Mapping and zapping

Impact paragraph

RELEVANCE

Epilepsy is one of the top 5 most common brain diseases and a major health problem, affecting more than 70 million people worldwide.[1] Persistent epileptic seizures carry serious neurological, cognitive, psychological and social consequences. On a societal level, epilepsy has significant economic implications due to chronic health care demands and lost productivity of work.[2] In addition to its high prevalence and burden, people living with epileptic seizures unfortunately still suffer from stigma, discrimination and even human rights violations which may lead to difficulties in education and employment (www.who.int). Consequently, epilepsy has a high medical, social and economic burden in our current society.

Most patients with epilepsy become seizure free with the first two antiepileptic drug regimens. However, for over 30% of patients, antiepileptic drugs do not result in seizure control and adding an additional drug only offers less than 5% additional probability of seizure control.[3] The burden of epilepsy is therefore highest among patients with uncontrolled seizures, also termed drug resistant epilepsy, accounting to 86% of all costs related to epilepsy in the United Stated (totalling $12.5 billion).[4] These numbers illustrate that we are still in need of an effective therapy control seizures in patients with drug resistant epilepsy.

Deep brain stimulation (DBS) of the anterior thalamus is a safe and potential treatment option for patients with drug resistant focal epilepsy, when epilepsy surgery or other less invasive neuromodulation strategies are not possible or failed to control seizures. DBS is thus a promising effective therapy for the most severely affected patients and may be a last resort for many patients. However, DBS response rates vary across patients and there is only a 50% probability that it will lead to 50% reduction in seizure frequency 1 year after surgery. Knowledge gaps on the predictors of response, optimal stimulation site and brain networks that are potentially crucial for achieving seizure control with DBS impede its widespread use as a standard neuromodulation therapy. With the aim of increasing the control of seizures by anterior thalamic DBS, we performed a series of animal, human and computational studies to identify the optimal stimulation site and brain networks that are crucial for achieving seizure control.

The main finding of this thesis is that there is an optimal stimulation site for seizure control in anterior thalamic DBS for drug resistant epilepsy and that these stimulation

sites are functionally connected to an intrinsic brain network that may play a causal role in lesion-related epilepsy.

TARGET AUDIENCE

The primary target audience will eventually be patients with severe epilepsy. The findings from this thesis could lead to better seizure control for patients with drug resistant epilepsy receiving anterior thalamic DBS and a better quality of life for patients and their family. Attaining seizure control is expected to result in patients being able to lead more normal lives, including a steady job, less dependency on relatives or healthcare workers, driving (when seizure free), and ultimately less risk of physical harm or sudden death in epilepsy. Effective treatment of patients with drug resistant epilepsy will also result in a marked decrease of the financial burden of epilepsy to our society, as productivity increases, and health care costs associated with uncontrolled seizures decrease.

However, the expected positive outcomes to patients and society may only be realized if our findings are *innovated* by the academic community, *adopted* by neuromodulation companies, and *implemented* by health care workers; constituting the other three target audiences of this thesis.

INNOVATION

In this thesis, we have contributed to the academic literature that studies effective stimulation sites in anterior thalamic DBS for drug resistant epilepsy. Our results were consistent with previously published smaller case series,[5,6] and innovative in three important ways: 1) we show that the junction between the mammillothalamic tract and anterior nucleus of the thalamus (ANT-MTT junction) is a reliable neuroanatomical target that can be visualized across different MRI field strengths, 2) we show that the stimulation sites (volume of activated tissue) of responders overlap at the ANT-MTT junction, and 3) we provide evidence and propose a role for modulation of fiber tracts in the efficacy of anterior thalamic DBS. In doing so, our study (among others) has inspired a retrospective analysis of the DBS lead locations implanted in the randomized controlled trial that led to FDA approval for anterior thalamic DBS (SANTE study),

which replicated our results.[7] In the short-term, we expect to see more replication studies of independent cohorts across the world and in the long-term, we hope that neurosurgeons and neurologists will adapt their surgical approach and DBS programming strategy to improve stimulation of this 'sweet-spot' for anterior thalamic DBS. Eventually we expect that identification of this optimal stimulation sites will lead to improved clinical outcome across patients and centers. One new insight gained from this research is that fiber tracts (or white matter) may have a role in the mechanism of action of anterior thalamic DBS, which warrants further studies using more sophisticated neuroimaging techniques that can visualize these fibers. In the future, this insight may even revive the use of several fiber tract targets historically used to treat epilepsy before the invention of modern neuromodulation devices. A second new insight is that intrinsic functional connectivity of the stimulation site is associated with clinical outcome after anterior thalamic DBS. This finding may seem surprising, but is in line with historical animal and human data showing that distant brain regions may have an effect on seizures, independent of where the seizures are starting in the brain (i.e. the seizure-onset zone).[8–12] We significantly extend this concept, by showing that lesions causing epilepsy and DBS sites treating epilepsy are functionally connected to a common intrinsic brain network, suggesting a role for a network distant from the seizure-onset zone in the cause and treatment of lesion-related epilepsy. We hope this finding leads to widespread testing by other academics into the role of this brain network in the cause and treatment of epilepsy.

