Neuromodulation, from the sideline to center stage

Prof.dr. Paul Boon
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INAUGURAL LECTURE

Neuromodulation, from the sideline to center stage

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DEPARTMENT OF ELECTRICAL ENGINEERING

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Presented on December 16, 2022
at Eindhoven University of Technology

Dear colleagues, dear family and friends,

It is my particular honor and pleasure today to deliver my inaugural lecture as Professor of Neuromodulation at Eindhoven University of Technology (TU/e). The actual planning has been tedious as the date that was originally set had to be postponed twice due to Covid-related restrictions. I am truly honored to stand here in front of a prestigious corona of fellow scholars and colleagues in the nice 'Blue Aula' of the prestigious academic institution that is Eindhoven University of Technology. This is the main academic institution of Brainport Eindhoven, the knowledge hub of the Netherlands, consisting of more than 5000 IT and technology companies and startups and accounting for more than one third of Dutch R&D. For the purpose of fostering and facilitating biomedical research and development, TU/e has strong, longstanding relationships with care institutions in the region, such as Kempenhaeghe, and international networks in which Ghent University and Ghent University Hospital play an important role. The latter was the subject of the formal signing of a Memorandum of Understanding in October 2017 in the presence of the Prime Ministers of the Dutch and Flemish governments. In my roles of R&D director of Kempenhaeghe and co-director of the Institute for Neuroscience at Ghent University, I have been interacting for a long time with many members of the TU/e academic community on scientific projects, PhD trajectories and common research platforms for neurotechnological research (Neu3Ca and Neuroplatform). With the generous support of the Royal Epilepsy Fund, EpilepsieNL, a professorship was created at TU/e and the title was officially granted to me by the Rector Magnificus on February 1, 2019.

As a neurologist and neuroscientist, working amidst engineers and technologists has become second nature for me. My clinical and preclinical research requires as much mathematical, analytical and technological input as medical and neurobiological input. It is therefore not surprising that my first two PhD students were engineers rather than medical doctors. Since then, I have established a large and fruitful collaborative network with biomedical engineers in Belgium, the Netherlands and many other countries in and outside of the European Union (EU).

At least one in three people have a **neurological disease**, making this the most burdensome and costly group in the noncommunicable diseases. In the field of clinical neurology, my specific interest lies in disorders of consciousness, more specifically epilepsy. **Epilepsy** means that a person has experienced at least two epileptic seizures. Epileptic seizures are defined as sudden changes of consciousness, behavior and emotions as the result of a hypersynchronous discharge at the level of the cerebral cortex. At least 1% of the population has epilepsy, which puts it among the most common serious and chronic neurological disorders. The diagnosis can be made on the basis of the patient's history, a careful description of the events, confirmatory information from an electroencephalogram (EEG) and neuroimaging studies such as computerized tomography (CT) and magnetic resonance (MR), which may demonstrate an underlying structural lesion. Epileptic seizures are typically treated with antiseizure medications (ASMs) that may have various mechanisms of action, such as interfering with ion channel function (typically blocking sodium channels or interfering with other ion channels), enhancing inhibitory neurotransmission, decreasing excitatory neurotransmission or interfering with the intracellular transport of neurotransmitters. Approximately two thirds of patients will become seizure-free without side effects when one or two ASMs are prescribed. In one third of patients, seizures cannot be controlled and/or the patients experience unacceptable side effects. These patients are referred to as refractory or drug-resistant epilepsy (DRE) patients. Despite the development of more than 25 different ASMs, many of which have become available in the past 15 years, the number of DRE patients has not significantly decreased. These patients are amenable to additional non-pharmacological treatments. An important limitation of practically all pharmaceutical trials in epilepsy is the self-reporting of seizures using patient diaries, which are notably unreliable due to either underreporting or overreporting of events. Devices that allow continuous monitoring and the recording of EEG signals or other biomarkers for the occurrence of seizures would substantially improve the reliable evaluation of therapeutic outcomes. Additionally, they would provide a means of alarm for seizures and would inform closed-loop interventional devices.

Epilepsy surgery is a treatment option that aims to render DRE patients seizure-free by removing the epileptogenic zone, which is the area of brain cortex that is necessary and sufficient for initiating seizures and of which removal or disconnection is necessary for the complete abolition of seizures. Epilepsy surgery requires a thorough presurgical evaluation, including establishing the presence of drug resistance, delineating the epileptogenic zone and avoiding additional neurological deficits. The presurgical evaluation comprises complete history-taking, video EEG monitoring, MRI, neuropsychological assessment (evaluation of memory, attention, language, dexterity and language dominance), positron emission tomography (PET), magnetoencephalography (MEG), functional MRI (fMRI) and the intracarotid amobarbital procedure (WADA test). In selected patients, invasive video EEG monitoring using subdural and/or depth electrodes will be performed to further confirm the localization of the epileptogenic area. The presurgical evaluation may eventually lead to resective surgery, such as anterior temporal lobectomy or amygdalohippocampectomy in patients with temporal lobe epilepsy and hippocampal sclerosis or lesionectomies in other brain regions. A large multicenter randomized clinical trial has confirmed the superior efficacy of resective surgery in refractory focal epilepsy compared to standard therapy with ASMs alone. More than 60% of patients will remain seizure-free five years after resective surgery. Temporal lobe epilepsy and the presence of a lesion are associated with a higher likelihood of long-term seizure freedom. Only 30-40% of patients with extratemporal and non-lesional epilepsy remain seizure-free during long-term follow-up. Resective epilepsy surgery carries risks, with major complications occurring in 1.5% of patients. The most common but usually reversible complications are bacterial infections (3.0%) and intracranial hematoma, typically asymptomatic (2.5%). Mortality associated with epilepsy surgery is 0.4-1%. Patients rejected for resective surgery in whom the epileptogenic zone is not identifiable or is located in eloquent cortex are amenable to disconnective epilepsy surgery, which also has the potential to substantially reduce seizures. This comprises procedures such as corpus callosotomy, hemispherotomy and multiple subpial transections.

