III. INTERNATIONAL CONFERENCE ON DEEP BRAIN STIMULATION

– virtual meeting –

November 20 – 21, 2020

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Movement decoding from cortical and subcortical oscillations based on spatial filtering in patients with Parkinson's disease

Victoria Peterson[1], Timon Merk[2], Witold Lipski[3], Andrea Kühn[2], Vadim Nikulin[4], Wolf-Julian Neumann[2], Mark Richardson[1]

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Deep brain stimulation (DBS) is an effective therapy for Parkinson's disease (PD) patients with motor complications. With conventional DBS, the target area is chronically stimulated at high frequencies, potentially leading to side-effects. Closed-loop or adaptive DBS (aDBS) systems aim to overcome such limitations by adjusting the stimulation parameters in real-time. Decoding voluntary movements from brain signals may improve aDBS, by allowing adaptation to the concurrent motor state, which is fundamental for human behavior. Although it has been shown that the combination of different spectral band-power features improves movement prediction from invasive recordings, most existing decoding algorithms are based on single-electrode approaches (or mass univariate). Here, we use electrocorticography (ECoG) and subthalamic nucleous (STN) local field potential (LFP) recordings combined with a spatial filtering technique and a filter bank analysis to construct a movement decoding model. We show that this multivariate approach can be used to decode voluntary movement using either cortical or subcortical recordings.

Simultaneous ECoG and subthalamic LFP recordings were obtained in 11 PD patients who participated in a grip-force task during DBS electrode implantation. The recorded brain activity can be modeled as a linear combination of different individual sources. Spatial filtering approaches aim at finding such linear combinations of activity from individual channels which would result in the desired properties of the obtained components. In particular, the Source Power Comodulation (SPoC) aims to find the neural oscillations with power time courses correlating (or anti-correlating) with an external target variable. To predict the force, we used SPoC as a spatio-spectral feature extraction method together with a regularized linear regression model. We evaluated the method by using beta band power (13 – 35 Hz) as well as a filter-bank (FB) approach. The prediction pipeline was implemented following a fully real-time compatible setup. The approach was compared to single electrode (SE) models, commonly used for movement decoding from invasive recordings. The goodness in the prediction was measured by the R2 coefficient.

We consistently found that decoding based on ECoG data performed better than STN LFP data, and that the highest R2 values could be achieved for contralateral movements. Contralateral ECoG with SPoC performed significantly better than the single electrode approach when only a single band power feature (beta activity) was used (SPoC R2=0.10, SE R2=0.07, p-value=0.038) as well as for the filter-bank decomposition (FB-SPoC R2=0.20, FB-SE R2=0.18, p-value=0.038). The topography maps of the most relevant spatial pattern also revealed that the location of the underlying source corresponds to the sensorimotor cortex.

In this work we have shown for the first time that spatial filtering approaches can be used for real-time compatible voluntary movement decoding from invasive ECoG and STN LFP data in patients with Parkinson's disease. The SPoC approach extracts neuronal sources by using spatial information distributed over different channels to find the component most correlated with the target variable of interest. Exploring optimized multivariate decoding methods for clinical symptoms and movement is important for the next generation of intelligent clinical brain computer interfaces.

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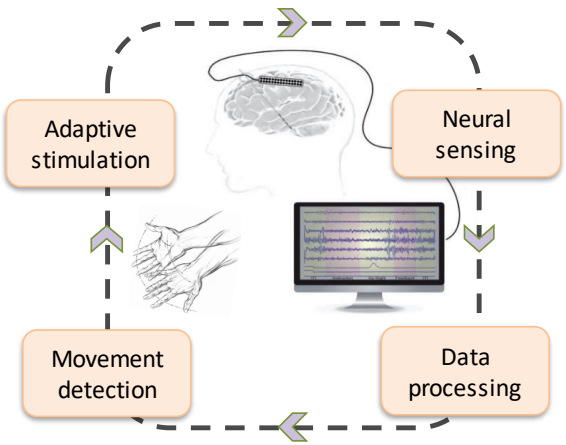
Movement decoding from cortical and subcortical oscillations based on spatial filtering in patients with Parkinson's disease

Victoria Peterson, Timon Merk, Witold Lipski, Andrea A. Kühn, Vadim Nikulin, Wolf-Julian Neumann*, Mark Richardson*

Background:

- For the development of adative DBS **online movement decoding** should be done based on **invasive brain signal recordings**.
- **Multivariate** (multichannel) brain decoding algorithms allow to impose spatial information to the model.
- **Multimodal** brain recording could enhance the next generation of aDBS.



*equal contribution

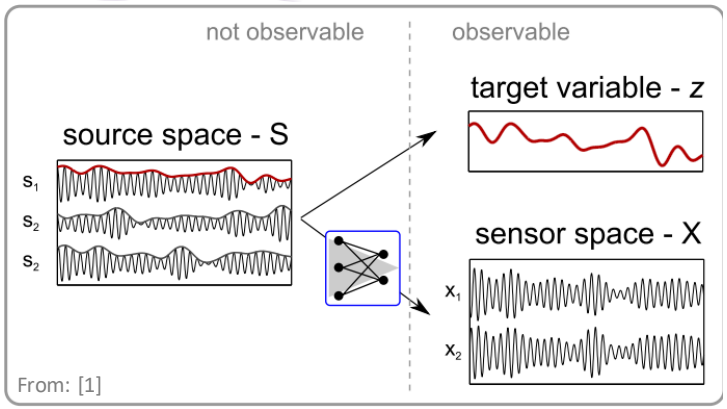
Methods:

1. Cortical and subcortical recordings

- Intraoperative ECoG and LFP-STN simultaneous recording.
- 11 PD patients.
- Grip-force task.

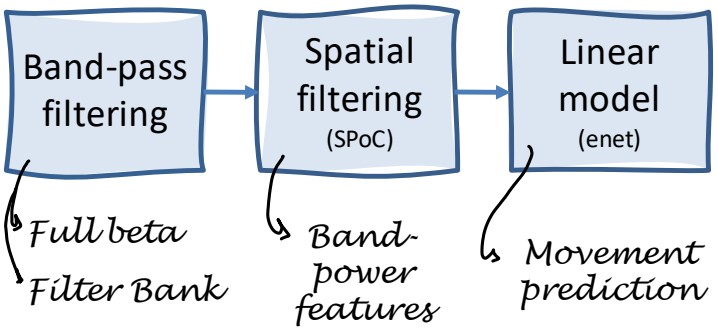
2. Source Power Comodulation (SPoC) [1]

- Supervised spatial filtering approach

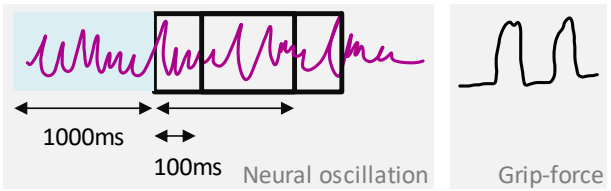


[1] Dähne, S., et. al (2014). SPoC: A novel framework for relating the amplitude of neuronal oscillations to behaviorally relevant parameters. https://doi.org/10.1016/j.neuroimage.2013.07.079

3. Movement decoding approach



"Fully real-time compatible setup"

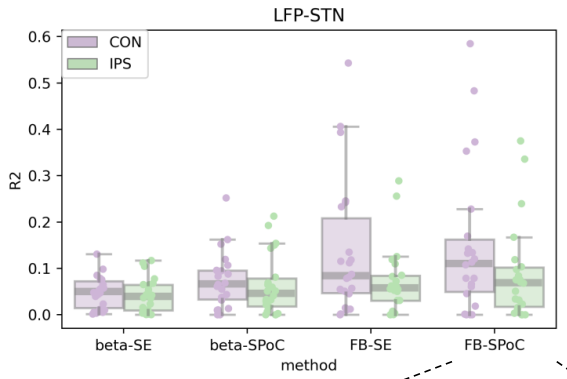


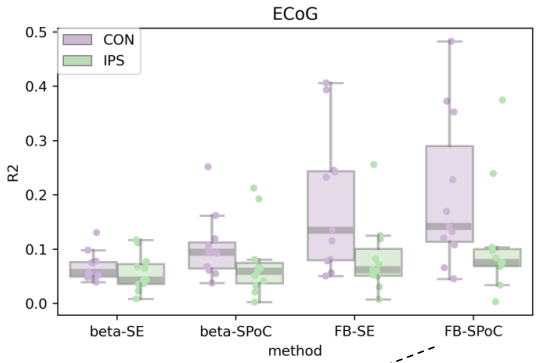
- 3-folds validation scheme.
- Hyperparameter search based on Bayesian Optimization.
- Compared against a single electrode (SE) approach.

Results:

Comparative Results

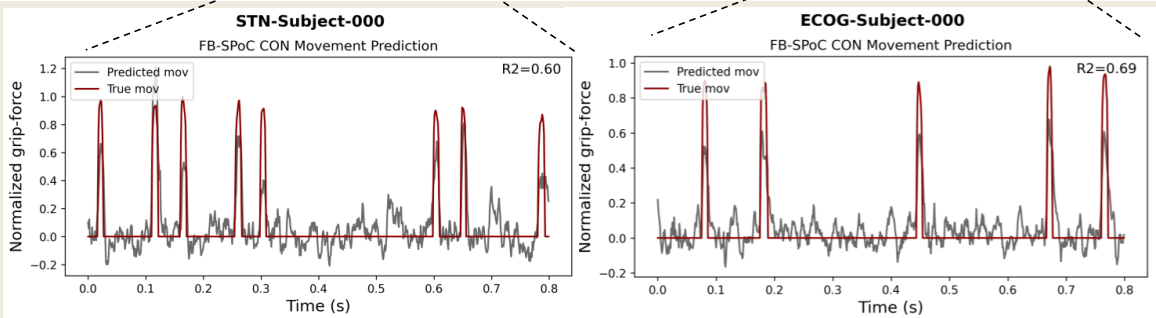
"Movement prediction using contralateral ECoG based on a filter bank analysis combined with spatial filtering performs best."





- ✓ ECoG CON > ECoG IPS (p-value=0.04)
- ✓ ECoG CON > STN CON (p-value=0.06)
- ✓ ECoG: beta-SPoC > beta-SE (p-value=0.03)
- ✓ ECoG: FB-SPoC > beta-SPoC (p-value=0.03)
- ✓ ECoG: FB-SPoC > FB-SE (p-value=0.03)

Example of predicted movement



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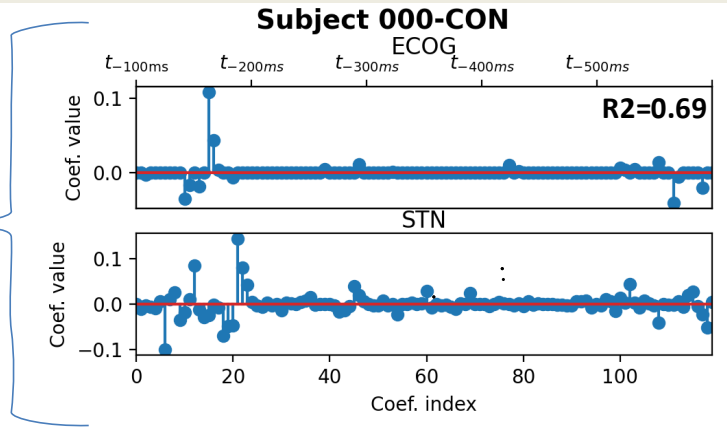
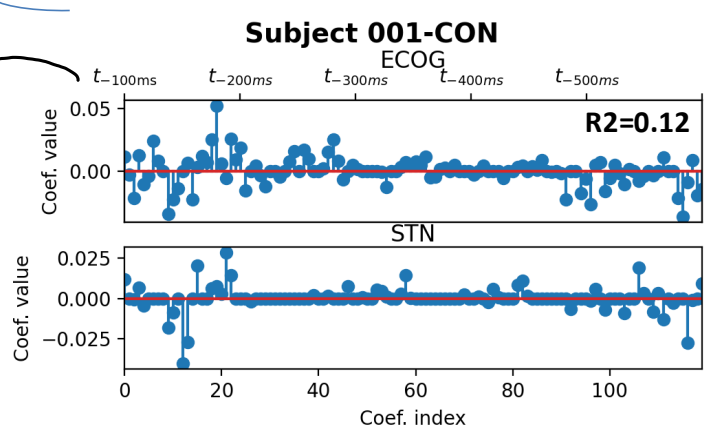
Results:

Selected features

3 band-power features
x
8 freq. Bands
x
5 time-lags

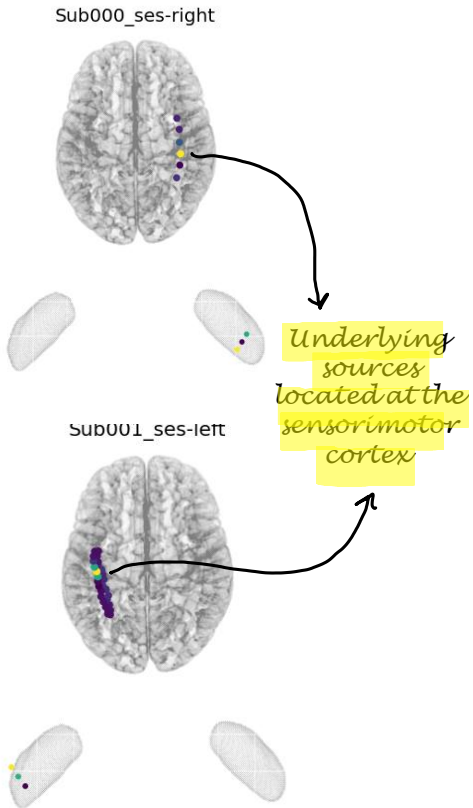
120 features





More non-zero coefficients

Patterns in full beta band



Conclusion:

Spatial filtering approaches can be used for real-time compatible voluntary movement decoding from invasive ECoG and STN LFP data in patients with Parkinson’s disease.

By means of SPoC we were able to extracts those neuronal sources that where most correlated with the grip-force output.

The combination of filter bank analysis with spatial filtering allowed us to gather spectral and spatial information to boost movement decoding performance.

The combination of STN LFP and ECoG features might improve the decoding performance.

Exploring optimized multivariate decoding methods for clinical symptoms and movement is important for the next generation of intelligent clinical brain computer interfaces.

Sensorimotor electrocorticography (ECoG) vs. Subthalamic local field potential (LFP) based decoding of grip force in patients with Parkinson's disease

Timon Merk[1], Victoria Peterson[2], Witold Lipski[3], Benjamin Blankertz[4], Tom Mitchell[5], Andrea A. Kühn[1], Robert S. Turner[3], Wolf-Julian Neumann[1], R. Mark Richardson[2]**

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* These authors contributed equally to the study.

The human cortico-basal ganglia circuit encodes critical information underlying kinematic control and movement vigor. Machine learning based decoding of kinematic signals may augment clinical brain computer interfaces to support motor function in patients with neurological disorders. Although this strategy has been studied primarily using cortical population activity, recent studies using local field potentials (LFP) from the subthalamic nucleus (STN) have shown promising advances in patients with Parkinson's disease (PD). [1] Subthalamic deep brain stimulation (DBS) is an effective treatment for PD patients with motor complications that gives unique access to invasive neurophysiology. Real-time adaptation of DBS parameters based on brain signal decoding bears significant potential to further improve therapeutic efficacy for patients with movement disorders, but optimal decoding strategies remain to be elucidated. The present study compares the decoding performance of grip force from subdural electrocorticography (ECoG) and subthalamic LFP signals in patients with Parkinson's disease.

Subdural sensorimotor ECoG signals were recorded simultaneously with STN-LFP in 11 Parkinson's disease patients performing a grip force task during awake functional neurosurgery. Neural sources (Cortex vs. STN), signal features (band power from Theta, Alpha, Beta and Gamma oscillations) and machine learning methods were compared in a systematic and fully real-time compatible manner. Band power features were used to train Linear Models (LM), Neural Networks (NN) and ensemble based methods (XGBOOST) within a Bayesian Optimization hyperparameter search to decode grip force. Performance was quantified as the proportion of grip force variance explained by the model and depicted as coefficient of determination (R^2). Correlation of decoding performance with anatomical location and PD motor sign severity (UPDRS-III) was estimated using linear mixed effects models and correlations.

We have developed and evaluated an optimal real-time enabled machine learning strategy for ECoG and LFP signals. Our results consistently show that there is a significant performance advantage of motor cortex ECoG over STN signals for movement decoding. We highlight the utility of gradient boosted ensemble methods, which outperformed linear models and artificial neural networks. Negative correlation of PD motor signs with decoding performance hints toward deterioration of neural coding capacity in the hypodopaminergic state. Although the implantation of ECoG strip electrodes is currently not a part of routine clinical practice, our results show that ECoG promises significant advantages for BCI based decoding for next-generation neurostimulation approaches, such as intelligent adaptive DBS for Parkinson's disease [2].

References

[1] S. A. Shah, H. Tan and P. Brown, „Continuous force decoding from deep brain local field potentials for Brain Computer Interfacing," 2017 8th International IEEE/EMBS Conference on Neural Engineering (NER), Shanghai, 2017, pp. 371-374, doi: 10.1109/NER.2017.8008367

[2] Neumann, W., Turner, R.S., Blankertz, B. et al. Toward Electrophysiology-Based Intelligent Adaptive Deep Brain Stimulation for Movement Disorders. Neurotherapeutics 16, 105–118 (2019). https://doi.org/10.1007/s13311-018-00705-0

PRESENTER:
Timon Merk

Sensorimotor electrocorticography (ECoG) vs. Subthalamic local field potential (LFP) based decoding of grip force in patients with Parkinson's disease

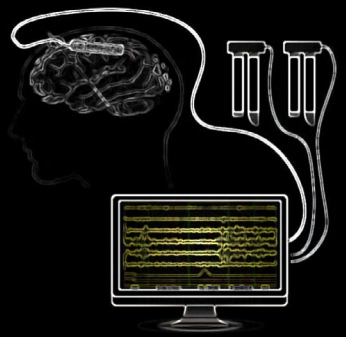
BACKGROUND

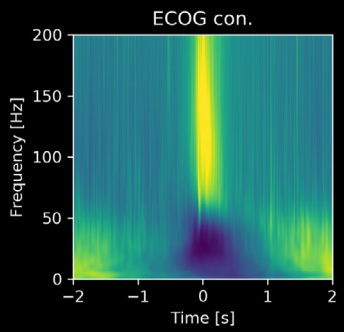
- Movement decoding could be used to inform **adaptive Deep Bran Stimulation** (aDBS) for Parkinson's disease (PD) [1]
- Movement decoding was described for ECOG [2] and STN [3] signals in separate patient cohorts

GOAL

Decoding performances comparison using different Machine Learning algorithms across cortex and STN in a single cohort of PD patients.

- **11** Parkinson Disease (PD) patients
- **Grip force task**
- **Simultaneous** intraoperative subdural electrocorticographical (ECoG) and subthalamic (STN) local field potential (LFP) recordings





Timon Merk[1], Victoria Peterson[2], Witold Lipski[3], Benjamin Blankertz[4], Andrea A. Kühn[1], MD, Robert S. Turner[3], Wolf-Julian Neumann[1]*, R. Mark Richardson[2]* (*equal contribution)

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[2]Department of Neurological Surgery, Massachusetts General Hospital, Boston, USA
[3]Department of Neurobiology, University of Pittsburgh, Pittsburgh, USA
[4]Department of Computer Science, Technische Universität Berlin, Berlin, Germany

[1] Closed-loop DBS triggered by real-time movement and tremor decoding based on thalamic LFP's for essential tremor (He et al 20)
[2] Decoding Movement From Electrocorticographic Activity: A Review (Volkova et al 20)
[3] Decoding voluntary movements and postural tremor based on thalamic LFPs as a basis for closed-loop stimulation for essential tremor (Tan et al 19)

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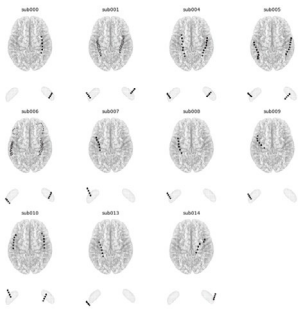
Patient individual electrode placement



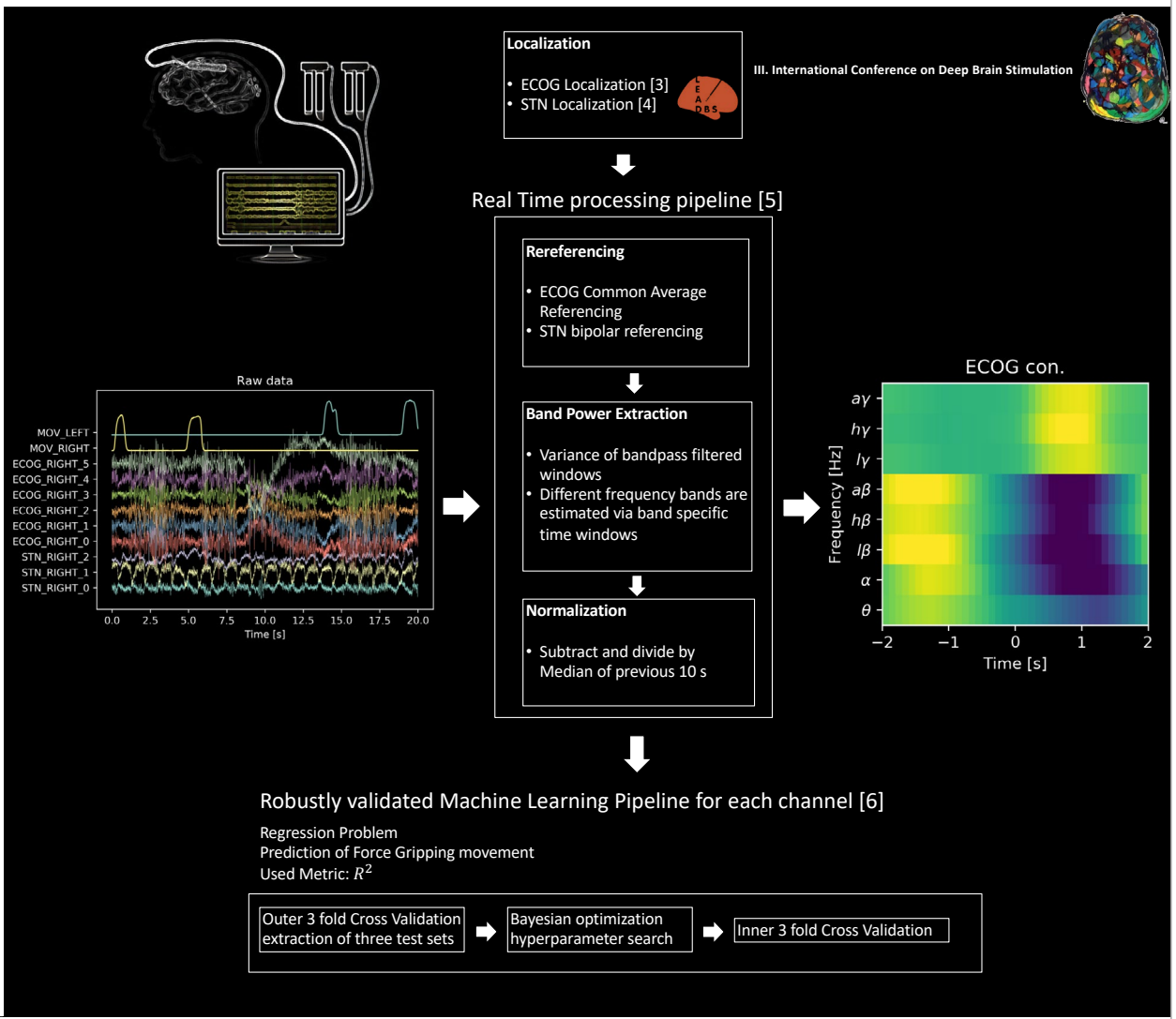
Methods

Data Structure

- Band power downsampled to 10 Hz
- For each channel 8 frequency bands are concatenated for 5 time points (40 features)
- Localization of electrodes in MNI space using Lead-DBS and a custom ECOG specific package

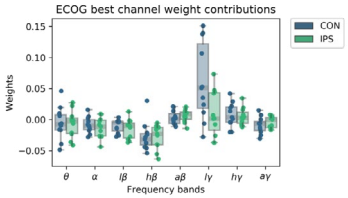
Machine Learning models

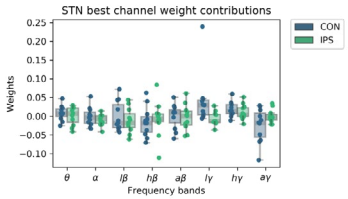
- Elastic Net Regularized Linear Model
- Different Neural Network Architectures
- Source Power Comodulation (SPOC) [1]
- Extreme Gradient Boosted Trees (XGBOOST) [2]



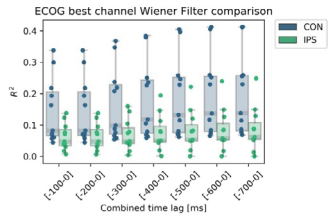
[1] SPoC: A Novel framework for relating the amplitude of neuronal oscillations to behaviorally relevant parameters (Dähne et al 14)
[2] https://xgboost.readthedocs.io/en/latest/
[3] Three-dimensional localization of cortical electrodes in deep brain stimulation surgery from intraoperative fluoroscopy (Randazzo et al 16)
[4] https://www.lead-dbs.org/
[5] https://github.com/neuromodulation/icn/tree/master/icn_m1
[6] https://github.com/neuromodulation/icn/tree/master/ECOG_vs_STN

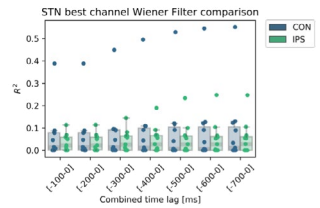
Best channel LM Results





Wiener Filter Best channel performances





Results feature parametrization

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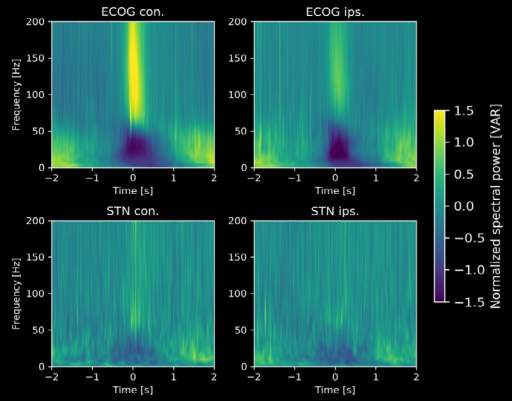
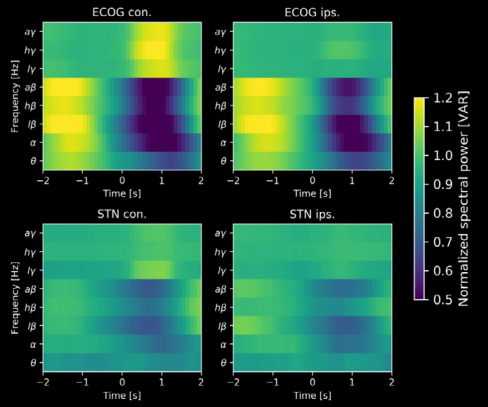
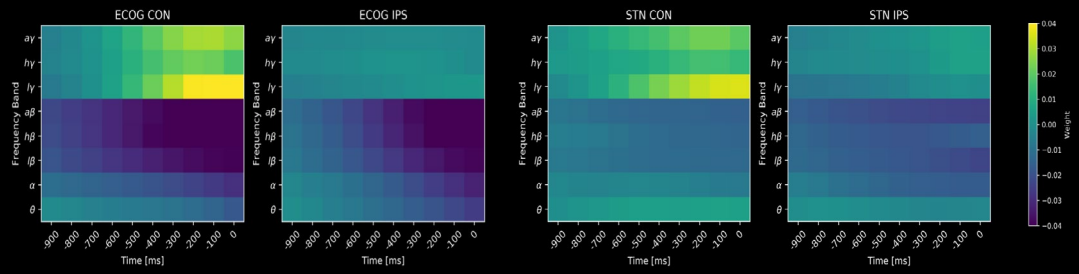
All channels movement aligned time frequency plots



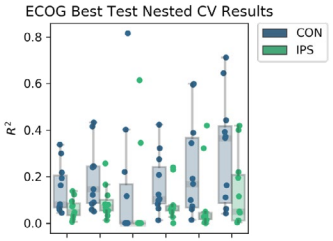
All channel movement aligned normalized spectral power features

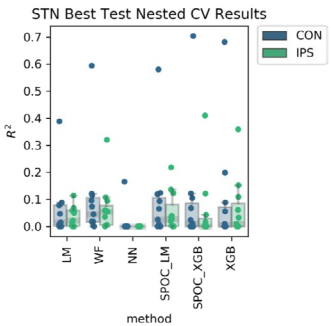


Best channel specific time – band specific coefficients

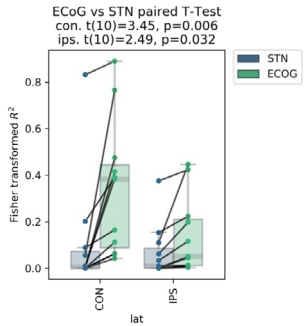


Machine Learning model selection results





Best ECOG vs best STN channels



Results

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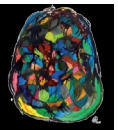
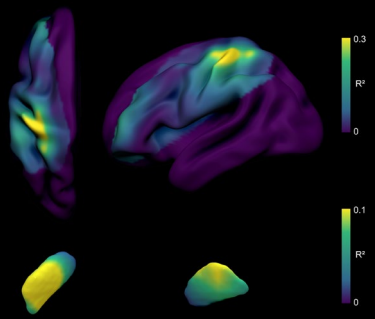
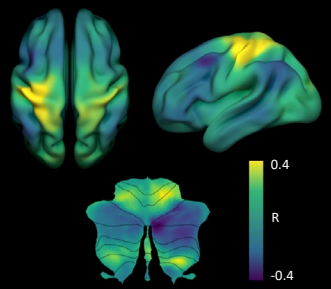


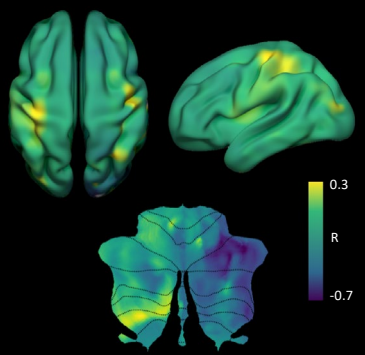
Interpolated XGB Performance overlays with **sensorimotor cortex** and **optimal PD DBS stimulation target in STN**



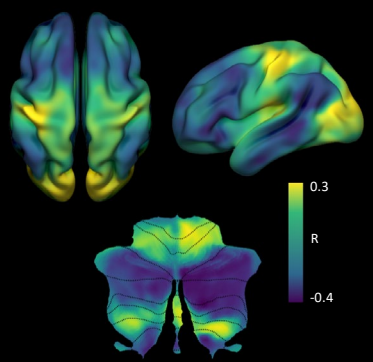
SPM Random Effect Analysis



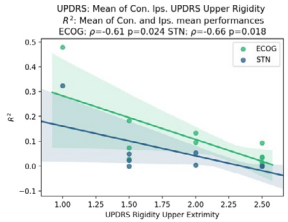
Fingerprint Analysis
Structural connectivity

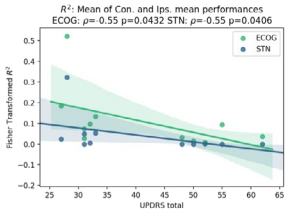


Fingerprint Analysis
Functional connectivity

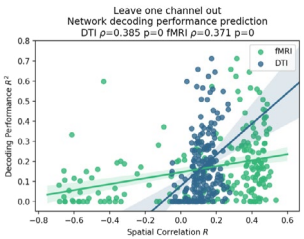


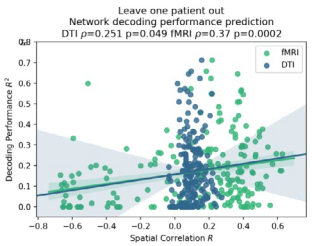
Clinical correlation analysis





Connectivity Analysis





Conclusions

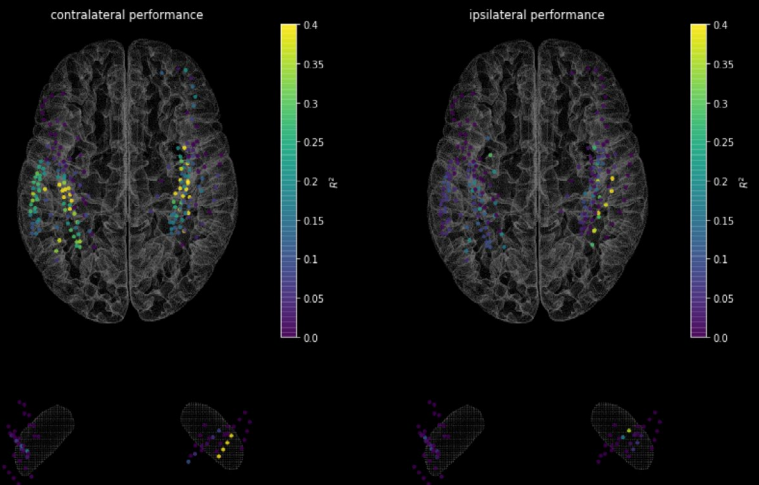
1. ECoG signals significantly outperformed STN LFP recordings

2. XGBOOST performances outperformed Linear models as well as state of the art spatial filter

3. Functional structural performance predicting network identification

4. Best performances were obtained by using all channels

Best channel mean weight features for individual time / frequency models



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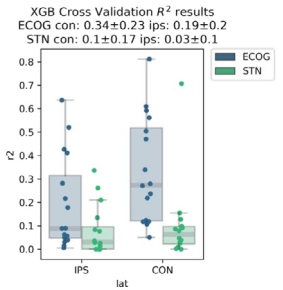
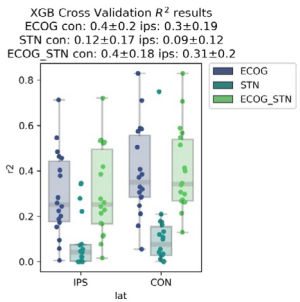
5. Adding STN to ECOG channels does not yield higher performances





6. Real time specific movement decoding pipeline

https://github.com/neuromodulation/icn/tree/master/icn_m1

Comparison of intra-cranial recordings simultaneous with Video-EEG recordings in a DBS for epilepsy patient.

Frans Gielen[1], A.J. Colon[2], J.P. Van Dijk[2], G. Leogrande[3], R, Rouhl[2], Y. Temel[2], G.L. Wagner[2]

[1] Medtronic PLC, Netherlands, [2] University Medical Center, Heeze and Maastricht, The Netherlands, [3] Medtronic Bakken Research Center, Netherlands

Deep brain stimulation (DBS) for focal epilepsy in the Anterior Nucleus of the Thalamus (ANT) is an established therapy for drug refractory epilepsy. Recently, a new type of implantable neurostimulator with sensing capabilities received CE approval for DBS. This device enables simultaneous DBS stimulation and recording from electrode contacts on the DBS lead offering. the possibility to simultaneously record chronic intra-cranial local field potentials (LFP) in the ANT and extra-cranial signals, e.g. electroencephalogram (EEG) combined with video recordings. Such combined recordings enable the comparison of intra- and extra-cranial signals and might result in the identification of a patient and epilepsy type specific biomarker or template, in analogy with the B-frequency peak related to Parkinson Disease (PD) symptoms in DBS for PD, which may be used in the optimization of the DBS for epilepsy therapy.

Methods and Materials:

An epilepsy patient received bilateral DBS for epilepsy in the (ANT) in 2015 after first receiving insufficiently effective vagal nerve stimulation (VNS). The patient reported about 50% reduction of seizures after start of the DBS. The VNS stimulator was simultaneously ON in order to not lose the, albeit insufficient, gain of VNS. A new stimulator (Percept™ PC, Medtronic plc.) was implanted due to battery depletion of the previously implanted neurostimulator. The Percept device with sensing features enabled simultaneous DBS stimulation and intracranial recording of LFPs from DBS lead electrode contacts. Both, LFP's and the simultaneously performed recording of video-EEG were synchronized and compared during a 4 days video-EEG session.

Several seizures were recorded simultaneously with the Percept and the video-EEG recording equipment during 2 chronic overnight recording sessions of about 7 hour each. An analysis of the recordings as well as a first result of the potential identification of a patient and epilepsy type specific biomarker or template will be presented during the conference. Intra-cranial recordings from externalized DBS leads in the week after the DBS lead implants in 2015 will also be shown.

Conclusion and Discussion:

Recorded seizure signals were of good quality and seizures could be recognized in the LFP. Identification of reliable biomarkers or templates is the first step for the ultimate goal of automatic seizure detection and potentially closed loop or Adaptive DBS in patients with DBS for epilepsy. More recordings with different patients are needed to learn whether there is a universal biomarker or an epilepsy patient individual biomarker will be necessary for this goal.

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Comparison of intra-cranial recordings simultaneous with Video-EEG recordings in a DBS for epilepsy patient.

Authors:

AJ Colon[1], JP van Dijk[1], F Gielen[3], VHBM van Kranen-Mastenbroek[2], G Leogrande[3], RPW Rouhl[2], Y Temel[2], GL Wagner[1]

[1]Academic Center for Epileptology, Epilepsy Center Kempenhaeghe/Maastricht, University Medical Center, Oosterhout, Heeze and Maastricht, The Netherlands

[2] Maastricht University Medical Center, Department of Neurosurgery and Neurology, The Netherlands

[3] Medtronic Bakken Research Center, Maastricht, The Netherlands

Background:

- Deep brain stimulation (DBS) for focal epilepsy in the Anterior Nucleus of the Thalamus (ANT) is an established therapy for drug refractory epilepsy.
- 3 Jan. 2020, a new type of implantable neurostimulator (Percept™ PC, Medtronic PLC) with sensing capabilities received CE approval for DBS.
- This device enables simultaneous DBS stimulation and recording from electrode contacts on the DBS lead, offering the possibility to analyze simultaneously recorded intra-cranial EEG named Local Field Potentials (LFP) in the ANT and scalp EEG signals, combined with video recordings.
- Goal of research: Is it possible to identify a (patient specific) biomarker that can be used for closed-loop stimulation in DBS for epilepsy?

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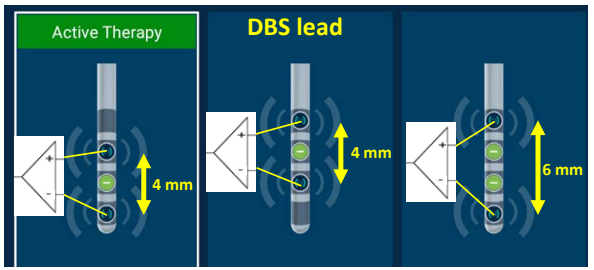
Methods:

- A male focal onset epilepsy patient received bilateral DBS for epilepsy in the (ANT) in 2015 after first receiving ineffective vagal nerve stimulation (VNS). The patient reported about 50% reduction of seizures after start of the DBS.
- In Jan 2020 a new stimulator (Percept™ PC, Medtronic plc.) was implanted following battery depletion of the previously implanted neurostimulator.
  - LFP's were recorded with Percept from bilaterally implanted DBS leads, each containing 4 cylindrical PtIr electrode contacts: 1. 5 mm long; 1.3 mm diameter and 0.5 mm separation between contacts.
  - The LFP's were differentially recorded to eliminate or strongly reduce the artefact resulting from simultaneously occurring stimulation.

