka MA, Corcos DM, Leurgans SE, Vaillancourt DE (2006) Three-dimensional locations and boundaries of motor and premotor cortices as defined by functional brain imaging: a meta-analysis. *Neuroimage* 31:1453–1474.
- Mazzoni P, Hristova A, Krakauer JW (2007) Why don't we move faster? Parkinson's disease, movement vigor, and implicit motivation. *J Neurosci* 27:7105–7116.
- Miller KJ, Sorensen LB, Ojemann JG, den Nijs M (2009) Power-law scaling in the brain surface electric potential. *PLoS Comput Biol* 5:e1000609.
- Minka T (2008) Automatic Selection of Dimensionality for PCA. MIT Media Lab Percept Comput Sect Tech Rep No 514.
- Mitra PP, Pesaran B (1999) Analysis of dynamic brain imaging data. *Biophys J* 76:691–708.
- Mohseni HR, Kringelbach ML, Probert Smith P, Green AL, Parsons CE, Young KS, Brittain J-S, Hyam JA, Schweder PM, Stein JF, Aziz TZ (2010) Application of a null-beamformer to source localisation in MEG data of deep brain stimulation. *Conf Proc . Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Annu Conf* 2010:4120–4123.
- Mohseni HR, Kringelbach ML, Woolrich MW, Baker A, Aziz TZ, Probert-Smith P (2013) Non-Gaussian probabilistic MEG source localisation based on kernel density estimation. *Neuroimage* 87:444–464.
- Mohseni HR, Smith PP, Parsons CE, Young KS, Hyam JA, Stein A, Stein JF, Green AL, Aziz TZ, Kringelbach ML (2012) MEG can map short and long-term changes in brain activity following deep brain stimulation for chronic pain. *PLoS One* 7:e37993.
- Moore DJ, West AB, Dawson VL, Dawson TM (2005) Molecular pathophysiology of Parkinson's disease. *Annu Rev Neurosci* 28:57–87.
- Moran A, Bergman H, Israel Z, Bar-Gad I (2008) Subthalamic nucleus functional organization revealed by parkinsonian neuronal oscillations and synchrony. *Brain* 131:3395–3409.
- Moran RJ, Mallet N, Litvak V, Dolan RJ, Magill PJ, Friston KJ, Brown P (2011) Alterations in Brain Connectivity Underlying Beta Oscillations in Parkinsonism. *PLoS Comput Biol* 7:e1002124.
- Mormann F, Fell J, Axmacher N, Weber B, Lehnertz K, Elger CE, Fernández G (2005) Phase/amplitude reset and theta-gamma interaction in the human medial temporal lobe during a continuous word recognition memory task. *Hippocampus* 15:890–900.
- Nagano-Saito A, Liu J, Doyon J, Dagher A (2009) Dopamine modulates default mode network deactivation in elderly individuals during the Tower of London task. *Neurosci Lett* 458:1–5.
- Nambu A (2008) Seven problems on the basal ganglia. *Curr Opin Neurobiol* 18:595–604.
- Neuper C, Pfurtscheller G (1996) Post-movement synchronization of beta rhythms in the EEG over the cortical foot area in man. *Neurosci Lett* 216:17–20.
- Niv Y, Rivlin-Etzion M (2007) Parkinson's disease: fighting the will? *J Neurosci* 27:11777–11779.

- Nolte G (2003) The magnetic lead field theorem in the quasi-static approximation and its use for magnetoencephalography forward calculation in realistic volume conductors. *Phys Med Biol* 48:3637–3652.
- Nolte G, Bai O, Wheaton L, Mari Z, Vorbach S, Hallett M (2004) Identifying true brain interaction from EEG data using the imaginary part of coherency. *Clin Neurophysiol* 115:2292–2307.
- Okada Y (1983) Neurogenesis of Evoked Magnetic Fields. In: In: Williamson, S.H;Romani, G.L; Kaufman, L;Modena, I editors. *Biomagnetism: an Interdisciplinary Approach*. NewYork: Plenum press, pp 399–408.
