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Neuromagnetic investigations of mechanisms and effects of STN-DBS and medication in Parkinson's disease

Department of Clinical Medicine

Kousik Sarathy Sridharan

PhD dissertation

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asato mā sad gamaya,

tamaso mā jyotir gamaya,

mṛtyor mā amṛtaṃ gamaya

From transitory existence, lead me to the Eternal truth!

From ignorance, lead me to Knowledge!

From fear of death, lead me to the knowledge of Immortality!

~ Bṛhadāraṇyakopaniṣat

Preface

This thesis is based on the three following manuscripts:

1. Sridharan KS, Højlund A, Johnsen EL, Sunde NA, Johansen LG, Beniczky S, Østergaard, K. Differentiated effects of deep brain stimulation and medication on somatosensory processing in Parkinson's disease. Clin Neurophysiol 2017. doi:10.1016/j.clinph.2017.04.014.

2. Sridharan KS, Højlund A, Johnsen EL, Sunde NA, Beniczky S, Østergaard, K. Deep brain stimulation and dopaminergic medication differentially modulate motor cortical oscillations and corticomuscular coherence in Parkinson's disease. **(in review)**

3. Sridharan KS, Højlund A, Johnsen EL, Sunde NA, Beniczky S, Østergaard, K. . How do treatments modulate oscillatory dynamics in PD at rest? **(manuscript prepared)**

English summary

Parkinson's disease (PD) is a neurodegenerative disorder cardinally marked by motor symptoms, but also sensory symptoms and several other non-motor symptoms. PD patients are typically treated with dopaminergic medication for several years. Many patients eventually experience periods where medication might not be able to effectively control symptoms and experience side-effects of long-term dopaminergic treatments. Deep brain stimulation (DBS) is an option as the next therapeutic recourse for such patients. DBS treatment essentially involves placement of stimulating electrodes in the subthalamic nucleus (STN) or the globus pallidus internum (GPi) along with an implanted pulse generator (IPG) in the sub-clavicular space. STN-DBS alleviates motor symptoms and leads to substantial improvements in quality of life for PD patients. Although DBS is known to improve several classes of symptoms, the effect mechanism of DBS is still not clear. While there is a lack of electrophysiological investigation of sensory processing and the effects of treatments in PD altogether, the electrophysiological studies of the cortical dynamics during motor tasks and at rest lack consensus.

We recorded magnetoencephalography (MEG) and electromyography (EMG) from PD patients in three studies: (i) at rest, (ii) during median nerve stimulation, and (iii) while performing phasic contractions (hand gripping). The three studies focused on cortical oscillatory dynamics at rest, during somatosensory processing and during movement, respectively. The measurements were conducted in DBS-treated, untreated (DBS washout) and dopaminergic-medicated states. While both treatments (DBS and dopaminergic medication) ameliorated motor symptoms similarly in all studies, they showed differentiated effects on: (i) increased sensorimotor cortical low-gamma spectral power (31-45 Hz) (but no changes in beta power (13-30 Hz)) at rest only during DBS, (ii) somatosensory processing with higher gamma augmentation (31-45 Hz, 20-60 ms) in the dopaminergic-medicated state compared to DBS-treated and untreated states, and (iii) hand gripping with increased motor-related beta corticomuscular coherence (CMC, 13-30 Hz) during dopaminergic medication in contrast to increased gamma power (31-45 Hz) during DBS.

Firstly, we infer from the three studies that DBS and dopaminergic medication employ partially different anatomo-functional pathways and functional strategies when improving PD symptoms. Secondly, we suggest that treatments act on pathological oscillatory dynamics differently at cortical and sub-cortical levels and may do so through more sophisticated mechanisms than mere

suppression of the pathological spectral power in a particular band. And thirdly, we urge exploring effect mechanisms of PD treatments beyond the motor system. The effects of dopaminergic medication on early somatosensory processing has opened the door for exploring the effects of treatments and studying their mechanisms using electrophysiology, especially in higher order sensory deficits. Integration of such research findings into a holistic view on mechanisms of treatments could pave way for better disease management paradigms.

Dansk resumé

Parkinsons sygdom (PS) er en neurodegenerativ sygdom som især er karakteristeret ved motoriske symptomer, men også sensoriske symptomer og flere andre non-motoriske symptomer. PS-patienter bliver typisk behandlet med dopaminerg medicin i adskillige år. Mange patienter oplever dog efterhånden tilbagevendende perioder hvor medicinen ikke effektivt kan kontrollere symptomerne samt bivirkninger fra længerevarende dopaminerg behandling. Dyb hjernestimulation (DBS) er en mulighed som alternativ behandlingsmetode for disse patienter. DBS-behandlingen indebærer placering af stimulations-elektroder i nucleus subthalamicus (STN) eller globus pallidus interna (GPi) i hjernen sammen med en indopereret pulsgenerator (IPG) på forsiden af brystet. STN-DBS afhjælper de motoriske symptomer og fører til markante forbedringer i livskvalitet for PS-patienter. Selvom det er kendt at DBS forbedrer flere forskellige typer symptomer, er selve effekt-mekanismen bag DBS endnu ikke fuldt forstået. Mens der generelt mangler elektrofysiologiske undersøgelser af PS-behandlingers påvirkning af den sensoriske bearbejdning, er de eksisterende elektrofysiologiske undersøgelser af PS-behandlingernes påvirkning af de kortikale dynamikker under bevægelse og hvile præget af manglende konsensus.

Vi målte med magnetoencefalografi (MEG) og elektromyografi (EMG) fra PS-patienter i tre forsøg: (i) under hvile, (ii) under stimulering af nervus medianus (ved håndleddet), og (iii) under udførelse af gentagne håndbevægelse (sammentrækning og udstrækning af fingrene). De tre forsøg var således målrettet dynamikkerne i de kortikale frekvensbånd under hhv. hvile, sensorisk bearbejdning og bevægelse. MEG-målinger blev udført på PS-patienter i tre tilstande: DBS-behandlet, ubehandlet (udvaskning af DBS-effekt) og behandlet med dopaminerg medicin. Mens begge behandlinger (DBS og dopaminerg medicin) forbedrede bevægelsessymptomerne i lige høj grad i alle tre studier, viste de forskelligartede resultater: (i) forhøjet aktivitet i det sensori-motoriske kortikale gamma-bånd (31-45) Hz under hvile og kun ved DBS-behandling; (ii) forhøjet aktivitet i gamma-båndet (31-45 Hz, 20-60 ms) relateret til bearbejdning af sensorisk-relaterede stimuli ved medicinsk behandling sammenlignet med DBS og ingen behandling; og (iii) øget kortikomuskulær kohærens (CMC) mellem motor-kortex og underarmsmusklen i beta-båndet (13-30 Hz) ved medicinsk behandling i modsætning til øget aktivitet i gamma-båndet (31-45 Hz) i motor-kortex ved DBS-behandling.

Først og fremmest udleder vi på baggrund af de tre studier at DBS og dopaminerg medicin virker gennem delvist forskellige anatomisk-funktionelle forbindelser og implementeringer i deres forbedring af PS-symptomerne. Dernæst foreslår vi at behandlingerne påvirker de uhensigtsmæssige (patologiske) frekvens-dynamikker forskelligt på det kortikale og subkortikale niveau, og at de gør dette via mere sofistikerede mekanismer end bare at understrykke selve den uhensigtsmæssige spektrale aktivitet i de relevante frekvensbånd. Og endelig opfordrer vi til yderligere undersøgelse af effekt-mekanismerne bag PS-behandlingerne ved at se ud over bevægelses-netværket. Påvirkningerne fra dopaminerg medicin på den følesansrelaterede bearbejdning har åbnet en dør for elektrofysiologiske undersøgelser af behandlingernes effekt-mekanismer, især i relation til mere komplekse følesans-relaterede forringelser. Integrationen af sådanne forskningsresultater i et mere bredt og overodnet blik på behandlingernes mekanismer kan bane vej for bedre administration og behandling af sygdommen.

Acknowledgements

At the outset, I would like to express my profound gratitude to Prof. Karen Østergaard, my supervisor, for her calm and superlative guidance through my work. She let me to carry out the research in a way that I was comfortable with, while offering course corrections when I hit brick walls. I'm indebted to Sándor Beniczky, my co-supervisor, for his sharp and incisive comments during meetings and on the manuscripts that helped trim down and focus on the aspects of utmost importance.

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Words cannot express my gratitude to my parents for all they have done. I would have never taken up this work had my mom not encouraged me and has remained a pillar of strength and support throughout. I'm eternally indebted to my dad who had always encouraged me to pursue my dreams and laid a strong scientific spirit in me. If there was one reason I got through the last year unscathed, it was my wife, who helped me stay emotionally strong and reminding me subtly of the important things in life beyond work. The animated and funny discussions we had on many issues were all welcome diversions from the rigmarole. What would have I done without you! I'm grateful to my wonderful in-laws for their good wishes and their morale boosting presence. Thanks to my dear friend Chaitanya Srinivas, who was instrumental in convincing me to take up this position.

Table of Contents

Chapter - 1

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder, for which the prevalence increases exponentially with age (de Rijk et al., 1997; Pringsheim et al., 2014). PD affects 2.3 people per hundred above the age of 65 globally (de Rijk et al., 1997), and this number is set to double in the United States alone by 2040 (Kowal et al., 2013). An estimated USD 14 billion was the expenditure on treatments, and the economic impact due to loss of productivity was an estimated USD 6.3 billion in 2010 in the United States (Kowal et al., 2013). With such a large socio-economic impact (de Rijk et al., 1997; Kowal et al., 2013; Pringsheim et al., 2014; Bovolenta et al., 2017), understanding the disease and improving the management assumes obvious importance.

PD is cardinally marked by motor symptoms, but also sensory symptoms, cognitive decline, autonomous dysfunction, psychiatric symptoms and sleep disorders are prevalent (Lang and Lozano, 1998; Kalia and Lang, 2015). Once patients are diagnosed with PD, they are typically treated with dopaminergic medication (levodopa, dopamine agonists and other classes of drugs) for several years (Kalia and Lang, 2015). Some patients experience time periods where there is a reduction of symptom control, as well as side effects such dyskinesias due to long-term treatment with medication (Lang and Lozano, 1998; Rascol et al., 2000). For these patients who otherwise respond well to levodopa, but are no longer experiencing optimal effects of dopaminergic medication, deep brain stimulation (DBS) may be the next therapeutic recourse. Treatment with DBS involves placement of electrodes in specific subcortical nuclei in the brain, the efficacy of

which was first demonstrated by placing electrodes in the ventralis intermedius (VIM) nucleus of the thalamus to reduce tremor in PD patients (Benabid et al., 1988).

Following the work in animal models of Parkinson's disease, where it was shown that lesions in the subthalamic nucleus (STN) could reverse PD symptoms (Bergman et al., 1990; Aziz et al., 1991), Limousin et al. (1995) showed for the first time that PD symptoms could be suppressed with DBS of the STN. It was later shown that the internal segment of the globus pallidus (GPi) is also an effective target for DBS in suppressing PD symptoms (Pahwa et al., 1997; Ghika et al., 1998; Volkmann et al., 1998). Empirical and follow-up data show that DBS of the STN and GPi alleviates motor symptoms and leads to substantial improvements in quality of life (Kumar et al., 1998; Lang and Lozano, 1998; Limousin et al., 1998; Zgaljardic et al., 2003; Deuschl et al., 2006; Kleiner-Fisman et al., 2006). DBS is now a mainstay in symptom management for advanced PD.

Although DBS is known to improve several classes of symptoms, the effect mechanism of DBS is still not clear (Vitek, 2002; Kringelbach et al., 2007; Johnson et al., 2008; Montgomery and Gale, 2008; Chiken and Nambu, 2016). Several studies with animal models as well as a plethora of techniques from cellular level neurophysiology (Hammond et al., 2007; Nambu and Tachibana, 2014) to optogenetics (Gradinaru et al., 2009) have attempted to explain the mechanisms of DBS, but have still fallen short of unravelling the precise mechanisms, and hence, further advancement in disease management paradigms is till limited.

Moreover, several clinical studies have delved into effects of PD treatments (DBS and dopaminergic medication) on motor symptoms (Kumar et al., 1998; Limousin et al., 1998; Deuschl et al., 2006) and non-motor symptoms such as sensory and sensorimotor symptoms (Abbruzzese and Berardelli, 2003; Conte et al., 2013; Patel et al., 2014). They have showed varied effects of treatments (Abbruzzese and Berardelli, 2003; Conte et al., 2013; Patel et al., 2014), triggering electrophysiological investigations on changes in the cortical and sub-cortical structures during motor tasks (Salenius et al., 2002; Brücke et al., 2008; Hirschmann et al., 2011, 2013; Pollok et al., 2012) and rest (Brown et al., 2001; Cassidy et al., 2002; Kühn et al., 2006, 2008; Crowell et al., 2012; Cao et al., 2015, 2017; Oswal et al., 2016). However, to date there are no studies that explain the impact of PD treatments on electrophysiology related to sensory processing. Studies relating to motor tasks and resting state have evaluated the motor cortical and sub-cortical electrophysiology, but the literature lacks consensus regarding the treatment effects as well as

suffers from methodological issues (Salenius et al., 2002; Park et al., 2009; Hirschmann et al., 2013; Airaksinen et al., 2015; Cao et al., 2015, 2017; Oswal et al., 2016).

In the current thesis, I intend to extend the current understanding of the effects and mechanisms of PD treatments (i.e., DBS and dopaminergic medication) using somatosensory, movement-related and resting state protocols. As the first, our group has examined how DBS influences early cortical somatosensory processing. We have used magnetoencephalography (MEG) to measure cortical activity during various tasks in DBS-treated PD patients. For this, we have employed an elaborate experimental paradigm where PD patients were tested in DBS-treated, untreated and medicated states in order to properly assess and delineate the effects of each of the treatments as well as the DBS washout effects.

1.1 Aims and hypotheses

The overall objective of this thesis is to investigate the effects of STN-DBS and dopaminergic medication on cortical oscillations in PD patients. In this regard, we focus on cortical dynamics during sensory processing, during movement and during rest, as reflected in the accompanying three studies.

The purpose of Study I was to investigate the effects of treatments on somatosensory processing in PD patients. Though clinical effects of both DBS and dopaminergic medication have been assessed clinically, the effects on cortical oscillations have not yet been studied. We focused our analyses on early induced somatosensory beta, low-gamma and high-gamma oscillations following median nerve stimulation. Based on earlier studies on changes of metabolism and cerebral blood flow in the sensory cortical areas and on clinical studies on the impact of treatments on sensory symptoms, we hypothesized that both treatments would have an effect on early cortical somatosensory processing.

The intent behind Study II was to understand how STN-DBS and dopaminergic medication modulate motor cortical oscillations and corticomuscular connectivity, which we measured with spectral power and corticomuscular coherence (CMC), respectively. We hypothesized that dopaminergic medication would affect the beta-CMC as shown before, while DBS would more likely affect motor-related spectral power.

The object of Study III was to investigate effects of treatments on resting state cortical activity in PD patients. Similar to Study II, the focal points were to explore the effects of treatments on cortical spectral power (beta and low-gamma, in particular), but during rest. We focused our analyses spatially on sensorimotor cortex to better link all three studies conceptually and because PD is primarily characterized as a movement disorder. Based on Study II and a few earlier studies, we hypothesized that DBS would affect low-gamma power, but not beta power, in the sensorimotor area.

Chapter -2

Background

The main object of the thesis was to study the effects of DBS and dopaminergic medication on cortical areas in PD patients. Before we delve into the actual studies and methods used, it is important to understand the anatomical structures and the functional circuits involved in PD. Basal ganglia (BG) are intimately involved in motor control and the basal ganglia-cortical loop plays a crucial role in streamlining movement (Mink, 1996; Utter and Basso, 2008; Prodoehl et al., 2009; Brittain and Brown, 2014).

In this chapter, I go through the physiological and pathophysiological nature of the BG circuitry and explain their relevance to the PD pathology. I then introduce key PD symptoms relevant to this thesis, namely motor and sensory and discuss the proposed pathophysiology associated with them. Furthering these basic concepts, I present the current literature on cortical neurophysiological measures, their links to PD symptoms apart from the influence of DBS and medication on these measures. This chapter will lay the basis for the discussion of the findings in the thesis work.

2.1 Parkinson's disease

Parkinson's disease was first described by James Parkinson more than 200 years ago in 1817 in a seminal essay titled "An essay on shaking palsy". The essay opens with an explanation of the major symptoms such as tremor, stooping gait and posture, problems in action of bowels and speech problems (Parkinson, 2002). James Parkinson paints vivid and dramatic pictures of six cases of PD, each of whom he used to advance his understanding of the disease. The

understanding of PD, its etiology, pathology, diagnosis and treatment has evolved much since the first report from James Parkinson.

PD, as we know now, is principally caused by the degeneration of dopaminergic neurons in substantia nigra pars compacta which are situated in the mid brain along with the loss of dopamine transporters (DaT) located on dopaminergic terminals in striatum, that play a major role in transporting excess dopamine back into the presynaptic neuron (Jankovic, 2008; Booth et al., 2015). Clinical diagnosis is largely based on manifestation of bradykinesia with either rigidity or tremor or both (Postuma et al., 2015). A standard step in diagnosis is the drug challenge test, where the clinical effect of dopaminergic drugs are used to obtain a differential diagnosis in favor of PD. But the drug challenge test has also shown to be inconclusive due to the high false-negative rate especially in de-novo patients in predicting the long-term efficacy of L-Dopa treatment for them (Berardelli et al., 2013). Dopamine transmitter single photon emission tomography (DaT-SPECT) is standard neuroimaging technique used for the differential diagnosis of PD and atypical parkinsonian disorders from other forms of parkinsonianism, by binding to the nigrostriatal dopaminergic terminals and enabling their visualization. DaT is confined to the presynaptic nerve endings and generally lead to a maximal signal in the putamen and caudate where they innervate striatal GABAergic projection neurons expressing either D1 or D2 receptors. The degeneration of nigrostriatal innervations leads to a decreased signal in PD patients compared to patients with other disorders like essential tremor (ET) (Berardelli et al., 2013; Booth et al., 2015). See fig. 2.1 for DaT-SPECT images comparing PD with ET patient and also various stages of PD. It can be seen from Fig. 2.1 (top) that there is a marked reduction in the uptake of the radiotracer in the putaminal region as well as the asymmetry in the uptake. This shows the degeneration of the dopaminergic projections. The Fig. 2.1 (bottom) shows the comparison of DaT-SPECT images between different diseases and healthy subjects. In ET and in vascular parkinsonianism, though, the radiotracer uptake is normal.