In patients who are not amenable to epilepsy surgery or who have undergone unsuccessful surgical procedures, neurostimulation is an alternative option. **Neurostimulation** is defined as delivering electrical, magnetic or ultrasound energy to the nervous system with the aim of alleviating neurological symptoms. The focus of my presentation shall be on the electrical stimulation of brain structures. Electricity, mainly from electric fish, was used for thousands of years to treat conditions such as pain. From the 1760s, it became possible to control electricity and store electrical energy, and electrical devices were used for numbing pain during dental operations but also as quackery. Medically uncontrolled and chronic pain syndromes started to be treated with deep brain stimulation (DBS) in the 1960s, followed by spinal cord stimulation in the 1970s. As it was found that pain is the result of a series of complex dynamic processes in the nervous system and that damage to the nervous system itself may cause chronic (neuropathic) pain, surgical resective or lesioning procedures made way to potentially reversible

and less invasive treatments that exerted both an acute (neurostimulatory) effect and a chronic, potentially disease modifying (neuromodulatory) effect. Currently, the applications of therapeutic electrical stimulation are very diverse and new applications are being developed. The treatment of medically refractory chronic pain is the commonest indication, particularly neuropathic pain and in some cases ischemic pain due to a lack of oxygenated blood flow to muscles. Spinal cord stimulation (SCS) is the commonest modality and its use is well-established in the treatment of neuropathic pain. In addition, it is used in the treatment of ischemic pain such as angina and chronic critical limb ischemia, visceral pain such as that which can occur after chronic pancreatitis, and pelvic pain disorders. Beginning in the mid-2010s, new waveforms and SCS settings evolved, such as high frequency or burst modes of stimulation. Innovative devices are able to deliver multiple simultaneous waveforms and engage multiple mechanisms of pain relief. In recent years, devices have been designed to target wider and different regions of the spinal cord and nerve structures in the lower back area, allowing tailored neurostimulation. Moreover, since 2019, closed-loop systems have been available that are able to detect the effect of the stimulation on the targeted nerves in the form of evoked compound action potentials. Sensing this feedback enables automatic stimulation adjustment for steady treatment regardless of movement, posture or coughing, which might otherwise cause a momentary dip or surge in stimulation.

The modern era of neuromodulation started with the 1987 publication of a paper by Professor Benabid in Grenoble on the use of **deep brain stimulation (DBS)** for suppressing the tremors of Parkinson's disease. Thanks to modern imaging, including functional imaging and improved surgical techniques, neurosurgeons are now able to implant DBS electrodes virtually anywhere in the brain with a high degree of accuracy and relative safety. Increased understanding of the neural circuits involved in various neurological, psychiatric, cognitive and behavioral disorders makes it tempting to use the nondestructive stereotactic technique of DBS to modulate these circuits in the hope of alleviating symptoms. The success of this approach on the motor symptoms of Parkinson's disease – essential tremor and dystonia (the most common indications for DBS) – has led to enthusiasm for applying DBS beyond movement disorders in neurology and in the therapeutic domains of psychiatry, behavior and cognition. To date, DBS trials have targeted no fewer than 40 different brain sites for at least 30 clinical indications. The common denominator of these investigational applications of DBS is their intention to treat symptoms of illnesses and diseases that are refractory to nonsurgical management, be they tinnitus or obesity, depression or dementia, epileptic seizures or phantom pain.

Peripheral nerve stimulation for pain relief in neuropathic pain or chronic migraine and chronic cluster headache has also gained increasing attention. Intractable epilepsy has been treated variously with deep brain stimulation, cerebellar cortex stimulation and vagal nerve stimulation. Vagus nerve stimulation (VNS) was also observed to have a mood elevating effect and received regulatory approval for depression. VNS that stimulates part of the autonomic nervous system gained further interest starting in the 2010s in relation to addressing autoimmune inflammatory diseases such as rheumatoid arthritis, with these methods sometimes referred to as 'bioelectronic medicine'. In 2020, a handheld VNS device received approval for use by asthmatics experiencing difficulty in breathing in association with Covid-19 infection. VNS was also investigated to treat critically ill Covid-19 patients in whom there was evidence of a cytokine storm. Neuromodulation treatment for certain types of heart failure and hypertension also became possible in the 2010s with regulatory approvals for a device that stimulates the baroreceptors in the heart. The use of DBS to treat severe intractable depression, obsessive compulsive disorder, Tourette syndrome and Alzheimer's disease is being actively explored. In light of past experiences with psychosurgery, more specifically the overuse or abuse of lobotomies for various psychiatric conditions as advocated by Freeman and colleagues in the 1960s, stereotactic lesions (capsulotomy, cingulotomy) and DBS in psychiatric patients are under particular scrutiny. There are some limited studies into DBS to potentially treat intractable obesity, addiction and chronic pain. Motor cortex stimulation by means of brain surface electrodes was introduced in 1991 to potentially treat pain suffered by stroke patients and in patients with trigeminal nerve damage. The management of urinary and fecal incontinence or retention by means of electrical nerve stimulation has been optimized and is becoming more widely available. Sacral nerve stimulation and posterior tibial nerve stimulation are established treatments for pain syndromes available within advanced healthcare systems. Refractory angina pectoris, chronic pancreatitis and chronic pelvic pain are continuing areas of research. Neuropathic and visceral pain associated with cancer and cancer treatments is another growing therapeutic area among cancer survivors. The application of functional electrical stimulation (FES) had its origins in the management of spinal injury and post-stroke care. After severe spinal cord injury, it is currently becoming feasible to enhance physical rehabilitation by restoring upper and lower limb function, bladder, bowel and sexual function and chest ventilation. A number of external and implantable devices have been designed