- Oostenveld R, Fries P, Maris E, Schoffelen J-M (2011) FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Comput Intell Neurosci* 2011:156869.
- Oostenveld R, Oostendorp TF (2002) Validating the boundary element method for forward and inverse EEG computations in the presence of a hole in the skull. *Hum Brain Mapp* 17:179–192.
- Oswal A, Brown P, Litvak V (2013a) Movement related dynamics of subthalamo-cortical alpha connectivity in Parkinson's disease. *Neuroimage* 70:132–142.
- Oswal A, Brown P, Litvak V (2013b) Synchronized neural oscillations and the pathophysiology of Parkinson's disease. *Curr Opin Neurol* 26:662–670.
- Oswal A, Litvak V, Brown P, Woolrich M, Barnes G (2014) Optimising beamformer regions of interest analysis. *Neuroimage* 102 Pt 2:945–954.
- Oswal A, Litvak V, Sauleau P, Brown P (2012) Beta reactivity, prospective facilitation of executive processing, and its dependence on dopaminergic therapy in Parkinson's disease. *J Neurosci* 32:9909–9916.
- Oswal A, Ogden M, Carpenter RHS (2007) The time course of stimulus expectation in a saccadic decision task. *J Neurophysiol* 97:2722–2730.
- Özkurt TE, Butz M, Homburger M, Elben S, Vesper J, Wojtecki L, Schnitzler A (2011) High frequency oscillations in the subthalamic nucleus: a neurophysiological marker of the motor state in Parkinson's disease. *Exp Neurol* 229:324–331.
- Ozkurt TE, Sun M, Sclabassi RJ (2006) Beam-space magnetoencephalographic signal decomposition in spherical harmonics domain. *Conf Proc IEEE Eng Med Biol Soc* 1:5743–5746.
- Palva S, Palva JM (2007) New vistas for alpha-frequency band oscillations. *Trends Neurosci* 30:150–158.
- Parent A, Hazrati LN (1995a) Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. *Brain Res Brain Res Rev* 20:128–154.
- Parent A, Hazrati LN (1995b) Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. *Brain Res Brain Res Rev* 20:91–127.

- Park H, Kim JS, Paek SH, Jeon BS, Lee JY, Chung CK (2009) Cortico-muscular coherence increases with tremor improvement after deep brain stimulation in Parkinson's disease. *Neuroreport* 20:1444–1449.
- Parkinson J (1817) *An essay on the shaking palsy*. London: Sherwood, Neely and Jones.
- Pedrosa DJ, Reck C, Florin E, Pauls KAM, Maarouf M, Wojtecki L, Dafsari HS, Sturm V, Schnitzler A, Fink GR, Timmermann L (2012) Essential tremor and tremor in Parkinson's disease are associated with distinct "tremor clusters" in the ventral thalamus. *Exp Neurol* 237:435–443.
- Pezzoli G, Cereda E (2013) Exposure to pesticides or solvents and risk of Parkinson disease. *Neurology* 80:2035–2041.
- Pfurtscheller G, Lopes da Silva FH (1999) Event-related EEG/MEG synchronization and desynchronization: basic principles. *Clin Neurophysiol* 110:1842–1857.
- Pfurtscheller G, Neuper C, Kalcher J (1993) 40-Hz oscillations during motor behavior in man. *Neurosci Lett* 164:179–182.
- Pogosyan A, Gaynor LD, Eusebio A, Brown P (2009) Boosting cortical activity at Beta-band frequencies slows movement in humans. *Curr Biol* 19:1637–1641.
- Pogosyan A, Kühn AA, Trottenberg T, Schneider G-H, Kupsch A, Brown P (2006) Elevations in local gamma activity are accompanied by changes in the firing rate and information coding capacity of neurons in the region of the subthalamic nucleus in Parkinson's disease. *Exp Neurol* 202:271–279.
- Pogosyan A, Yoshida F, Chen CC, Martinez-Torres I, Foltynie T, Limousin P, Zrinzo L, Hariz MI, Brown P (2010) Parkinsonian impairment correlates with spatially extensive subthalamic oscillatory synchronization. *Neuroscience* 171:245–257.