FIG.1: Guarding differential recording concept. Recording electrode contacts were "guarding" the active Negative polarity stimulation electrodes. Positive electrode at the remote sub-clavicular stimulator housing.



- For 2 nights simultaneous scalp EEG recordings plus video and Percept recorded LFP's in ANT were acquired during ongoing therapeutic stimulation with Percept.
  - Cycling stimulation protocol: 1 min. stim=ON; 5 min.'s stim=OFF; f_{stim}145 Hz; 90 usec Pulse width

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Results:

- 19 seizures were detected by qualified nurses via the vEEG system during 2 nights.
  - 10/19 (52.6%) of the seizures recorded by the EEG started during the stimulation ON phase.
- ~ 10hrs of raw LFP signals were recorded in ANT in sessions of 30 or 60min during the same 2 nights.
  - ECG artifact was recorded in the stimultation ON phase of each stimulation cycle.
  - EEG and LFP synchronization achieved via timestamps and (cycled) stimulation.
  - Simultaneous LFP and EEG recordings are available for 12/19 seizures.
  - Each of these 12 seizures can be recognized in the LFP visually (FIG. 2) and/or by spectral analysis (FIG. 3).

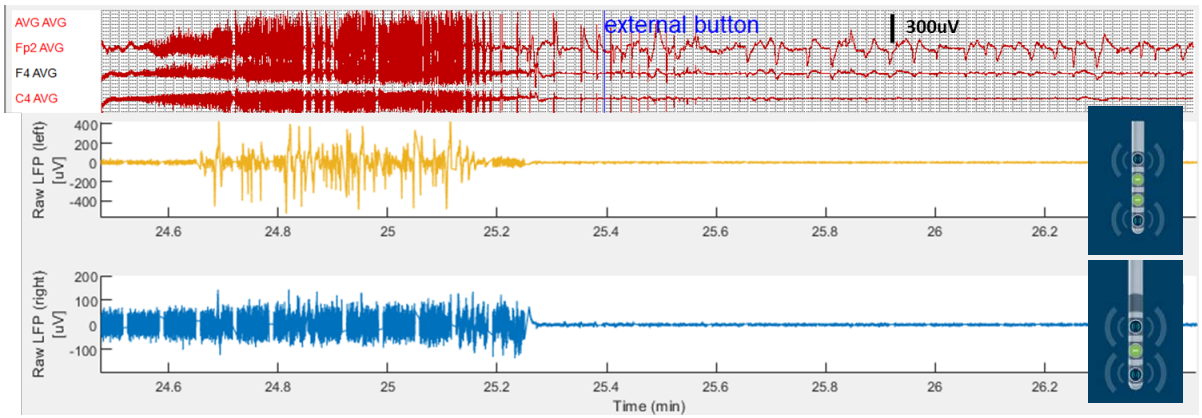

FIG. 2: example of seizure and inter-ictal activity. Signals from vEEG (red) were synchronized with LFP's from left ANT (yellow) and right ANT (blue). Recording gaps in the LFP's have a technical origin.

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Results (cont'd):

- The amount of relative power in the empirically selected band 26+/-2.5Hz of the LFP was measured and recorded directly by the Percept stimulator.

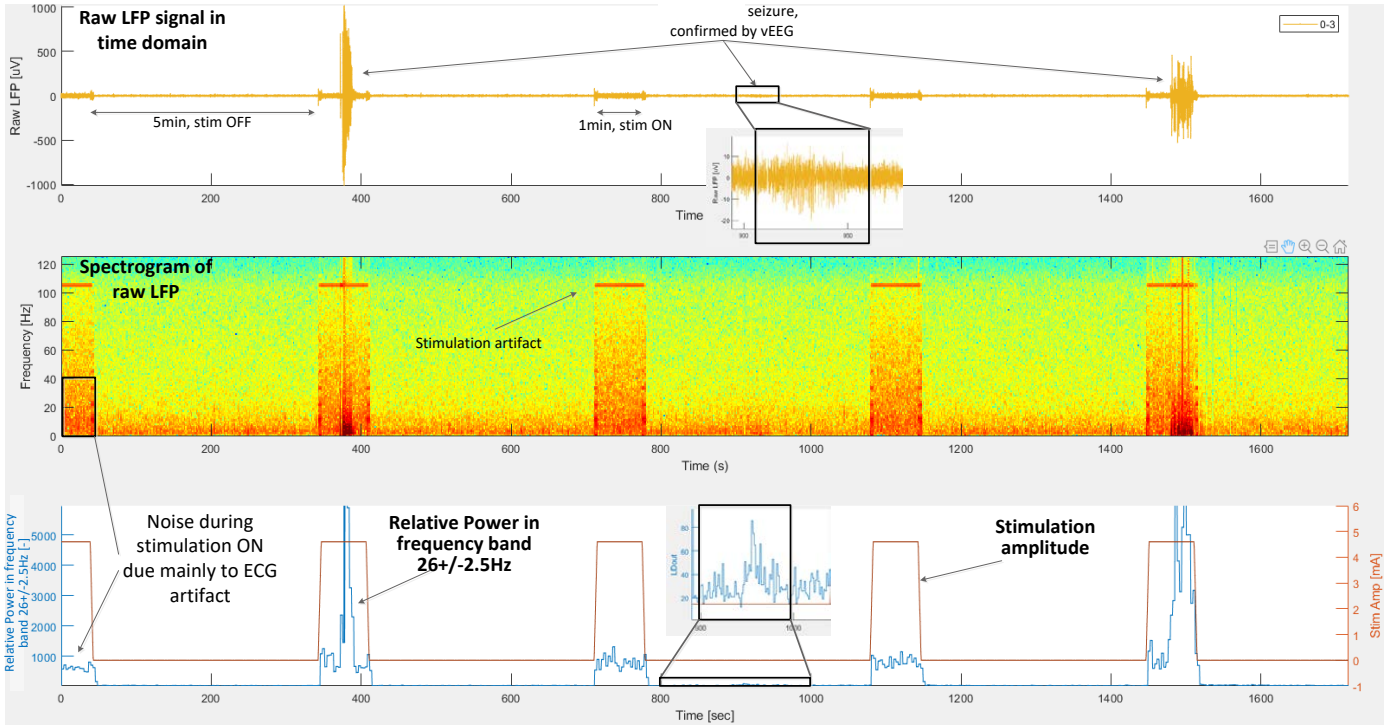

FIG. 3: example of seizures recorded during periods with stimulation ON and OFF. Raw LFP from left ANT (yellow), spectrogram, relative power in selected frequency band in LFP (blue) and stimulation (red) recorded by the Percept.

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Conclusion:

- Seizures were recorded succesfully in ANT with Percept.
- The signal-to-noise ratio for the Percept recorded LFP's is enough to identify seizures.
  - Despite simultaneously ongoing DBS stimulation in ANT and ECG artifacts in the LFP signals.
  - ANT recorded Seizure LFP amplitudes are comparable with scalp EEG amplitudes: +/- 500 uVtt.
- 10/19 (52.6%) of the recorded seizures started during the stimulation ON period
  - NOTE: Cycling stimulation protocol: 1 min. stim=ON; 5 min. stim = OFF.
  - If seizures would start independent of stimulation ON period, then about 16.6 % of the seizures would start during the stimulation ON period.
  - This suggests that scalp EEG and LFP's can be used to relatively quickly identify seizures as adverse effects of stimulation.
- The patient had abundant inter-ictal events seen in the scalp EEG
  - Inter-ictal events were not always identified in the LFP due to the low amplitude of these signals.
  - Seizures as identified from the scalp EEG were clearly seen in the LFP's recorded in ANT.
- The power in specific frequency bands could be used to detect seizures in this set of data
  - Optimization of the selection of the band could enable fully automatic detection of seizures.

Adaptive DBS Algorithm for Personalized Therapy in Parkinson's Disease: ADAPT-PD Trial: a prospective single-blind, randomized crossover, multi-center trial of deep brain stimulation adaptive algorithms in subjects with Parkinson's disease.

Helen Bronte-Stewart[1], Andrea Kühn[2], Lisa Tonder[3], Robert Raike[3], Scott Stanslaski[3], Kassa Lynch[3]

[1] Stanford, USA, [2] Charité Berlin, Germany, [3] Medtronic, USA

Deep brain stimulation (DBS) is an effective therapy for Parkinson's disease (PD) symptoms, though opportunities exist to improve the efficiency and efficacy. Commercially approved DBS is programmed to run continuously (cDBS) at specified programming parameters. In contrast, adaptive DBS (aDBS) algorithms may individualize and optimize PD therapy by adjusting stimulation based on objective signals. The algorithm technology used in this study is uniquely embedded in the device, which allows for out-of-clinic assessments. Local field potentials (LFPs) represent population-level neuronal oscillations surrounding the DBS electrode and can be used as aDBS control signals.

The objective of this study is to demonstrate safety and effectiveness of adaptive deep brain stimulation (aDBS) algorithms in subjects with Parkinson's disease (PD).

Subjects will have been implanted with DBS leads either in the Globus Pallidus interna (GPi) or the subthalamic nucleus (STN) connected to a commercial DBS system capable of sensing LFPs. An investigational feature will be unlocked to allow programming of two different aDBS modes using low frequency (8-30 Hz) LFP control signals. Subjects will enter a 30-day Baseline Phase in their current cDBS programming configuration, followed by an aDBS Set-up and Adjustment Phase. Subjects tolerating both aDBS modes will then enter a 2-period randomized crossover Evaluation Phase and receive each aDBS mode over 30-day periods, followed by a Long-Term Follow-up Phase over 10 months. The aDBS evaluations will involve measures of On time, quality of life, speech, movement, sleep, patient preference and satisfaction, and total electrical energy delivered (TEED).

The primary effectiveness endpoint will measure On time without troublesome dyskinesia from the PD Home Diary. Other endpoints will include TEED, output from a wearable device, Voice Handicap Index, UPDRS, EQ-5D-5L, PDSS-2, PDQ-39, and patient preference and satisfaction. Safety will include evaluation of stimulation-related adverse events (AEs), AEs, and device deficiencies.

This international, multi-center, chronic aDBS study is expected to generate data to support safety and effectiveness for both aDBS modes in PD subjects.

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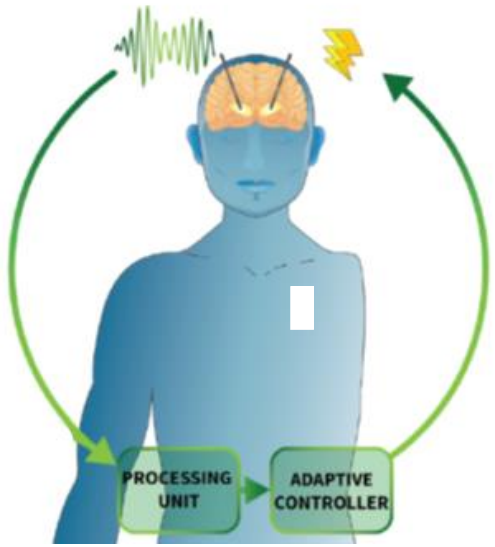
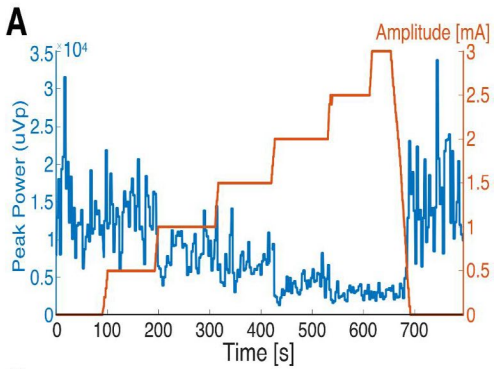
ADAPT-PD Trial: a prospective single-blind, randomized crossover, multi-center trial of deep brain stimulation adaptive algorithms in subjects with Parkinson's disease

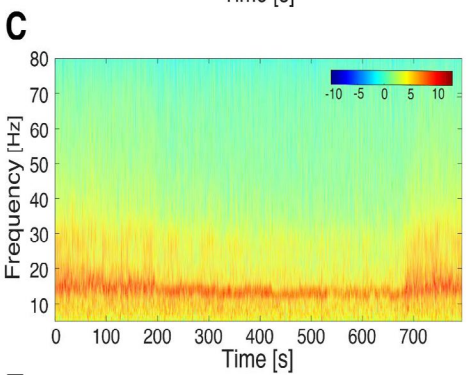
Andrea Kühn[1], Lisa Tonder[2], Robert S. Raike[2], Scott Stanslaski[2], Kassa Lynch[2],Helen Bronte-Stewart[3]

[1]Department of Neurology, CharitéUniversity of Berlin, Berlin, Germany 10117; [2]Medtronic Neuromodulation, Medtronic, Minneapolis, MN 55432; [3]Stanford Movement Disorders, Stanford University, Stanford, CA 94305

Background: Concept of Adaptive DBS and Study Design

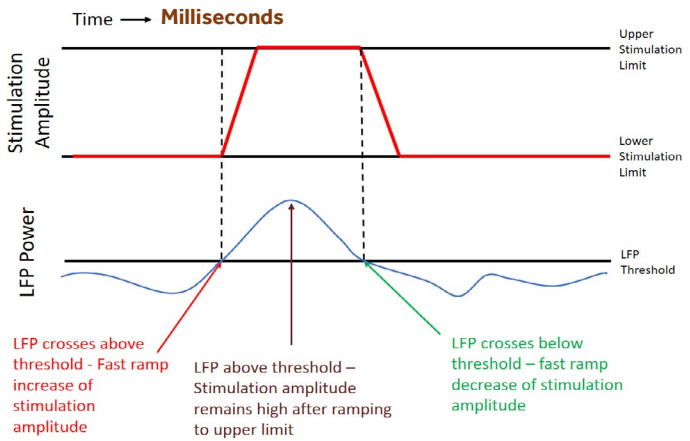






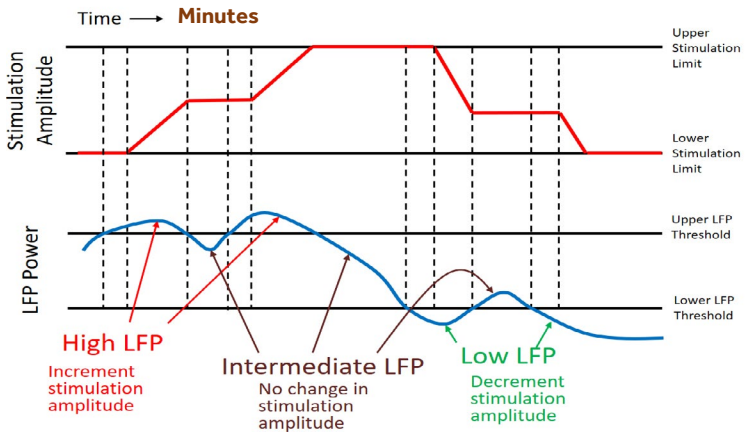
Methods: Two Different Algorithms for Adaptive Stimulation

Single Threshold: Faster ON-OFF stimulation changes



Average of 250 ms, Beta Burst tracking

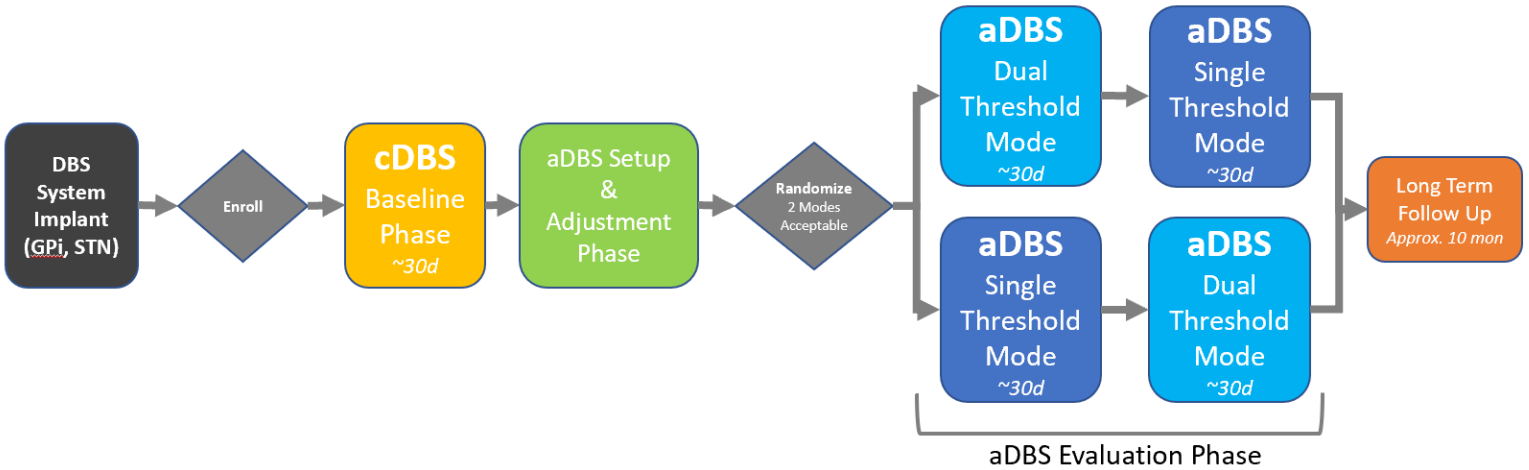
Dual Threshold: Amplitude modulation over longer time frame



Average over 2.5 min, adaptation to medication cycle

Methods: ADAPT-PD Trial

Helen Bronte-Stewart (USA)
Andrea Kühn (Europe)



Primary Endpoint: ON Time without troublesome dyskinesias (patient diary)
Secondary Endpoint: Total electrical energy delivered (TEED)

Medtronic

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Conclusion:

- This international, multi-center, chronic aDBS study is expected to generate data to support safety and effectiveness for both aDBS modes (single threshold and dual threshold) in PD subjects

Modulation of Subthalamic Nucleus Local-Field Potentials by speech

Leonor Correia Guedes[1], Ines Cardoso[1], Patrícia Lobo[1], Begona Cattoni[1], Herculano Carvalho[1], António Gonçalves Ferreira[1], Miguel Coelho[1]

[1] **Hospital de Santa Maria, Portugal**

Closed-loop deep brain stimulation (DBS) is emerging as an opportunity for a possible more personalized treatment for Parkinson's disease (PD) as compared to traditional open-loop stimulation systems depending on frequently laborious and punctual programing adjustments. Having the capacity to measure Local Field Potentials (LFPs) surrounding different stimulation electrodes, closed-loop systems will use LFPs as electrophysiological surrogate markers of clinical motor signs to automatically adapt stimulation, optimizing treatment over time.

There is evidence that PD is associated with exaggerated, pathological, synchronization of basal ganglia neurons in the beta frequency band (13–35 Hz) and that dopaminergic medications, as well as STN-DBS, induce a decrement of beta-band activity in the LFPs. Studying the possible influence of motor activity in the LFPs sensed in closed-loop systems is of utmost importance to better understand the specificity of the device for modulating feed-back dependent stimulation. Our study aimed to investigate the influence of 3 different motor tasks on beta-band activity in LFPs.

One patient submitted to STN-DBS,was tested in two different conditions, ON and OFF dopaminergic medication, in each condition performing sequential timed periods performing: 1- speech; 2- hand movements; 3- gait, alternating with rest. LFPs were measured using the implanted DBS leads and a newly commercially available Implantable Pulse Generator (IPG) with sensing capacity.

We could identify a consistent modulation of the beta-band with speech both in ON and OFF medication.

Our preliminary results indicate a possible influence of speech on beta-band LFPs, support further investigation on voluntary motor activity in closed-loop systems sensed LFPs and have possible implications for research in both neurophysiological and clinical applications of these new DBS systems.

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Modulation of Subthalamic Nucleus Local-Field Potentials by speech

Leonor Correia Guedes, Inês Cardoso, Patrícia Pita Lobo, Anabela Valadas, Begona Cattoni, Herculano Carvalho, António Gonçalves Ferreira, Miguel Coelho

Department of Neurosciences and Mental Health, Neurology and Neurosurgery Departments, Hospital de Santa Maria, CHULN, Lisbon, Portugal

Background

Closed-loop deep brain stimulation (DBS) is emerging as an opportunity for a possible more personalized treatment for Parkinson's disease (PD).

PD is associated with exaggerated, pathological, synchronization of basal ganglia neurons in the beta frequency band. Dopaminergic medications and STN-DBS, induce a decrement of beta-band activity.

Closed-loop systems will use Local Field Potentials (LFPs) as electrophysiological surrogate markers of clinical motor signs to automatically adapt stimulation, optimizing treatment over time.

We hypothesized that speech and voluntary motor activity may influence STN LFPs. It is known that activating maneuvers as speech tasks and motor tasks worsen motor signs of PD. Furthermore, there is evidence that STN is itself involved in speech production.

Studying the possible influence of motor activity and speech in the LFPs sensed in closed-loop systems is of utmost importance to better understand the specificity of the device for modulating feed-back dependent stimulation.

Aims

Our study aimed to investigate the influence of speech and additional motor tasks on STN LFPs.

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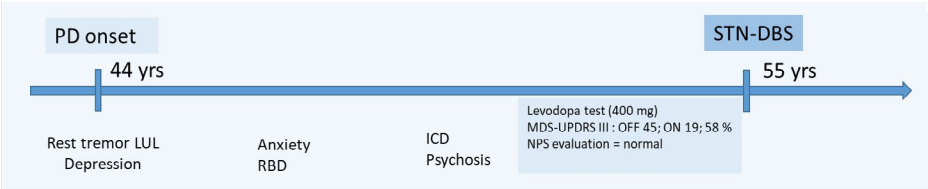
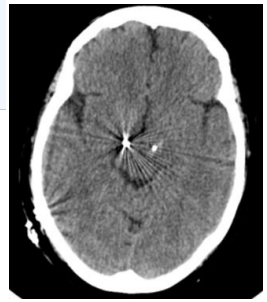
Methods:

Clinical case



Right Electrode			Left Electrode		
X	Y	Z	X	Y	Z
10.0	-1.16	-4.02	-10.0	-1.42	-3.96

Target Coordinates



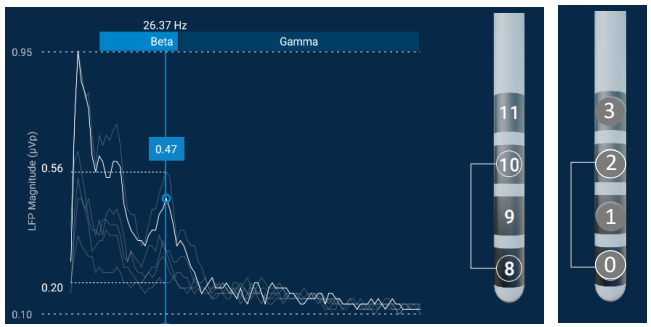
Post-operative CT Scan

Test conditions

Two different conditions, ON and OFF dopaminergic medication/ STIM OFF

Each condition - sequential timed periods : 1- speech; 2- hand movements; 3- gait, alternating with rest.

LFPs measured using the implanted DBS leads and a newly commercially available Implantable Pulse Generator (IPG) with sensing capacity.



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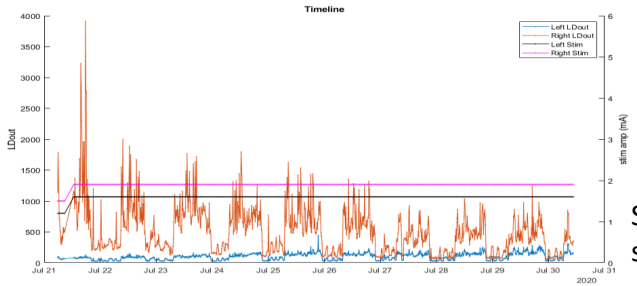
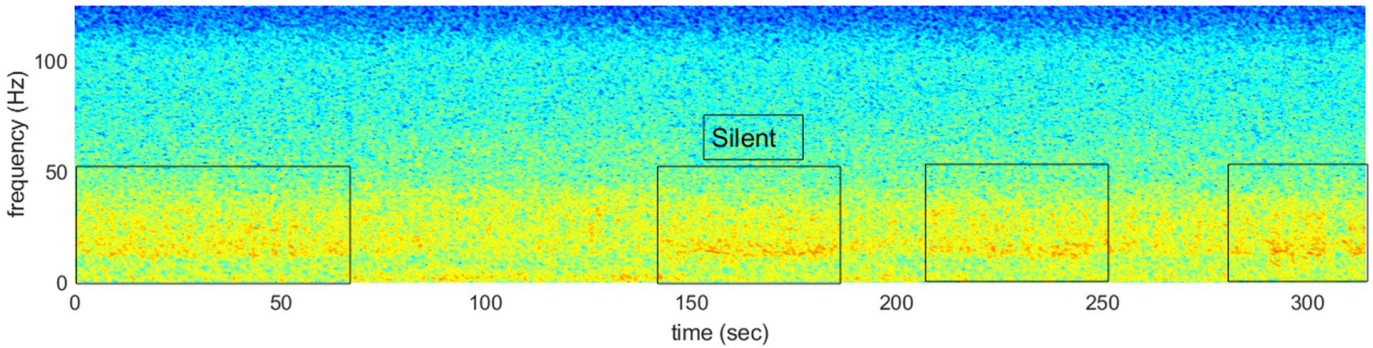
Results:



Suppression in time after stimulation adjustment

Modulation of STN LFPs by speech



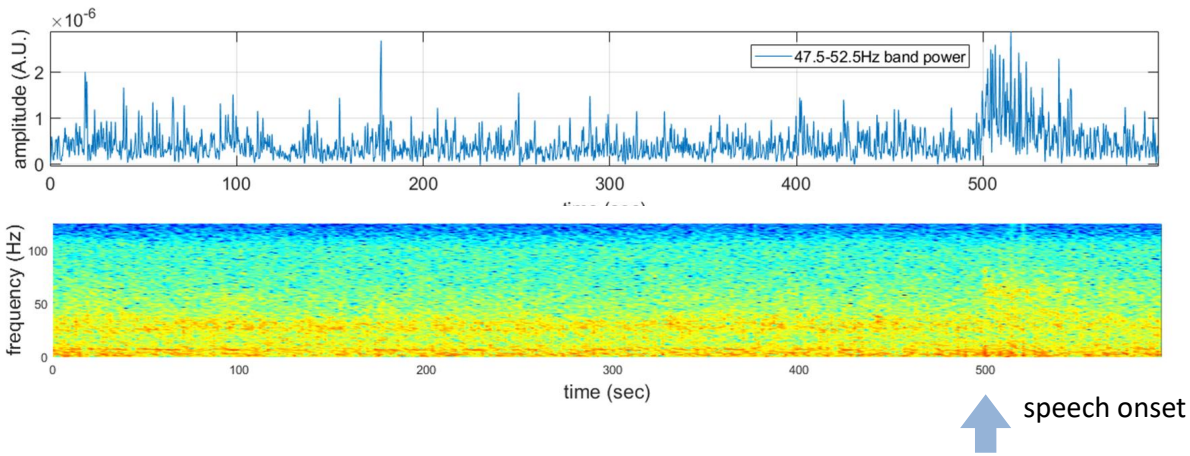
Beta fluctuations during speech exercises

Boxes highlight moments when patient was silent – higher Beta power – alternating with moments when patient was executing speech exercises – lower Beta power.

Time axis coherent with the sequence of exercises: patient is silent (1min); speaks (1min); silent (1min); speaks (30secs); silent (30secs); speaks (30secs); silent (30secs).

Results:

Modulation of STN LFPs by speech



Finger tapping, gait and speech exercised were performed during Streaming Session using Percept PC™. Last exercise on the list was Speech exercise coherent with Gamma increase.

Conclusion:

Our preliminary results indicate a possible influence of speech on beta and Gamma band LFPs, support further investigation on speech and voluntary motor activity in closed-loop systems sensed LFPs and have possible implications for research in both neurophysiological and clinical applications of these new DBS systems.

Acknowledgments
Scott Stanslaski Msc, PhD , Medtronic USA, Minneapolis
Armando Fernandes Msc, Medtronic Portugal, Lisboa

Impaired movement-related beta band modulation precedes freezing episodes: hypothesis from upper limb freezing for novel STN sensing technology

Maria-Sophie Breu[1], Marlieke Scholten[2], Alireza Gharabaghi[3], Daniel Weiss[1]

[1] Clinic of Neurology, University Hospital Tübingen, Germany, [2] Hertie-Institut for clinical Brain Research, Germany, [3] University Hospital Tübingen, Germany

Freezing phenomena in Parkinson's disease (PD) constitute an important unaddressed therapeutic need. Changes in cortical neurophysiological signatures may precede a single freezing episode and indicate the evolution of abnormal motor network processes. Here, we hypothesized that the movement-related power modulation in the beta-band observed during regular finger tapping deteriorates in the transition period between regular tapping and upper limb freezing (ULF).

We analyzed a 36-channel EEG of 13 patients with idiopathic PD during self-paced repetitive tapping of the right index finger. In offline analysis, we identified ULF episodes and compared the period immediately before ULF ('transition') with regular tapping regarding movement-related cortical frequency domain activity and cortico-cortical phase synchronization.

From time-frequency analyses, we observed that the tap cycle related beta-band power modulation over the contralateral sensorimotor area was diminished in the transition period before ULF. Furthermore, increased beta-band power was observed in the transition period compared to regular tapping centered over the contralateral centro-parietal and ipsilateral frontal areas.

Here, we demonstrate that impaired beta power modulation precedes freezing in upper limb movement. From this work, we generate the hypothesis that beta band related power modulations may also precede freezing of gait episodes. We will translate this finding to freezing of gait by analyzing local field potentials (LFPs) of the subthalamic nucleus in patients with next generation impulse generators with available sensing technology (Medtronic, Percept™ PC) Deterioration of beta power modulation prior to freezing has potential to evolve as biomarker in order to treat and prevent freezing of gait episodes with adaptive stimulation.

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– virtual meeting –
November 20 – 21, 2020

Impaired movement-related beta band modulation preceding freezing episodes:

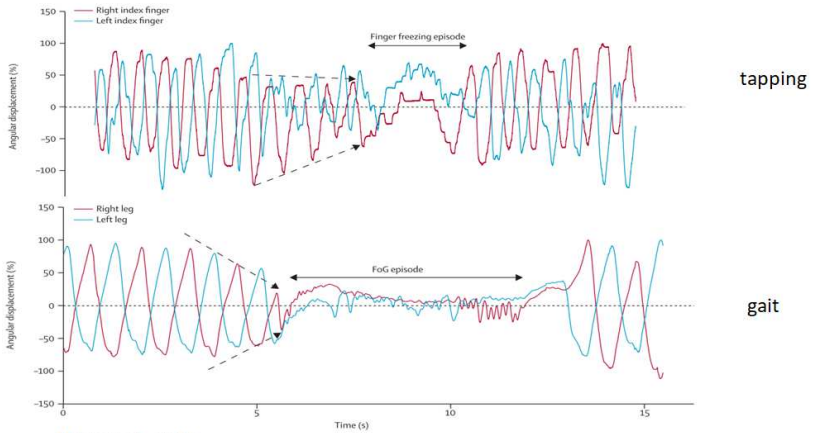
Upper limb freezing and freezing of gait

Breu M-S, Schneider M, Garabaghi A, Weiss D

Background:

Similar kinematic and neurophysiological characteristics in Upper Limb Freezing (ULF) and Freezing of Gait (FoG)

->increase in frequency and decrease in amplitude



Nutt et al., 2011

III. International Conference on Deep Brain Stimulation

Methods:

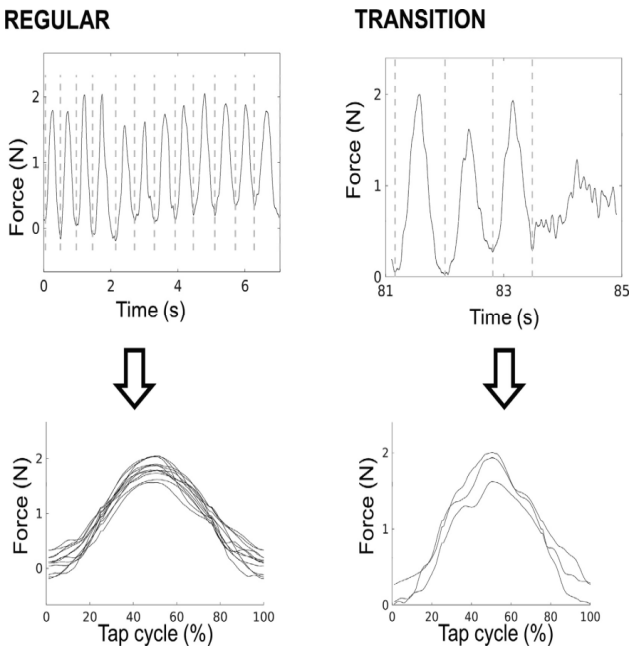
- Patients with PD
(akinetic-rigid, after overnight withdraw of medication)

- Finger-tapping-paradigm

- Interpolating each tap
(time warping)

- `Transition´ period
before ULF

- Analyzing cortical activity in EEG

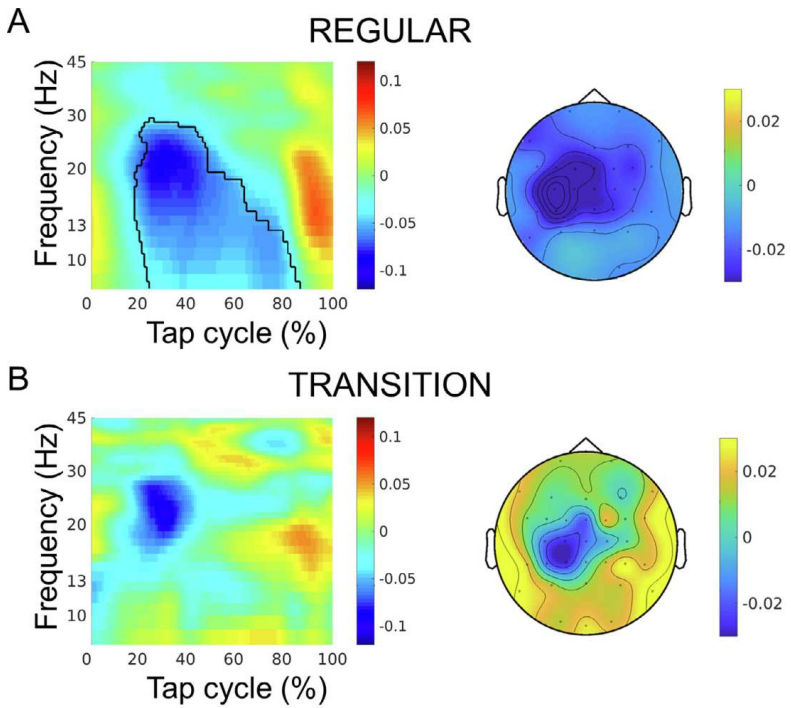


Scholten et al., 2020

III. International Conference on Deep Brain Stimulation

Results:

- Movement related power modulation in regular finger tapping but not in `Transition´



Scholten et al., 2020

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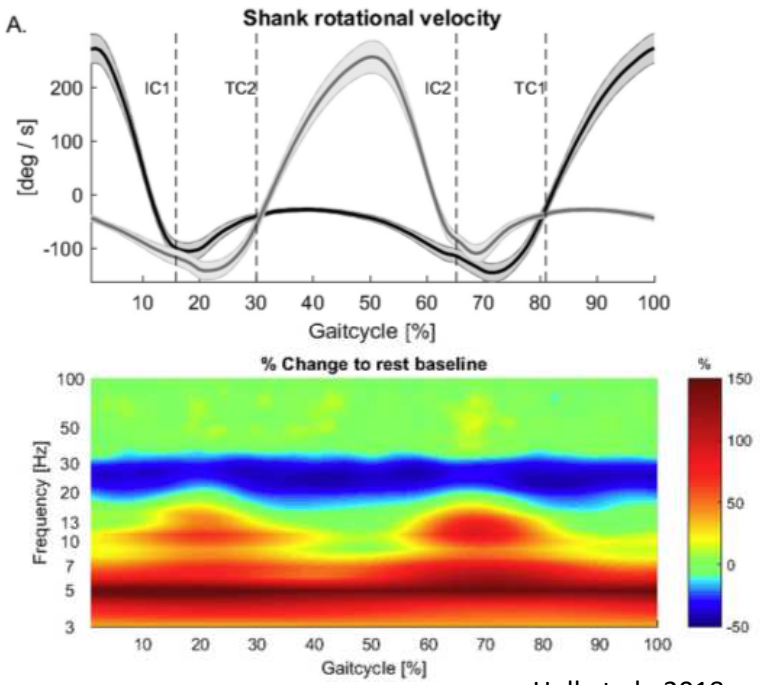
State of the Art:

•Movement-related beta-band modulation in STN during bicycling (Storzer et al. 2016), stepping (Fischer et al. 2018) and regular gait (Hell et al. 2018)



Hell et al., 2018

III. International Conference on Deep Brain Stimulation

Preview/Conclusion:

- Gait paradigm to provoke Freezing of Gait
- Percept™PC BrainSense™ Technology to analyze Local Field Potentials (LFP) of the subthalamic node (STN) and Substantia nigra (SNr)

- Pathological cortical motor processing precedes freezing episodes in the upper limb
- Validate if impaired beta modulation precedes FOG to customize preventive neuromodulation treatment

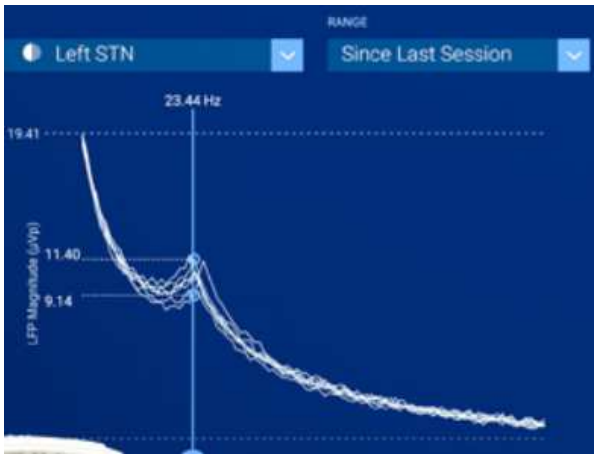


Image Provided Courtesy of Medtronic, Inc.