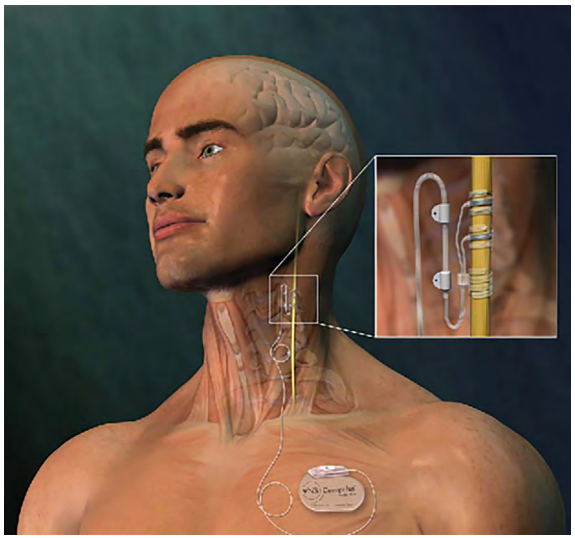
and manufactured to restore useful function in an otherwise intact nervous system, such as cochlear implants for hearing impairment and visual prosthetic systems for restoring visual perception. Cortical EEG sensing, allowing people with severe paralysis to use a brain-machine interface to sense motor intentions and operate a computer cursor or robotic arm, is currently under wider investigation.

The technology supporting the implantable devices used for neuromodulation has steadily improved over the last several decades. As the hardware becomes smaller and more user-friendly for both clinician and patient, it seems likely that the use of neuromodulation will grow. Up to 100,000 units were already implanted annually by the 2020s, but this represents only a small proportion of those who could benefit. However, the penetration of neuromodulation has not matched the growth of existing indications nor the developments of new indications. Access may be restricted by a lack of awareness in patients and referring clinicians, a lack of experienced implant sites and lack of healthcare resources and reimbursement. The global neurostimulation device market was valued at $4,300 M in 2021 and is expected to double by 2028, with the compound annual growth forecast estimated to be 12.5%. The key industrial players are Boston Scientific, Medtronic, Abbott, Nevro, Livanova, Axonics Modulation Technologies, Neuropace, EndoStim, NDI Medical, Cochlear and Neuronetics, among others. The main drivers of this growth are believed to be Alzheimer's disease, Parkinson's disease, epilepsy, stroke and pain.

The **invasive modalities of neuromodulation** for epilepsy include vagus nerve stimulation, anterior nucleus of the thalamus stimulation and responsive neurostimulation.

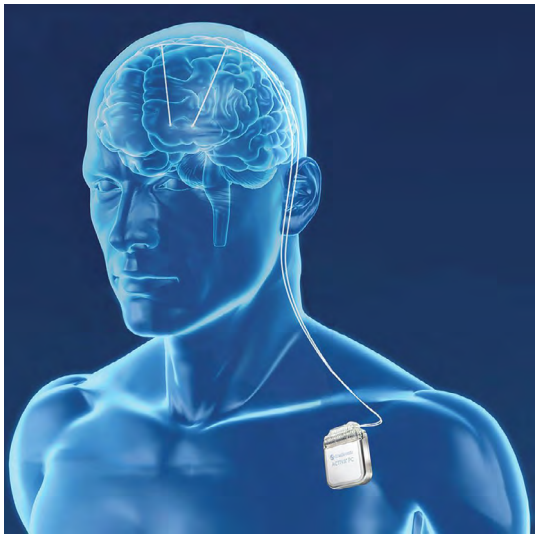
Vagus nerve stimulation (VNS) (LivaNova) is an adjunctive treatment for patients with drug-resistant epilepsy, available since 1997 and with more than 150,000 patients treated worldwide. It is the most frequently used neurostimulation treatment option for epilepsy. The system consists of a programmable pulse generator implanted in the subclavicular region and a bipolar lead that connects the generator to the left vagus nerve in the neck, where a helical electrode is wrapped around the vagus nerve. Stimulation output current ranges from 0-3.5 mA, pulse width from 130-1000 µs and frequency from 1-30 Hz. Stimulation is typically delivered with a 30 s on / 5 min off duty cycle. The mechanism of action of VNS involves afferent vagus nerve fibers modulating the activity of brainstem nuclei such as the nucleus of the solitary tract and its projections, including the locus coeruleus and the raphe nucleus with widespread (mainly) noradrenergic

and serotonergic projections in the brain. The efficacy of VNS was demonstrated in two large randomized controlled trials (RCTs) showing significant reductions in seizure frequency after three months of treatment with a high stimulation paradigm compared to a low stimulation (subtherapeutic) paradigm. A more than 50% reduction in seizure frequency was found in 31% and 23.4% of patients respectively. Long-term open-label trials have confirmed ≥50% seizure reductions in up to 65% of patients after five years. Long-term seizure freedom can be reached in 10% of patients. SUDEP rates in implanted patients are lower compared to patients with drug-resistant epilepsy who have no VNS. Side effects are mild and include hoarseness, throat paresthesia or pain, coughing and dyspnea occurring during the stimulation and can be relieved by adjusting parameter settings. Innovative VNS generators are able to detect ictal tachycardia and then automatically deliver additional stimulation to abort the seizure or reduce its duration and/or severity and can deliver complex pre-programmed stimulation schedules, allowing more flexibility and less frequent ambulatory clinic visits.

