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Abstracts

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Network-wide modulation and therapeutic effects of DBS I

P002

Subjective patient rating as a novel feedback signal for DBS programming in Parkinson's disease

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Background: Deep brain stimulation of the subthalamic nucleus (STN-DBS) effectively alleviates motor fluctuations in Parkinson's disease (PD). Optimal electrode placement and effective programming significantly influence outcomes. From a patient"s perspective, DBS should relieve motor symptoms while avoiding side effects. However, there is a lack of programming routines that consider patients' subjective feedback for parameter adjustment.

Objective: This study assessed the usefulness of patients' subjective ratings as feedback for DBS programming.

Methods: We analyzed 260 DBS settings from 11 STN-DBS patients, pairing each volume of tissue activated (VTA) with a subjective rating measured by a visual analogue scale (VAS). We performed sweet spot mapping and connectivity analyses, utilizing voxel-wise and nonparametric permutation statistics to identify neuroanatomical regions and connectivity profiles associated with the highest VAS ratings. To validate our findings, we cross-validated the results in an independent test dataset of 6 patients (189 settings) to determine if the sweet spot and connectivity profile could predict the subjective patient perception.

Results: VTAs with the highest VAS scores were localized to the dorsolateral STN, consistent with published sweet spots derived from clinical data. Connectivity with the supplementary motor area (SMA) and primary motor cortex (M1) was associated with a more positive subjective perception. Connectivity profiles derived from one dataset successfully predicted outcomes in an independent dataset, as validated through leave-one-cohort-out cross-validation.

Conclusions: Mapping patients' subjective perceptions using VAS yields conclusive anatomical results that align with objective clinical and imaging measures. VAS-guided programming could provide an additional feedback mechanism for both acute and chronic DBS parameter adjustments.

Keywords:
Visual Analogue Scale (VAS); Parkinson"s disease (PD); Deep Brain Stimulation (DBS); Connectomics

P003

The deep brain stimulation response network in Parkinson's disease operates in the high beta band

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Deep brain stimulation (DBS) of the subthalamic nucleus improves motor symptoms in patients with Parkinson"s disease. Using functional MRI, optimal DBS response networks have been characterized. However, neural activity associated with Parkinsonian symptoms is magnitudes faster than what can be resolved by this method. While both *spatial* and *temporal* domains of these networks appear critical, no single study has yet investigated both domains simultaneously.

Here, we aim to close this gap by analyzing electrophysiological data from a total of N = 127 hemispheres. Using subthalamic local field potentials that were concurrently recorded alongside whole-brain magnetoencephalography in a multi-center cohort of patients that underwent subthalamic DBS for the treatment of Parkinson"s disease (N = 100 hemispheres), we analyzed the DBS response network in both spatial and temporal domains. In every cortical vertex, cortico-subthalamic coupling was correlated with stimulation outcomes.

The high beta network spatially resembled fMRI-based findings (R = 0.40, P = 0.039) and explained significant amounts of variance in clinical outcomes (*bstd* = 0.30, P = 0.002), while theta-alpha and low beta coupling did not show significant associations with DBS response (theta-alpha: *bstd* = -0.02, P = 0.805; low beta: *bstd* = -0.08, P = 0.426). The "optimal" high beta coupling map was robust when subjected to various cross-validation designs (10-fold cross-validation: R = 0.29,P = 0.009; split-half design: R = 0.31, P = 0.026) and was able to predict outcomes across DBS centers (R = 0.74;*P(1)* = 8.9e-5).

We identified a DBS response network that i) resembles the previously defined MRI network and ii) operates in the high-beta band. Maximal connectivity to this network was associated with optimal DBS outcomes and was able to cross-predict clinical improvements across DBS surgeons and centers.

P004

Thalamic deep brain stimulation restores implicit motor adaptation in essential tremor

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Introduction

Essential Tremor (ET) impairs sensorimotor adaptation and deep brain stimulation (DBS) of the ventral intermediate nucleus of the thalamus (VIM) exacerbates this deficit. However, because motor adaptation arises from the operation of multiple learning mechanisms, it remains unclear which mechanisms are disrupted by ET and DBS.

Goals

Our pre-registered study used two tasks, one that isolates implicit adaptation and the other that isolates explicit strategy use. We examined how ET and VIM-DBS impact these two learning processes.

Materials & Methods

We tested patients with ET (N=31) in DBS ON and DBS OFF conditions, along with age- and sex-matched healthy controls (N=32). We used a KINARM system to present the stimuli and collect kinematic data. To induce learning, we manipulated the position of a feedback cursor during reaching movements. Clamped feedback was used to isolate implicit adaptation and delayed feedback was used to isolate explicit strategy use.

Results

ET patients showed reduced implicit adaptation compared to healthy controls when DBS was OFF. However, contrary to previous reports, turning DBS on restored, rather than disrupted, implicit adaptation. Notably, these recovery effects cannot be explained by DBS- induced tremor reduction. Explicit strategy use was not impacted by ET nor DBS.

Summary

DBS restored implicit adaptation in patients with ET while leaving explicit learning strategies intact. We will discuss potential circuit-level mechanisms through which thalamic DBS modulates sensorimotor adaptation and consider broader clinical implications of our findings.

P005

Action vs. rest tremor map to different networks within primary motor cortex

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Introduction

Tremor is a prominent symptom in Parkinson"s disease and essential tremor, yet the neural substrates underlying different tremor types remain poorly defined. Deep brain stimulation effectively reduces both rest and action tremor, but it is unclear whether these symptoms respond to modulation of the same or distinct cortical subnetworks. A recent study identified a convergent tremor treatment network involving cerebellum and primary motor cortex, motivating a finer analysis of tremor topography within functional subdivisions of motor cortex [1].

We aimed to test whether rest and action tremor preferentially engage different subnetworks within primary motor cortex, specifically effector versus inter-effector regions [2]. A secondary goal was to determine whether clinical DBS programming already reflects differential engagement of these symptom-specific networks.

Methods

We analyzed three international DBS cohorts across Parkinson"s disease and essential tremor, including STN and VIM targets. Tremor scores were evaluated at the hemisphere level. Electrode locations and stimulation volumes were reconstructed using Lead-DBS. Functional connectivity was computed using a large normative connectome, and connectivity was correlated with clinical improvement to generate tremor-specific therapeutic maps. We quantified network engagement within effector and inter-effector regions using permutation testing. For each patient, we also generated theoretical stimulation settings in silico, optimized to target either the rest or action tremor map, and compared these to actual clinical settings.

Results

Across disorders and DBS targets, rest tremor improvement was linked to stronger connectivity with effector-specific regions of primary motor cortex, while action tremor improvement aligned with inter-effector regions. This dissociation was significant in both STN and VIM cohorts. Cerebellar connectivity also differed between tremor types. Clinical stimulation settings reflected these distinctions: in Parkinson's disease, settings more closely aligned with rest tremor networks, while in essential tremor, settings aligned with action tremor networks. Although implantation site influenced network access, most electrodes could be reprogrammed to stimulate either network. Optimizing stimulation for one network demonstrated a tradeoff, in which targeting one network reduced engagement of the other.

Conclusions

Rest and action tremor map to distinct subnetworks within primary motor cortex. Rest tremor preferentially engages effector-specific regions, while action tremor engages inter-effector regions linked to broader action control. These findings refine the cortical organization underlying tremor treatment and show that clinical programming already aligns with symptom-specific circuits. Mapping tremor phenotypes onto motor cortical subdivisions provides a mechanistic basis for personalized neuromodulation and may improve targeting and programming strategies across movement disorders.

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P006

Gray matter atrophy in Parkinson's disease patients with GBA mutation and its predictive role for motor and cognitive outcome after STN-DBS

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Background: Patients with Parkinson"s disease (PD) carrying Glucocerebrosidase 1 (GBA) variants (GBA+PD) are more prone for a severe motor and non-motor disease course with higher frequency of cognitive decline and dementia. The impact of subthalamic nucleus deep brain stimulation (STN-DBS) on cognition in GBA+PD patients, although known to be effective for motor sympoms in advanced PD with and without GBA mutation, remains controversial and counceling of GBA+PD patients challenging. **Methods:** We applied voxel-based morphometry (VBM) using the CAT12 toolbox (SPM12, Matlab R2019b) to identify GBA-specific atrophy patterns in GBA+PD patients versus PD patients without genetic mutations (GBA-PD) at the timepoint of evaluation for STN-DBS. Region of interest (ROI) volumes were retrieved from the Jülich Brain Atlas (Version 3.1). Clinical scores comprised the Unified Parkinson"s Disease Rating Scale motor part (UPDRS-III), medication including Levodopa equivalent dosage (LED), and non-motor measures, including BDI-II, Starkstein-Apathy Scale, PDQ-39, QUIP-RS and Mini-Mental-State Examination (MMSE). **Results:** In the group comparison, 20 GBA+PD patients showed atrophy of the right fusiform gyrus subunit 5 compared to 30 GBA-PD patients (p=0.0018, Holm-Bonferroni-corrected). Furthermore, atrophy of the left entorhinal cortex (p=0.003, uncorrected), left nucleus basalis of Meynert (p=0.017, uncorrected) and greater volume of the left frontal operculum subunit 9 (FOp9, p=0.009) have been detected in GBA+PD. 18 of the 20 GBA+PD patients underwent STN-DBS. Volume of right FOp9 predicted less MMSE decline at 12 months follow-up in GBA+PD (*F[1,17]=9.5, p=0.007**, R2=0.373*). MMSE deterioration did not occur more frequently in GBA+PD compared to GBA-PD one year after STN-DBS. GBA+PD and GBA-PD patients both profited regarding motor symptoms with significant improvement on UPDRS-III, including axial subitems. **Conclusion:** We detected pronounced medial temporal lobe atrophy and reduced volume of the nuleus basalis of Meynert in GBA+PD patients. Volume of FOp predicted post-DBS cognitive outcome in the GBA+PD cohort and might be a structural correlate of the cognitive reserve. In our cohort, STN-DBS proved to be effective for the treatment of motor symptoms in GBA+PD without significant cognitive deterioration one year after surgery. These findings are in line with recent data published by Avenali et al. (PMID: 41124650), indicating that GBA+PD patients should not be withheld from STN-DBS due to genetic status alone. A validation of these findings is planned through a multicenter cohort study, utilizing the infrastructure and clinical core dataset of Retune TRR 295.

P007

Neurophysiological recordings to create personalized deep brain stimulation programs in Parkinson's disease: Brain-recordings Utilized For Field Shaping (BUFFS)

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Background: Modern deep brain stimulation therapy for Parkinson"s disease (PD) may be personalized to neuroanatomy, symptom burden and disease progression. Efforts to automate parameter refinement propose the use of imaging, local field potential electrophysiology and objective symptom metrics. Many of these solutions focus on mono- or bi-polar configuration settings. Approaches to automating and evaluating complex multi-contact configurations based on electrophysiology remain underexplored.

Objective: Compare the clinical outcomes between electrophysiology defined single contact and multi-contact configurations for DBS therapy in PD.

Methods: Six PD patients (2F/4M, post-diagnosis = 12.00 ± 4.58 years; on/off percent change = 46.92 ± 12.32) with bilateral subthalamic nucleus (STN) DBS were recruited. A single and multi-contact configuration derived from measuring beta power (13-30 Hz) was evaluated for each hemisphere. MDS-UPDRS Part III assessments for unilateral symptoms, therapeutic amplitude range, slope of rigidity improvement, quantitative kinematics, and volume of tissue activation overlap within motor-STN were compared between the configuration settings.

Results: Multi-contact configurations resulted in a clinically meaningful significant difference in MDS-UPDRS III compared to single contact (multi-contact = 94.33%, single contact = 73.26%; p = 0.039). No significant differences were observed for TW amplitude, slope in improvement during monopolar review, or individual subgroups of canonical motor symptoms. Finally, multi-contact configurations revealed greater overall with motor STN compared to single contact at minimal amplitude required for maximal rigidity improvement (multi-contact = 34.63%, single contact = 16.32%; p = 0.004).

Conclusion: This study demonstrates that contact selection predicated upon multi-contact beta representation may be an effective method for deriving complex configurations for personalizing STN-DBS in PD.

P008

Real-world clinical and safety outcomes from a prospective, multicenter deep brain stimulation registry of essential tremor patients

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Question

What are the real-world clinical and safety outcomes of deep brain stimulation (DBS) using multiple independent constant current (MICC) directional systems for patients with medication-refractory essential tremor (ET)?

Methods

This ongoing prospective, multicenter, international registry (NCT04032470) was designed to capture real-world outcomes of MICC-based DBS systems (Vercise DBS Systems, Boston Scientific) in ET patients. Up to 500 subjects are planned across 50 sites. Devices include Vercise, Vercise PC, Gevia, and Genus systems with Vercise and Cartesia leads. Baseline and follow-up assessments include tremor severity (TETRAS performance and activities of daily living), quality of life (QUEST summary index), tremor hours per day (QUEST diary), and clinician/subject global impression of change. Safety data are collected per standard of care. Preliminary results are reported for 88 enrolled subjects, 73 of whom were activated, with follow-up through two years.

Results

At baseline, patients had a mean age of 66 years, disease duration of 20 years, and reported an average of 14 hours per day with tremor. Following DBS activation, tremor hours decreased substantially: by six months patients reported 8.3 hours with tremor, falling further to 7.0 hours at one year and 7.6 hours at two years. This corresponds to a mean gain of 7.5 tremor-free hours per day, representing a 46% improvement. Quality of life improved in parallel. The QUEST summary

index increased by 17.4 points at six months, 21.6 points at one year, and 23.4 points at two years, all exceeding the threshold for clinical significance. Tremor severity, measured by TETRAS performance, improved by 41% at six months and remained stable through two years. Activities of daily living showed even greater benefit, with a 60% improvement sustained over the same period. Importantly, both clinicians and patients consistently reported high satisfaction: more than 95% of clinicians and 93% of patients noted improvement at six months, with these rates maintained at one and two years. Safety outcomes were consistent with established DBS practice, with no unexpected adverse events observed.

Conclusion

Preliminary results from this prospective, multicenter registry demonstrate that MICC-based directional DBS systems provide sustained, clinically meaningful improvements in tremor control, quality of life, and daily functioning for ET patients over two years. Patients experienced an average of 7.5 additional tremor-free hours per day, significant reductions in tremor severity, and improved activities of daily living. Both clinicians and patients reported high satisfaction and sustained benefit. These findings support the long-term effectiveness and safety of MICC directional DBS in real-world practice and highlight its role as a durable therapy for essential tremor.

P009

Automated image guided programming algorithm supports clinicians during DBS programming for Parkinson's disease patients

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Question

Can an automated image-guided programming (aIGP) algorithm provide motor outcomes comparable to standard-of-care (SoC) programming in Parkinson's disease (PD) patients, while improving efficiency and supporting clinicians during DBS programming?

Methods

This prospective, multicenter, double-blinded, acute and chronic cross-over study enrolled 15 PD patients (12 male) implanted with bilateral DBS systems targeting the subthalamic nucleus (STN, n=13) or globus pallidus internus (GPi, n=2). All patients had been on stable SoC programs for at least four weeks. The aIGP algorithm (Illumina 3D, Boston Scientific) generated stimulation settings designed to maximize sensorimotor target coverage while minimizing spread to non-target regions. Acute efficacy was assessed using MDS-UPDRS III scores in both medication OFF and ON states. Chronic outcomes were evaluated via patient motor diaries. Clinician optimization of aIGP-derived settings was permitted, and stimulation field models (SFM) were analyzed to compare initial algorithmic settings with final optimized programs.

Results

In the acute setting, aIGP-derived DBS programs significantly improved motor symptoms compared to DBS-off. In the medication-OFF state, initial aIGP stimulation reduced MDS-UPDRS III scores by 39% ($p<0.0001$), a benefit statistically indistinguishable from optimized SoC programming ($p=0.44$). In the medication-ON state, clinician-optimized aIGP settings achieved a 54% improvement versus DBS-off ($p<0.0001$), again comparable to SoC ($p=0.33$). Chronic evaluation via motor diaries revealed that aIGP-guided programs provided an average of 25 additional minutes of ON time per day and 58 fewer minutes of ON time with dyskinesias compared to SoC, although group-level differences did not reach statistical significance. Importantly, stimulation field model analysis showed that clinician adjustments to aIGP settings were minimal, with a high degree of overlap (DICE coefficient 0.83 ± 0.16), underscoring the accuracy of the algorithm in identifying clinically effective stimulation parameters. Safety outcomes were consistent with established DBS practice, with no unexpected adverse events reported.

Conclusion

Automated image-guided programming achieved motor outcomes comparable to optimized standard-of-care programming in PD patients, both acutely and chronically. The algorithm provided accurate initial settings requiring only minor clinician adjustments, reduced dyskinesia burden, and supported durable motor benefits. By rapidly synthesizing patient-specific anatomical data to generate optimal stimulation fields, aIGP offers a practical tool to streamline DBS

programming, reduce patient burden, and enhance clinical efficiency. These findings highlight the potential of automated programming to complement clinician expertise and improve long-term management of Parkinson's disease with DBS.

P010

The Vercise Registry: three-year outcomes of the so far largest registry of directional deep brain stimulation of the subthalamic nucleus for Parkinson's disease.

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Question

Do directional deep brain stimulation (DBS) systems with multiple independent current control (MICC) improve motor function and quality of life in patients with Parkinson"s disease (PD) under real-world clinical practice conditions?

Methods

This ongoing, prospective, multicenter international registry was designed to collect real-world outcomes of MICC-based DBS systems (Vercise, Boston Scientific) using directional leads (Vercise Cartesia). Up to 1,500 patients are planned across 70 sites. Key assessments include the Movement Disorder Society–Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS III, meds OFF), Parkinson"s Disease Questionnaire (PDQ-39), Clinical Global Impression of Change (CGI, subject and clinician), and Schwab and England Scale (SE). Safety was monitored through adverse event reporting. Preliminary results are reported for 815 patients implanted with directional leads, with follow-up extending to two years.

Results

At baseline, patients had a mean age of 60.9 years, mean disease duration of 10.3 years, and mean MDS-UPDRS III score of 46.4 in the medication-OFF condition. Following implantation, motor function improved significantly, with MDS-UPDRS III scores reduced by 35% ($p<0.0001$), and this benefit was sustained up to two years post-implant. Quality of life also improved: PDQ-39 summary index scores demonstrated significant gains at one year ($p<0.0001$), with a mean change of 4.8 points, exceeding the minimal clinically important difference threshold of 4.7. Importantly, these improvements were maintained at two years despite the expected decline in quality of life due to disease progression. Clinical Global Impression of Change assessments revealed that more than 80% of patients and 90% of clinicians reported sustained improvement at two years. Safety outcomes were favorable, with no unanticipated adverse events, lead fractures, or breakages reported. The overall safety profile was consistent with established DBS practice.

Conclusion

Preliminary results from this large, ongoing registry demonstrate that directional DBS systems with MICC provide sustained improvements in motor function and quality of life for patients with Parkinson's disease in real-world practice. Benefits were maintained for up to two years, with high

satisfaction reported by both patients and clinicians. The directional lead design expands the therapeutic window, enhances programming flexibility, and maintains an acceptable safety profile. These findings support the clinical utility of next-generation directional DBS systems as durable, patient-tailored therapies for Parkinson's disease.

P011

Varying patterns of association between cortical large-scale networks and subthalamic nucleus activity in Parkinson's disease

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Question

The rising prevalence of Parkinson's disease has created an urgent need for brain activity markers guiding diagnosis and treatment strategies. While abnormal basal ganglia activity is known to synchronise with specific cortical regions, the temporal dynamics and cortical network architecture of this coupling remain unclear.

Methods

To address this, we analysed simultaneous magnetoencephalography (MEG) and subthalamic nucleus (STN) local field potential recordings from 27 individuals with Parkinson's disease, both on and off dopaminergic medication. Applying a time-delay embedded Hidden Markov Model to the MEG data, we identified dynamic large-scale cortical networks. For each network, we then quantified STN-cortical coupling and the temporal overlap between STN beta bursts and cortical network activations.

Results

STN-supplementary motor area synchrony increased during visits to the sensorimotor network and the posterior default mode network (DMN). The former was further associated with power in the 9.5-23 Hz range and beta bursts in the STN, and the latter with power in the 5-16.5 Hz range in the STN. Dopaminergic medication preferentially reduced STN beta power in networks lacking enhanced STN-motor synchrony.

Conclusions

These findings suggest that large-scale cortical networks show varying patterns of association with STN activity, and that the sensorimotor and posterior DMN may provide temporal windows into subcortical processing. Such network signatures in non-invasive recordings offer promising candidates for markers of subcortical-cortical activity in Parkinson's disease and may provide targets for treatment strategies, including closed-loop stimulation.

P012

Effects of 30 Hz subthalamic nucleus deep brain stimulation on cortical oscillations and response inhibition

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Introduction: Patients with Parkinson"s disease (PD) typically show strong beta-band oscillations in the subthalamic nucleus (STN) and other parts of the basal ganglia, which can be modulated by deep brain stimulation (DBS). High-frequency DBS (> 100 Hz) reduces STN beta activity and correlates with motor improvement, whereas low-frequency stimulation (10–30 Hz) slows down movement, suggesting a causal role of beta oscillations for behavior. Beyond motor control, the STN also contributes to cognitive processes such as response inhibition and has been described as a "brake" in response control. At the electrophysiological level, this brake-like function may be mediated by beta oscillations within a fronto-subthalamic network.

Question: This study aimed to clarify the effect of 30 Hz STN-DBS on response inhibition and the underlying neural dynamics.

Methods: 20 PD patients with STN DBS implants underwent magnetoencephalography (MEG) recordings. Continuous bipolar DBS at 30 Hz was applied to the left STN (DBS ON) or switched off (DBS OFF). During both conditions, patients performed a cued Go/NoGo task in which a preparatory cue indicated whether the upcoming stimulus would require a button press (Go) or response withholding (NoGo).

Results: Behavioural analyses revealed a robust effect of cue–stimulus congruency: incongruent trials exhibited longer reaction times and higher commission error rates than congruent trials. On electrophysiological level, we did not find an effect of congruency but observed that Go trials showed a longer and stronger peri-movement beta suppression than NoGo trials.

Beta-band DBS boosted baseline beta power and selectively influenced Go trials. In the DBS ON condition, patients showed slower reaction times and a stronger beta suppression in the left sensorimotor cortex, compared to DBS OFF. The behavioural and the electrophysiological effect correlated, i.e. longer reaction times were associated with a steeper beta suppression. Commission error rates were unaffected by DBS.

Conclusion: Our results suggest that beta power needs to fall below a certain threshold before a response can be initiated. 30 Hz STN DBS appears to delay this process by elevating the baseline level of beta power. Interestingly, this artificial slowing effect did not go along with a reduction of commission errors, differentiating it from voluntary slowing in situations requiring caution.

