University of Szeged

Albert Szent-Györgyi Medical School

Doctoral School of Clinical Medicine

Neuromodulation of the sensory system: a computer-brain-spine interface to aid balance and gait

PhD Thesis

László Halász, MD

Supervisor: Loránd Erőss, MD, Ph.D

Szeged

2024

Publications directly related to this thesis

Kelemen, Andrea; **Halász, László**; Muthuraman, Muthuraman; Erőss, Loránd; Barsi, Péter; Zádori, Dénes; Laczó, Bence; Kis, Dávid; Klivényi, Péter; Fekete, Gábor
Clinical parameters predict the effect of bilateral subthalamic stimulation on dynamic balance parameters during gait in Parkinson's disease
FRONTIERS IN NEUROLOGY 13 Paper: 917187, 9 p. (2022)

IF: 3.4

Halász, László; Sajonz, Bastian E A; Miklós, Gabriella; van Elswijk, Gijs; Hagh Gooie, Saman; Várkuti, Bálint; Tamás, Gertrúd; Coenen, Volker A; Erōss, Loránd
Predictive modeling of sensory responses in deep brain stimulation
FRONTIERS IN NEUROLOGY 15 Paper: 1467307, 11 p. (2024)

IF: 2.7

Várkuti, Bálint; **Halász, László**; Hagh Gooie, Saman; Miklós, Gabriella; Smits Serena, Ricardo; van Elswijk, Gijs; McIntyre, Cameron C; Lempka, Scott F; Lozano, Andres M; Erōss, Loránd
Conversion of a medical implant into a versatile computer-brain interface
BRAIN STIMULATION 17: 1 pp. 39-48., 10 p. (2024)

IF: 7.6

1. Introduction

Neuromodulation offers a wide range of opportunities to engage with both the peripheral and central nervous systems. Since the first report by Pollak and Benabid on deep brain stimulation (DBS) and the early work by Shealy on spinal cord stimulation (SCS), there have been significant advancements in these therapies. We can now visualize the fibers we are stimulating using non-invasive magnetic resonance imaging, and we can also describe the underlying network principles related to the dysfunction of these systems. Ongoing research and improvements in the design of the initial neurostimulators have enabled us to target different neural structures more selectively. Despite these advancements and the expansion of our available tools in recent years, managing late-stage symptoms of neurodegenerative diseases, such as Parkinson's disease (PD), remains challenging.

1.1 Principles of deep brain stimulation

Deep brain stimulation is an invasive procedure wherein a stimulation lead is placed into a targeted structure,

followed by the implantation of a pulse generator in the infraclavicular fossa. To reach the necessary area, such as the internal part of the globus pallidus (GPi) for dystonia or Parkinson's disease, the ventral intermediate nucleus (as defined by Hassler) (VIM) for essential tremor (ET) or tremor-dominant Parkinson's disease, and the subthalamic nucleus (STN) for Parkinson's disease ventriculography combined with standard coordinate-guided stereotactic surgeries have been the mainstay at the beginning. Subcortical regions were extensively studied, and atlases standardizing the basal ganglia were created. Microelectrode recordings and awake procedures have allowed for precisely optimizing the final lead's location. Moreover, advancements in magnetic resonance imaging have enabled a transition to procedures conducted under general anesthesia with direct anatomical guidance targeting.

1.2 Advanced-stage Parkinson's disease and deep brain stimulation

Various studies have examined the optimal timing for implementing deep brain stimulation to treat Parkinson's

disease. As a consensus, DBS in PD is still determined by the therapeutic response and the onset of fluctuations, and most patients undergo surgery 14-15 years after the diagnosis.

Although initial therapeutic results improve motor symptoms and quality of life, several factors begin to decline in the years following treatment initiation of DBS. Freezing of gait and balance problems are still hard to manage as the initial effects of DBS tend to fade in the first 3 years.

1.3 Deep brain stimulation in Parkinson's disease, a network principle

In current clinical practice, deep brain stimulation is regarded as the gold standard therapy for movement disorders. The optimal electrode placement targets the dorsolateral region of the subthalamic nucleus. High-frequency stimulation via electrodes in this area helps inhibit cellular hyperactivity. While cell stimulation has long been viewed as the primary mechanism of this effect, recent publications highlight the significance of white

matter stimulation, leading to a shift to a network-based paradigm.