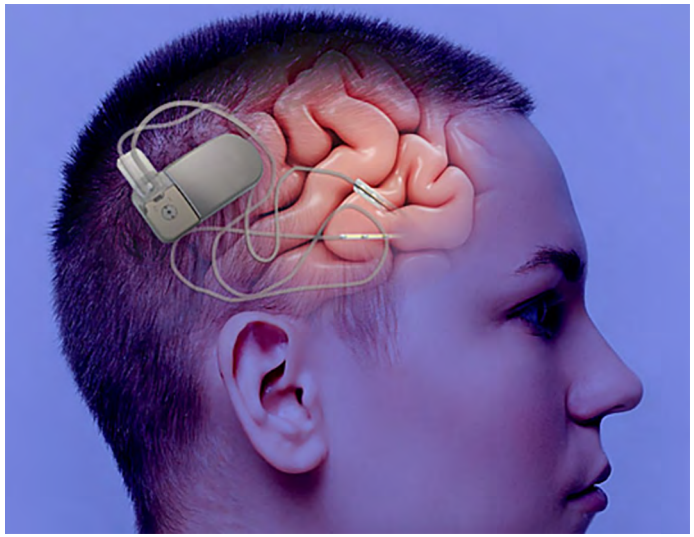


Deep brain stimulation (DBS) and (responsive) cortical stimulation (RNS) are invasive intracranial neurostimulation techniques that have been investigated as a treatment option for refractory epilepsy patients for more than 40 years. Following positive results in two large RCTs, FDA approval has been granted to both responsive stimulation of the ictal onset zone (2013) and anterior thalamic

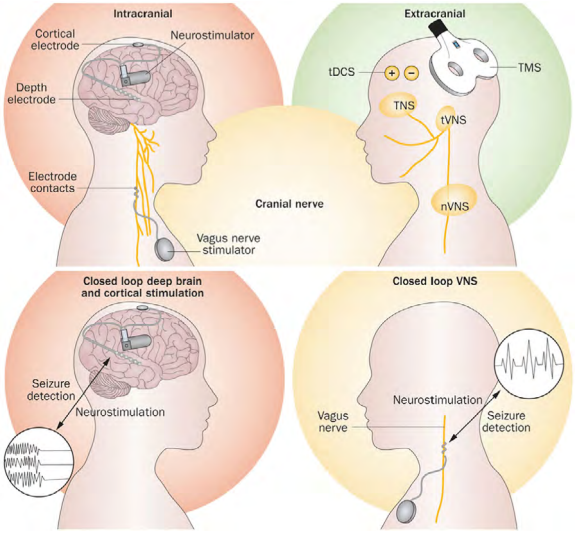
deep brain stimulation (2018) as a treatment for medically refractory focal epilepsy patients. **Anterior thalamic nucleus deep brain stimulation (ATN-DBS)** (Medtronic) consists of the bilateral stimulation of the anterior nucleus of the thalamus via the stereotactic implantation of two 4-contact electrodes using a transventricular or extraventricular trajectory. The efficacy and safety of ANT-DBS, both in the short and long-term follow-up (SANTE trial patient cohort), showed a median seizure frequency decrease of -41% after one year and -69% after five years, with responder rates of 43% and 68%. At the five-year assessment, 11 out of 83 patients (13.2%) had been seizure-free for at least six months. The median reduction was 44% after one year and 76% after five years for temporal lobe epilepsy, 53% after one year and 59% after five years for frontal lobe epilepsy and 34% after one year and 68% after five years for the remainder of seizure onset locations. Previous resective surgery or VNS was not associated with a worse response to ATN-DBS. Furthermore, there were significant reductions in seizure severity, about half of patients showed a clinically significant improvement in quality of life and there was a gradual improvement in attention, executive function, depression, tension/anxiety, total mood disturbance and subjective cognitive function. The most frequent adverse events included implant site pain, paresthesia at the stimulator site, implant site infection, lead(s) not within target, memory impairment and depression. The SUDEP rate was similar or lower than reported in literature. Open-label trials published since 2013 have reported similar long-term outcomes, including a large EU pragmatic trial published in 2022 (MORE patient registry). The presence of electrode contacts with an actual location at the anterior (and superior) aspect of ATN on MRI were associated with a more favorable outcome. The stimulation of brain areas, both cortical and deep brain stimulation, is commonly performed in an open-loop modality, which means that the targeted brain area is stimulated continuously or with a duty cycle, irrespective of the occurrence of seizures. A different, somewhat more sophisticated approach is to administer electrical current only when a seizure has just started or even beforehand when the likelihood of the occurrence of seizures is higher. This approach is referred to as closed-loop neurostimulation.



The **responsive cortical stimulation (RNS)** device (Neuropace) is available in the USA and a number of other countries for patients with drug-resistant epilepsy and consists of a generator case that is implanted in the convexity of the skull bone and connected to a sensing EEG electrode that continuously records EEG from the presumed epileptogenic area as well as a second stimulating electrode that is placed in the neighborhood. When the embedded seizure detection paradigm detects a seizure, a stimulation train is delivered to the area of seizure onset, which may result in the abortion of the ongoing seizure. The efficacy and safety of RNS was demonstrated in a large RCT and long-term open-label studies. After three to six years of stimulation, median seizure reductions typically ranged from 60-65%, with 55-60% responder rates and a substantial improvement in quality of life. Patients with seizure onset in temporal and extratemporal lobes responded equally well. More than 10% of patients became seizure-free for at least one year. Adverse events included implant site infections, medical device removal, intracranial hemorrhage, device lead damage and revisions. Improvements in some measures of cognitive flexibility, visual spatial abilities and language were reported. There was no negative effect on mood and improvements were reported in mesial temporal lobe epilepsy patients.