P013

Improving DBS treatment response-prediction in cervical dystonia by combining neurophysiological and neuroimaging markers

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Introduction: Deep brain stimulation (DBS) is an established therapy for cervical dystonia (CD), yet programming remains challenging due to delayed therapeutic responses and complex network effects. fMRI-based connectivity of active contacts explains some variability in treatment response, but current models do not account for differences that arise when stimulation parameters are changed at the same location. DBS can modulate distinct oscillatory frequency bands in opposing directions—for example, increasing anti-kinetic beta while suppressing pro-kinetic theta activity—potentially contributing to variable benefit and side effects such as bradykinesia. We therefore propose that integrating neurophysiological markers with neuroimaging-derived predictors may improve DBS response modeling and support individualized programming.

Goals: To improve prediction of clinical response to pallidal DBS in CD by identifying network dynamics underlying therapeutic benefit and stimulation-induced bradykinesia, and by testing whether combining MEG-derived oscillatory features with fMRI connectivity increases explained variance in treatment outcomes.

Methods: We recruited 25 patients with CD receiving pallidal DBS. Symptom severity was assessed with the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) in DBS ON and OFF states. Whole-head MEG was recorded during randomized ON/OFF stimulation, and source-reconstructed multispectral oscillatory features were extracted as predictors of clinical response. Electrodes were localized, and volumes of tissue activated (VTAs) were computed. Connectivity profiles of each VTA were estimated using a normative resting-state fMRI connectome. For each patient, similarity between their VTA connectivity and the optimal CD DBS-response network (Horn et al., 2022) was calculated. The same framework was used to map network features associated with stimulation-induced movement slowing based on kinematic assessments. Finally, we aim to test whether combining neurophysiological and neuroimaging-derived network features improves prediction of clinical outcomes compared with either modality alone.

Results: DBS produced significant improvement in TWSTRS scores and significant movement slowing relative to OFF stimulation. Connectivity associated with clinical improvement replicated prior findings emphasizing the precentral gyrus, and additionally highlighted the dorsolateral premotor and dorsolateral prefrontal cortices. Connectivity linked to stimulation-induced bradykinesia was dominated by bilateral supplementary motor area involvement, consistent with networks implicated in bradykinesia in Parkinson"s disease. Prediction analyses using oscillatory, connectivity-based, and combined models are underway; we expect multimodal integration to enhance outcome prediction.

Summary: In 25 patients with CD, DBS improved dystonia severity but induced measurable slowing of movement. Networks supporting benefit involved precentral, dorsolateral premotor, and dorsolateral prefrontal regions, while bradykinesia was associated with supplementary motor areas. Ongoing multimodal modeling aims to establish integrated neurophysiological–connectivity markers as a foundation for precision DBS programming.

P014

Reduced white matter integrity in the left STN-vmPFC pathway is associated with pre-surgical apathy in PD

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Question

Apathy is a common and disabling non-motor symptom in Parkinson"s disease (PD) that can reduce the therapeutic benefit of subthalamic nucleus deep brain stimulation (STN-DBS), Zoon *et al.,* 2021. Our previous work (de Bruin *et al.,* 2025) demonstrated that co-stimulation of the left ventromedial prefrontal cortex (vmPFC) can compensate for apathy following levodopa withdrawal in PD patients treated with STN-DBS. This finding suggests a functional interplay between the STN and vmPFC, highlighting the importance of the limbic-cortical–basal ganglia circuitry in modulating apathy. Building on these findings, we investigated the presurgical white matter integrity of the STN-vmPFC pathway and a potential structural correlate of apathy pre DBS.

Methods

We examined T1-weighted and diffusion tensor imaging (DTI) data from 119 PD patients undergoing STN-DBS. Based on pre-surgical Starkstein Apathy Scale (SAS) scores, patients were classified as apathetic (SAS ≥ 14; N = 67) or non-apathetic (N = 52). Data preprocessing followed the standard neurosurgical workflow. Skeletonized fractional anisotropy (FA) maps were generated using FSL"s Tract-Based Spatial Statistics (TBSS) pipeline. Voxel-wise comparisons were performed with FSL"s *randomise* tool, using threshold-free cluster enhancement (TFCE) and 5,000 permutations for multiple comparisons correction. Analyses were limited to a bilateral STN–vmPFC mask derived from probabilistic tractography of a previously published cohort (N = 28), de Bruin *et al.,* 2025, combining tracts from both STN-to-vmPFC and vmPFC-to-STN directions.

Results

A significant cluster (74 voxels) in the left STN–vmPFC pathway showed reduced FA in the apathetic group compared to the non-apathetic group (TFCE-corrected peak p = 0.0294), suggesting decreased white matter integrity.

Conclusion

Pre-surgical apathy in PD is associated with reduced white matter integrity in the left STN–vmPFC pathway. These results align with prior findings showing that DBS targeting this pathway can improve apathy, particularly during medication reduction. This study extends previous work by identifying a pre-stimulation structural correlate of apathy. Incorporating white matter integrity markers into pre-surgical assessments may help better predict and optimize apathy-related outcomes following DBS.

P015

Effects of cognitive-load on motor performance are differentially modulated by deep brain stimulation

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Multitasking situations that require the simultaneous performance of motor and cognitive tasks can increase the debilitating motor symptoms of patients with Parkinson"s disease (PD). While deep brain stimulation (DBS) improves motor symptoms like bradykinesia, its influence on goal-directed movements during multitasking is unclear. To investigate this, we used a motor-cognitive dual-task paradigm consisting of a custom gamified reaching task and a serial subtraction task with low and high load (subtracting by one or seven, respectively).

Twenty-two PD patients with DBS performed the tasks under single- and dual-task conditions with stimulation on and off. Overall motor and cognitive performance were assessed by the number of targets reached and correct subtractions. For a more detailed quantification of performance, temporal and spatial kinematic features were extracted for each movement, and the audio signal was analyzed using voice-activation detection. Detected speech was aligned to each reaching movement, allowing to examine the underlying behavioral strategies during multitasking. Linear mixed-effects models assessed the effects of cognitive load and stimulation on overall behavioural performance, movement kinematics, and speech-movement coupling.

Our results show that overall motor and cognitive performance decreased under dual-tasking conditions with low load and that this decline was amplified under high load. DBS improved motor performance across conditions without affecting cognitive performance. Kinematic analyses showed that high load slowed movement initiation and execution, mainly through prolonged deceleration time and reduced peak velocity, indicating greater reliance on feedback-driven motor control. DBS had the opposite effect, shortening reaction and deceleration times and increasing peak velocity, leading to a more efficient feedforward control. The dual-task strategy analysis revealed that under high cognitive load, patients reduced speech during demanding movement phases (i.e., when moving faster or approaching the target), thus adopting a "motor-first" strategy. DBS attenuated this speech suppression, leading to a general improvement in patients" capacity to engage in motor and cognitive processing during multitasking.

Together, these findings highlight how cognitive load and DBS differentially modulate dual-task performance and reveal a mechanistic interaction between attentional control and motor execution that shapes the allocation of cognitive-motor resources during multitasking. Finally, this multimodal framework can serve as a basis for future efforts to link complex behavioural outcomes to neural correlates to advance state-dependent and adaptive DBS approaches.

P016

Paradoxical targeting: overlap between optimal and gait-impairment stimulation sites in essential tremor

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Background: Deep brain stimulation (DBS) is an effective treatment for medication-refractory essential tremor (ET), typically targeting the ventral intermediate nucleus (VIM), posterior subthalamic area (PSA), or dentato-rubro-thalamic tract (DRTT). However, up to one-third of patients develop gait impairment, possibly due to stimulation of unintended or overlapping pathways. This study investigated stimulation areas specifically linked to gait impairment.

Methods: We retrospectively analyzed clinical data from 40 ET patients (80 hemispheres) treated with DBS. Tremor improvement was assessed with the Fahn-Tolosa-Marin (FTM) tremor rating scale and gait impairment was assessed with the first item of the Scale for Assessment and Rating of Ataxia (SARA). Volume of tissue activated (VTA) were modeled using Lead-DBS, and voxel-wise associations were examined with Spearman-rank correlations and Wilcoxon signed-rank test, from which a heatmap was generated. Mixed effects regression was used to evaluate clinical and stimulation-related covariates.

Results: Regions linked to both tremor reduction and gait impairment overlapped with the VIM, PSA, and DRTT ($p<0.05$, FDR corrected). No distinct region was exclusively associated with gait impairment. Stimulation location was not significantly related to postoperative gait outcome ($p > 0.05$). Patients with more severe baseline gait ataxia were more likely to deteriorate, although this association was not significant after bootstrapping.

Conclusion: Our findings suggest that DBS may simultaneously engage therapeutic and adverse pathways within the DRTT. A potential somatotopic organization of the cortico-thalamo-cerebellar (CTC) network may underlie this overlap, though it could not be disentangled in this study. Future work integrating functional connectivity and tractography may help delineate specific pathways, enabling more precise targeting and improved outcomes for ET patients.

P017

Tuning evoked resonant activity to optimize the neuronal impact of DBS in downstream structures

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Introduction

Deep Brain Stimulation (DBS) of the subthalamic nucleus (STN) provides symptomatic relief in Parkinsons Disease (PD). Evoked resonant neural activity (ERNA), elicited shortly after DBS pulses, has been shown to predict therapeutic efficacy (Sinclair et al., Annals of Neurology, 2018; Wiest et al., Neurobiol. Dis, 2020) and has been suggested to be reflective of the neuronal circuit intervention that underlies its local mechanism of action (Steiner et al. 2024; Nature Communications). However, neuronal recordings concurrent to the appreciation of ERNA have been limited to the site of stimulation, limiting interpretability of the circuit intervention it provides throughout the basal ganglia.

Goals

To develop a paradigm to provide single neuron physiology data to tailor intermittent burst stimulation paradigms.

Materials & Methods

Here, we present a novel a dual-site stimulation and recording strategy implemented during DBS implantation surgery in PD patients that allows for parallel recording of ERNA at the stimulation site with concurrent ERNA and single unit recordings in a downstream structure. Specifically, we apply intermittend burst macro-contact stimulation to the STN while recording ERNA from STN and neuronal activity for the Substantia Nigra pars reticulata (SNr).

Results

We present data that allows us to directly appreciate the neuronal impact of evoked resonant activity while monitoring the circuit invention of subthalamic DBS at two sites in parallel. We leverage our setup to study novel paradigms of intermittent patterned stimulation and find that intermittent burst paradigms that optimize in ERNA entrainment also produce most pronounced neuronal inhibition in downstream structures.

Summary

Our findings suggest that single-cell readouts of subthalamic DBS at downstream structures can not only help us gain insight into the single cell mechanism of subthalamic DBS, but may provide critical input for physiology-driven for the refinement of DBS strategies.

P018

Tracking the role of the subthalamo-temporal network in speech: a DBS-EEG study

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Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment for motor symptoms in Parkinson"s disease. However, stimulation-related dysarthria can limit its tolerability, and the underlying mechanism remains unclear. Cortico-subthalamic alpha connectivity may support speech initiation and error correction (1,2). Local field potential (LFP) streaming from Medtronic Percept® in chronically implanted patients, combined with EEG, enables monitoring of the acute effects of DBS on this network.

Goal

To determine whether STN–cortical alpha connectivity is modulated during speech initiation or correction of perceived phonetic errors, and whether DBS acutely disrupts this network during these processes.

Materials and Methods

Twenty patients with Parkinson"s disease and STN DBS (Medtronic Percept, 20/20 Sensight leads), off medication and six months post-implantation, were recruited. Each underwent LFP streaming and 64-channel EEG co-recording. Signals were acquired during resting state (5 minutes) and during an altered auditory feedback task, both OFF and ON DBS (3). The task comprised two sets of 100 vocalisation trials of the vowel /æ/: 50 unperturbed and 50 perturbed by pitch (F0) or first formant (F1) shifts (indicative of tongue height/mouth opening) (separate sessions; upward shift: 100 cents (a semitone) for F0, 30% frequency shift for F1). STN–cortical alpha connectivity was quantified as alpha envelope correlation (αEnv) between synchronised STN LFPs and source-level cortical signals during resting state, unperturbed trials, and perturbed trials. Connectivity changes induced by vocalisation and feedback were compared between OFF and ON DBS using a cluster-based permutation approach. Task performance was analysed with ANOVA.

Results

Participants showed the expected downward pitch (F0) compensation, which did not differ between ON and OFF DBS, but no F1 compensation. Vocalisation reduced STN–opercular αEnv and increased STN–premotor αEnv, whereas perception of an F1 error increased STN–opercular αEnv. DBS significantly attenuated these αEnv modulations. F0 perturbation did not affect αEnv.

Summary

Vocalisation and perception of F1 errors modulate STN–opercular and STN–premotor alpha connectivity. DBS acutely disrupts these dynamics, suggesting that its effects on speech may partly result from interference with this network.

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P019

Investigating deep brain stimulation effects on pallido-cortical interactions in patients with dystonia, an EEG-LFP study

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Introduction

Globus pallidus internus (GPi) deep brain stimulation (DBS) is an established treatment for dystonia. The development of stimulators capable of local field potential (LFP) streaming, such as the Medtronic Percept®, enables monitoring of DBS effects on GPi–cortical connectivity in chronically implanted patients, well beyond the microlesion period and after DBS-induced plasticity has stabilised (1,2). Isolating the acute impact of DBS on dystonia networks may support the development of neurophysiology-guided stimulation settings.

Goal

We aimed to determine the effect of DBS on GPi–cortical connectivity during resting state and movement in chronically implanted dystonia patients.

Materials and Methods

We studied 11 patients with dystonia (3 cervical dystonia, 2 myoclonus dystonia, 6 generalised dystonia) with chronic GPi-DBS implants (8 with "3389" leads, 3 with "Sensight" leads). Patients underwent 64-channel EEG and LFP recordings during resting state (RS), active and passive hand and foot movements, both OFF and ON DBS (30 minutes washout). Connectivity between GPi and cortex was computed at the source level using imaginary coherence for RS and pre- and post-movement phases (five conditions in total). Connectivity maps for each canonical band (theta, alpha, low-beta, high-beta, gamma) were entered into a general linear model to identify significant frequency bands expressed in each condition. Significant maps were then used as regions of interest (ROIs) for further analysis of DBS state and task phase interactions via a linear mixed-effects model. Additionally, we examined power spectral density (PSD) in the ON condition for DBS-entrained gamma and localised GPi–cortical coherence at the entrainment frequency using beamforming.

Results

Significant GPi–cortical connectivity was observed in the theta band across all five conditions at bilateral frontal, temporal, and parietal regions, and in the alpha band only during resting state and passive movement at ipsilateral opercular, sensorimotor, and angular areas. ROI analysis revealed a significant DBS-induced increase in theta connectivity at RS and a significant reduction in alpha connectivity irrespective of task. No interaction between lead type and coherence levels was found.

In cases with gamma entrainment, resting coherence at half the stimulation frequency was localised to ipsilateral motor areas.

Summary

Our findings demonstrate that GPi-DBS in dystonia patients acutely modulates GPi–cortical connectivity in the alpha and theta bands. Furthermore, we confirm the loss of alpha coherence between basal ganglia structures and temporo-opercular cortex during active movement (3). Acknowledging that the interval between OFF and ON DBS was short, these results may nevertheless inform neurophysiology-guided stimulation strategies in dystonia.

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P020

Subthalamic and nigral activity differ in GBA and idiopathic Parkinson's disease

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Introduction: Parkinson"s Disease (PD) is characterised by alterations in subthalamic neural activity, which can be targeted with deep brain stimulation (DBS). Mutations in the GBA gene influence PD symptomatology and may impact the clinical outcome of DBS. We hypothesised that GBA mutations alter subthalamic neural activity and contribute to distinct clinical features.

Goals: To investigate the neurophysiological basis of PD in patients with and without GBA mutations.

Materials and methods: We compared the neural activity of idiopathic and GBA-mutated PD patients undergoing DBS surgery. We analysed intraoperative microelectrode recordings from 14 PD patients with pathogenic GBA mutations and compared them with 28 genetically negative PD patients. We assessed spiking activity and oscillations in neurons of the subthalamic nucleus (STN) and the substantia nigra (SNr).

Results: GBA-mutated patients showed distinctive STN neural activity. In GBA-mutated patients, bursty STN neurons exhibited a higher firing rate and an increased oscillatory activity in the high-beta range (i.e., 21–35 Hz) compared to idiopathic PD patients. These neural activity changes correlated with DBS clinical outcome. SNr neural activity also differed between GBA-mutated and idiopathic PD patients.

Summary: Our findings provide evidence that GBA mutations impact STN neurophysiological activity and differentiate GBA-mutated and idiopathic PD patients, possibly explaining their clinical differences.

P021

Neural signatures of nucleus accumbens stimulation in children with severe, refractory self-injurious behaviour

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Objective

Self-injurious behaviour (SiB) is a phenomenon that occurs in some children with profound autism. Mechanistically, cortico-striatal networks involving the nucleus accumbens (NAcc) are implicated in restricted and repetitive behaviours similar to SiB in autism spectrum disorder. Therefore, deep brain stimulation (DBS) targeting the NAcc has been implemented in attempt to reduce the frequency of SiB. Stimulation-evoked potentials (SeP) can be useful physiological biomarkers to study network connections. These are thought to arise from concurrent activations of population-level synaptic currents. Therefore, SePs can be used to identify various clusters of afferent inputs, allowing for network mapping in humans. Currently, NAcc structural connectivity is virtually unexplored in humans, and we lack a concrete understanding of its role in SiB pathophysiology and DBS benefit. Therefore, in this work, we conducted a thorough investigation of NAcc SeP profiles in children with SiB.

Methods

Intracranial recordings were taken using a Ben-Gun array in 7 children undergoing NAcc-DBS surgery. At every millimeter along the surgical trajectory, stimulation was delivered from one macroelectrode at varying frequencies, while responses were recorded in a second macroelectrode 2 mm away. Following pulses, compound evoked signatures were disaggregated and individually fit using a specialized function estimating population-level synaptic currents. For each isolated component, we investigated its morphology and dependencies on time and stimulation frequency. We then reconstructed surgical trajectories within patient imaging and normalized stimulation sites to a template brain in order to visualize spatial distributions of individual fields. Next, we conducted a thorough review of the preclinical literature related to post-synaptic potentials sourced in different striatal networks. These waveforms were compared to our recordings in humans to identify similarities in evoked responses and thus, identify possible network inputs to the human NAcc. From this, we generated a structural network model of the NAcc that may produce the SeP responses we recorded in humans.

Results

We identified 4 distinct SeP components occurring with NAcc stimulation. Each varied in its characteristic morphology and latency depending on time, location, and stimulation frequency. These were positive inflections of potential at 2, 5, and 10 ms peak latencies and a broad negative inflection with an 8-10 ms trough latency. The positive peaks of extracellular potential are hypothesized to reflect aggregate inhibitory inputs as the synaptic currents are hyperpolarizing the intracellular space. Preclinical comparisons corroborate the shortest latency responses (2 and 5 ms) as potentially arising from inhibitory fast-spiking interneurons and striatal recurrent collateral activations, respectively. The negative inflection may emerge from aggregate glutamatergic action through the activation of inputs from mostly the prefrontal cortex, but also hippocampus, thalamus, etc. These excitations would then produce a feedforward reactivation of inhibitory neurons, generating the latter positive peak (10 ms latency).

Conclusions

Distinct SeP phenomena were identified within the NAcc. These may provide insights into the

structural organization of human NAcc afferent pathways and can be coupled with clinical observations to optimize DBS targeting and stimulation programming in the striatum for SiB.

P022

The structural and functional network architecture of globus pallidus stimulation

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Question

To characterize network architectures, synaptic dynamics, and spatial organization of stimulation-evoked responses of the globus pallidus (GP) in Parkinson"s disease, and to establish how these signatures relate to the mechanistic underpinnings of therapeutic efficacy.

Methods

In people with Parkinson's, we recorded stimulation responses every millimetre along the surgical trajectory during microelectrode procedures. Evoked responses were stratified into classes based on waveform morphology, and temporal dynamics and single-neuron correlates were characterized for these classes. Evoked responses were also mapped across the spatial extent of GP and correlated with UPDRS outcome. Finally, a biophysical conductance-based model was constructed, which considered anatomically constrained circuit architectures involving striatum, GP internus/externus (GPi/e), and subthalamic nucleus (STN) engaged by stimulation, and functional properties of the engaged synapses modeled via experimentally informed short-term plasticity.

Results

We: (i) identified five distinct classes of stimulation-evoked responses within the GP (striatum-mediated, GPe-mediated, ERNA (evoked recurrent STN/GPe-mediated neural activity), and two mixed striatum-linked variants); (ii) used a computational model of the basal ganglia to infer plausible anatomical circuit architectures and functional properties underlying each class; (iii) observed class-specific inter-stimulus firing-rate dynamics; (iv) demonstrated that while the isolated striatal, GPe, and ERNA responses exhibit unique temporal characteristics, features remain relatively consistent when those pathways appear within mixed responses; (v) mapped the spatial distribution of all five classes across the GP, revealing regions of both segregation and overlap; and (vi) related the spatial patterns to clinical targeting, showing the potential relevance of ERNA and striatum-mediated responses with clinical benefit.

Conclusion

Our framework identifies putative network architectures engaged by GPi-DBS, defines the synaptic dynamics that govern pathway-specific effects, elucidates the anatomical organization of the basal ganglia circuits, and links activation patterns to clinical outcomes. This provides a foundation for pathway-specific targeting and synaptic-level tuning of basal ganglia circuits.

P023

Algorithm-based compared to visual contact selection using pseudomonopolar LFP recordings in STN-DBS for Parkinson's disease

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Introduction: Subcortical local field potentials, particularly activity in the beta frequency range (13-30 Hz), may guide the selection of effective deep brain stimulation parameters in Parkinson's disease. Pseudomonopolar recordings (BrainSense Electrode Identifier) with the Percept PC or RC system are accompanied by an on-board algorithm that suggests potential stimulation contacts.

Goals: We aimed to compare contact selection based on the on-board algorithm with contact selection based on visual assessment of the corresponding power spectral densities (PSDs).

Materials & Methods: We conducted a single-center retrospective study. Pseudomonopolar recordings were obtained from 51 patients (n = 97 hemispheres) implanted with a Medtronic Percept PC or RC system. Recordings were performed on average 6.8 years after electrode implantation (SD 5.3 years). The neurologist who visually evaluated the PSDs was blinded to both the algorithmic output and the clinically optimized contact. Recordings were included for analysis only when both algorithmic and visual assessments of PSDs provided spatially discriminative information across stimulation contacts. For each hemisphere, contacts identified by the algorithm and those identified by visual assessment of the PSDs were compared with the purely clinically optimized contact configuration. The proportion of hemispheres with an overlapping configuration was calculated for both methods. Proportions were compared using McNemar's test, as the two contact selection methods were applied to the same hemispheres, resulting in paired data. A chi-square test was not appropriate due to this dependency. Statistical significance was set at a threshold of 0.05.