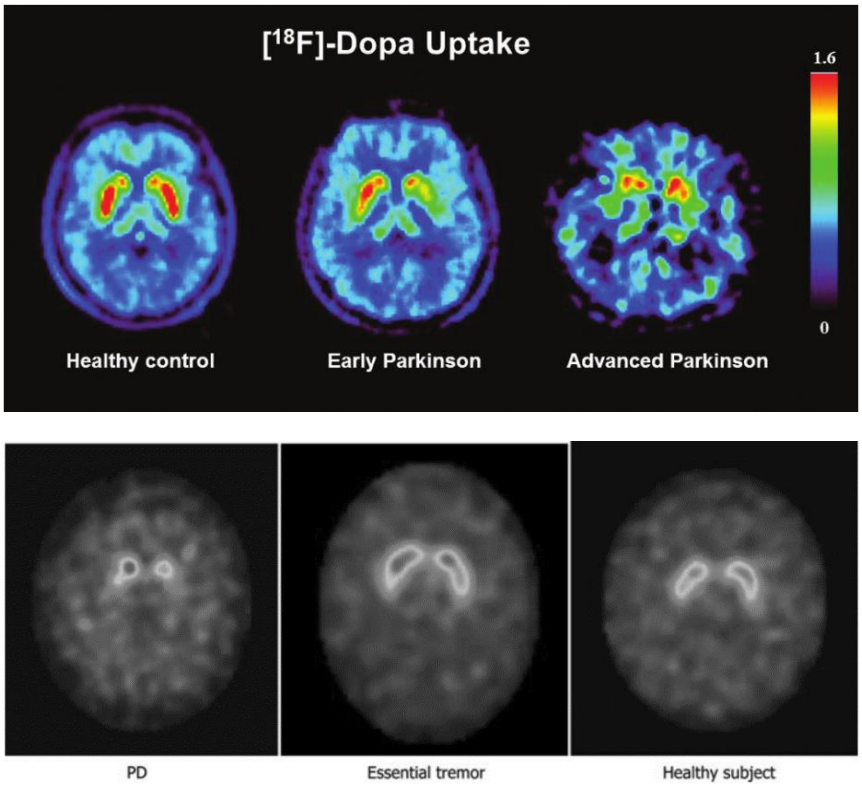

Fig 2.1: DaT-SPECT images from PD patients in various stages of the disease compared to healthy control **(top)** (Booth et al., 2015) and compared to an ET patient **(bottom)** (Berardelli et al., 2013)

The clinical diagnosis of PD begins after the patient presents with the motor symptoms, though there are a host of prodromal symptoms which are non-motor in nature (Kalia and Lang, 2015; Postuma et al., 2015). Non-motor prodromal symptoms such as olfactory abnormalities, constipation, depression, rapid eye movement sleep behavior disorder (RBD) are common (Kalia and Lang, 2015). Early markers of PD are now being studied and RBD figures as a possible biomarker, as is gastro-intestinal dysfunction (Postuma et al., 2006; Knudsen et al., 2017). Post-diagnosis, as motor symptoms progress, non-motor symptoms progress as well (Kalia and Lang, 2015), and hence is becomes important to assess the effects and possible mechanisms of treatments on non-motor symptoms, as is normally done with motor symptoms (See Fig. 2.2).

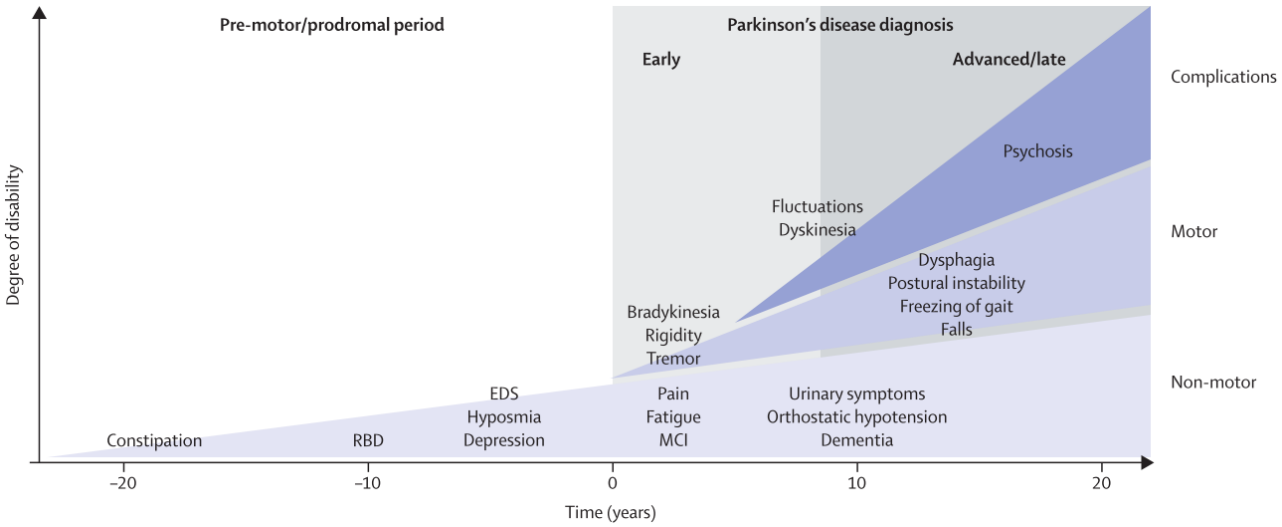

Fig 2.2: Progression of clinical symptoms in PD: Though the diagnosis is largely after the occurrence of motor symptoms, a number of non-motor sub-clinical symptoms may precede the PD diagnosis. As disease progresses several motor and non-motor symptoms may develop (Kalia and Lang, 2015). EDS: excessive daytime sleepiness; MCI: mild cognitive disorder; RBD: REM sleep behavior disorder.

2.2 Basal ganglia-cortical motor loop and PD

2.2.1 Basal ganglia-cortical circuitry

Basal ganglia (BG) or the basal nuclei are a collection of nuclei and part of the cerebrum that are involved in several functions such as sensory processing, motor control, sensorimotor integration, motor learning, executive functions and emotions (Lanciego et al., 2012). BG mainly consists of the striatum (putamen, caudate), globus pallidus (GP pars externa and interna), subthalamic nucleus (STN) and substantia nigra (pars reticulata, pars compacta). Striatum is the main input nucleus in the BG system receiving glutamatergic (excitatory) inputs from several parts of the cerebral cortex (Bolam et al., 2000; Hammond et al., 2007; Utter and Basso, 2008). Recent evidence also shows that the STN receives wide excitatory connections from the cortical areas including the motor cortex via the so-called hyperdirect pathway (Nambu et al., 2000; Fernandez-Miranda et al., 2012; Petersen et al., 2017). Striatum receives dopaminergic innervation from substantia nigra pars compacta (SNc) while the ventral tegmental area (VTA) projects to limbic and frontal cortex, both nuclei with a large proportion of dopaminergic neuronal populations. These

connections are called the nigro-striatal and mesolimbic and mesocortical dopaminergic pathways respectively (See Fig. 2.3).

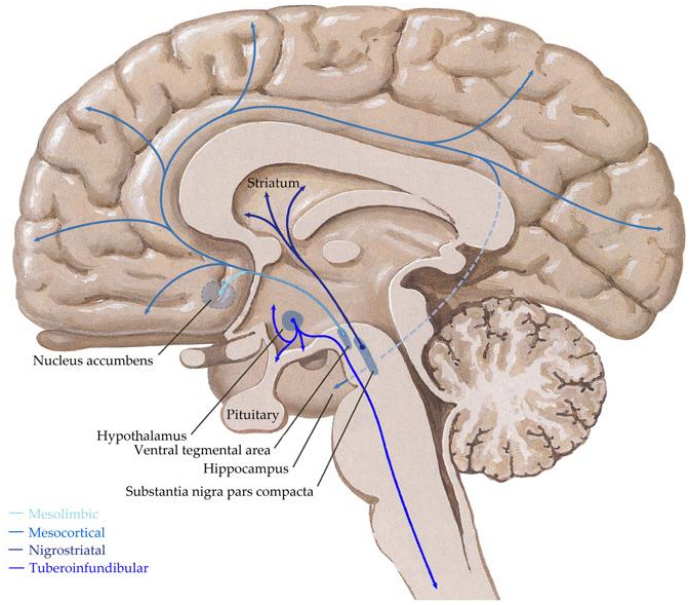

Fig 2.3: Dopaminergic projection system in humans: Multiple dopaminergic pathways exist. Each of the pathway is color-coded (Scarr et al., 2013)

Of the five main dopaminergic receptors, there are two in the striatum (and in BG) namely D1 and D2. Dopamine binding to D1-receptors causes an increase in probability of excitation, whereas dopamine binding to D2 leads to inhibition. Thus depending on the level of dopamine in the BG system, the influence of cortical inputs into BG via the striatum will vary (Hammond et al., 2007; Obeso et al., 2008; Utter and Basso, 2008). Striatal output is mostly routed through GABAergic medium spiny neurons projecting to the globus pallidus interna or externa. Fig. 2.4 shows the BG-cortical network along with the functional nature of the connectivity in healthy and PD state.

Anatomically medial to the putamen, globus pallidus has two separate sets of nuclei, GPi and GPe with a separating layer of 'border' cells. The external segment is positioned laterally and the internal segment medially. Both pallidal segments receive inhibitory GABAergic input from striatum, GPi receives inputs from GABA/substance-P-containing neurons also expressing dopamine D1 receptors, while GPe receives its inputs from GABA/enkephalin-containing neurons, also expressing dopamine D2 receptors. The former is known as the "direct" pathway and the latter as the first part of the "indirect" pathway. The projection from striatum to GPe is

routed onwards to GPi through the STN in an indirect manner, hence its name. The substantia nigra pars reticulata (SNr) also receives inhibitory input from the striatum, whereas the final leg of the indirect pathway, the STN-GPi projection, is glutamatergic, i.e., excitatory in nature. Thus the cortico-striatal system influences the GPi via two pathways, the direct and indirect, by which it exerts an inhibitory effect on GPi via the D1-projection and eventually disinhibits the excitatory thalamic drive to the cortex and an excitatory effect on GPi via the GPe-STN-GPi pathway through the D2-projections that leads to an inhibition of the excitatory thalamic drive. The GPi along with the SNr are the main output nuclei of the BG system with inhibitory projections to several nuclei of the thalamus (ventrolateral, ventroanterior), which in turn project back to the cortex (Wichmann and DeLong, 2006; DeLong and Wichmann, 2007; Hammond et al., 2007; Obeso et al., 2008; Utter and Basso, 2008; Nambu, 2011).

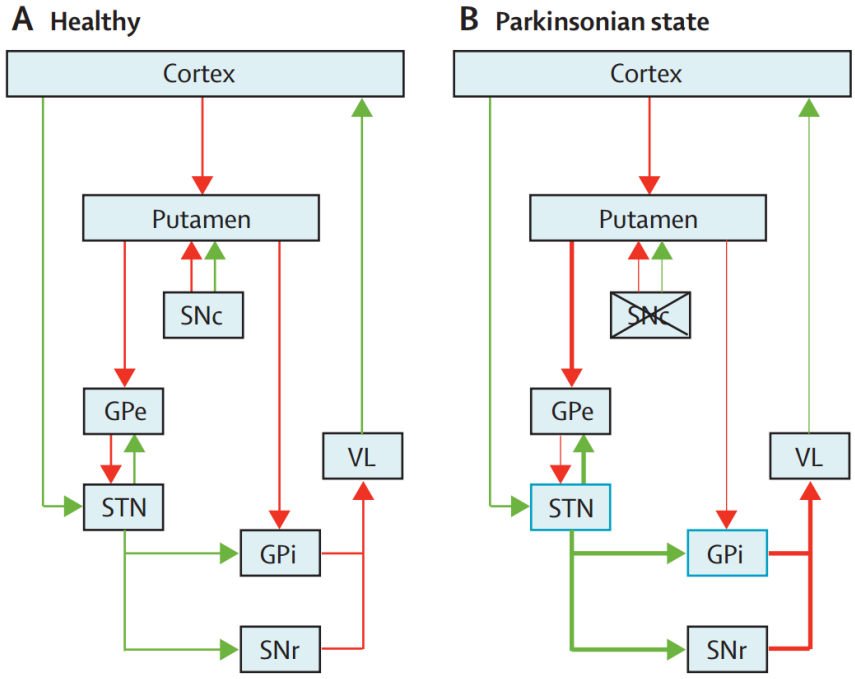

Fig 2.4: (a) Schematic diagram BG-cortical network. The functional nature of the connectivity is color-coded. **(b)** Changes in the functional network in PD state. Thicker arrows denote higher level of activity than healthy state whereas thinner arrows denote lower level of activity than healthy state. Green denotes excitatory innervation while red denotes inhibitory innervation (Rodriguez-Oroz et al., 2009)

STN receives afferent fibers from GPe and also shares reciprocal connections with it. STN furthermore receives profuse glutamatergic inputs from the cortical areas (motor, premotor) evidenced from anatomical (Monakow et al., 1978; Kitai and Deniau, 1981; Nambu et al., 2002) and tractography studies (Lambert et al., 2012; Petersen et al., 2017), these connections are referred to as the "hyperdirect" pathway. Moreover, STN is the only nucleus in the BG circuitry with an excitatory output drive (Kitai and Deniau, 1981) and it exerts a direct influence on the main output nucleus of the BG circuit (GPi). GPi and STN are the most preferred targets for DBS treatment in PD patients since both targets lead to similar effects on motor symptoms and increase the time for which treatment is effective with a reduction of "off" periods compared with best medical treatment (Deep-Brain Stimulation for Parkinson's Disease Study Group et al., 2001; Deuschl et al., 2006; Follett et al., 2010). While GPi-DBS leads to direct improvement of dyskinesias, STN-DBS leads to a greater reduction in medication dosage and indirectly improves dyskinesias, and can be administered with a shorter pulse-width and lower amplitude of stimulation thereby extending battery life (Limousin et al., 1998; Deep-Brain Stimulation for Parkinson's Disease Study Group et al., 2001; Follett et al., 2010; Okun, 2012).

2.2.2 Motor pathways and their functional significance

The two pathways, direct and indirect, are thought to represent to contrasting functional purposes, though it is not completely clear how they do so. It is speculated that the direct pathway provides a channel for active motor programs while the indirect pathway provides a channel for passive ones. If we happen to flex our wrist, we need the flexors to actively contract while the extensors have to passively expand. An imbalance between these two actions will make motor action difficult (Mink and Thach, 1991; Mink, 1996; Nambu et al., 2000). Nambu et al., (2002) proposed a center-surround model to explain the possible functional relationship between the indirect and direct pathways which largely follows the above explanation with distinct pathways for active and passive motor programs.

Moreover, speculating about the functional significance of the hyperdirect pathway, they hint at a possible role of a pre-inhibition of the areas in the thalamus that might be involved in the selected and other competing motor paradigms. They propose a sequential processing system whereby, once the initial inhibition is in place, the selected motor paradigm disinhibits the areas and allows movement whilst, in parallel, the indirect pathway keeps the targets of the competing

motor paradigms inhibited through the movement (Mink and Thach, 1991; Mink, 1996; Nambu et al., 2000, 2002, 2014; Nambu and Tachibana, 2014), however, the validity of the model is evidenced by a computational study that proposed a competitive model where the information streams from direct and hyperdirect pathways compete to enable motor paradigm selection and hence still begs more experimental verification. It was shown with this model that depletion of dopamine could cause an imbalance between the two pathways (direct and indirect) and lead to loss of selectivity (Leblois et al., 2006) similar to the functioning of dopamine-depleted BG circuitry.

2.2.3 BG in sensory processing and pathophysiology

The BG system also has a profound impact on sensory processing, which in turn affects motor action (Kaji and Murase, 2001; Juri et al., 2010). The main input nuclei of the BG, striatum, is known to respond to sensory stimuli (Carelli and West, 1991; Flaherty and Graybiel, 1991; Schneider, 1991; Hoover et al., 2002), as well as to inputs from motor and somatosensory cortical areas which have been shown to synapse at the striatal parvalbumin-positive (PV^+) GABAergic neurons (Ramanathan et al., 2002). PV^+ GABAergic interneurons may synapse with GABAergic projection neurons are also innervated by the nigro-striatal pathway, whereby striatum may subserve sensorimotor integration (Ramanathan et al., 2002). Hence, the depletion of dopamine in the nigro-striatal pathway may have an impact not just on sensory processing and motor control but also on sensorimotor integration (Ramanathan et al., 2002; Juri et al., 2010; Lyoo et al., 2012; Conte et al., 2013; Aman et al., 2014).

2.2.4 BG motor circuit pathophysiology

The GPe-STN structures that have reciprocal connections are often characterized as the pacemaker of the BG circuitry (Nambu and Tachibana, 2014). Primate models are used to isolate pathways and study the pathophysiology related to PD. It involves injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin, over a 2 week period which leads to degeneration of dopaminergic neuronal populations (Bergman et al., 1994). It is known from such MPTP-based animal PD models that beta power (8-15 Hz) is increased in GPe, GPi and STN (Soares et al., 2004; Tachibana et al., 2011) apart from an overall increase in burst strengths in the above nuclei (Wichmann and Soares, 2005). It was also shown that administration of levodopa decreased the pathological beta-rhythm (Brown et al., 2001; Cassidy et al., 2002; Tachibana et al.,

2011). This implied that the abnormal pathology was definitely dopamine dependent. The originator of the pathological beta rhythm was still under question. Blocking of the STN output decreased the pathological beta power in GPi (Tachibana et al., 2011) but blockade of the GABAergic striatal-GPe inputs to STN and reduction in GPe activity by lesioning did not lead to an appreciable change in the GPi pathological activity (Soares et al., 2004; Tachibana et al., 2011), which taken together informed that the driver of the pathological rhythm might be the STN through its glutamergic inputs to GPi. Lesion of the STN has been shown to alleviate the motor symptoms in MPTP-treated primates (Bergman et al., 1990; Aziz et al., 1991), which also like the above-mentioned studies, suggests that the pathological downstream effects of dopamine imbalance in BG may propagate from and through the STN to the BG output nucleus, GPi. The depletion of dopamine in the BG system likely leads to an imbalance between the direct and indirect pathways and hence cause abnormal pacing in the BG (Leblois et al., 2006; Nambu and Tachibana, 2014). Fig. 2.4 shows the schematic representation of BG in PD state.