Diffusion tensor imaging (DTI) and tractography provide a novel method to deconstruct fiber structures entering and traversing the subthalamic area. Individualized parcellation of the subthalamic nucleus might advance to find the optimal target for DBS.

1.4 Sensory system and deep brain stimulation

In conditions such as essential tremor or Parkinson's disease, it's important to avoid stimulating the sensory fibers, particularly the medial lemniscus. Utilizing probabilistic or deterministic tractography to locate these fibers during the planning phase can help minimize the risk of unwanted paresthesia. Additionally, implementing current steering after the implantation of segmented leads can further expand the therapeutic window in complex cases.

In patients with ET, optimal placement of the DBS electrode targets the area within or near the dentate-thalamic (DRT) tract. The medial lemniscus runs closely

alongside the DRT until it reaches the thalamus. Stimulation of the lemniscal area, which induces transient paresthesia, is a reliable indicator for determining the final lead position when optimal tremor control is achieved. In Parkinson's disease, the medial lemniscus is located posterior to the STN; thus, transient paresthesia could be evoked even on an optimal lead placement.

1.5 Principles of spinal cord stimulation

Spinal cord stimulation is an invasive procedure wherein an electrode is implanted into the dorsal epidural space through percutaneous technique or direct surgical exploration. The electrode is usually placed at the ThIX-X vertebral level. Then it is externalized for a short 3-4 week testing period through an extension cable and connected to an external neurostimulator. The main indications for SCS are neuropathic pain syndromes, but its use was also explored in bladder dysfunction and even regaining motor functions after spinal cord injury.

2. Aims and objectives

2.1 To assess kinematic predictors related to balance and gait in Parkinson's disease

We wanted to explore the possibility of finding specific parameters or kinematic predictors related to dynamic balance and gait in PD using 3D movement analyses. We also wanted to obtain spatial and stimulation-related information by examining lead positions in our patients' brains.

2.2 To create artificial balance through sensory substitution using DBS and SCS

In recent years, the development of brain-computer interface systems has allowed us to tap into deep brain or spinal cord fibers to test novel therapeutic options. We created our experimental system for two distinct purposes:

We wanted to explore the parameter space (frequency, pulse width, amplitude, active contact locations) and the therapeutic window in DBS programming. We proposed an algorithm based on machine learning to reliably predict

stimulation-induced paresthesia and rule out unwanted side effects during DBS programming. We also wanted to create intentional, reproducible paresthesia in a predictable fashion for further use through sensory substitution in possible new indications in DBS therapy

We wanted to intentionally create stimulation-induced, reliable, reproducible paresthesia using SCS to provide artificial balance information through the sensory system.

3. Materials and Methods

3.1 Predicting clinical parameters influencing dynamic balance in Parkinson's disease

To assess clinical factors influencing dynamic balance in Parkinson's disease, including double support, peak turning velocity, range of motion, and trunk velocity in 3 planes (sagittal, coronal, and axial), we obtained and analyzed datasets of 20 patients (24 enrolled). Motion sensor data, DBS lead location, and demographic factors, such as disease duration and levodopa dose, were also considered.

To obtain motion data, we used six wireless Opal monitors. Supplied dataset from each provided gyroscopic and accelerometric parameters in a three-dimensional reference system.

Instrumented Timed Up and Go and Instrumental Clinical Test of Sensory Integration and Balance tests were conducted, and the resulting parameters were assessed in four stimulation conditions after a 12-hour-long medication withdrawal. Stimulation conditions were as follows: bilateral stimulation OFF (OFF), bilateral stimulation ON (StimON), unilateral stimulation right side ON (R-StimON), unilateral stimulation left side ON (L-StimON). Stimulation parameters were set according to therapeutic stimulation; no changes were made in the optimal active contacts, amplitude, frequency, or pulse width.

Disease-related parameters were collected to be included in a quantifiable dataset. The Unified Parkinson's Disease Rating Scale part III (UPDRS III) provided calculated results of levodopa responsiveness in preoperative ON and OFF states, while age, disease duration, preoperative and

postoperative Hoehn-Yahr stage, and time elapsed since the operation were also obtained. International Parkinson and Movement Disorders Society UPDRS III (MDS-UPDRS III) in stimulation ON and OFF states indicated stimulation responsiveness during our examination.