- Pollok B, Krause V, Martsch W, Wach C, Schnitzler A, Südmeyer M (2012) Motor-cortical oscillations in early stages of Parkinson's disease. *J Physiol* 590:3203–3212.
- Pollok B, Makhouloufi H, Butz M, Gross J, Timmermann L, Wojtecki L, Schnitzler A (2009) Levodopa affects functional brain networks in Parkinsonian resting tremor. *Mov Disord* 24:91–98.
- Ponce FA, Lozano AM (2010) Deep brain stimulation state of the art and novel stimulation targets. *Prog Brain Res* 184:311–324.
- Ponsen MM, Stoffers D, Booij J, van Eck-Smit BLF, Wolters EC, Berendse HW (2004) Idiopathic hyposmia as a preclinical sign of Parkinson's disease. *Ann Neurol* 56:173–181.
- Priori A, Foffani G, Pesenti A, Tamma F, Bianchi AM, Pellegrini M, Locatelli M, Moxon KA, Villani RM (2004) Rhythm-specific pharmacological modulation of subthalamic activity in Parkinson's disease. *Exp Neurol* 189:369–379.
- Raethjen J, Lindemann M, Schmaljohann H, Wenzelburger R, Pfister G, Deuschl G (2000) Multiple oscillators are causing parkinsonian and essential tremor. *Mov Disord* 15:84–94.

- Raichle ME, Snyder AZ (2007) A default mode of brain function: a brief history of an evolving idea. *Neuroimage* 37:1083–1090; discussion 1097–1099.
- Ramírez RR, Kopell BH, Butson CR, Hiner BC, Baillet S (2011) Spectral signal space projection algorithm for frequency domain MEG and EEG denoising, whitening, and source imaging. *Neuroimage* 56:78–92.
- Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE (2000) A Five-Year Study of the Incidence of Dyskinesia in Patients with Early Parkinson's Disease Who Were Treated with Ropinirole or Levodopa. *N Engl J Med* 342:1484–1491.
- Ray N, Kringelbach M, Jenkinson N, Owen S, Davies P, Wang S, De Pennington N, Hansen P, Stein J, Aziz T (2007) Using magnetoencephalography to investigate brain activity during high frequency deep brain stimulation in a cluster headache patient. *Biomed Imaging Interv J* 3:e25.
- Ray NJ, Brittain J-S, Holland P, Joundi RA, Stein J, Aziz TZ, Jenkinson N (2011) The role of the subthalamic nucleus in response inhibition: Evidence from local field potential recordings in the human subthalamic nucleus. *Neuroimage*.
- Ray NJ, Jenkinson N, Kringelbach ML, Hansen PC, Pereira EA, Brittain JS, Holland P, Holliday IE, Owen S, Stein J, Aziz T (2009) Abnormal thalamocortical dynamics may be altered by deep brain stimulation: using magnetoencephalography to study phantom limb pain. *J Clin Neurosci* 16:32–36.
- Ray NJ, Jenkinson N, Wang S, Holland P, Brittain JS, Joint C, Stein JF, Aziz T (2008) Local field potential beta activity in the subthalamic nucleus of patients with Parkinson's disease is associated with improvements in bradykinesia after dopamine and deep brain stimulation. *Exp Neurol* 213:108–113.
- Ray S, Maunsell JHR (2010) Differences in gamma frequencies across visual cortex restrict their possible use in computation. *Neuron* 67:885–896.
- Reck C, Florin E, Wojtecki L, Krause H, Groiss S, Voges J, Maarouf M, Sturm V, Schnitzler A, Timmermann L (2009) Characterisation of tremor-associated local field potentials in the subthalamic nucleus in Parkinson's disease. *Eur J Neurosci* 29:599–612.
- Rehncrona S, Johnels B, Widner H, Törnqvist A-L, Hariz M, Sydow O (2003) Long-term efficacy of thalamic deep brain stimulation for tremor: double-blind assessments. *Mov Disord* 18:163–170.