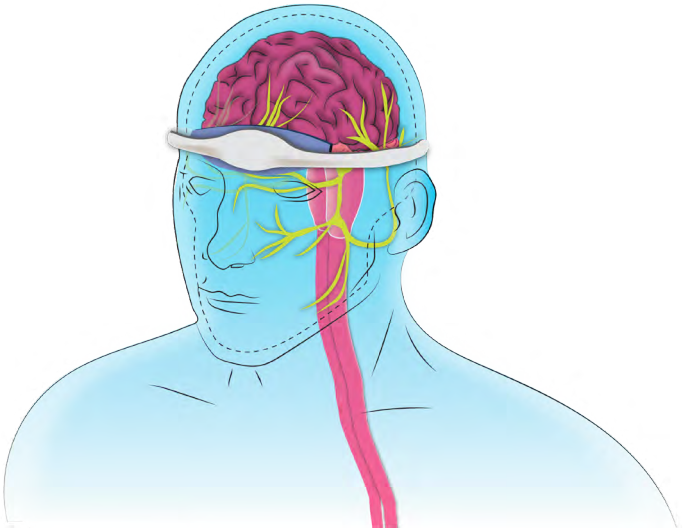
Deep brain stimulation in regions other than the anterior thalamic nuclei (centromedian nucleus, nucleus accumbens, hippocampus, commissural structures) has also been investigated but has seen less general application. Among the different targets that have been stimulated, the hippocampus is of particular interest. Small open-label trials in patients suffering from refractory temporal lobe epilepsy showed a 60% seizure reduction and a 78% responder rate, even when interictal epileptiform discharges were not reduced. A randomized double-blind controlled trial with 16 refractory temporal lobe epilepsy patients showed significant seizure reductions and high responder rates during a six-month period. Long-term follow-up studies confirmed mean seizure reductions of more than 70%. The side effects of hippocampal stimulation are similar to ANT-DBS. Neuropsychological evaluations, including memory assessment, did not show significant changes in short and long-term follow-up.



Different targets and stimulation strategies for drug resistant epilepsy

Neurostimulation for epilepsy can also be administered via **noninvasive modalities.**

Trigeminal nerve stimulation (TNS) consists of noninvasive transcutaneous bilateral stimulation of the supraorbital branches of the trigeminal nerve. After promising results in a pilot trial, an RCT with 50 patients aimed at evaluating the efficacy, tolerability and safety of TNS failed to show a statistically significant difference between the high stimulation group and the low (subtherapeutic) stimulation group during the entire 18-week study period. However, increasing efficacy was shown over time in a significant number of responders after 18 weeks of high stimulation. Open-label extended follow-up studies confirmed substantial reductions in seizure frequency after 12 months, with up to one third of patients experiencing a ≥50% seizure reduction. Adverse events include anxiety, headaches and skin irritation.

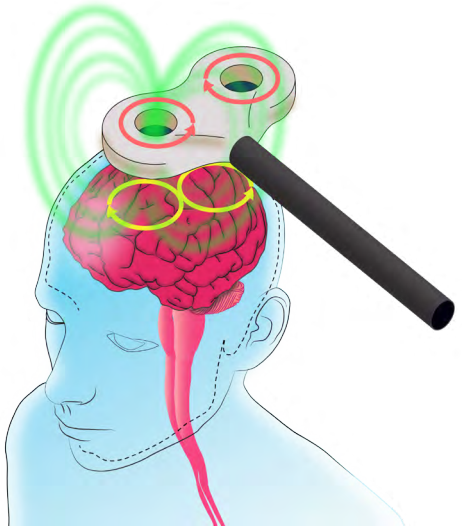


Transcranial direct current stimulation (tDCS) does not induce action potentials but presumably modulates neuronal excitability by changing the resting membrane potential through the constant transcranial delivery of weak currents of 1-10 mA via two electrodes. Cathodal tDCS suppresses seizures by inducing membrane hyperpolarization and has been investigated in single 20-minute tDCS session RCTs in which only a few found a significant reduction in the number of interictal epileptiform discharges in patients. Only two other studies showed significant and borderline reductions in seizure frequency compared to sham stimulation. Other studies evaluated the effect of three to five sessions of cathodal tDCS, showing mixed results. How crucial the location of the stimulation electrodes is and whether personalized stimulation based on a prior or simultaneous determination of the epileptogenic zone can reduce seizures is currently under investigation. Reported adverse events include tingling sensations, mild itching, moderate headaches and skin burn. Transcranial alternating current stimulation (tACS) provides a variable excitation waveform that can mimic natural brain rhythms such as the theta band (~4 Hz) associated with memory and create high-frequency impulses for blocking seizures and pain. Similar to tDCS, the choice of electrode placement is important to engaging the desired neural circuits. As part of my professorship at TU/e, a large multidisciplinary project team obtained a grant from Health Holland's Top Sector Life Sciences and Health to investigate the actual delivery of current using different tDCS stimulation parameters in experimental

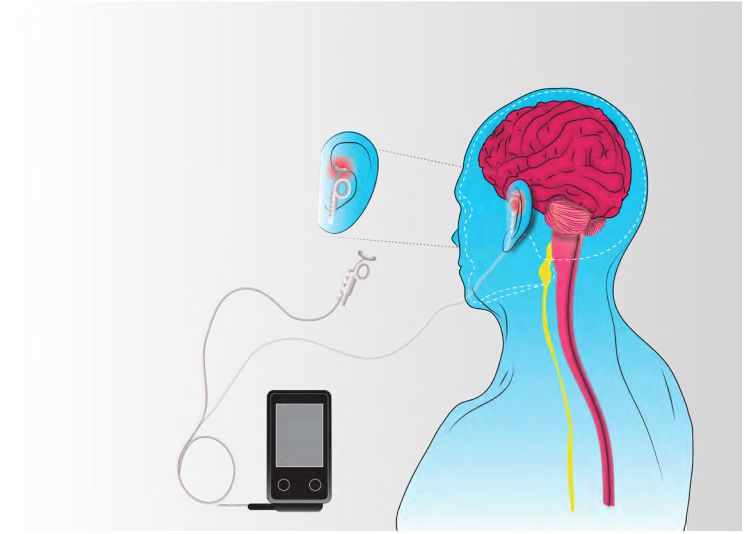
conditions and to evaluate the effect of personalized tDCS on neurophysiological readouts (evoked potentials, EEG, ictal EEG) in healthy volunteers and epilepsy patients. This project (PERSTIM) is a collaboration between TU/e, Ghent University Hospital, Kempenhaeghe, Philips and the Dutch Royal Epilepsy Fund.