Spatial dependence of beta bursts determined by segmented DBS electrodes

Matthias Sure[1], Jan Vesper[1], Alfons Schnitzler[1], Esther Florin[1]

[1]University Hospital Düsseldorf, Germany

Beta band bursts in the STN play an important role in the pathophysiology of Parkinson's disease (PD) and can be used as a trigger in closed-loop DBS. However, so far it is not known, how these bursts are spatially distributed within the STN. Using directional DBS leads we here investigate the occurrence of beta burst with higher spatial resolution compared to the traditional omnidirectional DBS leads. Thereby we identify if beta band bursts have differing characteristics for the functional subsystems of the STN.

Patients power spectra had individual peaks in the beta range (22.3 ± 5.9 Hz). However, not in every recording channel, a peak was determined. The power at the BPf and within the hBB was significantly reduced by medication. In the hBB, the power of the anterior recording direction was greater than at medial and lateral.

Burst density increased for all directions and frequencies in OFF medication compared to ON. Additionally, for the BPf more bursts occurred in the lateral direction than anterior in ON medication. The burst duration in the hBB and the BPf increased without medication. Only for hBB bursts, the amplitude was found to be reduced at anterior in the ON.

The results show reducing effects of dopaminergic medication on the burst density, duration, and, overall power, whereas the burst amplitude seems to be less affected. That most effects were found for the hBB and the BPf highlights the frequency specificity of beta bursts for the pathology of PD. Density and duration contribute to the overall power and may accumulate in the individual beta peaks. As peaks in the power spectrum are only present at some contacts supports a non-homogeneous distribution of beta activity in the STN.

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Spatial dependence of beta bursts determined by segmented DBS electrodes

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[a] Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty, Heinrich Heine University Düsseldorf, Germany

[b] Department of Functional Neurosurgery and Stereotaxy, Medical Faculty, University Hospital Düsseldorf, Germany

Background

- Subthalamic (STN) beta bursts pathological hallmark of Parkinson's disease (PD)
- DBS and medication reduce the number of bursts[1]
- Beta bursts as a trigger in closed-loop DBS[2]

Objectives

- Is beta burst activity homogeneous within the STN?
- Is pathological beta burst activity in PD specific to a beta subband?

Clinical Neuroscience Düsseldorf

Methods

- LFPs from the left and right STN of 26 PD patients at rest
- 30 minutes with (ON) and without dopaminergic (OFF) medication
- Directional leads sorted according to anterior, medial, and lateral
- Bursts detected for 12-24 Hz (lBB), 24-35 Hz (hBB), and ± 3 Hz around the individual beta peak frequency (BPf)
- Raw data z-score normalized
- Detection threshold: 75th-percentile of the Morlet wavelets amplitude

Results

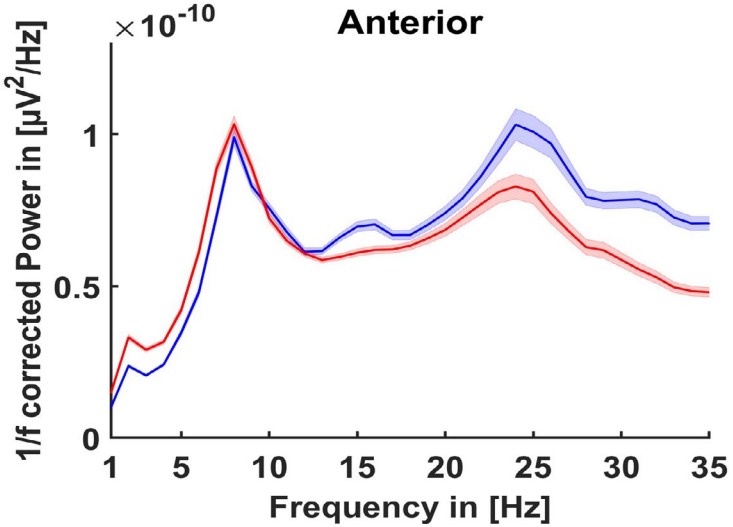

Figure 1: The 1/f corrected power spectra of the anterior contact is displayed for the medication OFF state in blue and the ON state in red. The coloured shaded areas indicate the standard deviation of the mean.

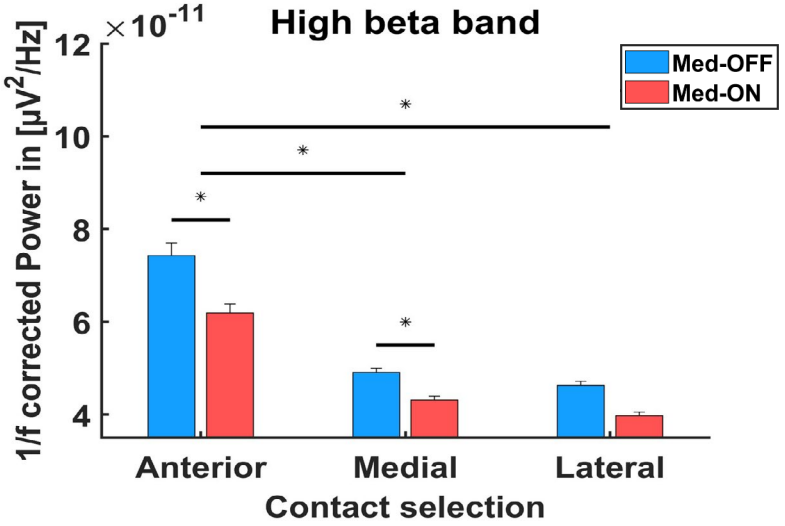

Figure 2: The mean power with the standard error of the mean for the high beta band is shown. Stars indicate a significant difference with $p < 0.005$.

- **Beta peaks were found at individual frequencies (Mean ± SD: 22.1 ± 5.8 Hz)**
- **Peaks not found at all LFPs (Anterior: 25 times; Medial: 20; Lateral: 19)**
- **Power differences between OFF and ON and between LFPs for the hBB and BPf**

Results

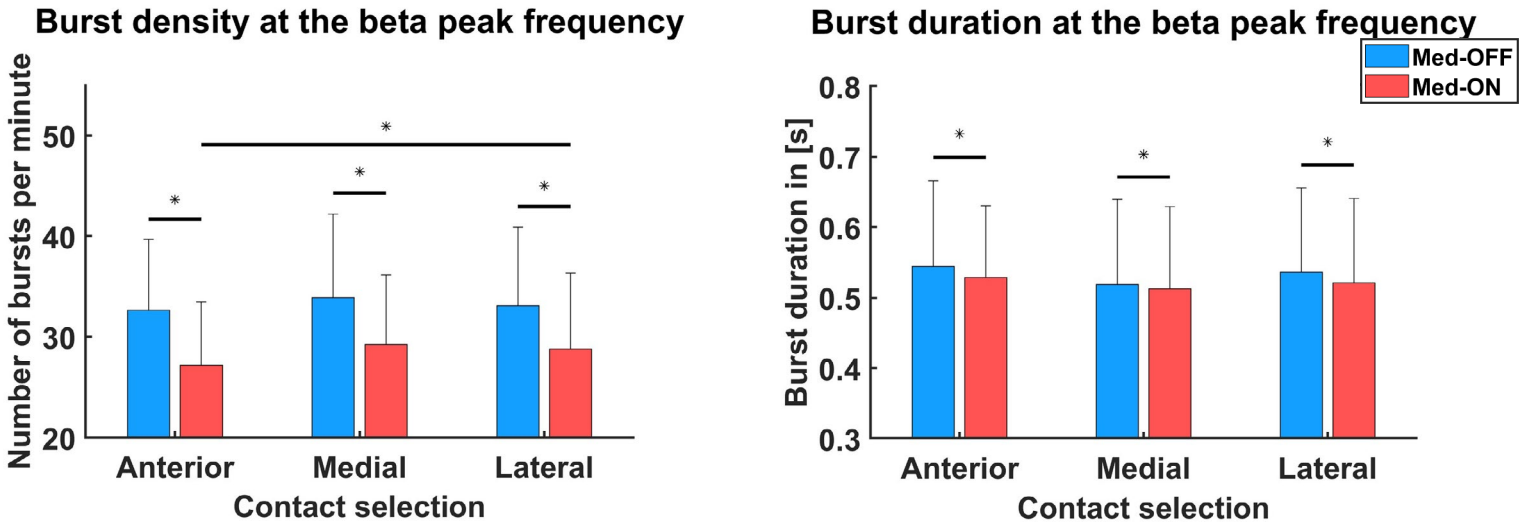

Figure 3: The mean with standard deviation is plotted for the burst density (left) and the burst duration (right) at the individual beta peak frequency. The values are presented separately for the anterior, medial, and lateral orientation. Stars indicate a significant difference with $p < 0.005$.

- **Density is reduced by medication in all frequency bands**
- **Only for the BPf more bursts at lateral than anterior direction ON medication**
- **Duration is longer OFF than ON medication for hBB and BPf**

Conclusion

- Effect of medication depends on beta frequency definition
- Medication effect on duration more frequency specific than on density
- Beta activity is non-homogenously distributed in the STN
  - Orientation dependency of power and burst density maybe caused by different functional STN subregions
  - No specific region for pathologically elevated beta activity

References:
1. Ray NJ, Jenkinson N, Wang S, et al. Local field potential beta activity in the subthalamic nucleus of patients with Parkinson's disease is associated with improvements in bradykinesia after dopamine and deep brain stimulation. Experimental neurology 2008; 213(1):108–13.
2. Arlotti M, Marceglia S, Foffani G, et al. Eight-hours adaptive deep brain stimulation in patients with Parkinson disease. Neurology 2018; 90(11):e971-e976.

Acknowledgements:
Esther Florin gratefully acknowledges support by the Volkswagen Foundation (Lichtenberg program 89387).

The effect of directional DBS and/or short pulse width on attenuation effects in VIM/PSA-DBS for tremor.

Julian Köchert[1], Christian Hartmann[1], Petyo Nikolov[1], Philipp Jörg Slotty[1], Jan Vesper[1], Alfons Schnitzler[1], Stefan Jun Groiss[1]

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Deep brain stimulation (DBS) of the ventral intermediate thalamic nucleus and/or the posterior subthalamic area (VIM/PSA) is a highly effective treatment for essential tremor. However, chronic VIM/PSA-DBS may be associated with attenuation of treatment efficacy, which in turn requires adaption of stimulation amplitudes increasing the applied energy to allow for sustained tremor control. Recently, short pulse (e.g. 40µs) and DBS via segmented leads (directional DBS, dDBS) has been suggested as superior stimulation strategies towards conventional DBS with omnidirectional stimulation (oDBS) and usage of longer pulse widths (e.g. 60µs). So far, it has not been investigated whether these recommended strategies also have an impact on attenuation effects.

A total of 10 patients who priorly underwent VIM/PSA-DBS surgery were recruited for this study. For each patient, monopolar review of segmented contacts was performed by a blinded rater to identify the preferable height and segmented contact for chronic DBS. This information was subsequently utilized to set-up dDBS40µs, dDBS60µs, oDBS40µs, and oDBS60µs in a randomized sequence for a 4-week-period, respectively. Tolosa-Marin Tremor Rating Scale (TRS) and the Essential Tremor Rating Assessment Scale (TETRAS), the Scale for the assessment and rating of ataxia (SARA), the International Cooperative Ataxia Rating Scale (ICARS), and a multimodal gait analysis utilizing the Zebris® FDM 3 measurement platform were obtained after withdrawal of prior DBS settings for 60 minutes, immediately after initiation of a new DBS setup, and after the associated 4-week treatment period. Linear mixed models (LMM) were utilized to delineate the effects of DBS directionality (dDBS vs. oDBS) pulse width (40µs vs. 60µs), and time (immediate assessment vs. 4-week follow-up) on tremor control potential and side effects.

All DBS conditions (dDBS40µs, dDBS60µs, oDBS40µs, oDBS60µs) led to a significant tremor reduction. No significant difference of tremor reduction or side effects could be observed between the 4 treatment conditions. However, DBS-mediated tremor suppression significantly deteriorated after 4 weeks of chronic stimulation, compared to immediate assessment. Again, no significant difference between stimulation paradigms was observed.

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The effect of directional DBS and/or short pulse width on attenuation effects in VIM/PSA-DBS for tremor.

Köchert J[1], Hartmann CJ[1,2], Nikolov P[1], Slotty PJ[3], Vesper J[3], Schnitzler A[1,2], Groiss SJ[1,2].

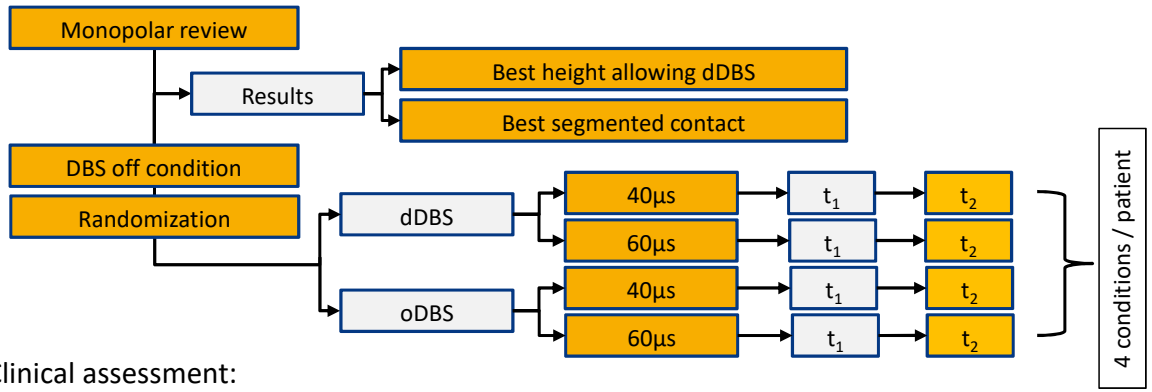
[1]Institute of Clinical Neuroscience and Medical Psychology, [2]Department of Neurology, [3]Department of Neurosurgery, Medical Faculty, Heinrich-Heine-University Düsseldorf, Germany

Background:

- Deep brain stimulation (DBS) of the ventral intermediate thalamic nucleus and/or the posterior subthalamic area (VIM/PSA) is a highly effective treatment for essential tremor but may be associated with attenuation of treatment efficacy.[1]
- Recently, application of short pulse widths (e.g. 40µs) and DBS via segmented leads (directional DBS, dDBS) has been suggested as superior stimulation strategies towards conventional DBS with omnidirectional stimulation (oDBS) and usage of longer pulse widths (e.g. 60µs).[2,3]
- Aim of this study was to investigate whether these recommended strategies also have an impact on attenuation effects.

Methods:

- 10 patients who already underwent VIM/PSA-DBS surgery were recruited.
- Study design:



- Clinical assessment:

  DBS off state (withdrawal of DBS for 60 minutes), DBS on-state (t1: immediately, t2: 4-week follow-up) for each treatment condition.

- Clinical measures:

  Tolosa-Marin Tremor Rating Scale (TRS), Essential Tremor Rating Assessment Scale (TETRAS), Scale for the assessment and rating of ataxia (SARA), International Cooperative Ataxia Rating Scale (ICARS), Gait analysis (Zebris® FDM 3 measurement platform)

- Statistical analysis:

  Linear mixed models (LMM) using R and its lme4 package accounting for repeated measurements

Results:

- All DBS conditions (dDBS40µs, dDBS60µs, oDBS40µs, oDBS60µs) led to a significant reduction of TRS and TETRAS performance scales.
  LMM: lmer(value ~ time (off/t_1/t_2) +(1 | subject)
- Tremor deteriorated in each condition after 4 weeks (t_2), compared to immediate assessment (t_1)
  LMM: lmer(value ~ pulse width (40/60µs)* time (t_1/t_2) * mode (oDBS/dDBS) + (1 | subject).

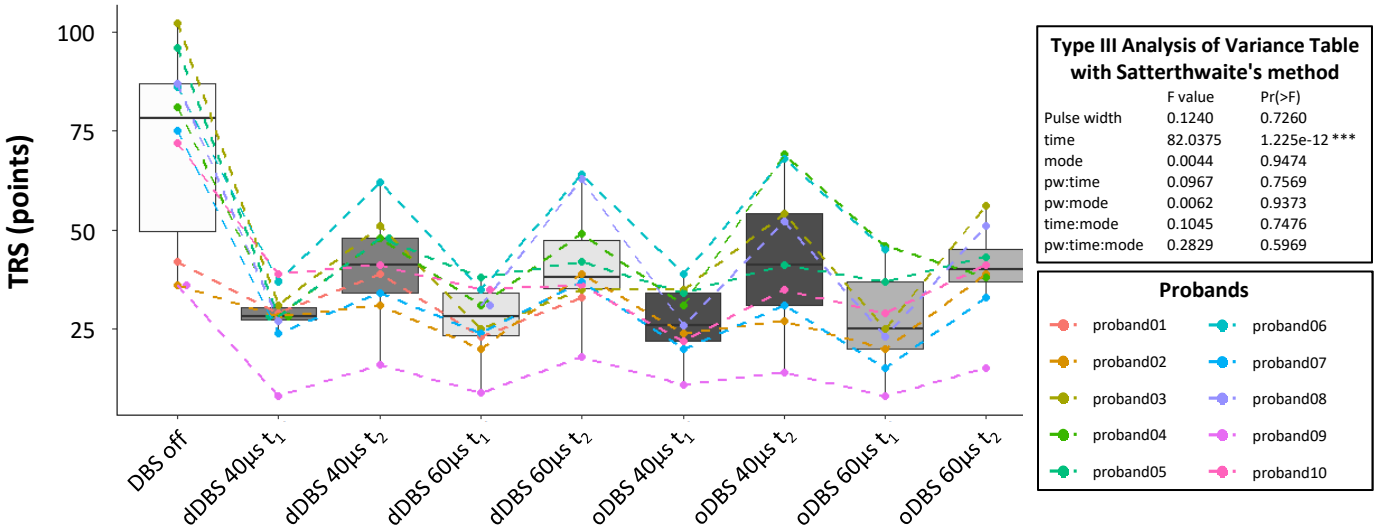


Fig. 1: Effects of DBS on tremor severity on TRS. DBS lead to a significant tremor reduction, regardless if oDBS/dDBS or pulse widths of 40/60µs were applied. In addition, significant worsening of tremor could be observed over time (t_1 vs. t_2) in every DBS condition.

Results:

- Compared to off state, DBS did not lead to changes of ataxic symptoms, as assessed with SARA and ICARS, or features of gait and stance, as assessed with Zebris® FDM 3 measurement platform.
- In addition, no significant differences of ataxic symptoms or features of gait and stance could be observed between the 4 treatment conditions.
- LMM: lmer(value ~ pulse width (40/60µs)* time (t_1/t_2) * mode (off/oDBS/dDBS) + (1 | subject)

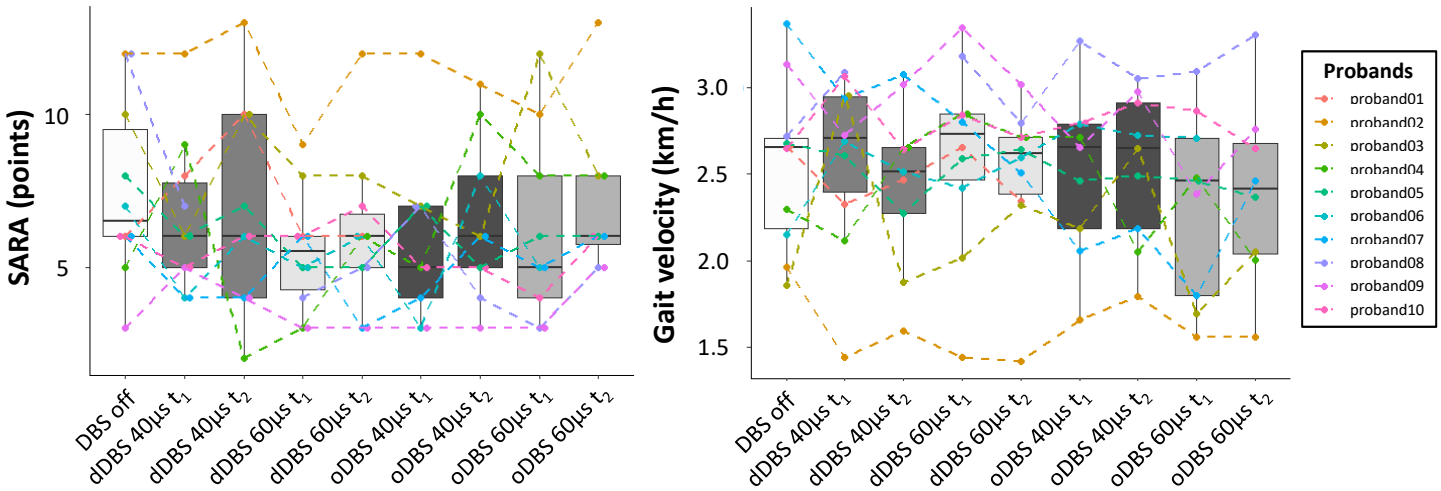


Fig. 1: Assessment of ataxic symptoms using SARA (left), and gait gait velocity, right). LMM analyses did not reveal significant effects of applied pulse width, time, or DBS mode. Moreover, no significant effects between DBS off and DBS on conditions could be observed. Similar observations were made for ICARS as well as other features of stance and gait, respectively.

Conclusion:

- To the best of our knowledge, this is the first study evaluating the effects of pulse width and directional stimulation on attenuation effects in VIM/PSA-DBS.
- Compared to conventional stimulation paradigms (oDBS and pulse width of 60µs), neither dDBS nor shorth pulse width reduced the risk or the amount of attenuation effects in our small study cohort.
- Hence, our data suggest that the risk of habituation effect cannot be easily overcome by such advanced DBS paradigms. However, the utility of applying short pulse width <60µs and dDBS increases the degrees of freedom for chronic DBS settings and therefore may provide more options to continuously switch DBS settings and hence to compensate attenuation effects.
- Since no DBS-induced worsening of gait, stance, and ataxic symptoms could be observed, further studies with a larger number of probands and longer observation period (> 4 weeks) may be necessary to better address the impact of dDBS and/or short pulse width on these features.

References:

1. Fasano A, Helmich RC. Mov Disord. 2019 Dec;34(12):1761-1773.
2. Bruno S, Nikolov P, Hartmann CJ, Trenado C, Slotty PJ, Vesper J, Schnitzler A, Groiss SJ. Neuromodulation. 2020 Jul 15.
3. Moldovan AS, Hartmann CJ, Trenado C, Meumertzheim N, Slotty PJ, Vesper J, Schnitzler A, Groiss SJ. Brain Stimul. 2018 Sep-Oct;11(5):1132-1139.

Real World Clinical Outcomes Using a Novel Directional Lead from a Multicenter Registry of Deep Brain Stimulation for Parkinson's Disease

Roshini Jain [1], Günther Deuschl [2], Steffen Paschen [3], Michael Barbe [4], Andrea Kühn [5], Jan Vesper [6]

[1] Boston Scientific, USA, [2] University of Kiel, Germany, [3] University Medical Center Schleswig-Holstein, Germany, [4] University Hospital Cologne, Germany, [5] Charité – Universitätsmedizin Berlin, Germany, [6] Heinrich Heine Universität Düsseldorf, Germany

Deep Brain Stimulation (DBS) systems have historically used ring-shaped electrodes that produce stimulation fields with limited control over field shape and volume of tissue activated. Directional current steering may permit a more personalized DBS approach with respect to individualized shape and pattern of electrical field and corresponding volume of tissue activated. In this report, on-going real-world registry outcomes using a directional lead with a Deep Brain Stimulation (DBS) system capable of multiple independent current source control (MICC) for use in managing symptoms of levodopa-responsive Parkinson's disease (PD) are reported.

The Vercise DBS Registry (ClinicalTrials.gov Identifier: NCT02071134) is a prospective, on-label, multi-center, international registry sponsored by Boston Scientific. Subjects were implanted with a directional lead included as part of a multiple source, constant-current directional DBS system (Vercise Cartesia, Boston Scientific). Subjects were followed up to 3-years post-implantation where their overall improvement in quality of life and PD motor symptoms was evaluated. Clinical endpoints evaluated at baseline and during study follow-up included Unified Parkinson's disease Rating Scale (UPDRS), MDS-UPDRS, Parkinson's disease Questionnaire (PDQ-39), and Global Impression of Change.

Enabling fractionalization of current using MICC can permit application of a well-defined, shaped, electrical field. This ongoing registry represents the first comprehensive, large scale collection of real-world outcomes using a directional lead and an MICC-based DBS system.

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– virtual meeting –
November 20 – 21, 2020

Abstract title / authors:

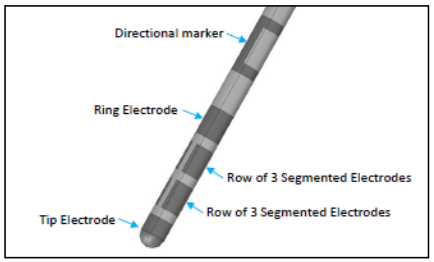
Real World Clinical Outcomes Using a Novel Directional System from a Multicenter Registry of Deep Brain Stimulation for Parkinson's Disease

Guenther Deuschl[1], Roshini Jain[2], Heleen Scholtes[2], Alex Wang[2], Michael T. Barbe[3], Steffen Paschen[1], Jens Volkmann[4], Chong Sik Lee[5], Andrea Kühn[6], Jan Vesper[7]

1. University Hospital Schleswig-Holstein, Kiel, Germany
2. Boston Scientific, Valencia, CA USA
3. University Hospital Cologne, Cologne, Germany
4. University Hospital Würzburg, Würzburg, Germany
5. University of Ulsan, ASAN Medical Center, Seoul, South Korea
6. Charité - Universitätsmedizin Berlin, Berlin, Germany
7. Heinrich Heine University, Düsseldorf, Germany

Background:

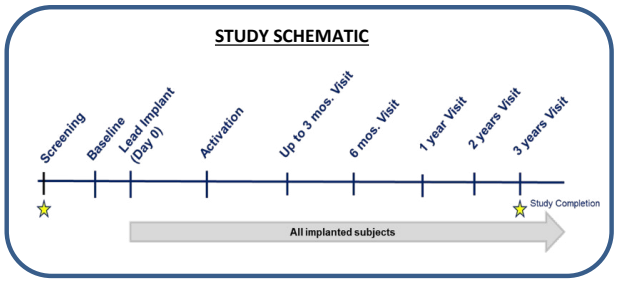
- Deep Brain Stimulation (DBS) systems have historically used ring-shaped electrodes that produce stimulation fields with limited control over the shape of the field and volume of tissue activated.
- Directional current steering may permit a more personalized DBS approach with respect to the individualized shape and pattern of the electrical field and corresponding volume of tissue activated.



The directional DBS lead has four electrode levels, of which the two middle levels are split into three segments spanning ~120° (highest and lowest levels consist of ring-shaped electrodes).

This analysis reports real-world outcomes using a directional lead with a DBS System capable of multiple independent current source control (MICC) for use in the management of symptoms of levodopa-responsive Parkinson's disease (PD).

Methods:

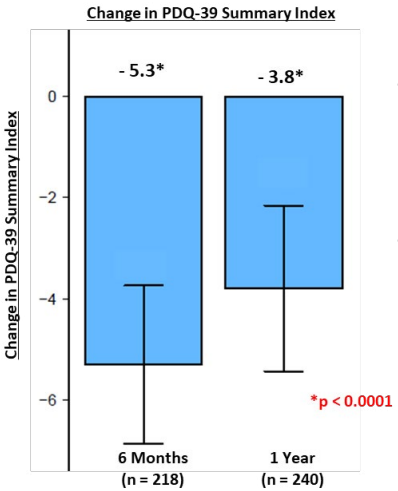


Primary Objective	• To compile real-world outcomes of an MICC-based DBS system (Vercise, Boston Scientific) using a directional lead (Vercise Cartesia, Boston Scientific)
Coordinating Investigators	• Prof. Dr. med Günther Deuschl • Prof. Dr. med Jan Vesper
Subjects/Sites	• Up to 1000 implanted subjects at up to 70 international sites
Key Study Assessments	• Parkinson's Disease Questionnaire (PDQ-39) • Unified Parkinson's Disease Rating Scale (UPDRS) or MDS-UPDRS • Clinical Global Impression of Change as assessed by Subject, Caregiver and Clinician • Schwab and England Scale (SE) • EQ-5D-5L
Safety	• Adverse events were reported

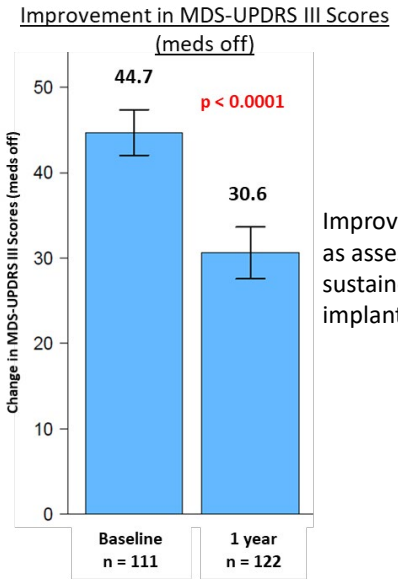
BASELINE CHARACTERISTICS (Subjects Enrolled: 434 / Implanted: 433 as of February 2020)	
Age (years) - Mean (SD) N	60.8 (8.7) 433
Gender – Male %	70.3%
PD Related Symptoms	**Mean (SD) N**
UPDRS III Scores (meds OFF)	37.6 (12.3) 158
MDS-UPDRS III Scores (meds OFF)	45.0 (15.5) 224
Disease Duration (years)	10.2 (4.7) 431
PDQ-39 Summary Index Score	28.7 (14.6) 423

Results:

Improvement in Quality of Life and Motor Function



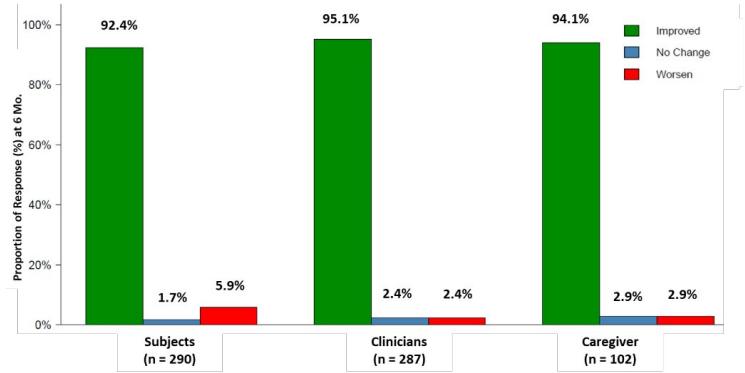
- Improvement in Quality of Life ($p < 0.0001$) following Directional DBS Implant up to 1-year post-implant (n = 240)
- Several subdomains showed statistical significant improvement ($p < 0.0001$) at 6 months that was sustained at 1-year post- implant

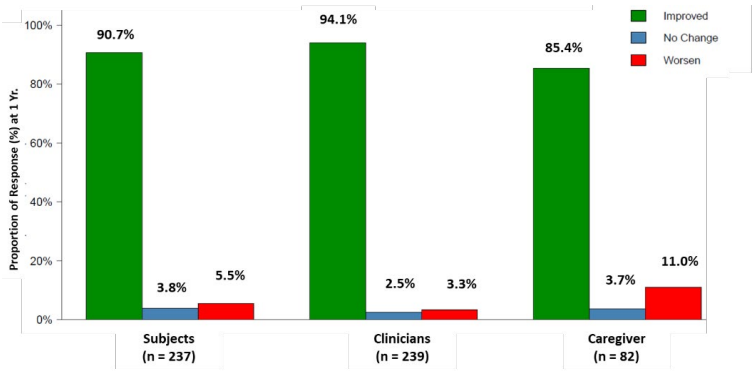


Improvement in motor function as assessed by UDPRS III scores sustained up to 1-year post-implant ($p < 0.0001$)

Results:

Clinical Global Impression of Change assessed by clinicians, subjects & caregivers





Improvement in PD symptoms:

- At 6 months: Over 90% of subjects, physicians and caregivers
- At 12 months: Over 90% of subjects, physicians and 85% of caregivers

Safety

- No unanticipated adverse events
- No lead breakages/fractures
- A total of 231 serious adverse events in 131 subjects were reported

Conclusion:

This on-going registry represents the first comprehensive, large scale collection of real-world outcomes using Directional DBS Systems (MICC-based)

- Overall improvement in Quality of Life and motor function
- Over 90% of subjects, caregivers, clinicians reported improvement in PD symptoms
- The overall safety profile is acceptable

Deep Brain Stimulation (DBS) for Parkinson's Disease International Study (REACH-PD): Final Outcomes from China

Huifang Shang[1], Yuqing Zhang[2], Ling Chen[3], Bomin Sun[4], Xuelian Wang[5], Jun Wang[6], Jian Wang[7], Kahrin Stromberg[8], Sarah Wibben[8], Dogni Xie[9], Ayse Bovet[10]

[1] West China Hospital – SiChuan University, China, [2] Xuanwu Hospital of Capital Medical University, China, [3] The First Affiliated Hospital of Sun YatSen University, China, [4] Ruijin Hospital Shanghai Jiao Tong, China, [5] Tangdu Hospital of Fourth Military Medical University, China, [6] The First Hospital of China Medical, China, [7] Huashan Hospital – Fudan University, China, [8] USA, [9] China, [10] Switzerland

Deep brain stimulation (DBS) at the subthalamic nucleus (STN) and globus pallidus interna (GPi) is effective in improving symptoms of levodopa-responsive, idiopathic Parkinson's disease (PD). This has been shown in several randomized control trials mostly in Europe and in the US. DBS Therapy has become an established treatment for PD patients with medically intractable fluctuations and dyskinesia and has shown long-term efficacy.

There is however a consistent need for evidence in many regions around the world such as Asia and Latin America. This study was the first prospective, multi-center, post-market international study with a primary purpose of assessing PD-related health outcomes with adequate statistical power to generate evidence in China and Brazil.

The primary objectives of this study were to demonstrate significant improvements in PD-related quality of life (PDQ-8) from baseline to 12 months and in motor score (Unified Parkinson's Disease Rating Scale (UPDRS III) from baseline (Off medication) to 12 months (On stimulation/Off medication). Additional measures such as UPDRS I, II, IV, Hoehn and Yahr Staging Scale, overall health status and patient satisfaction were also included. Results from China are presented here

PD patients were implanted and completed follow-up visits at 3, 6, and 12 months following DBS therapy activation. Changes in PDQ-8 and UPDRS III (Off med) from baseline to 12 months were evaluated for all implanted patients, with a negative change indicating an improvement from baseline in PD-related quality of life and motor function. Additionally, changes in UPDRS I, II, IV and in Hoehn and Yahr Staging Scale, overall health status and patient satisfaction were included.

The study met both primary objectives. Patients demonstrated a significant improvement in PD related quality of life and in motor function (On stimulation/Off medication) at 12 months post-device activation. Improvement was also observed in the additional measures: motor functioning, mentation, behavior, and mood; activities of daily living; complications of therapy; overall health status; and healthcare outcomes. Patient satisfaction was high, with 95.3% of patients satisfied with their DBS surgery results, and 98.8% of patients indicating they would recommend the therapy to a friend with PD.

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Deep Brain Stimulation (DBS) for Parkinson's Disease International Study (REACH-PD): Final Outcomes from China

Authors: Yuqing Zhang, Ling Chen, Bomin Sun, Xuelian Wang, Jun Wang, Jian Wang, Kathrin Stromberg, Sarah Wibben, Dongni Xie, Ayse Bovet and Huifang Shang

Objective:

Understand DBS therapy effectiveness as measured by clinician and patient reported health outcomes data through one year of follow-up in China.

Introduction:

- Deep brain stimulation (DBS) at the subthalamic nucleus (STN) and globus pallidus interna (GPi) is effective in improving symptoms of levodopa-responsive, idiopathic Parkinson's disease (PD). This has been shown in several randomized control trials mostly in Europe and in the US. DBS Therapy has become an established treatment for PD patients with medically intractable fluctuations and dyskinesia and has shown long-term efficacy. There is however a consistent need for evidence in many regions around the world such as Asia and Latin America.

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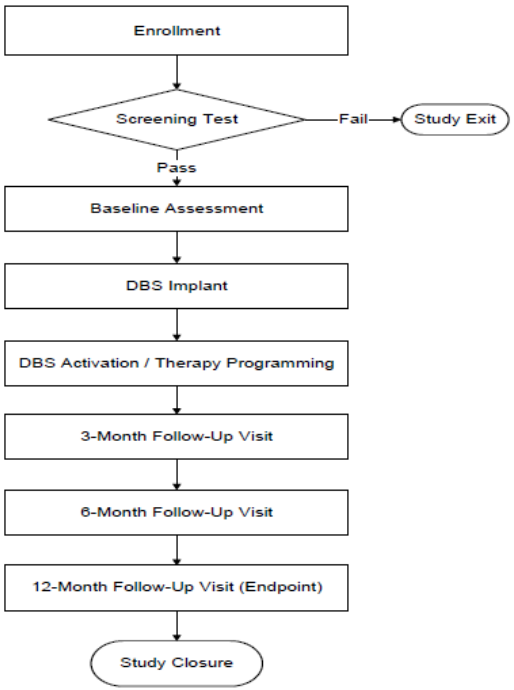
Methods:

- PD patients were implanted and completed follow-up visits at 3-, 6-, and 12-months following DBS therapy activation. Changes in PDQ-8 and UPDRS III (Off med) from baseline to 12 months were evaluated for all implanted patients, with a negative change indicating an improvement from baseline in PD-related quality of life and motor function.
- Additionally, changes in UPDRS I, II, IV and in Hoehn and Yahr Staging Scale, overall health status and patient satisfaction were included.



Results:

Seven centers in China implanted 89 patients (68.5% male, mean (SD) age 58.3 (9.4)); 86 patients completed the 12-month visit.

Figure 11-1. PDQ-8 primary analysis (ITT Analysis Set)

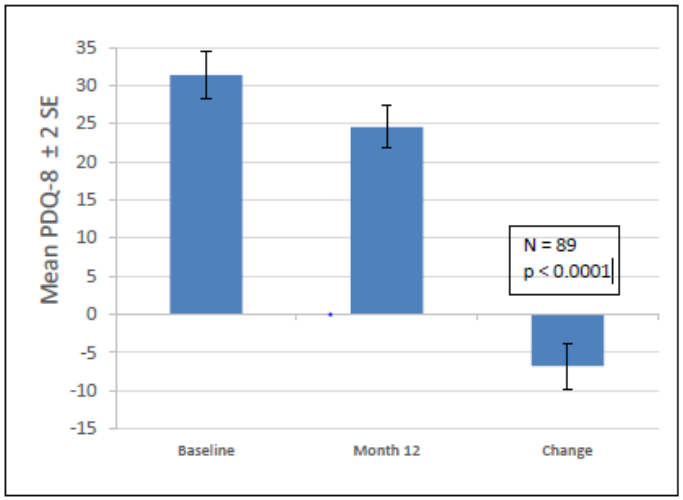
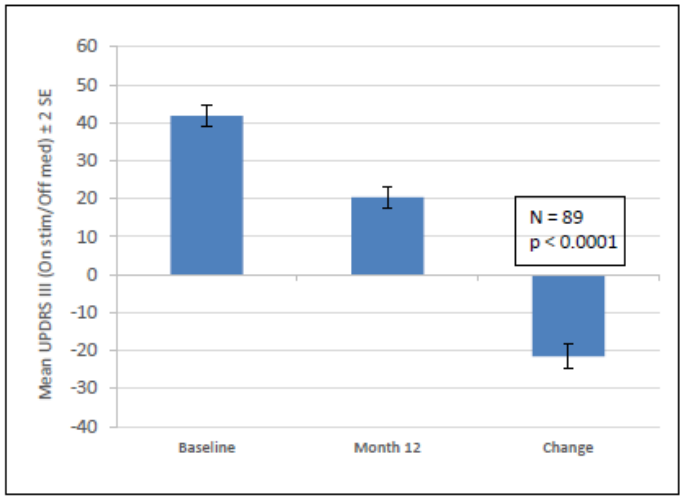


Figure 11-3. UPDRS III (On stim/Off med) primary analysis (ITT Analysis Set)



Conclusion:

- The study met both primary objectives. Patients demonstrated a significant improvement in PD related quality of life and in motor function (On stimulation/Off medication) at 12 months post-device activation.
- Improvement was also observed in the additional measures: motor functioning, mentation, behavior, and mood; activities of daily living; complications of therapy; overall health status; and healthcare outcomes.