- Rivlin-Etzion M, Marmor O, Heimer G, Raz A, Nini A, Bergman H (2006) Basal ganglia oscillations and pathophysiology of movement disorders. *Curr Opin Neurobiol* 16:629–637.
- Rodriguez-Oroz MC et al. (2005) Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up. *Brain* 128:2240–2249.
- Rodriguez-Oroz MC, López-Azcárate J, Garcia-Garcia D, Alegre M, Toledo J, Valencia M, Guridi J, Artieda J, Obeso JA (2011) Involvement of the subthalamic nucleus in impulse control disorders associated with Parkinson's disease. *Brain* 134:36–49.

- Rodriguez-Oroz MC, Rodriguez M, Guridi J, Mewes K, Chockkman V, Vitek J, DeLong MR, Obeso JA (2001) The subthalamic nucleus in Parkinson's disease: somatotopic organization and physiological characteristics. *Brain* 124:1777–1790.
- Rodríguez-Rivera A, Baryshnikov B V, Van Veen BD, Wakai RT (2006) MEG and EEG source localization in beamspace. *IEEE Trans Biomed Eng* 53:430–441.
- Rogers D, Lees AJ, Smith E, Trimble M, Stern GM (1987) Bradyphrenia in Parkinson's disease and psychomotor retardation in depressive illness. An experimental study. *Brain* 110 (Pt 3:761–776.
- Rohenkohl G, Nobre AC (2011) α oscillations related to anticipatory attention follow temporal expectations. *J Neurosci* 31:14076–14084.
- Rosin B, Slovik M, Mitelman R, Rivlin-Etzion M, Haber SN, Israel Z, Vaadia E, Bergman H (2011) Closed-loop deep brain stimulation is superior in ameliorating parkinsonism. *Neuron* 72:370–384.
- Rossi L, Foffani G, Marceglia S, Bracchi F, Barbieri S, Priori A (2007) An electronic device for artefact suppression in human local field potential recordings during deep brain stimulation. *J Neural Eng* 4:96–106.
- Rossi L, Marceglia S, Foffani G, Cogiamanian F, Tamma F, Rampini P, Barbieri S, Bracchi F, Priori A (2008) Subthalamic local field potential oscillations during ongoing deep brain stimulation in Parkinson's disease. *Brain Res Bull* 76:512–521.
- Salamone JD, Correa M, Farrar AM, Nunes EJ, Pardo M (2009) Dopamine, behavioral economics, and effort. *Front Behav Neurosci* 3:13.
- Salenius S, Salmelin R, Neuper C, Pfurtscheller G, Hari R (1996) Human cortical 40 Hz rhythm is closely related to EMG rhythmicity. *Neurosci Lett* 213:75–78.
- Samejima K, Ueda Y, Doya K, Kimura M (2005) Representation of action-specific reward values in the striatum. *Science* 310:1337–1340.
- Sauleau P, Eusebio A, Thevathasan W, Yarrow K, Pogosyan A, Zrinzo L, Ashkan K, Aziz T, Vandenberghe W, Nuttin B, Brown P (2009) Involvement of the subthalamic nucleus in engagement with behaviourally relevant stimuli. *Eur J Neurosci* 29:931–942.
- Schoffelen J-M, Oostenveld R, Fries P (2005) Neuronal coherence as a mechanism of effective corticospinal interaction. *Science* 308:111–113.
- Schoffelen J-M, Poort J, Oostenveld R, Fries P (2011) Selective movement preparation is subserved by selective increases in corticomuscular gamma-band coherence. *J Neurosci* 31:6750–6758.
- Sharott A, Magill PJ, Harnack D, Kupsch A, Meissner W, Brown P (2005) Dopamine depletion increases the power and coherence of beta-oscillations in the cerebral cortex and subthalamic nucleus of the awake rat. *Eur J Neurosci* 21:1413–1422.

- Silberstein P, Pogosyan A, Kühn AA, Hotton G, Tisch S, Kupsch A, Dowsey-Limousin P, Hariz MI, Brown P (2005) Cortico-cortical coupling in Parkinson's disease and its modulation by therapy. *Brain* 128:1277–1291.