Adoption

The findings of this thesis may also be relevant for neuromodulation companies such as Medtronic, NeuroPace, Boston Scientific and many others. Our results show that there is an optimal stimulation site and there are crucial network connections associated with increased seizure control after anterior thalamic DBS. By mapping increased seizure control to a brain region, the eventual template map of this region could be used to guide DBS surgery and programming. Neuromodulation companies are invested to deliver the best possible outcome for their patients, reduce side effects, shorten the time to therapeutic response, and streamline technology for clinicians to broaden adoption of the offered neuromodulation device. More specifically, Medtronic offers a software program, called Suretune (www.medtronic.com) that localizes the DBS lead in patient space and visualizes the lead location in respect to a thalamic atlas to assist postoperative programming by the neurologist. There are also open-access software tools available that

offer similar applications for research purposes, such as Lead-DBS (https://www.lead-dbs.org). The optimal stimulation site in this thesis may be converted into a region of interest (similar to an anatomical atlas) and transformed into patient space, to give the treating neurologist visual feedback of the optimal stimulation target to aim for during DBS programming. A similar approach can be taken using the optimal brain network connections identified in this thesis. A map of intrinsic connectivity to the basal ganglia and cerebellum could be derived from a normative connectome from healthy individuals, or even a patient specific connectome derived from functional MRI scans of that patient. This connectivity profile could be transformed into native space to assist the neurosurgeon and neurologist in modulating these connections with DBS. I hope and expect that widespread collaborations between engineers, clinicians, neuroimaging experts and medical device companies will adopt these findings and, in a wider framework, move the field toward network-neuromodulation for epilepsy.

Implementation

Knowledge obtained in this thesis has been and will be shared through paper contributions to the academic literature, presenting to scientific audiences in both Europe and the US, and inspiring new insights and studies in the field. We hope that the findings from this thesis will be picked up by both basic, translational and clinical researchers studying epilepsy and its treatment with neuromodulation. On the short term, the results of this thesis are relevant for neurosurgeons and neurologists treating drug resistant epilepsy with anterior thalamic DBS, who may use our stimulation site and intrinsic brain network to guide neuromodulation treatment in their daily clinical practice. These health care workers are also essential to independently validate and replicate our results across different centers and patient groups. I am currently collecting data around the world to test whether our identified intrinsic brain network associated with epilepsy may predict outcome in independent cohorts of anterior thalamic DBS. External replication is an important step towards testing whether this brain network may be used as an improved therapeutic target in randomized controlled clinical trials. Furthermore, the results of this thesis are relevant to brain stimulation neurologists, and to general and stroke neurologists treating patients with brain lesions. Brain lesions inherently increase the risk of epilepsy. Neurologists designing trials to test antiepileptogenic drugs may use our identified brain network to stratify patients into low and high risk for epilepsy. Using damage to our brain network as a selection criterion, one could enrich antiepileptogenic drug trials with patients at high risk of epilepsy.

Trials enriched with patients at high risk of epilepsy will drastically decrease the time to reach the specified inclusion numbers and eventually also the financial cost of such trials. In the long term, the findings of this thesis will need to be implemented in randomized clinical controlled trial designs that will be setup by health care workers specialized in stroke, epilepsy and neuromodulation.

While the findings of this thesis can already be used in the current daily clinical care of patients with anterior thalamic DBS, the new insight that 'intrinsic brain connectivity' may play a role in the cause and modulation of epilepsy may result in the largest scientific and social impact of this thesis. The current dogma in both the scientific and clinical arena of epilepsy and neuromodulation, is that epilepsy diagnosis and treatment should be focused on a patient's individual epilepsy network, not a common brain network across patients. The new insights from this thesis could therefore lead to a paradigm shift in how we understand the cause and perform the treatment of epilepsy. In the basic scientific community, studies that investigate whether intrinsic brain networks distant from the seizure focus may have a causal influence in epileptogenesis could open up new avenues. For example, one could design antiepileptic drug treatments or neuromodulation therapies that optimally modulate these distant brain networks. In the translational scientific community, studies that measure and perturb brain activity within these intrinsic brain networks may open up new treatment targets for neuromodulation. In the epilepsy centers, a focus away from mapping individual epilepsy network to common networks across patients may result in changes in how they work-up patients with drug resistant epilepsy to either treatment with epilepsy surgery or neuromodulation.

Overall, *innovation*, *adoption* and *implementation* of the findings described in this thesis may lead to a new way of '*mapping and zapping*' brain networks in epilepsy with substantial scientific, clinical and social impact.

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