Results: 43 hemispheres were included. 54 hemispheres were excluded for the following reasons: unreliable or artefactual spectra as per visual assessment (n = 20), absent beta peak as per visual assessment (n = 15), spatially inseparable beta activity as per visual assessment (n = 5), spatially inseparable beta activity as per algorithmic assessment (n = 14). Algorithm-guided contact selections overlapped with clinically determined contacts in 30 of 43 hemispheres (69.8%). Visual assessment-guided contact selections overlapped with clinically determined contacts in 40 of 43 hemispheres (93.0%). The difference between these proportions was statistically significant (p = 0.006). We investigated potential bias and found that visual assessment identified more possible stimulation contacts than the algorithm. Specifically, visual assessment identified four potential contacts in 19 hemispheres (44.2%), compared with none (0%) by the algorithm. Three potential contacts were identified by visual assessment and the algorithm in 10 (23.3%) and 7 hemispheres (16.3%), respectively.

Summary: When using pseudomonopolar LFP recordings in STN-DBS for Parkinson's disease to select a stimulation contact, visual assessment of PSDs may have advantages over algorithm-based selection. However, visual assessment may be affected by overestimation bias. Prospective studies are needed to further evaluate the clinical utility of pseudomonopolar recordings.

P024

Cortical oscillations during different behavioral states of levodopa-induced dyskinesia in OPM-MEG

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The majority of Parkinson"s disease (PD) patients develops levodopa-induced dyskinesia (LID), characterized by involuntary movements that impair quality of life as a side effect of dopaminergic treatment akinetic-rigid symptoms. LID is associated with impaired cortical synaptic plasticity and pathological hyperactivity within the cortico-basal ganglia network. Based on invasive cortico-subthalamic recordings, we showed in previous work the distinct oscillatory patterns in multiple spectral bands between movement-dependent dyskinetic sub states. However, the full cortical oscillatory dynamics remain unknown, as well as the oscillatory patterns during the behavioral sub state of motor suppression during LID. Here, we applied state-of-the-art optical pumped magneto-encephalography (OPM) to differentiate whole-brain cortical oscillations during movement execution, suppression, and rest in LID, to unravel the cortex" role in hyperdopaminergic motor (dis)-inhibition and to elucidate the behavioral relevance of cortical LID biomarkers.

PD patients receiving dopaminergic replacement medication and with a positive LID history performed repetitive resting state and a modified go/no-go task recording. Recordings were performed starting in a dopaminergic wearing-off state and, following a supra-treshold dosage of fast-acting levodopa, were continued until dyskinesia onset. OPM-compatible accelerometer and EMG recordings could successfully differentiate between behavioral states of movement execution, movement suppression, and rest without motor activity that were provoked during the go/no-go task. Prefrontal, SMA, and sensorimotor cortical areas showed oscillatory changes in theta/alpha, beta, and gamma bands that were movement-dependent and differed between non-dyskinetic and dyskinetic movement. Voluntary movement suppression during LID demonstrated an increased state of motor inhibition, with a lower success-rate leading to involuntary movements.

Understanding the role of the cortex in the hyperdopaminergic states of movement execution and inhibition improves our understanding of cortico-basal-ganglia motor inhibition networks and can attribute to more robust biomarker development for adaptive neuromodulation.

P025

Implementing an intraoperative experimental paradigm to record and manipulate STN efferences in patients with Parkinson's disease

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Introduction

Despite recent advances in understanding deep brain stimulation (DBS) mechanisms at the single-neuron level (Neumann*, Steiner*, Milosevic; Brain, 2023), the neuronal impact of recruiting STN efferent (outgoing fibers) pathways remains contentious. In rodent models, activation of subthalamic nucleus (STN) efferents has been identified as a driver of DBS-induced network effects (Ji et al 2024; *Cell reports*), and early human studies reported fast excitatory transmission via monosynaptic STN–subtanstia nigra pars reticulata (SNr) projections, while also suggesting global suppression of firing rates (Galati et al., 2006, *EJN*; Maltête et al., 2007, *J Neurophysiol*).

Goals

To clarify the cellular impact induced by STN efferent recruitment, providing prerequisites for the translation of novel cellular-physiology driven stimulation paradigms from preclinical to human DBS.

Materials & Methods

We developed a novel intraoperative stimulation–recording paradigm enabling simultaneous single-unit microelectrode recordings from the substantia nigra pars reticulata (SNr) and patterned stimulation delivered through the STN macro-contact during DBS implantation surgery in Parkinsons disease (PD) patients. For each identified SNr neuron, low-frequency (LFS, 10 Hz) and high-frequency stimulation (HFS, 100 Hz) in the STN at amplitudes of 1, 2, and 3 mA was applied. SNr firing rates were extracted and interstimulus interval (ISI) histograms were analysed in the spatial domain considering stimulation and recording sites in MNI space.

Results

Across the recorded SNr neurons from PD patients, ISI analyses revealed significant firing rate increases within the early post-stimulus window, consistent with fast excitatory input from monosynaptic STN–SNr projections. A subset of neurons instead showed early poststimulus inhibition, suggesting heterogeneous microcircuit responses to STN activation. Under LFS, firing rates remained stable across amplitudes, with no significant group differences. In contrast, HFS produced a clear amplitude-dependent suppression. Relative to 1 mA, firing was significantly reduced at 2 mA and further suppressed at 3 mA. Our topographical analysis suggests that stimulation parameters critically define the subset of fibers recruited thereby imposing topographically organized impact on neuronal firing in downstream structures.

Summary

Together, these findings demonstrate that subthalamic DBS exerts stimulation intensity- and frequency- dependent, spatially organized response topologies in downstream structures. These insights may establish important prerequisites for the development of cellular-physiology driven stimulation paradigms in PD patients.

P026

Deep brain stimulation in Parkinson's disease: investigating apathy and motivation

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Introduction: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has been shown to effectively alleviate motor symptoms in Parkinson's disease. However, the disease is also associated with a range of non-motor symptoms. As STN-DBS itself can induce or worsen non-motor symptoms, a better understanding of the underlying networks and how they are influenced by DBS is needed to improve symptom management. This study aims to investigate apathy and motivation in patients with Parkinson's disease.

Methods: 14 patients with Parkinson's disease completed the Monetary Incentive Delay task, a behavioural task assessing reward and loss anticipation and outcome processing. The task was completed twice, once with DBS off and once with DBS on. Simultaneous subthalamic local field potential and electroencephalography data was collected during the task, allowing us to investigate subcortical and cortical activity during reward/loss anticipation and outcome processing, as well as potential stimulation-induced changes.

Results: Behavioural analyses are showing reaction times to be significantly faster in reward trials compared to neutral trials ($p = 0.003$). Reaction times in loss trials, relative neutral trials, are following the same trend ($p = 0.071$). There is no significant difference in reaction times off and on DBS ($p > 0.05$).

Discussion: Preliminary findings suggest that behaviour is modulated by potential reward and loss, with greater incentive to respond faster during reward/loss trials, regardless of DBS. Analyses of the electrophysiological data, investigating differences in anticipation and processing of reward and loss, is ongoing.

P027

Neural microstates in the cortico-subthalamic system differentiate physiological movement from Levodopa-induced dyskinesia in Parkinson's disease

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Levodopa remains the most effective symptomatic therapy for Parkinson"s disease (PD), yet its long-term use can trigger involuntary hyperkinetic movements known as levodopa-induced dyskinesia (LID). Neural oscillations representing LID as a global state are currently used as input signals for adaptive neuromodulation. However, the pathophysiological neural mechanisms associated with single dyskinetic movements remains poorly understood. Differentiating physiological motor execution from dyskinetic movements may increase the robustness of potential biomarkers.

Here, we recorded local field potentials (LFP) from the subthalamic nucleus (STN) and electrocorticograms (ECoG) simultaneously during a self-paced hand-tapping task performed by PD patients in MED-OFF, MED-ON, and LID states. The recordings were segmented into pre-, event-, and post-movement epochs. Power spectral density (PSD) of both cortex and STN was estimated using Welch"s method. Functional connectivity was quantified with weighted Phase Lag Index (wPLI), and directed coupling was assessed using net time-reversed Granger causality (net-TRGC).

Dopaminergic treatment consistently suppressed STN beta power and enhanced top-down cortical drive, as shown by a stronger cortical bias in the net-TRGC. During dyskinetic movement, gamma power was increased in the STN during all movement periods, but only in event and post-event periods in the cortex. Functional connectivity between the STN and cortex in the gamma range markedly increased during LID movements, most prominently during the event and post-event phases, consistent with a state-dependent microcircuit. In contrast, theta connectivity showed a pronounced dissociation: although elevated before and after movement, it transiently decreases during dyskinetic movements. The cortical drive, measured by the net-TRGC, decreased during LID and shifted towards a subcortical drive, similar to what was seen in the MED-OFF state.

Together, these findings demonstrate that dyskinesia is defined by movement-phase dependent changes in oscillatory power and connectivity. The results suggest that dyskinesia is not a single global state (so-called macrostate) but consists of discrete microstate transitions that could be monitored and targeted in adaptive deep brain stimulation (aDBS) strategies.

P028

Patient reported feedback suggests an alternative sweet spot for DBS programming in essential tremor

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Background: Deep brain stimulation (DBS) of the ventral intermediate nucleus (VIM) and caudal zona incerta (cZi) is an established therapy for essential tremor (ET). Clinical outcomes depend on precise electrode placement and optimal stimulation parameters. Effective programming must balance tremor suppression with side-effect risk, yet systematic incorporation of patient-reported feedback remains limited.

Objective: To assess whether subjective patient feedback, quantified via a visual analogue scale (VAS), can guide DBS programming for effective tremor control.

Methods: In 15 VIM-DBS patients, 1,253 unique stimulation settings were collected, each rated with a VAS reflecting perceived clinical benefit. Associated volumes of tissue activated (VTA) were mapped and analyzed. VAS-optimized settings were compared to standard-of-care (SoC) programming. Voxel-wise permutation statistics identified stimulation sweet and sour spots, while structural and functional connectivity analyses determined neural correlates of subjective benefit.

Results: VAS-optimized stimulation achieved tremor suppression comparable to SoC settings but with lower energy consumption. Sweet spots correlated with high VAS ratings localized to the dorsal VIM, whereas sour spots were ventral. Connectivity between sweet spots and prefrontal, frontal, and insular regions positively correlated with perceived benefit.

Conclusions: Integrating patient-reported feedback offers a structured, individualized approach to DBS optimization in ET. VAS-guided programming identifies patient-specific sweet spots and delineates connectivity profiles associated with clinical benefit. Notably, VAS-derived sweet spots were more dorsal than previously suggested targets, highlighting the importance of incorporating subjective feedback to refine optimal stimulation regions.

P029

Psychometric reliability of patient-reported visual analogue scales in STN-DBS programming for Parkinson's disease

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Background: Subthalamic nucleus deep brain stimulation (STN-DBS) is an established therapy for Parkinson"s disease (PD), yet programming relies heavily on subjective feedback. Visual analogue scales (VAS) have been proposed to structure patient-reported outcome measures during programming, but their psychometric reliability has not been systematically assessed.

Objective: To evaluate the reliability and contextual stability of VAS ratings in STN-DBS programming.

Methods: Fifteen patients with bilateral STN-DBS underwent four structured experiments: (i) test–retest consistency, (ii) effect of stimulation duration (15, 60, 120 s), (iii) impact of unilateral DBS withdrawal intervals (0, 10, 30 min), and (iv) contralateral stimulation ON versus OFF. Across experiments, patients provided >3,000 VAS ratings. Reliability was analyzed using correlation, regression, and Bland–Altman methods, with subgroup analyses by motor phenotype, cognition, and disease burden.

Results: VAS ratings showed strong test–retest reliability ($r = 0.70$, $R^2 = 0.53$), with 83% of repeated scores within ±2 points. Reliability was reduced in tremor-onset compared to non-tremor patients ($p = 0.04$), but unaffected by cognition or quality of life. Stimulation duration influenced absolute scores, with 15 s ratings systematically lower than 60–120 s ($p < 0.001$), though relative scaling was preserved. DBS withdrawal intervals did not affect group means but increased trial-level variability. Contralateral stimulation ON versus OFF yielded modest correspondence ($r = 0.31$, $R^2 = 0.13$), suggesting hemispheric interactions in subjective perception.

Conclusions: VAS ratings provide reproducible, quantifiable feedback during STN-DBS programming, though reliability depends on motor phenotype, stimulation duration, and bilateral context. Incorporating structured VAS feedback may enhance programming workflows, remote care models, and future multimodal closed-loop DBS strategies.

P030

Deep brain stimulation for Tourette syndrome: from voxels to networks

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Question: Deep brain stimulation (DBS) for Tourette Syndrome (TS) has shown comparable outcomes are across targets[1]. Yet, optimal stimulation sites and the tic-related inter-target networks are unknown. Identifying specific connections responsible for clinical improvement will be pivotal for advancing understanding of TS-DBS and refining targeting.

Methods: An imaging dataset for TS-DBS (n=115) across three target structures, thalamus (n=43; CM/Voi or CM/Pf), pallidum (n=56; amGPi, pvGPi, or GPe) and STN (n=16), was included. We calculated the tic response map of thalamus and pallidum using the sweetspot mapping pipeline available in Lead-DBS[2]. The tic response was defined as the percent change of Yale Global Tic

Severity Scale[3] at 6 months. We calculated the spatial correlation of electrical fields (E-Fields) of STN patients to the combined map of thalamus and pallidum cohorts to test for a potential common network. The similarity to the tic response map was correlated with tic improvement across patients. Combined response map of all cohorts revealed tract-like voxel clusters resembling sub-bundles of three pathways: ansa lenticularis (al), fasciculus lenticularis (fl) and efferent pathways of intralaminar thalamic nuclei. The potential pathways were modelled into streamlines using CurveToBundle module available in 3DSlicer[4]. Peak E-field magnitudes along streamlines were correlated with tic improvement. Streamlines with significant correlations ($p<.05$, uncorrected) were retained for further analysis. We tested model variance explained across the full and target-specific cohorts. Permutation testing provided a stability check.

Results: The tic response maps revealed three peaks each for the thalamus and pallidum cohorts. The spatial similarity of E-fields of the STN cohort with the combined response map of thalamus and pallidum correlated significantly with tic improvement in the STN cohort ($R=0.53$; $p=.034$). The three-tract model explained 22% variance. Permutation testing suggested that the observed correlation ($R=0.39$) was higher than expected by chance ($p=.007$). Results remain hypothesis-generating due to circularity. External validation of our results could improve patient care and may contribute to the understanding of anatomical underpinnings of TS-DBS.

Conclusions: Our results identify optimal tic response target peaks for thalamus and pallidum. We propose a common tic improvement network composed of the al, fl and efferent pathways of intralaminar nuclei. These pathways include the motor, associative and limbic domains.

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P031

Modulation of subcortical-cortical networks by chronic deep brain stimulation and medication in people with Parkinson´s disease

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Parkinson's Disease (PD) is characterised by elevated beta power (13-30 Hz) in the subthalamic nucleus (STN) and high-beta (21-30 Hz) synchronisation between the STN and motor cortex (Oswal et al., 2016). Dopaminergic medication and STN-deep brain stimulation (STN-DBS) can attenuate beta power and synchronisation. Current evidence about these neurophysiological alterations is limited to measurements directly after DBS electrode implantation, which are confounded by the stun effect. In addition, the stimulation parameters are not established. New DBS devices, i.e., the Percept system, allow local field potential (LFP) recordings from implanted electrodes, even when the generator is implanted. This allows for post-operative measurements in an optimally stimulated state without the stun effect. We aim to classify the effect of medication and stimulation on cortical and STN power, as well as STN-cortex synchronisation using magnetoencephalography (MEG) with concurrent LFP streaming via the Medtronic Percept device to investigate treatment mechanisms in the chronically stimulated state and identify potential biomarkers for adaptive DBS programming.

Seventeen participants completed a 15-minute resting-state MEG measurement with concurrent LFP streaming in the medication (med) ON and medOFF state, with their respective stimulation (stim)ON and stimOFF conditions. The MEG data was cleaned from the DBS artefact using temporal Signal Space Separation and Hampel filtering. Additionally, the data was manually cleaned to remove any residual artefacts. Based on each participant's individual MRI, the MEG sensor data were projected on the cortex using minimum norm estimation. Power was computed for each cortical source and for each STN. Coherence was calculated between each cortical source-STN pair.

Cortical beta band power did not change in response to medication or stimulation, while STN beta power was reduced due to medication and stimulation ($p<.05$, respectively). When subdividing the beta band into low- and high-beta, medication significantly decreased power in both bands ($p<.05$, respectively), while stimulation reduced power only in the high-beta band ($p<.05$). Beta coherence between the STN and cortex was attenuated by medication and stimulation, especially in the high-beta band (Cluster-based permutation $p<.05$). These modulations localized in the case of high-beta to medial and mesial regions of the motor cortices.

These post-operative results align with previous peri-operative research indicating distinct treatment mechanisms for medication and STN-DBS in PD. We identified biomarkers that remain responsive to treatment in the chronically stimulated state and exhibited similar treatment-related modulations in the peri-operative state. While medication has a broad effect across the beta band on both STN power and STN-cortex coherence, STN-DBS specifically modulates activity in the high-beta range. High-beta coherence between the STN and cortex is believed to reflect hyperdirect pathway communication, whereas low-beta activity is associated with indirect pathway communication (Oswal et al., 2016). These recordings from the chronically stimulated state provide detailed insights into disease and treatment mechanisms and help optimise adaptive DBS programming strategies.

Network-wide modulation and therapeutic effects of DBS II

P032

Neural signatures and clinical effects of cerebellar deep brain stimulation in dyskinetic cerebral palsy

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Introduction

Managing symptoms of dyskinetic cerebral palsy (DCP), which includes dystonic and choreoathetotic forms, is difficult because medications often provide only modest improvement. Deep brain stimulation (DBS) of the basal ganglia or thalamus has become an effective tool in managing severe isolated dystonia, but it has shown limited efficacy in CP-related dystonia, likely due to structural damage in these regions. As the cerebellum is typically spared from hypoxic ischemic damage and plays a role in the pathophysiology of dystonia, it may serve as an alternate stimulation target.

Goals

In this clinical trial (NCT06122675), we aim to evaluate the safety and therapeutic efficacy of cerebellar DBS in dyskinetic CP. Further, we aim to identify electrophysiological and kinematic markers reflecting disease severity and response to neuromodulation in DCP to get an understanding of the underlying disease.

Materials and Methods

Three pediatric and young adult patients with DCP were implanted with the Medtronic Percept and SenSight electrodes targeting the dorsal motor region of the dentate nucleus. Local field potentials (LFPs) were recorded one day postoperatively from the implanted device, with DBS turned off, during rest and arm movements. A frequency in the alpha/low-beta range (8–12 Hz / 13–21 Hz) was selected at each patient's individual LFP power peak and its amplitude was continuously tracked every 10 minutes throughout day and night. Beginning one month after surgery, stimulation was activated. At monthly visits, LFPs were recorded during various motor tasks such as walking, sitting, standing, reaching, stomping and lying. Movement kinematics were simultaneously captured using a video-based, markerless motion-tracking system. Moreover, symptoms were evaluated using validated clinical questionnaires.

Results

Recordings one day after surgery showed prominent alpha and low-beta activity at rest, which decreased during voluntary movement. A similar movement-related reduction in alpha and beta activity was observed when DBS was activated. Long-term monitoring revealed circadian

fluctuations, with alpha activity increasing at night and beta activity decreasing. Stimulation modulated alpha activity, but the directionality of effects varied across patients. Continuous tracking also suggested that alpha activity may become more variable throughout the clinical trial during active stimulation. All three patients and their families reported modest symptomatic improvements, such as reduced involuntary movements at rest. These subjective improvements are supported by formal kinematic analysis.

Summary

Our study is among the first to characterize neural activity recorded from the human cerebellum. Our findings show that cerebellar oscillatory dynamics share features with activity patterns in other motor regions, such as the basal ganglia and motor cortex, including modulation by movement and circadian variation. Furthermore, our results support the safety of cerebellar DBS and highlight its potential to improve symptoms in DCP. Understanding how DBS-induced changes in neural activity relate to clinical improvements will be important for identifying a reliable physiomarker in DCP.

P034

Monitoring motor fluctuations in Parkinson's disease: linking subthalamic beta-band local field potentials with wearable-derived motor metrics

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Introduction: Local field potentials (LFPs) recorded from the subthalamic nucleus (STN) provide valuable insights into oscillatory activity within the basal ganglia in Parkinson"s disease (PD). In particular, beta-band oscillations (13–30 Hz) have been associated with bradykinesia and rigidity, whereas their suppression correlates with improved motor performance [1, 2]. Continuous and objective monitoring of motor symptoms using the Parkinson"s KinetiGraph™ (PKG; Global Kinetics Corporation, GKC) enables quantification of bradykinesia and dyskinesia during activities of daily living. While both LFPs and PKG-derived metrics have independently been linked to motor states, it remains unclear how wearable-derived bradykinesia and dyskinesia scores correspond to subthalamic beta-band activity in real-life conditions, and how these measures reflect medication effects and ON/OFF fluctuations.

Goals: This study aims to: (1) examine the relationship between beta-band activity in the STN and PKG-derived bradykinesia and dyskinesia; (2) assess changes in beta-band activity following levodopa intake; and (3) compare LFP beta activity between OFF and ON motor states.

Materials & Methods: At the six-month follow-up, n=16 PD patients implanted with STN-DBS electrodes were equipped with a PKG watch and instructed to wear the device continuously for seven consecutive days in their home environment. The PKG provided 30-minute rolling averages of bradykinesia and dyskinesia, capturing motor performance under naturalistic conditions. Concurrently, LFPs were recorded from the STN via the Percept™ neurostimulator (B35200/B35300) at 10-minute intervals. Beta-band power was computed within a narrow 5-Hz window centered on each patient"s individual beta peak. Statistical analyses are planned using linear mixed-effects models to account for repeated measures and inter-subject variability.

Results: The current analyses are investigating the temporal and quantitative relationships between subthalamic beta-band activity and PKG-derived motor metrics over seven days. We aim to characterize how beta fluctuations correspond to bradykinesia or dyskinesia and respond to levodopa. LFP beta features will be compared between medication OFF and ON states to assess their relationship with wearable-derived motor measures. This multimodal approach will clarify the extent to which peripheral data reflect central neural oscillations in real life.

Summary: This work establishes a framework for integrating wearable motor data with chronic subthalamic LFP recordings in Parkinson"s disease. By assessing relationships between PKG metrics and beta activity, it aims to elucidate the neural correlates of bradykinesia and dyskinesia in daily life. Findings may advance objective monitoring of motor fluctuations, improve understanding of medication effects, and guide patient-specific adaptive DBS strategies.