- Singh A, Levin J, Mehrkens JH, Bötzel K (2011) Alpha frequency modulation in the human basal ganglia is dependent on motor task. *Eur J Neurosci* 33:960–967.
- Sochurkova D, Rektor I (2003) Event-related desynchronization/synchronization in the putamen. An SEEG case study. *Exp Brain Res* 149:401–404.
- Stam CJ (2010) Use of magnetoencephalography (MEG) to study functional brain networks in neurodegenerative disorders. *J Neurol Sci* 289:128–134.
- Stoffers D, Bosboom JLW, Deijen JB, Wolters EC, Berendse HW, Stam CJ (2007) Slowing of oscillatory brain activity is a stable characteristic of Parkinson's disease without dementia. *Brain* 130:1847–1860.
- Stoffers D, Bosboom JLW, Wolters EC, Stam CJ, Berendse HW (2008) Dopaminergic modulation of cortico-cortical functional connectivity in Parkinson's disease: an MEG study. *Exp Neurol* 213:191–195.
- Sweeney-Reed CM, Nasuto SJ (2007) A novel approach to the detection of synchronisation in EEG based on empirical mode decomposition. *J Comput Neurosci* 23:79–111.
- Tachibana Y, Iwamuro H, Kita H, Takada M, Nambu A (2011) Subthalamo-pallidal interactions underlying parkinsonian neuronal oscillations in the primate basal ganglia. *Eur J Neurosci* 34:1470–1484.
- Tan H, Pogosyan A, Anzak A, Foltynie T, Limousin P, Zrinzo L, Ashkan K, Bogdanovic M, Green AL, Aziz T, Brown P (2013) Frequency specific activity in subthalamic nucleus correlates with hand bradykinesia in Parkinson's disease. *Exp Neurol* 240:122–129.
- Tan H, Pogosyan A, Ashkan K, Cheeran B, FitzGerald JJ, Green AL, Aziz T, Foltynie T, Limousin P, Zrinzo L, Brown P (2015) Subthalamic Nucleus Local Field Potential Activity Helps Encode Motor Effort Rather Than Force in Parkinsonism. *J Neurosci* 35:5941–5949.
- Tanner CM (1992) Epidemiology of Parkinson's disease. *Neurol Clin* 10:317–329.
- Tanner CM, Ottman R, Goldman SM, Ellenberg J, Chan P, Mayeux R, Langston JW (1999) Parkinson disease in twins: an etiologic study. *JAMA* 281:341–346.
- Taulu S, Kajola M, Simola J (2004) Suppression of interference and artifacts by the Signal Space Separation Method. *Brain Topogr* 16:269–275.
- Taulu S, Simola J (2006) Spatiotemporal signal space separation method for rejecting nearby interference in MEG measurements. *Phys Med Biol* 51:1759–1768.
- Temperli P, Ghika J, Villemure J-G, Burkhard PR, Bogousslavsky J, Vingerhoets FJG (2003) How do parkinsonian signs return after discontinuation of subthalamic DBS? *Neurology* 60:78–81.

- Tessitore A, Amboni M, Esposito F, Russo A, Picillo M, Marcuccio L, Pellecchia MT, Vitale C, Cirillo M, Tedeschi G, Barone P (2012) Resting-state brain connectivity in patients with Parkinson's disease and freezing of gait. *Parkinsonism Relat Disord* 18:781–787.
- Thatcher RW, Krause PJ, Hrybyk M (1986) Cortico-cortical associations and EEG coherence: a two-compartmental model. *Electroencephalogr Clin Neurophysiol* 64:123–143.
- Thomson D (1982) Spectral estimation and harmonic analysis. *Proc IEEE* 70:1055–1096.
- Thut G, Nietzel A, Brandt S a, Pascual-Leone A (2006) Alpha-band electroencephalographic activity over occipital cortex indexes visuospatial attention bias and predicts visual target detection. *J Neurosci* 26:9494–9502.