In PD patients, withdrawal from dopaminergic medication led to an increase in the lower frequency oscillations (mainly beta band (<30 Hz)) in the GPi and STN (Brown et al., 2001; Cassidy et al., 2002; Kühn et al., 2006). This pathological beta synchrony in BG extends to the motor cortical area, as well. Studies have shown exaggerated coupling between gamma amplitude and beta phase in M1 (de Hemptinne et al., 2013, 2015), and that M1 gamma activity drives the STN spiking activity (Shimamoto et al., 2013). Taken together, these studies attest that dopaminergic depletion not only affects synchrony in the BG system but also in the cortical areas, and that the pathological beta synchrony is coterminous with motor symptoms (Brown et al., 2001; Magill et al., 2001; Kühn et al., 2006).

2.2.5 Effect of treatments on BG pathophysiology

Dopaminergic medication, possibly acting through the D1 and D2 receptors of the GABAergic projection neurons, has been shown to lead to a decrease in beta band synchrony and an increase in gamma (>70 Hz) synchrony in STN. The decrease in beta synchrony was correlated with improvement of motor symptoms (Brown et al., 2001; Cassidy et al., 2002; Kühn et al., 2006; Hammond et al., 2007).

DBS has also been shown to reduce the pathological beta synchrony in the STN (Kühn et al., 2008), as well as normalize the exaggerated phase-amplitude-coupling (PAC) in M1 (de Hemptinne et

al., 2013, 2015). The causal role of antidromic stimulation of the hyperdirect pathway in the DBS effect mechanism was shown in an optogenetic study where optical stimulation of cortical layer V neurons alone could alleviate motor symptoms similarly to STN stimulation in the 6-hydroxydopamine (6-OHDA) rat model of PD (Gradinaru et al., 2009). STN stimulation furthermore influenced motor cortical excitability (Kuriakose et al., 2010), which fits with the results from pharmacological blockage of glutamatergic inputs from the cortex via the hyperdirect pathway leading to a decrease in the beta rhythm in STN (Tachibana et al., 2011).

2.3 Symptoms, pathophysiology, treatments

2.3.1 Motor symptoms and their pathophysiology

PD patients suffer from the so-called triad of motor symptoms: rigidity, akinesia and rest tremor, however approximately 1/3 of PD patients do not experience rest tremor. Apart from this, they also suffer from postural instability and gait disturbances (Hughes et al., 2001; Jankovic, 2008; Rodriguez-Oroz et al., 2009).

Rigidity is characterized by increased muscle tone during passive movement of the limb and increased resistance to stretching (Wilson, 1925; Jankovic, 2008; Rodriguez-Oroz et al., 2009). Rigidity is especially elevated when patients engage in slow flexion and may occur in both distal and proximal structures. The Froment's maneuver, where voluntary movement of the contralateral limb is generally used to reinforce rigidity is a classic test for rigidity (Jankovic, 2008; Rodriguez-Oroz et al., 2009).

Akinesia broadly consists of two categories, bradykinesia and hypokinesia, where the former is poverty of movements while the latter is lack of amplitude in movements. Bradykinesia is characterized by problems during repetitive or rhythmic movements, such as walking where timing is key. Central pattern generators play a key role in such rhythmic movements, and as such, this ability is impaired in PD patients (Artieda et al., 1992; Berardelli et al., 2001; Rodriguez-Oroz et al., 2009). Hypokinesia, on the other hand, refers to attenuated amplitude of movement (Johnsen et al., 2009) and occurs due to lower neuronal recruitment or lower drive from the central nervous system.

Rest tremor as PD symptom generally occurs in 4-6 Hz range and is more prominent in the extremities than in proximal body parts. Apart from rest tremor, PD patients also experience

postural tremor when trying to hold a posture, such as holding the hand in a raised position. Postural tremor is often more disabling than rest tremor and may be an early marker for PD (Jankovic et al., 1999; Jankovic, 2008; Rodriguez-Oroz et al., 2009).

Freezing of gait is a specific type of akinesia in advanced PD, where the patient's motor function involved in walking is blocked. Freezing occurs particularly during walking and is heightened by changes in the environment, such as a door, a narrow passage, changing direction of walking or when trying to handle obstacles to reach a target (Bloem et al., 2004; Jankovic, 2008).

Effects of DBS and dopaminergic medication treatments

Dopaminergic medication is known to improve all motor symptoms but is less efficient in handling tremor and midline symptoms as gait and balance disturbances and dysarthria (Jankovic, 2008; Rodriguez-Oroz et al., 2009; Connolly and Lang, 2014). After several years of treatment, phases where the dopaminergic medication occasionally does not alleviate the motor symptoms occur. These so-called off-periods with worsening of PD symptoms, often at first as wearing-off symptoms later as unpredictable off-periods, are especially experienced by early-stage PD patients (Kleiner-Fisman et al., 2006). When PD patients begin to experience the phasic loss of effect of medication, they may be eligible for DBS treatment. DBS has been shown to significantly alleviate motor symptoms (quantified by UPDRS parts II (activities of daily living) and III (motor)), including tremor and "daily off" periods (time periods when symptom management is not efficient), as well as lead to reduced levodopa equivalent daily dosage (LEDD) and significant amelioration of dyskinesias (involuntary movements) (Limousin et al., 1998; Østergaard et al., 2002; Deuschl et al., 2006; Kleiner-Fisman et al., 2006; Follett et al., 2010). In 4-year and 10-year follow-up studies, significant and sustained improvements in total motor function, activities of daily living and reduction of off periods were observed (Krack et al., 2003; Østergaard and Aa Sunde, 2006; Castrioto, 2011; Bang Henriksen et al., 2016), which shows that DBS is a viable long-term treatment when dopaminergic medication is no longer a viable option.

Pathophysiology

The pathophysiology of each of the PD motor symptoms is still debatable (Berardelli et al., 2001; Rodriguez-Oroz et al., 2009; Magrinelli et al., 2016). Akinesia is thought to be a disorder related to failure of timing mechanisms in the basal ganglia circuitry. Since dopamine plays an important role in central pattern generators, loss of the neurotransmitter may lead to timing problems

(Buhusi and Meck, 2005; Yuste et al., 2005; Magrinelli et al., 2016). Self-paced movements show more marked pre-movement abnormalities than externally paced ones, again suggesting timing mechanisms as a potential root cause (Jahanshahi et al., 1995; Berardelli et al., 2001; Buhusi and Meck, 2005).

Bradykinesia, on the other hand, may occur due to an imbalance between the direct and indirect pathways, where the indirect pathway outputs tend to suppress activity in the motor cortex (Mink and Thach, 1991; Mink, 1996; Nambu et al., 2000). Though a simplistic model, it seems to be evidenced by the underactive supplementary motor area (SMA) during movement and sensory stimulation in PD states and administration of dopaminergic medication leads to the restoration of the activity in the SMA (Jenkins et al., 1992; Rascol et al., 1992; Berardelli et al., 2001; Rodriguez-Oroz et al., 2009; Pollok et al., 2013; Shirota et al., 2013). It has also been shown that both the pre-movement beta suppression and post-movement beta rebound, classical oscillatory correlates of movement preparation and post-movement recalibration, are reduced in PD and possibly points to ineffective engagement of neuronal populations involved in movement (Heinrichs-Graham et al., 2014).

Microelectrode recordings show that cells in both ventro-lateral thalamus and internal segment of the globus pallidus fire at tremor frequencies (4-8 Hz) (Lozano et al., 1996; Jankovic et al., 1999) and that STN neuronal populations are synchronized at frequencies higher (>10 Hz) than the tremor frequencies (Levy et al., 2000). Tremor is improved with pallidotomy (Lozano et al., 1996) and with STN-DBS (Limousin et al., 1998) which both show that the abnormal oscillatory dynamics in PD may play a role in tremor pathophysiology (Jankovic et al., 1999; Rodriguez-Oroz et al., 2009).

2.3.2 Sensory symptoms and their pathophysiology

PD patients have abnormal sensory perception (Shin et al., 2005; Conte et al., 2010; Ciampi De Andrade et al., 2012) and their tactile spatial acuity is decreased (Sathian et al., 1997; Conte et al., 2010, 2013; Lyoo et al., 2012). Clinical studies investigating the sensory symptoms use sensory detection and discrimination tests to assess the degree of abnormality in sensory perception (Gierthmühlen et al., 2010; Spielberger et al., 2011; Ciampi De Andrade et al., 2012; Doty et al., 2015). While sensory thresholds relate to earlier processing of stimuli involving prefrontal cortex, postcentral gyrus and basal ganglia, sensory discrimination is markedly later in time and involves

processing in higher order areas (Lacruz et al., 1991; Artieda et al., 1992; Pastor et al., 2004). The anatomical basis of the discrimination comes from studies on patients with focal cerebral lesions where, lesions in the striatum, medial thalamus and lenticular nucleus led to abnormal temporal discrimination thresholds indicating a basal ganglia role in temporal discrimination (Lacruz et al., 1991).

Artieda and colleagues (1992) elaborately studied the flawed temporal discrimination in PD patients. With a relatively large cohort of 44 PD patients, they studied temporal discrimination problems in PD patients with various modalities such as tactile, auditory and visual stimuli. PD patients showed abnormal discrimination thresholds over all three modalities, as well as a significant correlation between disease severity and the temporal discrimination thresholds. Much later, these results were confirmed by a different group, showing increased somatosensory temporal discrimination thresholds (STDTs) for PD patients (Conte et al., 2010).

Using a grating orientation task, Sathian and colleagues (1997) showed that PD patients have increased tactile spatial thresholds, implying decreased sensitivity in judging the changes in groove width on a grating. PD patients' discrimination capabilities were 2-3.5 times more impaired compared to age-matched controls. The asymmetry in the patients' tactile impairment was similar to the asymmetry in presentation of their symptoms, with the more affected side showing higher tactile impairment.

Shin et al., (2005) used the same grating orientation task to investigate the effect of dopamine on tactile spatial acuity. To this end, they tested the threshold for spatial discrimination on drug naïve PD patients before and after long-term levodopa administration (several months). They found that significant improvement of sensory dysfunction paralleled improvement in motor symptoms alluding to a role of dopamine in the spatial acuity apart from a link between sensory function and motor symptoms.

A more direct experiment assessing the effect of the striatal dopaminergic denervation on the discrimination threshold showed that levodopa improved somatosensory discrimination, and that dopamine transporter uptake levels in the striatum (measured with positron emission tomography (PET))) correlated with the STDT values when PD patients were OFF dopaminergic medication (after at least 18 hours without anti-Parkinsonian medication) (Lyoo et al., 2012).

These findings establish a more direct link between striatal dopaminergic denervation and the dysfunction of somatosensory discrimination.

Studies have also been performed on tactile thresholds rather than discrimination. PD patients have been shown to have increased tactile detection thresholds, more specifically, higher mechanical and vibration detection thresholds (Ciampi De Andrade et al., 2012).

Effects of DBS and dopaminergic medication treatments

Some aspects of the impaired somatosensory perception in PD patients are affected by treatments for PD. The sparse literature seems to suggest that impaired behavior on sensory tasks involving discrimination (e.g., grating orientation and STDT) can be improved by dopaminergic medication (Artieda et al., 1992; Shin et al., 2005; Conte et al., 2010; Lyoo et al., 2012), whereas DBS seems to worsens such sensory symptoms (Lacruz et al., 1991; Conte et al., 2010). Yet, PD patients' impaired behavior on sensory tasks involving purely detection of tactile input (e.g., mechanical and vibratory detection as tested by quantitative sensory testing, QST) does not seem to be affected by DBS or dopaminergic medication (Gierthmühlen et al., 2010; Spielberger et al., 2011; Ciampi De Andrade et al., 2012; Doty et al., 2015).

This apparent discrepancy in effects of treatments on different sensory tasks is likely due to involvement of different cortical and subcortical structures in sensory discrimination tasks compared to sensory detection tasks. It has been shown in both animal models and humans that discrimination tasks involve additionally higher order areas such as posterior parietal cortex, striatal and other BG structures, and pre-supplementary motor area apart from the structures involved in sensory detection, which are mainly post-central gyrus and inferior parietal lobule (Lacruz et al., 1991; Artieda et al., 1992; Pastor et al., 2004).

Pathophysiology

The pathophysiology involving sensory processing problems and the effect of PD treatments on them are still debatable. One view is that the BG may not be directly involved in sensory processing but have an indirect influence on the somatosensory processing and discrimination (Sathian et al., 1997). It is also pertinent to note that most of the reported sensory symptoms of PD were sensorimotor in nature where the task required a kinesthetic or motor response to a sensory stimulus (Schneider et al., 1986, 1987).

The improvement in sensory discrimination function from dopaminergic replacement by levodopa shows that the deficit is at least partially modulated by dopamine depletion (Shin et al., 2005; Juri et al., 2010). Striatum receives descending cortical motor and sensory inputs onto the same PV^+ neurons, which synapse with GABAergic projection neurons. These PV^+ neurons are influenced by dopamine, which in turn affects sensory processing indirectly through the BG-cortical connections in a systemic manner (Ramanathan et al., 2002). The deficit may also be related to the loss of specificity to a stimulus, as an increased number of basal ganglia neuronal populations responded to passive limb movement (Filion et al., 1988; Conte et al., 2013). The increase in the response population suggests a possible role of dopamine in regulating gain and selectivity.

2.4 Functional importance of oscillations

2.4.1 Oscillations in motor cortex

Voluntary movement is accompanied by alpha, beta and gamma oscillatory components in the motor cortex (Crone et al., 1998a, 1998b; Pfurtscheller and Lopes da Silva, 1999; Pfurtscheller et al., 2003; Neuper et al., 2006; Muthukumaraswamy, 2010). Gastaut (1952), is referenced as the first to investigate and report on the rolandic rhyhtms related to movement.

Chatrian et al. (1959) used a 19-channel EEG recorder with an ink-writing unit to record encephalographic and electromyographic activity. Their intent was to study the so-called "wicket rhythm", or alpha/mu rhythms as it is now commonly known. Participants performed voluntary movement, passive movement of limbs, and reflex movements (patellar reflex) during the EEG recording. Chatrian et al. (1959) showed that all three kinds of experiments led to a decrease in the "wicket rhythm". They also showed that the mu rhythm suppression happened in both ipsi- and contralateral rolandic regions and that the suppression preceded movement.

In a more digitized experimental setting, Pfurtscheller and Aranibar (1979) described changes in alpha band power in central areas when subjects were asked to respond to auditory and visual stimuli with button presses. They showed a mu rhythm phasic event-related desynchronization (ERD) prior to movement. The ERD was mostly bilateral though more pronounced in the ipsilateral side in the central-vertex region. It was also later shown that the ERD and the event-related synchronization (ERS) in the low-beta and mu-bands are somatotopically specific such

that an activation of the hand induces an ERD in the hand area and an ERS in the foot area, and vice versa during foot activation (Pfurtscheller and Lopes da Silva, 1999).

In an elaborate study on the topography of the alpha, beta and gamma oscillations, Crone et al. (1998a, 1998b) performed spectral analyses of electro-corticographic (ECoG) data during rest and movement. The topographies obtained were compared to the somatotopic maps from direct cortical stimulation. It was shown that during movement, the alpha-ERD phenomenon was more prominent than the beta-ERD. Though both were somatotopically specific to the hand area, beta-ERD was more focally localized.

While beta and mu-oscillations are suppressed during movement, gamma oscillations (>40 Hz) are augmented (Pfurtscheller and Aranibar, 1979; Pfurtscheller et al., 2003; Huo et al., 2010). Gamma activity is an interesting oscillatory component to observe as it is known to represent an aspect of the underlying spiking activity (Cardin et al., 2009). During self-paced finger movements, 40 Hz oscillations were reported to be enhanced while beta oscillations were suppressed (Pfurtscheller and Neuper, 1992; Pfurtscheller et al., 1993, 2003; Salenius et al., 1996; Ohara et al., 2001; van Wijk et al., 2012). Using ECoG data during movement, gamma-ERS was found to accompany movement. Topographic mapping showed that the gamma-ERS was localized to areas similar to maps obtained from cortical stimulation (Crone et al., 1998a; Szurhaj et al., 2005, 2006). Interestingly, two different bands in the gamma range were identified (35-50 Hz; 75-100 Hz) with distinct topographies suggesting that the two bands may not simply be harmonics of one another but instead have independent origins (Crone et al., 1998a).

Motor cortical gamma oscillations have been shown to peak 100-250 ms after movement onset as measured by EMG and to be scaled with movement amplitudes (Cheyne et al., 2008; Muthukumaraswamy, 2010). Gamma oscillations have also been shown to scale during repetitive movements and to dampen after the first movement cycle (Muthukumaraswamy, 2010). While they were present during both cued and self-paced movements, gamma oscillations were not prevalent during passive movement of limbs (Cheyne et al., 2008; Muthukumaraswamy, 2010; van Wijk et al., 2012). Functionally, beta oscillations are thought to signal status quo while gamma activity is thought to underlie active processing in the underlying neuronal population (Fries, 2009; Manning et al., 2009; Engel and Fries, 2010). For instance, the enhanced beta-band oscillations in STN and motor cortex are accompanied by motor symptoms in PD (Pollok et al., 2012; Whitmer et al., 2012). Dopaminergic treatment and DBS suppress beta-activity and boost

gamma-activity in the STN and this is shown to correlate with better motor symptoms (Kühn et al., 2006, 2008).

Resting state motor cortical activity recorded using electro-corticograms (ECoG) has yielded conflicting results. While Whitmer et al. (2012)s showed that DBS in STN suppresses motor cortical beta band power, others showed no effect of DBS on beta (13-30 Hz) or broadband gamma (50-200 Hz) oscillations (de Hemptinne et al., 2013; Rowland et al., 2015). The only two available studies using MEG and testing PD patients ON and OFF DBS in resting state also showed no effect of beta power at rest, though gamma power (34-38 Hz) was affected by DBS (Cao et al., 2015, 2017). Another MEG study with early-stage PD patients showed no effect of dopaminergic medication on cortical beta power at rest (Pollok et al., 2012).

While the influence of the treatments on STN oscillatory activity is clear, their effects on cortical beta and gamma rhythms is sparse. High-frequency DBS in the STN (and slightly dorsal to it) reduced the resting state beta power in cortex (Whitmer et al., 2012), a phenomenon observed in the STN, as well, and the reduction is known to correlate with improved motor performance (Kühn et al., 2006, 2008). ECoG studies with sophisticated metrics like phase-amplitude coupling (PAC) have shown that the pathological exaggerated PAC between beta-phase and gamma amplitude in the motor cortex is suppressed with DBS (de Hemptinne et al., 2013, 2015).

