Basic mechanisms of DBS for Parkinson’s disease: computational and experimental studies on neural dynamics
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Chapter 7

General Discussion
Deep Brain Stimulation: fad, fashion or function

Deep Brain Stimulation (DBS) has become an accepted therapy of last resort for Parkinson's disease (Benabid et al. 1996; Benabid et al. 1991; Benabid et al. 2005; Deuschl et al. 2006; Krack et al. 2003; Kumar et al. 1998; Obeso et al. 2001; Rodriguez-Oroz et al. 2005). The acceptance of DBS for the management of Parkinson’s disease motor symptoms is based on its success rate and contrasts sharply with ones understanding of the pathophysiology underlying the disease state. Implanted electrodes allowed researchers to collect extensive information from animal models (Hashimoto et al. 2003; Plenz and Kital 1999; Sharott et al. 2005; Sharott et al. 2004) and humans (Dostrovsky et al. 2000; Hammond et al. 2007; Kuhn et al. 2004; Moro et al. 2002; Sharott et al. 2005). Identification of possible nuclei which could be targeted for the management of Parkinson’s disease motor symptoms is ongoing together with establishment of reliable patient selection criteria. Success of DBS for Parkinson’s disease also tempted clinicians to apply DBS for the treatment and management of many other difficult to treat brain pathologies such as obsessive compulsive disorder, depression, epilepsy, schizophrenia, and so forth. (Alexander and Crutcher 1990; Alexander et al. 1986; Benabid et al. 1996; Benabid et al. 1991; Benabid et al. 2005; Delong 1990; Deuschl et al. 2006; Krack et al. 2003; Kumar et al. 1998; Obeso et al. 2001; Rodriguez-Oroz et al. 2005).

Parkinson’s disease

DBS parameters used for the management of Parkinson’s disease motor symptoms have been derived empirically (Benabid et al. 1991; Moro et al. 2002). Experiments have shown that high frequency stimulation of the subthalamic nucleus (STN) or the globus pallidus internum (GPI) leads to a reduction in firing rates at the stimulated nucleus (Benazzouz et al. 2000; Boraud et al. 1996). Computational studies indicate that suppression of activity at the stimulated nucleus is dependent on the balance between hyperpolarizing and depolarizing effects of the electric field on the dendrites and activation of afferent GABAergic fibers impinging on the stimulated nucleus (McIntyre et al. 2004). These studies have also shown that passing and projecting myelinated fibers can be activated by DBS resulting in alterations in down-stream
activity patterns (Holsheimer et al. 2000; McIntyre et al. 2004). Alterations in down-stream activity patterns have also been experimentally recorded (Hashimoto et al. 2003). Specifically in the context of Parkinson’s disease, target nucleus for DBS is either the STN or the GPi. During STN-DBS, activity patterns in the GPi would be regularized as a result of high frequency activation of glutamatergic projections from the STN (Hashimoto et al. 2003; Miocinovic et al. 2006). During GPi-DBS however, phasic inhibition of the thalamocortical relay neurons would be replaced with constant inhibition from the GPi (Johnson and McIntyre 2008). Overall, it is hypothesized that high frequency stimulation has an effect on the pathological synchronization of the Basal Ganglia nuclei in the theta and beta frequency bands and when applied to key nuclei in the basal ganglia-thalamocortical loop, prevents relay of these pathological oscillations further down the loop (Brown 2003). Generalization of this explanation for the effects of DBS to other brain circuits is most likely an oversimplification that first needs thorough experimental and computational support.