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P035

GAITDBS study: Longitudinal insights into STN-DBS effects on gait and balance in Parkinson's disease

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Introduction Subthalamic nucleus deep brain stimulation (STN-DBS) is an established therapy for advanced Parkinson"s disease (PD), providing sustained improvement in motor symptoms and quality of life. However, its long-term impact on axial symptoms—gait, balance, and freezing of gait (FOG)—remains insufficiently characterized, as most studies focus on early postoperative outcomes. This gap underscores the need to evaluate the trajectory of axial symptoms at multiple postoperative stages to understand the long-term impact of STN-DBS on postural instability and gait disorders (PIGD). Quantitative, sensor-based assessments combined with standardized clinical scales may provide more accurate insights into the evolution of PIGD. **Goal** To demonstrate that isolated STN-DBS does not adversely affect gait and balance in PD patients, through longitudinal evaluation combining standardized clinical scales and wearable inertial sensor-based movement analysis. **Methods** A prospective, observational before–after study was conducted in six Spanish centers including 11 PD patients eligible for bilateral STN-DBS. Assessments were performed preoperatively and at 6 months,1 year,2 years and 3 years postoperatively. Evaluations were carried out under four experimental conditions: OFF med/OFF stim, OFF med/ON stim, ON med /OFF stim and ON med/ON stim. Outcome measures included MDS-UPDRS parts III and IV, Mini-BESTest, FOG score, Hoehn & Yahr, MoCA test, fall frequency, Clinical Global Impression (CGI), and quantitative gait and balance metrics using APDM Mobility Lab®. Dopaminergic medication (LEDD) and stimulation parameters (TEED) were recorded. Statistical analyses included descriptive statistics, paired-samples t-tests or Wilcoxon signed-rank tests. Normality was evaluated using the Shapiro–Wilk test. PResults Postoperatively, a significant reduction in dopaminergic medication was observed (p=0.001). STN-DBS produced robust and sustained improvement in motor symptoms, with significant reductions in MDS-UPDRS III scores under ON stimulation at all follow-up points through 36 months. Mini-BESTest significantly improved under ON stimulation compared to baseline, especially during the first 24

months. FOG scores showed a significant reduction only at 12 months under ON stimulation ($p<0.05$). Although clinical improvements were observed at other time points, they did not reach statistical significance, likely due to high baseline variability combined with small sample size and attrition over successive visits. Hoehn & Yahr significantly improved under stimulation at all time points. No increase in fall frequency nor cognitive decline (measured by MoCA test) was detected throughout the follow-up. Both patients and clinicians consistently reported sustained subjective improvement across all postoperative evaluations. **Conclusions** STN-DBS produced consistent motor benefits, reduced medication needs, and improved balance and gait without adversely affecting cognition or fall risk. Furthermore, FOG scores showed significant improvement at 12 months under stimulation. While this effect was not sustained at later time points due to variability and sample attrition, clinical benefits were consistently observed. Overall, STN-DBS demonstrated a favorable safety and efficacy profile for gait and balance outcomes in PD patients over mid-term follow-up

P037

Real-time monitoring of beta frequency LFP activity in Parkinson's disease patients following STN-DBS: insights into the microlesion effect and personalized treatment optimization

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Background

Parkinson"s disease (PD) is a progressive neurodegenerative disorder characterized by motor symptoms such as rigidity and bradykinesia. Deep brain stimulation (DBS) is a widely used treatment for PD, targeting the subthalamic nucleus (STN) to alleviate symptoms. Recent advances in brain sensing technology have enabled continuous monitoring of local field potentials (LFPs) during DBS, providing new opportunities to explore the underlying electrophysiological changes associated with symptom relief, particularly the microlesion effect (MLE) that occurs in the immediate postoperative period.

Objective

This study aimed to examine the relationship between beta frequency LFP activity and the MLE in PD patients following bilateral STN-DBS. The goal was to investigate how LFP patterns correlate with symptom relief and to better understand the dynamics of MLE, with a focus on the potential of LFP monitoring to optimize DBS settings and patient outcomes.

Methods

Eleven advanced PD patients underwent bilateral STN-DBS. LFP data were continuously recorded over a period of up to 30 days post-surgery, and the power of beta frequency oscillations was assessed every 10 minutes. The median power of the last three recorded days for each hemisphere was defined as 100%, allowing for normalization of data. Statistical analysis was performed to identify differences in LFP power before and after the onset of the MLE.

Results

The analysis of data of eleven patients with PD following DBS-implantation revealed the detection of electrophysiologic MLE through evaluation of beta frequency LFP activity. Significant interpatient and even interhemispheric variability was observed, with a statistically significant reduction in LFP ($p<0.001$), that did not consistently correlate with the duration relief of PD-symptoms. After initiating the DBS-stimulation, patients showed an average improvement of 33.3 % (7 points fo UPDRS), along with LED-reduction of 36.5 % (379 mg).

Conclusions

Continuous monitoring of LFP activity provides unique insights into the individualized responses to DBS in PD patients. Our findings indicate that LFP patterns, particularly in the beta frequency range, reflect electrophysiological changes that extend beyond clinical symptom relief, suggesting a need for more personalized and adaptive DBS treatment strategies. By leveraging real-time LFP data, clinicians could optimize DBS settings and timing, enhancing treatment outcomes and reducing the risk of complications in the immediate postoperative period. Further research is needed to explore the neurophysiological mechanisms underlying these findings and to expand the application of LFP monitoring to other movement disorders treated with DBS.

P038

Mapping symptom-specific gait networks in neuromodulated tremor patients: insights into divergent forms of Ataxia

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Stimulation-induced ataxia hinders deep brain stimulation (DBS) for essential tremor (ET), limiting clinical outcomes, but the mechanisms involved remain unclear. We combined within-subject, symptom-specific DBS perturbations and deep phenotyping for a clinical characterization. We used recent advances in multimodal brain network integration to combine and compare results from normative functional connectivity and dual-condition [^{18}F]FDG PET in 14 ET patients to identify the involved networks. We found two distinct clinical phenotypes of stimulation-induced ataxia with dissociable networks: (i) a supratherapeutic appendicular dysmetria linked to dysfunction in a thalamo–striatal network encompassing thalamus, pallidum, and putamen, with possible partial compensation in (pre)motor cortex; and (ii) a delayed-onset axial gait syndrome linked to a posterior midline network centred on the cerebellar vermis, posterior cingulate, and precuneus. In an independent cohort (n=49), patients with likely delayed-onset ataxia showed greater connectivity to the delayed-onset network (p=0.002). Together, our results indicate that stimulation-induced ataxia should be differentiated into two distinct clinical phenotypes underlying different network mechanisms. Multimodal imaging and clinical phenotyping converged to distinguish these phenotypes within patients and across cohorts, providing candidate network markers, clinically meaningful differences, and a framework for hypothesis-driven validation in larger, prospective studies.

P040

Asymmetric frontal cortex activation explains how deep brain stimulation improves gait adaptation

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Introduction: Adapting gait to environmental challenges is essential to safely navigate the surroundings. Impairment of gait adaptation is common in Parkinson"s disease (PD), negatively affecting mobility and quality of life. Current therapeutic options offer limited effectiveness, likely due to our insufficient understanding of the neural mechanisms underlying gait adaptation.

Goals: to study the neural underpinnings of gait adaptation in PD and their improvement under subthalamic deep brain stimulation (STN-DBS).

Materials & Methods: 12 subjects with PD and bilateral STN-DBS underwent a [18F]fluorodeoxyglucose positron emission tomography (FDG-PET) after suspension of all antiparkinsonian medications in three different conditions on three different days: i) resting, ii) walking-, after an overground gait adaptation task in virtual reality (VR) with DBS switched off, iii) walking+, after performing the same VR task with active stimulation. Movement kinematics and cortical oscillatory activity were recorded during each task before the FDG-PET scan, using inertial measurement units and electroencephalography, respectively. Kinematic data were analyzed using a principal component analysis to derive a composite gait adaptation score, which summarized performance quality and provided individualized levels of DBS-related improvement. Eight age-matched healthy subjects completed the same kinematic assessment to provide normative data.

Results: Compared to resting, the walking- condition increased metabolic activity in the cerebellum and sensorimotor cortex. By comparing walking- and walking+, we showed that STN-DBS improved gait adaptation performance in all subjects and distinctively enhanced thalamic and superior frontal gyrus (SFG) activity, while reducing cerebellar uptake. In both walking- and walking+ conditions, right-lateralized SFG metabolism significantly correlated with gait adaptation performance (walking-: r=-0.685, P=0.020; walking+: r=-0.689, P=0.019). Moreover, DBS-driven shifts toward greater right-lateralized SFG activity predicted the magnitude of DBS-related improvement (OR=-0.683, P=0.020). This effect was independent of baseline asymmetry in clinical impairment, electrode placement, or structural connectivity of the activated regions. EEG analyses confirmed a lateralized network modulation, with SFG theta-band asymmetry mirroring FDG-PET findings.

Summary: Our multimodal approach revealed a lateralized thalamo-cortical control of gait adaptation in PD and highlighted the central role of the right SFG. We also showed that STN-DBS can rebalance neural network activity across the hemispheres, dynamically recalibrating cortico-thalamic circuits to enable effective gait adjustments.

P041

Structural networks of Lesion-induced dystonia

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Dystonia is a common movement disorder causing involuntary muscle spasms that result in abnormal posturing of body parts such as the neck, arms or legs. Evidence has demonstrated that dystonia is a network disorder, with symptoms arising from disrupted brain circuits rather than damage to single anatomical regions. DBS in dystonia is targeted to the globus pallidus internus (and less commonly, the subthalamic nucleus), and recent work has revealed distinct networks are associated with subsequent improvement in dystonic symptoms across different body regions (Butenko et al., 2025). Given this, identifying the causal networks underlying dystonic phenotypes is the next step to provide evidence for the optimisation of neuromodulation therapy. Therefore, this study sought to delineate the structural brain networks connected to lesions causing 8 dystonia phenotypes - arm, blepharospasm, cervical, face, foot, hand, leg and trunk dystonia (total N=179). To do this, we used the fiber filtering tool in Lead-DBS (Neudorfer et al., 2023) and a normative structural connectome from the Human Connectome Project (N = 985, Elias et al., 2024) to identify the top 1000 streamlines that are most commonly connected to lesions causing each of 8 dystonia phenotypes. This creates a structural connectivity profile per phenotype, i.e. "subtype networks". We then assessed the specificity of each subtype network in two ways. First, proportion tests determined which streamlines were more associated with lesions causing each phenotype (e.g. cervical) compared to lesions not causing that phenotype. Second, spatial correlations were used to determine whether structural connectivity profiles *within* dystonic types were more similar to each other, than to profiles of the other dystonic types (e.g., that connectivity patterns of lesions causing cervical dystonia are more similar to each other, than to patterns of lesions causing hand dystonia). Overall, these tests showed differential brain networks underlying the dystonic phenotypes and revealed an anterior to posterior gradient spanning the corona radiata, with each network showing connections between the cortex, basal ganglia, and brain stem. Networks of limb dystonias (arm, hand, leg and foot) showed similar connectivity patterns resembling the corticospinal tract, whereas blepharospasm and face dystonia showed connectivity to more anterior frontal regions and the sensorimotor cortex. Notably, cervical dystonia showed a distinct connectivity pattern localising predominately to cerebellar pathways. This evidence furthers our understanding of the neural bases of dystonia and may provide a framework to support the optimisation of DBS targeting and modelling of symptom modulation in dystonia phenotypes.

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P042

Zona incerta exhibits attenuated beta activity: implications for adaptive deep brain stimulation in Parkinson's disease

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Introduction: Adaptive deep brain stimulation (aDBS) algorithms allow stimulation delivery tailored to the patient"s clinical state, inferred from subthalamic nucleus (STN) beta power. With the Percept device, however, the reliability of beta-power estimates is constrained by bipolar recordings: when both contacts capture similar neural activity, common-mode rejection can inadvertently cancel out relevant beta signals. In this context, neighboring subthalamic structures with distinct oscillatory properties, and ideally minimal beta activity, may help improve the computation of STN-specific beta power.

Goals: To characterize oscillatory activity in the STN, zona incerta (ZI), and substantia nigra pars reticulata (SNr) in PD patients with bilateral STN-DBS.

Materials and methods: We retrospectively analyzed local field potentials (LFP) recorded in PD patients implanted with bilateral STN-DBS (Percept, Medtronic, PLC) at the University Hospital of Würzburg in the period 2019-2025. All recordings were acquired during routine programming in the medicated state. Contact pairs were anatomically localized in patient-specific MRI–CT reconstructions (Brainlab Elements) and classified as STN, ZI, SNr, or border zones (i.e., with the two recording contacts in different neighboring regions). Recordings obtained within three months post-implantation or contaminated by artefacts were excluded. A custom MATLAB pipeline processed BrainSense Survey recordings (21-second epochs, 250 Hz) by computing the normalized power spectral densities in the theta (5-8 Hz), alpha (8-12 Hz), beta (13-30 Hz), and gamma (31-80 Hz) bands. Regional differences were assessed using linear mixed-effects models.

Results: A total of 141 recordings of 24 patients met the inclusion criteria. The STN displayed the highest beta power across the regions analyzed, with the ZI showing significantly lower beta power ($p < 0.001$) and distinctively higher theta power ($p = 0.0037$). SNr recordings exhibited beta amplitudes comparable to the STN.

Summary: This study provides the first chronic electrophysiological characterization of the subthalamic region in PD patients. The ZI showed a distinct oscillatory profile characterized by attenuated beta synchronization. ZI-referenced sensing may improve the computation of STN beta power, thus supporting contact selection and aDBS treatment.

P043

Basal ganglia pathway recruitment determines bidirectional motor speed modulation by DBS in humans

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The introduction of optogenetics has facilitated profound updates on the basal ganglia function, while the striatal neural differentiation into direct and indirect pathways has remained the basis. In contrast to animal studies, research on deep brain stimulation in humans has been rather anatomically descriptive than neuroscientifically conclusive. Selective stimulation of specific neural populations in humans remains elusive, entangling the question of pathway-specific effects of permanent DBS.

We used a set of advanced imaging methods to examine retrospective cohorts of PD patients with STN DBS (N=59) and GPi DBS (N=39), a retrospective cohort of dystonia patients with GPi DBS (N=46) and validated our results on a prospective STN DBS PD cohort (N=15). We quantified disturbances of the movement velocity as a normalised sum of MDS-UPDRS III items 4-8 and the stimulation effect as its preoperative to postoperative difference, or STIM OFF to STIM ON difference in case of the prospective experiment, always in MED OFF (BDS – bradykinesia difference index). We employed Lead DBS toolboxes to process the imaging data and perform fibrefiltering (using the Petersen atlas) and FSL randomize to analyse normative functional connectivity patterns.

The mean BDS in the GPi PD cohort was -0.21±0.74, in the STN PD cohort -0.71±0.77, in the GPi dystonia cohort 0.18±0.56, and in the prospective STN PD cohort -0.56±0.63, demonstrating antibradykinetic effect of DBS in PD and probradikinetic effect in dystonia when evaluated at the cohort level. The individual effects, nevertheless, were bidirectional in all cohorts. The joint fibrefiltering of the retrospective PD data revealed a clear pathway differentiation into the lenticular fasciculus (LF), increasing bradykinesia scores, and a part of the hyperdirect pathway (HF), reducing bradykinesia scores. This fibre model performed well in the leave-one-out cross-validation ($R=0.38$, $p<0.0001$) and permutation tests ($p = 0.004$). The functional connectivity pattern of the induced bradykinesia, defined as voxel clusters with familywise corrected $p<0.05$ from the GLM analysis, involved the thalamic areas receiving pallidal input through the LF, further validating the result. The cross-prediction of bradykinesia induction in dystonic patients with GPi DBS using the LF fibres defined by the fibrefiltering in PD was significant ($R=0.25$, $p=0.048$), as well as the cross-prediction of the prospective STN PD cohort ($R=0.21$, $p=0.04$). Moreover, the sole stimulation of the fibrefiltering-derived LF fibres predicted the occurrence of induced bradykinesia when tested prospectively ($p=0.035$). Last but not least, we contrasted the antiparkinsonian and antidystonic effects of pallidal DBS on a single fibre level and found a fascicle of Edinger´s comb, interconnecting GPe and STN (being part of the indirect pathway), significantly more antiparkinsonian than antidystonic, and some LF fibres and Edinger´s fibres in posterior GPi, vice versa. The antiparkinsonian fascicle of interest was predictive in the subsequent hypothesis-driven analysis ($R=0.37$, $p=0.02$), whereas the antidystonic fibres were not.

In summary, these results provide the first clear evidence that the effects of DBS in humans can be assigned to particular pathways, relating pallidothalamic connectivity to induced bradykinesia

with direct clinical implications. On the neuroscientific level, supported by our results and literature, we infer an upmodulation of movement velocity by hyperdirect pathway DBS, generally antiparkinsonian effects of indirect pathway DBS, and most importantly, movement disruption at the level of the joint BG output in the lenticular fasciculus, likely resulting from DBS interference with direct pathway activity.

P044

Cross-domain network interactions of STN-DBS: mapping motor–cognitive interactions in Parkinson's disease

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Background: Deep brain stimulation of the subthalamic nucleus (STN-DBS) effectively improves tremor, rigidity, and bradykinesia in Parkinson"s disease (PD), yet gait disturbances, cognitive decline, and mood changes may persist or emerge de novo after the surgery. Although connectomic studies have identified networks associated with clinical change in single domains (e.g., global motor or memory networks), capturing cross-domain interactions remains challenging and limits imaging-driven strategies to optimize stimulation for both motor and non-motor outcomes.

Methods: We retrospectively analyzed 75 PD patients undergoing STN-DBS with clinical assessment at baseline and 1-year follow-up. Lead localization, volume of tissue activated modeling, and normative functional connectivity were performed using Lead-DBS V.3.0 and the 1,000-subject GSP connectome. Principal component analysis (PCA) was applied to delta scores of the motor and cognitive domains, resulting in domain-specific latent components. These components were used as covariates in DBS network mapping with FSL PALM. Domain-specific networks were then entered into a moderation analysis to identify regions supporting motor-cognitive interactions. A multivariate stepwise regression model was applied to determine which regions jointly explained cross-domain clinical variance.

Results: PCA identified two motor components (explaining >60% variance, reflecting improvement in mobility, gait, and freezing of gait, asymmetry of bradykinesia & rigidity) and one cognitive component (explaining >60%, reflecting memory improvement). PC-motor network mapping revealed improvement-associated connectivity in higher-order association cortex, whereas PC-cognitive improvement localized to sensorimotor and visuospatial cortex. Moderation analysis identified seven network nodes showing synergistic motor-cognitive interactions. Cross-domain motor-cognitive improvement was best captured by coordinated modulation between the frontal orbital cortex and the cerebellar vermis (Lobule IX) (Multivariate model: AIC = 15.47, 15.1% motor and 23.8% cognitive variance explained, $p < 0.05$).

Conclusion: Distinct yet partially overlapping functional networks support motor and cognitive clinical changes after STN-DBS. Integrating dual-domain network mapping with multivariate modeling can identify new targets to enhance individualized stimulation strategies aimed at optimizing both motor and cognitive outcomes.

P045

Pallidal bursting correlates with dystonia severity

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Introduction. Deep brain stimulation (DBS) of the globus pallidus internus (GPi) is an effective therapeutic option for medically refractory dystonia, although up to 25% of patients experience only limited clinical improvement. Intraoperative microelectrode recordings (MER) provide a unique opportunity to explore disease pathophysiology and to advance our understanding on DBS action.

Goals. We aim to assess whether intraoperative pallidal recordings encode disease severity in patients with dystonia and can inform clinical improvement after surgery.

Materials & Methods. We analysed single-unit neuronal activity recorded from GPi during DBS surgery in 13 dystonia patients (6F; mean age at surgery 50±15yrs) focusing on firing rate, regularity, burst and pause dynamics. For firing rate and regularity-related neural biomarkers, four markers were included: inter-spike interval (ISI), firing rate (FR), coefficient of variation, and local variance. Pauses were detected using the Poisson-Surprise method and characterized by pause index (PI; ratio between ISIs >50ms and ISIs <50ms), intra-pause firing rate (IPFR), pause duration (PDR; average length of pauses within the spike train), and pause spike count. Bursts were identified with the Rank Surprise method and described by burst index, inter-burst interval (IBI; mean time between consecutive bursts), intra-burst firing rate, intra-burst interval (InBI; mean interval within bursting activity), and burst spike count. Disease severity was assessed preoperatively and at 1-year follow-up using the Toronto Western Spasmodic Torticollis Rating Scale. Baseline preoperative scores were normalized for cross-patient comparability as follows: (preoperative TWSTRS score ÷ maximum total TWSTRS score) ×100. Improvements at follow-up were also defined as percentage changes. These values were then correlated with neural features.

Results. Preoperative disease severity averaged 42% (range, 6–74%), with 100% corresponding to the maximum TWSTRS score. Relative to the preoperative assessment, ten patients showed a good response to DBS (43-87% improvement), whereas three patients showed limited benefit (<30% improvement). Median FR of bursting neurons, and IPFR negatively correlated with preoperative disease severity ($p<0.05$). In contrast, IBI, InBI, PI, and PDR showed positive correlations ($p<0.05$). Multiple regression identified InBI as the only independent predictor of preoperative severity. No neural features correlated with DBS-related clinical improvement.

Summary. GPi InBI correlated with dystonia severity, supporting a direct role of pallidal bursting in dystonia pathophysiology. Prolonged GPi bursts may promote abnormal low-frequency synchronization and impair motor network communication.

P046

Impact of low-frequency mesiotemporal deep brain stimulation on memory performance: a report of two patients with incorrect electrode placement

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Introduction

Deep brain stimulation (DBS) is an established therapy for movement disorders such as Parkinson"s disease, essential tremor, and dystonia. Its application to enhance cognitive functions remains experimental. Prior studies suggest that fornix stimulation at 20 Hz and mesiotemporal stimulation can modulate memory-related networks. We report two patients with misplaced DBS leads contacting the medial temporal regions bilaterally and examine cognitive effects of stimulation in this region.

Methods

Two female patients were referred for correction of misplaced DBS leads. Patient 1 (55 years) had Meige syndrome; patient 2 (47 years) presented with generalized dystonia. Both had initially undergone globus pallidus internus (GPi) stimulation at another center, but symptoms persisted and lead misplacement was identified. Leads were located ventro-caudally to the GPi, within medial temporal region near the hippocampal formation. As DBS showed no antidystonic effect, revision surgery was planned. Initial positions were documented in Montreal Neurological Institute (MNI) coordinates at the lowest contact.

To assess cognitive impact, neuropsychological testing was performed under three stimulation conditions: (i) baseline (0 Hz), (ii) high-frequency (120 Hz, 4.5 mA), and (iii) low-frequency (20 Hz, 4.5 mA). Testing followed a pseudo-randomized, double-blind design. Each condition was repeated three times, yielding nine sessions per patient. The battery included verbal memory, working memory, verbal fluency, and Stroop tasks. Results were compared with five dystonia patients successfully treated with GPi stimulation. Given the small sample, Bayesian models were applied, supplemented by numeric differences between conditions. The study was approved by the local ethics committee; all participants provided written informed consent.Results

Electrode reconstruction with Lead-DBS localized contacts in MNI space: patient 1, right x=22.91, y=–6.23, z=–10.29; left x=–31.00, y=–9.05, z=–9.51. Patient 2, right x=20.75, y=–13.60, z=20.57; left x=–21.38, y=–15.88, z=22.19.