- Timmermann L, Gross J, Dirks M, Volkmann J, Freund H-J, Schnitzler A (2003) The cerebral oscillatory network of parkinsonian resting tremor. *Brain* 126:199–212.
- Timmermann L, Wojtecki L, Gross J, Lehrke R, Voges J, Maarouf M, Treuer H, Sturm V, Schnitzler A (2004) Ten-Hertz stimulation of subthalamic nucleus deteriorates motor symptoms in Parkinson's disease. *Mov Disord* 19:1328–1333.
- Tort ABL, Komorowski RW, Manns JR, Kopell NJ, Eichenbaum H (2009) Theta-gamma coupling increases during the learning of item-context associations. *Proc Natl Acad Sci U S A* 106:20942–20947.
- Trottenberg T, Fogelson N, Kühn AA, Kivi A, Kupsch A, Schneider G-H, Brown P (2006) Subthalamic gamma activity in patients with Parkinson's disease. *Exp Neurol* 200:56–65.
- Tsang EW, Hamani C, Moro E, Mazzella F, Saha U, Lozano AM, Hodaie M, Chuang R, Steeves T, Lim SY, Neagu B, Chen R (2012) Subthalamic deep brain stimulation at individualized frequencies for Parkinson disease. *Neurology* 78:1930–1938.
- Turner RS, Desmurget M (2010) Basal ganglia contributions to motor control: a vigorous tutor. *Curr Opin Neurobiol* 20:704–716.
- Twelves D, Perkins KSM, Counsell C (2003) Systematic review of incidence studies of Parkinson's disease. *Mov Disord* 18:19–31.
- Tzagarakis C, Ince NF, Leuthold AC, Pellizzer G (2010) Beta-band activity during motor planning reflects response uncertainty. *J Neurosci* 30:11270–11277.
- Uhlhaas PJ, Singer W (2006) Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. *Neuron* 52:155–168.
- Van den Broek SP, Reinders F, Donderwinkel M, Peters MJ (1998) Volume conduction effects in EEG and MEG. *Electroencephalogr Clin Neurophysiol* 106:522–534.
- Van Veen BD, van Drongelen W, Yuchtman M, Suzuki A (1997) Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. *IEEE Trans Biomed Eng* 44:867–880.

- Wager TD, Keller MC, Lacey SC, Jonides J (2005) Increased sensitivity in neuroimaging analyses using robust regression. *Neuroimage* 26:99–113.
- Wakabayashi K, Tanji K, Mori F, Takahashi H (2007) The Lewy body in Parkinson's disease: molecules implicated in the formation and degradation of alpha-synuclein aggregates. *Neuropathology* 27:494–506.
- Walters JR, Ruskin DN, Allers KA, Bergstrom DA (2000) Pre- and postsynaptic aspects of dopamine-mediated transmission. *Trends Neurosci* 23:S41–S47.
- Weaver FM et al. (2009) Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA* 301:63–73.
- Weinberger M, Hutchison WD, Dostrovsky JO (2009) Pathological subthalamic nucleus oscillations in PD: can they be the cause of bradykinesia and akinesia? *Exp Neurol* 219:58–61.
- Weinberger M, Mahant N, Hutchison WD, Lozano AM, Moro E, Hodaie M, Lang AE, Dostrovsky JO (2006) Beta oscillatory activity in the subthalamic nucleus and its relation to dopaminergic response in Parkinson's disease. *J Neurophysiol* 96:3248–3256.
- Weiss D, Klotz R, Govindan RB, Scholten M, Naros G, Ramos-Murguialday A, Bunjes F, Meisner C, Plewnia C, Krüger R, Gharabaghi A (2015) Subthalamic stimulation modulates cortical motor network activity and synchronization in Parkinson's disease. *Brain* 138:679–693.
- Whitmer D, de Solages C, Hill B, Yu H, Henderson JM, Bronte-Stewart H (2012) High frequency deep brain stimulation attenuates subthalamic and cortical rhythms in Parkinson's disease. *Front Hum Neurosci* 6:155.