Dystonia

Use of DBS was extended to the treatment of primary dystonia (Coubes et al. 2004; Kupsch et al. 2006; Vidailhet et al. 2005). Comparable to Parkinson’s disease, dystonia is also predominantly based on alterations observed in the basal ganglia-thalamocortical circuit (Wichmann and DeLong 2006). Dystonia is associated with reduced activity levels in the GPi both at rest and during movement (Starr et al. 2005). Similar to Parkinson’s disease, activity patterns in the Basal Ganglia nuclei are altered during dystonia and increased levels of synchrony have been reported, especially in the theta frequency band (Silberstein et al. 2003). High frequency stimulation applied to the GPi leads to significant clinical improvement and suppression of dystonic symptoms (Coubes et al. 2004; Kupsch et al. 2006; Vidailhet et al. 2005). In comparison with Parkinson’s disease, the efficacy of high frequency stimulation for dystonia has been seen as paradoxical on account of the differences observed in the firing rates in the Basal Ganglia: i.e. reduction in the GPi firing rate during dystonia in contrast to hyperactivity of the GPi during Parkinson’s disease. One explanation for this
seemingly paradoxical efficacy could be rooted in regularization of the oscillatory activity patterns observed during dystonia in the basal ganglia-thalamocortical circuit by high frequency stimulation; comparable to the hypothesized mechanism underlying the efficacy of DBS for Parkinson’s disease. Similar to lesioning of the GPi for the treatment of dystonia, suppression of symptoms as a result of DBS take up to six months to establish (Benabid et al. 2005; Wichmann and DeLong 2006). This indicates that unlike Parkinson’s disease, where motor symptom suppression occurs immediately as a result of DBS or lesioning, suppression of dystonic symptoms likely involves slow alterations to certain network dynamics (Benabid et al. 2005).

Obsessive Compulsive Disorder and Tourette’s Syndrome

DBS has also been used in the treatment of disorders such as obsessive compulsive disorder and the Tourette’s syndrome (Ackermans et al. 2006; Ackermans et al. 2008; Greenberg et al. 2006; Houeto et al. 2005; Mink et al. 2006; Nuttin et al. 2003a; Nuttin et al. 2003b). Both obsessive compulsive disorder and the Tourette’s syndrome are correlated with dysfunction of the basal ganglia-thalamocortical loop (Wichmann and DeLong 2006). Limited trials made in this field have shown promising results in alleviation of disease symptoms (Ackermans et al. 2006; Ackermans et al. 2008; Greenberg et al. 2006; Houeto et al. 2005; Mink et al. 2006; Nuttin et al. 2003a; Nuttin et al. 2003b). Obsessive compulsive disorder is believed to be linked to a dysfunction of the non-motor portions of the basal ganglia-thalamocortical loop; more specifically hyper-activity of the frontal corticostriatal projection (Delong 1990; DeLong and Wichmann 2007). A possible target nucleus emerging from trials for the treatment of the obsessive compulsive disorder is the ventral striatum; high frequency stimulation of this nucleus aims at modulating and reducing the frontal corticostriatal hyperactivity (Greenberg et al. 2006; Nuttin et al. 2003a; Nuttin et al. 2003b). The Tourette’s syndrome has both cognitive and motor features and therefore been linked to dysfunction of both the frontal cortex and the motor basal ganglia-thalamocortical circuit (DeLong and Wichmann 2007; Peterson et al. 1998; Wichmann and DeLong 2006; Ziemann et al. 1997). It is hypothesized that the motor basal ganglia-
thalamocortical circuit is impaired during the Tourette’s syndrome giving rise to inability to perform action selection and to suppress movements; resulting in characteristic tics (Ackermans et al. 2006; Ackermans et al. 2008; DeLong and Wichmann 2007; Wichmann and DeLong 2006). The efficacy of DBS is limited in the treatment of the Tourette’s syndrome (Wichmann and DeLong 2006). This could be a direct consequence of the involvement of both the motor and non-motor circuits in the manifestation of the Tourette’s syndrome. Our lack of understanding of the complete circuitry that underlies the Tourette’s syndrome makes identification of a successful target region difficult and it may well require stimulation of multiple regions to successfully treat the symptoms. For the management of the Tourette’s syndrome, possible targets include the GPi and ventral thalamus (Ackermans et al. 2006; Ackermans et al. 2008; Houeto et al. 2005; Mink et al. 2006; Visser-Vandewalle et al. 2003).

