Mapping and zapping

Summary

The aims of this thesis were to identify the optimal stimulation site and brain networks that are potentially crucial to engage for achieving seizure control with ANT-DBS in drug-resistant focal epilepsy. To address this aim, we have performed the following animal (*Part I*), human (*Part II*) and computational (*Part III*) studies:

The introduction **in Chapter 1** provides a brief background on the treatment of patients with drug resistant focal epilepsy and formulates the *problem statement* of this thesis. Patients with drug-resistant focal epilepsy are left with few therapy options if epilepsy surgery is not possible or fails to control seizures. Anterior thalamic DBS (ANT-DBS) is a potentially effective neuromodulation therapy for these patients, but knowledge gaps on the predictors of response, optimal stimulation site and brain networks that are potentially crucial for achieving seizure control with ANT-DBS, impede its widespread use as a standard neuromodulation therapy.

PART 1 - ON ANIMAL STUDIES

In Chapter 2, we review the literature on the animal evidence for ANT-DBS. We found that most rodent studies were performed in acute seizure models and focused on the modulation of the seizure threshold by ANT-DBS, not the modulation of spontaneous recurrent seizures. Only a few studies performed ANT-DBS in rodent models of chronic epilepsy, exhibiting spontaneous recurrent seizures, and results were mixed between different models of epilepsy. Some studies tested whether unilateral or bilateral thalamic stimulation is more effective and found that, in line with common clinical practice, bilateral stimulation was associated with more seizure reduction. No study tested different stimulation sites within the ANT and a comparison of different targets within the ANT could therefore not be made. Stimulation parameters differed between studies (high and low frequency) and, surprisingly, none of these studies performed the clinical stimulation paradigm that was used in the human trials: a cycled stimulation mode of 1 minute ON and 5 minutes OFF for 24 hours a day. In conclusion, rodent studies support the use of bilateral stimulation over unilateral stimulation, find that both low and high frequency stimulation can be effective in reducing seizures, but no study models the clinically used 24 hours a day cycled stimulation paradigm (1 min ON, 5 min OFF).

In Chapter 3, we report on a rat model of electrically induced epilepsy, exhibiting spontaneous recurrent seizures, that allows for the assessment of chronic ANT-DBS under controlled experimental conditions. To the best of our knowledge, this is the first

rodent study that applied cycled ANT-DBS for 7 consecutive days (24 hours a day), using a clinically relevant stimulation paradigm to test therapeutic efficacy and behavioural side effects. In the limited number of animals (n=5) that completed the study, we did not observe an effect of cycled ANT-DBS on seizure frequency. In this animal model of epilepsy, characterized by reduced spatial memory, cycled ANT-DBS did improve spatial memory, yet recognition memory, anxiety and locomotion remained unchanged. Due to the unexpectedly large loss to follow-up, the power of the current study, and the conclusions that may be made from it, are limited. We therefore turned to existing human data that was collected in patients receiving ANT-DBS to test whether neurophysiological or neuroanatomical characteristics of the ANT target area may identify an optimal stimulation site.

PART 2 - ON HUMAN STUDIES

In Chapter 4, we review the rationale, safety, clinical efficacy, and the proposed mechanisms of action of ANT-DBS in humans. We found that the clinical implementation of ANT-DBS in standard clinical practice still faces great challenges, as there is only a 50% chance of a 50% reduction in seizure frequency after 1 year of treatment. We focused on whether there are specific patient characteristics or other factors related to the treatment that could identify patients that respond or do not respond to ANT-DBS. We identified multiple opportunities for improving the localization of the DBS target area, including its neurophysiological characteristics and neuroanatomical surroundings, to eventually improve seizure control.