- Patient satisfaction was high, with 95.3% of patients satisfied with their DBS surgery results, and 98.8% of patients indicating that they would recommend the therapy to a friend with PD.

PO 15

European expert opinion on ANT-DBS therapy for drug-resistant focal epilepsy (Delphi method)

Elisabeth Kaufmann[1], Fabrice Bartolomei[2], Paul Boon[3], Stéphan Chabardes[4], Albert Colon[5], Loránd Eross[6], Dániel Fabó[7], Antonio Goncalves-Ferreira[8], Lukas Imbach[9], Wim Van Paesschen[10], Jukka Peltola[11], Ricardo Rego[12], Tom Theys[10], Berthold Voges[13]

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Deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS) is supported by high-level clinical evidence (the SANTE randomized controlled trial) and is CE marked for patients with drug-resistant focal epilepsy. However, open questions remain concerning patient selection, patient management and outcome evaluation and guiding reports on practical treatment principles remain scarce. This initiative thus aimed to evaluate the current knowledge on ANT-DBS therapy and to share European experts´ opinion and experience.

The Expert Panel (EP) encompassed 10 neurologists and 4 neurosurgeons from eight different European countries. A Delphi approach was used, which included (1) a review of the current literature on ANT-DBS as first step. The literature search was limited to reports on at least 3 patients published between 01/2000 and 01/2019. The extracted data was summarized as pre-reading material and served as a basis for the creation of the survey questions. The online survey (2) was completed anonymously by the EP prior to a (3) face-to-face meeting held in November 2019. After discussing the first survey round results and modifying the questions, a second survey round was completed by the EP. An agreement level of ≥71% (10/14 panellists) was considered as consensus.

The literature search yielded a total of 323 publications, whereof 46 studies were selected for data extraction of the most reported criteria for patient selection, management, and outcome. The EP board agreed on the importance of a presurgical evaluation of ANT-DBS candidates and achieved consensus on 4 complementary parameters for patient selection and management, i.e. patient´s preference, operability, occurrence and frequency of psychogenic seizures, and psychiatric history. Patients with temporal lobe epilepsy having no resective therapy option, as well as patients who failed prior VNS and/or resection were classified as good patient candidates. Reasons for concern were seen in unreliable seizure documentation, history of frequent psychogenic seizures, progressive etiologly, history of psychosis or depression, especially in case of an history of suicidal attempts, and general MRI contraindications. Due to the low level of evidence on device programming, it was not possible to give strict recommendations. The EP thus shared their clinical practice instead: all centres start with monopolar stimulation and typically (79%) use the cycling mode. Stimulation frequency and pulse width are mostly (93%) set according to the SANTE parameters, whereas half of the experts prefer to start with lower amplitudes than 5V. Agreement was further achieved on strategies for electrode selection and management of side effects or insufficient clinical response. A set of 7 outcome parameters was defined to be monitored during the follow-up in order to evaluate the clinical response and promptly assess side-effects.

The expert opinion report on ANT-DBS provides scientific and strategic advice on patient selection, stimulation strategies, management of side effects and insufficient clinical response and presents recommendations for outcome evaluation. Although current evidence is too low for definite practical guidelines, this EP report could support clinicians in adopting the therapy.

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European expert opinion on ANT-DBS therapy for drug-resistant focal epilepsy (Delphi method)

Elisabeth Kaufmann[1], Fabrice Bartolomei[2,3*], Paul Boon[4*], Stéphan Chabardes[5, 6*], Albert J Colon[7, 8*], Loránd Eross[9, 10*], Dániel Fabó[11*], Antonio Gonçalves-Ferreira[12*], Lukas L Imbach[13*], Wim Van Paesschen[14*], Jukka Peltola[15*], Ricardo Rego[16*], Tom Theys[17*], Berthold Voges[18*]

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Background:

- ANT-DBS therapy is approved for patients with drug-resistant focal epilepsy
- high-level clinical evidence (the SANTE randomized controlled trial)
- open questions on patient selection / management / outcome evaluation
- no guideline available

European initiative: (1) evaluate current knowledge on ANT-DBS
(2) share European experts´ opinion
(3) provide strategic advice

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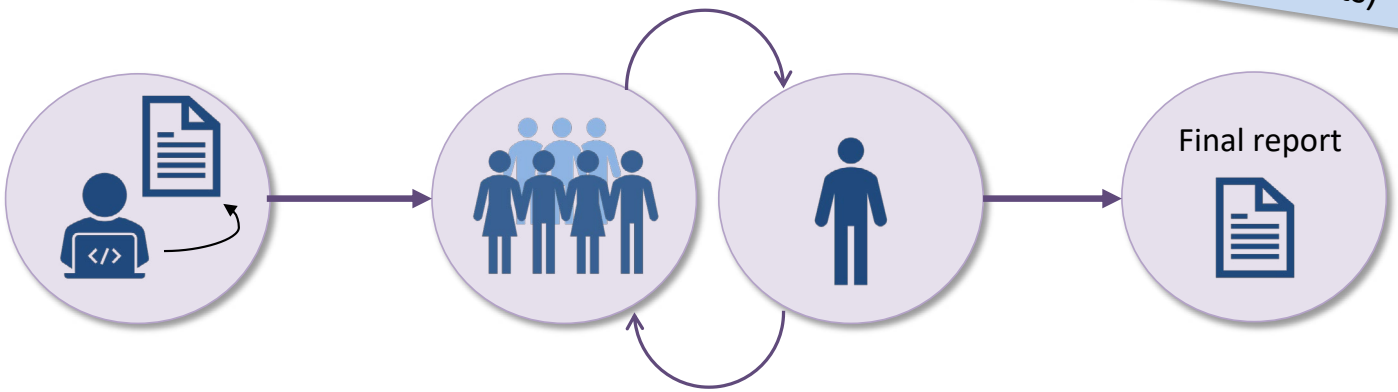
Methods:

- **Expert Panel (EP)**: 10 neurologists & 4 neurosurgeons (8 European countries)
- **DELPHI approach:**

consensus = agreement level of ≥71% (10/14 panellists)



- literature review (2000-2019)
- creation of pre-reading material
- creation of first survey round

- 1st survey round (anonymous)
- Face-to-Face meeting
- 2nd survey round (anonymous)

- appraisal of level of agreement
- publication of final report

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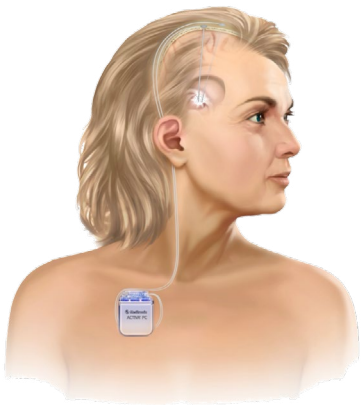
Results (1)

- Literature review: 323 publications → 46 selected for data extraction
- Patient selection: Presurgical evaluation
  Patient´s preference
  Operability
  Psychogenic seizures? Psychiatric history?
- Good candidates: Temporal lobe epilepsy (TLE)*
  Patients who failed prior VNS and/or resection
- Reasons for concern: Unreliable seizure documentation
  History of frequent psychogenic seizures
  Progressive etiologly
  History of psychosis/depression/suicidal attempts
  General MRI contraindications



*who failed surgery or are no candidate for resective therapy

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Results (2)

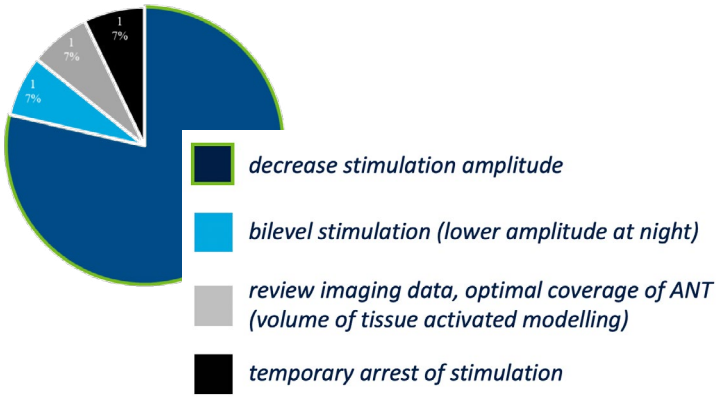
❖ Electrode selection*

- Based on location on coregistered CT/MRI (86%)
- Anterior / superior location within ANT

❖ Initial programming:

- monopolar stimulation (100%)
- cycling mode (79%)
- stimulation frequency 130-145 Hz (93%)
- pulse width 90µs (93%)
- amplitude: 5V (50%) vs. < 5V (50%)

❖ Strategies in case of side effects:



❖ Outcome measures:

- Affective symptoms
- Seizure frequency
- Memory/cognitive perform.
- Quality of Life
- Seizure severity
- Infection
- Sleep quality

*transventricular approach: n=13
extraventricular approach: n=8

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Conclusion:

- Scientific & strategic advice on patient selection / management / stimulation strategies
- Recommendations for outcome evaluation
- ***Support clinicians in adopting ANT-DBS therapy***

FUNDING: All authors received speaker honoraria by **Medtronic Inc.** The face-to-face meeting was held in the European Medtronic Headquarter in Tolochenaz, Switzerland, upon invitation by Medtronic

Publication: Kaufmann et al., *Seizure*, 81 (2020) 201-209

Power Demand and Battery Longevity: 5-year Results from a Multi-Center Global Registry

Peter Konrad[1], George M. Plotkin[2], Stephane Palfi[3], Emmanuel Cuny[4], Jean-Philippe Azulay[5], Tomas Witt[6], Tom Theys[7], Yasin Temel[8], Gayle Johnson[9], Kulwant Bhatia[9], Todd Weaver[9]

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Several published articles on the impact of programmed settings and impedance on battery longevity in DBS patients implanted with Activa PC have been compared with predecessor Kinetra IPGs.1-3 However, Activa PC contains hardware and programming capabilities that provide physicians greater flexibility in managing patient symptoms. The difference in battery longevity between Activa PC and Kinetra may be due to a number of design improvements for patient comfort and therapy optimization. In addition, sample size, diagnosis and duration of disease, stimulation settings including longitudinal impedance changes, and length of follow-up vary widely in these studies. The effect of these electrical parameters is better understood when a standardized approach across diverse centers and global patient populations is used.

The Product Surveillance Registry (PSR) is a prospective long- term, multi-center global registry. The stimulation settings were analyzed for 612 patients at 35 centers in 11 countries; 452 were first- time implanted IPGs and 215 were replacement IPGs. IPG longevity was estimated as the time to replacement due to battery depletion. TEED (µJ) per lead was estimated from the actual device reported stimulation parameters and impedances over the lifetime of the battery. Statistical analysis was completed using Cox Proportional Hazards regression and Kaplan-Meier methods.

The present analyses represent battery longevity from a global patient population reflecting standard practice patterns at most DBS centers without protocol constraints regarding the management of these patients. IPG longevity was quite similar in PD and ET patients but shorter in replacement IPGs, likely due to higher energy demand in replacement IPGs. The increase in TEED over time and higher TEED in replacement IPG may reflect changes in stimulation settings, usage patterns, or local tissue impedance fluctuations. Overall this analysis demonstrated the expected performance of 3-5 years of primary cell battery longevity in PD and ET patients.

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POWER DEMAND AND BATTERY LONGEVITY: 5-YEAR RESULTS FROM A MULTI-CENTER GLOBAL REGISTRY

Authors: Konrad P, MD, PhD[1], Plotkin G, MD, PhD[2], Palfi S, MD, PhD[3], Cuny E, MD, PhD[4], Azulay JP, MD[5], Witt T, MD[6], Theys T, MD, PhD[7], Temel Y, MD, PhD[8;] Johnson G, MPH[9], Bhatia K, PhD[9], Weaver T, PhD[9]

[1]Vanderbilt University Medical Center, Nashville, Tennessee, USA; [2]University of Texas Health Science Center at Tyler, Tyler, Texas, USA; [3]AP-HP, Groupe Hospitalier Henri-Mondor, Paris, France; [4]Universite de Bordeaux, Bordeaux, France; [5]Hôpital de la Timone, Marseille, France; [6]Indiana University Health, Indianapolis, Indiana, USA; [7]Universitair Ziekenhuis Leuven, Leuven, Belgium; [8]School of Mental Health and Neuroscience, Maastricht University, The Netherlands; [9]Medtronic Clinical Research, Minneapolis, MN, USA

- Recent articles reported impact of DBS stimulation settings and impedance on total electrical energy delivered (TEED) and consequently, battery longevity in DBS patients[1-4]
- Sample size, diagnosis, duration of disease and length of follow-up vary widely in these single-center studies
- We analyzed the electrical features of long-term DBS settings for Parkinson's Disease (PD) and Essential Tremor (ET) patients and the impact on battery longevity in primary cell DBS IPG's
- The data is derived from a global, multi-center registry tracking real-world use of the device

METHODS

- Data collected from the Post-market Surveillance Registry (PSR): a prospective, long-term, multi-center global DBS registry monitoring Medtronic DBS systems
- TEED analysis on 612 patients collected at 35 centers who were implanted with Activa™ PC devices for PD and ET from July 2009 through April 2019
- TEED (μJ) per lead was calculated as the average energy used in left and right DBS leads over the lifetime of the device
    - Actual impedance (ohms) values were used, data with missing impedance was excluded
    - Observations in first 6 months in first-time implanted devices and 1-month in replacement devices were excluded from the analysis
- Statistical analysis: Cox Proportional Hazards regression and Kaplan-Meier methods

$$\text{TEED} = \mathcal{E}_{(\mu J)} = \frac{\mathcal{V}^2.pw.f}{\mathcal{R}} \quad (1s)$$

$\mathcal{E}$ = Energy (micro Joules)
$\mathcal{V}$ = Voltage (volts) - intensity
pw = pulse width (msec)
f = frequency (1 / sec)
$\mathcal{R}$ = resistance ~ impedance (ohms)

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RESULTS

TABLE 1. MEDIAN BATTERY LONGEVITY OF ACTIVA™ PC

	PD – Median (Q1, Q3)			ET – Median (Q1, Q3)		
	First-time implanted Device	Replacement Device	P-value	First-time implanted Device	Replacement Device	P-value
Number of Patients	760	424	NA	321	117	NA
Number of Devices	760	545	NA	321	159	NA
Median Battery Longevity -years	4.5 (3.7, NA)	2.9 (2.0, 4.4)	<0.0001	4.3 (3.2, 6.3)	2.8 (1.9, 4.1)	0.0001

- First-time implanted IPG longevity higher than replacements

TABLE 2. STIMULATION SETTINGS AND BATTERY

Variables	PD – Median [Q1, Q3]			ET – Median [Q1, Q3]		
	First-time Implanted Device N=361	Replacement Device N=202	p-value	First-time Implanted Device N=91	Replacement Device N=40	p-value
Amplitude (V)	2.6 [2.2, 3.2]	3.2 [2.7, 3.7]	<0.0001	2.5 [2.0, 3.1]	3.2 [2.7, 3.7]	0.0001
Pulse width (µs)	72.5 [60.0, 90.0]	84.9 [60.0, 90.0]	0.0002	75.0 [60.0, 90.0]	90.0 [60.0, 105.0]	0.4099
Frequency (Hz)	130.0 [125.0, 132.7]	130.0 [125.0, 150.0]	0.2485	130.0 [130.0, 150.0]	130.0 [130.0, 180.0]	0.1841
Impedance (Ω)	1090.8 [956.0, 1221.0]	932.7 [792.5, 1085.5]	<0.0001	995.0 [857.7, 1216.2]	889.5 [764.8, 1078.7]	0.1739
TEED/Lead (µJ)	62.5 [41.8, 97.7]	123.5 [78.4, 167.0]	<0.0001	66.2 [41.3, 114.0]	174.9 [97.9, 248.1]	<0.0001
Battery Longevity (years, 95% CI)	4.7 (3.8, 6.3)	3.1 (2.2, 4.3)	<0.0001	4.5 (3.3, 6.3)	2.6 (1.9, 3.9)	<0.0001

- Amplitude (V) settings differ significantly between first-time vs replacement implants
- TEED significantly higher in replacement groups for both PD and ET patients (p<0.0001) and hence the reduced battery longevity in the replacement group

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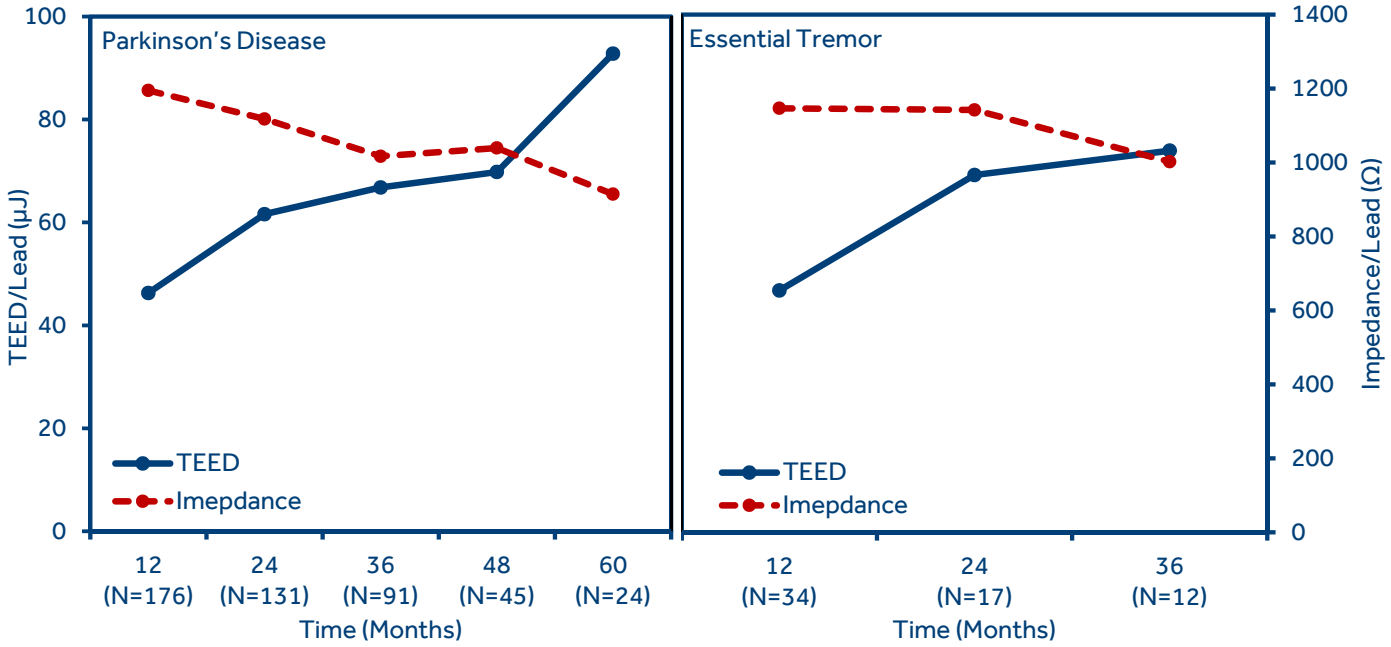
RESULTS

CHANGE IN TEED AND IMPEDANCE OVER TIME



- TEED increased over time in PD ($p<0.001$) and ET ($p=0.386$) patients in first-time implanted device
- A significant downward trend in impedance was also observed in both PD and ET patients ($p<0.0001$) leading to higher energy use over lifetime of lead

CONCLUSION

- DBS primary cell IPG battery longevity of 3 to 5 years follows expected performance
- Data derived from real-world, global DBS patient population
- IPG longevity is quite similar in PD and ET patients but shorter in replacement IPGs, likely due to an increased power demand in replacement IPGs
  - Intensity adjustments account for largest change in TEED
  - Impedance drops over time which leads to increased power delivery without change in settings
- The increase in TEED over time and higher TEED in replacement IPGs may reflect changes in stimulation settings, usage patterns, or local tissue impedance fluctuations

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Asleep Surgery May Improve the Therapeutic Window for Deep Brain Stimulation of the Subthalamic Nucleus

Farhad Senemmar[1], Christian Hartmann[1], Philipp J. Slotty[1], Jan Vesper[1], Alfons Schnitzler[1], Stefan Jun Groiss[1]

[1] **Heinrich Heine University, Germany**

The effect of anesthesia type in terms of asleep vs. awake deep brain stimulation (DBS) surgery on therapeutic window (TW) has not been investigated so far. The objective of the study was to investigate whether asleep DBS surgery of the subthalamic nucleus (STN) improves TW for both directional (dDBS) and omnidirectional (oDBS) stimulation in a large single-center population.

A total of 104 consecutive patients with Parkinson's disease (PD) undergoing STN-DBS surgery (80 asleep and 24 awake) were compared regarding TW, therapeutic threshold, side effect threshold, improvement of Unified PD Rating Scale motor score (UPDRS-III) and degree of levodopa equivalent daily dose (LEDD) reduction.

Asleep DBS surgery led to significantly wider TW compared to awake surgery for both dDBS and oDBS. However, dDBS further increased TW compared to oDBS in the asleep group only and not in the awake group. Clinical efficacy in terms of UPDRS-III improvement and LEDD reduction did not differ between groups.

Our study provides first evidence for improvement of therapeutic window by asleep surgery compared to awake surgery, which can be strengthened further by dDBS. These results support the notion of preferring asleep over awake surgery but needs to be confirmed by prospective trials.

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Abstract title / authors:

"Asleep surgery may improve the therapeutic window for deep brain stimulation of the subthalamic nucleus"

Farhad Senemmar, Christian J. Hartmann, Philipp J. Slotty, Jan Vesper, Alfons Schnitzler, Stefan Jun Groiss,

Background:

- The effect of anesthesia type in terms of asleep vs. awake deep brain stimulation (DBS) surgery on therapeutic window has not been investigated so far.
- The objective of the study was to investigate whether asleep DBS surgery of the subthalamic nucleus (STN) improves TW for both directional (dDBS) and omnidirectional (oDBS) stimulation in a large single center population

Methods:

- 104 consecutive PD patients (75 male, 29 female) who underwent bilateral STN-DBS surgery using directional leads at the center of movement disorders in Düsseldorf from 2016 to 2019 were retrospectively analysed
- 80 asleep patients and 24 awake patients
- Both groups were compared regarding:
  1. therapeutic window
  2. therapeutic threshold
  3. side effect threshold
  4. improvement of Unified PD Rating Scale motor score (UPDRS-III)
  5. degree of LEDD reduction
  6. baseline characteristics (age, disease duration, H&Y stage, UPDRS off medication pre, LEDD pre, MDRS pre, MoCa pre, number of trajectories, duration of surgery)

Results:

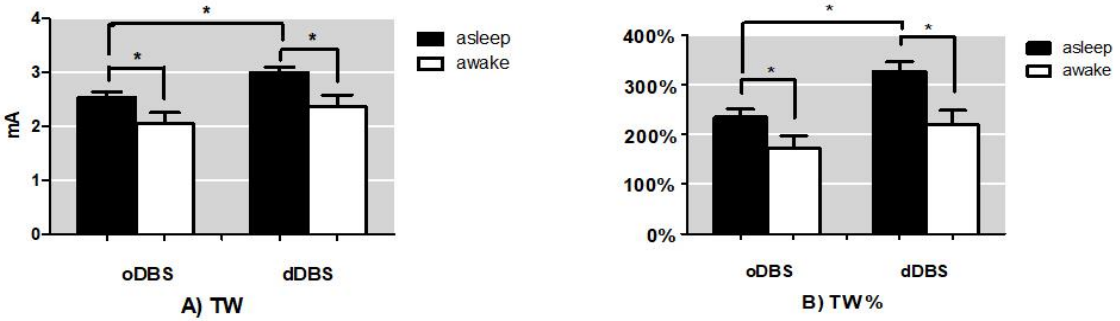

Figure 1: Therapeutic windows (mean ± SE) A) in absolute stimulation amplitude and B) relative to therapeutic threshold, significance level was set to p<0.025. TW = therapeutic window, TW% = therapeutic window percentage.

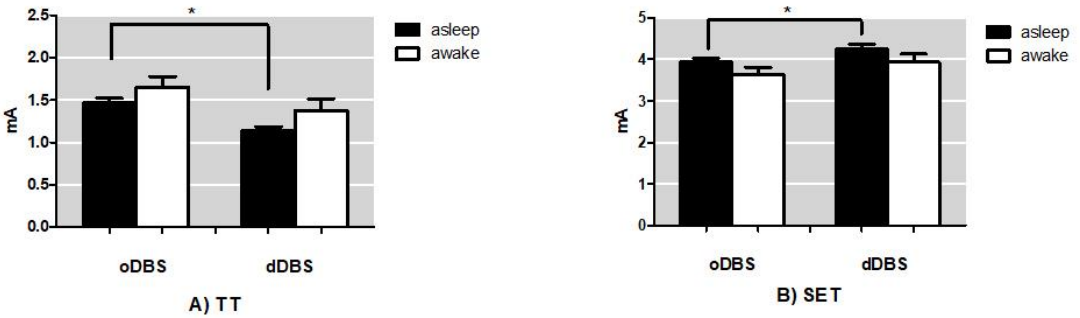

Figure 2: A) Therapeutic and B) side effect thresholds (mean ± SE), significance level was set to p<0.025. TT = therapeutic threshold, SET = side effect threshold

Results:

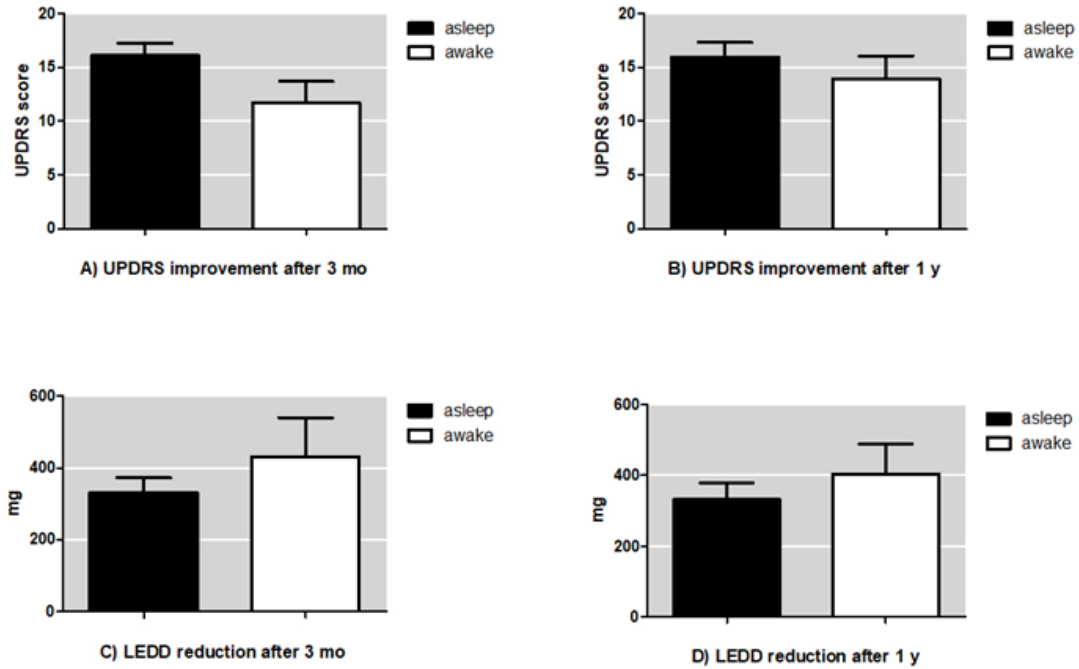

Figure 3: Clinical outcomes in terms of UPDRS-improvement (mean ± SE) A) 3 month and B) 1 year postoperatively and LEDD reduction (mean ± SE) C) 3 month and D) 1 year postoperatively. UPDRS = Unified Parkinson Disease Rating Scale, LEDD = Levodopa Equivalent Daily Dosage, mo = month, y = year

Conclusion:

- Asleep DBS surgery led to significantly wider TW compared to awake surgery for both dDBS and oDBS
- dDBS further increased TW compared to oDBS in the asleep group only and not in the awake group
- Clinical efficacy in terms of UPDRS-III improvement and LEDD reduction did not differ between groups.

- **Our study provides first evidence for improvement of therapeutic window by asleep surgery compared to awake surgery, which can be strengthened further by dDBS.**
- **These results support the notion of preferring asleep over awake surgery but needs to be confirmed by prospective trials.**

ACTIVA systems for deep brain stimulation: an analysis on a prospective, multicenter Product Surveillance Registry (PSR) to meet the reimbursement requirements of the French Haute Autorité de Santé (HAS)

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Following reimbursement of ACTIVA DBS systems, the French Haute Autorité de Santé (HAS) requested a five-year follow-up registry of implanted DBS patients to maintain the reimbursement of the devices. The aim of the study was to characterize adverse events and quality of life measures by DBS indication.

A prospective, non-randomized, observational, multicenter study was conducted, as part of the Product Surveillance Registry (PSR), an ongoing, prospective, long-term multi-center registry. Patients were enrolled from June 2013 until October 2018. A sampling of patients (n=400) from 7 representative French implanting centers were pooled with data from other global centers enrolling in the PSR. The eligible centers in France were analyzed by quartiles representing implant volume. To limit bias, changes in EQ-5D score were analyzed for therapy-naïve PSR patients who completed both baseline and follow-up questionnaires.

The results of this five years follow-up study support the continued safety and effectiveness of the ACTIVA systems for their intended use in real world conditions.

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ACTIVA systems for deep brain stimulation: an analysis on a prospective, multicenter Product Surveillance Registry (PSR) to meet the reimbursement requirements of the French Haute Autorité de Santé (HAS)

Stéphane Palfi , Créteil (FRA); Emmanuel Cuny, Bordeaux (FRA); Jean-Philippe Azulay, Marseille (FRA); Luc Defebvre, Lille (FRA); Soledad Navarro, Paris (FRA); Keisha Sandberg, Minneapolis (USA).

Background:

- Following reimbursement of ACTIVA DBS systems, the French Haute Autorité de Santé (HAS) requested a five-year follow-up registry of implanted DBS patients to maintain the reimbursement of the devices.
- **The aim of the study was to characterize adverse events and quality of life measures by DBS indication.**

Methods:

- A prospective, non-randomized, observational, multicenter study was conducted, as part of the Product Surveillance Registry (PSR), an ongoing, prospective, long-term multi-center registry.
- Patients were enrolled from June 2013 until October 2018.
- A sampling of patients (n=400) from 7 representative French implanting centers were pooled with data from other global centers enrolling in the PSR.
- The eligible centers in France were analyzed by quartiles representing implant volume. To limit bias, changes in EQ-5D score were analyzed for therapy-naïve PSR patients who completed both baseline and follow-up questionnaires.

Results:

Patient enrollment :

- At the time of the final study report (June 2019), 2 537 patients were enrolled at 38 global sites, including 491 (19,4%) from France.
- Most patients were treated for Parkinson's disease (PD) (64,2%) and Essential Tremor (22,9%).
- The average length of follow-up time was 31 months (0 – 106,7 months).
- France enrolled a higher proportion of PD patients (71,1% vs 58,3%; $p<0,0001$) and patients receiving a replacement device (45,6% vs 36,7%; $p<0,0001$).
- There was no statistically significant difference in enrolled patients from France versus patients from other geographies in age and gender.

Adverse events :

- Overall, 1 427 events were reported for 768 patients (30,2%). Of those, 381 events were classified as serious (26,7%) for 294 patients (11,6%).
- A total of 331 events were reported for 197 French patients (40,1%). Of those, 109 events were classified as serious (32,9%) for 89 patients (18,1%).
- The rates of adverse events and serious adverse events in France were not significantly different from other European countries.

Results:

Hospitalizations :

- Overall, 693 hospitalizations were reported (376 in France). Of these 221 (31,9%) were due to events. The most common adverse events related to hospitalizations were for medical device site or wound infections, worsening tremors or dyskinesia, high impedance, psychiatric disorders (e.g. depression, anxiety), gait disturbances, and device migrations.
- There was a difference in hospitalization rates between patients in France and other geographies, that may be attributable to regional variation in care patterns (e.g more hospitalizations in France for device re-programming vs. outpatient care).
- Overall, there were 171 deaths (6,7%) and 17 deaths (3,5%) in France. None of deaths were reported as a direct result of a product performance event.

Quality of life:

- Patients from France and other geographies showed a statistically significant improvement in EQ-5D index and VAS scores through first follow-up.
- For therapy-naïve PD patients from France (N=135), change across time was statistically significant with average improvements between baseline and first follow-up (6 or 12 months) of 0,12 in EQ-5D index score ($p<0,0001$) and a significant improvement in EQ-5D VAS score of 12,4 units or 22,9% change between baseline and first follow-up.

Conclusion:

The results of this five years follow-up study support the continued safety and effectiveness of the ACTIVA systems for their intended use in real world conditions.

Three-Year Follow-Up of a Prospective, Double Blinded Multi-Center RCT Evaluating DBS with a Multiple Source, Constant-Current Rechargeable System for Treatment of Parkinson's Disease

Roshini Jain [1], Jerrold Vitek [2], Lilly Chen [1], INTREPID Study Group [1], Philip Starr [3]

[1] Boston Scientific, USA, [2] University of Minnesota School of Medicine, USA, [3] University of California, San Francisco, USA

STN-DBS is an established therapeutic option for managing the motor symptoms of Parkinson's disease (PD); however, it has not been previously evaluated in a double-blind RCT with sham control using a device capable of MICC. We conducted a double-blinded randomized controlled trial (RCT) with a sham control using a device capable of multiple independent contact control (MICC) to assess subthalamic nucleus Deep Brain Stimulation (STN-DBS) in Parkinson's disease (PD). In this report, outcomes out to 3-years follow-up are presented.

INTREPID (Clinicaltrials.gov identifier: NCT01839396) is a multi-center, prospective, double-blinded randomized controlled trial (RCT) sponsored by Boston Scientific. Subjects with advanced PD were implanted bilaterally in the STN with a multiple-source, constant-current DBS system (Vercise, Boston Scientific). Subjects were randomized to either receive active versus control settings for 12 weeks. Upon completion of the 12-week blinded period, subjects received their best therapeutic settings in the open-label phase up to 5 years. During long-term follow-up, motor improvement and quality of life was evaluated using UPRDS, PDQ39, and Schwann and England. Adverse events were also collected.

Results of the INTREPID RCT demonstrate that use of a multiple-source, constant current DBS system is safe and effective for treatment of PD motor symptoms. Long-term follow-up on the use of this system and associated outcomes will be presented.

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Abstract title / authors:

A Three-Year Follow-Up of a Prospective, Double Blinded, Multi-Center Randomized Controlled Trial Evaluating Deep Brain Stimulation with a New Multiple Source, Constant-Current Rechargeable System for Treatment of Parkinson's Disease (INTREPID)

Jerrold Vitek[1], Roshini Jain [2], Lilly Chen [2], Alexander Tröster [3], Lauren Schrock[1], Paul House[4], Monique Giroux[5], Sierra Farris[2], Adam Hebb[6], Donald Whiting[7], Timothy Leichliter[7], Jill Ostrem[8], Marta San Luciano[8], Nicholas Galifianakis[8], Leo Verhagen Metman [9], Sepehr Sani [9], Jessica Karl [9], Mustafa Siddiqui [10], Stephen Tatter [10], Ihtsham ul Haq [10], Andre Machado [11], Michal Gostkowski[11], Michele Tagliati [12], Adam Mamelak [12], Michael Okun [13], Kelly Foote [13], Guillermo Moguel-Cobos [3], Francisco Ponce [3], Rajesh Pahwa [14], Jules Nazarro [14], Cathrin Buetefisch [15], Robert Gross [15], Corneliu Luca [16], Jonathan Jagid [16], Gonzalo Revuelta [17], Istvan Takacs [17], Michael Pourfar [18], Alon Mogilner [18], Andrew Duker[19], George Mandybur [19], Joshua Rosenow [20], Scott Cooper [1], Michael Park [1], Suketu Khandhar [21], Mark Sedrak [22], Fenna Phibbs [23], Julie Pilitsis [24], Ryan Uitti [25], Philip Starr [8]

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6. Kaiser Permanente of Colorado, Denver, CO, USA 7. Allegheny General Hospital, Pittsburgh, PA, USA 8. University of California, San Francisco, San Francisco, CA, USA 9. Rush University Medical Center, Chicago, IL, USA 10. Wake Forest University School of Medicine, Winston-Salem, NC, USA
11. Center for Neurological Restoration at the Cleveland Clinic, Cleveland, OH, USA 12. Cedars-Sinai Medical Center, Los Angeles, CA, USA 13. University of Florida, Gainesville, FL, USA 14. University of Kansas Medical Center, Kansas City, KS, USA 15. Emory University Medical Center, Atlanta, GA, USA
16. University of Miami School of Medicine, Miami, FL, USA 17. Medical University of South Carolina, Charleston, SC, USA 18. New York University Medical Center, New York, NY, USA19. University of Cincinnati Medical Center, Cincinnati, OH, USA 20. Northwestern University Medical Center, Chicago, IL, USA
21. Kaiser Permanente, Sacramento, Sacramento, CA, USA, 22 Kaiser Permanente of Redwood City, Redwood City, CA,USA, 23. Vanderbilt University Medical Center, Nashville, TN, USA 24. Albany Medical Center, Albany, NY, USA 25. Mayo Clinic, Jacksonville, FL, USA

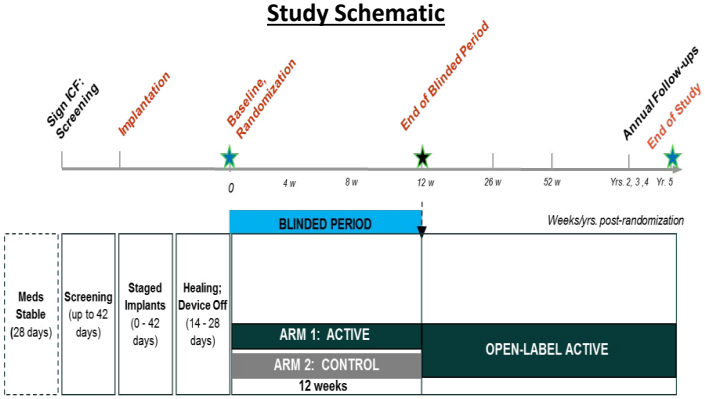
Background:

- Deep Brain Stimulation (DBS) is an effective treatment for the motor signs and fluctuations associated with Parkinson's disease (PD).
- Although DBS efficacy has been substantiated by several randomized controlled trials (RCTs), the degree of improvement varies significantly.
- The INTREPID Study assessed improvement in motor function and quality of life in PD patients following bilateral subthalamic nucleus (STN) DBS using a new device with multiple independent current sources that allows for selective activation of individual contacts on the DBS lead thereby permitting a defined distribution of applied current.