Major Depression

Currently DBS is also experimentally applied for the treatment of major depression (Gutman et al. 2009; Johansen-Berg et al. 2008; Mayberg et al. 1999; Mayberg et al. 2005). In recent years imaging techniques such as positron emission tomography (PET) and diffusion tensor imaging (DTI) have been extensively utilized in identification of brain regions involved in the manifestation of major depression and in determination of the connectivity levels between these regions (Gutman et al. 2009; Johansen-Berg et al. 2008). Several nuclei have been used as target nuclei for DBS; some of which were based on the side-effects observed during STN-DBS, used for the management of Parkinson’s disease symptoms (Benabid et al. 2005). During STN-DBS depending on the electrode location and the stimulation parameters (most specifically pulse amplitude) adverse side-effects including mood changes are observed (Funkiewiez et al. 2004). Based on imaging studies indicating over activity of the subgenual cingulate region area 25 during major depression; DBS has been applied to this region with success in some patients (Mayberg et al. 2005). Recent imaging studies have also highlighted that the subgenual cingulate region area 25 is strongly connected to various brain regions, implicated in major depression (Gutman et al. 2009;
Johansen-Berg et al. 2008). There are several difficulties involved with the application of DBS for major depression. Firstly, major depression is a heterogeneous psychiatric disorder making patient selection for DBS challenging. Additionally, limited knowledge about the mechanisms underlying depression, lack of animal models and agreement upon the complete circuitry implicated in the manifestation of major depression together with wide spread functionality of the nuclei already implicated in major depression (i.e. hypothalamus) pose significant challenges (Nestler et al. 2002).

Epilepsy

Last but not least, currently trials are being conducted for application of DBS for the management of epilepsy (Hodaie et al. 2002; Nagel and Najm 2009; Vercueil et al. 1998; Vonck et al. 2002). Epileptic seizures are episodic and epileptic brain switches between a “normal” state and epileptic activity (Lopes da Silva et al. 2003; Nagel and Najm 2009). Treatment techniques utilized in the management of epilepsy aims at predicting/detecting onset of the epileptic activity and suppressing it or extending the duration the brain remains in the “normal” state by continuously modulating the networks involved in generation of epileptic seizures (Nagel and Najm 2009). There are two main streams of research regarding application of DBS: 1) closed loop stimulation in conjunction with seizure detection and 2) open loop stimulation (i.e. continuous stimulation) (Chabardes et al. 2002; Cooper et al. 1976; Cooper and Upton 1978; Fountas et al. 2005; Handforth et al. 2006; Kossoff et al. 2004; Osorio et al. 2005; Osorio et al. 2007; Velasco et al. 2007; Velasco et al. 2000; Velasco et al. 1987; Velasco et al. 1995). DBS is used to reduce the likelihood of a seizure together with reducing the severity of the seizures (Nagel and Najm 2009). Several nuclei have been tried as target nuclei such as the cerebellum, substantia nigra, caudate nucleus, STN and anterior thalamic nucleus (Chabardes et al. 2002; Cooper et al. 1976; Cooper and Upton 1978; Fountas et al. 2005; Handforth et al. 2006; Kossoff et al. 2004; Osorio et al. 2005; Osorio et al. 2007; Velasco et al. 2007; Velasco et al. 2000; Velasco et al. 1987; Velasco et al. 1995). Both animal and human studies have shown mixed results when DBS has been applied to these nuclei (Chabardes et al. 2002; Cooper et al. 1976; Cooper and Upton 1978;
Several points need to be addressed regarding application of DBS for epilepsy such as target nucleus, stimulation parameters and reliable patient selection criteria (Nagel and Najm 2009).

As use of DBS is becoming more and more accepted, several clues are emerging regarding the mechanism of action of DBS (McIntyre and Hahn 2010). At the stimulated nucleus, effect of DBS is dependent on the stimulation parameters used, 3D morphology of the neurons, and the afferent fibers impinging on the stimulated nucleus (Johnson and McIntyre 2008; McIntyre and Hahn 2010; McIntyre et al. 2004; Miocinovic et al. 2006). Modulation of the average firing rate at the stimulated nucleus relies on the combined hyperpolarizing and depolarizing effect of the electric field on the dendrites of the neurons, together with the effect of activated glutamatergic and GABAergic fibers projecting on to the stimulated nucleus (Johnson and McIntyre 2008; McIntyre and Hahn 2010; McIntyre et al. 2004; Miocinovic et al. 2006). Activation of passing fibers is dependent on the orientation of the fibers within the electric field together with the dimensions of the passing fibers (Holsheimer et al. 2000; Johnson and McIntyre 2008; McIntyre and Hahn 2010; McIntyre et al. 2004; Miocinovic et al. 2006). The overall effect that one wishes to achieve with DBS is also dependent on which passing fibers are activated and whether these passing fibers are in turn impinging on the desired downstream nuclei (Hashimoto et al. 2003; Johnson and McIntyre 2008; McIntyre and Hahn 2010; McIntyre et al. 2004; Miocinovic et al. 2006). Therefore, details of the underlying neural circuitry are highly relevant for the overall effect of DBS on a micro to macro level.