Word-cued recall revealed an estimated group difference of –6.14 (95% CI –9.21 to –2.97), indicating lower performance in controls. Group × stimulation interaction was largest at 20 Hz (estimate –8.8, 95% CI –12.2 to –5.2), versus baseline (–4.6, 95% CI –8.1 to –1.1) and 120 Hz (–5.5, 95% CI –8.5 to –1.5). Patients with misplaced leads remembered on average 4 more cued word pairs at 20 Hz than at 0 Hz, and 0.3 more at 120 Hz. In contrast, the control group recalled 8.2 cued word pairs at 0 Hz, with 0.3 fewer at 20 Hz and 0.1 fewer at 120 Hz, indicating no relevant stimulation effect. The memory improvement at 20 Hz in patients with misplaced leads was also observed in free recall, while no significant differences between stimulation conditions were found for the other tasks in either group.

Summary

We report neuropsychological findings of two patients with DBS lead misplacements in the medial temporal region bilaterally. Memory performance improved under 20 Hz stimulation, suggesting modulation of medial temporal networks. Ongoing imaging studies aim to identify the specific fiber connections involved, to better characterize networks supporting memory formation under DBS.

P047

STN-DBS modulates subthalamic low-frequency oscillations during turning in Parkinson's disease

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Introduction: Turning is a particularly demanding locomotor task for people with Parkinson"s disease (PD) and is associated with an increased risk of falls. Deep brain stimulation of the subthalamic nucleus (STN-DBS) is a well-established therapy for PD, but its benefit on gait and balance, particularly during postural transitions, remain limited. A clearer understanding of how DBS influences postural transitions may guide the development of more effective neuromodulation strategies.

Goals: To investigate the effect of DBS on STN neural activity during turning in PD.

Material & Methods: We recorded bilateral subthalamic local field potentials (LFPs) during turnings in eight patients with idiopathic PD (age: 62±5 years; disease duration: 10±5 years; UPDRS-III meds-off/stim-off: 40±12; mean±standard deviation) implanted with the Percept device (Medtronic, PLC), assessed after overnight suspension of dopaminergic drugs (meds-off), in stim-on (under clinically optimized stimulation) and stim-off (45min after pausing DBS) conditions. Patients were instructed to walk back and forth on a 10m walkway with 180° turns at the end of each walking trial. We analysed the kinematic performance during turnings (11-88 turnings) by means of a sternum-mounted inertial measurement unit (Opal, APDM). To quantify the overall turning performance, we derived a kinematic composite score (turn index) by combining key parameters: turn duration, root mean square (RMS) of the vertical angular velocity and RMS of the linear acceleration along the anterior-posterior axis. For each turn, we analysed the time-frequency dynamics of LFPs during each turning window and its subphases, by classifying each STN as contralateral or ipsilateral to the internal leg relative to the turning direction.

Results: In the stim-off condition, the turn index correlated negatively with the "Gait" sub-item of the UPDRS-III (Pearson"s $r = -0.85$, $p < 0.05$). Turn index significantly improved in the stim-on than in the stim-off condition ($p < 0.05$). At the neural level, cluster-based permutation analysis revealed a significant increase in low-frequency oscillatory (LFO; 4–12 Hz) power in the contralateral STN in stim-on versus stim-off between turn onset and peak angular velocity. Specifically, in stim-off, LFO power within this subphase was significantly reduced than the pre-turn window ($p < 0.05$); the magnitude of this suppression correlated negatively with the turn index (Pearson"s $r = -0.84$, $p < 0.05$), indicating that greater suppression was associated with better turning performance. In contrast, in the stim-on condition, LFO power within this sub-window did not differ from the pre-turn window.

Summary: Our findings indicate that subthalamic LFO are modulated during turning in PD, and that STN-DBS mitigates their suppression. We provide evidence in PD for a lateralised, frequency-specific role of subthalamic activity in turning control.

P048

Frequency-dependent inhibition during deep brain stimulation of thalamic ventral intermediate Nuclei as a physiological correlate for essential tremor

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Deep brain stimulation (DBS) of the thalamic ventral intermediate nucleus (Vim) has been a standard therapy for essential tremor. It has been shown that high frequency (≥100Hz) DBS suppresses Vim firing and tremor activity, however, the underlying mechanisms are not fully understood. Here, we investigate whether neuronal suppression during high-frequency DBS occurs at cellular levels or is influenced by network-level effects. Using human in vivo recordings of Vim neurons during different DBS frequencies, we detected a positive-going evoked-field potential during high-frequency Vim-DBS in some recording sites. Interestingly, it was observed that (i) neuronal suppression is stronger in neurons with the evoked potential, implying that inhibitory engagement during high-frequency DBS can further suppress neuronal firing, (ii) the evoked potential emerges after the transient burst, i.e., the latter may give rise to the former, and (iii) applying microstimulation to neurons with the evoked potential results in increased tremor reduction. By utilizing a novel artifact removal and characterizing dynamics of the evoked potential, we showed that the occurrence of inhibitory activity is negatively correlated with firing, and neurons with the evoked potential are significantly more suppressed than those without. Moreover, we utilized accelerometer recordings and an objective evoked potential detection algorithm to verify that stimulation sites with the evoked potential are significantly correlated with increased measurable tremor reduction. We propose a framework that explains DBS effects at both cellular and network levels, i.e., high-frequency DBS not only depresses synapses, but also enables the recruitment of inhibitory neurons. A transient burst in the spiking activity is likely providing sufficient network engagement to recruit inhibitory neurons that are silent during low-frequency DBS. Also, engaging this cellular and network DBS mechanism likely increases clinical efficacy. These results suggest that an excitatory-inhibitory balance could regulate Vim activities during high-frequency DBS. Our findings shed light on potential network mechanisms underlying Vim-DBS, which can provide insight for intraoperative targeting and optimizing DBS.

P049

Cortical evoked responses correlate with DBS-induced clinical improvement in dystonia: MEG-based analysis across contacts and pulse widths

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Introduction: Deep brain stimulation (DBS) in globus pallidus internus (GPi) is an effective therapy for dystonia, yet stimulation programming remains challenging because clinical improvement often appears only hours or days after parameter adjustments, making monopolar review insufficiently reliable. Objective physiological markers could, therefore, support more individualized DBS programming.

Objective: To determine whether amplitude of cortical evoked responses (cER) are associated with DBS-induced clinical improvement (Stim ON vs OFF), and whether cER characteristics differ between clinically optimal and non-optimal stimulation contacts.

Methods: Fifteen patients with dystonia underwent 2-minute MEG recordings during 2 Hz left GPi stimulation. cERs were recorded from all four contacts using two pulse widths (90 and 120 µs), with stimulation amplitude set to the clinically effective level. Sensor-level analysis revealed two significant time windows, corresponding to two distinct cER peaks, which were subsequently analyzed as an early (19–80 ms) and a late (95–250 ms) component. Based on source analysis, these peaks were extracted in four regions of interest (ROI): frontal, frontolateral, precentral, and postcentral cortices.[AS1]

Clinical improvement was quantified as the percentage change between Stim OFF and Stim ON using BFMDRS (Burke-Fahn-Marsden Dystonia Rating Scale) scale (total and severity subscores). Spearman correlations with FDR correction were performed for amplitude of both peaks. Peak parameters were also compared between best-clinical and non-clinical contacts.

Results: Significant FDR-corrected correlations were observed between cER peak amplitudes and DBS-induced clinical improvement. For 90-µs stimulation, late-peak amplitude showed a strong positive correlation with BFMDRS improvement in the precentral and postcentral regions ($r>0.7$, $p=0.01$-0.03, FDR-corrected). For 120-µs stimulation, both early- and late-peak amplitudes positively correlated with BFMDRS improvement in frontal and frontolateral cortices ($r>0.7$, $p=0.01$–0.04, FDR-corrected).

No significant amplitude differences were detected between best-clinical and non-clinical contacts, indicating that cER peak amplitude likely capture patient-specific cortical–basal ganglia physiology and the degree of DBS-induced benefit, rather than serving as a reliable marker for distinguishing between stimulation contacts.

Conclusion: cER amplitudes partially track DBS-induced clinical improvement, supporting their potential as patient-specific physiological markers for guiding DBS programming in dystonia.

P050

Cross Frequency Coupling (CFC) in patients with Parkinson`s disease(PD) treated with DBS: local field potentials and surface EEG - a pilot study

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Introduction

Deep Brain Stimulation in patients with PD has become a very important treatment option. Increasingly more techniques are available. The most prominent side-effects beside surgical complications are dyskinesia and reduction of speech fluency.

Speech disturbances are often associated with motor signs but the pathomechanism of this relation remains unknown. Muthumaran et al. detected 2020 the cross-frequency coupling in brain area M1, PMC, STN and cerebellum: in STN, suppression of beta frequency is negatively correlated to the increase of gamma frequency. The optimum of clinical effect with only few side effects is at minimal ratio of beta to gamma power, measured as local filed potentials in the STN.

Goals

To replicate the CFC data in STN, and to observe whether a similar ratio of global relative beta to gamma power in the surface EEG (256-channels) in patients with or without motor and speech complications.

Material and Methods

Resting state 256-channel EEG from 24 patients with PD (12 with DBS,12 without) will be analyzed in combination with a neurological and neuropsychological assessment with specific focus on speech analyses. The local field potentials in STN will be recorded in operated patients using the Brainsense-tool (Medtronic).

Results

In a pilot study, one patient with DBS was tested with respect to practicability and feasibility of the measuring procedures. The patient tolerated the recordings and examinations without any problems and the QEEG-analyses could be performed successfully.

Summary

It is likely that the CFC-effect could be replicated even with surface-EEG, allowing characterizing the CFC-coupling in unoperated patients, too.

Reference

Muthuraman, M. et al. Brain 2020

P051

COMEDD study: modulation of electrophysiological resting state activity in monopolar review recordings at 3-months follow-up

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Question: To date, most research in electrophysiological biomarkers in dystonia has been done post-operatively. Pallidal theta band activity has been associated with dystonic symptom severity, and beta band activity emerged as a biomarker for bradykinesia in chronic pallidal (GPi) deep brain stimulation (DBS). While it is the most effective symptomatic therapy, DBS programming in dystonia can be very challenging. As stimulation effects may occur with a delay, the programming process can be lengthy and on a trial-and-error basis. The Chronic Outcome Measures in Dystonia with DBS (COMEDD, NCT07244549) study aims to leverage the potential of sensing-enabled neurostimulators for the understanding of chronic electrophysiological biomarkers and ultimately improve therapy optimization based on electrophysiology. In a first analysis, we here investigate the reaction of different frequency bands to DBS at 3 months-follow-up as the first major DBS optimization timepoint.

Methods: 9 patients with various types of dystonia implanted with pallidal DBS and the sensing-enabled Percept neurostimulator were included in the study. At three-months follow-up, we performed a monopolar review recording on the clinically used contacts. Stimulation was increased on the clinically used contact in 0.5 mA steps of approximately 30 sec. We recorded local field potentials (LFP) at a sampling frequency of 250 Hz in a bipolar configuration adjacent to the DBS contacts. Data was high-pass filtered at 2 Hz and low-pass filtered at 98 Hz and transformed to the time-frequency domain using short fourier transformation. Normalization was performed to % total sum. Mean spectra (over visually selected artifact free resting-state activity of 17-35 sec, mean 22.8 +- 3.7 sec) were generated for the different stimulation amplitudes. DBS amplitudes were grouped by % clinical DBS amplitude. Spectral parametrization was applied for differentiation of periodic and aperiodic components.

Results: 6 patients suffered from cervical dystonia, 3 patients from generalized dystonia, (overall age range: 5-65 years, female:male 4:5). After visual inspection for artifacts, 17/18 GPi could be included for final analysis. There was a significant suppression by DBS in the low-frequency band (8-10Hz, mean power OFF DBS: 3.97±1.6, ON DBS at best clinical amplitude: 3.03±1.2 % total sum, paired t-test, p=0.032). Beta band activity was variable, without a significant increase at three months short-term recordings (13-20Hz, mean power OFF DBS: 2.56±1.8, ON DBS at best clinical amplitude: 2.3±2.03 % total sum, paired t-test, p=0.61). In 4/9 patients, gamma entrainment occurred at 1:2 of the stimulation amplitude.

Conclusions: Deep brain stimulation at an effective therapy amplitude leads to a reduction in low frequency activity in chronically implanted patients. In some patients, gamma entrainment occured at clinically used amplitudes. Correlation with long-term clinical outcomes will provide further insights into the applicability of these biomarkers for electrophysiologically guided DBS optimization. In future, these biomarkers might be used to inform adaptive algorithms in dystonia.

P052

Low-frequency stimulation improves dynamic obstacle avoidance during gait in patients with Parkinson's disease

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Introduction: Advanced Parkinson's disease (PD) is frequently associated with gait disturbances, particularly during gait modulation tasks. High-Frequency Deep Brain Stimulation (HFS) is remarkably effective in alleviating the cardinal motor signs of PD; however, its effects on gait are inconsistent and may be even detrimental in some patients. Preliminary studies suggest that lower-frequency stimulation (LFS, 60–80 Hz) may preferentially ameliorate axial symptoms, including gait impairment. Nevertheless, quantitative, standardized assessments of the effects of LFS on gait, especially during real-life, transition-dependent gait tasks, remain limited.

Goal: To assess the effects of LFS on dynamic obstacle avoidance during gait in patients with PD.

Methods: Eight patients with PD (age 63.4±6.3 years; disease duration 9.0±4.4 years) treated with chronic HFS were recruited. Patients were tested after overnight withdrawal of dopaminergic medication under two stimulation conditions: chronic HFS and acute LFS. Disease severity was scored with the Unified Parkinson's Disease rating scale motor part (UPDRS-III). Gait analysis was assessed with at least 10 trials of unperturbed overground linear walking and a dynamic obstacle-avoidance task (30 trials per session) in a fully-immersive Virtual Reality (VR) environment [1]. The VR paradigm elicited standardized gait perturbations via a Virtual Agent (VA) crossing the participant's walking trajectory, presented through a head-mounted display (Vive Pro, HTC). Whole-body kinematics were captured with an optoelectronic motion-capture system (SMART-DX, BTS). Linear walking was evaluated based on gait cycle parameters (stride length, average and max velocity, stride elevation, stance and double-support duration) and steady-state walking speed. Obstacle negotiation was assessed by evaluating the duration of the gait modulation window (i.e., from the onset of speed reduction to the return to steady-state walking) and the magnitude of velocity change. Preservation of personal space was evaluated on the transverse plane as the cross-sectional area maintained around the participant's position relative to the VA trajectory. The average values were compared across HFS and LFS conditions using a Wilcoxon signed rank test.

Results: HFS and LFS provided comparable benefits when assessed clinically. During linear walking, six patients showed, under LFS, increased stride elevation and reduced double-support phases. In four of these patients, higher walking speed, longer strides, and faster stride velocity were also observed. During the dynamic obstacle-avoidance task, seven patients exhibited, under LFS, a shortening of the gait modulation window ($p=0.06$), and six of these patients also maintained a higher minimum walking speed.

Summary: Our findings suggest that the additional benefit perceived by patients with PD under LFS may be related to smoother gait control during dynamic obstacle avoidance. Notably, conventional clinical rating scales were unable to capture these differences. Validation in larger cohorts is warranted to confirm these preliminary observations and to identify patients most likely to benefit from LFS.

[1] Palmisano et al. Front. Hum. Neurosci. 2022

P053

Selective modulation of cortico–subthalamic and corticomuscular networks by deep brain stimulation in Parkinson's disease

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Subthalamic nucleus deep brain stimulation (STN-DBS) is an established treatment for Parkinson"s disease (PD), increasingly implemented in adaptive systems that target pathological beta oscillations. However, beta activity also supports physiological motor control, which prompts questions about whether DBS might interfere with the neural mechanisms necessary for maintaining stable posture.

Here we combined simultaneous recordings of subthalamic local field potentials, motor cortical electro-encephalography, and limb electromyography in 24 patients with PD to examine how STN-DBS modulates oscillatory activity and connectivity across the cortico–basal ganglia–muscle system during rest and sustained posture task.

We found that STN-DBS robustly reduced subthalamic beta power and enhanced gamma power both during sustained posture and rest. At the network level, DBS selectively reorganized cortico–subthalamic coherence by inducing a transient reduction of beta-band coherence during sustained posture, while increasing gamma-band coherence across both rest and posture conditions. In contrast, corticomuscular coherence, a readout of corticospinal motor output, was not altered by DBS. Furthermore, DBS-induced changes in cortico–subthalamic coherence were not correlated with changes in corticomuscular coherence in either frequency bands, suggesting independent modulation of these distinct, functional pathways by DBS. Furthermore, changes in cortico–subthalamic coherence, but not corticomuscular coherence, related to clinical motor improvement.

These findings reveal a functional dissociation between upstream cortico–basal ganglia and downstream corticospinal processes. STN-DBS selectively suppresses pathological beta synchrony and promotes gamma communication within cortico–subthalamic circuits while preserving corticomuscular coupling required for postural control. This dissociation provides mechanistic evidence that beta-targeted (adaptive) DBS can alleviate motor impairment without compromising physiological motor output.

P054

Subthalamic stimulation reduces subthalamic high beta – cortical high gamma phase-amplitude coupling in Parkinson's disease

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Question

Subthalamic stimulation (STN-DBS) in Parkinson's disease may operate via the hyperdirect pathway by suppressing high-beta connectivity between the STN and motor cortical areas and promoting gamma motor cortical processing. In this study, we examined how subthalamic beta activity shapes the pattern of cortically generated gamma rhythm and how STN-DBS influences this coupling.

Methods

Thirty-eight patients with akinetic-rigid Parkinson's disease treated with bilateral STN-DBS were recruited. First, four levels of contralateral stimulation were selected to improve bradykinesia based on kinematic testing (0: DBS OFF, 1-3). A 64-channel electroencephalogram was recorded at rest and while patients drew self-paced and traced spirals with their more affected hand on a digital tablet, five times at the four selected stimulation levels. After using a beamformer inverse solution dynamic imaging for coherent sources, we analyzed time-resolved inter-regional phase-amplitude coupling (irPAC) between the following subthalamic beta and cortical (primary, supplementary motor, dorsal and ventral premotor cortex) gamma frequency band pairs: subthalamic low beta (SLB; 13-20 Hz) – cortical low gamma (CLG; 31-60 Hz), subthalamic low beta – cortical high gamma (CHG; 61-100 Hz), subthalamic high beta (SHB; 21-30 Hz) – cortical low gamma, and subthalamic high beta – cortical high gamma. Drawing speed was assessed as tangential velocity, and its stimulation-induced improvement, as slope, was correlated with stimulation-induced changes in irPAC values across the two spiral drawing tasks.

Results

The irPAC value during the resting state was significantly higher than during the two movement tasks ($p<0.001$), whereas it did not differ during the two motor tasks ($p=0.76$). The calculated irPAC values did not differ between the four subthalamic-cortical pathways ($p=0.08$). The irPAC value was higher in the pairs of the high beta band than that of the low beta band ($p<0.001$). However, no significant difference was found between the SLB-CLG vs. SLB-CHG ($p=0.42$) and the SHB-CLG vs. SHB-CHG ($p=0.99$). When adjusting the stimulation level, only subthalamic high beta–cortical high gamma irPAC decreased on the fourth stimulation level ($p<0.001$), and its stimulation-induced decrease along the STN-M1 and STN-dorsal premotor cortex hyperdirect pathways correlated significantly with the increase in spiral drawing speed. The three-dimensional distance from the subthalamic centroid to the active lead contact and the preoperative levodopa-equivalent dose best predicted changes in coupling strengths, according to a Support Vector Machine model.

Conclusion

Pathological subthalamic high-beta activity abnormally drives high-gamma motor cortical processing in Parkinson's disease, and subthalamic stimulation decreases this effect. Stimulation-induced decrease in phase-amplitude coupling along the hyperdirect pathways comprising the primary motor and the dorsal premotor cortex correlates with the improvement of bradykinesia during spiral drawing.

P055

Subthalamic deep brain stimulation improves dynamic aspects of locomotor control in Parkinson's disease: a study on ground reaction forces in immersive virtual reality

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Introduction: Gait disturbances are among the most disabling symptoms of Parkinson"s disease (PD) and often respond suboptimally to dopaminergic therapy and deep brain stimulation (DBS). In particular, gait adaptation to environmental challenges remains highly problematic, increasing the risk of freezing of gait and falls. Quantitative evidence on the impact of high-frequency stimulation (HFS) of the subthalamic nucleus (STN) on the ability to adapt gait to obstacles in ecologically valid contexts is still limited. Anterior-posterior ground reaction forces (AP-GRFs) provide a sensitive kinetic measure of braking and propulsive control during walking adaptation and may complement clinical evaluation of DBS impact on gait.

Goals: To quantify the effects of STN-DBS on AP-GRF patterns during an obstacle avoidance task performed in an immersive virtual reality (VR) environment in patients with PD.

Materials and methods: Eight PD patients (age 63.4 ± 6.3 years; disease duration 9.0 ± 4.4 years) with bilateral STN-DBS performed an overground walking task in a fully immersive VR environment under two conditions: without obstacles (VR/VA-) and with a virtual agent (VA) crossing their path in a standardised manner (VR/VA+). All patients underwent overnight withdrawal of antiparkinsonian medications. The task was performed both with active HFS and after at least one hour following DBS deactivation (OFF). GRFs were recorded using four force plates (P6000, BTS) embedded in the gait laboratory walkway, and AP-GRF signals were segmented in correspondence of the steps performed on the force plates. For the VR/VA+ condition, steps performed on the force plates were clustered based on their timing relative to the onset of the obstacle presentation into two groups: Group I, comprising the first and second strides after VA onset, and Group II, comprising the third and fourth strides after VA onset. For each stance phase, we analysed braking and propulsive peak forces, their timing within the gait cycle, the force zero-crossing time, and braking and propulsive impulses normalised to body weight. Variables were compared within condition (VR/VA- and VR/VA+, separately for Group I and Group II) across stimulation modes (HFS vs. OFF) with a Wilcoxon signed rank test ($p=0.05$).

Results: In the unperturbed condition (VR/VA-), HFS significantly increased the propulsive impulse (HFS: 2.24 [1.06–2.87] vs OFF: 2.00 [0.55–2.66], $p < 0.05$; median [range]) and showed a near-significant increase in the braking impulse (HFS: 2.57 [1.22–3.09] vs OFF: 2.40 [0.69–2.77], $p = 0.06$). Additionally, HFS was associated with a reduction in the percentage zero-crossing time (HFS: 50.92% [46.12–61.74] vs OFF: 54.04% [45.13–62.51], $p = 0.06$). In the perturbed condition (VR/VA+), despite improvement trends similar to those observed in the VR/VA- condition, no significant differences emerged between stimulation modes. This may reflect the limited number of steps recorded on the force plates and the inter-individual variability in gait modulation strategies.

Summary: Our findings suggest that DBS can positively influence dynamic aspects of gait performance in PD. AP-GRFs proved sensitive to stimulation-induced changes, supporting their use as quantitative biomarkers to refine DBS outcome assessment and inform the development of targeted rehabilitation strategies. Further studies in larger cohorts are warranted to confirm these preliminary observations.