2.4.2 Oscillations in sensory cortex

As explained in Section 2.3.2 PD patients have somatosensory deficits. Median nerve stimulation and the subsequent oscillatory dynamics such as somatosensory evoked fields (SEF) or potentials (SEP) are effective tools to study somatosensory processing (Gaetz and Cheyne, 2003; Fukuda et al., 2008, 2010). Median nerve stimulation involves placing a bipolar stimulation electrode near the wrist, where the median nerve runs superficially and stimulating it with a current of 2-15 mA and with a pulse width of 150 μs. The sign of a stimulated nerve is a visible twitch of the thumb. Depending on whether the experiment requires a supra-threshold or sub-threshold stimulation the stimulation current can be varied.

Somatosensory evoked fields

The first cortical response to median nerve stimulation is termed N20(m) and peaks at about 20 ms after the stimulation. It reflects the initial excitatory postsynaptic potential (EPSP) at SI

pyramidal neurons, largely those in area 3b occupying the major part of the posterior wall of the central sulcus (Hari and Forss, 1999; Ikeda et al., 2005). Following the N20m peak, another peak occurs at 30 ms post-stimulus called N30(m). N20 evoked potentials are susceptible to changes based on wakefulness (Yamada et al., 1988) while N30 evoked potentials are affected by stimulation settings (inter-stimulus interval) (Tiihonen et al., 1989) and concomitant movement (Cheron and Borenstein, 1987; Huttunen and Lauronen, 2012).

SEPs and SEFs have been used widely on PD patients to test the sensory processing and also the effects of dopaminergic medication and DBS. Insola et al. (2005) showed that N20 amplitude did not vary significantly with either apomorphine (DOPA-agonist) or with GPi- or STN-DBS. In Pierantozzi et al. (1999), N20 showed no significant effect when DBS was turned ON or OFF whereas Priori et al. (2001) showed that switching OFF DBS increased N20 amplitude. Although these two studies present contradictory results, it is hard to compare them due to methodological differences including differences in EEG montages and electrode referencing. It must also be borne in mind that both studies have heterogeneous and small cohorts (Pierantozzi et al., 1999: 6 PD patients: 4 GPi-DBS and 2 STN-DBS; Priori et al., 2001: 9 PD patients treated with STN-DBS).

Recently, Airaksinen et al., (2011) showed, with a relatively larger cohort (n=12), that DBS treatment had no significant effect on the N20m, however, they observed considerable inter-/intra-individual differences. Such lack of effects could partly be explained by patients being on medication during both DBS ON and DBS OFF conditions.

Somatosensory gamma oscillations

Gamma oscillations reflect underlying spiking activity and changes might be due to involvement of more neuronal populations or increased synchrony between neuronal populations (Srinivasan et al., 1999; Cardin et al., 2009; Manning et al., 2009). Gamma oscillations in general have been found to modulate the synchrony in local excitatory activity and is seen as an index of cortical computation (Fries, 2009). Gamma oscillations that were recorded in rat somatosensory cortex (SI & SII) were not global but restricted to somatosensory areas (MacDonald and Barth, 1995), and in humans, short latency power increases found in broadband gamma power (40-100 Hz) were confined to contralateral S1 (Hirata et al., 2002; Ihara et al., 2003; Gaetz and Cheyne, 2006; Fukuda et al., 2008, 2010).

Studies investigating the role of oscillatory activity in information processing show that rhythm-inducing cell types, especially fast-spiking interneurons, play an important role in regulating activity (Traub et al., 1997; Fries et al., 2007). The excitatory pyramidal neurons are provided with inhibitory post-synaptic potentials from the inhibitory interneuron network (Bartos et al., 2007). The pyramidal neurons fire in a phase-locked manner in response to a sensory stimuli and are accompanied by gamma oscillations. These gamma oscillations and the firing of the excitatory pyramidal cells are modulated by inhibitory network activity (Fries et al., 2001, 2007). The parvalbumin-positive (PV^+) inhibitory interneurons oscillate at higher frequencies producing cyclic inhibitory temporal windows during which excitatory pyramidal neurons can discharge synchronously (Bartos et al., 2007; Cardin et al., 2009) and thus might play a role in channeling afferent information (Jones and Barth, 1997).

Synchrony can functionally enhance the saliency of relevant stimuli, and enhancement of response saliency will enable selection of subsets of neuronal responses for further processing (Engel et al., 2001) as well as increase the relevance of stimuli on downstream circuits (Fries et al., 2001; Suffczynski et al., 2014). Hence, early gamma augmentation in somatosensory cortex can be considered an early aspect of somatosensory information processing (Fukuda et al., 2008, 2010), mainly produced by excitatory pyramidal neurons within temporal windows created by inhibitory interneurons. Modulation of the amplitudes of such gamma augmentations might reflect recruitment of additional neuronal populations or increased precision in synchronization (Srinivasan et al., 1999).

2.4.3 Connectivity between M1-muscle

Physiological relevance of corticomuscular coherence

Corticomuscular coherence (CMC), especially in the beta-band, is used to study directed corticospinal drive (Conway et al., 1995; Salenius et al., 1997; Schoffelen et al., 2005). Corticomuscular coherence and corticospinal coherence are terms that are interchangeably used in the literature. CMC is found in both beta and gamma bands (Kilner et al., 2000; Gwin and Ferris, 2012). CMC studies often involve tasks with limb movements of one kind or another, and these movements are generally classified as isotonic or isometric. Isotonic movements involve maintaining a required tone in the muscle including changing the limb position to maintain the tone. Isometric movements involve maintaining the limb in a fixed posture.

A study performed with both isotonic and isometric contractions showed that beta coherence is slightly higher during isometric contractions than during isotonic contractions in healthy subjects (Gwin and Ferris, 2012). Beta-CMC in general has spurred research interest since it provides a gateway to study corticomuscular interaction and data acquisition is non-invasive.

During voluntary isometric contractions, motorneuron pools oscillate in a synchronous manner as evidenced by the firing patterns of motor unit pairs recorded with needle electrodes (Datta and Stephens, 1990). The results from the above study were extended, where similar motor unit pair recordings were made during isometric contractions in the first dorsal interosseous muscle and the biceps brachii muscles of healthy subjects (Farmer et al., 1993). It was shown that the motor units were in synchrony in the range of 16-32 Hz and reflected the common firing pattern among the motorneuron pool (Farmer et al., 1993). Furthermore, studies on patients with peripheral and central neurological lesions showed that the drive for the 16-32 Hz synchrony might arise from a central generator rather than from a peripheral one (Farmer et al., 1993; Kilner et al., 2004).

Furthering the study into the central drive of the synchronized rhythms in the hand muscles, Conway et al. (1995), using a single-channel MEG, obtained measurements from a grid over the sensorimotor cortical area, which was determined by pre-experimental magnetic stimulation. EMG was recorded from the first dorsal interosseous muscles (1DI) using standard Ag-AgCl surface electrodes. They showed coherence in the range of 13-35 Hz between motor cortex and the motorneuron pool at the spinal level as measured by the EMG. Although they observed cortical activity in other frequency ranges such as ~10 Hz (mu-rhythm) and gamma (40-50 Hz), none of them were synchronous with the muscular activity.

Salenius et al. (1997) showed the similar beta-CMC (15-33 Hz) during sustained isometric contractions, using a 122-channel MEG. They extended the previous results on beta-CMC (Conway et al., 1995) and showed that it is directional and that the cortical activity preceded the motor unit firing by 12-53 ms. They also showed that the lags increased as the examined muscle groups moved from proximal to distal areas, thereby clearly indicating the involvement of a central drive for synchrony in the motorneuron pool. But beta-CMC is not only a cortical drive on the muscles, it also has contributions from ascending pathways. Riddle et al., (2005) cooled the peripheral nerves, thereby slowing down the conduction velocity, which was confirmed with the peripheral motor conduction time (PMCT) test. When the precision hand gripping task was repeated when the peripheral nerves were cooled, apart from a reduction in the CMC, the delay

calculated had a rise of twice the delays from PMCT test. The extra delay cannot be accounted with a model that assumes only afferent contributions and hence it was suggested that afferent feedback also plays a role in the generation of beta-CMC.

Following the original studies showing beta-CMC during isometric tasks (Datta and Stephens, 1990; Farmer et al., 1993; Conway et al., 1995; Salenius et al., 1997) several studies have elaborated on it using subtle variations to obtain a better understanding of CMC. With a hold-move-hold task, (Kilner et al., 2000) using time-resolved beta-CMC it was shown that it was elevated during hold phases while suppressed during move phases. Moreover, beta-CMC was found to be even further elevated during the hold phase after movement compared to the hold phase before movement. Clearly, beta-CMC was dependent on the motor state and its parameters (Kilner et al., 2000). In another study, a similar increase in beta-CMC during hold phases was also shown during bimanual tasks (Gross et al., 2005). Interestingly, beta-CMC has also been found during rest, and hence, it has been taken to represent a continuous corticospinal influence (Gross et al., 2005).

An experiment with varying motor tasks before a hold state showed that beta-CMC was modulated depending on the computational load of the preceding motor activity (Omlor et al., 2011). For larger movements such as changes in length of muscles, angles of joints, the beta-CMC during the following rest phase was increased compared to after smaller movements (Witte et al., 2007). This pointed to a possible role of beta-CMC in re-calibration mechanisms (Kristeva et al., 2007; Omlor et al., 2011). Increases in beta-CMC was also accompanied by improved compliance and decreased errors (Kristeva et al., 2007), which may suggest that increased beta-CMC improves integration of somatosensory information leading to better motor performance (Kristeva et al., 2007; Witte et al., 2007; Omlor et al., 2011).

Effects of PD treatments on beta-CMC

The literature on the effects of DBS on beta-CMC is not consistent. Very preliminarily, Park et al. (2009) investigated three PD patients, of which two were OFF dopaminergic medication for at least 24 hours, and showed elevated beta-CMC during DBS ON compared to DBS OFF while performing isometric contractions. In a MEG-study with a larger cohort of PD patients (n=19), Airaksinen et al. (2015) showed that DBS variedly affected beta-CMC with large inter-patient variability, and the relation between beta-CMC and motor performance was not consistent. The

authors mention a limitation that the patients remained on dopaminergic medication during both DBS ON and OFF conditions which may have contributed to the variance in the outcomes.

For the effects of dopaminergic medication on beta-CMC, it has been shown that while PD patients have low beta-CMC compared to controls, dopaminergic medication seems to normalize it (Salenius et al., 2002). This normalization of beta-CMC was construed to reflect an improved coupling between motor cortex and the spinal motorneuron pool. However, Hirschmann et al. (2013) showed no effect of dopaminergic medication on beta-CMC. The patients were on apomorphine medication (until about ~2 hours before the measurements), and this may have confounded the observed effects or lack thereof, although apomorphine is known to have a very short half-life. However, a similar study with de-novo patients and early-stage PD patients on dopaminergic medication did not show any group differences on beta-CMC (Pollok et al., 2012).

Chapter - 3

Methods

The Methods chapter is intended to provide a general primer on the methods used, while the specifics of the methods used are available in the manuscripts attached in the Appendices. The chapter opens with an introduction to MEG and its electrophysiological basis. Time-frequency analysis techniques used in this thesis are then introduced. This is followed by a section on the physics behind MEG, the forward and inverse solutions (specifically DICS). Finally, since we use Bayesian inference in this thesis, there is a section formally introducing Bayes Factors.

3.1 Magnetoencephalography

Magnetoencephalography (MEG) is a neuroimaging technique, by which the functional activity in the brain are measured as the magnetic components of the activity-associated electrical fluctuations. These measurements may eventually be mapped onto anatomical images to obtain source localization for the observed brain activity. In other words, MEG is the magnetic homologue of electroencephalography (EEG). In this section, I briefly introduce the instrumentation of the MEG system as well as the electrophysiological basis of the signals that are measured with MEG.

3.1.1 The MEG system

The measurement of the magnetic fields associated with neuronal currents is based on the principles of electromagnetism, which is illustrated by the classic 'right hand rule'. It basically says that the magnetic lines of force due to an electric current flow, follows the curl of the fingers when grasping the current conductor with your right-hand thumb pointing in the direction of the

current flow. The magnetic fields from the brain are extraordinarily weak compared to the environmental fluctuations in the magnetic fields, which is illustrated in Fig.3.1, below. The magnetic fields from the brain are at least 7-8 orders of magnitude smaller than the earth's magnetic field and at least 1-3 orders of magnitude weaker than those stemming from the strong bioelectric activity of heart rhythms and eye movements. This necessitates a sophisticated setup to both reject the external noise as well as pick up the miniscule magnetic fluctuations from the brain. Hence, the MEG is placed inside a magnetically shielded room (MSR) to reduce the external interference to the widest extent possible.

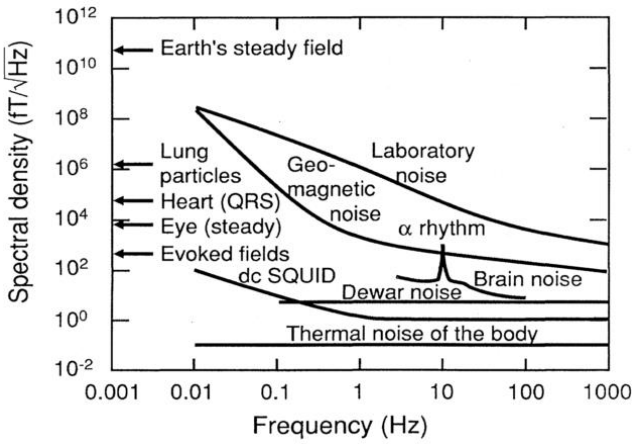

Fig. 3.1: Spectral densities of common biomagnetic fields (Hämäläinen et al., 1993)

The principal component of the MEG system is the sensor which is a superconducting quantum interference device (SQUID). The conception is based on the mathematical relationship between current and voltage across the weak link in a superconducting device called the Josephson junction. Brian D. Josephson conceived the formulation for this and was awarded the Nobel Prize in Physics for his work on quantum tunneling and superconductivity. In practice though, the flux quantum is not directly measured. In the MEG system, the SQUID sensor works through a feedback mechanism where a compensatory magnetic flux of the opposite sign is applied to hold the output of the SQUID at a constant. So the signal that is recorded is actually the compensating signal which tracks the magnetic flux linearly. To maintain the SQUID and the flux transformer setup in a superconducting state, the setup needs to be cooled with liquid helium (T=4.2K). The

setup therefore is enclosed in a thermally shielded enclosure which limits the proximity of the sensors with respect to the head surface.

There are generally three types of SQUID sensors: magnetometers and planar gradiometers (found in Elekta systems) and axial gradiometers (found in CTF systems). Besides the SQUID, a typical sensor also consists of a flux transformer, also in superconducting state, which is coupled to the SQUID loop. A flux transformer serves merely to expand the surface area for better coupling of the magnetic field to the sensor. In the case of an axial gradiometer, the flux transformer can contain two coils, a pick-up coil and a compensation coil. Placed a few millimeters above the pick-up coil, the compensation coil acts as a compensation for magnetic fields arising from external sources (Fig. 3.2 (a)). The flux transformer may also contain the two coils differentially coupled but laying on the same plane by which it picks up the planar derivative of the magnetic flux and thus makes up a planar gradiometer (Fig. 3.2 (a)). Planar gradiometers always appear in pairs with orthogonal orientations so that they may record the planar derivative of the magnetic flux at the sensor location optimally (Fig. 3.2 (b,c)).

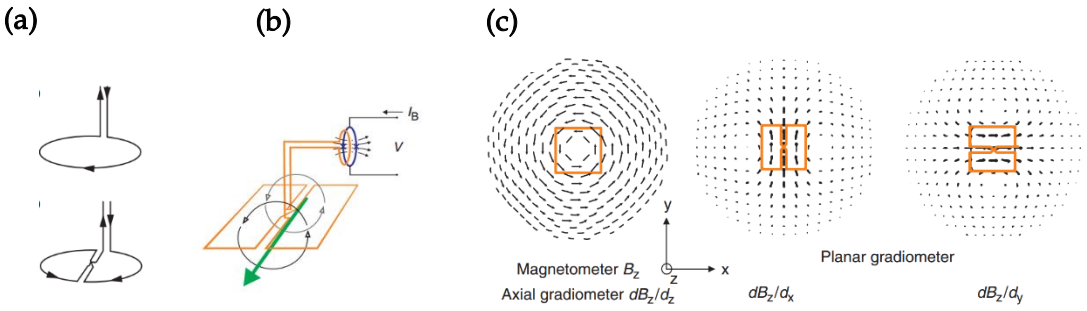

Fig. 3.2: (a) Coil design of the magnetometer **(top)** and planar gradiometer **(bottom)**. **(b)** Illustration of the magnetic field gradient picked up from a source current (green line) that leads to a magnetic field (blue) which are coupled to the SQUID **(c)** Leadfields of different types of sensors in the Neuromag TRIUX system. Leadfields of magnetometers and axial gradiometers are similar while planar gradiometers picking up the X and Y gradients of the magnetic fields are most sensitive to source right below sensor (Hansen et al., 2010).

3.1.2 Electrophysiological basis

The fundamental informational units of the nervous system are neurons. When a neuron is activated by action potentials arriving at the dendrites, ionic currents are generated as postsynaptic potentials. The neuronal activation can lead to a fast depolarization of the cell body resulting in an action potential unfolding within one or two milliseconds, which, in turn, entails slower changes in potentials mediated by the transmitter systems at the terminal buttons where this neuron's axon connects with 100s or 1000s of dendrites from other neurons. These slower postsynaptic potentials unfold over a timescale of 10 milliseconds and therefore sum up more easily across neurons than the relatively faster action potentials. The postsynaptic potentials can be either excitatory or inhibitory postsynaptic potentials (EPSPs or IPSPs), and the relatively slower excitatory post-synaptic potentials arising from the pyramidal neurons in the cerebral cortex form the electrophysiological basis of the MEG signals.

There are two aspects of the pyramidal neurons that most likely lead to measureable signals at the scalp: structural organization and temporal precision. The pyramidal neurons at the cortex are arranged in columns where the apical dendrites are arranged perpendicular to the cortical surface, which means that the postsynaptic potentials generated along the apical dendrites have very similar direction. The temporal precision of the pyramidal cells allows for thousands of pyramidal cells to "fire" in synchrony, i.e., within only a few milliseconds, leading to a super-position of the post-synaptic potentials (See Fig. 3.3).