Methods:

Study Design	Multi-center, prospective, double-blind, randomized (3:1) with sham control
Study Device	Vercise DBS System (Boston Scientific, Valencia, CA, USA)
Number of Subjects	N = 160
Primary Endpoint	Mean change in ON time from baseline to 12 weeks post-randomization between active and control groups (PD diary)
Secondary Endpoints	• UPDRS III Scores (stim on/meds off) • Parkinson's Disease Questionnaire (PDQ-39)

Study Schematic



BASELINE CHARACTERISTICS	
Age (years) - Mean (SD) n	59.9 (7.95) 160
Gender – Male (n %)	72.5% (116/160)
Parkinson's Disease Related Symptoms	
UPDRS III Scores (meds OFF) – Mean (SD) n	43.4 (9.60) 153
UPDRS III Scores (meds ON) – Mean (SD) n	18.5 (8.26) 157
Disease Duration (years) - Mean (SD) n	10.1 (3.61) 160
PD diary: OFF time ON time with troublesome dyskinesias ON time without dyskinesias ON time with non-troublesome dyskinesias Asleep	 6.91 ± 2.99 hours 4.35 ± 2.63 hours 4.65 ± 2.67 hours 3.65 ± 1.90 hours 7.20 ± 1.47 hours

Key Inclusion Criteria

- Diagnosis of bilateral idiopathic PD with ≥ 5 years of motor symptoms.
- In the meds off condition: modified H&Y≥ 2; UPDRS-III score of ≥ 30
- Greater than or equal to 6 hours of poor motor function (OFF time plus ON time with troublesome dyskinesias) per day as assessed by PD diary
- Greater than or equal to 33% improvement in UPDRS-III scores following meds
- DRS-2 (Dementia Rating Scale -2) score ≥ 130 and BDI-II score < 17
- An appropriate candidate for the surgical procedures required for bilateral STN DBS

Key Exclusion Criteria

- Any intracranial abnormality or medical condition that would contraindicate DBS surgery
- Have any significant psychiatric condition likely to compromise the subject's ability to comply with requirements of the study protocol
- History of suicide attempt or current active suicidal ideation as determined by a positive response to items 2 -5 of suicide ideation sub-scale of C-SSRS

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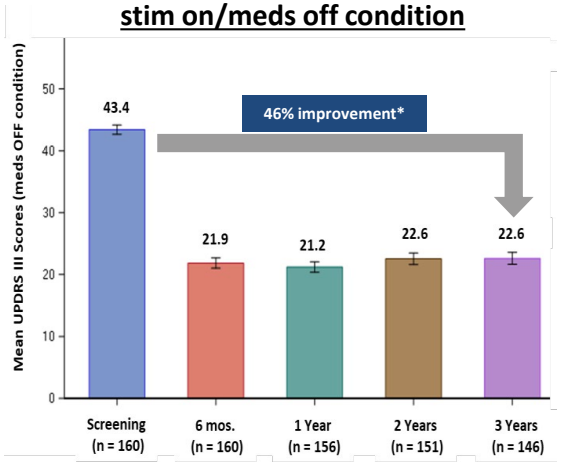
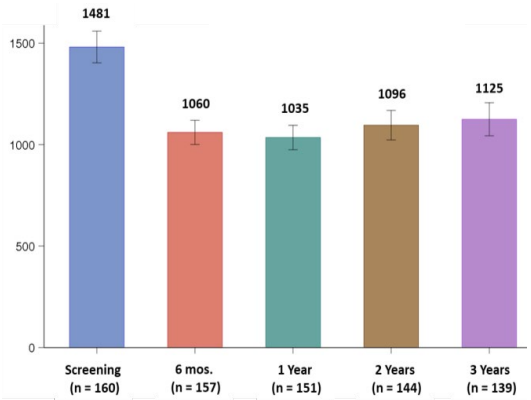
Results:

UPDRS III scores in stim on/meds off condition



- A 46% improvement in UPDRS III scores (n = 160) was reported at 3-years follow up
- Reports in the published literature at 3 years follow-up include:
  - 30% (Weaver FM, et al. *Neurology* 2012 Jul 3;79[1]:55-65.)
  - 35% (Odekerken VJ, et al. *Neurology.* 2016 Feb 23;86(8):755-612016.)

Change in antiparkinsonian medications (LED)



- Anti-parkinsonian medication reduction (LED) was stable up to 3 years follow up

Results:

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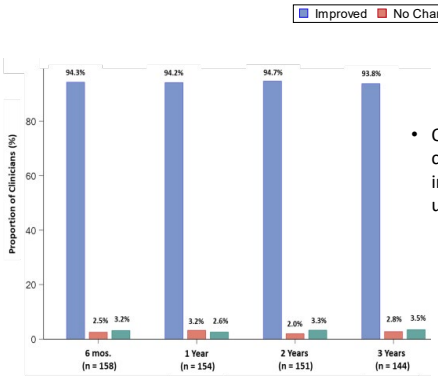
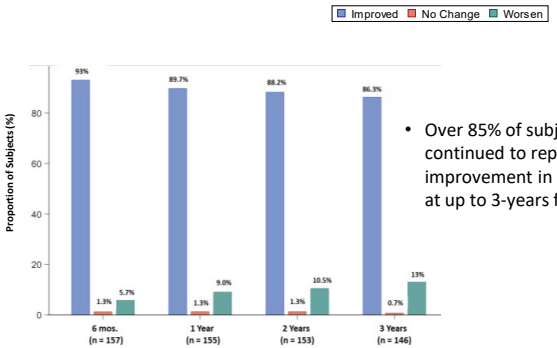
Clinical Global Impression of Change – Clinician



- Over 90% of clinicians continued to report improvement in subjects at up to 3-years follow-up

Clinical Global Impression of Change – Subject



- Over 85% of subjects continued to report improvement in subjects at up to 3-years follow-up

Treatment Satisfaction

Overall Satisfaction	1 year	2 year	3 year
Extremely Satisfied	42.9%	35.1%	43.8%
Very Satisfied	25.6%	33.8%	33.3%
Satisfied	17.3%	16.9%	11.8%
Somewhat Satisfied	5.1%	7.8%	7.6%
Dissatisfied	3.2%	0.6%	2.8%
Very Dissatisfied	1.9%	1.3%	0.0%
Extremely Dissatisfied	3.8%	4.5%	0.7%

- At 3 years, 89% reported being satisfied/very satisfied/extremely satisfied with treatment

Surgical complications across all patients who underwent implantation (n = 196) [whether or not they went on to be randomized in the study]

Event	Number of Events (Subjects)	Rate
Infection occurring in first 6 months of surgery associated with partial/total hardware removal (SAE)	7 (7)	7/196 (3.6%)
Symptomatic Perioperative Intracranial Hemorrhage (SAE) occurring during surgery or postsurgical hospitalization	4 (4)	4/196 (2.0%)
Symptomatic Peri Lead Edema (SAE)	6 (6)	6/196 (3.1%)
Return to OR due to electronic malfunction	7 (6)	6/196 (3.1%)
Return to OR due to lead breakage/lead migration	0 (0)	0/196 (0%)
Return to OR due to hardware erosion occurring > 6 mos. after implantation	2 (2)	2/196 (1.0%)

- Deaths: 7 deaths (unrelated to study-device and/or implant procedure)
- No unanticipated adverse events
- No lead breakage/lead fractures

Conclusion:

- The study successfully met the primary endpoint and several secondary endpoints based on outcomes reported during the 12-week blinded period (Vitek J., et al. AAN Congress, 2018).
- At 1 year, UPDRS III scores (stim on/meds off) improved 49.2% ($p<0.001$) and ON time without troublesome dyskinesias (PD-diary) increased 6±3.8 hours compared with screening ($p<0.001$).
- At 3-years Follow-Up:
  - 46% improvement in UPDRS III scores (stim on/meds off) reported compared with screening ($p < 0.001$)
  - Anti-parkinsonian Medication reduction continued to be stable
  - Significant improvement in overall Quality of Life and satisfaction with therapy
  - Safety profile of the DBS System continues to be comparable to other published reports

Utilization of a Visualization Software Tool for Deep Brain Stimulation Programming in a Subset of Subjects with Parkinson's Disease Who Participated in the INTREPID Randomized Clinical Trial

Roshini Jain [1], Michele Tagliati [2], Lilly Chen [1]

[1] Boston Scientific, USA, [2] Cedars-Sinai Medical Center, USA

Typically, optimization of DBS programming involves an ongoing, and sometimes lengthy or inefficient, trial-and-error process of various stimulation parameters that relies on clinician assessment and subject reporting of clinical benefit. The use of a new visualization tool that can illustrate the location of the DBS lead in the patient's own-segmented anatomy may help to improve the efficiency of achieving programming optimization and outcomes specific to the individual patient (Pavese, S. et al. [Abstract]. 20th International Congress of the International Parkinson and Movement Disorders Society, 2016). This report will describe the utilization and parameters associated with the use of a new visualization tool for Deep Brain Stimulation (DBS) programming in a subset of Parkinson's disease (PD) subjects participating in the INTREPID Randomized Controlled Trial.

INTREPID (ClinicalTrials.gov Identifier: NCT01839396) was a multi-center, prospective, double-blinded randomized controlled trial (RCT) sponsored by Boston Scientific. Subjects with advanced PD were implanted bilaterally in the STN with a multiple-source, constant current DBS System (Vercise, Boston Scientific). In the long-term follow-up phase of the study, a subset of subjects was assessed and programmed, as needed, using a newly available visualization tool (GUIDE XT, Boston Scientific).

Data collection with use of the visualization tool, implemented in up to 30 subjects, is currently ongoing. Preliminary analysis suggests an improvement in motor function and better resolution of adverse effects. Detailed analysis of programming parameters correlated with volume of tissue activated will be presented. Additionally, any case reports of instances where the use of tool help fine tune their settings and associated impact on outcomes will also be presented.

Use of a visualization tool to help guide DBS programming, may offer an opportunity to enhance the overall experience of DBS, thereby potentially contributing to achieving highly effective and desired clinical outcomes.

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– virtual meeting –
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Abstract title / authors:

Utilization of a Visualization Software Tool for Deep Brain Stimulation Programming in a Subset of Subjects with Parkinson's Disease Who Participated in the INTREPID Randomized Clinical Trial

Michele Tagliati[1], Rajesh Pahwa[2], Cathryn Beutefisch[3], Lilly Chen[4], Roshini Jain[4]

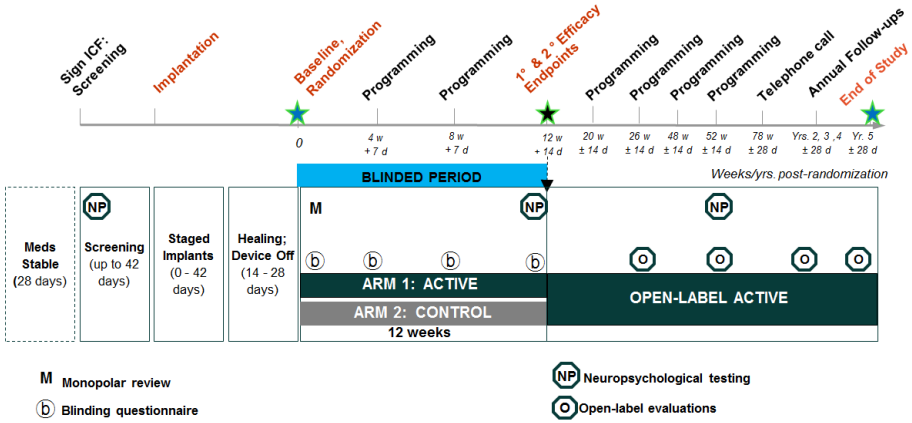
1. Cedars-Sinai Medical Center, Los Angeles, CA USA 2. University of Kansas Medical Center, Kansas City, KS USA
3. Emory University Medical Center, Atlanta, GA USA 4. Boston Scientific Neuromodulation, Valencia, CA USA

Background:

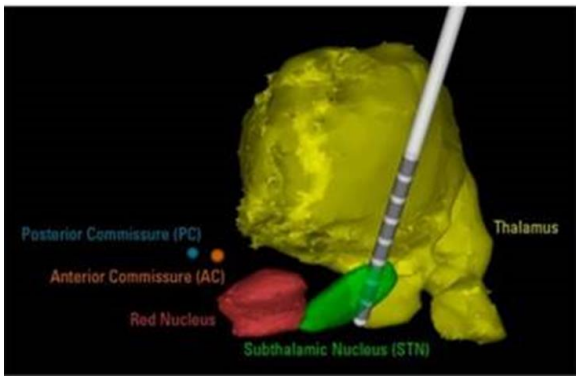
- Typically, optimization of DBS programming involves an ongoing, and sometimes lengthy or inefficient, trial-and-error process of various stimulation parameters that relies on clinician assessment and subject reporting of clinical benefit.
- The use of a new visualization tool that can illustrate the location of the DBS lead in the patient's own-segmented anatomy may help to improve the efficiency of achieving programming optimization and outcomes specific to the individual patient (Pavese, S. et al. [Abstract]. 20th International Congress of the International Parkinson and Movement Disorders Society, 2016).
- This report will describe the utilization and parameters associated with the use of a new visualization tool for Deep Brain Stimulation (DBS) programming in a subset of Parkinson's disease (PD) subjects participating in the INTREPID Randomized Controlled Trial.

Methods:

STUDY SCHEMATIC



- All INTREPID subjects upon completion of the 12-week blinded period are in the open-label phase and followed up to 5 years post- randomization
- Subjects are being assessed and/or programmed as needed using a new visualization tool.



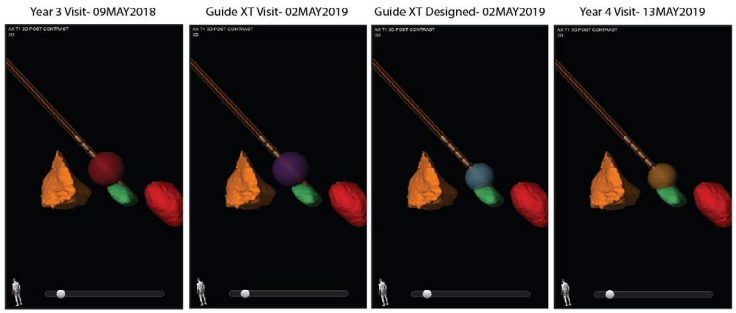
- GUIDE XT (Boston Scientific) is a visualization tool that may help improve the efficiency of achieving programming optimization and outcomes specific to the individual patient
- Utilizes each subject's pre-op MRI and post-op CT to create patient specific anatomy
  - Visualization based-programming
  - DBS lead relative to anatomical targets

Results:

Case Subject 1

- Female
- Age: 59 years
- Duration of Disease: 19 years
- Received Vercise Implant on April 14, 2015
- Screening UPDRS III scores (meds off): 53

Subject received programming settings based on GUIDE XT recommendations and returned for follow up 11 days after with same settings



Guide XT 3D software image of the left lead (left STN)

Guide XT 3D software image of the left lead (right STN)

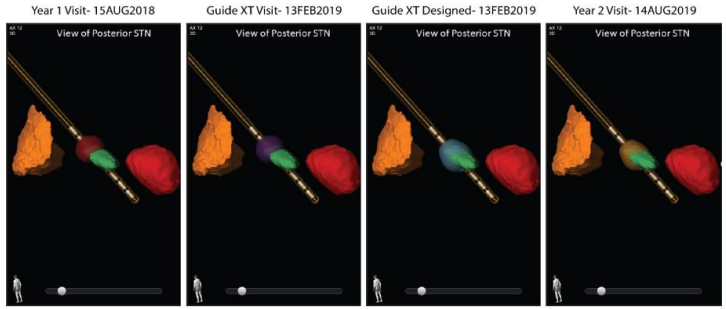
- Stimulation parameters and Volume of tissue activated (VTA) modified based on visualization of lead
- A clinically significant improvement in UPDRS III scores (meds off) [38 → 32] was reported with the use of recommend settings

Results:

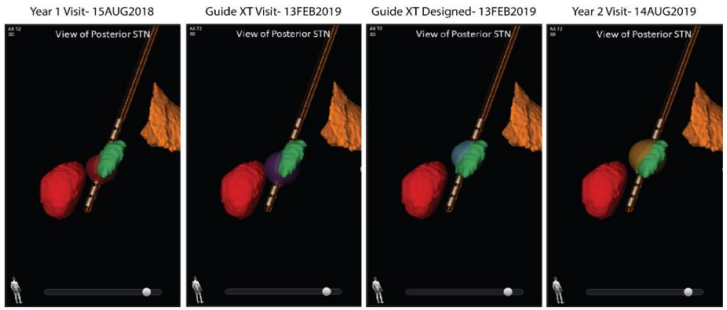
Case Subject 2

- Female
- Age: 57 years
- Duration of Disease: 17 years
- Received Vercise Implant on July 24, 2017
- Screening UPDRS III scores (meds off): 30

Subject received programming settings based on GUIDE XT recommendations and returned for follow up 182 days after with same settings



Guide XT 3D software image of the left lead (left STN)



Guide XT 3D software image of the left lead (right STN)

- Stimulation parameters and Volume of tissue activated (VTA) modified based on visualization of lead
- A clinically significant improvement in UPDRS III scores (meds off) [38 → 32] was reported with the use of recommend settings

Conclusion:

- In this case series of two subjects (with over two years of stimulation as part of the INTREPID Study), the new visualization tool recommended stimulation parameters that led to clinically significant motor improvement –
  - ➢ as assessed by UPDRS III scores in the meds off condition.
- Use of a visualization tool to help guide DBS programming, may offer an opportunity to enhance the overall experience of DBS –
  - ➢ thereby potentially contribute to achieving highly effective and desired clinical outcomes.

Outcomes of a Prospective, Multicenter, International Registry of Deep Brain Stimulation for Parkinson's Disease

Roshini Jain [1], Günther Deuschl [2], Steffen Paschen [3], Michael Barbe [4], Andrea Kühn [5], Jan Vesper [6]

[1] Boston Scientific, USA, [2] University of Kiel, Germany, [3] University Medical Center Schleswig-Holstein, Germany, [4] University Hospital Cologne, Germany, [5] Charité – Universitätsmedizin Berlin, Germany, [6] Heinrich Heine Universität Düsseldorf, Germany

The effectiveness of Deep Brain Stimulation(DBS) for reducing motor complications of Parkinson's disease (PD) has been substantiated by randomized controlled trials (Schuepbach et al., 2013). Additionally, motor improvement is sustained for up to 10 years (Deuschl et al. 2013). Large patient data registries may facilitate insights regarding real world, clinical use of DBS. Furthermore, no registry database currently exists for a multiple source, constant current DBS system.

The Vercise DBS Registry (ClinicalTrials.gov Identifier: NCT02071134) is a prospective, on-label, multi-center, international registry sponsored by Boston Scientific. Subjects were implanted with a directional lead included as part of a multiple source, constant-current directional DBS system (Vercise Cartesia, Boston Scientific). Subjects were followed up to 3-years post-implantation where their overall improvement in quality of life and PD motor symptoms was evaluated. Clinical endpoints evaluated at baseline and during study follow-up included Unified Parkinson's disease Rating Scale (UPDRS), MDS-UPDRS, Parkinson's disease Questionnaire (PDQ-39), and Global Impression of Change.

This DBS registry represents the first comprehensive, large scale collection of real-world outcomes and evaluation of safety and effectiveness of a multiple-source, constant-current DBS system.

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Abstract title / authors:

Outcomes of a Prospective, Multi-Center, International Registry of Deep Brain Stimulation for Parkinson's Disease

Guenther Deuschl[1], Roshini Jain[2], Heleen Scholtes[2], Alex Wang[2], Michael T. Barbe[3], Steffen Paschen[1], Jens Volkmann[4], Chong Sik Lee[5], Andrea Kühn[6], Jan Vesper[7]

1. University Hospital Schleswig-Holstein, Kiel, Germany
2. Boston Scientific, Valencia, CA USA
3. University Hospital Cologne, Cologne, Germany
4. University Hospital Würzburg, Würzburg, Germany
5. University of Ulsan, ASAN Medical Center, Seoul, South Korea
6. Charité - Universitätsmedizin Berlin, Berlin, Germany
7. Heinrich Heine University, Düsseldorf, Germany

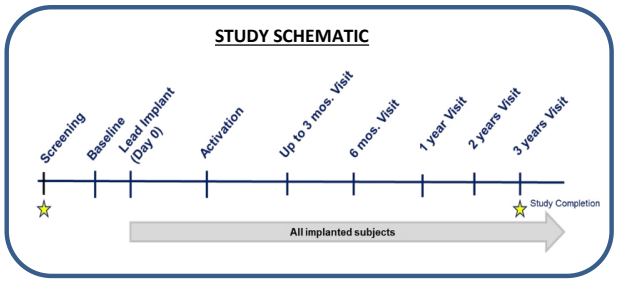
Background:

- Deep Brain Stimulation (DBS) is an effective strategy in reducing the motor complications in Parkinson's disease (PD) as substantiated by several randomized controlled trials

- This motor improvement has shown to be sustained for up to 10 years (Deuschl et al. 2013). Large patient data registries documenting overall improvements in PD disease symptoms, quality of life may facilitate new insights regarding the real-world, clinical use and outcomes of DBS.

- Hence, a large scale, on-going registry was initiated to compile effectiveness and safety-related real-world outcomes of a DBS System capable of multiple independent current source control (MICC) in the management of symptoms of levodopa-responsive PD.

Methods:



Primary Objective	• To compile real-world outcomes of an MICC-based DBS system (Vercise, Boston Scientific) using a directional lead (Vercise Cartesia, Boston Scientific)
Coordinating Investigators	• Prof. Dr. med Günther Deuschl • Prof. Dr. med Jan Vesper
Subjects/Sites	• Up to 1000 implanted subjects at up to 70 international sites
Key Study Assessments	• Parkinson's Disease Questionnaire (PDQ-39) • Unified Parkinson's Disease Rating Scale (UPDRS) or MDS-UPDRS • Clinical Global Impression of Change as assessed by Subject, Caregiver and Clinician • Schwab and England Scale (SE) • EQ-5D-5L
Safety	• Adverse events were reported

BASELINE CHARACTERISTICS (Patients Enrolled: 645 / Implanted: 574 as of Feb. 2020)	
Age (years) - Mean (SD) N	60.3 (8.9) 574
Gender – Male %	70.8%
PD Related Symptoms	**Mean (SD) N**
UPDRS III Scores (meds OFF)	38.4 (12.5) 221
MDS-UPDRS III Scores (meds OFF)	44.9 (15.5) 264
Disease Duration (years)	10.2 (4.8) 572
PDQ-39 Summary Index Score	29.1 (14.3) 561

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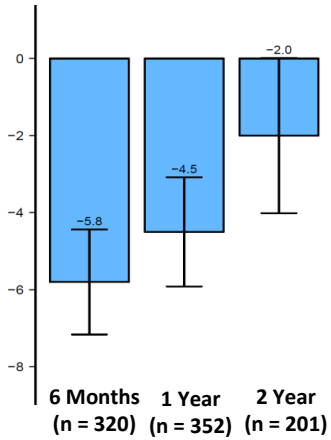
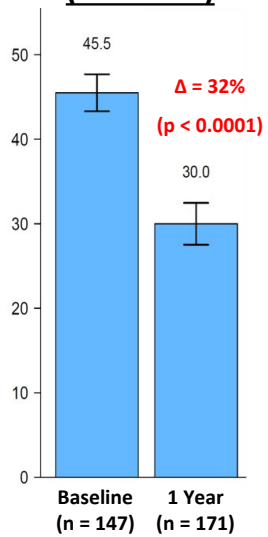
Results:

Change in Parkinson's Disease Questionnaire (PDQ-39)



- PDQ-39 Summary Index demonstrates improvement in Quality of Life (QoL) ($p < 0.0001$) following implant at 6 months and up to 2-year post-implant (n = 201)
- Several subdomains showed statistically significant improvement ($p < 0.0001$) at 6 months that was sustained at 1-year post-implant
  - Mobility, Activities of Daily Living, Stigma, Bodily Discomfort

Improvement in MDS-UPDRS III (meds off)



Improvement in motor function (32%) assessed by UDPRS III scores sustained up to 1-year post-implant ($p < 0.0001$)

Results:

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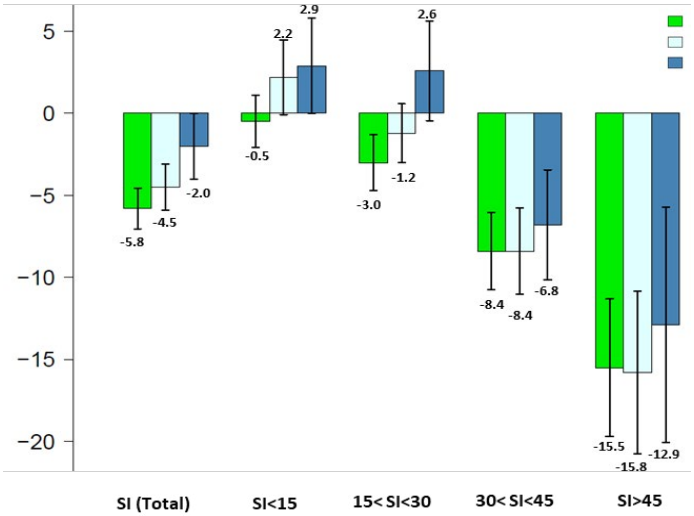
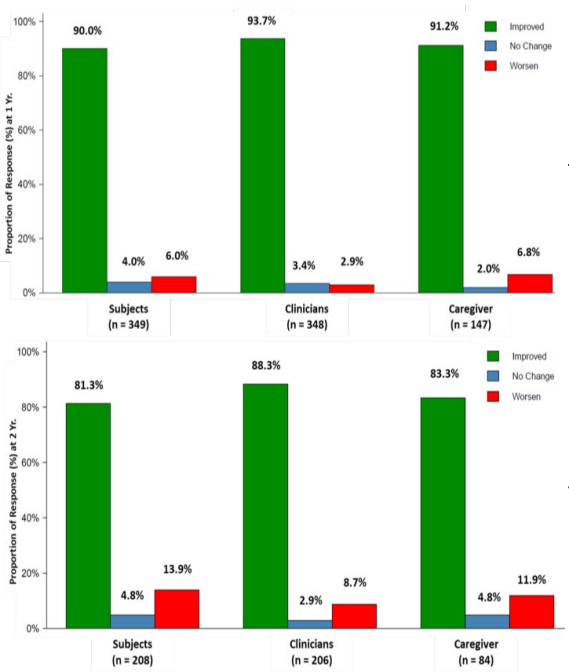
Change in PDQ-39 Summary Index based on Baseline QoL



Higher improvement in Quality of Life (QoL) was noted in patients with worse QoL at Baseline.

- At 6 months, a 15.5-point improvement was noted that was sustained up to 2 year follow up (SI > 45 group)

Clinical Global Impression of Change assessed by clinicians, subjects & caregivers



- Over 80% of patients, physicians, and caregivers noted an improvement in PD symptoms out to 2-years post-implant

Safety

- No unanticipated adverse events
- No lead breakages/fractures
- A total of 297 serious adverse events in 164 patients reported

Conclusion:

This registry is the first large scale collection of outcomes using a DBS System capable of multiple independent current source control.

Preliminary analysis demonstrates that at 6-months, 1-year, and 2-years post-lead implantation:

- Overall improvement in Quality of Life (PDQ-39, EQ-5D-5L and SE)
- Significant improvement in motor function demonstrated by MDS-UDPRS III scores (32%, $p<0.0001$), in the meds off condition
- Over 80% of patients, caregivers, clinicians reported improved PD symptoms
- The overall safety profile is acceptable

Multi Recharge: A multicentric trial on acceptance, convenience, and complications of neurostimulators for deep brain stimulation in movement disorder patients

Martin Jakobs[1], Ann-Kristin Helmers[2], Philip J. Slotty[3], Judith Anthofer[4], Andreas W. Unterberg[1], Karl L. Kiening[1]

[1] University Hospital Heidelberg, Germany, [2] University Hospital Schleswig-Holstein, Campus Kiel, Germany, [3] University Hospital Düsseldorf, Germany, [4] University Hospital Regensburg, Germany

Rechargeable neurostimulators for deep brain stimulation have been available since 2008, promising longer battery life and fewer replacement surgeries compared to non-rechargeable systems. Long-term data on how recharging affects movement disorder patients is sparse. This is the first multicenter, patient-focused, industry-independent study on rechargeable neurostimulators in DBS patients with movement disorders

Four German neurosurgical centers sent a questionnaire to all adult movement disorder DBS patients with a rechargeable neurostimulator implanted at the time of the trial. The primary endpoint was the convenience of the recharging process rated on an ordinal scale from very hard (1) to very easy (5). Secondary endpoints were charge burden (time spent per week on recharging), user confidence, and complication rates. Endpoints were compared for several subgroups (age, sex, indication, primary vs. secondary implant, user confidence, person performing recharge, recharging below 25%).

Datasets of 195 movement disorder patients (66.1% of sent questionnaires) with Parkinson's disease (PD), tremor, or dystonia were returned and included in the analysis. Patients had a mean age of 61.3 years and the device was implanted for a mean of 40.3 months. The overall convenience of recharging was rated as easy (4). The mean charge burden was 122 min/wk and showed a positive correlation with duration of therapy; 93.8% of users felt confident recharging the device. The rate of surgical revisions was 4.1%, and the infection rate was 2.1%. Failed recharges occurred in 8.7% of patients, and 3.6% of patients experienced an interruption of therapy because of a failed recharge. Convenience ratings by PD patients were significantly worse than ratings by dystonia patients. Caregivers recharged the device for the patient in 12.3% of cases. Patients who switched from a non-rechargeable to a rechargeable neurostimulator found recharging to be significantly less convenient at a higher charge burden than did patients whose primary implant was rechargeable. Recharging at below 25% or not feeling confident with the device did not coincide with more interruptions of therapy. Age and sex did not have a significant impact on any endpoint.

Considering the usage of rechargeable neurostimulators in this cohort, 78 replacement of non-rechargeable neurostimulators could be avoided.

Patients with movement disorders rated recharging as easy, with low complication rates and acceptable charge burden.

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Multi Recharge: A multicentric trial on acceptance, convenience, and complications of neurostimulators for deep brain stimulation in movement disorder patients

Jakobs M.[1], Helmers A.-K. [2], Slotty P. [3], Anthofer J. [4], Unterberg A.W. [1], Kiening K. [1]

[1]Universitätsklinikum Heidelberg, Neurochirurgische Klinik, Heidelberg, Deutschland
[2]Universitätsklinikum Schleswig-Holstein, Kiel, Neurochirurgische Klinik, Kiel, Deutschland
[3]Universitätsklinikum Düsseldorf, Stereotaktische und Funktionelle Neurochirurgie, Düsseldorf, Deutschland
[4]Universitätsklinikum Regensburg, Neurochirurgische Klinik, Regensburg, Deutschland

Background:

Rechargeable neurostimulators for deep brain stimulation have been available since 2008, promising longer battery life and fewer replacement surgeries compared to non-rechargeable systems.

Long-term data on how recharging affects movement disorder patients is sparse.

This is the first multicenter, patient-focused, industry-independent study on rechargeable neurostimulators in DBS patients with movement disorders.

Methods:

Four German neurosurgical centers sent a questionnaire to all adult movement disorder DBS patients with a rechargeable neurostimulator implanted at the time of the trial.

The primary endpoint was the convenience of the recharging process rated on an ordinal scale from very hard (1) to very easy (5).

Secondary endpoints were charge burden (time spent per week on recharging), user confidence, and complication rates.

Endpoints were compared for several subgroups:

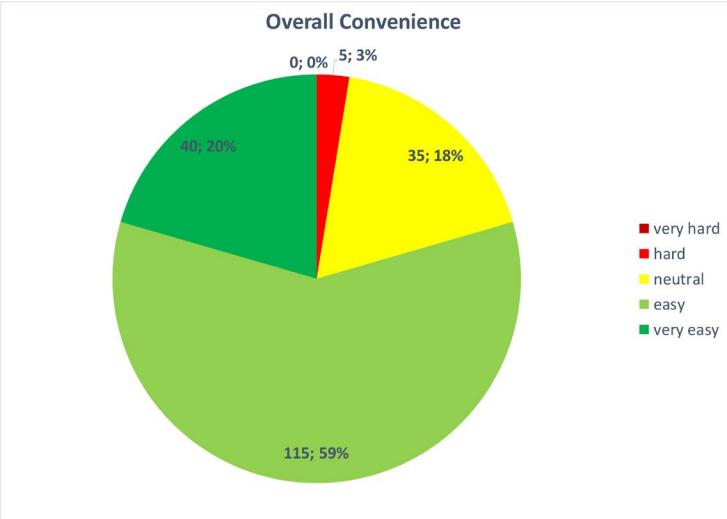
age, sex, indication, primary vs. secondary implant, user confidence, person performing recharge, recharging below 25%).

Results:

- n=195 datasets available (66.1% return rate)
- Age: 61.3 years with 40.4 months experience
- 28.7% were switched to a rechargeable device

- **Primary endpoint:**
  - overall convenience: 4.0 „easy“

- **Secondary endpoints:**
  - User confidence: 93.8%
  - Failed charges: 8.7%
  - Interruption of therapy: 3.6%
  - Charge burden: 122 min/week



Factors influencing primary endpoint:

- Type of movement disorder: PD < dystonia
- Timepoint of implantation: primary < secondary

Factors influecing charge burden:

- Type of movement disorder: dystonia > PD
- Timepoint of implantation: secondary < primary
- Type of neurpstimulator: Activa RC > Brio/Vercise RC

Charge burden positively correlates with duration of therapy.

Factors influencing complications:

- Timepoint of implantation: secondary > primary

12.3% of patients have caregivers perform the recharging process.

Conclusion:

Patients with movement disorders rated recharging as easy, with low complication rates and an acceptable charge burden (ca. 2h/week).

Rechargeable neurostimulators seem to be better accepted and produce less complications when implanted as primary, rather than secondary neurostimulators.

PO 10

Effects of DBS on delayed feedback learning in Parkinson‘s disease patients

Henning Meyer-Wilm[1], Benjamin Weismüller[2], Alfons Schnitzler[1], Christian Bellebaum[2], Markus Butz[1]

[1] Universitätsklinikum Düsseldorf, Germany, [2] Heinrich-Heine-Universität Düsseldorf, Germany

The neural mechanisms of feedback learning from immediate and delayed feedback are different. In a study by Foerde et al. (2011), it was demonstrated that patients suffering from Parkinson‘s disease (PD) perform worse than healthy controls when learning from immediate feedback. In contrast, there were no differences between both groups, if the feedback was delayed by 7 s. In healthy individuals, activity in the striatum could be observed by fMRI during learning with immediate feedback, whereas with delayed feedback activity in the hippocampus was seen (Foerde et al., 2011). A study by Meissner et al. (2016) revealed that DBS in the subthalamic nucleus (STN) facilitates active feedback learning in PD patients, especially in more severely affected patients. However, there has not been a direct comparison between learning from immediate feedback and delayed feedback in PD patients with DBS yet. Therefore, this study was designed to examine the effects of DBS on feedback learning from immediate vs. delayed feedback. To this end, learning performance of PD patients during active and no stimulation (DBS ON vs. OFF) was compared with each other and with the performance of an age-matched healthy control (HC) group. In particular, we aimed to answer the question, if the number of correct reactions and the reaction times of PD patients differ between feedback learning with immediate and delayed feedback and if DBS has a modulating effect.

18 PD patients (65,2 +/- 7,7 y) and 20 healthy control subjects (64,7 +/- 5,3 y) were tested. Both groups performed a feedback learning task, each comprising two parts, one with immediate and one with delayed feedback. Both parts consisted of three blocks in which participants were to learn associations between stimulus and feedback in three conditions with different reward probabilities (100%, 80%, 60%). The measurements were carried out on two separate days, with PD patients varying whether they were initially examined with or without active DBS.

The learning performance of the healthy control group was overall better than the performance of the PD patients ($p = .012$). As became clear from an interaction between group and block ($p = .001$), the increase in correct reactions across blocks was greater in the controls than in the PD patients. In addition, a comparison of the three reward probabilities revealed that the 100% condition could be learned better by the control group ($p = .01$), whereas there was no difference to the PD patients in the two other conditions (80%, 60%). Moreover, there were no significant effects of feedback timing (immediate vs. delayed) and DBS (ON vs. OFF).

Patients with PD demonstrate impaired learning from feedback compared to healthy age-matched controls. However, the timing of feedback and DBS did not modulate learning performance in the present study.

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Abstract title / authors:

Effects of DBS on delayed feedback learning in Parkinson's disease patients

Henning Meyer-Wilm, Dr. Benjamin Weissmüller, Prof. Dr. Alfons Schnitzler, Prof. Dr. Christian Bellebaum, PD Dr. Markus Butz

Background:

The neural mechanisms of feedback learning from immediate and delayed feedback are different. In a study by Foerde et al. (2011), it was demonstrated that patients suffering from Parkinson's disease (PD) perform worse than healthy controls when learning from immediate feedback. In contrast, there were no differences between both groups, if the feedback was delayed by 7 s. Yet, there has not been a direct comparison between learning from immediate feedback and delayed feedback in PD patients with DBS.

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Question:

(1) Does DBS influence the number of correct reactions and the reaction time?

(2) Is there any effect of feedback delay?