Repetitive transcranial magnetic stimulation (rTMS) uses a large magnetic field (approximately 1 T for peaks over 100 µS), which induces a countercurrent that can excite the nervous system in areas as deep as two centimeters. Low-frequency repetitive TMS has been shown to induce long-lasting reductions in cortical excitability and has consequently been proposed as a treatment for epilepsy. TMS is also licensed for depression and some forms of migraine and is used for investigation when mapping the brain before surgery. Of many RCTs evaluating the efficacy of five to ten days of low-frequency (0.33-1 Hz) rTMS in refractory focal epilepsy patients, only three trials could demonstrate a significant reduction in seizure frequency compared to the baseline. In contrast to the limited effects on seizure frequency, all five studies that evaluated the effect of rTMS on the number of interictal epileptiform discharges observed significant reductions. Reported adverse events include headaches, dizziness and tinnitus. Unresolved questions remain with regard to patient selection, the optimal stimulation protocol (parameters and targets), the duration of the treatment effect and how to adequately blind participants. To overcome the spatial limitations of tDCS

and rTMS and allow access to deeper intracranial structures, more advanced transcranial techniques might be applied, such as 'paired stimulation' that aims to synchronize different regions of the brain according to the concept that "neurons that fire together wire together" and temporal interference (TI) that superimposes different stimulation patterns to deliver therapy more deeply in the brain.



Transcutaneous VNS (tVNS) was developed as a noninvasive alternative to vagus nerve stimulation and stimulates the auricular branch of the vagus nerve. Two uncontrolled open-label trials each demonstrated 50% reductions in seizure frequency and 50% responder rates. Of three RCTs, one showed no significant difference between 1 Hz (subtherapeutic) and 25Hz (therapeutic) stimulation groups in seizure frequency and responder rates, and two trials found a statistically significant treatment effect between transcutaneous auricular vagus and non-vagus nerve stimulation in terms of seizure frequency and responder rates. The side effects of transcutaneous VNS include local skin irritation and headaches. Larger RCT are clearly needed to confirm these results.



Low-intensity focused ultrasound (LIFU) has recently been studied based on the results of several preclinical mechanistic studies. LIFU in experimental rodent models has been shown to have inhibitory effects on excitatory cell populations. Apart from a decrease in average EEG amplitude after LIFU, it was seen that LIFU significantly decreased the brain network connection strength across multiple brain regions. Besides neuromodulation, LIFU can also be used to temporarily open the blood brain barrier (BBB). In this way, drugs can be specifically targeted toward certain brain regions. Various studies showed that LIFU can lead to a decrease in seizure frequency in rodent epilepsy models but there is still limited evidence. Further investigations evaluating both efficacy and safety are required to provide conclusive data. Only recently, the first pilot study testing LIFU in epilepsy patients was published with promising results, although the sample size was small and no control group was included. There is a need for controlled clinical trials with larger study groups and long-term follow-up. As part of my professorship, I have opened a second research line alongside tDCS research by initiating a Dutch-Belgian collaboration between TU/e, Donders Institute Nijmegen and Ghent University/ Ghent University Hospital (BENEFUS). The purpose is to investigate the potential of LIFU in reducing EEG abnormalities and seizures in both experimental epilepsy models and epileptic patients. Initial grants for equipment have been awarded and a series of additional grant proposals have either been submitted, are under review or are in a preparatory phase.

While invasive neurostimulation for neurological disorders has become more widely available, the therapy is typically offered in a tertiary referral center by a multidisciplinary team of neurologists, neurosurgeons, neuroradiologists and neuropsychologists. Presurgical and surgical protocols based on clinical evidence are available. Based on the refractoriness and longstanding history of their conditions, patients are usually very much motivated to undergo surgery. The patients should be fully informed about the level of invasiveness and risks of the surgical procedure that is required to install a DBS or other invasive neurostimulation device. Informed consent is typically easily obtained and ethical concerns about the invasive procedures are minor or absent. Concerning ethical guidelines for DBS in psychiatric indications, DBS for psychiatric illness is less established and should be conducted in a multidisciplinary fashion on patients with documented refractory illnesses who have the capacity to consent, with long-term follow-up using established evaluation scales and with dissemination of all results, both positive and negative. Neurosurgery for psychiatric disorders should never be performed for political, law enforcement or social purposes, but with therapeutic intent aimed at the restoration of normal functioning and the amelioration of distress and suffering. While improved understanding of the dysfunctional brain structures underlying abnormal antisocial behavior or violence can lead to specific treatments using deep brain stimulation or other new noninvasive neuromodulation techniques, considerable debate on the efficacy,