Apart from the structural arrangement of the pyramidal cells, it is also important to note that the cortex itself is folded into gyri and sulci. As already stated, the magnetic fields run perpendicular to the direction of the underlying electrical potential. This entails that the MEG system cannot measure from neuronal populations that are aligned perfectly radially to the skull since their magnetic fields simply decay as they pass along the inside of the skull (Fig. 3.3 (c)). And likewise, MEG is thus most susceptible to magnetic fields produced by the neuronal columns arranged tangentially to the skull, which means that MEG mainly measure signals generated along the walls and curvatures of the sulci and gyri, but very rarely so from those generated at the most radially oriented peaks of the gyri and the most radially oriented troughs of the sulci. Fig. 3.3, below, show the relationship between the microscopic potentials in the neuronal cells and the fields that are picked up by the MEG.

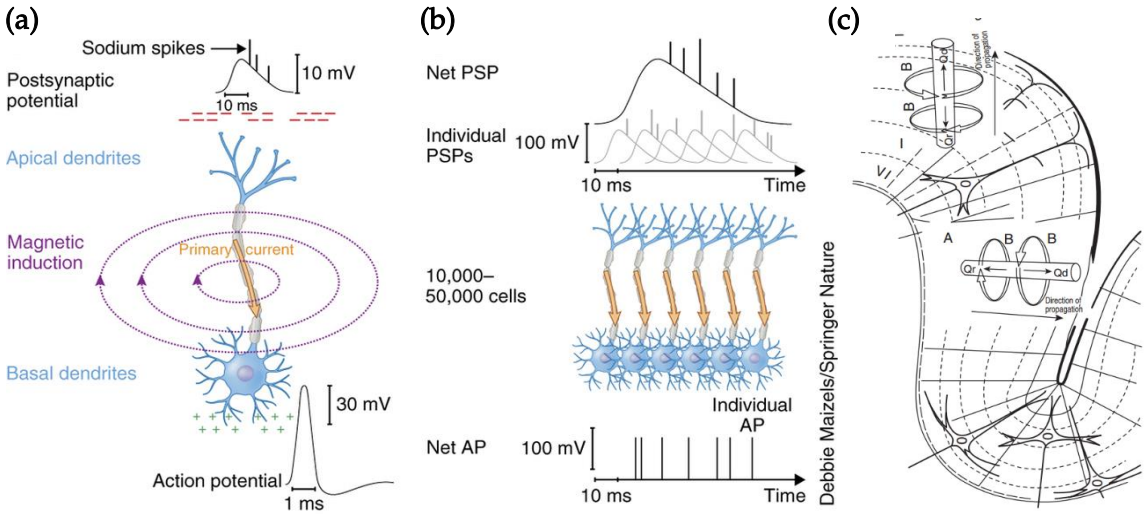

Fig. 3.3: (a) Cortical pyramidal neuron with the primary current and the magnetic field due to primary current flowing along the axon (Baillet, 2017). **(b)** Post-synaptic potentials, which unfold slower than action potentials, overlap in time without the need for exact synchronization creating a net signal measureable with MEG (Baillet, 2017). **(c)** Arrangement of radial and tangential sources along with the corresponding magnetic fields (Hansen et al., 2010).

3.2 Preprocessing

This section contains the preprocessing techniques used to clean the data and enable application of other advanced processing methods.

3.2.1 Filtering

MEG data is generally sampled at 1000 Hz with a manufacturer-specified frequency range of 0.01 to 330 Hz. Since the response of the sensors drop off with increasing frequency (1/f), analyses are generally restricted to below 100-150 Hz. In our preprocessing, we generally use a two-pass, 2nd order Butterworth filter to filter all MEG, ECG (electrocardiography), EOG (electrooculography) and EMG (electromyography) data. A Butterworth filter is an IIR (infinite impulse response) filter with a flat pass-band response, i.e., the pass-band of the Butterworth filter does not have ripples (oscillatory jitter of small amplitude). One limitation of the filter is its potentially non-linear phase response, which can be circumvented by running the filter twice, once forward and once

backwards, aptly called the two-pass filtering method. Filters also are defined by the 'order' which controls the roll-off rate or rate at which the output amplitude of the filter attenuates. Filter choices that do not account for the inherent limitations of filter may affect some measures such as coherence, since non-linear changes in the phase may distort the phase-relationships between signals.

3.2.2 Artefacts

MEG data is usually corrupted by jump artefacts, eye blinks and eye movements, heart beats, muscular and other high-frequency artefacts and, most relevant for this thesis, DBS artefacts. For study II, we used the independent component analysis-based (ICA) artefact rejection routine in MNE-Python (Gramfort et al., 2013) to factor out mainly eye blinks and heart beats. For study I and III, we used a z-scoring-based artefact rejection method implemented in the Fieldtrip toolbox (Oostenveld et al., 2011) to account for corruptions from all of the above-mentioned artefact sources except for DBS. The DBS artefacts, on the other hand, were suppressed using Maxfilter, a commercial implementation of the spatio-temporal signal space separation (tSSS) method (Taulu and Simola, 2006). Each of these methods are explained below.

Maxfilter

Although the MSR suppresses external magnetic interferences, the interferences arising near the sensors due to DBS stimulation and its metallic components still corrupt the MEG signals. Therefore, the temporal expansion of the signal space separation (SSS) method, the tSSS was used to first separate the data into components that arise from inside and outside the measured space (Taulu and Kajola, 2005; Taulu et al., 2005), and second to identify and separate out the components that are common, i.e., highly correlated, between both spaces. Since the DBS artefacts are high in energy and since they are captured by inner and outer expansions, they tend to appear as correlated components in both spaces. This way, brain signals in the inside space, which should generally be uncorrelated between the two spaces are retained (Taulu and Simola, 2006) whereas DBS-generated signals that are common to both the inside and outside spaces are separated out. Studies using the tSSS method have shown to reliably reject DBS and nearby artefacts while still retaining sensible brain signals (Taulu and Hari, 2009; Airaksinen et al., 2011, 2012).

ICA-based artefact rejection

MNE-Python (Gramfort et al., 2013) provides an implementation based on ICA to reject EOG and ECG artefacts. ICA relies on statistical independence of the components it identifies, and this is used in an artefact rejection sense in order to identify artefact components that are independent of the components reflecting the brain signals of interest. This assumption is warranted by the fact that the artefacts arise as different biological phenomena from the brain signals, and ICA should thus be able to identify certain components reflecting the purely artefact-related contributions to the data. ICA belongs to a class of methods called blind source separation. The idea is to decompose signals into known number of independent sources which renders a mixing matrix.

$$x_j = a_{j1}s_1 + a_{j2}s_2 + \cdots + a_{jn}s_n \qquad \forall\, j \tag{3.1}$$

where, the signal x_j is denoted as $x_1, \ldots, x_n$, which are a set of n linear mixtures of n independent components, whose vector-matrix notation is $\mathbf{x} = \mathbf{As}$. Once the matrix **A**, through one of several techniques such as FastICA, mutual information etc (Hyvärinen and Oja, 2000) is calculated , the demixing matrix **W**, which is the inverse of **A**, is computed in order to demix the linear mixtures as follows: $\mathbf{s} = \mathbf{Wx}$, where **W** is the demixing matrix, **x** denotes the linear mixture of components **s**. The number of components in practicality is determined by an iterative process where the components explaining the maximal data variance are preserved.

The mixing matrix is calculated by using a cost function, e.g., reducing the mutual information between the estimated signal sources or by maximizing the non-gaussianity in the sources. The default MNE-Python method for ICA decomposition is FastICA (Hyvärinen and Oja, 2000) which maximizes non-gaussianity of the source estimates. This method works well for identifying the components reflecting EOG and ECG artefacts (Fig. 3.4). The EOG and ECG channels are used as reference signals to detect artefactual components. These automatic selections are verified using the topographical plots of the components and plots of the time-series of the components. ICA-based artefact rejection is advantageous due to minimal loss of trials, and it is especially useful in experimental settings containing relatively low number of trials. While the procedure is semi-automated, it does involve a necessary checking procedure to ensure non-artefactual components are not rejected.

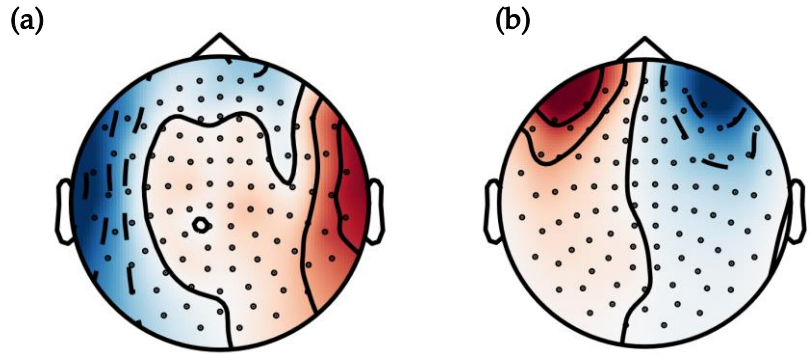

Fig. 3.4: Topographical representation of the ECG (a) and the EOG (b) artefacts picked up using ICA decomposition

z-score-based artefact rejection

While ICA can also be performed in Fieldtrip, the toolbox also has a z-score-based artefact rejection method implemented. This relies on the accumulated z-score of the data. The Hilbert-transformed envelope of all the channels are calculated and z-scored. These z-scored channels are then averaged to give a single time-series of z-scores. Since the artefactual components, mainly EOG and ECG, are picked up by several channels, averaging helps boost the artefactual component. Using a reference EOG and ECG channel, a threshold for the artefact can be set which can then pick up all artefact-corrupted epochs. Other than the EOG and ECG artefacts, data could also contain SQUID jumps which must be eliminated in order to make the frequency analysis effective. The downside of the approach is loss of trials while the upside is that the whole procedure is largely automated.

3.3 Data analysis and metrics

The following section is meant to introduce the frequency domain analysis methods used in the articles accompanying this thesis. A broad description of each of them are presented below primarily based on publications from Roach and Mathalon (2008) , Allen and MacKinnon (2010), and Gross (2014).

3.3.1 Frequency domain analysis

Unlike more classical event-related potential/field (ERP/ERF) analyses, the frequency domain representation of the electrophysiological data contains information on the oscillatory dynamics of the recorded brain signals (Tallon-Baudry and Bertrand, 1999; Allen and MacKinnon, 2010). Spectral analysis mainly involves decomposing the time series and representing them as a linear combination of pre-determined oscillatory basis functions of the form

$$X(\omega) = \sum_{k=0}^{N-1} x_k \, e^{-j\omega n} \tag{3.2}$$

where, ω is the normalized frequency, x is a time-series of N points, X is the Fourier domain signal of complex values (Allen and MacKinnon, 2010).

Fourier transform is the most common method to obtain spectral estimation and the fast-fourier transform implementation is one of the most efficient ways to perform the estimation. Although originally proposed by Jean Baptiste Fourier in 1807 to explain heat propagation in terms of sinusoids, today's Fourier transforms were not formalized until decades later when the Dirichlet boundary conditions were formulated dealing with the Fourier decomposition of discontinuous signals (Keithley, 1999:85). Thus, the basic principle of Fourier-based methods is the idea of representing any given frequency domain signal in terms of sinusoids.

The common procedure for computing the time-frequency representation (TFR) based on Allen and MacKinnon (2010) is as follows:

i. The data is first epoched into trials (either by means of triggers in the data or by arbitrarily defined epochs, e.g., 1 sec segments).
ii. Each trial is then subset into smaller time segments over which the TFR computation is performed. A windowing function or a taper is used to truncate the data for time-frequency computation. Such tapers are qualitatively different from mere subsetting of data, which is implied convolution with a boxcar taper and such a boxcar taper has high spectral leakage. The use of the windowing function like Hanning window is to prevent spectral leakage.

iii. These tapered or windowed time-segments are then subjected to Fourier transform which outputs a complex-valued spectrum, the absolute value of which is an estimate of the spectrum (whose phase is reflected in the imaginary component of the complex-valued spectrum).

iv. Steps (ii) and (iii) are repeated over the time-series with an overlap of the truncated time series to allow for optimal time resolution while ensuring long enough time windows for the frequency resolution of interest (see below for more details).

v. The integration of the spectral estimates across the overlapping moving windows thus results in a time-resolved frequency representation, a TFR.

To obtain only a spectral estimate without any temporal resolution, the estimates can be computed over the whole trial instead of with a moving-window method.

As briefly mentioned in step iv, there is an inherent limitation to any time-constrained frequency estimation, namely that the length of the taper directly determines the frequency resolution. If the taper length is given by L, say 100 ms, then the frequency resolution is 1/L, i.e., 1/100 ms = 10 Hz. If a frequency resolution below 10 Hz is desired, a longer taper is needed, which can to some extent be accomplished by oversampling the spectrum with zero-padding. Theoretically, it will improve the frequency resolution, but it is basically a correlate of interpolation, and hence, large amounts of zero-padding must be used with caution as it cannot compensate for signals that simply cannot be estimated due to the inherent limitations of the data dimensions.

Steps (ii) and (iii) in the above procedure can be performed using different methods such as Multitaper method and wavelet method, which are explained below. These methods are merely different methods of spectral estimations.

Multitaper-based Fourier analysis

A challenge for the standard Hanning window approach for the Fourier transform is that we assume that each estimate truly represents the signal components, i.e., the amplitude and phase at the frequency of interest (Mitra and Pesaran, 1999). By using a set of tapers instead of only one, we can reduce the variance in the estimate of the signal components for the frequency of interest while at the same time controlling the frequency smoothing due to the multiple tapers (Mitra and Pesaran, 1999). The degree of frequency smoothing increases with each taper, hence increasing the number of tapers increases smoothing. This approach is called the multitaper method, and

discrete prolate slepian sequences (DPSS) are one such set of tapers (Mitra and Pesaran, 1999; Gross, 2014). One of DPSS' key properties is that the tapers form an orthogonal basis. The orthogonality of the basis functions can be easily tested by taking the dot product of the slepian sequences as this must tend to zero. These basis functions are basically meant to pick up different aspects of the windowed time-series due to their orthogonality (Mitra and Pesaran, 1999). Increasing the number of tapers increases the frequency smoothing which can be observed by plotting the tapers and their spectral responses (Mitra and Pesaran, 1999).

Wavelet-based analysis

Wavelet-based analysis is conceptually similar to the Fourier analysis, except that the time-series is convolved with a different set of oscillatory basis functions called wavelets (Gross, 2014). Since convolution in the time domain is equivalent to multiplication in the Fourier domain and since multiplication is computationally more efficient than convolution, wavelet-based analyses are performed by Fourier transforming both the data time series and the wavelets and then multiplying them in the Fourier domain (Gross, 2014).

Morlet wavelet is one of the most commonly used wavelets in electrophysiological data analysis (Gross, 2014). A Morlet wavelet is a sine wave multiplied by a Gaussian envelope. The number of cycles fitted for each frequency is kept constant. Hence, if we fix the number of cycles to 5, then an alpha rhythm of 10 Hz requires a wavelet-length of 500 ms (5 cycles of 100 ms each since 1/100 ms = 10 Hz), and a low-gamma rhythm of 40 Hz requires a wavelet-length of 125 ms (5 cycles of 25 ms each since 1/25 ms = 40 Hz). By increasing the number of cycles, we can obtain better frequency resolution, but this happens at the expense of time resolution and vice-versa. Thus the time-frequency resolution is adapted to the estimated frequency (Gross, 2014).

3.3.2 Evoked vs induced activity

Stimulus-related oscillations generally fall into two broad categories, evoked and induced. Theoretically, evoked activity is both time-locked and phase-locked to the incoming stimulus. It is consistent in its temporal precision and has good repeatability. Induced activity, on the other hand, is not phase-locked and may or may not be precisely time-locked to the stimulus (Tallon-Baudry and Bertrand, 1999). Because of the temporal precision of the earliest somatosensory evoked response field (N20m) and its direct relation to the stimulus, it is thought to mainly reflect bottom-up sensory communication (Hari and Forss, 1999; Ikeda et al., 2005; Huttunen et al., 2006).

The induced activity, on the other hand, is thought to reflect local processing in the underlying neural substrate due to its non-phase-locked and non-time-locked nature (Pfurtscheller and Lopes da Silva, 1999; Tallon-Baudry and Bertrand, 1999). To compute the induced activity, the evoked activity (trial-averaged time series) is subtracted from each trial in the original data, which may then subjected to TFR analysis (Pfurtscheller and Lopes da Silva, 1999; Tallon-Baudry and Bertrand, 1999; David et al., 2006; Uhlhaas and Singer, 2010). This subtraction procedure assumes temporal stationarity of the evoked responses (Truccolo et al., 2002).

However, the precision of the phase-locked activity is not a given fact and the amplitudes may also vary across trials. Due to such variations in the onset of the evoked response and potential differences in the gain across trials, the subtraction procedure may leave residual evoked response in the estimated induced data (Truccolo et al., 2002; David et al., 2006). A trial-to-trial input jitter in the evoked responses is most of evident as a 'bleeding' of higher frequency components into the induced responses (David et al., 2006). It is therefore necessary to be cautious when interpreting induced responses obtained by the subtraction method, and it is advisable employ additional checks in order to ensure that the computed induced activity does not merely reflect residuals of the evoked activity.

3.3.3 Analysis of functional connectivity

There are generally three types of connectivity: anatomical, functional and effective connectivity (Friston, 1994; Lang et al., 2012; Bastos and Schoffelen, 2016). Anatomical connectivity refers to connections established through physical connection between neuronal cell assemblies (Bullmore and Sporns, 2009). Functional connectivity refers to the temporal dependence of oscillations in one brain region on those of another. Such functional connectivity may be driven through a network of cell assemblies (Bullmore and Sporns, 2009). Effective connectivity characterizes the causality in the functional communication between regions (Lang et al., 2012; Bastos and Schoffelen, 2016). An abstract example of such a causal link is when the transmission of oscillatory activity between two regions modulates the excitability of one of the regions (the target region) and hence alters the underlying neuronal activity (Lisman, 1997; Womelsdorf et al., 2007).

The connectivity measure relevant for this thesis is coherence co-efficient, or coherence in short. It is a non-directed connectivity measure, i.e., a measure of functional connectivity, and consists of a cross-correlation between two frequency spectra (Rosenberg et al., 1989; Conway et al., 1995).

Coherence, simply put, is the cross-spectrum between two signals normalized by the power-spectra of each of the signals. The normalized coherence metric is bound between 0 and 1 and is given by:

$$C_{xy} = \frac{\left|\frac{1}{n}\sum_{k=1}^{n} A_x(\omega,k)\, A_y(\omega,k)\, e^{i(\varphi_x(\omega,k)-\varphi_y(\omega,k)}\right|}{\sqrt{\left(\frac{1}{n}\sum_{k=1}^{n} A_x^2(\omega,k)\right)\left(\frac{1}{n}\sum_{k=1}^{n} A_x^2(\omega,k)\right)}} \quad (3.3)$$

A_x and A_y are two time-series for which we want to compute the coherence at frequency ω over n trials. When computing e.g. corticomuscular coherence, the two time series are thus the MEG channels and the EMG recordings. For more details on the usage of the method, see the section on Study II in the chapter on the original contributions.