Methods:

Screen-based learning task (17 “-monitor)

Factors:

- DBS: ON *vs.* OFF (ON medication state)
- Feedback Delay: 1 s *vs.* 7 s
- Contingency: 100% *vs.* 80% *vs.* 60%
- 3 Parts (1 *vs.* 2 *vs.* 3) with 60 trials each

Dependent variables:

- Correct reactions (%)
- Reaction time (RTs)

Focus on effects:

- Group
- Stimulation
- Delay

Parkisnon Patients (*n* = 18)	Healthy Controls (*n* = 20)
Age: 65,2 +/- 7,7 years	**Age:** 64,7 +/- 5,3 years
Gender: ♂:♀ = 13:5	**Gender:** ♂:♀ = 12:8
Disease Duration: 12,9 +/- 4 years	
UPDRS: MedON/StimOFF 25,2 +/- 11,1 MedON/StimON 15,3 +/- 7,0	

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Results:

Figure 1

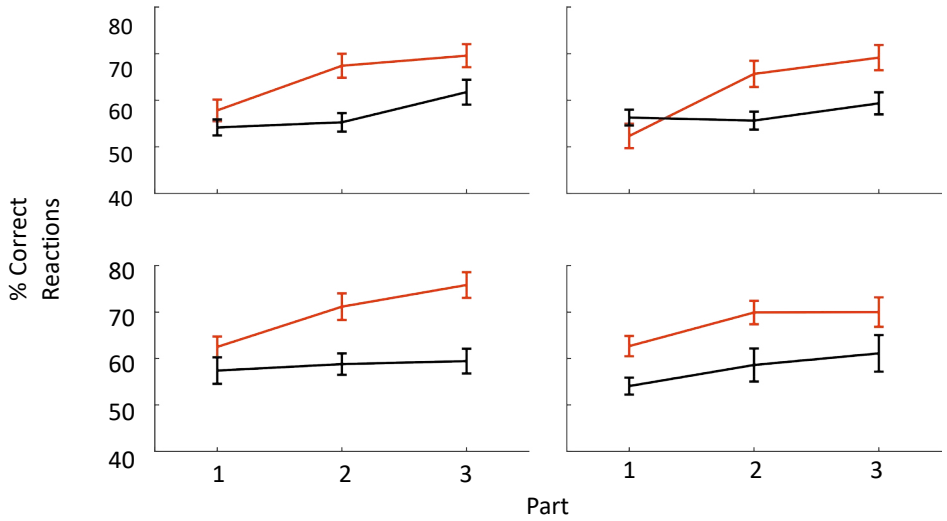


Fig.2 Learning performance of PD patients and control persons over the three blocks in the various test conditions. The data are averaged over the reward probabilities.

- **Main effect group** (p <.001): patients are generally impaired.
- **Interaction group x block** (p <.001): The learning growth over the Blocks is stronger in the controls than in the PD patients.
- **Interaction between group and contingency** (p <.001): Differences between the probabilities are greater for control persons than forPD patients.

Figure 2

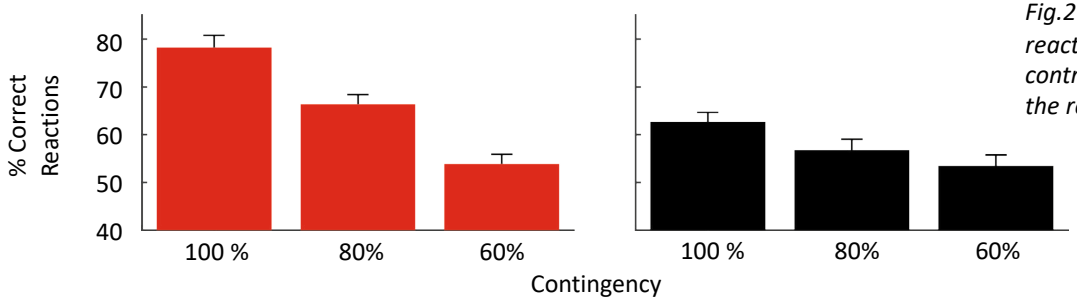
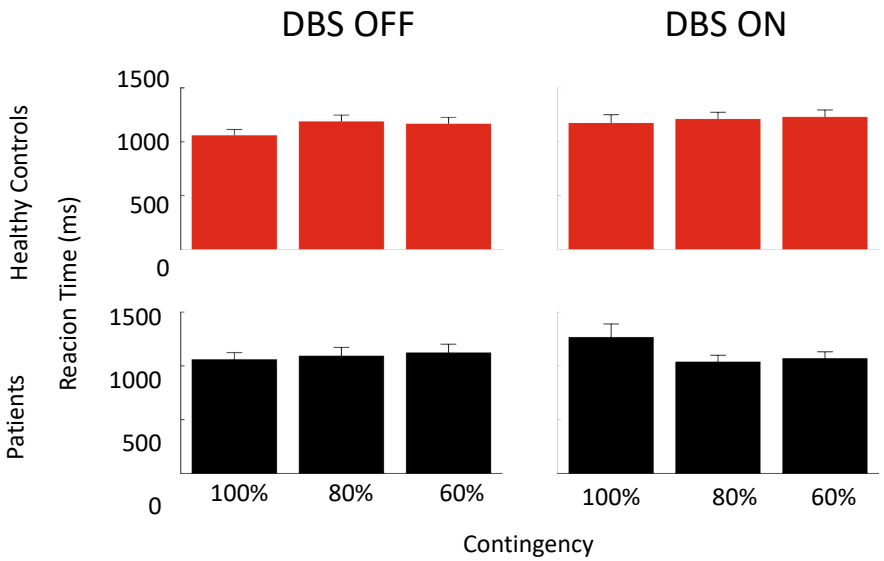


Fig.2 Number of correct reactions for PD patients and control persons depending on the reward probability.

Results:



RTs for PD patients and controls for the different reward probabilities THS OFF and THS ON.

- Interaction group x DBS x probability of reward (p <.05): RTs lowest for greatest probability of reward, except for PD patients DBS ON.
- Interaction group x block x delay (p <.05): RTs get smaller from block 1 to 3, only not in PD patients with delayed feedback.

Conclusion:

The results of this study confirm that Parkinson's patients are impaired in learning from feedback. This is shown above all in a flatter learning curve and for stimuli that are associated with high reward probabilities. In contrast to previous studies, no clear effects of feedback delay and DBS were found. Slower reaction times of patients under conditions with higher compared to low reward probabilities can be explained by increased impulsiveness under DBS.

A meta-analysis of studies assessing facial emotion recognition after subthalamic nucleus deep brain stimulation in Parkinson's disease

Stefania Kalampokini[1], Epameinondas Lyros[1], Piergiorgio Lochner[1], Klaus Fassbender[1], Marcus Unger[1]

[1] University Hospital of Saarland, Germany

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective established therapy for movement disorders including Parkinson's disease (PD). However, some neuropsychiatric symptoms are reported to change after STN DBS, among which the emotion recognition from facial expressions. Studies assessing facial emotion recognition (FER) after STN DBS in PD showed inconsistent findings.

To elucidate whether FER is worsening after DBS in PD, we conducted a literature search of the electronic databases MEDLINE and Web of science in English between 2000 and 2020 using the key search terms: facial emotion recognition, subthalamic nucleus, deep brain stimulation, Parkinson's disease and manual search of the references of the identified studies. We conducted a meta-analysis of studies comparing FER before and after STN DBS (2 months-1 year) in PD patients for the total score and separate basic emotions (happiness, sadness, fear, anger, disgust, surprise and neutral). We compared the pre-operative to the post-operative condition of the same PD patients with stimulation ON, both on medication.

We included 6 studies in the meta-analysis with a total of 108 PD patients. We found a negative effect of DBS on FER of PD patients (random model Hedges' g=-0.478, p=0.000, I2=40.117, P=0.138). Regarding specific emotions, we found a significant worsening after STN DBS for the emotions of sadness (Hedges' g= -0.486, p=0.000) and fear (Hedges' g= -0.531, p=0.000) and a tendency for the emotion of disgust (Hedges' g=-0.267, p=0.086). Publication bias was assessed using the funnel plot, which showed a slight asymmetry i.e. a tendency towards publishing studies with a negative effect of DBS on FER.

Our results suggest that, despite clinical and methodological discrepancies of studies, there seems to be a FER worsening after DBS in PD patients, particularly for the negative emotions (sadness, fear and tendency for disgust). FER worsening after STN DBS can be attributed to the functional role of the STN in limbic circuits and to the connections of STN with the limbic part of the basal ganglia, amygdala, pre- and frontal areas (orbitofrontal and anterior cingulate cortex), which are areas involved in FER. These outcomes improve our understanding of the key role of STN in multi-level integration of motor, cognitive and affective information. Our findings have also implications in patients' social interactions and relationships with others. Further future studies using standardized, FER testing and including larger patient samples are needed, in order to derive definite conclusions about the effect of STN DBS on emotional processing.

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A meta-analysis of studies assessing facial emotion recognition after subthalamic nucleus deep brain stimulation (STN DBS) in Parkinson's disease (PD)

S. Kalampokini, E. Lyros, P. Lochner, K. Fassbender, Unger MM.

Department of Neurology, University Hospital of Saarland, Homburg, Germany

***Background*:** Some neuropsychiatric symptoms are reported to change after STN DBS, among which the emotion recognition from facial expressions. Studies assessing facial emotion recognition (FER) after STN DBS in PD showed inconsistent findings.

Methods:

- We conducted a literature search of MEDLINE and Web of science in English between 2000 and 2020 with key search terms: ''facial emotion recognition'', ''subthalamic nucleus'', ''deep brain stimulation'', ''Parkinson's disease''.
- We conducted a **meta-analysis of studies** comparing FER before and after STN DBS in the same PD patients with stimulation ON, both on medication.
- We compared the total accuracy score and that of separate basic emotions (happiness, sadness, fear, anger, disgust, surprise and neutral i.e. no emotion) pre- and postoperative.

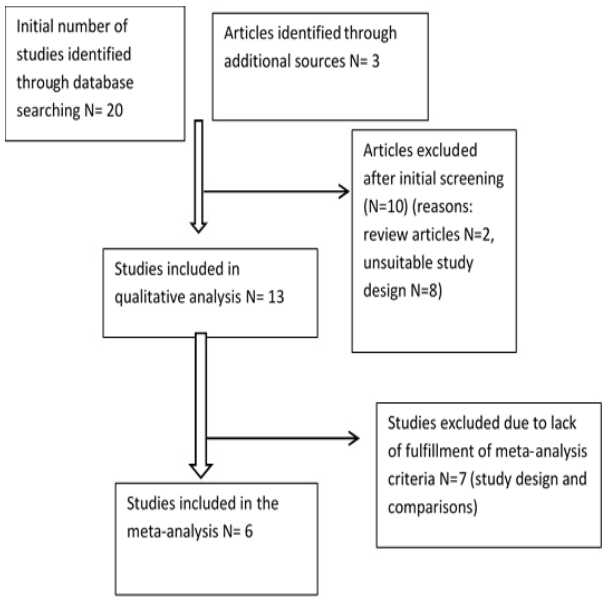

Figure 1. Flow diagram of studies

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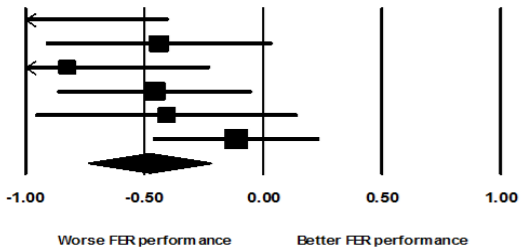
Results I:

- The meta-analysis included 6 studies with a total of 108 PD patients, who underwent bilateral STN DBS (assessment before and 3-12 months after DBS); mean age ranged 56.9-62.7 years, mean duration of disease 10.9-15.9 years.
- The most common facial stimuli used were from the Ekman and Friesen series. (P. Ekman and W. Friesen, Pictures of Facial Affect, Consulting Psychologists, Palo Alto, CA, 1976)
- We found a *negative effect of DBS on FER of PD patients* (random model Hedges' g=-0.478, *p*=0.000, I^2=40.117, P=0.138). (Figure 2)

Figure 2. FER accuracy pre- vs post- STN DBS

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Dujardin et al. 2004	-1.081	0.348	0.121	-1.762	-0.400	-3.110	0.002	10.73
Drapier et al. 2008	-0.438	0.243	0.059	-0.914	0.038	-1.804	0.071	17.38
Le Jeune et al. 2008	-0.824	0.306	0.094	-1.424	-0.225	-2.695	0.007	12.91
Peron et al. 2010	-0.457	0.208	0.043	-0.865	-0.049	-2.194	0.028	20.62
Aiello et al. 2014	-0.406	0.281	0.079	-0.957	0.145	-1.445	0.149	14.48
Albuquerque et al. 2014	-0.113	0.178	0.032	-0.463	0.237	-0.634	0.526	23.88
	-0.478	0.132	0.017	-0.736	-0.220	-3.634	0.000	



Results II:

- Regarding specific emotions, we found a *significant worsening after STN DBS* for the emotions of *sadness* (Hedges' g= -0.486, *p*=0.000) and *fear* (Hedges' g= -0.531, *p*=0.000) and a tendency for *disgust* (Hedges' g=-0.267, *p*=0.086).

Limitations

- Small number of studies (6), small sample sizes (<30 PD patients).
- Heterogeneity of studies: FER task (material, number of stimuli, time given), assessment time after DBS.
- Publication bias: Funnel plot showed a slight asymmetry i.e. tendency towards publishing studies with a negative effect of DBS on FER. (Fig.3)

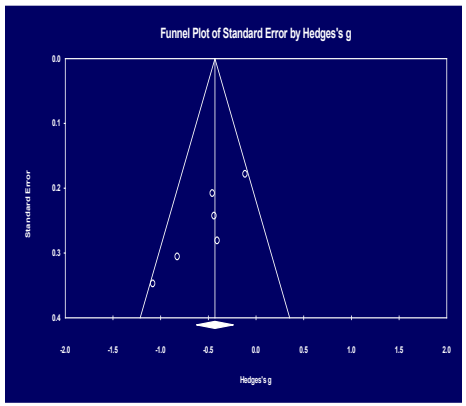


Figure 3. Funnel plot for publication bias

Conclusions:

- Despite clinical and methodological discrepancies of studies, there seems to be a FER worsening after STN DBS in PD patients, particularly for the negative emotions (sadness, fear and tendency for disgust).

- FER worsening after STN DBS can be attributed to the functional role of the STN in limbic circuits and to the connections of STN with the limbic part of the basal ganglia, amygdala, pre- and frontal areas (orbitofrontal and anterior cingulate cortex), which are areas involved in FER.

- The surgical trajectory, electrode positioning, stimulation (parameters), and current diffusion to nearby limbic STN territory might contribute to DBS effects on FER.

- These outcomes have implications in patients' social interactions and relationships with others.

STN has a key role in the multi-level integration of motor, cognitive and affective information.

Future studies using standardized FER testing and larger patient samples are needed, in order to derive definite conclusions about the effect of STN DBS on emotional processing.

Detecting Parkinson's Disease Tremor in Multimodal Neural Data

Dmitrii Todorov[1], *Alfons Schnitzler*[2], *Jan Hirschmann*[2]

[1] Centre de Recerca Matematica, Spain, [2] Heinrich Heine University, Germany

Many processes happening in Parkinson's disease, despite a long history of research, are still not completely understood. In particular, there is no clear understanding on how Parkinsonian rest tremor is generated and how it can be detected and distinguished from voluntary movements in neural recordings.

We employ several machine learning methods (PCA, LDA, t-SNE, UMAP) on multimodal data from the cortex (MEG) and basal ganglia (subthalamic nucleus LFP), recorded from intermittent tremor-presenting PD patients, to evaluate how distinguishable are distinct behavioral states (quiet rest, rest tremor, voluntary movements).

We developed a pipeline for multimodal data analysis and show that using both MEG and LFP data (in contrast to using just LFP) one can successfully distinguish different behavioral states. We also describe which data features (tremor, beta, gamma bands, coherence, cross-freq coupling, Hjorth parameters) contribute most to the classification.

Our research contributes to the basic science of Parkinson's disease by describing which electrophysiological markers are important to measure when analyzing tremor-related questions. It has potential applications for developing tremor-guided DBS and creating computational models of the tremor-generating circuit in PD.

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Parkinson's Disease Tremor Signs in Multimodal Neural Data

***Dmitrii Todorov (dtodorov@crm.cat),**
***Alfons Schnitzler, **Jan Hirschmann*
** = Centre de Recerca Matematica (Barcelona)*
*** = Heinrich Heine University (Düsseldorf)*

Background: to improve PD DBS one may seek to deliver simulation only in response to symptoms (e.g. tremor). In particular, **neural signatures of tremor** are of interest. Existing STN LFP-based methods cannot distinguish between tremor and voluntary movements.

STN LFP + MEG data helps to distinguish between tremor and voluntary movements

*Dmitrii was supported by EU-funded Marie Skłodowska-Curie Actions "OSCBAGDIS" IF

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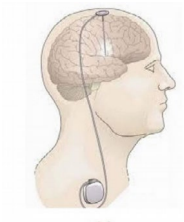
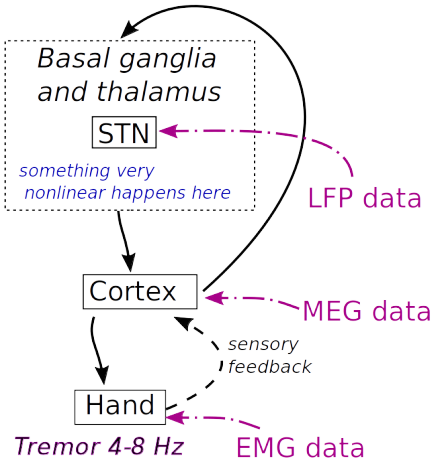
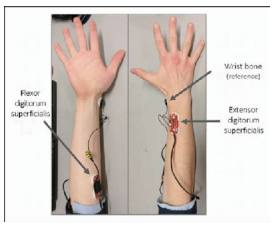
Methods:

- *10 Parkinson's disease patients with rest tremor waxing and waning over time*
- *Each* with tremor-dominant hand performing "hold" (45 deg from body) and "move" (grasp) tasks*

- STN LFP + MEG + hand EMG
- Tremor labeling
- MEG source reconstruction
- Machine learning







Two sets of MEG sources: **entire brain surface** or **8 regions of interest** (Hirschmann 2011, 2013)

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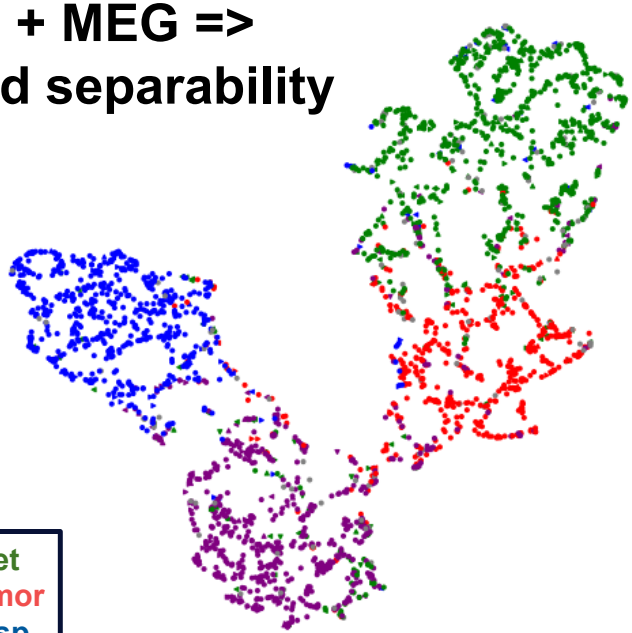
Results:

cortical features are necessary to distinguish tremor from voluntary movements

LFP + MEG => good separability



Only STN LFP => bad separability

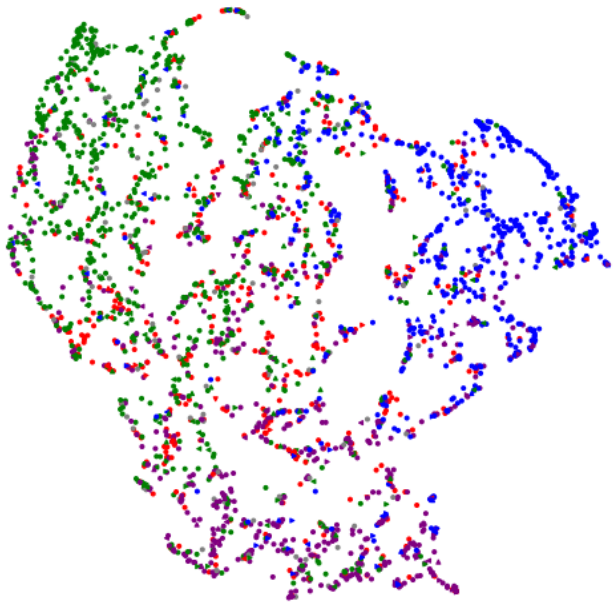


Fig: nonlinear projections of one subject data for different feature subsets

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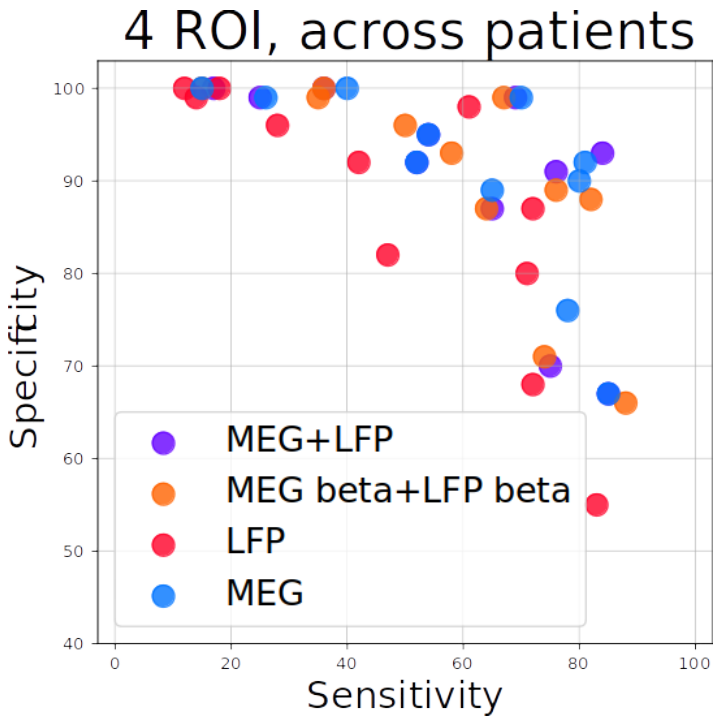
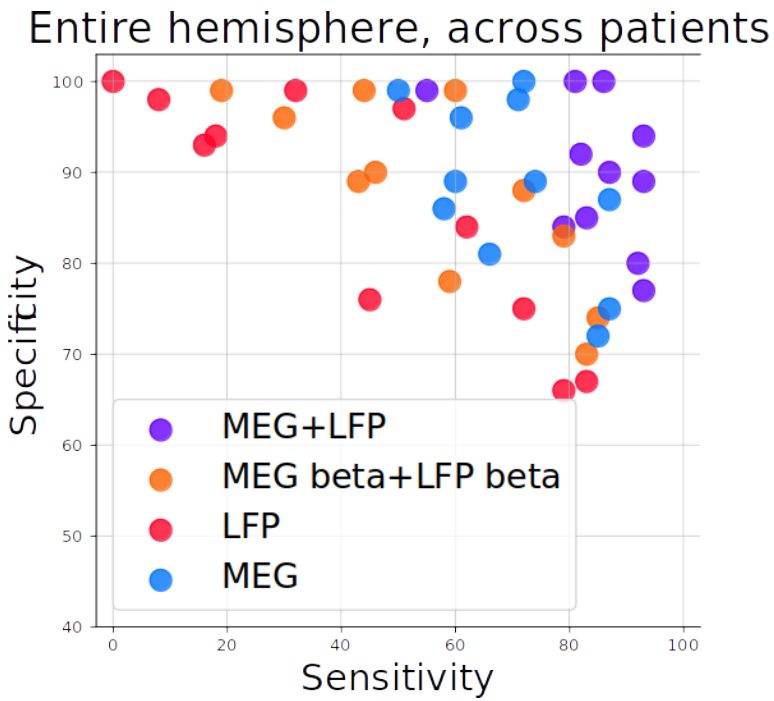
Results:

$$\text{sensitivity} = \frac{\text{true positive}}{\text{all positive}} \qquad \text{specificity} = \frac{\text{true negative}}{\text{all negative}}$$

Few MEG ROIs performance < entire cortex performance





Conclusion:

- Cortical data data allows to detect tremor better than STN LFP alone
- MEG has more tremor info than STN LFP
- Restricting to a single frequency band lowers performance
- Few ROI work worse than sources covering entire brain

Differential dopaminergic modulation of spontaneous cortico-subthalamic activity in Parkinson's disease

Abhinav Sharma[1], Esther Florin[2], Diego Vidaurre[3], Alfons Schnitzler[2], Jan Vesper[2]

[1] Uniklinik Duesseldorf, Germany, [2] HHU Düsseldorf/ Uniklinik Düsseldorf, Germany, [3] Oxford University England, United Kingdom

Pathological oscillations are a hallmark of neural activity in Parkinson's disease (PD). Time-averaged analyses are usually employed to study changes in spectral connectivity with and without dopaminergic intervention in PD. This prevents differentiating the pathological vs physiological nature of dynamically evolving oscillatory activity serving multiple functional roles. Taking into account both the between-subject and medication-induced heterogeneity, a characterization of the differential DRT effects has the potential to delineate pathologically versus physiologically relevant spectral connectivity in PD. In our present work we study PD brain activity via a Hidden Markov Model (HMM), a data-driven learning algorithm (Vidaurre et al., 2016; Vidaurre, Hunt, et al., 2018). This allows us to reveal the temporal properties of connectivity, offering a more complete description of the network activity

In order to study cortico-subcortical interactions in PD, we recorded combined resting-state whole-brain MEG and subthalamic nucleus (STN) local field potential (LFPs) from 17 PD patients and included both modalities into the model. We address the effect of DRT on spectral connectivity by acquiring data both OFF and ON medication (L-DOPA). We used a specific variety of the HMM, the time-delay embedded HMM (TDE-HMM), where the states are characterized by spectrally-defined networks at the whole-brain level, defined in terms of both power and phase-coupling. The Hidden Markov model is a data-driven probabilistic algorithm that finds recurrent network patterns in multivariate time series. Each network connectivity pattern is referred to as a "state" in the HMM framework, such that networks can activate or deactivate at various points in time.

We discovered three distinct network activity patterns. One network was related to adverse effects of increased dopamine, a second one maintained ON-medication spatio -spectrally selective cortico-STN connectivity and finally, a local STN-STN network emerged which indicated the inability of L-DOPA to modify local basal ganglia activity. Temporally we found that, ON medication, the cortico-STN and the STN-STN network increased in duration whereas the cortico-cortical network occurred less frequently. Our results provide a spectrally diverse and spatially specific understanding of transient network connectivity in PD on a whole-brain level, disambiguating temporal and spatial changes of the underlying networks.

By providing electrophysiological evidence for the differential effects of L-DOPA intervention in PD, our findings open further avenues for electrical and pharmacological intervention in PD. Our findings bring forth a dynamical systems approach for differentiating pathological vs physiologically relevant spectral connectivity in PD. Furthermore, we are able to demonstrate that a dynamical systems-level approach is able to uncover differential changes induced by altered levels of a neuromodulator.

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Differential dopaminergic modulation of spontaneous cortico-subthalamic activity in Parkinson's disease

Abhinav Sharma[1], Diego Vidaurre[2,3], Jan Vesper[4], Alfons Schnitzler[1], Esther Florin[1]

1 Institute for Clinical Neuroscience and Medical Psychology Medical Faculty HHU, 2 Department of Psychiatry Oxford University, 3 Department of Clinical Health Aarhus University, 4 Department of Neurosurgery University Hospital Düsseldorf

Background:

- Pathological oscillations are a hallmark of neural activity in Parkinson's disease (PD)
- Oscillations serve distinct functional roles at different points in time
- Time-averaged analyses prevent differentiating pathological vs. physiological oscillations
- **Here**: PD brain activity analysed via a data-driven dynamical learning algorithm

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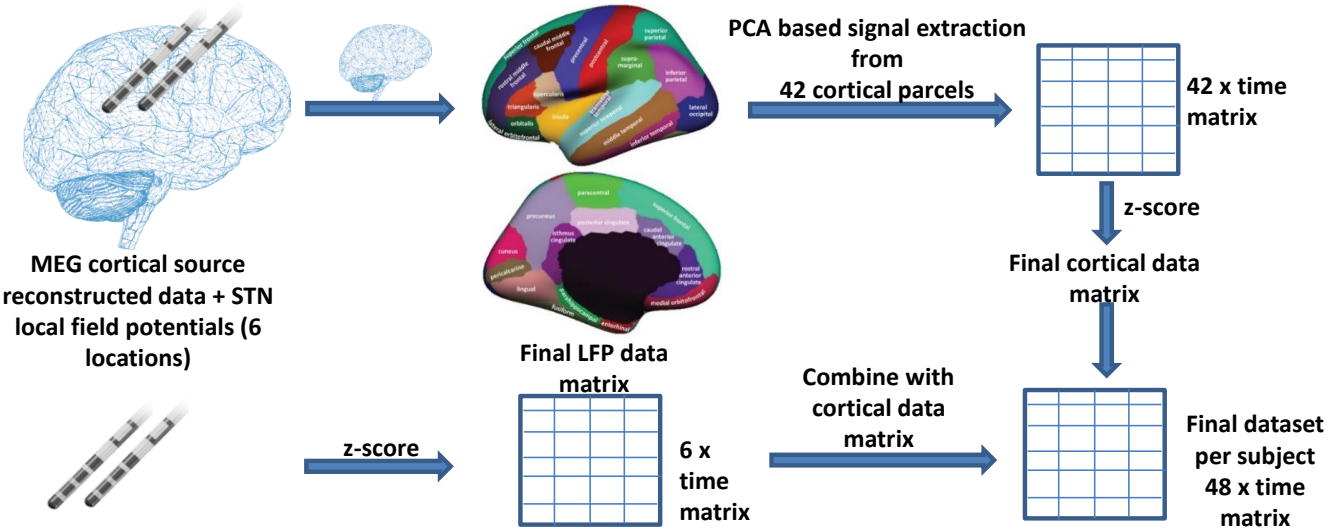
Methods:



- MEG-LFP (subthalamic nucleus) recordings of 17 PD patients OFF and ON medication (L-DOPA)
- Hidden Markov model (HMM) analysis
- HMM finds recurrent networks (states) in a multivariate time series
- Networks can activate or deactivate at various points in time

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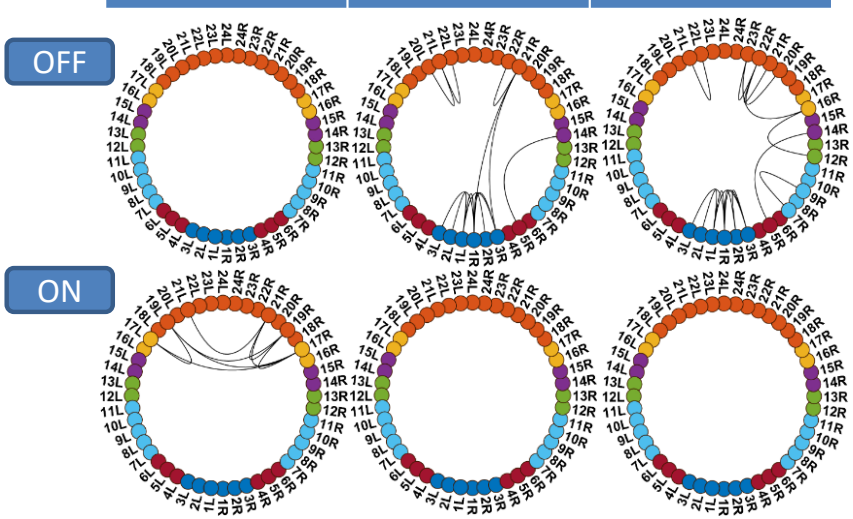
Results: Spectral properties of networks

STN	1	contact1 right
	2	contact2 right
	3	contact3 right
	1	contact4 left
	2	contact5 left
	3	contact6 left
Vis Ctx	4	cuneus
	5	lateral occipital
	6	lingual
Par Ctx	7	inferior parietal
	8	paracentral
	9	precuneus
	10	superior parietal
	11	supramarginal
Smr Ctx	12	postcentral
	13	precentral
Tmp Ctx	14	middle temporal
	15	superior temporal
	16	caudal middle frontal
Mpf Ctx	17	medial orbitofrontal
	18	insula
	19	lateral orbitofrontal
	20	parsopercularis
	21	parsorbitalis
Frnt Ctx	22	parstriangularis
	23	rostral middle frontal
	24	superior frontal

STN- Subthalamic nucleus, Vis- Visual, Par-Parietal, Smr-Sensory motor, Tmp-Temporal, Mpf-Medial prefrontal, Frnt-Frontal, Ctx- Cortex

Hyper-dopaminergic network



Each black curve in the ring plot represents coherence based connectivity between the two regions ($p<0.05$, corrected for multiple comparisons)

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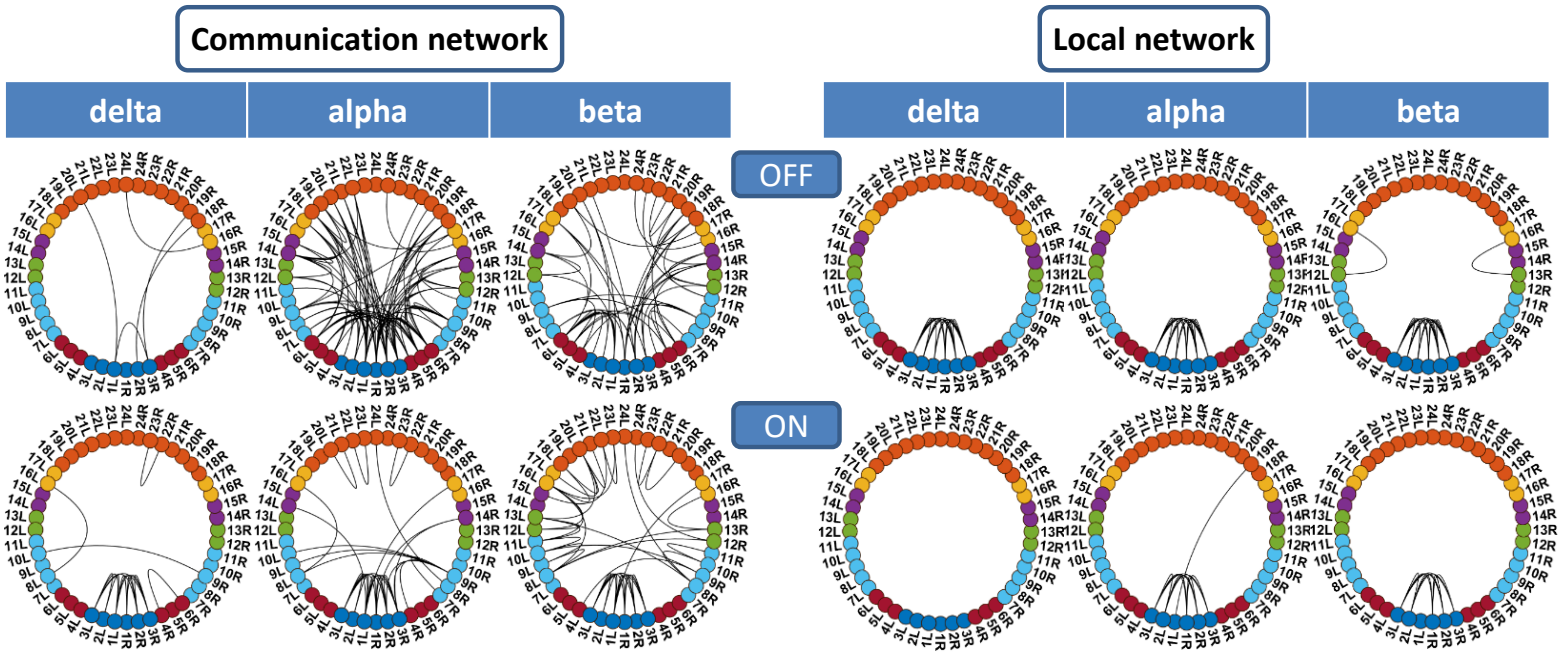
Results: Spectral properties of networks



Each black curve in the ring plot represents coherence based connectivity between the two regions ($p<0.05$, corrected for multiple comparisons)

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Conclusions:

- **Hyper-dopaminergic network:** Medial - orbitofrontal delta/theta coherence ON medication
- **Communication network**: Spectrally and spatially-specific cortico-STN connectivity and in the beta band fronto-parietal-motor network ON medication
- **Local network:** Selective modulation of STN-STN delta oscillations ON medication
- Spectrally similar connectivity under different whole brain networks
- Differential dopaminergic modulation of spectral connectivity in the networks
- Network results provide new markers for closed-loop DBS

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Simultaneous recording of thalamic local field potentials and long term video-EEG in a focal epilepsy patient: first insights

Ricardo Rego[1], Elodie Lopes[2], Angela Santos[1], Catarina Caldeiras[1], Clara Chamadoira[1], Joao Paulo Cunha[2], Rui Vaz[1]

[1] Centro Hospitalar Universitario de Sao Joao, Portugal, [2] Faculdade de Engenharia da Universidade do Porto, Portugal

Anterior thalamic nucleus deep brain stimulation (ANT-DBS) is safe and effective in focal refractory epilepsy. However, a significant proportion of patients are partial or non-responders. Data gathered from chronic ambulatory recording of local field potentials (LFP) from the ANT may help optimization of stimulation in these patients. Simultaneous recording of video-EEG seems essential in order to correlate the temporal dynamics of LFP with ictal semiology and conventional EEG signal.

A 54 year-old male focal refractory epilepsy patient with bilateral perisylvian ulegyria and frequent tonic seizures was implanted with ANT-DBS using Medtronic's Percept system and BrainSense (TM) technology. One month after implantation he was admitted for long term video-EEG monitoring, allowing for synchronous recording of LFP (in continuous streaming or timeline modes), video and EEG. This was made both before and after stimulation was turned on. SANTE settings (145 Hz, 90 us, 1 min on/5 minutes off) were chosen, as is standard practice in our center. An LFP alpha peak (~11 Hz) was found during survey and chosen for subsequent recordings. A detailed event log was kept for patient events (seizures, sleep/wake cycles, medications) and neurostimulator adjustments.

Time synchronization across devices (video-EEG and Percept) was achieved analyzing artifacts generated during gentle tapping of the skull close to lead entry areas. Simultaneous recording of video-EEG allowed for validation of signal changes in LFP during sleep-wake cycles. Seizures could be identified in LFP recordings, mostly through significant fluctuations in power apparently correlated with postictal EEG attenuation/suppression or high-amplitude slowing.

Correlating peri-ictal ANT LFP signals with long term video-EEG is feasible and shows promise in finding individual surrogate markers for future optimization of stimulation settings.

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Simultaneous recording of thalamic local field potentials and long term video-EEG in a focal epilepsy patient: first insights

Ricardo Rego[1], Elodie Lopes[2], Angela Santos[1], Catarina Caldeiras[1], Clara Chamadoira[3], João Paulo Cunha[2], Rui Vaz[3]

1. Neurophysiology Unit and Neurology Sevice, Centro Hospitalar Universitario Sao Joao (CHUSJ) 2. INESC TEC – FEUP, University of Porto 3. Neurosurgery Service, CHUSJ

Background:

Anterior thalamic nucleus deep brain stimulation (ANT-DBS) is safe and effective in focal refractory epilepsy. However, a significant proportion of patients are partial or non-responders. Data gathered from chronic ambulatory recording of local field potentials (LFP) from the ANT may help optimization of stimulation in these patients. Simultaneous recording of video-EEG is essential in order to correlate the temporal dynamics of LFP with ictal semiology and conventional EEG signal.