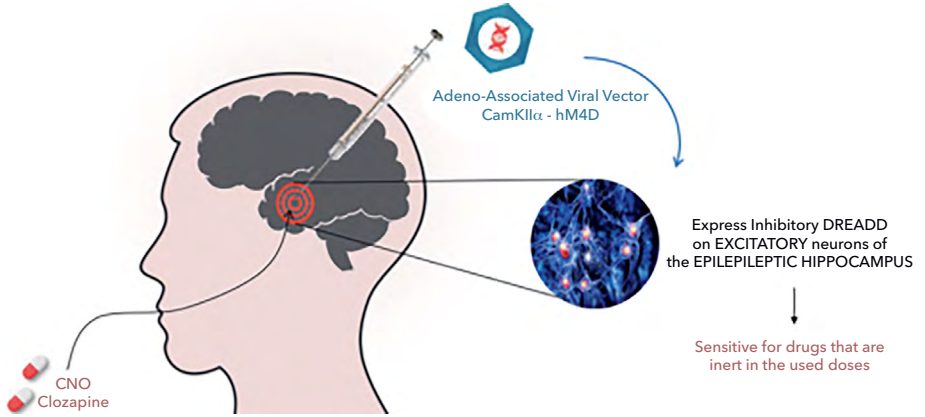
safety and ethical appropriateness remains. Due to its more widespread use for an increasing number of indications, DBS is now generally considered reversible and safe, not to say almost harmless, which disregards the inherent risks of hemorrhage and neurological deficit and the side effects of the chronic stimulation of various deep brain structures. This is particularly relevant to a trend of considering DBS interventions for the cognitive enhancement of healthy people. In that respect, noninvasive neurostimulation may become a more attractive option for further study in that domain.

Prospects for the future

Developing a neurostimulation device for patients requires a trade-off of sometimes conflicting constraints, such as invasiveness, precise targeting and patient acceptability. Noninvasive methods have the advantage of requiring no surgery, but typically require bulky wearables and doctor or patient intervention – the latter often resulting in lower levels of treatment adherence. Implantable devices provide higher spatial specificity and typically require less patient interaction. Critically important for invasive neurostimulation is the electrode-tissue interface where charge is carried from electrons in the electrode to sodium, potassium and chloride ions in the tissue. The charge transferred depends mainly on stimulation paradigms, material properties and tissue characteristics. When these are appropriately chosen, the electrode-tissue interface remains stable, enabling reliability in the stimulation of electrodes for preferably over at least ten years. Implanted materials should not cause inflammation or harm the surrounding tissue (biocompatibility) and the warm, wet and corrosive tissue environment should not damage the implant (biostability). The energy requirements (100 µW-10 mW) of an implanted device require innovative (and rechargeable) battery technology combined with much needed miniaturization. The possibility of storing and exchanging large datasets of ECG, EEG and other bio-signals recorded by neurostimulation devices, typically in the context of closed-loop stimulation, requires additional developments in data storage and transmitting modalities. To achieve these goals, various technical issues in the field of materials science, battery technology, electronics and data transmission and security must be solved.

Apart from the aforementioned technological challenges, what are the major knowledge gaps to be addressed by biomedical research in the coming years? I see the following challenges as the most important.

We need to improve our understanding of the different disease networks that underly major neurological conditions such as epilepsy and understand that even in a specific type of epilepsy, network abnormality may be different among patients. Inversely, a particular network abnormality may manifest itself in different clinical semiologies. A dysfunction of e.g., the amygdala may be expressed as seizures, posttraumatic stress disorder (PTSD) or other behavioral disorders. A major step towards improving insight into how epilepsy influences and disturbs brain networks will result from The Virtual Brain (TVB) project by the Human Brain Project (HBP) and its successor, EBRAINS. A clinical trial is currently underway to evaluate the personalized brain models of TVB as a new tool for epilepsy surgery planning, with promising first results. A better understanding of the effect of different stimulation parameters (output current, frequency, pulse width, duration, duty cycle, open or closed-loop paradigms) is essential to optimizing treatment outcome. A better understanding of the complex relationship between the acute and chronic effects of neurostimulation is equally important. Nearly all clinical studies have shown that the efficacy of therapeutic stimulation in epilepsy increases over time, while the true nature of this apparent neuromodulatory effect still escapes us. Improving automatic and reliable seizure detection, predicting periods of increased likelihood of seizure occurrence and the development of new biomarkers in other neurological conditions are other important issues to be addressed. The long-term monitoring of brain signals typically involves large datasets of which interpretation in real time requires advanced analytics that often rely on machine and deep learning and cannot be done without advanced computational capabilities. Alternative ways of selectively stimulating brain areas and even specific cell populations are to use chemogenetic or optogenetic approaches in which neurons are modified to express either designer receptors exclusively activated by designer drugs (DREADDs) or light-sensitive opsins that are then subsequently controlled by specific drugs such as clozapine or olanzapine or by the application of light. Early studies, some of which were performed in our group, have shown the potential of chemogenetic modulation to control seizures in experimental rodents. The potential therapeutic advantage of chemo and optogenetics is the specificity to cell types and the capability to directly inhibit or excite activity.



A variation on the theme of optogenetic modulation is to locally uncage antiseizure compounds by optic stimulation using photopharmacological methods. Again, early experiments on experimental animals performed in 4Brain have shown promising results. Translation to humans is not straightforward for technical reasons and concerns about the safety of viral vectors, the appropriate choice of the designer drugs, the power requirements for optical stimulation and the remaining need for an invasive trajectory for injecting compounds or photic stimulation.

The more widespread availability of neurostimulation devices to treat brain conditions clearly meets unmet therapeutic gaps and patient expectations. Patients want safe and effective devices, preferably less or non-obtrusive, that are accessible, affordable, easy to use and provide extra benefits such as control over their own health or brain data. The fact that many of these devices will be able to communicate with external platforms, transfer data and autonomously deliver stimulation based on biomarker analysis and the detection of events requires these systems to be safe not only in the biological sense of the word but also in terms of data management and data protection. The rapidly expanding market for neuromodulation devices also represents a challenge for reimbursement agencies and third-party payers. The regulatory requirements for bringing new devices to the market may be different from pharmacological therapies. The recent acquisitions of neurodevice-related expertise and device start-ups and companies by pharmaceutical companies, which often claim to offer therapeutic solutions rather than just drugs, should be seen in that light. When appropriately performed regulatory trials show benefit in terms of efficacy and risks, neurostimulation therapies should swiftly be brought to the market, approved by regulators and reasonably reimbursed. The rapid development of new neurostimulation devices may strain traditional administrative and regulatory approval procedures.