P056

Clinical improvement after deep brain stimulation is associated with the suppression of pallidal low-frequency oscillations in patients with dystonia

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Introduction: Deep Brain Stimulation of the Globus Pallidus internus (GPi) is a mainstay treatment for medically refractory dystonia, but clinical outcomes can vary significantly. The factors that predict response to DBS remain unclear, also due to our limited understanding of the neural dynamics underlying dystonia pathophysiology. New DBS devices allow the recording of neural activity with chronically implanted electrodes, providing insights into basal ganglia functioning and paving the way for the development of personalised neuromodulation strategies.

Goals: to investigate the relationship between pallidal activity and clinical response to GPi-DBS

Methods: We recorded bilateral pallidal local field potentials (LFP) of eight dystonic patients with GPi-DBS during rest, under chronic stimulation (stim-on), and after switching off stimulation for at least 30 minutes (stim-off). To reduce motion artifacts, synchronous muscular and kinematic recordings of dystonic tremor were regressed out from the LFP signals. Cardiac artifacts were mitigated using a singular value decomposition analysis based on cardiac peaks detected from heart rate monitoring, while stimulation artifacts in the stim-on condition were eliminated using the Period-based Artifact Reconstruction and Removal Method (PARRM). We compared the power spectral densities (PSDs) of the cleaned signals between stim-off and stim-on conditions and correlated them with the severity of dystonia and clinical improvement after surgery, and its percentual variation between pre- and post-DBS.

Results: We observed a suppression by GPi-DBS of power in the alpha (8-12 Hz) and low-beta (13-20 Hz) bands. DBS-induced relative power decrease positively correlated with clinical improvement after surgery in both bands (Pearson"s ρ, alpha band =0.79, beta band = 0.85, $p < 0.05$).

Summary: Our findings suggest that the clinical benefit of GPi-DBS in dystonia patients is linked to a reduction in alpha- and low-beta pallidal activity. Further research on larger cohorts is warranted to define the potential of these biomarkers for the development of novel and more effective adaptive DBS strategies.

P057

Interim report of a clinical trial of physiologically-inspred burst DBS for Parkinson disease

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Question: Adoption of DBS therapy for Parkinson"s disease is hindered, in part, by off-target side-effects, burden of generator replacement or charging, and possible limitations in clinical benefit, especially with respect to gait and non-motor symptoms. Recent optogenetic and computational modeling work has shown that finely tuned intermittent burst-patterned pallidal DBS can differentially modulate specific cell types and produce motor benefits that endure beyond stimulation cessation while reducing stimulation burden. Our team"s pilot study comparing pallidal conventional and burst-DBS (cDBS and bDBS) showed equal efficacy and tolerability, motivating further investigation. The tolerability and effectiveness of pallidal bDBS over longer periods of time and potential persistence of therapeutic benefit remain undefined.

Methods: We conducted a double-blind randomized controlled trial to compare the tolerability and effectiveness of bDBS vs cDBS. Patients with stable pallidal DBS therapy were randomized to either bDBS or cDBS (established clinically) for 1 week each, and assessed off medications after each week with serial UPDRS assessments for up to 3 hours. bDBS was delivered at the same contact(s) and amplitude as cDBS alternating 200ms on and 800ms off at 150 Hz.

Results: At interim analysis, 10 patients were enrolled, including 9 men, with an average age of 67.5y and UPDRS3 off of 36.1. Average duration of implant at time of enrollment: 28.7months. Five of 10 patients completed the two weeks of randomized stimulation. Reasons for not completing the trial included intolerance of being off medications(1), comorbid non-PD neurological symptoms(1), bDBS intolerance due to symptomatic worsening(2), intolerance of cDBS after experiencing bDBS(1). Of those completing two weeks of randomization, off-medication off-stimulation UPDRS3 scores were 28.4±7.7, cDBS off-medication 14.8±1.9, and bDBS off-medication 24.8±5.7. Subscore analyses for tremor, rigidity and bradykinesia suggest that poorer bDBS scores were attributable to lesser control of bradykinesia, whereas rigidity and tremor were generally equally modulated by cDBS and bDBS. While both cDBS and bDBS had similar magnitude of symptom recurrence between 15 and 60 minutes after stimulation termination, cDBS was associated with a greater magnitude of symptom worsening between 15 and 180 minutes after stimulation termination. Other non-motor and quality-of-life measures were equivalent between bDBS and cDBS, including MOCA, QUIP, PDQ39, and PHQ9. Of those completing the two weeks of randomization, 4 preferred cDBS and 1 reported no preference. One participant who strongly preferred bDBS due to improvement in gait and speech (despite attempted blinding) was excluded from final analysis due to not completing one week of cDBS randomization (UPDRS3 off: 45, cDBS: 38, bDBS 27).

Conclusions: This blinded randomized trial comparing cDBS and physiologically-inspired bDBS did not demonstrate predicted tolerance and benefit of bDBS. Interpretation is limited by low compliance with the protocol and assumptions about the optimal site and amplitude of burst-DBS based on prior cDBS settings. Understanding previously demonstrated equal efficacy in the acute setting and disproportionate benefit of bDBS in some patients warrants further investigation of physiologically-defined parameters for patient-specific optimization of bDBS and patient-specific factors that may predispose to benefits from bDBS.

P058

Pre-frontal network flexibility indexes major depression severity

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Major depressive disorder is considered a dysfunction of pre-frontal brain circuitry. We hypothesize that increased depression severity is associated with decreased brain network flexibility, or the ability of the brain to transition between network activity states. We also hypothesize that therapeutic deep brain stimulation (DBS) is associated with increased network flexibility, providing a potential biomarker of therapy.

We recorded resting state intracranial neurophysiology and temporally aligned symptom severity in 6 patients undergoing simultaneous implantation of sEEG and ventral-capsule/ventral-striatum (VC/VS) and subcallosal cingulate (SCC) DBS as part of a study of DBS for treatment-resistant depression. We employed a pairwise maximum entropy model on a network of 8 prefrontal regions using beta band-filtered activity (15-30 Hz). We inferred a shared energy landscape across recordings that enabled computation of an "effective temperature" parametrizing the dynamics of each recording. For each recording we identified attractor basins within the energy landscape, transition probabilities between attractor basins, and dwell times within attractor basins using a Markov model. We quantified group effects using linear mixed effects (LME) modeling after pooling data across patients. To compare our new model parameters to established biomarkers of depression severity, we computed the aperiodic exponent across the different regions using the slope of the power spectrum between 20 and 45 Hz in log-log space. We assessed the effect of therapeutic stimulation on network flexibility in 3 patients. We tested these changes using an LME model that accounted for both stimulation and model accuracy as main fixed effects and subject identity as a random effect to study the effect of stimulation while controlling for changes in model accuracy due to stimulation artifact.

Temperature and transition probability, which represent the brain"s flexibility to transition between states, were both significantly anti-correlated with depression severity across recordings in most patients, ($R = -0.438$ and $p < 10^{-8}$) and ($R = -0.334$, $p < 10^{-5}$) respectively. Mean dwell time, whose increase represents reduced dynamics, was correlated with depression severity ($R = 0.337$, $p < 10^{-5}$). We showed that temperature and transition probability were correlated, while dwell time was anti-correlated, with aperiodic exponent across most prefrontal regions, most strongly in dACC and vmPFC. Lastly, in 3 patients, we showed that VC/VS DBS acutely increased both temperature and transition probability ($p < 10^{-5}$) and decreased mean basin dwell time ($p < 10^{-3}$) while concurrently improving mood. SCC stimulation in one patient, where acute beneficial mood effects were not observed, did not appreciably change brain network flexibility measures, suggesting in part that changes in network flexibility are reflective of therapeutically effective DBS.

As depression severity decreases, prefrontal networks become more dynamic and have lesser propensity to dwell in attractor basins. These measures of network flexibility correlate with both behavioral measures of mood and established physiological markers of depression severity, both with spontaneous variation in mood and with therapeutic stimulation. Network flexibility may serve as a valuable biomarker to guide DBS therapy, both with respect to patient selection and guiding therapeutic interventions.

P059

A connectome approach to determine the risk for cognitive decline following STN-DBS in Parkinson's disease

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Background: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment for motor symptoms in Parkinson"s disease (PD), but cognitive outcomes are variable, with some patients experiencing stimulation-induced cognitive decline. Prior work has linked DBS-related cognitive impairment to connectivity between the stimulation site and distributed cognitive networks, 1,2 leading to a connectivity-based "heat map" that predicts cognitive risk by stimulation location. However, the prevalence of high-risk stimulation profiles in routine clinical practice and the availability of alternative electrode contacts to reduce cognitive risk remain unclear.

Objective: To determine the number of DBS patients in routine clinical practice at risk of cognitive impairment following STN-DBS and to determine whether alternative stimulation parameters can be identified that might mitigate the cognitive risk.

Methods: We studied 120 PD patients with STN-DBS treated at Brigham and Women's Hospital. Electrode locations were reconstructed using pre- and post-operative brain imaging, and clinical stimulation sites were generated using electric field modelling and DBS parameters extracted from the medical record. The intersection between each patient's clinical DBS site and a previously published "cognitive decline heat map" was computed and used to assess patients' risk based on pre-set cutoffs. A recently developed DBS reprogramming algorithm was applied to identify alternative contact configurations and stimulation intensities that minimized intersection with the cognitive decline heat map.

Results: Intersection of clinical DBS sites with the cognitive decline heat map classified 85 patients as low risk, 30 as medium risk, and 5 as high risk for cognitive impairment. The reprogramming algorithm identified alternative DBS settings that showed less intersection with the cognitive decline heat map (than the clinical setting) in 77% of patients.

Conclusion: 29% of patients who have undergone STN DBS at BWH were classified as medium or high risk of cognitive decline based on the location of their stimulation. 85% of these patients had alternative DBS settings on the same electrodes that might reduce this risk.

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P060

Purpose-built spinal cord neuroprothesis alleviates gait deficits in people with advanced Parkinson's disease

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Despite advances in neuromodulation therapies for Parkinson"s disease (PD), a large number of patients with advanced PD develop disturbances of gait and balance, including postural instability, festination, or freezing of gait, that are often refractory to existing treatments. These deficits lead to frequent falls and increase comorbid conditions. We previously reported that epidural electrical stimulation (EES) of lumbosacral spinal cord improved gait asymmetry, shuffling steps, imbalance, and freezing of gait in one patient with advanced PD (STIMO-PARKINSON clinical trial, NCT04956770). This proof-of-concept trial used re-purposed technology that was originally developed to treat chronic pain and is therefore suboptimal for this application.
To confirm our preliminary results, we are now conducting a clinical trial in 6 individuals with PD who presents severe gait and balance deficits (SparkL, NCT06295614). We also aim to resolve technological limitations of repurposed technologies with the evaluation of a purpose-built implantable platform designed for precise stimulation of the spinal cord and enhanced usability to support daily mobility. Our first participant so far demonstrated improved gait quality, extended walking capacities, decreased freezing of gait, and increased confidence during daily mobility. At-home monitoring confirmed these improvements, which translated into a reported increase in his quality of life. These results will have to be confirmed in the next participants.

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P061

Peri-lead edema in deep brain stimulation – how to deal with an unsolved miracle in deep brain stimulation

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Background: Peri-lead edema is an unsolved phenomenon in deep brain stimulation (DBS) with a tremendous impact on patients" clinical courses and increased incidences reported recently. Here, we analyze the evolution of incidences, clinical presentation, therapeutic strategies and outcome over a period of 15 years with a focus on prophylaxis and therapeutic measures.

Methods: In a prospective series of 643 DBS procedures, all patients were routinely investigated by a postoperative CT on day 0 or 1 to exclude complications and to identify lead positions and directional contact orientation by fusion with presurgical images. With a noticeable rise in peri-lead edema, in 2021, specific surgical measures to avoid any lead contamination were undertaken, and an additional CT scan on day 6 to 7 was added in 2022 to exclude or detect any severe perifocal lead edema as early as possible. In clinically symptomatic edema, methylprednisolone infusions were administered for 3 days. At the end of 2022 systematic edema prophylaxis with dexamethasone for three days was started at surgery. All incidences were documented and discussed at weekly interdisciplinary meetings. Patients" files were searched for further factors possibly related to edema formation.

Results: Among 643 DBS procedures, 106 patients with radiologically proven peri-lead edema, 70 asymptomatic (11%) and 36 (5.6%) with clinical symptoms were identified. Before the systematic repeat CT one week after implantation, the incidence of peri-lead edema was 2.8%, since then it has risen to 4.4% in 2022 to 2023, and to 8.8% in 2024 to 2025. Symptomatic patients presented with delirium in 10, with headaches in 3, hemiparesis in 1, with apathy and/or aphasia in 13 patients and with epileptic fits in 9 patients. All patients have recovered completely. Individual patient constitution and medication might increase their liability for hypersensitization, but need further investigation.

Conclusions: Peri-lead edema occurs more frequently than presumed and obviously has increased in recent years by incidence and by clinical severity and can no longer be named a benign symptom. Our protocol change to early repeat CT at one week after implantation has definitely detected more patients with peri-lead edema, also numerous asymptomatic cases, but has enabled early enhanced anti-edema medication and has prevented any long-term sequels. Especially, the prophylactic use of steroids has not caused any new infections.

P062

Identifying the neuromodulation blind spot for gait and balance control in Parkinson's disease

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Gait and balance impairments remain among the most disabling features of Parkinson"s disease and are only partially alleviated by today"s neuromodulation therapies. Subthalamic deep brain stimulation (STN-DBS) effectively improves major motor symptoms but often leaves gait and balance deficits untouched. Lumbosacral epidural electrical stimulation (EES) can restore locomotion and stability in selected cases, yet its mechanisms are not fully understood and do not resolve symptoms in all patients. These limitations point to a critical gap in our understanding of the neuronal architecture recruited by STN-DBS and EES, and suggest the existence of a neuromodulation blind spot—balance and gait circuits that neither therapy effectively engages.

To identify these missing circuits, we used a transgenic Parkinsonian mouse model (MCI-PD) that progressively develops the combined gait–balance impairments characteristic of the disease. Using a controlled behavioral paradigm requiring dynamic postural adjustments, we mapped whole-brain transcriptional activity in wild-type and MCI-PD mice to reveal circuit-level dysfunction underlying these deficits. We then performed the same mapping during STN-DBS and during lumbosacral EES to determine how each therapy engages the neuronal architecture of gait and balance control—and where their influence fails to reach.

This approach identifies the neuromodulation blind spot, the set of gait–balance circuits that escape recruitment by both STN-DBS and EES. By exposing these missing targets, our work provides a foundation for next-generation neuromodulation strategies designed to stimulate the full architecture required to restore stable locomotion in Parkinson"s disease.

Computational modelling and imaging in DBS

P063

Moving beyond trial and error: Interim analysis of the CONECT Trial (Comparative evaluation of standardized imaging-guided CONtact SelECTion for subthalamic deep brain stimulation in Parkinson's Disease)

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Background

STN-DBS provides effective motor symptom control in advanced Parkinson's disease. Conventional programming relies on trial-and-error monopolar reviews, which are time-intensive and subjective. Imaging guided programming promises increased efficiency and possibly improved outcomes. Our previous research suggests subtle variations in methodology significantly impact therapeutic effects. This prospective, double-blind, randomized crossover study evaluated a standardized imaging-guided contact selection protocol against conventional clinical programming.

Objective

Comparative Evaluation of Standardized Imaging-Guided Contact Selection for Subthalamic Deep Brain Stimulation in Parkinson's Disease

Methods

We recruited PD patients with directional STN-DBS (age 60.9±5.9 years, disease duration 9.9±4.4 years, DBS duration 1.8±1.7 years). Participants received reprogramming via clinical programming and imaging-guided contact selection. Both treatments were applied for one week in blinded random order with autonomous amplitude titration. Primary outcome was patient preference (Prescott Test). Secondary outcomes included MDS-UPDRS III, UPDRS IV, FOG-Q, and stimulation characteristics. This planned interim analysis included 18 subjects. This study was preregistered (DRKS00034229) and monitored, the study protocol has been submitted for publication.

Results

Imaging-guided programming was strongly preferred (77.8% vs 22.2%, p=0.03, RR 3.5, NNT 1.8, Cohen"s h=1.23). Both approaches improved MDS-UPDRS III (Med OFF) from baseline (38.8±12.4 pts), but imaging-guided programming achieved significantly greater motor symptom reduction at chronic assessment (64.9±10.5% vs 48.4±22.2%, p<0.001) and lower final scores (14.1±7.1 pts vs 19.6±8.8 pts, p<0.01), despite comparable acute effects. Imaging-guided reprogramming provided additional 23.1±3.9% symptom reduction versus baseline (p<0.001).

Imaging-guided selection led to more complex configurations with increased multilevel (72.2% vs 25.0%, p<0.001) and directional steering (97.2% vs 83.3%, p=0.074). Clinical selections showed

lower rigidity thresholds (1.47±0.63 mA vs 1.65±0.66 mA, p=0.012) and wider therapeutic windows (2.60±1.08 mA vs 2.09±0.70 mA, p<0.001). Final amplitudes were similar (2.18±0.81 mA vs 2.21±0.79 mA). Superior efficacy was driven by enhanced control of akinetic-rigid symptoms and reduced fluctuations.

Conclusion

Standardized imaging-guided DBS contact selection induced perceivably improved symptom control with greater motor improvements than traditional programming, possibly due to more sophisticated stimulation configurations. Benefits were not apparent during acute evaluation or predicted by thresholds, challenging established routines like monopolar review. These findings support integrating imaging guidance into routine DBS programming and emphasize the need for standardized protocols. The study protocol provides for early termination given the demonstrated non-equivalence between treatment arms.

P065

Cortical feedback and conduction delays determine STN beta burst dynamics and DBS response: clinical validation across on/off states

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Exaggerated beta oscillations (13-35 Hz) are a hallmark of Parkinson's disease (PD), prominently observed in local field potential recordings from the subthalamic nucleus (STN). At the millisecond timescale, these pathological oscillations manifest as bursts, whose duration distinguishes parkinsonian from physiological states. Deep brain stimulation (DBS) alleviates PD motor symptoms by suppressing these exaggerated beta oscillations through electrical impulses delivered via implanted electrodes. However, therapeutic optimization has been hindered by reliance on clinical trial-and-error testing of stimulation parameters and adaptive algorithms, imposing substantial burden on patients. To address this challenge, we developed a biophysical, conductance-based computational model of the cortex-STN-external globus pallidus network to investigate DBS effects on pathological beta bursts. Our results demonstrate that reproducing clinically-observed STN bursting dynamics and DBS responses requires explicit incorporation of cortical feedback and physiologically realistic synaptic delays. These components introduce critical non-linearities that govern burst generation and modulation. The resulting model accurately captures individual patient burst profiles across DBS ON and OFF states, validated against clinical recordings. This work establishes that cortical mechanisms and transmission delays are essential for developing in-silico models capable of predicting patient-specific DBS settings. Such computational frameworks could optimize stimulation parameters for sustained beta burst suppression, potentially improving motor outcomes while reducing the clinical programming burden in PD treatment.

P066

Electrophysiological correlates of reinforcement learning in the human ventral tegmental area

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Introduction

As the principal source of dopaminergic input to the human prefrontal cortex, the ventral tegmental area (VTA) is central to reinforcement learning. Yet direct electrophysiological evidence for reward-related signals in the human VTA during instrumental learning remains scarce. We used a clinical opportunity provided by VTA deep brain stimulation surgery to examine whether human VTA local field potentials show reinforcement learning signals consistent with those reported in animal studies.

Goals

To characterise how human VTA LFPs recorded during a probabilistic instrumental learning task encode outcome, the expected value of the chosen option and reward prediction error, and to relate these signals to behavioural and clinical measures.

Materials & Methods

Fourteen subjects (9 male, mean age 46 ± 10 years) with chronic cluster headache undergoing VTA DBS took part. During temporary electrode externalisation, they performed an instrumental learning task with three trial types (reward, loss, neutral). Bipolar VTA LFPs were recorded and epoched relative to stimulus, button press and outcome events. Behaviour was modelled with a hierarchical Rescorla-Wagner model with separate learning rates for rewards and losses and an inverse temperature parameter. For each trial type, subjects were assigned Random, Consistent or Gradual behavioural types based on model fit and choice trajectories. Single-trial outcome-locked LFP amplitudes were analysed using Statistical Parametric Mapping and linear mixed effects models including trial type, outcome label and clinical covariates.

Results

Clear evoked VTA responses were observed for stimulus and outcome events, except for one subject. Outcome-locked responses were significantly larger for wins than for losses or neutral outcomes, while loss and neutral responses did not differ reliably, indicating selective sensitivity to reward. In the linear mixed effects model (N = 13), all three trial types showed a positive effect of outcome label, with a large win minus nothing effect ($\beta = 0.309$, $p < 1\times10^{-15}$). Only 9 of 14 subjects developed a clear preference for the high-reward option, and among these learners 2 subjects displayed "Gradual", trial-by-trial learning, while the others adopted a "Consistent" win-

stay strategy. In a subset of eight subjects, whose reward choices allowed reliable estimation of trial-wise chosen value, activity around the button press correlated with the expected value of the chosen option. Analyses conditioning on outcome and value did not provide strong evidence for a distinct reward prediction error signal. Clinical scores and smoking status did not significantly correlate with the observed effects.

Summary

Human VTA population activity recorded from DBS electrodes is robustly tuned to rewarding outcomes and, when behaviour shows effective exploration and learning, reflects the expected value of the chosen option around decision time. We did not find clear evidence that VTA LFPs encode a distinct reward prediction error signal beyond outcome and value, in line with the suggestion that LFPs are representative of VTA inputs rather than its output. These findings show that human VTA activity carries reward-related signals consistent with reinforcement learning accounts from animal models and support the translational relevance of VTA DBS.

P067

Leveraging evoked cortical potentials to dissect pathway involvement in STB-DBS

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Question

DBS of the STN area may affect a wide variety of neuroanatomical structures and pathways. This study investigates whether different DBS evoked cortical potentials (DBS-ECPs) can be used as biomarkers for the recruitment of different neuroanatomical pathways and loops.

Methods

N = 20 subjects (n = 37 hemispheres) with PD and STN-DBS received high-density EEG recordings during monopolar stimulation at each available DBS contact with 10 Hz and amplitudes of 0.5 mA, 2.0mA, and 4.0mA (n > 800 DBS settings). DBS-ECPs were analysed by averaging EEG data over DBS pulses and identifying different ECPs using topographies and channel-wise statistics. We then used a variety of probabilistic voxel-wise mapping techniques to investigate the neuroanatomical origins of different ECPs.

Results

We identified three distinct ECPs: First, a positive deflection at 25 ms post-stimulus (P25), centred at the motor cortex, originated primarily from DBS medial to the STN. Further analyses and comparisons with TMS literature suggested that this ECP might be related to DBS of the cerebello-thalamo-cortical system by activation of the dentate-rubro-thalamic-tract (DRTT). Second, we identified a negative deflection at 55 ms post-stimulus (N55) and, third, another positive deflection at 80 ms post-stimulus (P80). Both N55 and P80 were centred at more prefrontal areas. Probabilistic voxel-wise mapping revealed that both N55 and P80 originated from stimulating an overlapping area lateral and dorsal to the STN. Furthermore, N55 and P80 amplitudes showed a strong correlation, suggestive of an oscillatory nature of the activity. An exploratory fiber-wise analysis suggested that these potentials might be related to stimulation of the direct and/or indirect pathways of the basalganglia-cortex system either by stimulating output pathways of the pallidum like the ansa lenticularis and the fasciculus lenticularis or by stimulating pathways connecting the STN to the pallidum and vice versa.