3.2 Predictive modeling of sensory responses in deep brain stimulation

We designed a study in which an externalized DBS system implanted in the surroundings of afferent sensory fibers would provide enough data to assess the sensory activations through controlled paresthesia.

Ten patients were enrolled in two centers: Semmelweis University, Institute of Neurosurgery and Neurointervention, and Medical Center of Freiburg University. Each patient received segmented DBS electrode systems (Vercise Cartesia, Directional Lead, DB2202, Boston Scientific Corporation, Marlborough, MA, United States). Two patients were implanted due to chronic, medically intractable pain; seven patients

received DBS for essential tremor; and one for tremor-dominant Parkinson's disease.

Pain patients were only stimulated on the thalamic electrodes, while essential tremor and Parkinson patients received bilateral stimulations with an external programmable neurostimulator. In Freiburg, we used a Neuro Omega stimulator, in Budapest, a CereStim stimulator was applied. The patients expressed feedback about stimulation-related sensations orally or via button press.

Paresthesia was evoked in almost every instance during our stimulation trials, with only a few cases where no paresthesia was reported. For this reason, we introduced "pseudotrials" with configurations in the parameter field that were synthesized from the empirical data, evoking no responses. By generating new combinations of stimulation parameters, we supplemented the dataset of stimulation-evoked parameters.

Two scenarios were defined to measure the strength of our prediction system. Stimulation energy-related parameters,

such as amplitude, frequency, and pulse width, along with the hemispheric location (left or right), were decisively chosen as classifiers to predict the occurrence of paresthesia effectively. For somatic representation, such as the paresthesia evoked in the finger, wrist, hand, or leg, the spatial information provided by the reconstructed VTA models was selected for training. The prediction models were trained using the LogiBoost algorithm and were evaluated with a nested two-level (K by L) cross-validation approach.

3.3 Artificial balance information induced in the sensory system at the level of the spinal cord

We recruited 20 patients who underwent standard externalized SCS lead implantation for medically intractable chronic pain to assess sensory information transmission through the spinal cord using conventional spinal cord stimulation systems.

Patients were sitting in front of a computer monitor; their externalized electrodes were connected to an external programmable neurostimulator (CereStim). For balance

studies, a card box or a baseball cap was used that had an Arduino circuit board with an embedded inertial sensor inside. A custom Matlab code and the Psychophysics Toolbox were used to deliver electrical, and visual stimuli and record input from the participants.

To obtain effective outcomes, sensations needed to be consistently elicited. Distinguishable dermatome regions where a certain sensation threshold was reached using specific parameters were termed perceptual channels. Each perceptual channel was subdivided according to different intensity levels of sensation.

Through the verification stage, we sought consistent reports from the participants using the same parameters. Sensation intensity levels were also verified in pairs, e.g., level 1 was lower than level 2, and level 2 was lower than level 3.

During balance tasks, three increasing amplitudes were used on two perceptual channels, indicating left and right. Patients had to reach an artificial equilibrium by considering only paresthesia-related factors. In the initial

trials, participants needed to achieve equilibrium by tilting a balance board to a randomly chosen angle determined by the computer. In the second set of trials, patients were required to tilt their heads according to the levels and directions indicated by the stimuli.

4. Results

We concluded that most factors influencing dynamic balance and gait cannot be improved through DBS as the disease progresses. Steering the stimulation field to a more posterior position could have a beneficial effect in the short term. Estimating activated fiber tracts should be necessary to achieve the best clinical results.

Double support, a part of walking the cycle when both feet are on the ground, is related to freezing. Its parameters did not change after switching on the stimulation on the group level and did not differ from control values. Individual changes in double support and horizontal range of trunk motion due to stimulation could be predicted by disease-related factors and the severity of the disease.

A more posterior lead position in the STN provided favorable dynamic balance outcomes. A superior lead position did not improve double support or dynamic balance.