3.4 Source reconstruction

Source localization is the process by which one may estimate the neuronal sources of the signals we measure at the MEG (or EEG) sensors. The measured signal reflects the magnetic fields created by two basic components, the primary currents and the volume currents. Of these, the primary currents are of most interest, since they reflect post-synaptic potentials arising the pyramidal cells as explained in a previous section (3.1.2 Electrophysiological basis). The first step in estimating the underlying currents that eventually lead to the magnetic flux measured at the scalp, is to understand how a current dipole projects to magnetic fields to the sensors near the scalp. For this purpose, we need the so-called leadfield matrix, which is the magnetic field projected onto a specified sensor by a current dipole of unit strength, and this is calculated with a given forward solution. With the information given by the leadfield matrix, we may then proceed to estimate the neuronal sources of a given signal projection. The dipole projection onto the scalp and the subsequent estimation of neuronal sources based on this projection form the forward and inverse problems, respectively.

Firstly, we setup the forward problem through equations for the magnetic fields created by a current dipole, which we estimate for a simple geometry and then extend with a correction for arbitrary volume conductors. This information from the forward model allows us to setup the mathematical model for estimating the neuronal sources of the signal, the inverse solution. The

following formulae and equations are adopted from the mathematical dispositions on MEG and source analysis procedures previously reported by Hämäläinen (1993), Leahy and colleagues (1998), Baillet and colleagues (2001) and Nolte (2003).

3.4.1 Forward model

In order to compute the forward model, the mathematical problem must be formulated in accordance with our assumptions. The following explanation follows from the elaborate derivations presentation in Hämäläinen et al., (1993). Firstly, the temporal decay of the electric signal is considered negligible and is quasi-statically approximated. The magnetic field $\mathrm{B}(r)$ created by a current density $J(r')$ at position r' and observed at position r in a closed volume V is given by the Biot-Savart law.

$$\mathrm{B(r)} = \frac{\mu_0}{4\pi} \int_{\mathrm{V}} \mathrm{J(r')} \times \frac{\mathrm{r} - \mathrm{r'}}{\|\mathrm{r} - \mathrm{r'}\|^3} \, \mathrm{dv'} \tag{3.4}$$

The total current density at the source consists of two parts: primary and volume currents. We know from anatomy that the head is composed of different materials such as scalp, skull, cerebrospinal fluid, and gray and white matter, all with different electrical conductivities. If we assumed each of these enclosed volumes have isotropic electrical conductivities, the total current emanating from the closed volume can be represented as vectors on a surface of the volume. Thus, the three-dimensional problem of the volume currents shrinks to a two-dimensional one and therefore only needs to be solved as surface integrals.

It has been shown that for a spherically symmetric volume conductor, the contributions from volume currents vanish and only the contributions from primary currents to the magnetic field remains (Hämäläinen et al., 1993). Since the magnetic field $\mathrm{B}(r)$ has contributions only from the primary currents (Hämäläinen et al., 1993). The forward model can be calculated analytically for specific geometries while only numerical solutions exist for realistic head models. From equation 3.4, it can be seen that the magnetic field $\mathrm{B}(r)$ is linearly related to the current dipole moment and non-linearly and inversely related to the distance between the observation point and the current dipole (Hämäläinen et al., 1993).

Realistic volume conductor

The above result can also be extended if the head is modelled as a set of concentric spheres of known conductivity and if they are each assumed to have isotropic conductivity profiles. The spherical models work fairly well for MEG signals mainly because of the absence of contributions from volume currents (Leahy et al., 1998).

The spherical model is still an approximation of the geometry of the head and hence it needs to be expanded with a correction to ensure that the leadfield obtained with a spherical approximation is still tangential at the outermost surface of the volume conductor. The method performs a forward calculation for a single shell of an arbitrary geometry (Nolte, 2003). The actual computation of the forward model consists of two steps: the initialization step obtains the spherical harmonics and the second step solves for the actual leadfield. Having calculated the forward solution which reflects the magnetic contributions of a given dipole for any specific MEG sensor, we can proceed to solve the inverse problem.

3.4.2 Mathematical model of the signal

The magnetic field $m(r)$ measured at sensor r is linearly related to the current dipole moment q as stated in the previous section. Given the dipole magnitude of q, the orientation of the dipole Θ is given by the argument of the dipole vector. The magnetic field $m(r)$ measured at location r is thus given by:

$$\mathrm{m}(r) = \mathrm{l}(\mathrm{r}, \mathrm{r_q}, \theta)\mathrm{q} \tag{3.5}$$

where $\mathrm{l}(\mathrm{r}, \mathrm{r_q}, \theta)$ is the forward solution from the previous section for a dipole of unit amplitude and orientation θ. Extending the above equation for p dipoles, we simply sum up the contributions of each of these dipoles by using the linear super-position of the contributions of each of the dipoles. The magnetic fields at N sensors created by p dipoles is thus given by:

$$\mathrm{m} = \begin{bmatrix} \mathrm{m}(\mathrm{r_1}) \\ \vdots \\ \mathrm{m}(\mathrm{r_N}) \end{bmatrix} = \begin{bmatrix} \mathrm{l}(\mathrm{r_1}, \mathrm{r_{q1}}, \theta_1) & \dots & \mathrm{l}(\mathrm{r_1}, \mathrm{r_{qp}}, \theta_\mathrm{p}) \\ \vdots & \ddots & \vdots \\ \mathrm{l}(\mathrm{r_N}, \mathrm{r_{q1}}, \theta_1) & \dots & \mathrm{l}(\mathrm{r_N}, \mathrm{r_{qp}}, \theta_\mathrm{p}) \end{bmatrix} \begin{bmatrix} \mathrm{q_1} \\ \vdots \\ \mathrm{q_p} \end{bmatrix} \tag{3.6}$$

$$= \mathrm{L}(\{\mathrm{r_{qi}}, \theta_{\mathrm{i}}\})\mathrm{Q}^{\mathrm{T}} \quad (3.7)$$

where $\mathrm{L}(\{\mathrm{r_{qi}}, \theta_{\mathrm{i}}\})$ is the gain matrix for a given dipole i at N sensor positions and T corresponds to transpose of a matrix. The above equation can also written with a time-component t. Given this signal model, the leadfield satisfies the following equation:

$$\mathrm{M} = \mathrm{L}(r)\mathrm{Q} \quad (3.8)$$

where $\mathrm{L}\ r$ is the leadfield matrix of dimension $\mathrm{N} * \mathrm{P}$ with N as the number of sensors and P as the number of points in source space, equivalent to $\mathrm{L}(\{\mathrm{r_{qi}}, \theta_{\mathrm{i}}\})$, and Q is a $\mathrm{P} * 1$ matrix with the unit dipole strengths.

3.4.3 Inverse solution

There are multiple ways to obtain an inverse solution such as dipole fitting (a parametric estimation method), beamforming (a scanning technique), distributed source models and Bayesian estimation of sources (Baillet et al., 2001). Since we have used the beamforming technique called dynamic imaging of coherent sources (DICS) (Gross et al., 2001) for our source localization calculations (see Study II), we will focus on this method in the following by providing its mathematical formulation and explaining its implementation. The equations follow presentation in Gross et al. (2001) that outlines the DICS method.

The objective of the inverse solution, especially when using scanning methods like beamforming, is to identify the strength of the neuronal activity at a given location in the source space. The inverse problem is a linear problem where the number of unknowns (source space points, given by *P* in equation 3.6) severely outnumbers the knowns (sensors, given by N in equation 3.6) and hence, the problem is underdetermined. This necessitates a need for constraints, some mathematical and some physiological, in order to limit the solution space and thus increase the chances of obtaining a plausible inverse solution. The main assumption when using beamforming is that all sources are uncorrelated with each other.

An ideal spatial filter W^{T} would satisfy conditions such that it passes all signals at an arbitrary source location r_0 but stops all signals outside r_0. Since $L(r)$ is the leadfield or the forward gain matrix for a unit dipole placed at an arbitrary position r, the conditions that the weighting matrix should satisfy can be written as below.

$$\mathrm{W}^{\mathrm{T}}\,\mathrm{L}(r) \tag{3.9}$$

for the conditions

$$\mathrm{W}^{\mathrm{T}}\,\mathrm{L}(r) = \begin{cases} \mathrm{I}, & \mathrm{r} = \mathrm{r}_0 \\ 0, & \mathrm{r} \neq \mathrm{r}_0 \end{cases} \tag{3.10}$$

for r∈G where G is the brain volume where I is an identity matrix. The resulting frequency dependent weighting matrix W(r, f) (or spatial filter) for a location r is given by:

$$\mathrm{W(r,f)} = \left(\mathrm{L}^{\mathrm{T}}(r)\mathrm{C_r}(f)^{-1}\mathrm{L}(r)\right)^{-1}\mathrm{L}^{\mathrm{T}}(r)\mathrm{C_r}(f)^{-1} \tag{3.11}$$

where $C_r(f) = C(f) + \lambda I$ with $C(f)$ as the cross spectral density function at frequency f and λ λ is the regularization parameter (Gross et al., 2001).

Now having the inverse solution, the aim is to compute the coherence between the external reference, an EMG signal in this case and the cortical sources. Coherence between a cortical signal x and a reference signal y for a given frequency f is given by: $|C_S(x,y,f)|^2/\left(P_s(x,f)P_{ref}(y,f)\right)$, where $P_s(x,f)$ and $P_{ref}(y,f)$ are the power spectral estimates of signals x and reference (EMG in case of CMC) at frequency f, $C_S(x,y,f)$ is the cross-spectral density between signal x and y at frequency f and subscript s denotes source-space.

Hence to compute the coherence at the sources, we need to obtain the source projection of the cross-spectral density and the power at the source level apart from the power of the reference signal, i.e., the power of the EMG signal. Spectral power can be readily obtained as explained in Section 3.3.1. To obtain the cross spectral density between two arbitrary sources we use,

$$\mathrm{C_s}(r_1, r_2, f) = \mathrm{W}(r_1, f)\mathrm{C}(f)A^{*T}(r_2, f) \tag{3.12}$$

where, $\mathrm{C_s}\ r_1, r_2, f$ is the cross-spectral density matrix for a given frequency f between signals at locations r_1 and r_2 given a spatial filter W.

For the cross-spectral density between a reference EMG signal and a cortical location, using equation 3.12,

$$\mathrm{C_s}(r,f) = \mathrm{W}^T(r,f)\mathrm{C_{ref}}(f) \tag{3.13}$$

where, $C_s\ r,f$ is the cross-spectral density between the reference signal and a source at position r and C_{ref} is the cross-spectral density between the EMG reference signal and the MEG sensors. Likewise, power estimate can also be derived from equation 3.12.

The inverse solutions generally contain three orientations and it is general practice to obtain the orientation of the dipole in the dominant direction by computing the singular value decomposition of the dipole strengths in all direction and picking the largest singular value. Using methods like multitapering (see Section 3.3.1), it is also possible to beamform over an entire frequency band, in which case f is the center frequency of the band.

3.4.4 Co-registration

Apart from the above-mentioned mathematical disposition, there is a more practical aspect that is also critical to the source localization procedure. It involves co-registering the anatomical image of the given participant (most often a T1-weighted magnetic resonance image (MRI)) with the functional data, i.e., the MEG signals. This is an important step because the calculation of the forward model and the inverse solution rely on the alignment between the functional data recorded with MEG and the anatomical data recorded with MRI.

To this end, before the MEG measurement is performed, it is general practice to place 4-5 head position indicator (HPI) coils on the participant's head and record their positions in a virtual 3D coordinate system using a Polhemus tracking system. Apart from recording the locations of the HPI coils, further anatomical landmarks are obtained including nasion, and left and right pre-auriclar points as well as 50-100 points denoting the head shape. Co-registration of the structural and functional data is then performed by approximate alignment of the corresponding anatomical landmarks on the MRI and the relevant head shape points from the MEG preparation, which is further optimized through an iterative closest point algorithm to find the best fit between the point cloud from the digitized head shape and the head shape from the MRI.

3.5 Bayesian statistics

Statistical inference in science is generally based on the classical null-hypothesis significance testing (NHST). Though all pervasive throughout science, they carry drawbacks such as inability to state evidence for the null and to some extent overstating the evidence against the null (Selke et al., 2001; Wagenmakers and Grünwald, 2006; Rouder et al., 2009) (however, see Läkens (2017) for alternatives within NHST for testing for null effects using equivalence tests). Using Bayes Factors (BFs) for statistical inference, on the other hand, allows for considering both the null and the alternative hypotheses on equal footing (Wagenmakers and Grünwald, 2006; Rouder et al., 2009; Dienes, 2014). BFs allow for comparisons of competing hypotheses. They do so by providing a measure of the relative likelihoods of the data given different hypotheses, and these relative likelihoods can thus be directly compared (Kass and Raftery, 1995; Wagenmakers and Grünwald, 2006; Jarosz and Wiley, 2014).

The mathematical formulation for Bayes Factors (BF) is provided below. Assume that data D have arisen under one of the two competing hypotheses, H_1 and H_2, with the prior probability density functions $P(D|H_1)$ and $P(D|H_2)$. The prior probabilities of the two hypotheses are given by $P(H_1) = 1 - P(H_2)$, and the posteriori probabilities are given by $P(H_2|D) = 1 - P(H_1|D)$.

Bayes theorem is given by:

$$\mathrm{P(A|B)} = \frac{\mathrm{P(B|A)P(A)}}{\mathrm{P(B)}} \tag{3.14}$$

Given two competing hypotheses, using Bayes' theorem we write,

$$\frac{\mathrm{P(H_1|D)}}{\mathrm{P(H_2|D)}} = \frac{\mathrm{P(D|H_1)}}{\mathrm{P(D|H_2)}} \frac{\mathrm{P(H_1)}}{\mathrm{P(H_2)}} \tag{3.15}$$

And thus,

$$Posterior\ odds = Bayes\ Factor * Prior\ odds \tag{3.16}$$

$$\mathrm{BF_{12}} = \frac{\mathrm{P(D|H_1)}}{\mathrm{P(D|H_2)}} \tag{3.17}$$

The prior odds, i.e., $P(H_1)$ and $P(H_2)$, are generally assumed to be equal (but can be specified differently if there are good *a priori* reasons for doing so) and hence, the BF is simply the ratio of the posterior odds in favor of H_1 (or H_2). The posterior probabilities, $P(D|H_1)$ and $P(D|H_2)$, are also called the marginal likelihoods M and are obtained by integrating the probability density function of the data under each hypothesis weighted by the distribution of the prior $p_H\ \theta$ on the parameters. φ_H denotes the parameter space and y denotes the data:

$$M_H = \int_{\theta\ \epsilon\ \varphi_H} f_H(\theta; y) p_H(\theta) d\theta \tag{3.18}$$

It can be readily seen that the prior $p_H\ \theta$ acts as a weighting function on the marginal likelihoods. The parameter space for a t-test between two normal distributions would be the mean the variance of the distributions. It can also be seen that the ratio of the marginal likelihoods that emerge are obtained based on the observed data.

A prior should be chosen such that it does not unduly favor an unlikely value for any given parameter. Priors can be informed either from previous experimental work and theoretical frameworks or by the assumptions on the parameters. Rouder et al. (2009) laid the basis for the so-called Jeffreys, Zellner and Sinow (JZS) prior, which is a combination of prior based on the assumptions placed on the effect size and variance of parameters. A detailed explanation of the prior choice, especially the JZS prior is provided by Rouder et al. (2012), which forms the basis for their R-based (R Core Team, 2016) BayesFactor package (Morey et al., 2015), which we have used for our stastical analyses in the three accompanying articles.

The interpretation of the BFs are also quite straightforward. Given two hypotheses, H_1 and H_2, and given a BF labelled BF_{12}, we can directly infer that H_1 is BF_{12} times more likely than H_2 given the observed data. This schema greatly simplifies the inferencing problems since BFs potentially could provide evidence for either hypotheses, but also inconclusive evidence, it follows from this that the BFs and the Bayesian framework allow for an actual interpretation of potential null effects.

Nevertheless, within the Bayesian framework there are several schools of thought on the exact weight of evidence that is necessary to infer that a hypothesis is valid for a given dataset. Kass and Raftery (1995) present a table that can be used to qualitatively interpret the BFs. They posit

that a BF of 1 to 3 is considered evidence barely worth a mention, 3 to 20 positive evidence, 20 to 150 strong evidence and more than 150 very strong evidence. There is, however, an alternative formulation positing that since the BFs are directly interpretable, they should be reported without using any more or less arbitrary cut-offs leaving the evaluation of the weight of evidence to the readers themselves (Rouder et al., 2009).

In the studies accompanying this thesis, we follow a hierarchical approach to perform Bayesian inference. We first evaluate if there is an effect of Condition (i.e., treatments for the PD patients and time for the controls) and then progressively test more constrained hypotheses informed by our *a priori* understanding of treatment effects on the measures of interest. Similar tests are also performed on the control data to see if we obtain any evidence for the alternative, which would signify an effect of Condition. The interpretation relies on progressively accumulating evidence to observe if any conditions differ enough from the others to make us update our priors.

It is also worth noting that Rouder et al. (2012) and Wetzels et al. (2011) showed the correspondences between t-values (from two-sample t-tests) and BFs for various sample sizes from 5 to 5000 (Fig.2: (Rouder et al., 2012: Fig. 2, Wetzels et al., 2011: Fig.3). Reading those plots informs us that for N=10/13, we would find for a $BF_{10}=3$ that the corresponding $t\approx2.5$ (and thus $p<0.05$). However, these correspondences are for t-tests (and not e.g., F-tests). Nevertheless, they serve as a useful reference for understanding some of the relations between BFs and p-values.

Chapter - 4

Original PhD contributions

In this chapter I introduce the three studies that accompany this thesis. A section with a general introduction to the methods specifically used in the studies is first presented, along with the experimental paradigm and the patient and control cohorts. The operational parts of the theoretical background, methods and results of the three studies are presented thereafter for each study separately. The complete details can be found in the manuscripts attached as Appendices.