- Williams A, Gill S, Varma T, Jenkinson C, Quinn N, Mitchell R, Scott R, Ives N, Rick C, Daniels J, Patel S, Wheatley K (2010) Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. *Lancet Neurol* 9:581–591.
- Williams D, Kühn A, Kupsch A, Tijssen M, van Bruggen G, Speelman H, Hotton G, Loukas C, Brown P (2005) The relationship between oscillatory activity and motor reaction time in the parkinsonian subthalamic nucleus. *Eur J Neurosci* 21:249–258.
- Williams D, Kühn A, Kupsch A, Tijssen M, van Bruggen G, Speelman H, Hotton G, Yarrow K, Brown P (2003) Behavioural cues are associated with modulations of synchronous oscillations in the human subthalamic nucleus. *Brain* 126:1975–1985.
- Williams D, Tijssen M, Van Bruggen G, Bosch A, Insola A, Di Lazzaro V, Mazzone P, Oliviero A, Quartarone A, Speelman H, Brown P (2002) Dopamine-dependent changes in the functional connectivity between basal ganglia and cerebral cortex in humans. *Brain* 125:1558–1569.
- Williams-Gray CH, Foltynie T, Brayne CEG, Robbins TW, Barker RA (2007) Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. *Brain* 130:1787–1798.
- Wingeier B, Tcheng T, Koop MM, Hill BC, Heit G, Bronte-Stewart HM (2006) Intra-operative STN DBS attenuates the prominent beta rhythm in the STN in Parkinson's disease. *Exp Neurol* 197:244–251.

- Wirdefeldt K, Adami H-O, Cole P, Trichopoulos D, Mandel J (2011) Epidemiology and etiology of Parkinson's disease: a review of the evidence. *Eur J Epidemiol* 26 Suppl 1:S1–S58.
- Witjas T, Kaphan E, Régis J, Jouve E, Chérif AA, Péragut J-C, Azulay JP (2007) Effects of chronic subthalamic stimulation on nonmotor fluctuations in Parkinson's disease. *Mov Disord* 22:1729–1734.
- Woolrich M, Hunt L, Groves A, Barnes G (2011) MEG beamforming using Bayesian PCA for adaptive data covariance matrix regularization. *Neuroimage* 57:1466–1479.
- Woolrich MW, Baker A, Luckhoo H, Mohseni H, Barnes G, Brookes M, Rezek I (2013) Dynamic state allocation for MEG source reconstruction. *Neuroimage* 77:77–92.
- Wooten GF, Currie LJ, Bovbjerg VE, Lee JK, Patrie J (2004) Are men at greater risk for Parkinson's disease than women? *J Neurol Neurosurg Psychiatry* 75:637–639.
- Worsley KJ, Evans AC, Marrett S, Neelin P (1992) A three-dimensional statistical analysis for CBF activation studies in human brain. *J Cereb Blood Flow Metab* 12:900–918.
- Worsley KJ, Friston KJ (1995) Analysis of fMRI time-series revisited--again. *Neuroimage* 2:173–181.
- Yarnall A, Rochester L, Burn DJ (2011) The interplay of cholinergic function, attention, and falls in Parkinson's disease. *Mov Disord* 26:2496–2503.
- Zaidel A, Spivak A, Grieb B, Bergman H, Israel Z (2010) Subthalamic span of beta oscillations predicts deep brain stimulation efficacy for patients with Parkinson's disease. *Brain* 133:2007–2021.
- Zetuský WJ, Jankovic J, Pirozzolo FJ (1985) The heterogeneity of Parkinson's disease: clinical and prognostic implications. *Neurology* 35:522–526.
- Zgaljardic DJ, Borod JC, Foldi NS, Mattis P (2003) A review of the cognitive and behavioral sequelae of Parkinson's disease: relationship to frontostriatal circuitry. *Cogn Behav Neurol* 16:193–210.
- Zrinzo L, van Hulzen ALJ, Gorgulho AA, Limousin P, Staal MJ, De Salles AAF, Hariz MI (2009) Avoiding the ventricle: a simple step to improve accuracy of anatomical targeting during deep brain stimulation. *J Neurosurg* 110:1283–1290.