For this reason, we designed two experimental systems to assess sensory stimulation to manage balance and gait. Using DBS, stimulation-induced paresthesia could be evoked in at least 2 different somatic areas in each patient, most frequently reported in the fingers, palm of the hand, and thumb.

Our machine learning-based algorithm could predict the occurrence of paresthesia by providing the system parameters related only to stimulation (hemisphere, frequency, pulse width, amplitude). Including VTA-related data for further analysis could even reliably predict the location of the paresthesia (hand, fingers, etc.)

These results indicate that our prediction model could effectively rule out unwanted paresthesia during a standard clinical programming session.

Utilizing information about VTA locations and stimulation parameters, the location of paresthesia can be reliably predicted and the sensation could be maintained in patients.

Using SCS, paresthesia could be evoked in each patient. After a short calibration phase perceptual channels could be successfully established. These perceptual channels had 3 distinct levels of stimulation-induced paresthesia in two body regions, each on one side of the body. Different levels of sensations could achieve artificial balance information, which the patients could utilize to change their body or head positions accordingly.

5. Discussion

Gaining insight into the activated network and identifying locations of the stimulating electrode contacts may be essential for correcting balance dysfunction. Our study suggests that dynamic balance can also be inferred from the positions of the active contacts. Our findings align with the observation that the pedunculo-pontine fibers run through the H2 Field of Forel, situated superior to the

STN, thus leading to no beneficial effect on stimulation. Previous research has indicated that high-frequency stimulation of the pedunculopontine nucleus can exacerbate axial symptoms. Our results reinforce the need for a more individualized, network-centric programming philosophy in DBS.

Persistent or severe transient paraesthesia induced by stimulation is generally uncomfortable and should be avoided during DBS programming. Recent advancements in neurostimulator system development have provided the ability to adjust the stimulation current to expand the therapeutic window and significantly increase the range of available parameters. In our study, we reported the possibility of predicting the occurrence and the location of these unpleasant sensations using artificial intelligence and predictive modeling.

An additional important insight from our findings is that stable and accurately predicted paresthesia can be achieved through specific stimulation parameters. This opens the potential to develop a computer-brain interface that uses the sensory system for sensory substitution.

For a successful sensory input in a computer-brain interface, stable paresthesia must be induced. In our study, we successfully elicited controlled sensation in 20 SCS patients, with each completing the system calibration phase in just 90 minutes.

The use of perceptual channels proved highly effective in encoding artificial balance information. In the balance task, while all participants performed above chance, many made some errors. Body positions, randomly assigned by the computer, could be reached by the patients in both standing and sitting positions. Body tilt could also be reached parallel to a balance board held by an investigator in blindsight.

6. Conclusions and limitations

Managing gait and balance in diseases such as Parkinson's disease remains challenging. Our results indicate that most factors related to dynamic balance are connected to disease-related factors and are hardly influenced by DBS in the long term. Thus, developing novel neuromodulation

systems or new stimulation paradigms is required to provide salvage therapy in advanced and late-stage PD.

We established that machine learning algorithms could accurately predict the occurrence of paresthesia. The locations of these sensory responses can be predicted by incorporating lead positions and VTA reconstructions. Such a tool can provide an option to reduce the occurrence of unwanted paresthesia during standard clinical programming. Still, it can also be an essential option to generate stable perceptual channels within the brain for sensory substitution. We could use such perceptual channels provided by paresthesia evoked by SCS in pain patients to create artificial balance information. Training time to understand this new information was short and possible in older patients. These findings further emphasize that CBI systems might be essential to treat disorders related to balance and gait. Our findings might also provide a base for developing neuroprosthetics and artificial sensation.

Our computer-brain interface studies were developed to be concluded in a short period of time during an

externalization phase. Thus, chronic use of these devices has yet to be evaluated. Selective activation of sensory fibers is still limited by the available technology of DBS or SCS and lead construction. Habituation to the elicited paresthesia was not observed by our group in the short term but might occur in a chronic setting. Our stimulation paradigm was generated by advanced stimulator systems; its use in actual patients in the long term might require the development of new neurostimulator systems. Our results are limited in showing the exact use of our proposed methods in an actual disease and should only be considered proof of concept. This indicates that further research is required in this field. Ideas proposed in this thesis are designed to be used with off-the-shelf neuromodulation devices in the future.