Methods:

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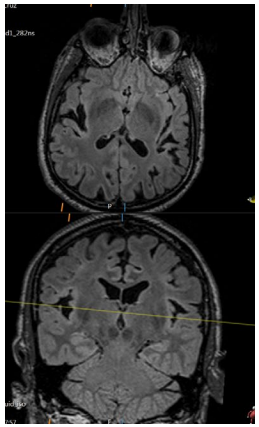
54 year-old right-handed patient; focal refractory epilepsy of perinatal hypoxic-ischemic etiology.

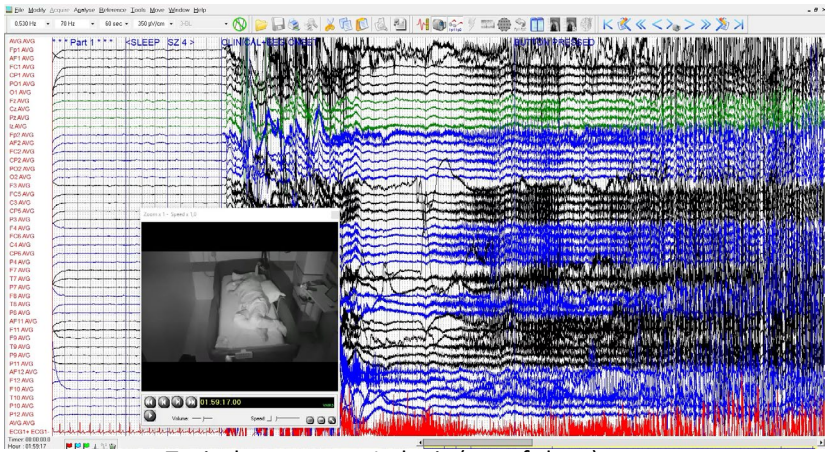
Seizures: (1) spasms (2) bilateral tonic > hypermotor > L clonic; activated by sleep. Non-lateralized/artifact obscured ictal EEG

Non-ressective → bilateral DBS-ANT (Percept™)

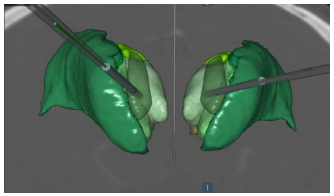
> 5-day vídeo+scalp EEG recording + simultaneous ANT-DBS recordings Brainsense™
- streaming
- timeline
- Events (tech activated)



MRI (FLAIR): bilateral perisylvian ulegyria



Tonic>hypermotor>L clonic (out of sleep) EEG: artifact obscured



Bilateral transventricular approach, 3389 electrodes SureTune™

Signal sync across systems:

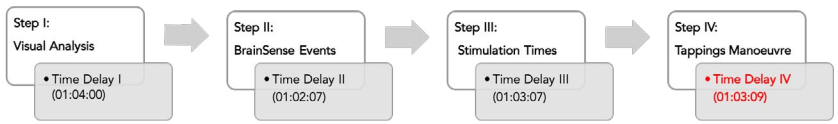
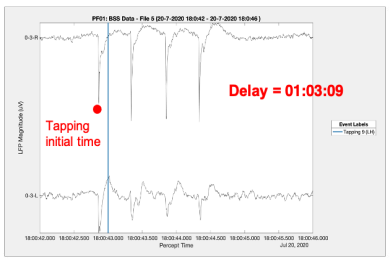


Figure: Methodology used to synchronize Percept PC and VEEG clocks. First, we analyze the Percept hour information, available in the Timeline viewer; The, we compared the times of LfpSnapShots and the first simulations hours; Finally, we have searched for tappings Manoeuvre in the Percept signal, also visible on the EEG.



Results: Timeline

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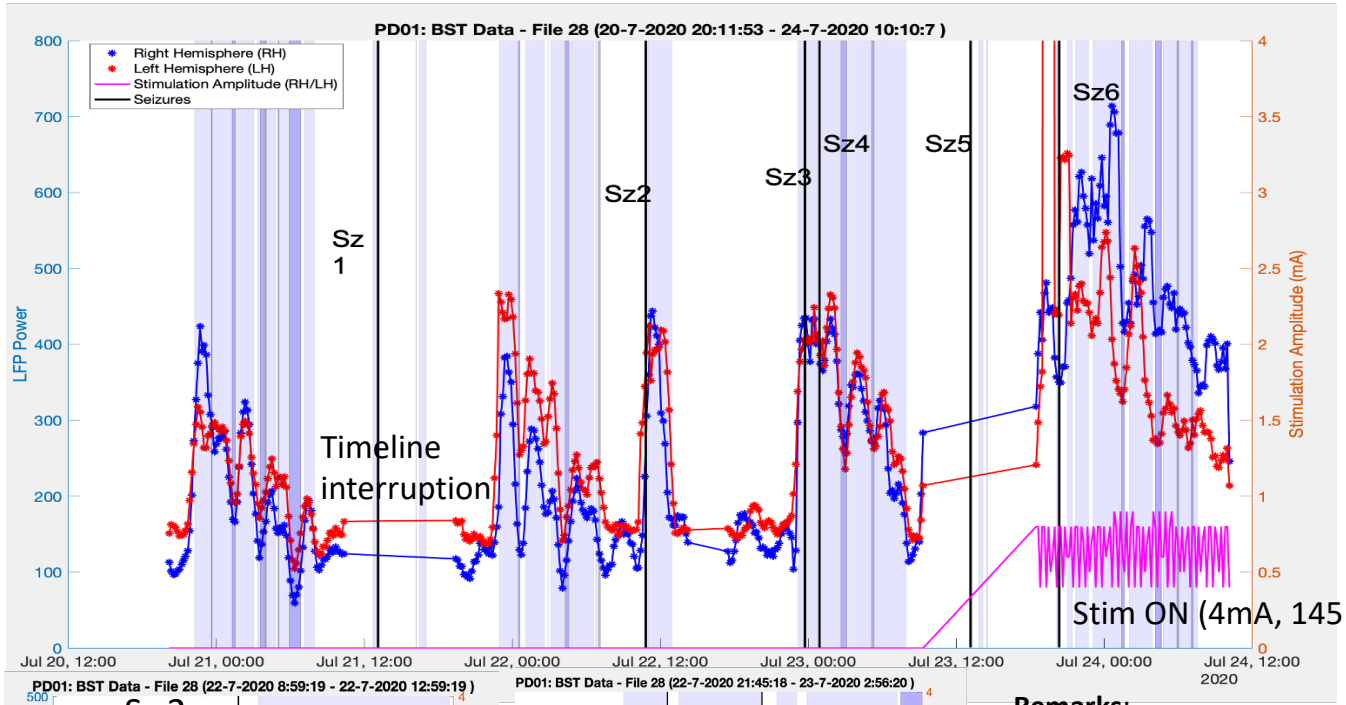
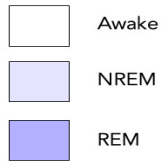
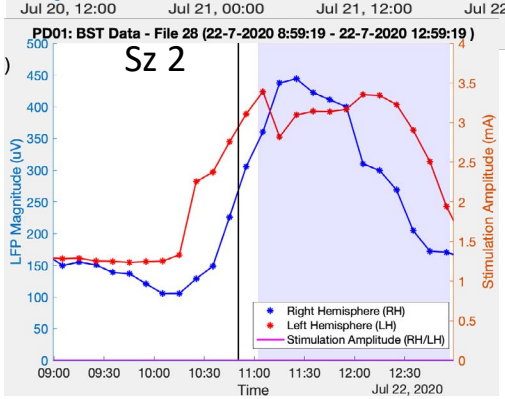
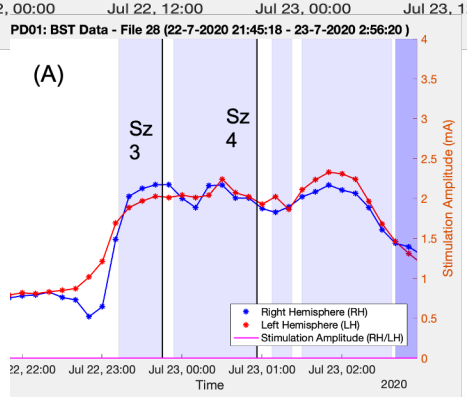




Stim ON (4mA, 145 Hz, 90 us)



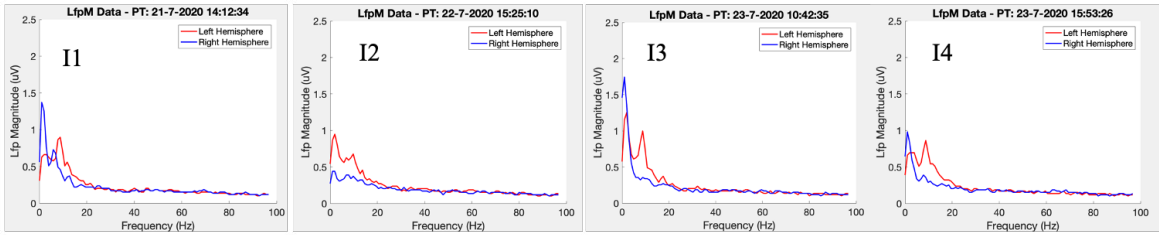


Remarks:

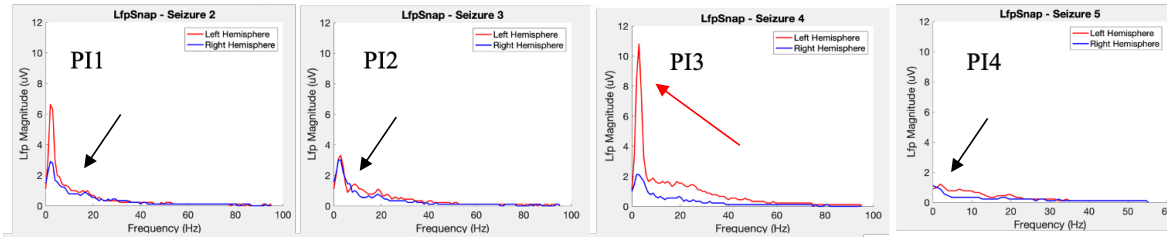
1. Wake-sleep transitions: LFP amplitude increases pre-EEG changes
2. Whole night sleep LFP patterns are similar
3. Sz occur on a setting of increased LFP power
4. After stim ON an overall increased LFP power was observed

Results: Events (LFP Snap)

Interictal (I) Activity



Peri-ictal (PI) Activity



Seizure #	Date	SZ ONSET	SZ OFFSET	EVENT	SZ DURATION	FROM SZ ONSET UNTIL EVENT	FROM EVENT BUTTON PRESSED UNTIL SZ OFFSET
2	22/07/20	11:53:28	11:54:44	11:54:20	00:01:16	00:00:52	00:00:24
3	23/07/20	00:48:27	00:49:29	00:49:10	00:01:02	00:00:43	00:00:19
4	23/07/20	01:59:30	02:00:57	02:00:13	00:01:27	00:00:43	00:00:44
5	23/07/20	14:14:33	14:15:04	14:15:38	00:00:31	00:01:05	button pressed after sz end

Table: Timing of seizures (Sz) and created events (LfpSnapShot). Seizure duration corresponds to the period between the onset and offset. Δt is the interval between the seizure initial and the time of the created event.. *Note that there is a time delay before the triggered event and its creation.*

Remarks:

1. Probably post-ictal LFP were recorded, except on Sz 4
2. Post-ictally the alfa peak is attenuated
3. On sz 4 an increase on the alfa peak is observed, probably late ictal

Note: no seizures were captured on multiple streaming sessions

Conclusions:

1. LFP recordings using Percept™ were optimized for PD but had valuable information on our epilepsy patient, at least during prolonged VEEG
2. Sleep-wake cycles were detectable and LFP changes preceded standard visual EEG staging of sleep
3. On Timeline mode seizures tended to occur at higher LFP power values
4. Technician-activated events usually resulted on a post-ictal sampling of LFP due to a long latency between button activation and recording onset; this was associated with peak attenuation
    a) Late ictal sampling was probably achieved on one seizure and associated with an unilateral „extreme“ alfa peak
5. Optimization of this device in epilepsy would require:
    1. Faster streaming onset upon event activation
    2. Ability to perform longer streaming sessions
    3. Denser Timeline data

Subthalamic beta bursts correlate with motor impairment in Parkinson‘s disease

Roxanne Lofredi[1], Liana Okudzhava[1], Friederike Irmen[1], Wolf-Julian Neumann[1], Joachim K. Krauss[2], Gerd-Helge Schneider[1], Andrea A. Kühn[1]

[1] Charité Universitätsmedizin Berlin, Germany, [2] Medizinische Hochschule Hannover, Germany

Intracerebral recordings in Parkinson‘s disease (PD) patients undergoing Deep Brain Stimulation (DBS) have allowed to identify increased subthalamic beta oscillations as biomarker for motor impairment in PD. Recently, the temporal dynamics of this exaggerated beta synchronization have come into focus. Instead of being continuously increased, beta amplitude synchronizes in brief periods, so called beta bursts. In small cohorts of PD-patients it has been shown that subthalamic beta burst duration is prolonged in the OFF-medication state and reduced by dopaminergic medication. We hypothesize that subthalamic beta burst duration is prolonged in the OFF when compared to the ON medication state. Moreover, beta burst duration correlates with motor impairment as assessed by the UPDRS, as does reduction of beta burst duration with motor improvement.

Subthalamic local field potentials were analyzed from archival rest recordings of 99 PD-patients that underwent DBS-surgery both ON- and OFF-medication. Continuous recordings were down sampled and filtered, before data was transferred into the frequency domain. For power analyses, amplitudes were averaged across contact pairs, spectra were normalized to the total sum and further expressed as a percentage of total power. For burst determination, wavelet amplitude was averaged across frequencies of interest, smoothed and z-scored over the entire recording. A common threshold was defined at the 75th percentile of the normalized signal amplitude distribution across medication states. Power and burst analyses were performed separately for the low beta (13–20 Hz) and high beta band (20-30 Hz), as differential dopamine-responsivity of these sub-bands has been reported. Nonparametric permutation tests, Spearman’s correlation and stepwise model selection were used for statistical analyses.

Here we show that low beta burst duration correlated with motor impairment across 99 PD-patients. More specifically, this correlation was driven by the amount of low beta bursts that exceeded 900 ms duration. With dopaminergic medication, burst duration decreased along with symptom alleviation.

Replicating previous findings in such a large cohort of PD-patients increases the confidence that an adaptive DBS-approach where stimulation would be triggered by beta amplitude threshold crossings of specific lengths might be advantageous in clinical settings. Large multicenter trials with first generations of commercially available sensing enabled devices are currently in development. We conclude that aDBS trials should look beyond the power threshold paradigms and consider temporal dynamics as a key hallmark that could inform next-generation multifeature approaches for aDBS in PD.

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Subthalamic beta bursts correlate with motor impairment in Parkinson's disease

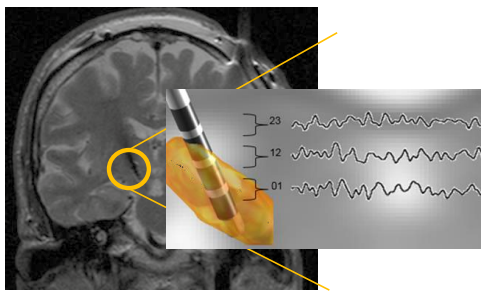
Roxanne Lofredi, Liana Okudzhava, Friederike Irmen, Wolf-Julian Neumann, Joachim K. Krauss, Gerd-Helge Schneider, Andrea A. Kühn

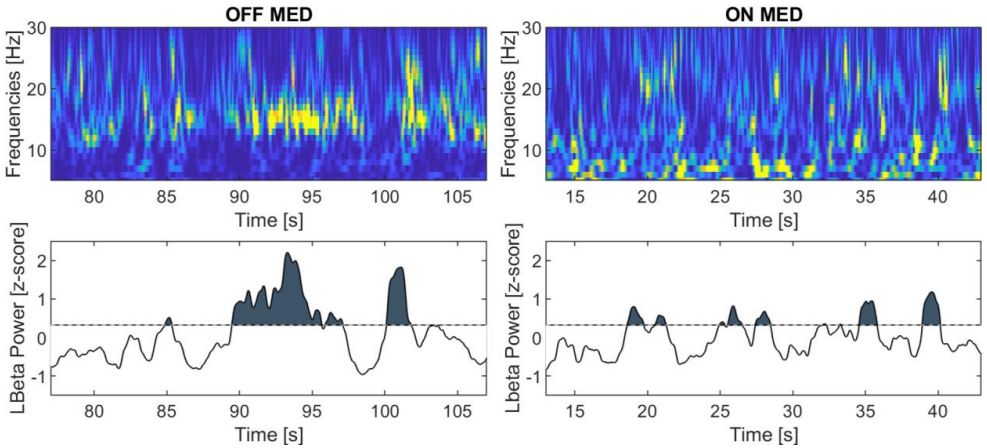
Background:

Pathologically increased oscillations in the human subthalamic nucleus have been described as a robust biomarker of motor impairment in Parkinson‘s disease (PD). Recently, it has been suggested that increased beta activity does not occur continuously but in bursts which are prolonged in PD. These could potentially serve as trigger for demand-adapted deep brain stimulation (DBS).

Methods:

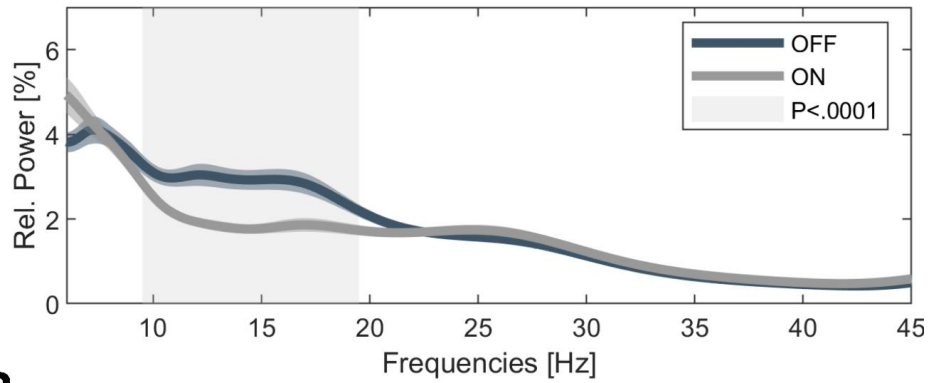
1. 99 PD-patients ON- and OFF-medication with externalized DBS-leads implanted in the subthalamic nucleus (STN).
2. Assessment of motor impairment ON- and OFF-MED using UPDRS-III.
3. Bipolar recordings of subthalamic local field potentials at rest.
4. Transfer in frequency domain using Morlet wavelets, before
   a) averaging low beta power (13-20 Hz) over time or
   b) filtering around low beta band and defining bursts as as the 75th percentile of the normalized signal amplitude distribution.





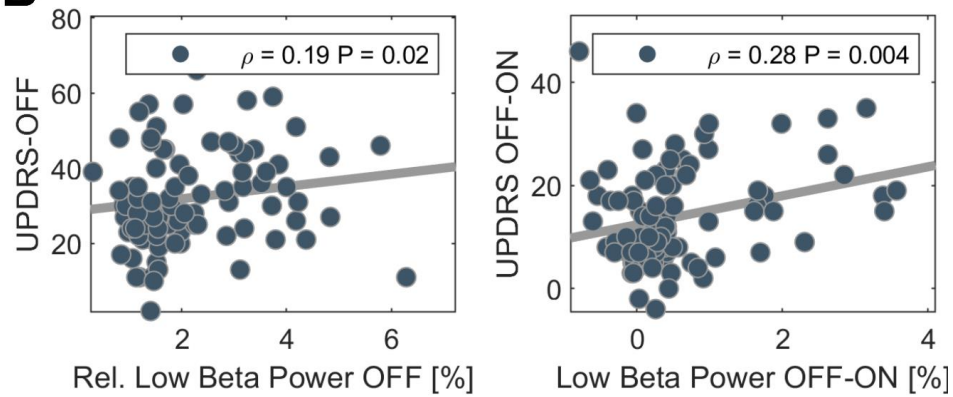
Results:

A



Significant power reduction with dopaminergic medication in frquencies predominatly confined to the low beta band.

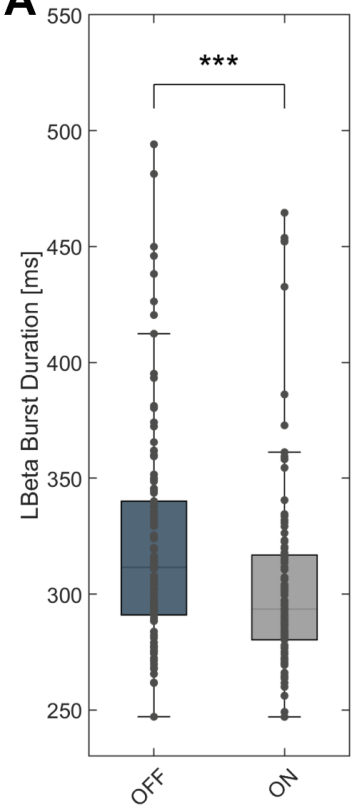
B



Averaged low beta power correlates with motor impairment in the OFF-state as does dopamine-dependent power reduction with symptom alleviation.

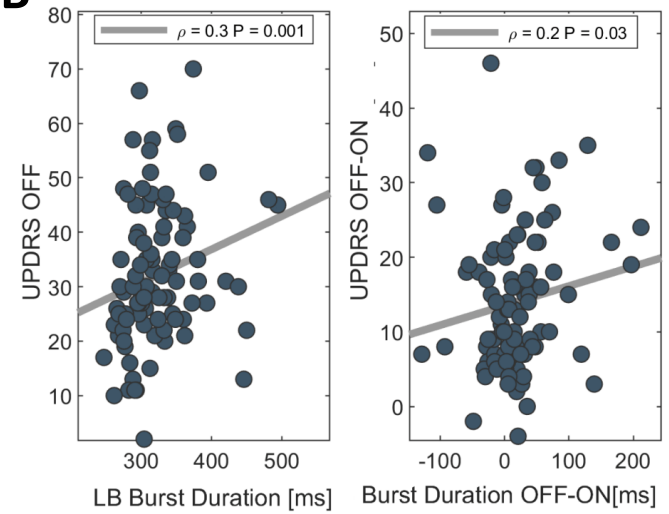
Results:

A



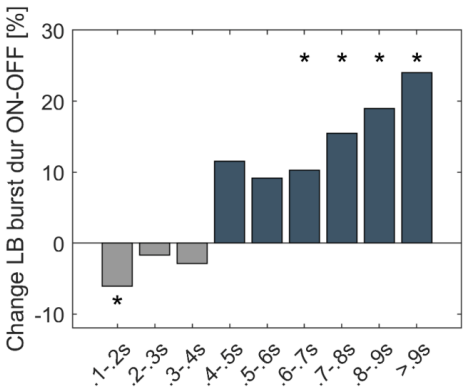
Significant reduction of mean burst duration with dopaminergic medication in the low beta band across patients.

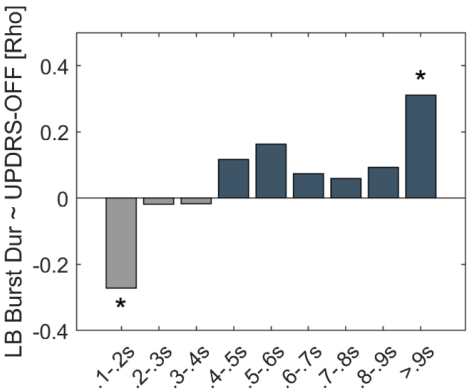
B



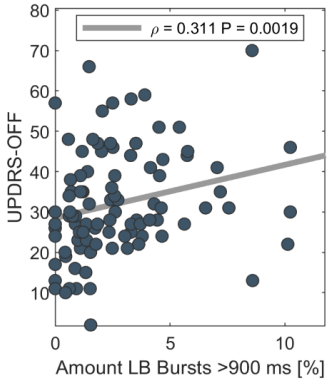
Mean burst duration correlates with motor impairment in the OFF-medication state as does ist shortening with symptom alleviation.

Results:





In the dopamine-depleted state, there is an increase of beta bursts >600 ms.



It is specifically the amount of very long beta bursts (>900 ms) that correlates with motor impairment in the OFF-medication state

Conclusion:

- We show that **burst duration correlates with motor impairment** in the OFF-medication state, which **explains more variance than beta power**. More specifically, this correlation was driven by the amount of beta **bursts that exceeded 900 ms duration**. Mean burst duration **decreased with dopaminergic medication**, which was linked to motor improvement in the ON-medication state. The observed effects were **frequency-specific** for the low beta band.
- Our findings highlight the importance of understanding temporal brain circuit dynamics.
- We conclude that large multicenter aDBS trials that are currently in development should look beyond the single or dual power threshold paradigms, and **consider temporal burst dynamics as a key hallmark of pathological basal ganglia activity** that could inform next-generation multifeature approaches for aDBS in PD.

Deep Brain Stimulation Does Not Modulate Auditory-Motor Integration of Speech in Parkinson's Disease

Bahne Bahners[1], Esther Florin[1], Julian Rohrhuber[2], Holger Krause[1], Jan Hirschmann[1], Ruben van de Vijver[1], Alfons Schnitzler[1], Markus Butz[1]

[1] Heinrich Heine University Düsseldorf, Germany, [2] Robert Schumann Hochschule, Germany

Deep brain stimulation (DBS) has significant effects on motor symptoms in Parkinson's disease (PD), but existing studies on the effect of DBS on speech are rather inconclusive. It is assumed that deficits in auditory-motor integration strongly contribute to Parkinsonian speech pathology. The aim of the present study was to assess whether subthalamic DBS can modulate these deficits.

20 PD patients (15 male, 5 female; 62.4 ± 6.7 years) with subthalamic DBS were exposed to pitch-shifted acoustic feedback during vowel vocalization and subsequent listening. Voice and brain activity were measured ON and OFF stimulation using magnetoencephalography (MEG). Vocal responses and auditory evoked responses time locked to the onset of pitch-shifted feedback were examined.

Subthalamic DBS appears to have no substantial effect on vocal compensations, although it has been suggested that auditory-motor integration deficits contribute to higher vocal response magnitudes in pitch perturbation experiments with PD patients. Thus, DBS seems to be limited in modulating auditory-motor integration of speech in PD.

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Deep Brain Stimulation Does Not Modulate Sensorimotor Integration of Speech in Parkinson's Disease

Bahne H. Bahners[1*], Esther Florin[1], Julian Rohrhuber[2], Holger Krause[1], Jan Hirschmann[1], Ruben van de Vijver[3], Alfons Schnitzler[1,4], Markus Butz[1]

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Background:

- Deep brain stimulation (DBS) has significant effects on **motor symptoms** in **Parkinson's disease (PD)**.
- Studies on the effect of DBS on **speech** are inconclusive.
- It is assumed that **sensorimotor deficits** strongly contribute to Parkinsonian speech pathology.

Objectives:

- Using **Magnetoencephalography (MEG)** we wanted to study if DBS can **modulate deficits** in sensorimotor integration of speech in a pitch perturbation experiment.

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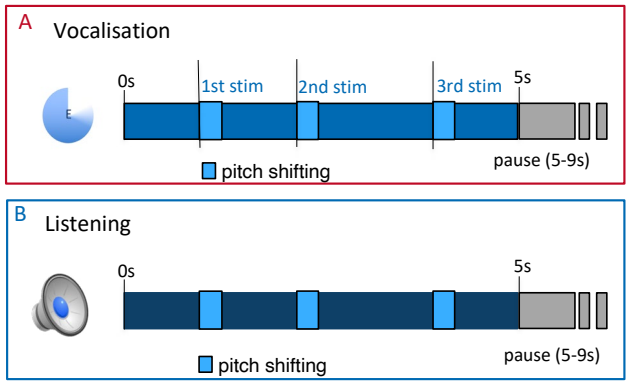
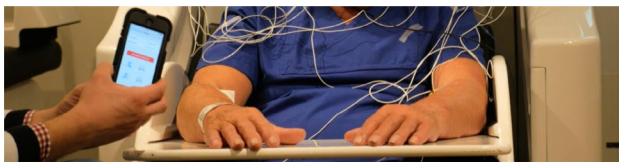
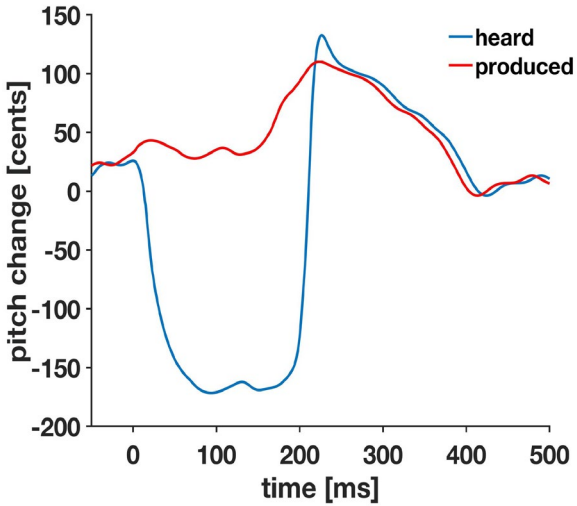
Methods:

- **20 PD patients** (5 f, 15 m; 62.4 ± 6.7 yrs) with subthalamic DBS (only **slightly magnetic hardware**)
- Significant therapeutic effect regarding UPDRS III (ON: 15 ± 6, p<0.001 vs. OFF: 28 ± 12).
- Pitch-shifted acoustic feedback during **vocalization** and **listening, OFF** and **ON stimulation.**
- **Vocal responses** and **auditory evoked responses** to pitch-shifted feedback.







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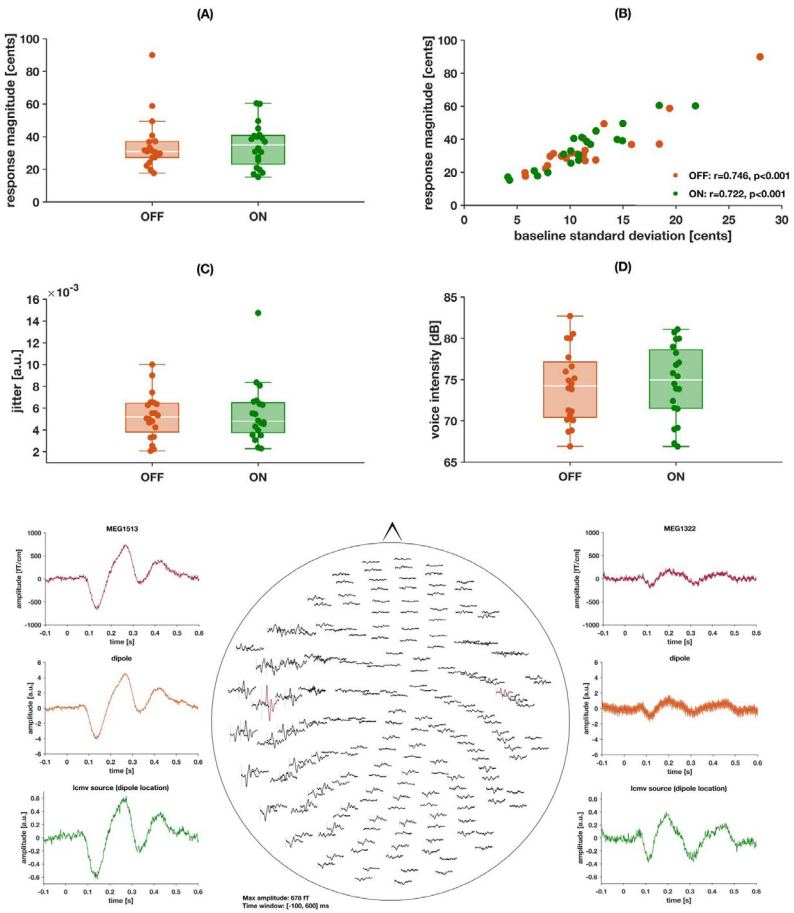
Results:

- A positive correlation between vocal **response magnitude** and **pitch variability**, stimulation OFF and ON (OFF: $r = 0.746$, $\mathbf{p<0.001}$, ON: $r = 0.722$, $\mathbf{p<0.001}$).
- No differences OFF vs ON of **vocal responses** to pitch-shifted feedback ($\mathbf{p=0.809}$, d= - 0.055) nor **voice intensity** ($\mathbf{p=0.419}$, d= - 0.185).
- Linearly Constrained Minimum Variance **(LCMV) beamforming**, reducing artefacts caused by movements of the magnetic DBS hardware components.



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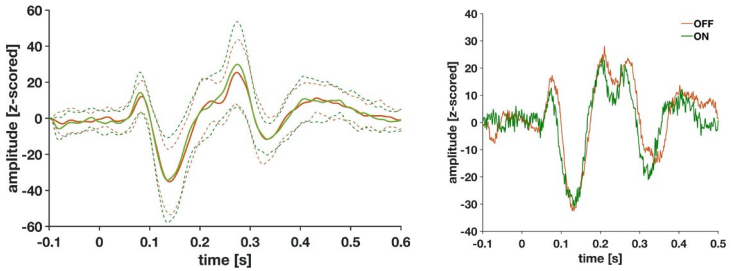
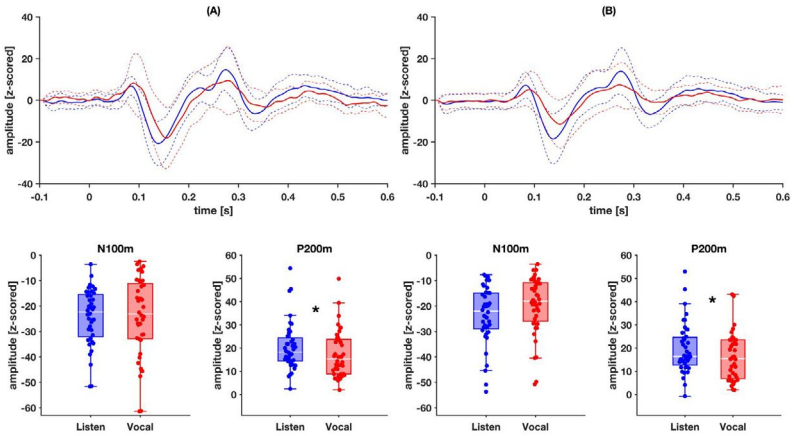
Results:

- Amplitudes and latencies did not reveal a significant difference between stimulation conditions (left AC: N100m: F(1,19)=0.337, ***p*=0.586**, f=0.133; P200m: F(1,19)=0.433, ***p*=0.518**, f=0.151)



- P200m amplitudes of left and right auditory cortex (AC) and superior temporal gyrus (STG) significantly larger during listening (AC: F(1,19)=7.124, ***p*=0.015**; STG: F(1,19)=5.244, ***p*=0.034**).



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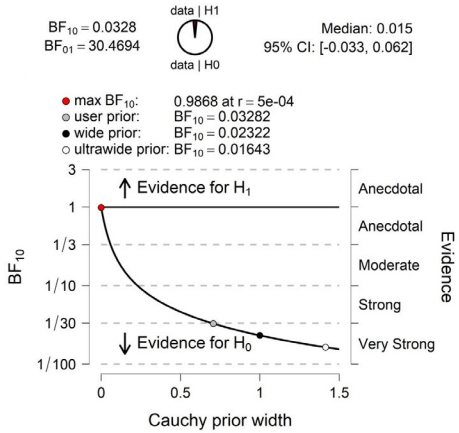
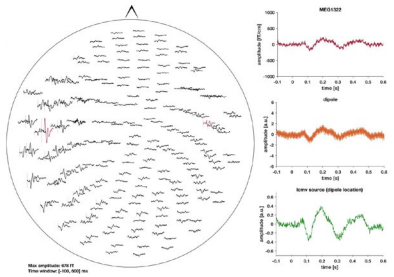
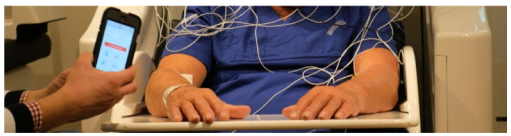
Conclusion:

- Given the behavioral data **Bayes statistics** confirmed that there was **very strong evidence** against an Effect of DBS on sensorimotor integration of speech (favoring H0) (BF10=**0.0328**, 95%-CI [-0.033, 0.062]).
- Thus, DBS seems to be **limited** in modulating **sensorimotor integration** of speech in PD.
- **Sensorimotor deficits** contribute to high response magnitudes in pitch perturbation experiments in PD.
- **LCMV beamforming** effectively reduces movement related DBS artefacts to study **evoked fields** in **MEG**.







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Calculation of the discrepancy between planning MRI and O-arm in deep brain stimulation.

F.W.R. Steup[1], Y.R. Willems[2], C.F. Hoffmann[2], R. Zutt[2], M.F. Contarino[2], N.A. Van der Gaag[2]

[1] Delft University of Technology, The Netherlands, [2] Haga Teaching Hospital, The Netherlands

Accurate implantation of electrodes is crucial in deep brain stimulation (DBS) treatment. The O-arm is used to verify electrode positioning intraoperatively. Intraoperative choices and choices in depth, according to microelectrode recording, have thus far not been taken into account for the comparison of O-arm and preoperative MRI coordinates, neither has a spherical correction been performed.

Imaging and intraoperative choices were retrospectively analyzed for 41 consecutive patients with movement disorders treated with DBS in 2017 to 2018. The O-arm images were registered to the preoperative Leksell frame-MR T1 imaging with StealthStation Surgical Navigation software (Medtronic, Minneapolis, Minnesota). A new algorithm taking into account both the chosen trajectory (defined by ring, arc, and target coordinates) and the intra-operative channel choice (central, medial, lateral, anterior or posterior) and depth, was used to calculate differences between preoperative MRI- and final O-arm coordinates. In this algorithm, calculation was performed using the command 'sph2cartvec' (MATLAB R2019b) to convert the spherical (arc, ring, depth, intraoperative channel choice) basis components to Cartesian (x,y,z) components, which potentially allows better correction for the real trajectory. The translation is the change in planned target coordinates resulting from intraoperative channel and depth choice on the preoperative planning MRI coordinates.

After application of a sophisticated spherical correction algorithm and correction for intraoperative channel choice the present study shows a significant difference between the x- and y-coordinates of MRI and intraoperative O-arm imaging. Further research to analyze this difference can be useful. However, the observed difference in this study is small and possibly not clinically relevant.