Discussion

Using a combination of high-density EEG recordings and DBS imaging techniques, our work clearly demonstrates how DBS-ECPs can be used to dissect the involvement of different pathways of the STN area. When combining these approaches with clinical data, DBS-ECP will serve as an important tool to identify the anatomical and physiological underpinnings of clinically effective DBS settings.

P068

Refining probabilistic mapping for deep brain stimulation: practical guidelines for parameters selection

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Introduction: Automated Deep Brain Stimulation (DBS) programming and prediction of DBS effects using probabilistic mapping of patient cohort data have gained increasing attention in recent years. Many existing studies rely on established workflows and default workflow parameters whereas few studies have investigated the influence of these parameters.

Goals: The present study aimed to provide guidelines for tuning probabilistic mapping workflows based on input data characteristics, with the final outputs being optimal stimulation areas (Probabilistic Sweet Spots, PSS) or regions associated with side effects.

Materials & Methods: The guidelines were developed based on intraoperative stimulation test data from 65 patients (23 with Essential Tremor and 42 with Parkinson"s disease) who underwent bilateral DBS implantation at the University Hospital of Clermont-Ferrand, France, and postoperative stimulation test data from 61 Essential Tremor patients treated at Norrlands University Hospital in Umeå, Sweden. PSS were generated for different patient groups by systematically varying workflow parameters, and their anatomical locations and geometrical characteristics were analyzed.

Results: The first critical parameter in probabilistic mapping is the choice of statistical test [1], which depends on the input data type. For discrete data, Bayesian t-tests (B) or Wilcoxon tests (W) are recommended; these tests, along with t-test (T) and linear mixed models (LMM), are also suitable for continuous data. LMMs are particularly useful when patient dependency needs to be modelled, and for B it is important to choose an appropriate prior probability distribution. Binary data, such as side-effect information, should be analyzed using binomial (Bin) tests. For small sample sizes, B are preferred due to their robustness, whereas larger cohorts (≥25 patients) allow the use of alternative tests. For B, W and T, an improvement threshold must be defined: a fixed threshold should be used if a clinically relevant score exists; otherwise, a flexible threshold (e.g., the cohort median) may optimize identification of effective stimulation areas. Bin, T and W require correction for multiple comparisons, with non-parametric permutation approaches preferred over False Discovery Rate corrections due to their consideration of the spatial distribution of electric fields. Voxels are subsequently assigned statistical values and classified as significantly or non-significantly associated with clinical effects. Commonly used significance thresholds are p-value<0.05 for Bin, W, T, and LMM, and Bayes Factor ≥10 for B. Voxels stimulated in too few patients or tests are discarded from the final volume, with stricter criteria resulting in smaller probabilistic volumes.

Summary: These steps yield probabilistic volumes that can inform downstream analyses, including programming algorithms and predictive models based on overlap or distance to stimulation-induced electric fields. Our studies underscore the critical influence of parameter selection, particularly the statistical test and improvement threshold, on the location and size of

probabilistic volumes, emphasizing the need for careful tuning to ensure reliable DBS mapping and programming.

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P069

Subthalamic Nucleus Stimulation in Parkinson's Disease and Impulsivity: A Multimodal Topographical Analysis of Theta and Beta Oscillations

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Introduction: Impulse control disorders (ICDs) are a common non-motor complication of Parkinson's disease (PD), often related to dopaminergic therapy [1]. In addition, subthalamic nucleus (STN) deep brain stimulation (DBS) may modulate impulsivity, especially when stimulation propagates into associative or limbic territories beyond the dorsolateral motor subregion [2]. Previous studies suggest that theta oscillations (4 – 8 Hz) within the STN are linked to impulsive behavior [3]. Yet, it remains poorly understood how these oscillations are spatially organized within the STN and how they relate to impulsive behavior.

Goals: The objective of this study is to characterize the spatial distribution of theta and beta (13 – 30 Hz) oscillations within the STN and their modulation by dopaminergic medication, using two complementary mapping approaches.

Materials & Methods: In n=25 PD patients with deep brain stimulation in the STN, local field potentials (LFPs) were recorded using Medtronic SenSight™ electrodes (B33005) and Percept™ neurostimulators (B35200/B35300). The examinations were performed 3, 6, and 12 months after implantation with stimulation turned off. Power spectra in the theta and beta bands were computed, and electrode positions were reconstructed and normalized to MNI space using Lead-DBS. Two mapping approaches were applied: (1) a coordinate-based method interpolating power across contacts to generate 3D topographies, and (2) a voxel-based model simulating the sigmoidal spatial decay of neuronal contributions within a ~2–3 mm influence radius, yielding probabilistic activity maps.

Results: Preliminary analyses revealed distinct spatial patterns of oscillatory activity within the STN across postoperative assessments at 3, 6, and 12 months. Theta-band power was predominantly localized in the ventromedial STN, overlapping with limbic–associative regions, whereas beta-band power was concentrated in the dorsolateral motor region. Both coordinate- and voxel-based mapping approaches produced highly consistent spatial distributions. These results suggest a robust, frequency-specific functional segregation within the STN, with theta and beta activity corresponding to limbic–associative and motor regions, respectively.

Summary: The findings shed new light on the frequency-specific functional segregation of STN oscillations revealed by multimodal mapping, showing ventromedial theta activity as a potential electrophysiological marker of impulsivity and dorsolateral beta activity delineating motor regions. This research offers significant insight into patient-specific DBS electrode placement and stimulation programming, supporting adaptive strategies to minimize ICD risk and enable targeted interventions to reduce impulsive behavior.

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P070

Prediction of STN-DBS outcome in Parkinson's disease using machine learning

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Question

Deep brain stimulation (DBS) targeting the subthalamic nucleus (STN) is an established therapy for advanced Parkinson's disease (PD) but outcomes vary significantly among patients. The ability to accurately predict clinical outcome in individual patients would facilitate the selection of suitable candidates for DBS surgery and improve expectation management for patients and clinicians. Our aim was to explore relevant predictors and assess the potential of machine learning (ML) models in predicting remaining motor symptom severity after STN-DBS treatment based on demographic and clinical information that is available before surgery.

Methods

We conducted a retrospective cohort study based on data from 408–420 PD patients (depending on outcome) collected as part of clinical routine care at the Amsterdam University Medical Center. The Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III and subscores for Tremor, Axial symptoms, and Bradykinesia & Rigidity obtained off medication on stimulation around 12 months afer surgery served as outcomes. Preoperative predictors included age, sex, disease duration, the presence of impulse control disorder, days between screening and postoperative follow-up, total levodopa equivalent dose, preoperative MDS-UPDRS-I-II-III-IV scores obtained on and off medication as well as improvement percentages in MDS-UPDRS-III post-levodopa administration, quality of life, and apathy scores. After feature extraction to narrow down the predictors to the most relevant, three different ML algorithms, Random Forest, Linear Regression, and LASSO, were trained for each outcome measure using 5-fold cross-validation. Their performance was evaluated by calculating the root mean square error (RMSE) between predicted and observed motor outcomes in a separate test dataset containing 20% of the available data. A SHAP (SHapley Additive exPlanations) analysis was performed to examine the individual contributions of features to the best performing model"s predictions.

Results

For both the total MDS-UPDRS-III model and the Axial symptom model, linear regression emerged as the best model type. The Random Forest Regressor was identified as the optimal model for Tremor and LASSO for the Bradykinesia & Rigidity model. The models explained 25%-30% of the variability in patient outcomes, achieving RMSE values of 9.1, 2.6, 2.5, and 5.3, respectively. The most influential factors were found to be the preoperative MDS-UPDRS-III scores in both on and off medication states, with age having a comparatively smaller impact. A more complex interplay of feature importance was observed for the Axial and Bradykinesia & Rigidity models.

Conclusions

These results demonstrate the ability of ML models to provide accurate predictions of remaining motor symptoms after STN-DBS in PD patients based on preoperative information alone, despite the heterogeneity of PD. This approach could in principle contribute towards refining patient selection by forecasting postoperative outcomes and enabling personalized treatment planning. Future iterations will explore additional predictors, such as neuroimaging data, to further improve model performance and support clinical decision-making in DBS therapy.

P071

Long-lasting concordance between imaging-guided and clinical-based STN-DBS programming enhances motor and axial outcomes in Parkinson's disease: a 3-year single-center study

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Question: Lead placement visualization softwires can facilitate subthalamic deep brain stimulation (STN-DBS) programming, especially in contact selection process. Does concordance between imaging-suggested (IGP) and standard clinical-programming (CP) selected stimulation contacts impact on STN-DBS motor outcomes in the long-term follow-up?

Methods: Thirty-five PD patients with bilateral STN-DBS were enrolled. Lead localization was reconstructed using Brainlab™. For each electrode, the predicted optimal vertical contact and, when applicable, directionality was identified and compared with stimulation parameters clinically activated three years post-surgery. Concordance, agreement and similarity IGP/CP metrics were calculated for both contact level and directionality. Postoperative changes in motor symptom severity were compared between concordant and discordant IGP/CP groups.

Results: Three years after surgery, IGP/CP concordance was 77.6% for active stimulation contact level and 66.7% for directionality. IGP reliably identified contacts and directional segments avoided by CP for chronic stimulation (negative predictive value 0.85 and 0.72, respectively). No significant difference was found in motor outcomes based on IGP/CP contact level concordance. Nonetheless, superior benefit in overall motor function and axial impairment (including speech) were reported in patients with clinically-activated directional stimulation concordant with that suggested by visual reconstruction.

Conclusions: Visualization software can simplify STN-DBS programming, especially by reducing the number of contacts warranting systematic clinical testing via monopolar review. Moreover, the combination of visualization and directional stimulation technologies can further improve outcomes, especially of those symptoms, like axial/speech impairment, often challenging subthalamic chronic stimulation.

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P072

Biophysical modeling of corticospinal tract activation predicts stimulation-induced motor contractions in STN-DBS

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Background: In Subthalamic Nucleus Deep Brain Stimulation (STN-DBS), the corticospinal tract (CST) lies in close proximity to the therapeutic target. Co-activation of the CST can elicit tonic motor contractions, a common side effect that restricts the therapeutic window of STN-DBS. Reliable estimation of stimulation-induced side-effect thresholds, both intraoperatively during electrode implantation and postoperatively during clinical programming, is therefore crucial to prevent reduced treatment efficacy. At present, these thresholds are determined through extensive clinical testing, which prolongs surgery and imposes considerable burden on patients and clinical staff during postoperative DBS optimization. Neuroimaging-based strategies are increasingly used to estimate side-effect thresholds. However, such estimations typically rely on experience or coarse anatomical metrics, limiting their predictive precision.

Aim: To develop and validate a data-driven model that predicts DBS-induced tonic motor contractions for both intraoperative test stimulations and postoperative programming using individual neuroimaging data and biophysical pathway activation modeling (PAM) of CST activation.

Methods: 42 patients with Parkinson's disease who underwent STN-DBS surgery were included. Intraoperatively, test stimulations were applied with 0.5 mA increments up to 7 mA or until motor contractions occurred, with pulse width fixed at 60 µs and frequency at 130 Hz. Additionally, 12 patients implanted with directional electrodes underwent postoperative monopolar review. Motor contraction thresholds were determined via electromyography and visual inspection. Intraoperative stimulation sites and postoperative electrode locations were reconstructed using stereotactic frame coordinates and CT artifacts, respectively. The CST was delineated from the HCP-1000 connectome and nonlinearly warped to patient space using multispectral symmetric diffeomorphic registration. PAM was performed using the OSS-DBS toolbox, incorporating biophysically plausible axon-diameter distributions and functional-anatomical gradients within the CST. Generalized linear mixed-effects models were applied to relate CST activation metrics to motor contractions. Model performance was evaluated using leave-one-patient-out cross-validation and quantified with R^2 and mean absolute error.

Results: During surgery, stimulation-induced motor contractions occurred at 331 of 356 intraoperative stimulation sites with a mean threshold of 3.9 ± 1.3 mA. PAM-based CST activation predicted intraoperative motor contraction thresholds and explained 31 percent of the variance, with a mean absolute error of 0.85 mA across all stimulation sites. Postoperatively, motor contractions were observed at 164 of 176 examined contacts with a mean threshold of 3.3 ± 1.0 mA. The model explained 31 percent of the variance in postoperative thresholds with a mean absolute error of 0.61 mA. Across all eight contacts, the model correctly identified the level with the lowest empirical motor contraction threshold in 11 of 22 cases and within directional lead levels it correctly identified the contact with the lowest threshold in 37 of 44 cases.

Conclusion: We developed and validated a predictive model for stimulation-induced motor contractions that may support stereotactic trajectory planning and postoperative programming of STN-DBS.

P073

Automated DBS programming of stn in Parkinson's disease: a study protocol comparing 3 programming modalities

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Introduction

Advances in neuroimaging have enabled imaging-guided DBS programming, which integrates structural MRI to personalise stimulation by visualising lead location, modelling volume of tissue activated, and estimating optimal configurations. Illumina3D is a newer platform that uses imaging and computational modelling to refine DBS programming, but its clinical equivalence to traditional programming, particularly for STN DBS in Parkinson"s disease (PD), remains unproven. Also, it remains to be established whether automated programming needs to be refined by the clinician to achieve full control of symptoms in people with PD and STN DBS.

Goals

This study evaluates whether pure or neurologist-guided Illumina3D programming matches conventional contact-based programming.

Materials and Methods

Comparisons include MDS-UPDRS III scores in OFF medication/ON stimulation, time spent in severe bradykinesia measured by PKG, gait and speech metrics recorded with gait and vocal analysis, and patient-reported outcomes to determine overall clinical effectiveness.

Eligible participants are ambulant people with PD (HY ≤3) who have Boston Scientific DBS programmed conventionally with contact review.

The study includes four visits over 4 weeks, with continuous PKG monitoring. At Visit 1, patients are tested under four DBS conditions: standard programming, pure automated programming by Illumina3D, neurologist-guided Illumina3D programming, and OFF medication/stimulation. After Visits 1–3, one of the three active programs is randomly applied for two weeks before reassessment in the OFF medication/ON stimulation condition.

Results

We will present the study protocol.

Summary

With this study, we seek to demonstrate the feasibility and modalities of automated DBS programming in clinic and his long-term effects at home in people with Parkinson"s disease treated with STN DBS.

P074

Neuroimaging analysis of small vessel disease effects on neuromodulatory prognosis

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In the last decade, a large body of neuroimaging literature was published addressing problems of neuromodulatory targeting and its effects on clinical and behavioral outcomes. However, despite an increase in accuracy and precision of targeting, not all patients reach a desired level of symptom alleviation. While many factors contribute to suboptimal outcomes, one potentially major factor is brain abnormalities, among which is small vessel disease (SVD). This is especially relevant for neurodegenerative disorders, such as Parkinson"s disease, dystonia and Alzheimer"s disease, which are often accompanied by profound neuroanatomical deficits. Classification and quantification of these deficits is crucial to address concerns regarding: disruption of neural substrate mediating neuromodulatory effect; disruption of distributed neural networks mediating neuromodulatory effect; changes in dielectric tissue properties and, consequently, stimulation effects.

Currently, SVD segmentation is a tedious semi-automated process. Although different software tools were developed to address this issue, they are limited to specific SVD manifestations. Therefore, to facilitate their use in a time-constrained clinical routine, we develop a dedicated MRI-based pipeline. For that, we first review and test currently available software tools for automated SVD segmentation. Based on their performance across different SVD manifestations (white matter hyperintensities, lacunes and enlarged perivascular spaces), we assemble a pipeline that provides optimal performance for the clinical population given available imaging data. Next, we assess clinical relevance of SVD segmentation across retrospective cohorts of patients, who underwent deep brain stimulation (DBS) for Parkinson"s disease and dystonia. In particular, we analyze the effects of SVD on motor outcomes using statistical mapping of stimulation sites as well as structural and functional network mapping. Finally, we deploy the pipeline for a use in clinical routine, including DBS work-up.

A proper delineation of SVD will provide crucial patient-specific information on the current brain state and its potential susceptibility to effective neuromodulation. Furthermore, together with lead localizations and electric field modeling, it will allow highly-informed image-based DBS programming, paving the way to individualized neuromodulatory treatment.

P075

Containerized and reproducible pipelines for cortico–subthalamic signal analysis in DBS studies

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1. Introduction Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an established therapy for Parkinson"s disease (PD), yet the neural mechanisms underlying its therapeutic effects—particularly the contribution of pathological beta-band synchronization (13–30 Hz) and its engagement of the hyperdirect cortico–subthalamic pathway—remain incompletely understood. Heterogeneous analytic pipelines, inconsistent preprocessing methods, and poor reproducibility across studies and species limit progress. A standardized computational framework is required to integrate multimodal neurophysiological data and advance mechanistic understanding and DBS optimization.

2. Goals This project aims to (i) develop a reproducible, platform-independent analytic framework for multimodal DBS-related electrophysiology; (ii) characterize frequency-specific cortico–subthalamic interactions with emphasis on beta-band dynamics; and (iii) validate directed connectivity patterns—particularly cortex → STN high-beta drive—using simultaneous EEG–STN-LFP data from PD patients.

3. Materials & Methods We developed fc_jupyter, a Docker-based, self-contained computational environment that standardizes preprocessing, spectral estimation, and directed connectivity analysis. The workflow integrates time-domain, frequency-domain, and information-theoretic causality estimators to capture linear, spectral, and nonlinear dependencies. Statistical robustness is ensured through bootstrapping, surrogate-based null models, and time-reversal analyses to confirm directionality.

The pipeline was validated using simultaneous EEG and STN-LFP recordings from seven PD patients undergoing DBS implantation, with stimulation frequencies of 55, 85, 110, and 125 Hz. Cortical sources (SMA, mesial M1) were reconstructed, and high-beta (21–30 Hz) versus low-beta (13–21 Hz) interactions were compared using non-parametric within-subject permutation tests. Directed connectivity was evaluated against surrogate distributions.

4. Results Across all seven patients, STN-LFPs showed prominent beta-band activity. Cortico–subthalamic coherence was significantly greater in the high-beta than low-beta band ($p < 0.01$), with SMA and mesial M1 consistently exhibiting the strongest coupling to the STN. Directionality analyses revealed a significantly high-beta cortex → STN influence ($p < 0.05$), while STN → cortex interactions did not exceed surrogate-based thresholds.

5. Summary This work introduces and validates fc_jupyter, a scalable and reproducible pipeline for multimodal DBS data analysis. By processing real patient datasets and recovering hallmark features of cortico–subthalamic high-beta interactions, the framework addresses key reproducibility challenges and enhances cross-study comparability. It establishes foundational methods for harmonizing multimodal and cross-species analyses and advances the mechanistic understanding of Parkinsonian beta dynamics. Future developments will extend the workflow to additional frequency bands and preclinical datasets, supporting both basic research and clinical refinement of DBS therapies.

P076

Distinct local and global functional network reorganization underlying STN versus GPi DBS in Parkinson's disease

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Question

While both Subthalamic Nucleus (STN) and Globus Pallidus internus (GPi) Deep Brain Stimulation (DBS) are effective treatments for Parkinson"s disease (PD), target selection remains largely empirical and personalized decision-making is challenging. Specifically, the differential modulation of local and global brain networks by these two targets is poorly understood. In this study, we investigated the stimulation-induced connectome to provide neuroimaging-based evidence supporting mechanistic differences in target selection.

Methods

Fifty-five PD patients (63.4 ± 7.9 years; 36 male, 19 female) underwent DBS targeting the GPi (n=28) and STN (n=27). Functional connectivity (FC) seeded from the Volume of Tissue Activated (VTA) was calculated using Pearson correlation following deep learning-based time-series filtering to isolate local functional associations. To probe global topological changes between stimulation conditions, we utilized functional gradients analysis. Finally, the Neurosynth decoder was utilized to link the identified brain network differences to normative functional annotations and cognitive domains.

Results

Locally, both STN and GPi DBS exhibited increased VTA-seeded functional connectivity with the motor cortex during the ON-stimulation state compared to OFF-stimulation (adjusted $p<0.05$), alongside distinct frontal region associations (adjusted $p<0.05$). Globally, however, the targets diverged: GPi DBS was associated with higher prefrontal gradients and lower temporal cortex gradients compared to STN DBS (adjusted $p<0.05$). These differences were predominantly situated in transmodal (non-sensory-specific) brain regions rather than primary sensorimotor networks, and were specifically annotated as being associated with the Inhibitory Control Network (rho = 0.34).

Conclusions

Our findings reveal critical functional dissociations between the two modulation targets. While both engage motor networks, GPi DBS distinctively preserves transmodal network organization, providing a mechanistic explanation for its more favorable cognitive side-effect profile compared to STN DBS. These network signatures offer potential biomarkers for predicting clinical outcomes and minimizing adverse cognitive effects and personalized surgical targeting.

P077

Diffusion MRI in STN-DBS - comparison with in-situ light intensity measurements

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Introduction

The use of tractography and connectomics in relation to DBS planning and follow-up is increasing. The calculations prior to visualization of the white matter tracts are based on mathematical models and statistical methods, which are difficult to verify. As a step towards intraoperative verification, we have implemented in-situ laser Doppler flowmetry recordings to measure backscattered total light intensity (TLI), i.e., a proxy for tissue grey-whiteness [1], and developed a workflow for probabilistic tractography from high-angular diffusion MRI [2].

Goals

To present a method for direct comparison of diffusion MRI with in-situ TLI measurements along the DBS insertion trajectory. Preliminary results from two patients are used for demonstration.

Materials and Methods

Patients referred for bilateral STN-DBS implantation were included after informed written consent (Dnr. 2024-02152-01). The day before surgery, diffusion MRI (dMRI, 2 mm isotropic voxels, b-values up to 2000 s/mm^2, 102 diffusion sensitizing gradient directions) and T1-weighted MRI (3 T Skyra, Siemens Healthineers, Germany) were acquired [2]. On the day of surgery, a stereotactic T_2w MRI (0.5x0.5x2 mm^3) was acquired for trajectory and target planning. During surgery, an in-house-developed fiber-optic probe was used for guidance and optical measurements (FluoRa 1.0, LiU, Sweden, [3]) of Perfusion (microcirculation) and TLI along the preplanned trajectories. With the probe attached in the Leksell Stereotactic System® (Elekta Instrument AB, Sweden), a mechanical insertion device was used to move the probe incrementally from cortex towards the target in steps of 5 mm (60-25 mm from target), 1 mm (25-10 mm from target), and finally 0.5 mm steps the last 10 mm [3]. Postoperatively, the average Perfusion and TLI were calculated over 5 s intervals and combined with data from corresponding positions in dMRI scalar maps (fractional anisotropy, FA; mean diffusivity, MD) and T_2w images. For comparison TLI, FA, MD and T2w were plotted for each trajectory. As a next step more data will be collected, and probabilistic tractography added.