In contrast to pharmacological alternatives of DBS for disease management which have widespread effect on the brain, DBS suppresses disease symptoms through localized modulation of the neural circuitry. This property of DBS puts further emphasis on understanding the circuitry underlying pathologies since efficacy of DBS is closely tied to understanding the end goal one wishes to achieve by stimulating the target nucleus and by modulating activity patterns of the downstream nuclei. Another key point which
emerges time and time again is heterogeneity associated with the disease of interest which has direct implications for patient selection. Additionally, possible network and neuronal differences underlying disease heterogeneity would also have implications on the selection of target nuclei.

Integration and use of information obtained from patient data, animal models, computational models and imaging studies continues to be instrumental in furthering the research field on DBS. In this thesis, we studied dynamics of the neural circuitry involved in Parkinson’s disease, using theoretical models and experimental recordings. In chapters 2 and 3, we looked into possible mechanisms underlying efficacy of DBS for the management of Parkinson’s disease. To this end, we studied in depth properties of the underlying circuitry both at a single cell and network level. Making use of a Basal Ganglia network model projecting onto a thalamocortical relay neuron model, we looked into mechanisms contributing to the efficacy of high frequency stimulation for suppression of Parkinson’s disease motor symptoms. We observed that high frequency stimulation is more effective in modulating the Basal Ganglia network away from oscillatory activity patterns together with preventing relay of pathological oscillations by the thalamocortical relay neurons to downstream nuclei (i.e. cortex). Low frequency stimulation on the other hand is not as effective in modulating neither the Basal Ganglia network nor the thalamocortical relay neurons away from relaying pathological oscillations to downstream nuclei. Additionally, high frequency stimulation is able to suppress relay of pathological oscillations at low stimulation amplitudes which does not impair relay of excitatory cortical inputs. At low stimulation frequencies, higher stimulation amplitudes are required in order to suppress relay of oscillatory Basal Ganglia activity patterns to the cortex. High stimulation amplitudes on the other hand, give rise to ‘informational lesion’ by also suppressing relay of excitatory cortical inputs. In chapter 4, based on the observations made using the theoretical models, we studied cellular properties of the thalamocortical relay neurons in-vitro. We first investigated modulatory effects of high frequency stimulation on the thalamocortical relay neurons. Based on ion channel properties of the thalamocortical relay neurons contributing to the modulatory effects of high frequency stimulation, we mimicked the effect that high
frequency stimulation has on thalamocortical relay neurons by using well timed pulse trains.

Understanding mechanisms involved in manifestation of the pathology is crucial for improving the therapies used in the management of the disease. There are several hypotheses regarding the mechanisms leading to oscillations and elevated levels of synchrony in the basal ganglia–thalamocortical network during Parkinson's disease. In chapter 6, we made use of cortical evoked potentials obtained from Parkinson's disease patients in order to study properties of the basal ganglia-thalamocortical network prior to and following administration of Levodopa. We inferred parameters dictating network dynamics based on cortical evoked potentials, obtained from Parkinson's disease patients and studied possible changes in connection strengths between different brain regions. These changes were used to capture the differences in the cortical evoked potentials, arising from alterations in dopamine levels.

Is feeding the network of interest with high frequency pulses the answer for the treatment of various diseases?