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Calculation of discrepancy between planning MRI and O-arm in DBS

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Background

- Accurate lead placement is essential in Deep Brain Stimulation (DBS)
- Targeting and trajectory planning is performed using preoperative stereotactic MRI
- Intraoperative findings (based on MER and macrostimulation) affect choice final lead position (trajectory, depth)
- Intraoperative CT (O-arm) verifies final lead position

Aim

To compare MRI target coordinates adjusted for intraoperative choices with final O-arm lead position coordinates using conventional and new methodology

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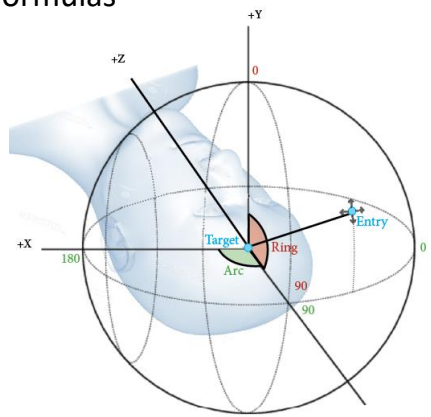
Methods

- Retrospective analysis of 41 Patients (81 trajectories) undergoing DBS with MER
- Co-registration of O-arm images to preoperative MR T1 images on StealthStation Surgical Navigation software *(Medtronic)*
- Comparison O-arm with MRI with conventional method
  - MRI coordinates adjusted for chosen trajectory and depth based on MER findings
  - Method: ±2 mm to either x or y direction (if not 'central') and reported mm z adjustment
- Comparison O-arm with MRI with new method *(mathematical algorithm)*
  - MRI coordinates adjusted for chosen trajectory and depth based on MER findings
  - Method: Cartesian vector analysis (x,y,z) through goniometric formulas *(based on centre-of-arc principle)*
- Calculation of differences between adjusted conventional and new planning MRI and O-arm coordinates
  - Directional distance $(\Delta x,\Delta y,\Delta z)$
  - Euclidean distance: $\sqrt{(\Delta x)^2+(\Delta y)^2+(\Delta z)^2}$



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Concept of Mathematical Algorithm

Spheric x, y, z alterations ***per*** MER trajectory and chosen depth, left or right

LEFT-SIDED

θ = 90 - ring (degrees)
φ = 180 - arc (degrees)
D = chosen depth (mm)

INTRAOPERATIVE CHOICE

ANTERIOR	0	X
	2*cos(θ)	Y
	2*sin(θ)	Z
LATERAL	2*sin(φ)	X
	-2*sin(θ)cos(φ)	Y
	2*cos(θ)cos(φ)	Z
CENTRAL		
MEDIAL	-2*sin(φ)	X
	2*sin(θ)cos(φ)	Y
	-2*cos(θ)cos(φ)	Z
POSTERIOR	0	X
	-2*cos(θ)	Y
	-2*sin(θ)	Z

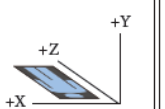
+

DEPTH CHOICE

-D*cos(θ)	X
-D*sin(θ)sin(φ)	Y
D*cos(θ)sin(φ)	Z

=

Effect in mm of intraoperative choice on electrode positioning



+X to left
+Y to anterior
+Z to caudal

Total Euclidean distance = $\sqrt{X^2+Y^2+Z^2}$

RIGHT-SIDED

θ = 90 - ring (degrres)
φ = arc (degrees)
D = chosen depth (mm)

INTRAOPERATIVE CHOICE

ANTERIOR	0	X
	2*cos(θ)	Y
	2*sin(θ)	Z
MEDIAL	2*sin(φ)	X
	2*sin(θ)cos(φ)	Y
	-2*cos(θ)cos(φ)	Z
CENTRAL		
LATERAL	-2*sin(φ)	X
	-2*sin(θ)cos(φ)	Y
	2*cos(θ)cos(φ)	Z
POSTERIOR	0	X
	-2*cos(θ)	Y
	-2*sin(θ)	Z

+

DEPTH CHOICE

D*cos(θ)	X
-D*sin(θ)sin(φ)	Y
D*cos(θ)sin(φ)	Z

=

Effect in mm of intraoperative choice on electrode positioning

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Results

- Planning MRI compared with O-arm according to conventional and new method
- Cartesian vector coordinates (mean ± sd)

		Left			Right		
	Coordinates	**X**	**Y**	**Z**	**X**	**Y**	**Z**
	Planning MRI	113.01 ±3.92	101.79 ±5.08	96.62 ±7.71	86.28 ±3.76	101.72 ±4.90	96.59 ±7.48
A	Conv. method planning MRI	113.16 ±3.88	102.24 ±5.31	99.30 ±7.69	86.18 ±3.76	102.60 ±4.90	99.24 ±7.54
B	New method planning MRI	112.19 ±4.27	101.35 ±5.51	98.99 ±7.74	87.19 ±4.40	101.77 ±5.08	99.12 ±7.46
	O-arm	111.47 ±4.39	100.01 ±5.50	98.35 ±7.95	86.98 ±4.44	100.70 ±5.32	98.42 ±7.60
A	Difference conv. vs. O-arm	-1.69 ±1.11*	-2.23 ±1.10*	-0.95 ±1.26*	0.80 ±1.09*	-1.90 ±1.54*	-0.82 ±1.43*
A	(Euclidean)	3.37 ±1.17 (range 0.59-5.64)**			2.98 ±1.24 (range 1.34-6.73)**		
B	Difference new vs. O-arm	-0.72 ±0.87*	-1.34 ±0.81*	-0.65 ±1.22*	-0.21 ±0.89	-1.07 ±1.17*	-0.70 ±1.37*
B	(Euclidean)	2.19 ±0.91 (range 0.51-4.51)**			2.20 ±0.89 (range 0.70-4.47)**		

*Significant (paired t-test, p<0.01)
**Significant (one-sample t-test, p<0.01)

Conclusion

- New method (mathematical algorithm), incorporating intraoperative trajectory adjustments, provides more accurate and realistic calculation of MRI target coordinates
- Final lead position on O-arm significantly more to the:
  - Right (-x), posterior (-y) and cranial (-z) for left-sided leads
  - Posterior (-y) and cranial (-z) for right-sided leads
- Mean euclidean difference both left and right around 2 mm
- New method shows significantly smaller discrepancy between planning and O-arm, compared to conventional method
- Future research is directed to elucidate remaining differences between planning MRI and intra- and postoperative verification imaging

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Cross-frequency coupling between gamma oscillations and deep brain stimulation frequency in cortico-subcortical networks in Parkinson's disease patients

Muthuraman Muthuraman[1], Manual Bange[1], Nabin Koirala[1], Dumitru Ciolac[1], Bogdan Pintea[2], Martin Glaser[1], Gerd Tinkhauser[3], Peter Brown[3], Gunther Deuschl[4], Sergiu Groppa[1]

[1] University Medical Center of the Johannes Gutenberg-University Mainz, Germany, [2] University Hospital of Bonn, Germany, [3] University of Oxford, UK, [4] Christian Albrecht's University, Germany

The disruption of pathologically enhanced beta oscillations is considered one of the key mechanisms mediating the clinical effects of deep brain stimulation on motor symptoms in Parkinson's disease. However, a specific modulation of other distinct physiological or pathological oscillatory activities could also play an important role in symptom control and motor function recovery during deep brain stimulation. Finely tuned gamma oscillations have been suggested to be prokinetic in nature, facilitating the preferential processing of physiological neural activity. In this study, we postulate that clinically effective high-frequency stimulation of the subthalamic nucleus imposes cross-frequency interactions with gamma oscillations in a cortico-subcortical network of interconnected regions and normalises the balance between beta and gamma oscillations.

To this end we acquired resting state high-density (256 channels) electro-encephalography from 31 patients with Parkinson's disease who underwent deep brain stimulation to compare spectral power and power-to-power cross-frequency coupling using a beamformer algorithm for coherent sources. To show that modulations exclusively relate to stimulation frequencies that alleviate motor symptoms, two clinically ineffective frequencies were tested as control conditions.

We observed a robust reduction of beta and increase of gamma power, attested in the regions of a cortical (motor cortex, supplementary motor area, premotor cortex) and sub-cortical network (subthalamic nucleus and cerebellum). Additionally, we found a clear cross-frequency coupling of narrowband gamma frequencies to the stimulation frequency in all of these nodes which negatively correlated with motor impairment. No such dynamics were revealed within the control posterior parietal cortex region. Furthermore, deep brain stimulation at clinically ineffective frequencies did not alter the source power spectra or cross-frequency coupling in any region.

These findings demonstrate that clinically effective deep brain stimulation of the subthalamic nucleus differentially modifies different oscillatory activities in a wide-spread network of cortical and subcortical regions. Particularly the cross frequency interactions between finely tuned gamma oscillations and the stimulation frequency may suggest an entrainment mechanism that could promote dynamic neural processing underlying motor symptom alleviation.

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Abstract title / authors:

Cross-frequency coupling between gamma oscillations and deep brain stimulation frequency in cortico-subcortical networks in Parkinson's disease patients

Muthuraman Muthuraman*, Manuel Bange*, Nabin Koirala, Dumitru Ciolac, Bogdan Pintea, Martin Glaser, Gerd Tinkhauser, Peter Brown, Günther Deuschl, Sergiu Groppa

Background:

- The disruption of pathologically enhanced beta oscillations is considered one of the key mechanisms mediating the clinical effects of deep brain stimulation on motor symptoms in Parkinson's disease.
- However, a specific modulation of other distinct physiological or pathological oscillatory activities could also play an important role in symptom control and motor function recovery during deep brain stimulation.

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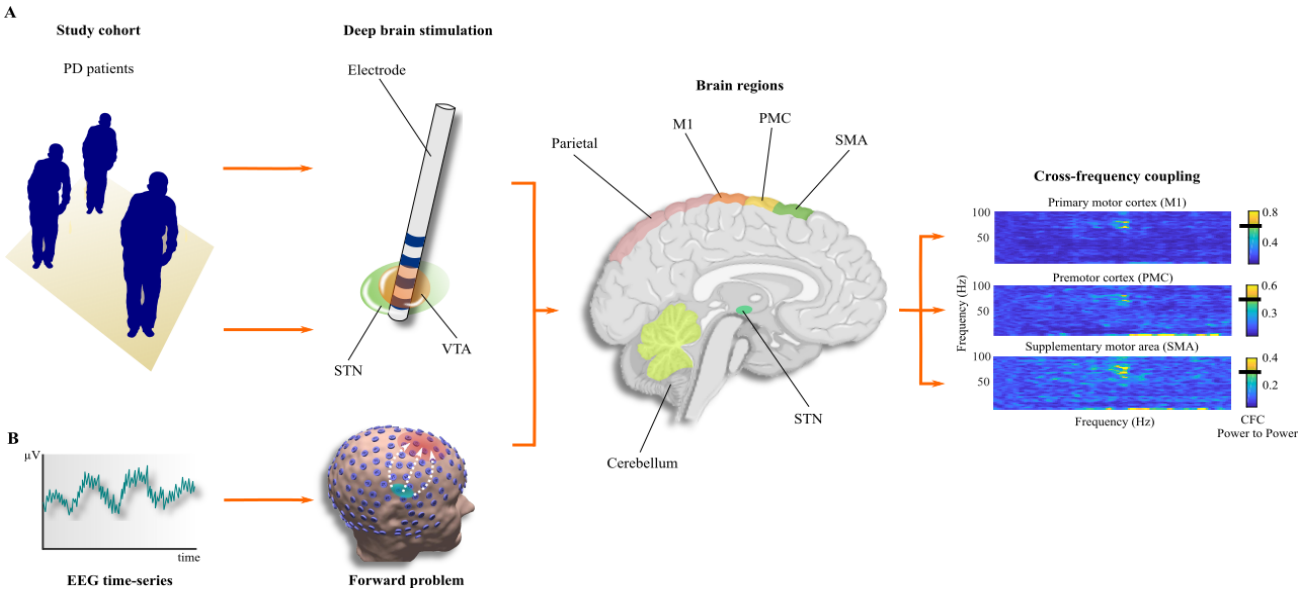
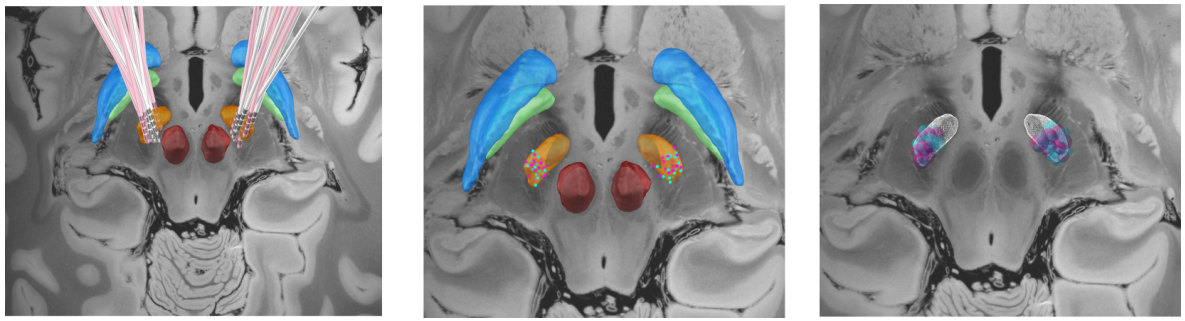
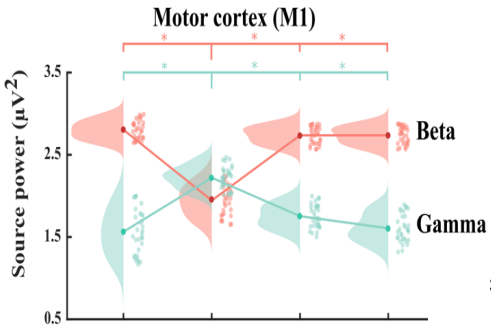
Methods:

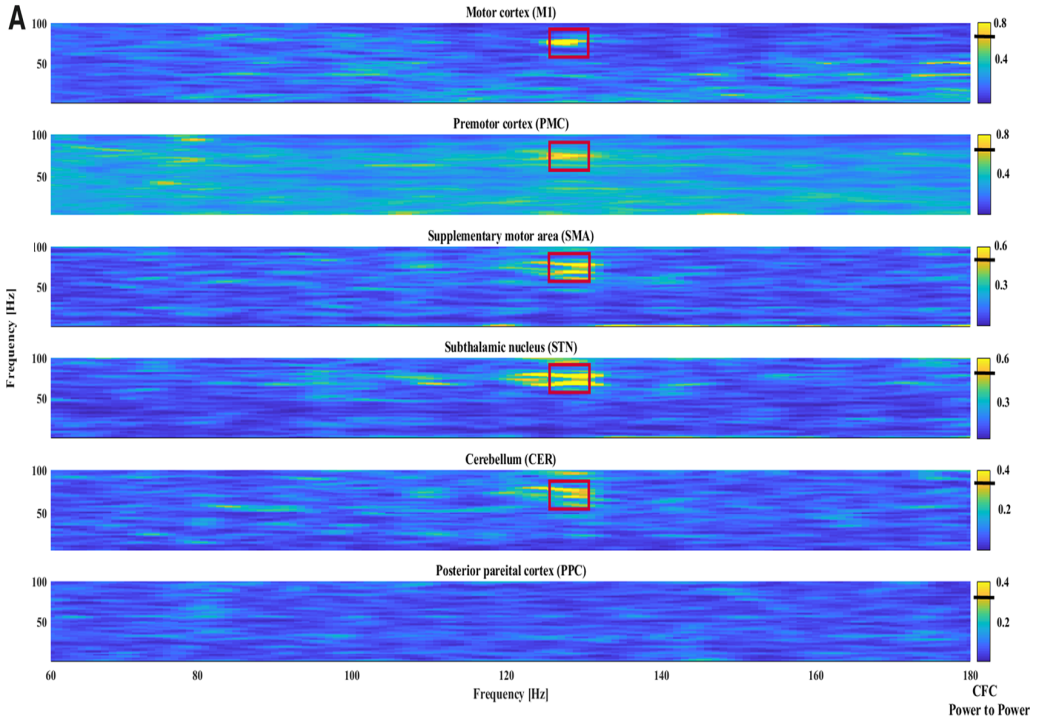




Muthuraman, M, et al., Brain. 2020 Nov 5:awaa297. doi: 10.1093/brain/awaa297

Results:





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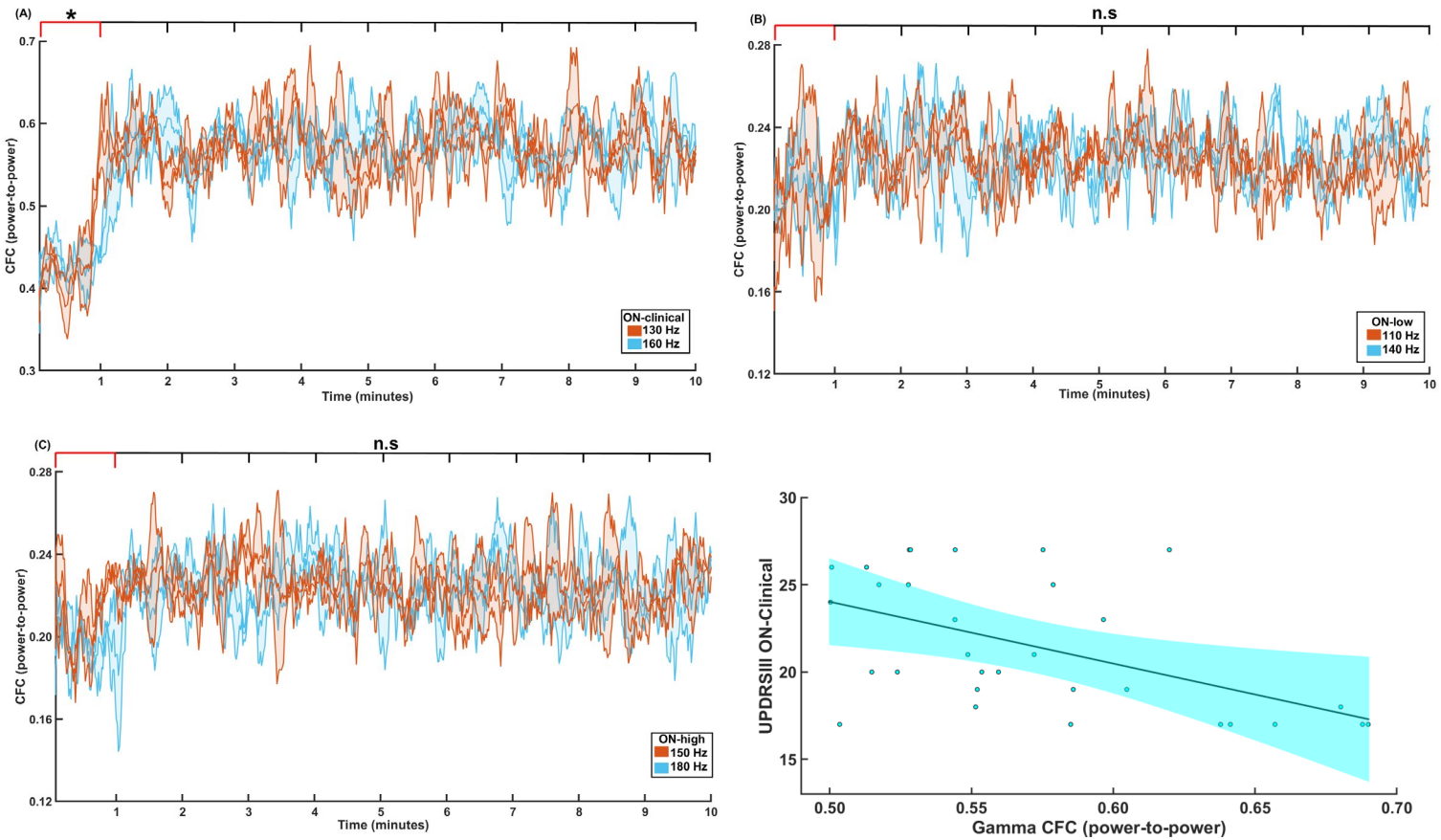
Results:



Muthuraman, M, et al., Brain. 2020 Nov 5:awaa297. doi: 10.1093/brain/awaa297

Conclusion:

- Deep brain stimulation at clinically ineffective frequencies did not alter the source power spectra or cross-frequency coupling in any region.

- These findings demonstrate that clinically effective deep brain stimulation of the subthalamic nucleus differentially modifies different oscillatory activities in a widespread network of cortical and subcortical regions.

- Particularly the cross-frequency interactions between finely tuned gamma oscillations and the stimulation frequency may suggest an entrainment mechanism.

Motor evoked potentials improve targeting in deep brain stimulation surgery

Petyo Nikolov[1], Verena Heil[1], Philipp J. Slotty[1], Jan Vesper[1], Alfons Schnitzler[1], Stefan J. Groiss[1]

[1] **Heinrich Heine University, Deutschland**

One of the main challenges posed by the surgical deep brain stimulation (DBS) procedure is the successful targeting of the structures of interest and avoidance of side effects, especially in asleep surgery. Here, intraoperative motor-evoked potentials might serve as tool to identify the pyramidal tract.

Motor potentials were evoked through both microelectrode and DBS-electrode stimulation during stereotactic DBS surgery on 26 subthalamic nuclei and 3 ventral intermediate thalamic nuclei. Internal capsule proximity was calculated for contacts on microelectrode-trajectories, as well as for DBS-electrodes, and correlated with the corresponding motor evoked potential -thresholds. Moreover, the predictivity of intraoperative motor evoked potential-thresholds on the probability of postoperative capsular side effects were calculated.

Intraoperative motor evoked potentials-thresholds correlated significantly with internal capsule proximity, regardless of the stimulation source. Furthermore, motor evoked potentials-thresholds were highly sensitive to predict the occurrence of postoperative capsular side effects.

Intraoperative motor evoked potentials provide additional targeting guidance, especially in asleep DBS surgery, where clinical value of microelectrode recordings and test stimulation may be limited. As this technique predicts future capsular side effects, it can directly be translated into clinical practice.

Motor evoked potentials improve targeting in deep brain stimulation surgery

Petyo Nikolov[1], Verena Heil[1], Christian J Hartmann, MD[1], Nikola Ivanov[1], Plilipp J Slotty, MD[2]
Jan Vesper, MD[2], Alfons Schnitzler, MD[1], Stefan J Groiss, MD[1]

[1] Department of Neurology, Medical Faculty, Heinrich Heine University, Düsseldorf &
Institute of Clinical Neuroscience and Medical Psychology, Heinrich Heine University, Düsseldorf
[2] Department of Functional Neurosurgery and Stereotaxy, Medical Faculty, Heinrich Heine University, Düsseldorf

Introduction:

- Deep brain stimulation (DBS) of the subthalamic nucleus (STN) and the ventral intermediate nucleus (VIM) are effective treatments for Parkinson´s disease (PD) and essential tremor (ET).
- One of the main challenges of the surgery is to target the structure of interest, while at the same time avoiding side effects.
- Here, intraoperative motor-evoked potentials (MEP) might offer additional support, especially in the context of asleep surgery.

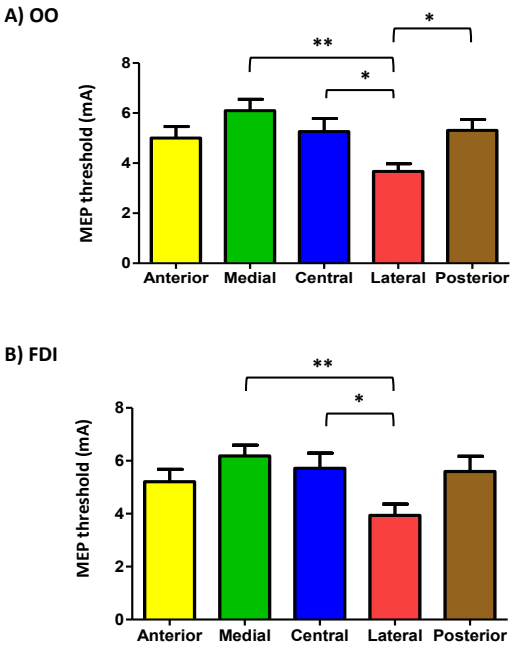
- **Hypothesis:**
  Intraoperative MEP thresholds
  1) correlate with internal capsule (IC) distance
  2) predict postoperative IC side effects occurrence.

Materials and Methods:

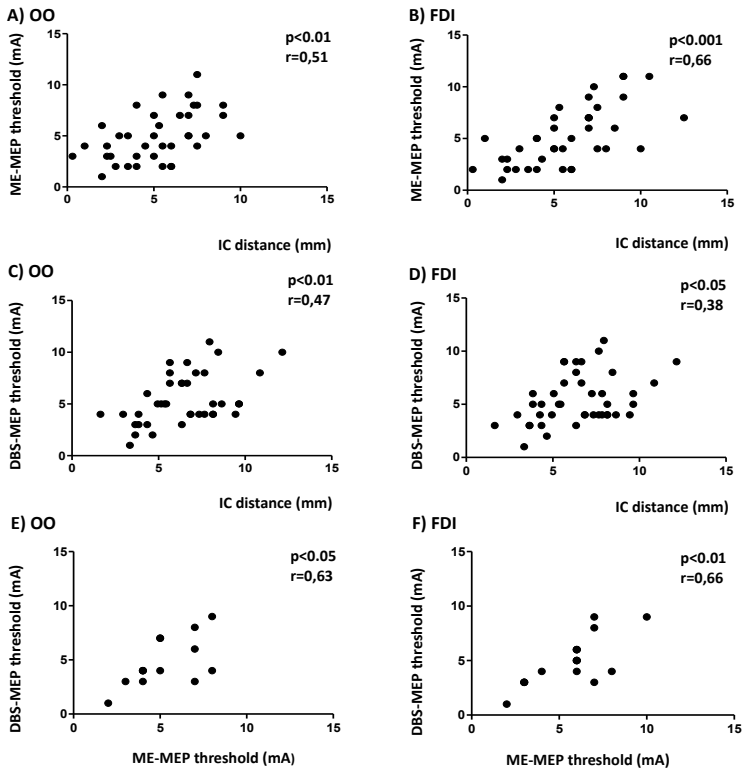
- 26 STN and 3 VIM from 16 patients
- Intraoperative stimulation:
  1) Microelectrode (ME) stimulation through different trajectories
  2) DBS electrode stimulation through different segments
- EMG-recordings:
  MEP from 1) orbicularis oculi (OO) and 2) first dorsal interosseous (FDI) muscles
- Clinical contact screening (monopolar review)
- MEP threholds were compared among different trajectories and correlated with IC distance.

Results:

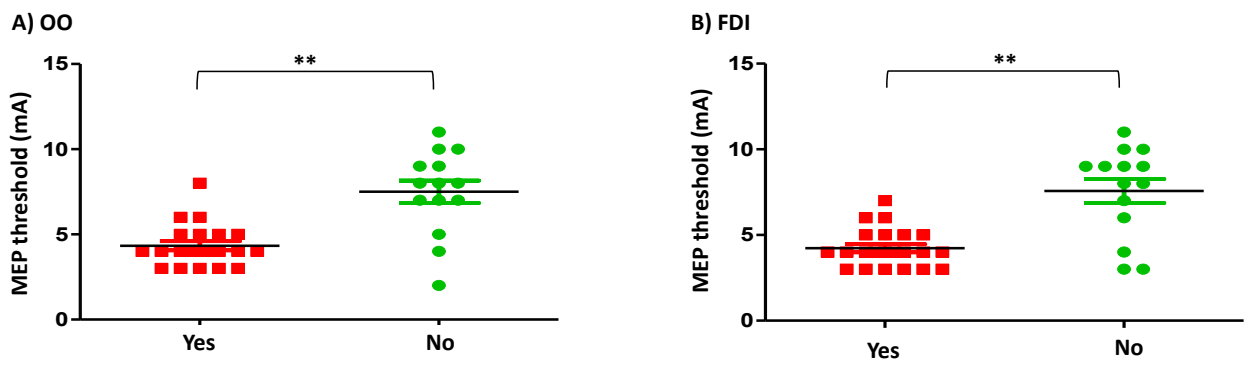
1) MEP-threshold was significantly reduced on the lateral trajectory.



2) MEP-threshold correlates with IC-distance



3) MEP-thresholds predict postoperative IC-side effects.



Conclusion: 1) Intraoperative MEP-thresholds provide additional targeting guidance and may especially be helpful within the context of asleep surgery, when clinical testing is limited.
2) The technique can easily be translated into clinical practice.

RechargePSYCH: Convenience, charge burden and complications of rechargeable implantable pulse generators in patients with deep brain stimulation for psychiatric disorders.

Martin Jakobs[1], David Hernán Aguirre-Padilla[2], Peter Giacobbe[3], Andreas W. Unterberg[1], Andres M. Lozano[4]

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Deep Brain Stimulation (DBS) for psychiatric indications such as major depression, anorexia nervosa or obsessive-compulsive disorder (OCD) has been established in clinical trials. Implantable pulse generator (IPGs) replacements represent the most common type of follow-up surgeries in these patients as stimulation parameters are usually higher compared to movement disorder patients. Rechargeable IPGs offer longer battery life and fewer additional surgeries combine with a smaller implant size. The impact of this technology on psychiatric patients as well as the amount of time necessary to maintain is still unknown.

A database analysis was performed to identify all DBS patients who were implanted with a rechargeable IPG for a psychiatric indication at the Toronto Western Hospital from 2003 to 2019. Patients that were still implanted with a rechargeable device at the time of the trial were invited to fill out a standardized online questionnaire. Primary endpoint was the rating of the convenience of recharging of the entire process and each individual step on an ordinal scale (0-10). Secondary endpoints were the rate of user confidence, satisfaction, complications (failed recharges, interruptions of therapy) and the charge burden (minutes per week necessary to recharge the IPG).

These endpoints were tested for differences in several subgroups (age, sex, indication, IPG model, confidence) as well as for associating factors (job, driver, smartphone user).

A total of 42 patients were implanted with rechargeable IPGs of which 32 were still implanted at the time of the trial. N=21 patients completed the questionnaire (return rate 65.6%) including n=13 patients with major depression, n=6 patients with anorexia and n=2 patients with OCD. More than 80% of patients were female. Mean age was 50.7 years with an average time of therapy with the rechargeable IPG of 31.8 months. Patients had undergone a median of 3 IPG replacements before receiving the rechargeable IPG.

Convenience of recharging was rated high (8.0 out of 10.0 points). Keeping the connection during the charging process (p=0.004) as well as putting on the charging belt (p=0.011) was rated worse compared to the convenience of charging the charger.

The mean charge burden was 286 minutes, which was regarded as acceptable by only 43% of patients. The mean acceptable charge burden was 121 minutes.

81% felt confident using the device. 66.7% would recommend and 62% would choose a rechargeable IPG again. 33% of patients experienced a failed recharge and 38% had an unintentional interruption of therapy.

Age, sex and the IPG model and none of the associating factors had no influence on any endpoint. Depression patients rated the convenience of recharging significantly worse compared with OCD patients (p=0.027). Patients that did not feel confident were less likely to recommend (p=0.006) or choose a rechargeable IPG again (p=0.012).

Rechargeable IPGs can be safely implanted in DBS patients with psychiatric indications. The convenience of the recharging process is high, however the amount of time necessary to recharge the device is more than twice as long as patients find acceptable.

III. INTERNATIONAL CONFERENCE ON DEEP BRAIN STIMULATION – virtual meeting – November 20 – 21, 2020

RechargePSYCH: Convenience, charge burden and complications of rechargeable implantable pulse generators in patients with deep brain stimulation for psychiatric disorders.

Jakobs M.[1,2], Aguirre-Padilla D.H.[1,3], Giacobbe P.[4], Unterberg A.W.[2], Lozano A.M.[1]

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Background:

DBS for psychiatric indications such as major depression, anorexia nervosa or obsessive-compulsive disorder (OCD) has been established in clinical trials.

Implantable pulse generator (IPGs) replacements represent the most common type of follow-up surgeries in these patients.

Rechargeable IPGs offer longer battery life and fewer additional surgeries combine with a smaller implant size.

The impact of this technology on psychiatric patients as well as the amount of time necessary to maintain is still unknown.

Methods:

- Database analysis of all psychiatric DBS patients from a single center (TWH) 2003-2019
- All patients with a rechargeable IPG implanted were invited for a standardized online-questionnaire

- Primary endpoint:
  convenience of recharging process, burden of care
  (ordinal scale 0-10 points; 0 lowest, 10 highest score)

- Secondary endpoints:
  charge burden (min/week), user confidence, user satisfaction, complication rates

– Endpoints were compared for several subgroups:
  age, sex, indication, IPG model, user confidence

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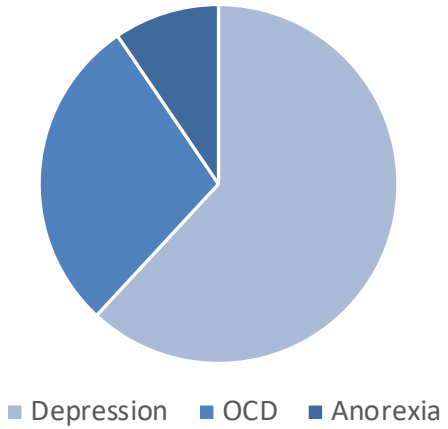
Results:

- n=21 datasets available (65.6% return rate)
- 50.7 years with 31.8 months of therapy
- 3.2 IPG replacements before rechargeable IPG



- **Primary endpoint:**
  convenience of recharging: 8.0/10.0 points
  burden of care: 7.0/10.0 points

- **Secondary endpoints:**
  Charge burden: 286 min/week (acceptable: 121 min/week)
  User confidence: 83%
  User satisfaction: 62%
  Failed recharges: 33%
  Interruption of therapy: 38%

Results:

Factors influencing primary endpoints:

Burden of care: Depressions > OCD/Anorexia

71.3% value fewer replacement surgeries more than not having to recharge.

Patient opinions:

Is recharging a reminder of illness? *5.5/10 points*

Does recharging make you feel in control of your therapy? *7.0/10 points*

Do you feel anxious about the recharging process? *7.0/10 points*

Conclusion:

Rechargeable IPGs can be safely implanted in DBS patients with psychiatric indications.

The convenience of the recharging process is high, however the amount of time necessary to recharge the device is more than twice as long as patients find acceptable.

Complication rates are several times higher compared to movement disorder patients.

Surgical long-term management of patients with deep brain stimulation for psychiatric disorders

Martin Jakobs[1], David Hernán Aguirre-Padilla[2], Peter Giacobbe[3], Andreas W. Unterberg[1], Andres M. Lozano[4]

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Deep Brain Stimulation (DBS) has implemented itself as a hallmark in movement disorder therapy by normalizing and stabilizing deranged neural circuits. As psychiatric disorders can be understood as such circuitopathies, DBS has been explored in clinical trials as an adjunct treatment. Data on how to surgically manage these patients long after the clinical trial has ended is currently lacking.

A database analysis was performed to identify all cases of DBS for psychiatric indications at the Toronto Western Hospital. Epidemiologic data, number and type of follow-up surgeries after initial implantation, rate of complications, long-term therapy and stimulation parameters were analyzed.

N=103 patients were implanted with a DBS system for a psychiatric indication (excluding dementias) between 2003 and 2019 with a mean follow-up of 106 months. Mean age was 43.1 years with two thirds being female. Indications were major depression (n=66), bipolar disorder (n=6), obsessive-compulsive disorder (n=6), anorexia nervosa (n=22) and Tourette's syndrome (n=3). The predominant target structure was the subgenual cingulate gyrus (CG25, 91% for depression, bipolar disorder and anorexia. The interthalamic peduncle (ITP, 6%) and the contromedian-parafascicular nucleus of the thalamus (CM-Pf, 3%). 48.5% of all patients still have an active DBS system with a mean follow-up of 94 months. 21.4% of patients had the system explanted with lack of efficacy being the most common one (77% of explants). IPG replacements were the most common scheduled surgery with an average of 2.3 replacements per patient. IPGs lasted for an average of 24.0 months with average stimulation parameters of 130Hz, 85µs and 5.3V. N=42 patients were switched to a rechargeable IPG with 24% being switched back to a non-rechargeable IPG later on. 37% of patients had unscheduled surgeries for wound-related complications (15.5% of patients), hardware related issues (10.6%) or suboptimal electrode placement (1.0%).

Patients with DBS for psychiatric disorders represent a separate entity compared to movement disorder patients. The rate of explants and unscheduled surgeries is higher. High stimulation parameters demand frequent IPG replacements generating a considerable rate of wound-related complications. Strategies to reduce the number of IPG replacements (optimization of stimulation parameters, use of rechargeable IPGs) could help to increase the rate of long-term responders in the future.

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Surgical long-term management of patients with deep brain stimulation for psychiatric disorders

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[4] Department of Psychiatry, Sunnybrook Health Sciences Centre, University of Toronto, Canada

Background:

Deep Brain Stimulation (DBS) has implemented itself as a hallmark in movement disorder therapy by normalizing and stabilizing deranged neural circuits.

DBS has been explored for psychiatric circuitopathies in clinical trials as an adjunct treatment.

Data on how to surgically manage these patients long after the clinical trial has ended is currently lacking.

Methods:

A database analysis was performed to identify all cases of DBS for psychiatric indications at the Toronto Western Hospital (2003-2019).

Analyzed items:

- Epidemiologic data
- numbers and types of follow-up surgeries after initial implantation
- rates and types of complications
- rate of long-term therapy
- stimulation parameters

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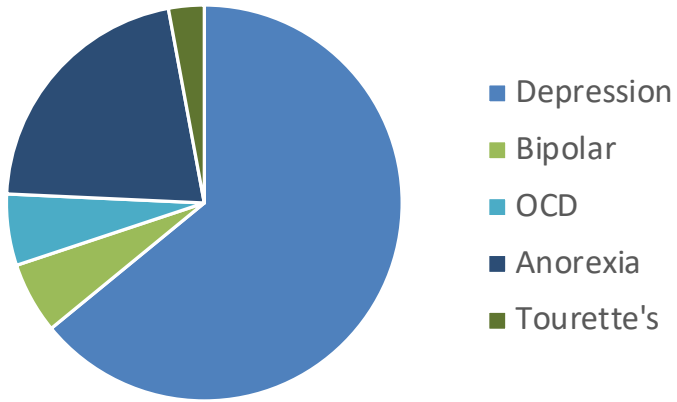
Results:

n=103 patients were operated for psychiatric circuitopathies (excluding dementias)

Targets:

- Subgenual cingulate: 91%
- Interthalamic peduncle: 6%
- CM-Pf: 3%



21.4% had the system explanted (after median 41 months)

- lack of efficacy: 77.3%
- infection: 9.1%

48.5% still have an active DBS system implanted (94 months of therapy)

- Deceased: 3,9%
- Lost to follow-up: 19,4%

Results:

63.1% of patients had unscheduled surgeries

- Skin erosion: n=4
- Infections: n=12
- Device failure: n=7
- IPG dyscomfort: n=4
- Misplaced electrodes: n=1
- Pocket hematoms: n=1
- IPG reversal (RC to PC): n=10

Stimulation parameters (median)
130Hz, 90µs, 5.5V
Single monopolar: 47% Double monopolar: 53%

n=235 scheduled IPG replacements (average 2.3 replacements)

- mean IPG duration: 24.0 months

N=42 patients were changed to a rechargeable IPG

- 23.8% were reversed to non-rechargeable IPGs

Conclusion:

Patients with DBS for psychiatric disorders represent a separate entity compared to movement disorder patients.

The rate of explants and unscheduled surgeries is higher.

High stimulation parameters demand frequent IPG replacements generating a considerable rate of wound-related complications.

Strategies to reduce the number of IPG replacements (optimization of stimulation parameters, use of rechargeable IPGs) could help to increase the rate of long-term responders in the future.

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