In Chapter 5, we explore the neurophysiological characteristics of the ANT in humans using microelectrode recordings obtained during DBS surgery (n = 10). The clinical utility of microelectrode recordings during ANT-DBS surgery remains unclear, as little is known about the neuronal firing properties of the ANT humans and even less about their relation to DBS lead placement or clinical outcome. Using data from 10 patients and a total of 19 trajectories, we found an incremental increase in firing rate when entering the ANT and a decrease in firing rate and burst rate when exiting the ANT. This pattern may hypothetically be associated with traversing the white matter of the medullary lamina of the thalamus. We then compared the trajectories of responders to non-responders and found no differences in the neuronal firing properties themselves nor their locations of peak firing/burst rate relative to the position of the active contact. We therefore conclude that single-cell firing rate detected by microelectrode recording

under general anesthesia can aid DBS lead placement within the ANT during surgery, but is not related to therapy response. In conclusion, single-cell recordings of the ANT target area did not identify neurophysiological characteristics of the ANT that could optimize seizure control by informing DBS surgery or programming.

In Chapter 6, we explore a potential role of white matter in seizure control by ANT-DBS and investigate whether stimulation of the mammillothalamic tract (MTT) is associated with optimal seizure control. Using data from patients that received ANT-DBS for drug resistant epilepsy (n = 20), we assessed the locations of both the ANT-MTT junction and the active contacts in stereotactic (or native) space. We found that the ANT-MTT junction can reliably be identified by two independent reviewers and can serve as a reproducible anatomical landmark for neurosurgical targeting. Active contacts more closely located to the ANT-MTT junction were associated with increased seizure control. The stimulation 'hot-spot' of responders was at the medio-ventral ANT in high vicinity to the ANT-MTT junction, in contrast to no evident hot-spot in non-responders. Accordingly, the ANT-MTT junction is not only a reliable neuroanatomical landmark for direct neurosurgical targeting, but also a potential optimal stimulation site for increased seizure control. In conclusion, we recommend planning a neurosurgical trajectory to target the ANT-MTT junction and programming the pulse generator to stimulate this region for optimal seizure control.

PART 3 - ON COMPUTATIONAL STUDIES

In Chapter 7, we introduce a novel technique, termed 'lesion network mapping' that combines a 'wiring diagram' of the human brain (the human connectome) with causal information from brain lesions and brain stimulation. Brain lesions cause damage to specific brain circuits which may lead to specific neuropsychiatric symptoms. Brain stimulation of these same circuits could potentially modulate these same neuropsychiatric symptoms. To determine whether brain lesion locations and brain stimulation sites modulating the same neuropsychiatric symptom converge on common brain circuits, we studied depression severity after brain lesions (n=461, five datasets), transcranial magnetic stimulation (TMS) (n=151, four datasets) and DBS (n=101, five datasets). We computed the functional connections between each lesion location and all other brain voxels using the resting state functional connectivity data from 1000 healthy participants (the human connectome). We found that lesions and brain stimulation sites most associated with depression severity were connected to a similar brain circuit.

Circuits independently derived from lesions, deep brain stimulation and transcranial magnetic stimulation were also similar, as were circuits derived from patients with major depression versus other diagnoses. Likewise, in an independent analysis in patients with Parkinson's disease, 29 lesions and 95 stimulation sites converged on a common brain circuit for motor symptoms of Parkinson's disease. We conclude that lesions, TMS and DBS map to common brain circuitry that may represent improved neurostimulation targets for depression or other neuropsychiatric diseases.

In Chapter 8, we apply lesion network mapping to epilepsy and test whether lesion-related epilepsy maps to a common brain network. We first studied lesion locations from patients with stroke-related epilepsy (n=76) and control lesions (n=625). Lesion locations were mapped to a common brain atlas and the brain network functionally connected to each lesion location was computed using the human connectome (n=1000). The functional connections associated with stroke-related epilepsy were identified. Generalizability to other lesion etiologies was assessed using four datasets with different lesion types (n=772). We then tested the therapeutic relevance of these connections using the outcome data from patients who received ANT-DBS for drug resistant focal epilepsy at our center (n=30). We found that lesion locations of stroke-related epilepsy map to a specific brain network defined by functional connectivity to nodes in the basal ganglia and cerebellum. Functional connectivity to these same nodes was associated with the risk of epilepsy across different lesion types and with therapeutic response to thalamic deep brain stimulation. We conclude that lesion-related epilepsy maps to a common brain network with therapeutic potential for neuromodulation.

The general discussion in **Chapter 9** provides an overview of the studies performed in this thesis, reflects on the methods used to map brain circuits, and provides a future perspective towards network-neuromodulation for epilepsy.