Understanding the physiological signals observed at the nuclei of interest and the changes that occur leading to the pathological state are of key importance for determining how the network should be modified during DBS. High frequency stimulation is highly efficient in modifying the network of interest away from synchronized oscillatory firing patterns during Parkinson's disease (Cagnan et al. 2009; Guo et al. 2008; Hashimoto et al. 2003; McIntyre and Hahn 2010; Rubin and Terman 2004). It still remains unknown though whether this is ideal for the treatment of other diseases. For instance use of continuous stimulation for epilepsy would inherently imply that the brain is also stimulated during the "normal state". Therefore it needs to be identified which patterns do not "jam" the physiological state of the brain while delivering the desired treatment outcome which in the case of epilepsy is controlling the excitability of different networks in order to minimize frequency of seizures (Nagel and Najm 2009). Similarly, for obsessive compulsive disorder, Tourette's syndrome and major depression one needs to observe the underlying pathological and physiological signals to understand whether the use of continuous high frequency
stimulation is most suitable for the modification of the pathological signals at hand.

Closed loop stimulation

Closed loop stimulation, during which a brain region would be stimulated using pulses dependent on the characteristic signals measured from a patient’s brain, remains one of the most important and challenging research topics in the field of DBS. There exist several challenges with the realization of closed loop stimulation. Despite increasing experimental and theoretical studies investigating mechanism of DBS, a consensus regarding the mechanism(s) has not yet been reached. Since the mechanism underlying the efficacy of open loop high frequency stimulation is not well understood, conversion of the system into closed loop is highly challenging. In the context of Parkinson’s disease, continuous oscillations in the theta and beta frequency bands are associated with Parkinson’s disease motor symptoms and one wishes to suppress these overtly synchronized continuous oscillations. On the other hand, beta frequencies are known to be utilized during voluntary movement. Therefore, for instance if the closed loop stimulation is designed to suppress beta band oscillations in the Basal Ganglia, one would need to make sure that “good” beta band oscillations utilized in movement control is not suppressed together with “bad” beta band oscillations, leading to Parkinson’s disease motor symptoms (Boraud et al. 2005). Basal ganglia-thalamocortical loop is a complex dynamic network. It is still not well understood, how synchronous beta band oscillations are generated in the network during Parkinson’s disease and how these oscillations are sustained within the network. There are several sub-cortical and cortical loops which are candidates for the generation of such oscillations: e.g. cortico-cortico, thalamocortical, STN and globus pallidus externum, and so forth. Of course, the difficulty faced in identifying a single sub-loop as the generator of beta band oscillations could imply that beta band oscillations result from complex interactions within the basal ganglia-thalamocortical loop, onset by a reduction in the dopamine level within the network and that all the nuclei forming the basal ganglia-thalamocortical loop contribute in one way or another in the generation of these oscillations. Last but not least, the implemented closed loop stimulation should be robust enough to withstand variability.
among Parkinson’s disease patients. In chapter 5 while working on automatic detection of the STN from MERs; we observed that there is not one MER feature which can be used to distinguish the STN from the surrounding structures and that there exist substantial variability among patients. Richness of the patient data points to potential difficulties in the realization of closed loop stimulation which should be robust enough in its implementation to ensure applicability to different patients.

Closed loop stimulation has also been considered for the management of epilepsy. The aim is to realize a system which can predict or detect onset of an epileptic seizure and deliver pulses in order to modulate the brain away from the epileptic state. One of the major obstacles remains the identification of a target nucleus which can be stimulated to achieve this goal. At this point, heterogeneity among patients poses a major barrier in identification of a single target nucleus. Moreover, it still remains unknown whether it is possible to modulate the brain away from an epileptic seizure following seizure detection or if it is simply too late at that stage.

DBS is a successful surgical treatment technique and compared to lesioning different brain regions, it is less invasive and reversible, making it an attractive alternative for the treatment of several diseases. Nonetheless, some caution needs to be taken in the extension of the application fields of this surgical technique. To make sure that desirable outcomes are achieved from the application of DBS, we need to know which regions we are trying to modulate, why we are trying to modulate specific regions, how we need to modulate them, what ideal stimulation frequencies are for different diseases and what ideal stimulation patterns are for different diseases. Incorporation of data from macro to micro scale and utilization of theoretical models to study neuronal dynamics both at a single cell and population level would play a significant role in furthering our understanding on obsessive compulsive disorder, Tourette’s syndrome, major depression and epilepsy and enable researchers to broaden the application of DBS together with achieving increased coherence in clinical outcome of DBS when used in the management of these afore mentioned diseases.
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