4.1 General methods

PD patients implanted with DBS at the Aarhus University Hospital were recruited for the studies. The main inclusion criterion was at least six months of bilateral STN-DBS. The exclusion criteria were any concurrent sensory or neurological deficits, mini-mental state examination (MMSE) score below 25, clinical significant depression as defined by the Major Depression Inventory (MDI). A total of 18 patients were recruited and participated in the three experiments. (For Experimental paradigm See Appendix-A; Fig. 1). Patients stopped taking anti-parkinsonian medication the night before the experiment (dopamine-agonists were last taken the morning before the experiment, hence 24 hours would have lapsed till the time the experiments were conducted). After the patients arrived, an initial Unified Parkinson's Disease Rating Scale part-III (UPDRS-III, motor part) was performed, and MDI and MMSE were administered. Ten healthy age-matched participants were recruited as controls and underwent all experimental paradigms and were mainly used to factor out any effects of time such as habituation, fatigue, etc.

All MEG measurements were performed with patients and healthy control in supine position. Each block (vertical bar) shown in the figure (See Appendix-A; Fig. 1) reflects a MEG

measurement. Patients and controls underwent seven MEG measurement blocks in total. Firstly, the patients were OFF medication, but still ON DBS, and underwent their first measurement block. After completing the three tasks comprising the three studies, namely, rest, hand gripping movements and somatosensory stimulation, the DBS was switched off. Five subsequent measurement blocks every 30 minutes were performed in the untreated state to track the potential washout phase of DBS. UPDRS-III scoring was performed after the first and the last MEG measurement blocks in the untreated state (blocks two and six, respectively). After the sixth MEG measurement block, patients were administered dopaminergic medication (200 mg of levodopa/50 mg carbidopa) and waited for an hour for it to take effect. UPDRS-III scoring was then performed, and finally, the last and seventh MEG measurement block was performed.

Since both patients and controls were placed in the supine position during the MEG recordings, their head positions were relatively stable during the actual recordings. We used their initial head positions for each recording (as measured with the head position indicators (HPIs)) as input to the MaxFilter process. In the DBS ON condition, we could not obtain any appropriate fits due to interference from the electrical stimulation. We therefore always made an extra dummy recording right after switching off the stimulator (or proceeded directly with the second recording after a short rest period) while ensuring the patient was still placed in the same position in the MEG device as during the just-finished DBS ON recording. We then used their head positions from this subsequent recording as input to the MaxFilter for the DBS ON condition.

Not all patients could undergo the whole paradigm and thus perform all tasks. E.g. one patient could not undergo median nerve stimulation at all since the patient considered it too be painful already at subthreshold current levels; and a subgroup of patients had been recorded with finger tapping, rather than hand gripping in the movement-related study. Therefore, the PD cohorts that qualified for the three different studies were of variable sizes and configurations, and all three are presented in more detail, below, under the corresponding studies.

4.2 Study I

Differentiated effects of deep brain stimulation and medication on somatosensory processing in Parkinson's disease

In this study, we looked at early somatosensory processing in PD and how it is affected by treatments. As the main index of somatosensory processing, we focused on oscillatory changes in the sensorimotor area after median nerve stimulation. To this end, we analyzed the earliest somatosensory component N20m and the early induced gamma augmentation (31-45 and 55-100 Hz) from 20-60 ms as well as the later beta suppression (13-30 Hz; 80-200 ms). Data from thirteen patients were passed onto final analysis (See Appendix-A- Tab. 1 for details of the cohort for this study). Time-frequency analysis was performed using Morlet wavelets.

The initial concern in the study and was the interference of DBS with oscillatory components like low- (31-45 Hz) and high-gamma (55-100 Hz) activity. Airaksinen et al., (2011) had already shown that they could successfully suppress DBS artefacts and study SEFs (and AEFs). But we were still uncertain about the signal quality during the DBS ON condition as well as the signal-to-noise ratio of the measured gamma oscillations due to the more general issue of the 1/f frequency response of the MEG sensors showing decreased sensitivity with increasing frequency (which is also true of many other time-domain measurements, including EEG – See previous section). We analyzed three pilot PD patients to obtain the N20m and the TFR around the N20m maximum in the sensor space. To confirm the origin of the gamma oscillations, we also performed source analysis and localized the broadband gamma (40-100 Hz) to the contralateral sensory cortex (S1).

To account for possible confounds of the impact of evoked activity on overall gamma activity, especially in the high-gamma band, we focused our analyses on induced components (rather than combined evoked and induced), which we obtained by subtracting the evoked fields from the original data (Tallon-Baudry and Bertrand, 1999). Since the induced activity is already a feeble measure, and because we had a functional localizer independent of the induced oscillations in the N20m, we did not perform source analysis of the results in this study.

We used Bayesian inferencing based on Bayes Factors (BF) in this study. A brief explanation of Bayes Factors is provided in Section 3.5. We set up hypotheses so as to test which conditions were potentially different from the others. We performed statistical analyses on the following

measures: UPDRS-III scores, low and high gamma augmentation, beta suppression and N20m amplitudes.

We showed differentiated effects of dopaminergic medication and DBS on early somatosensory cortical processing in PD patients in the low-gamma band (31-45 Hz) (Jones and Barth, 1997; Ihara et al., 2003; Cardin et al., 2009). Highest low-gamma augmentations were observed in the MED ON condition and the lowest in the untreated states (DBS OFF (0 min) through DBS OFF (120 min)) and the DBS ON condition (See Appendix-A-Tab. 2; Fig. 2, 4; Supp. Tab. 1). In comparison, the UPDRS-III scores indicating the severity of motor symptoms showed similar effects of both treatments. Thus, we take this to suggest differentiated effects of treatment on early somatosensory cortical processing, but not on the motor symptoms.

As explained in the Background chapter, somatosensory gamma oscillations play a role in sensory processing (Jones and Barth, 1997; Ihara et al., 2003; Cardin et al., 2009; Suffczynski et al., 2014). Hence, changes in gamma power in the macroscopic level at the cortex might indicate physiological changes in the microscopic neuronal level. The differentiation in effects of treatments are conceivable given the clinical studies on somatosensory processing. They suggest that problems in sensory discrimination are improved with dopaminergic medication (Artieda et al., 1992; Shin et al., 2005; Conte et al., 2010; Lyoo et al., 2012) whereas DBS may worsen them (Conte et al., 2010).

There are two plausible mechanisms that could drive effect of dopaminergic medication on early cortical gamma oscillations. Dopaminergic medication effects on somatosensory low-gamma augmentation may be driven by modulation of the excitability of the thalamic ventro-basal (VB) nuclei, which play an important role in the relay of sensory information (Felleman and Van Essen, 1991). On the other hand, dopaminergic medication may also cause its effect through the nigrostriatal dopaminergic pathway in contact with striatal spiny projection neurons. The above-mentioned mechanisms are elaborated the Discussion section of Appendix-A.

We furthermore showed null effects of both treatments on the N20m amplitudes, beta suppression and high-gamma augmentation (See Appendix-A-Tab. 2 Fig. 3; Supp. Tab. 1). Inspection of the data showed clear N20m and induced activity in beta as well as low and high gamma bands as also previously reported (Fukuda et al., 2008, 2010; Hagiwara et al., 2010). Lack of effects of treatments on N20m is in line with previous results (Pierantozzi et al., 1999; Priori et

al., 2001; Conte et al., 2010; Airaksinen et al., 2011) although some of these earlier studies may be partly confounded by methodological issues. We have extended these findings in a paradigm where treatments do not overlap and hence provide stronger bases for suggesting absence of effects of treatments on the arrival of the sensory stimuli at the cortical mantle.

The main limitation of this study is the lack of behavioral measures. Though we show an effect of dopaminergic medication on early cortical somatosensory processing through the increased augmentation in the low-gamma band, we were not able to fully characterize the functional importance of the increase. In this context, it should be noted that the experimental paradigm did not allow any extra time for a behavioral measure, but any future studies investigating sensory processing in PD would greatly enhance our understanding if also benchmarked against behavioral measures of sensory function.

4.3 Study II

Deep brain stimulation and dopaminergic medication differentially modulate motor cortical oscillations and corticomuscular coherence in Parkinson's disease

In this study, we looked at the modulation of motor cortical oscillations, especially beta and low-gamma, as well as of corticomuscular coherence (CMC) in the beta band. These measures were picked *a priori* since studies focused on voluntary movements have investigated these measures and their changes during various phases of movements (Crone et al., 1998a; Kilner et al., 1999, 2000; Muthukumaraswamy, 2010). It has also been shown that beta-CMC is increased after administration of levodopa (Salenius et al., 2002) and that beta power might not be affected by medication or DBS (Pollok et al., 2012; de Hemptinne et al., 2015). Since it has been shown that gamma rhythms are prokinetic and gamma oscillations are known to scale with the movement, we hypothesized that treatments might also affect gamma power (Brown et al., 2001; Kühn et al., 2006; Muthukumaraswamy, 2010).

Movement-related studies, especially in PD, most commonly use isometric contraction or extension tasks. It is probably easier for the patients to endure, and thus even during untreated states to achieve good task-compliance. Furthermore, it is possible to relatively easily modulate the extent of movement. We, on the other hand, used a hand gripping task. The primary reason for this was to more adequately capture the bradykinesia and also make the task more

ecologically valid as the task fits better with the grasping motions that a subject might perform in their day to day activities than an isometric task does. We did observe that patients found it difficult to keep up the hand gripping over long periods of time (~1 min). Hence, we broke the total ~2 minutes of recording into 30 s segments with equivalent breaks in between. This helped the patients to relax and continue with the task. Despite this accommodation of the paradigm, three patients among the ten included still could not steadily perform hand grips throughout the five DBS OFF conditions, mainly due to fatigue. We therefore measured hand gripping only in four conditions in these three patients: during DBS ON, DBS OFF (0 min), DBS OFF (120 min) and MED ON conditions. And in order to homogenize the data, we only analyzed data from these four conditions in all ten patients and all ten healthy controls.

We calculated the power and cross spectral densities (PSD & CSD) between MEG and EMG data using the multitaper method (Mitra and Pesaran, 1999). The section in the Methods chapter presents a brief introduction to the method. We limited our analysis to below 45 Hz in order not to confound the analysis with possible sub-harmonics of the electrical stimulation, which would be especially prone to mitigating confounds in the absence of a well-defined baseline period (unlike in Study I with clearly delineated median nerve stimulation epochs). The full details of the methods can be found in the Appendix-B-Methods section.

Increments in beta-CMC have been shown to improve performance with lesser errors that may lead to better compliance and performance (Kristeva et al., 2007; Witte et al., 2007; van Wijk et al., 2012). Beta-CMC has been shown to be incremented by dopaminergic medication in PD (Salenius et al., 2002) while the effects of DBS are inconsistent (Airaksinen et al., 2015). Studies with small cohorts showed that beta-CMC may also be increased by DBS (Marsden et al., 2001; Park et al., 2009), however, a recent MEG study with a larger cohort showed that DBS variedly affects beta-CMC and does not seem to lead to a group effect of treatment (Airaksinen et al., 2015).

Low-gamma power, on the other hand, has been shown to emanate from the motor cortex, to be somatotopically specific (Crone et al., 1998a), and is known to facilitate movement (Brown et al., 2001; Kühn et al., 2006; Cheyne and Ferrari, 2013) as well as to scale with the movement amplitudes (Muthukumaraswamy, 2010). The absence of effects on the beta power has been shown with ECoG and MEG studies where the beta power is not modulated by DBS (Pollok et al., 2012; de Hemptinne et al., 2015).

STN-DBS may influence motor cortical oscillations, especially low-gamma oscillations, by the antidromic activation of the hyperdirect pathway between M1 and STN (Nambu et al., 2002; Gradinaru et al., 2009; Nambu and Tachibana, 2014) . Such a pathway has now also been shown in humans (Fernandez-Miranda et al., 2012; Petersen et al., 2017). Dopamine effects, on the other hand, could be driven via nigro-striatal input going into the basal ganglia structures at the sub-cortical level while also affecting the oscillatory dynamics between the inhibitory interneurons and the excitatory pyramidal neurons at the cortical level and thus affecting the corticospinal drive. We suspect that the increase during dopaminergic medication may indicate a compensatory mechanism to augment the recalibration process and error reduction during motor action so as to facilitate a global improvement in motor behavior.

It could have been interesting to look at time-resolved changes in coherence and spectral power (Kilner et al., 2000; Kühn et al., 2008) for possible effects on various phases of movement. However, since our task was self-paced so as to better capture potential timing issues and bradykinesia setting in and since it was an unconstrained hand-gripping motion, it was not possible to analyze the separate phases of motion involved. Another aspect that could have been interesting to examine in more detail is the potentially transient nature of the spectral power. Recently, it has been shown that the cortical beta spectral power from primary somatosensory area averaged over an epoch is, in fact, a superposition of shorter beta events (Shin et al., pre-print). A higher rate and amplitude of such beta events may impair processing (Shin et al., pre-print). These results have been shown in both mice and humans, and it would be interesting to investigate if motor symptoms, like the setting in of bradykinesia, can be aptly characterized with such transient events.

4.4 Study III

How do treatments modulate oscillatory dynamics in PD at rest?

Our results in Study II showed that movement-related gamma oscillations were boosted by DBS, and given the impact of cortical oscillations on BG circuitry, it was pertinent to us to investigate the oscillatory dynamics during rest, as well. The improvements of PD motor symptoms brought about by STN-DBS and dopaminergic medication are accompanied by suppression of the pathological beta activity in STN and the BG circuitry (Brown et al., 2001; Cassidy et al., 2002;

Kühn et al., 2006, 2008). Apart from suppression of beta activity, the treatments also lead to an increase in gamma synchronization in the BG network (Brown et al., 2001; Cassidy et al., 2002; Kühn et al., 2006, 2008). The motor cortical gamma band activity, on the other hand, is elevated in the Parkinsonian state and hence might indicate functional differences in the oscillatory activity in STN and at cortex (Brown et al., 2001; Androulidakis et al., 2007). With these aspects in mind, the third study focused on oscillatory dynamics at rest.

Of the eighteen patients who underwent the MEG paradigm, one patient dropped out mid-way due to motor symptoms in the untreated state and one other patient was excluded from this analysis due to technical difficulties with the dataset. The cohort details can be found in Appendix-C Tab. 1. Detailed description of the methods is provided in Appendix-C- Methods section. We computed spectral power in two bands of interest drawing on the results from Study II, namely beta (13-30 Hz) and low-gamma power (31-45 Hz) in the sensorimotor area.

We showed that DBS increased the cortical sensorimotor low-gamma power in both hemispheres during rest and that neither treatment had any effects on beta resting state power. The observed increase in gamma power is in line with previous reports (Cao et al., 2017), and the absence of effect of treatments on beta resting state power also conforms to the previous reports from both ECoG and MEG studies (Pollok et al., 2012; de Hemptinne et al., 2015; Cao et al., 2017).

The few previous reports on resting state MEG in PD with DBS contain substantial methodological confounds that we attempted to address in our experimental paradigm. Firstly, Cao et al. (2015, 2017) used only magnetometers in their analyses, which measure a bipolar distribution of the underlying source (Hämäläinen et al., 1993). Analyzing magnetometer data in each of a set of very broadly defined regions (Elekta's default regions) separately in sensor space misses the nature of the particular topographical distributions of data from magnetometers (Hämäläinen et al., 1993). Secondly, Cao et al. (2015, 2017) only had a time gap of 10 minutes between switching off the stimulator and performing the DBS OFF measurement. By running a longer protocol with nearly 2 hours of washout measurements, we were able to capture the potential changes and stabilities in the oscillatory dynamics (and motor symptoms) over the washout phase.

Studies using other neuroimaging modalities (mainly PET and fMRI) have shown hemodynamic as well as metabolic changes in various areas in the cortex due to STN-DBS (Hershey et al., 2003;

Asanuma et al., 2006; Geday et al., 2009; Min et al., 2012; Knight et al., 2015) of which one of the studies specifically showed mesial sensorimotor areas influenced by DBS (Asanuma et al., 2006). Hence, our observed increase in low-gamma power with a topographical distribution over sensorimotor areas is in line with these imaging reports, though the exact functional nature of this effect is still under question.

As already explained in the Background chapter, gamma oscillations are known to reflect activation of the local neuronal population (Manning et al., 2009). Cortical sensorimotor gamma is elevated in PD patients compared to essential tremor and dystonia patients during rest (Crowell et al., 2012; Rowland et al., 2015), hinting at the possibility that the cortical neuronal populations are held at an active state to compensate for the antikinetic beta synchrony in BG (Rowland et al., 2015). In a recent study, it was shown that STN-DBS specifically suppressed the pathological beta synchrony between STN and mesial sensorimotor areas rather than lateral areas (Oswal et al., 2016), and this effect may be driven through the hyperdirect pathway (Gradinaru et al., 2009). We therefore speculate that our observed effect of DBS on low-gamma could be driven via the hyperdirect pathway through the cortico-subcortical functional coupling between the mesial sensorimotor areas and STN.

Recent publications on the shape of the waveforms have shown that prominent oscillations such as those in the beta-band, might be somewhat non-sinusoidal in PD (Gerber et al., 2016; Cole and Voytek, 2017; Cole et al., 2017). It has also been shown in PD patients that beta waveforms are sharper at the troughs than at the peaks in untreated states while DBS restores the smoothness of the beta waveform, i.e., makes it more sinusoidal (Cole and Voytek, 2017; Cole et al., 2017). These carry functional implications as the beta power itself might not undergo change, but the beta waveform that reflects the state of the underlying neuronal generators might be affected by treatments. This is a promising avenue for future investigations.

4.5 General comments

4.5.1 Potential confounds

DBS artefact

DBS artefacts and their subharmonics are a concern when looking for oscillatory components in MEG (and EEG) data, especially in the gamma range (>30 Hz). It has been shown that Maxfilter

can suppress these artefacts to a large extent (Airaksinen et al., 2011, 2013). In Study II and III, we investigated low-gamma power (31-45 Hz) without any clearly defined baseline, unlike in Study I where the median nerve stimulation provided clear events with an implicit baseline preceding immediately before the stimulation onset. So, in an attempt to factor out the possible contributions from DBS artefacts, we took several measures. Firstly, we also did a 'sham' analysis on power in the occipital area. Neither Study II nor III showed any effects of treatments in the occipital SOI in comparison to the observed effects over right and left sensorimotor regions. In addition to this, we also correlated the DBS voltages in each of the hemispheres with the corresponding low-gamma power during DBS. If artefacts from the electrical stimulation would directly influence the gamma estimates, we would expect the observed gamma power to correlate with the stimulation amplitude (i.e., the DBS voltages). This was not the case with any of the low-gamma summary values (or any other power values) obtained in Study II and III. Thus, we feel confident that our observed effects of DBS on movement-related and resting state oscillatory dynamics are not due to confounding artefacts from the electrical stimulation.