In conclusion, many neurostimulation treatments for patients whose chronic conditions cause suffering and disability often involve invasive technologies but can bring considerable relief and improvement to well-selected patients, often after other measures have failed. It is now clear that in most cases, neuromodulation therapy is no longer a treatment of very last resort and its earlier implementation may even modify the trajectory of some chronic conditions. Stimulation can be targeted to a dysfunctional brain focus, region or network and can be delivered as a single treatment continuously, according to a duty cycle or in response to physiologic changes. Programming can be titrated and modified based on the clinical response or a physiologic biomarker. The main challenge for clinicians, in addition to keeping pace with clinical and technological

developments, is to navigate complex ethical and economic considerations to ensure access to neuromodulation technology for a rapidly expanding population of patients. Neurostimulation for epilepsy is particularly well-established, with decades of experience with VNS and more recently DBS and RNS. Given the very active ongoing research in medical and technological research groups, including ours, into less obtrusive and highly innovative neurostimulation techniques, it seems very likely that neurostimulation for epilepsy and other neurological disorders will see a steep increase in development, accessibility and application for an increasing number of patients. Neurostimulation is no longer at the sideline but steadily moving to center stage.

I would like to end my inaugural lecture by thanking a number of people who have been supportive in my professional endeavors, more specifically in my work on neurostimulation for epilepsy and in my path to the professorship at TU/e. My mentor and PhD supervisor at Yale and Dartmouth Medical School, the late Professor Peter Williamson, Professor Susan Spencer, neurologist, Dennis Spencer, neurosurgeon, and Terry Darcey, biomedical engineer at Yale, who witnessed, first critically and later with much support, my increasing interest in neurostimulation for epilepsy. Professor Kristl Vonck, with whom I established the VNS program at Ghent University Hospital and performed the first preclinical research on rodents. Gert Van Hoey and Bart Van Rumste were my first PhD students from the Faculty of Engineering at Ghent University; both have had remarkable careers. From early on and for many years, I could count on the technical and intellectual support of Michel D'Havé, an engineer and, yes, one of my closest friends. Professors Vijay Thadani and Barbara Jobst from Dartmouth-Hitchcock Medical Center and Arthur and Christine Cukiert from Sao Paulo University, with whom we are doing many collaborative projects and who have become dear friends. Professor Christian Elger and Professor Johannes Schramm from Bonn, Professor Andreas Schulze-Bonhage from Freiburg and Professor Michel Baulac and his team from Pitié-Salpêtrière in Paris are acknowledged for their wonderful collaboration in many shared projects up to today. I want to mention the fruitful collaboration with the Katholieke Universiteit Leuven and Professor Lieven Lagae, Professor van Loon, Professor Bart Nuttin, Professor Tom Thys and Professor Marc Van Hulle. I am indebted to my colleagues at the Vrije Universiteit Brussel and Professor Ilse Smolders and her group, to Professor Jacques Brotchi, Dr. Benjamin Legros, Professor Chantal Depondt and Professor Xavier Detiège at the Université Libre de Bruxelles and to Professor Riem El Tahry and Dr. Susana Santos at the Université Catholique de Louvain. I want to thank my fellow chairmen of the Flemish academic neurology departments in Antwerp, Leuven and Brussels, Professors

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Micromed, who have all contributed to fruitful and stimulating collaborations that ultimately benefitted neurological patients. I need to mention my patients, who really are the reason for the existence of any clinician. For more than three decades up to today, I have met so many motivated and courageous individuals, most of whom were beacons of positive expectation and hope. I dedicate this professorship to them. Finally, I would like to thank Professor Meno Kok, CEO EIT and Carmen Van Vilsteren, with whom I shared many stimulating moments in the Board of Directors of EIT Health. In the context of EIT Health, thank you Rector Professor André Oosterlinck for your mentorship and friendship. My sincere gratitude goes to the TU/e leadership, to past and present deans Professor Ton Backx and Professor Bart Smolders and to Rector Magnificus Frank Baaijens for their trust and faith in me over the previous years and in the years to come. You all make me feel a proud member of the TU/e community.

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Curriculum Vitae

Prof.dr. Paul Boon, neurologist and chairman of the Department of Neurology at Ghent University Hospital, was appointed professor of Neuromodulation at the Department of Electrical Engineering at Eindhoven University of Technology on February 1, 2019. His chair is supported by Epilepsie.NL.

After completing studies at Ghent University Medical School, Belgium and Yale University Medical School, USA, Paul Boon became a faculty member in the department of Neurology at Ghent University Hospital in 1990. He started the epilepsy monitoring unit, expanded facilities for patients with epilepsy and neurological sleep disorders, and founded an experimental laboratory for translational brain research (4Brain). In 1994, Dr. Boon was awarded a PhD after defending a doctoral thesis entitled “Refractory lesional epilepsy, clinical and neurophysiological localization”. Paul Boon has been a Full Professor of Neurology since 2007. He has served and is currently serving in various leadership positions such as R&D director, and strategic advisor to the board of directors of Kempenhaeghe and chairman of the Division of Head, Movement and Senses at Ghent University Hospital. He has published widely (> 600 publications) in peer reviewed international journals (including The Lancet and The New England Journal of Medicine and Nature), presented his work in the field of epilepsy, neurophysiology, neuroimaging and neuromodulation worldwide, and trained a large group of neurology residents and PhD students. Professor Boon is President of the European Academy of Neurology.

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