Dopamine agonists

One potential confound for our observed lack of effects of treatments on N20m amplitudes, high-gamma augmentations and beta suppression in Study I is that most patients were medicated with dopamine agonists with long half-lives. And since various dopaminergic medications are known to affect cortical excitability differently (Ziemann et al., 1997; Strafella et al., 2000), differences in agonist doses between patients could potentially have contributed with further heterogeneity in our observations whereby potential consistencies across participants would be lost due to the increased heterogeneity. However, all the patients' dopamine agonists had half-lives ranging from 6-24 hours and since the patients had not taken any dopamine agonists for at least 24 hours before the MEG recording, we assess that their effects on the patients' cortical excitability at the time of the recordings would be negligible.

4.5.2 Experimental design

Control group

As already stated, the two main purposes of the controls in the present study were to give us an estimate of "healthy/normal" processing and to help us address potential confounds of the experimental protocol such as fatigue and repetition/habituation effects. Our aim was not to

compare controls and PD patients directly, but rather to test for effects of treatments/conditions in each group separately and thereby use the healthy controls as a quality control for any potential effects found in the PD group. The strength of our experimental paradigm is the repeated measures design (i.e., the same patients being recorded on/off stimulation and on/off dopaminergic medication within one day), which relies on the self-referential nature of the data. But since we could not randomize the order of the treatment conditions (because the washout time of levodopa and DBS are not easily comparable), we needed a control group to go through the same experimental paradigm without treatment interventions in order to control for sheer effects of time and repetition. In all our statistical tests, we analyzed the two groups (PD and controls) separately. We did so in order to avoid random influences of the control group in our analysis of the effects of Condition within the PD group.

Another potential option for a control group would have been to include a PD group without DBS. We did not opt for this option due to an evaluation of patient well-being vs. experimental outcome value. PD patients without DBS would have had to endure a full night and half a day off dopaminergic medication, which would have been a challenging task for these patients (matched on disease progression with the DBS cohort), compared to which patients in our cohort had to endure ~2 hours in the completely untreated condition under the supervision of a movement disorders specialist. One alternative to complete withdrawal overnight for PD patients without DBS would have been to keep the patients under subcutaneous medication (apomorphine) (Hirschmann et al., 2011, 2013) for 12-24 hours prior to the experiment, but this would still have been a drastic intervention in the patients' well-being when they would "merely" serve as control patients.

Measuring the best treated state

One could also consider the option of performing one more MEG measurement block with both DBS and dopaminergic medication at the very end of the experiment. However, our main focus was to explore the potentially different effects of dopaminergic medication and DBS on cortical sensory and motor processing. We therefore intended to record the patients in "pure" DBS/medicated states, meaning that the patients were practically on only one treatment modality at a time. We found this to be a major improvement over previous studies such as Airaksinen et al. (2011, 2015) where the patients were kept on dopaminergic medication during the DBS recordings, which makes it considerably more difficult to discern the DBS-specific effects.

Moreover, the potential interactions between DBS and dopaminergic medication is not well described, and we therefore predicted that the inclusion of a DBS ON/MED ON condition in the design would further complicate, rather than clarify, our understanding of the results. Furthermore, the complete paradigm from the time the patient arrived for the initial assessments to its finish was around 6 hours. In terms of patient well-being, we found this to be the maximum extent endurable.

Extent of washout measurements

Regarding the temporal extent of the washout period, we also had to weigh patient well-being against experimental outcome value. It has previously been shown that the washout of the DBS effect and the related deterioration of motor symptoms occur to almost full extent within 3-4 hours of turning off the stimulator with axial signs returning the slowest (Temperli et al., 2003). However, from Temperli et al. (2003) it was also evident that tremor, bradykinesia and rigidity returned almost fully within 1-2 hours. From our preliminary experience with testing DBS-treated PD patients off medication and with their stimulators turned off, we knew that ~2 hours of complete off time were tolerated reasonably well by most patients. Bearing in mind that the patients also had to go through five MEG measurements during this washout period, we therefore opted for a maximum washout period of ~2 hours. Our motivation for recording several sessions during the washout period instead of just one after ~2 hours was to investigate whether we could observe a similar washout effect on our neurophysiological measures of interest to those observed for the motor symptoms as quantified by UPDRS-III.

Chapter - 5

General discussion

The previous chapter summarized and discussed the three individual studies on which this thesis is based. This has paved the way for a general discussion based on three themes. Firstly, all three studies point at a differentiation in the mechanisms of the treatments based on differentiations of their effects on the employed measures. Secondly, the effects of treatments on oscillatory dynamics are different at the cortical and subcortical structures and they work through more sophisticated functional mechanisms that necessitates measures other than merely spectral power. Thirdly, results from the effects of treatments on somatosensory processing at the cortical level highlights the necessity to look beyond the motor system in order to fully understand the effects and mechanisms of the PD treatments. Finally, a few perspectives on future studies are presented.

5.1 Differentiated mechanisms of treatments

Results from all three studies, using three different task settings, have shown that the two PD treatments (DBS and dopaminergic medication) affect the oscillatory dynamics at the cortical level differently. It is pertinent to also note that both treatments led to similar improvements in motor symptoms. Taken together, these results strongly suggest that the treatments work through differentiated mechanisms to improve motor symptoms, as well as sensorimotor cortical processing more generally.

The following sub-sections discuss the probable mechanisms in a more general context than in the previous chapter (Original PhD contributions) and in the appended manuscripts (Appendix A, B and C).

5.1.2 Effect-mechanisms of dopaminergic medication

The dopaminergic projection system has multiple pathways projecting to several sub-cortical and cortical areas (Albanese et al., 1986) as presented in Chapter 2. Of most interest are the mesocortico-limbic and the nigrostriatal pathways, which project from the ventral tegmental area (VTA) to the prefrontal cortical areas and from the SNc to the striatum (especially the caudate and putamen) (Albanese et al., 1986; Scarr et al., 2013). Apart from the projection systems, dopamine is known to act on interactions between local neural circuits, such as interneuron circuitry, which in turn affects the activity of pyramidal neuron circuitry (Gao and Goldman-Rakic, 2003; Gao et al., 2003). It has been shown in primates and in rats that motor cortex has dopaminergic innervation (Gaspar et al., 1991; Hosp et al., 2011; Vitrac et al., 2014) and such dopaminergic projections can control pyramidal neuron activity in the cortex (Vitrac et al., 2014). It is thus not clear whether the beneficial effect of dopaminergic medication on PD motor symptoms arise entirely from its sub-cortical impact or also from its influence at the cortical level (Koller and Rueda, 1998).

In our studies, we observed two effects of dopaminergic medication. Study I showed an effect of dopaminergic medication on the oscillatory dynamics of early cortical somatosensory processing while Study II showed an effect on the connectivity between motor cortex and the forearm muscle (CMC). The more plausible mechanism for the effect on somatosensory processing at the cortical level is through the nigrostriatal system, i.e., at the striatum (Surmeier et al., 2007), which is known to play a role in sensory processing (Ramanathan et al., 2002; Juri et al., 2010). In this context, it is interesting to note that it has been shown in PD patients that their degree of striatal dopamine loss correlated with the worsening of their sensory discrimination ability (Lyoo et al., 2012), pointing to an effect of striatal dopamine on sensory function, and by extension possibly also sensory processing.

In contrast to this, the dopaminergic effect on CMC is most likely through the systemic cortical influence of dopamine, and thus through its effects on the direct and indirect BG-thalamo-cortical network (Surmeier et al., 2007; Nambu and Tachibana, 2014). However, as stated above, dopamine can control cortical pyramidal activity (Vitrac et al., 2014) through its cortical projections which may also have played a role in the modulation of CMC. Taken together, our

results thus suggest that dopaminergic medication may affect sensory and motor related processing at both the cortical and sub-cortical levels.

5.1.3 Effect-mechanisms of DBS

There is substantial work on the mechanism of DBS and the possible neural networks and circuits that DBS influences using animal studies (Chomiak and Hu, 2007; Li et al., 2007; Gradinaru et al., 2009) as well as intra-operative and post-operative human studies (Airaksinen et al., 2011; Hirschmann et al., 2011, 2013; Walker et al., 2012; de Hemptinne et al., 2015).

GPi-DBS decreases activity in thalamic structures in line with excitation of inhibitory pallido-thalamic connections (Anderson et al., 2003), which is somewhat paralleled in STN-DBS which also seems to increase GPi activity consistent with excitatory STN-GPi projections (Hashimoto et al., 2003; Brown et al., 2004). However, recent focus has moved beyond the internal structure of the BG since the demonstration of a causal relationship between stimulation of neurons in the deep layers of the motor cortex and alleviation of motor symptoms (Gradinaru et al., 2009). In support of this, cortical effects of DBS have been shown through ECoG and MEG studies (including our own studies), and other studies have also shown that DBS affects pathological cortical synchronization (Pollok et al., 2012, 2013; de Hemptinne et al., 2015) and has been posited previously.

Experimental and computational studies have proposed various models of DBS mechanisms. It has been suggested that while an orthodromic drive may suppress the propagation of pathological oscillations in the BG-cortical loop (Kang and Lowery, 2014), antidromic cortical activation may rectify the pathological cortical activity (Gradinaru et al., 2009; Walker et al., 2012; de Hemptinne et al., 2015). Computationally, STN-DBS has also been shown to affect the relay fidelity of thalamo-cortical relay cells by correcting the pathologically irregular bursts of inhibitory transmission from GPi (which compromise the effectiveness of the relay of excitatory inputs in thalamus), supposedly through shifting GPi output to a tonic high-frequency inhibitory state (Rubin and Terman, 2004; Guo et al., 2008). It is therefore plausible that DBS works through multiple mechanisms (both orthodromic and antidromic), not restricted to the target nucleus (STN) and the first-order projections from these nuclei (GPi/GPe) (Montgomery and Gale, 2008), and hence, its mechanisms may not be restricted to the correction of pathological activity in the motor system alone, nor to the rectification of internal BG activity alone.

In the studies in this thesis, we have shown effects of DBS on movement-related cortical oscillations (Study II) and at rest (Study III), but interestingly not on early somatosensory processing (Study I). It has been shown in animal models that there are projections from sensory cortical areas to the STN (Canteras et al., 1988, 1990; Degos et al., 2008; Lambert et al., 2012), and any antidromic propagation of the electrical stimulation would most likely have affected somatosensory areas to some extent, but it did not (Study I). On the other hand, DBS did have an effect on the cortical oscillations in Studies II and III. Considering these results together, it is possible that DBS works not only antidromically via the hyperdirect pathway, but also orthodromically on the BG-thalamo-cortical network. Moreover, the mechanisms may differ based on the cortical areas and sensorimotor functions involved.

5.2 Pathological oscillations and their alleviation

The initial publications showing pathological beta-synchronization in PD led to a spurt in studies unravelling changes in spectral power at both cortical and sub-cortical structures in PD and the effects of treatments on them. Among other findings, this led to findings of treatments affecting spectral power differently in cortical and sub-cortical structures. Our studies have reinforced this notion by showing no modulation of beta power at the cortical level due to treatments, which has otherwise been consistently shown to be modulated by both DBS and dopaminergic medication at the subcortical level.

Recent work with ECoG measurements have gone beyond the more simple metrics of spectral power and shown that the functional coupling (PAC) within motor cortex is pathological in nature in PD, whereas the spectral power in the beta or the broadband gamma band (50-200 Hz) is not affected. It was also shown that the abnormal PAC is suppressed with DBS (de Hemptinne et al., 2013, 2015). These studies (de Hemptinne et al., 2013, 2015) suggest that more sophisticated metrics can add knowledge which may not be possible to see using only spectral power.

And as we showed in Study II where dopaminergic medication solely affected the beta-CMC and not the spectral components and DBS affected spectral power and not beta-CMC, we thereby observed effects of both treatments on movement-related cortical activity which would not have been possible using spectral measures alone. These results suggested that DBS modulating gamma band power (low-gamma) affected the underlying spiking activity (Manning et al., 2009), whereas dopaminergic medication affected the communication between cortex and periphery

(Baker et al., 1997; Salenius et al., 1997; Kilner et al., 2000; van Wijk et al., 2012). Thus observing effects of both treatments along with the equivalent improvements in motor symptoms, we could surmise that the effect mechanisms of the two treatments may be brought about by different functional pathways.

5.3 Beyond the motor system

The results from Study I showed that while DBS does not affect early cortical somatosensory processing, dopaminergic medication does. This result has opened the door for exploring effects of treatments on sensory processing using electrophysiology, especially higher order sensory deficits such as sensory discrimination.

The literature suggests that somatosensory discrimination is degraded with DBS, but improved by dopaminergic medication (Artieda et al., 1992; Lee et al., 2005; Conte et al., 2010; Lyoo et al., 2012). On the other hand, somatosensory detection do not seem to be affected by either treatment (Gierthmühlen et al., 2010; Spielberger et al., 2011; Ciampi De Andrade et al., 2012). This apparent discrepancy in effects of treatment is likely due to the involvement of different cortical and subcortical structures in sensory discrimination tasks compared to sensory detection tasks. It has been shown in both animal models and humans that discrimination tasks involves higher order areas such as posterior parietal cortex, striatal and basal ganglia structures, pre-supplementary motor area, in addition to the structures also involved in sensory detection, namely post-central gyrus and inferior parietal lobule (Lacruz et al., 1991; Artieda et al., 1992; Pastor et al., 2004). In Study I, we looked at the early cortical somatosensory processing after median nerve stimulation, without any behavioral correlates. Such a passive experimental task is most likely more similar to a detection task. And thus, we may speculate that investigating higher order sensory function, such as discrimination, using electrophysiological measures may lead to a different pattern of effects of treatments and thus further our understanding of the effect mechanisms of both treatments.

BG circuitry has also been shown to play a role in sensorimotor integration (Ramanathan et al., 2002; Abbruzzese and Berardelli, 2003; Konczak et al., 2009) and it is noteworthy that both DBS and dopaminergic medication have effects on sensorimotor function (Abbruzzese and Berardelli, 2003; Conte et al., 2013; Wagle Shukla et al., 2013; Aman et al., 2014). This facet of sensorimotor integration, beyond merely motor behavior, has not yet been adequately addressed in

electrophysiological investigations and may also expand the current understanding of the mechanistic effects of the treatments when properly investigated.

5.4 Perspectives

Fortunately, PD and the effect mechanisms of DBS and dopaminergic medication are already being addressed from several methodological vantage points (including MEG, LFPs, ECoG, and PET). Clinical studies have provided a broad understanding of the disease and the effects of treatments on motor, sensory, cognitive and psychiatric symptoms, while experimental work using invasive and non-invasive electrophysiology, in particular, has provided valuable insights into the pathological neural network of PD and the mechanisms underlying the treatments' effects on this. However, it is still difficult to fully interpret many of the obtained measures due to the complexity of the underlying neural sources. In this respect, multimodal approaches combining MEG (or EEG) with imaging of the dopamine or GABA neurotransmitter systems (using PET) may help improve our interpretation of the observed changes in oscillatory dynamics (Muthukumaraswamy et al., 2013; Kujala et al., 2015). While we found in our studies that DBS and medication affected cortical gamma oscillations, their functional and behavioral implications are not easily discernable. Hence, combining MEG experimentation similar to the one adopted in this thesis with behavioral measures as well as imaging techniques mapping out relevant details on relevant neuroreceptors, such as GABA receptor density (Kujala et al., 2015), may improve the neurophysiological basis for interpreting our current results, and thus our understanding of the impact of treatments on particular neuronal elements, and their relation to behavioral effects and the possible underlying mechanisms.

Communication between brain regions forms an important component in neural processing, and hence, cortico-cortical and cortico-subcortical coupling during sensory and movement-related tasks may also provide interesting information on the treatment effects. While cortico-cortical coupling can be obtained with non-invasive measures, the more informative details from cortico-subcortical coupling needs invasive procedures such as LFP recordings from externalized DBS leads. However, invasive measurements such as ECoG and LFP recordings from intra-operative procedures and externalized leads are accompanied by considerable ethical issues. Newer technology with the ability to wirelessly transfer data outside from the implanted pulse generator may improve the access to recordings from deeper structures (Quinn et al., 2015), which may thus

enable recording from deeper brain structures without externalization of leads. Wireless transmission of deep brain data along with mobile EEG setups can enable experiments where PD patients are mobile, compared to the relatively immobile setup in our studies with patients lying in supine position. The mobility of PD patients opens up for interesting possibilities of studying cortico-subcortical oscillatory dynamics during disease symptoms such as dyskinesia or freezing of gait and during dynamic experimentation settings like biking (Gratkowski et al., 2016; Swann et al., 2016).

Another facet of DBS technology that is undergoing a sea-change with the advent of steerable stimulation, is the structural makeup of the stimulating electrodes (Hariz, 2014; Pollo et al., 2014; Timmermann et al., 2015; Steigerwald et al., 2016). For now, steerable (or directional) stimulation has been shown to improve the therapeutic window without much impact on the motor outcome itself (Pollo et al., 2014; Steigerwald et al., 2016). Further improvement of the motor outcomes are most likely dependent upon developing realistic means for modeling the volume of tissue activated (Butson et al., 2007; Butson and McIntyre, 2008) as well as a better understanding of the effect and mechanisms of DBS.

It has been shown that the region stimulated in the target nucleus determines the outcome (Zaidel et al., 2010), and there is also suggestive evidence in support of sub-optimal lead placement causing side effects such as verbal fluency (Højlund et al., 2017). It has been recently shown that combining information on spectral activity and anatomical connectivity can aid in specifying the optimal site for stimulation (Accolla et al., 2016; Horn et al., 2017). The combination of anatomical connectivity and spectral signatures can possibly be extended using steerable stimulation to activate even more specific areas in the target nucleus, which may lead to optimization of the therapy and even further increases in the therapeutic window. In addition to this, the steerable DBS system can also be used to target other areas in the STN, such as those that are known to have stronger connectivity with prefrontal areas in order to study the effect of DBS on executive functions (Frank et al., 2007; Jahanshahi, 2013), thereby enhancing our understanding of the mechanisms underlying the effects of DBS on cognitive functions, as well as other non-motor functions.

Moreover, replications of the results reported within this thesis are necessarily needed in order to fully understand the extents of their generalizability and thereby increment and solidify the

current understanding of the disease and the effect mechanisms of the treatments as they have been laid out in the preceding chapters.

And when the closely controlled experimentation used in this thesis paves the way for an integration of basic research findings into a more holistic and systemic view of both the disease and the mechanisms of the available treatments, management of PD symptoms should improve and may even enable patient- and symptom-specific disease management paradigms.

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