Results

Of 178 measurement positions, 12 presented slightly increased Perfusion of which 9 were found in the cortical region. The TLI trajectories agreed with previously presented STN-curves [1] with low TLI in the cortical region, increased TLI along the internal capsula and a small decrease when in target. Similar trends between T_2w, TLI and MD curves were found along the respective trajectories. The FA presented inverse trends with the lowest FA in the cortical region. This workflow will be further developed and fine-tuned for the investigation of tractography reconstruction and its relation to high-resolution in-situ measurement of light intensity matter. A long-term goal is to develop a method that can help verify tractography with in-situ measurements.

Summary

A workflow for combining diffusion MRI and optical measurements in relation to DBS-implantations has been presented. The combination of probabilistic tractography with in-situ measurements of tissue light intensity is a potential method for verification of white matter tracing.

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P078

Computational models to investigate the effect of weak DBS fields on the (de)synchronization of neurons

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Introduction

Deep brain stimulation (DBS) is an established treatment for alleviating the motor symptoms of Parkinson"s disease (PD). Yet, the therapeutic mechanism remains debated. Traditionally, DBS has been explained as working purely through the influence of strong electric fields. However, recent findings from non-invasive brain stimulation show that weak sinusoidal electric fields [1,2] can synchronize and desynchronize neuronal activity. While DBS applies short, pulsed stimulation, it remains unclear whether the resulting weak electric fields also modulate neural synchronization. This work addresses this question at the level of individual neurons, by focusing on the synchronization (entrainment) of single cell models.

Goal

Investigate the effect of weak electric DBS fields on the entrainment of cortical neurons

Methods

We simulated morphological realistic multicompartment models, representing cortical neurons [3]. Five different cell types from different layers of the cortex were simulated. An external electric field with typical high frequency DBS pulses was applied to all models. We assessed the effect of the electric field and its amplitude on the entrainment to the stimulation, using the phase-locking value (PLV).

Results

Weak DBS fields alter neuronal spike timing. Specifically, spike times tend to cluster immediately after each DBS pulse, creating a non-uniform distribution of spike times. This clustering increases the phase-locking value (PLV), indicating a stronger neural entrainment. Neurons with different morphologies exhibit distinct entrainment patterns. While most show a linear increase in PLV with stimulation amplitude, others display only subtle fluctuations. Moreover, neuron type influences the specific phase the neuron is locking to.

Conclusion

Electric DBS-like fields with low amplitudes (<10 V/m) can modulate cortical neural dynamics by entraining single neuron activity to the stimulation frequency. This suggests that such weak electric fields may contribute to the therapeutic mechanism of DBS or its side-effects, possibly through interactions with the strong electric fields present near the target site. Future work will extend these results to a network model of two-compartment neurons, to test whether these effects are amplified by network-level interactions and to investigate the potential for DBS-induced desynchronization.

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P079

Personalization of basal ganglia circuitry for clinical application

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Introduction

The basal ganglia are essential nodes of the motor control system and play a critical role in various neurological conditions such as movement disorders and stroke. However, their complex fiber architecture severely limits their in vivo mapping, even with the most advanced diffusion MRI (dMRI) techniques. Therefore, connectomic data are often obtained from normative atlases, which provide high anatomical detail but fail to capture individual variability [1-3].

Goals

To bridge the gap between anatomical precision and individual specificity, we developed SUBMARINE - Subcortical Ultraprecise Bundle Mapping for Anatomical Refinement in Individualized Neuroimaging, a novel pipeline that integrates a high-resolution normative basal ganglia fiber atlas with mesoscopic information extracted from individual dMRI data, generating personalized basal ganglia circuitry maps.

Methods

The SUBMARINE pipeline transfers and refines a basal ganglia atlas into the individual"s brain space, using synthetic diffusion images generated from the atlas" fiber architecture 4. SUBMARINE then maps these synthetic images to the patient"s empirical dMRI data, leading to topological refinement and personalization of the fiber bundles represented in the atlas. We implemented the pipeline to one example patient, testing both the Macroscale Human Connectome Atlas 5 and an internally developed normative 3D atlas with highly accurate anatomical representation of subcortical structures. For each atlas, we qualitatively assessed how well the personalized fibers aligned with the diffusion orientations observed in the patient"s dMRI. We then compared this to the alignment of the original, non-personalized atlas bundles, in order to understand whether SUBMARINE improved anatomical correspondence.

Results

In the tested patient, SUBMARINE showed an improved fiber personalization to the diffusion orientation in comparison with the corresponding fibers in the normative atlases. This improvement was evident for both tested atlases, supporting the effectiveness of the implemented pipeline.

Summary

Our results indicate that SUBMARINE can enhance the anatomical specificity of basal ganglia circuitry maps by combining atlas structures with individual diffusion MRI data. This suggests that

our approach holds promise for improving personalized connectomic analyses in clinical and research settings.

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P080

Imaging-informed guidance for subthalamic DBS: adapting group models to individual contacts

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Introduction

Motor outcomes in patients with Parkinson"s disease undergoing subthalamic deep brain stimulation (STN-DBS) vary depending on electrode position and stimulation parameters [1–3]. Imaging-based models may help explain these differences, but most have been designed to analyze shared variance across large cohorts rather than to identify optimal stimulation contacts in individual patients [4–6].

Goals

We aimed to explore the potential of models primarily trained to explain between-subject variance to account for within-subject differences. To achieve this, we introduced a novel framework that integrates multiple imaging-based predictors into a single model to provide insights for DBS programming.

Methods

Patients with Parkinson's disease treated with STN-DBS were assessed using UPDRS-III scores. In the training cohort of 129 patients, we combined imaging data with clinical improvement to derive five predictors of DBS outcome. These included contact coordinates, sweet-spot mapping, fiber-tract analysis, and structural and functional connectivity [2]. The features of these predictors were integrated using ridge regression to build a group-level model. The resulting model was tested on two independent datasets, including a monopolar review cohort for evaluating individual clinical contacts.

Results

Across 604 stimulation sites from 236 patients, the model trained on 129 patients explained 11% of the variance in a separate group-level cohort of 89 patients (R^2 = 0.11, p = 0.001). At the individual level, using 18 additional monopolar review patients (N = 21 electrodes), the model correctly identified the optimal clinical contact or its neighboring contact in all but one case (mixed-effects R^2 = 0.31, p < 0.001).

Conclusions

The model achieved the expected performance at the group level and demonstrated potential utility for contact selection, suggesting that imaging-informed approaches may help inform DBS programming.

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P081

Preoperative structural MRI in DBS: high effort, low impact?

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INTRODUCTION: High-resolution structural MRI is routinely obtained before deep brain stimulation (DBS) to detect lesions and vascular anomalies, but its impact on clinical decision-making is unclear.

GOALS: To assess the frequency of treatment adjustments based on structural MRI findings in patients screened for DBS surgery.

MATERIALS & METHODS: We performed a single-centre, retrospective analysis of 100 randomly selected patients implanted with DBS electrodes (2017–2023). Demographics, underlying disease, target, timing and findings of structural MRI and planning MRI for stereotactic targeting, and documented critical responses to imaging were extracted from a standardized audit template. Structural MRI findings were categorized as unremarkable, incidental but irrelevant, or incidental and potentially contraindicating. A critical response was defined as any imaging-driven change in management (additional imaging, trajectory modification, cancellation of DBS). Analyses were descriptive.

RESULTS: Mean age was 60 ± 13 years (range 15–77). Underlying diagnoses were Parkinson"s disease (68%), essential tremor (14%) and dystonia (13%); main targets were subthalamic nucleus (71%), Globus pallidus internus (14%) and thalamic targets (VIM ± STA, 15%). A dedicated structural MRI was available in 97/100 patients; 88/97 (91%) were classified as unremarkable, 6/97 (6%) as incidental but irrelevant and 3/97 (3%) as incidental and potentially contraindicating (e.g. cavernoma or developmental venous anomaly near the target). Overall, a critical response to imaging was documented in 9/100 patients (9%): 5 additional imaging studies, 3 trajectory modifications and 1 DBS cancellation. All three patients with potentially contraindicating structural findings triggered a critical response. Considering any structural abnormality, 8/50 patients (16%) with an abnormal structural MRI prompted a critical response, compared with 1/50 (2%) without structural abnormalities, where the reaction was driven by a new lesion detected only on planning MRI. In 5/9 patients (56%) with discrepant findings between structural and planning MRI, the discrepancy was attributable to contrast-enhanced or anaesthesia-related effects, while 4/9 (44%) reflected true structural change or improved depiction of pre-existing lesions. Median interval between structural MRI and surgery was 142 days (IQR 101–267), and 4 days between planning MRI and surgery (IQR 3–8). Trajectory haemorrhage occurred in 4/99 patients (4%). No significant association between haemorrhage and abnormalities on structural or planning MRI was detected (Fisher"s exact $p>0.05$).

SUMMARY: In this DBS cohort, preoperative structural MRI led to an explicit change in management in only a small minority of patients, while clearly critical findings were consistently addressed. The majority of discrepancies between structural and planning MRI were related to contrast or anaesthesia rather than an actual new pathology. This underscores the need for cautious interpretation of findings on planning MRI, as they may be influenced by contrast administration and anaesthesia-related effects and could otherwise lead to unnecessary delays or inappropriate exclusion from DBS. MRI abnormalities did not reliably predict trajectory haemorrhage, suggesting a residual multifactorial bleeding risk beyond imaging. Prospective work is needed to define which MRI protocols and timings are truly necessary and efficient in routine DBS workup.

P082

Can we trace the ORT with deterministic fibertracking? – Real-world approach

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1. Introduction

Tractography based target planning in DBS has emerged throughout the last decades and is now frequently used, for example in the case of the dentato-rubro-thalamic tract for Essential Tremor. This individual approach is taking the patients individual anatomy into account. Description of OCD (obsessive compulsive disorder) reducing fibers (ORT, OCD response tract), firstly described by Li et al. 1, has set focus on tractrographic targeting in the context of OCD. Since slMFB (superolateral branch of the medial forebrain bundle) based DBS for OCD has been firstly reported by Coenen et al., it is now to be closer investigated which fibers are targeted for optimal OCD therapy2. In this context, we try to understand white matter anatomy with the help of commonly used "down to earth" deterministic tractography in individual patient data.

2. Goals

We try to understand and replicate the complicated and refined structural anatomy included in OCD networks with deterministic tractography in individual patient imaging. Since DBS targets for treatment of OCD are in close proximity to each other, overlap of stimulation effects might be possible, especially of involved fibertracts. Therefore, we want to depict and analyze fiber-connections of commonly used OCD targets and their structural connectivity with brain regions involved in OCD pathology. Furthermore, we try to delineate fibers stimulated by BNST DBS (bed nucleus of the stria terminalis). Last, we try to compare our findings with the described ORT and slMFB courses.

3. Material & Methods

We retrospectively analyzed imaging data of 11 consecutive patients that underwent BNST DBS in our department. Imaging data were acquired on a 3T scanner (Magnetom Prisma, Siemens) and tractography was executed on diffusion weighted images with deterministic fibertracking (Elements, Brainlab).

Individual connectomic analysis was conducted with regions of interest (ROIs) set in the vALIC (ventral anterior limb of the internal capsule), BNST, N. accumbens, amSTN (antero medial subthalamic nucleus) and VTA (ventral tegmental area) for the slMFB. For depiction of BNST-DBS stimulated fibers, ROIs were set in all four electrode poles after fusion of postoperative CT images with DWI data.

4. Results

Most fibers delineated with the individual connectomic approach, pass through a spot slightly lateral to the BNST. Fibers depicted by electrode-

pole ROIs did not show significant differences in connections to several OCD associated brain areas except for the gyrus rectus, the medial temporal gyrus, the amygdala and the occipito-frontal fasciculus.

Fibers traversing the area lateral to the BNST seem to overlap with fibers related to the slMFB and ORT.

5. Summary

Depiction of OCD related fibers with deterministic fibertracking in individual patient data is possible and feasible. Its accuracy and plausibility must be validated by probabilistic approaches. A spot slightly lateral to the BNST might be promising for further evaluation concerning tractography based DBS targeting.

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P083

Optimizing STN-DBS through AI and image guidance: a clinical and DTI study

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Introduction Subthalamic nucleus stimulation is an established therapy for advanced Parkinson"s disease, yet postoperative programming remains highly operator-dependent and only partially informed by patient-specific anatomy. Imaging-guided workflows and algorithm-based tools may offer more precise and reproducible strategies than conventional monopolar review.

Goals To compare clinical, imaging-guided, and algorithm-assisted programming in terms of anatomical precision, programming efficiency, and recruitment of corticospinal and corticobulbar tracts (CST and CBT).

Materials & Methods We prospectively studied 20 PD patients implanted with the Boston Scientific Vercise Genus™ system using 8-contact directional leads. Preoperative 3T MRI and postoperative CT were fused in Brainlab Elements™ for individualized lead localization. Three programming paradigms were evaluated: (1) conventional clinical practice, (2) imaging-guided programming based on 3D anatomical reconstruction, and (3) Illumina 3D algorithm-assisted programming targeting the dorsolateral STN while avoiding adjacent structures. Each program was maintained for one month in randomized sequence. Motor outcomes, side-effect thresholds, activities of daily living, and quality of life were systematically assessed. Probabilistic tractography of CST and CBT was used to quantify their spatial relationship with the volume of tissue activated (VTA) at the thresholds of motor side-effect

Results Preliminary analyses in 20 patients showed high concordance between imaging-guided and algorithm-based contact selection. Both approaches reduced programming time compared to conventional review. Algorithm-assisted programming minimized CST/CBT recruitment at motor side-effect thresholds, suggesting improved safety margins.

Summary Imaging-guided and algorithm-enhanced programming strategies appear more anatomically precise, reproducible, and efficient than conventional clinical programming. Integrating neuroimaging, tractography, and computational modeling may optimize therapeutic windows and streamline postoperative management in STN DBS.

P084

Cortical E-fields in simulations of deep brain stimulation in Parkinson's disease patients exceed typical E-field magnitudes of transcranial electrical stimulation

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Deep Brain Stimulation (DBS) is an established surgical intervention for Parkinson"s disease (PD). In spite of its clinically proven efficacy, the exact mechanism is still under investigation. Current hypotheses state that the strong electric fields (E-fields) in the immediate surroundings of the active stimulation contacts affect their surgical targets, often the subthalamic nucleus or globus pallidus pars interna. Via E-fields strong enough to affect the spiking rates of surrounding neurons, DBS may steer basal ganglia output patterns away from pathological behaviour and thereby alleviate motor symptoms. E-fields outside of this limited local environment are so far neglected. However, from transcranial alternating current stimulation (tACS) literature we know that even weaker E-fields can have a measurable effect on neuron dynamics, not by affecting spiking rates, but by affecting spike timings. During DBS the E-fields are not isolated to the deep subcortical environments, but will also be present throughout the brain.

Our goal is to characterize and quantify the whole-head E-field distribution of DBS in PD patients.

Our dataset includes T1- and T2-weighted magnetic resonance imaging and computed tomography scans, clinical stimulation settings and electrode information for 23 PD patients. We used patient-specific head models created by SimNIBS and included the DBS electrode geometry based on the trajectory reconstructions provided by LeadDBS. Electrode geometry was integrated by overlaying masks for the encapsulation layer and insulation shaft into an upsampled segmentation image, which was used to create the volumetric head model. The masks were created by aligning 3D surface meshes for the encapsulation and electrode shafts with the LeadDBS reconstructed trajectory. Electrode contacts were added by superimposing surface meshes for the contacts with the insulation shaft in the volumetric head model and relabelling insulation elements that fell within the closed surfaces.

We simulated the E-field distributions for the patients clinical stimulation settings per hemisphere, yielding a total of 45 simulations. Based on the Brainnetome atlas parcellations we calculated the mean and 99.9th percentile E-field magnitudes across cortical regions.

We found that, on average, the mean E-field magnitude exceeds 0.1 V/m in all cortical regions. The lowest mean magnitude was reached in the superior parietal lobule with a value of 0.13 V/m, and the highest mean magnitudes were reached in the insular and cingulate gyri with values of 0.94 V/m and 0.63 V/m, respectively. On average, the 99.9th percentile exceeded 1 V/m in the superior frontal gyrus, inferior frontal gyrus, orbital gyrus, superior temporal gyrus, parahippocampal gyrus, insular gyrus, and cingulate gyrus. For 6 patients, the maximum values reached in the insular gyrus exceeded 5 V/m.

We created a novel framework to create patient-specific head models while incorporating DBS electrode geometry. We simulated the E-field distributions in 23 PD patients and found that on mean E-field magnitudes throughout the brain exceeded 0.1 V/m. Furthermore, 99.9th percentile values for the majority of cortical regions exceed 0.5 V/m. These magnitudes are comparable or higher than values typically reported in tACS literature. If neurons are responsive to DBS at these magnitudes and how this compares to tACS waveforms will need to be investigated further.

P085

Translating the transcriptome: a connectomic approach for gene network decoding and clinical integration

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Introduction

Understanding how genetic factors shape brain circuitry is essential for unraveling disease mechanisms and developing targeted treatments. Surgicogenomics, the tailoring of surgical interventions based on individual genetic profiles, represents a promising frontier in precision medicine[1]. However, conventional approaches often fail to capture the biological circuits underlying regional molecular variability. Imaging transcriptomics addresses this gap by linking gene expression patterns to brain organization[2]. Here, we introduce Gene Network Mapping (GNM), a framework integrating spatial transcriptomics with functional connectivity to identify networks associated with neuropsychiatric disorders.

Objectives

To develop and validate GNM as a tool for identifying disease-relevant functional circuits and informing neuromodulation strategies.

Methods

We analyzed microarray data (~20,000 genes) from the Allen Human Brain Atlas[3]. Regional expression patterns were mapped onto a 430-region atlas and related to whole-brain functional connectivity derived from resting-state fMRI (n=1,000)[4] using voxel-wise linear models. This yielded gene-specific network maps, which were aggregated across disease-associated genes to generate disease-network maps for parkinsonism, dystonia, and obsessive-compulsive disorder (OCD). Validation included comparison with pharmacological fMRI and PET data, spatial overlap with lesion network maps (n=971 lesions), and prediction of deep brain stimulation (DBS) outcomes across 176 patients from ten international centers.

Results

GNM successfully identified functional circuits based on local gene expression, highlighting key anatomical structures implicated in each condition. Gene-network co-activation maps correlated significantly with pharmacological fMRI findings ($R=0.49$, $p<0.001$), outperforming local gene co-expression and PET co-localization approaches. Disease-network maps showed greater spatial similarity with lesions causing the same syndrome than with lesions causing other conditions, confirming anatomical specificity. Critically, alignment between DBS stimulation profiles and disease-network maps predicted clinical improvement in dystonia ($R=0.56$), Parkinson's disease ($R=0.47$), and OCD ($R=0.44$; all $p<0.001$).

Conclusions

GNM bridges transcriptomics and connectomics, demonstrating that genetically derived and lesion-derived networks converge on shared circuits. Its predictive validity for DBS outcomes

across multiple disorders suggests potential for guiding circuit-based therapies using genetic information.

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P086

Structural connectivity mapping in pediatric patients with dystonia: Insights from diffusion MRI probabilistic tractography

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Introduction:

DBS of the globus pallidus internus (GPi) has been increasingly applied in pediatric patients with pharmacorefractory dystonia over the last decades. However, outcomes vary considerably depending on the underlying etiology. Genetic and acquired forms of dystonia differ in their pathophysiological mechanisms, yet the neuroanatomical connectivity underlying these clinical differences remains poorly understood (2). This study investigates the white matter structural connectivity in children and adolescents with genetic and acquired dystonia using quantitative probabilistic tractography and connectomic measurements in a priori regions of interest.

Methods:

Twenty-eight pediatric patients (18 genetic, 10 acquired dystonia) who underwent GPi-DBS at the University Hospital Cologne were retrospectively investigated. Diffusion MRI Imaging analysis was performed using several state-of-the-art imaging pipelines to develop patient-specific probabilistic tractography. Subject-specific connectomes were normalized to pediatric MNI space. Whole-brain tractography was conducted, and connectivity metrics were extracted between a priori regions of interest implicated in motor control, including pallidal, subthalamic, and thalamo-cortical pathways. Streamline-count metrics between a priori ROIs were extracted bilaterally, and group differences were assessed using Shapiro-Wilks test, Student's t-test and Bonferroni-correction test.

Results:

Preliminary results revealed that structural connectivity between the STN and thalamus was reduced in acquired compared with genetic dystonia. In the left hemisphere, mean streamline counts were 2,877 ± 1,455 for the genetic group and 1,948 ± 491 for the acquired group, representing a 66% difference in variability. In the right hemisphere, a similar trend was observed, with a 47% difference in standard deviation between groups. A significant reduction in left STN-thalamic streamline count was detected in the acquired group relative to the genetic group ($p = 0.018$), indicating decreased structural integrity of this pathway in acquired dystonia.

Conclusions:

This study represents, to our knowledge, the first patient-specific structural connectomic comparison between genetic and acquired pediatric dystonia. This pilot study supports the probe of concept that genetic and acquired pediatric dystonia can be associated with distinct structural network phenotypes, that may underlie varying DBS responsiveness. These findings support the feasibility of diffusion MRI-based connectomics as a promising tool for structural biomarkers for patient selection, guiding individualized targeting and programming strategies in pediatric DBS. Further work with advanced statistical models on larger cohorts are needed for integrating clinical phenotypes, genetic variants, and connectomic data, which enables the application of precision neuromodulation approaches tailored to etiology-specific network dysfunctions.

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Hardware innovations and technological needs

P087

Code-free visualization and analysis of percept™ DBS sensing data: bridging clinical annotations with neural recordings

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Introduction Next-generation Percept™ PC/RC deep brain stimulation (DBS) systems combine therapeutic stimulation with continuous neural recording, enabling adaptive DBS based on patient-specific biomarkers. However, managing the resulting complex multimodal datasets typically requires programming expertise, limiting accessibility for clinicians and researchers. Existing tools fail to integrate patient information, stimulation parameters, and neural signals within a unified, code-free environment.

Methods We developed PerceptLab, a Python-based desktop application (PyQt framework) for code-free analysis of Percept™ data. The tool processes JSON-formatted sensing data and TSV clinical annotations through an intuitive graphical interface. Features include: integrated dashboard for patient metadata and stimulation parameters; synchronized visualization across time-frequency domains; automated artifact removal; and structured data/figure export. The software runs on Windows and macOS.

Results PerceptLab has been successfully deployed for analyzing data from ~20 patients across multiple conditions (Parkinson's disease, OCD, chronic pain). The application enables: (1) immediate data exploration without programming knowledge; (2) synchronized multi-modal visualization of stimulation and sensing data; (3) rapid identification of potential biomarkers through integrated temporal-spectral analysis and clinical annotations; (4) streamlined research workflows with automated processing and export functions.

Conclusions PerceptLab addresses a critical gap in DBS data analysis by providing a user-friendly, code-free environment for exploring Percept™ recordings. While currently designed as a research support tool, it facilitates the identification of neural biomarkers and stimulation-response patterns essential for developing personalized adaptive DBS strategies. By eliminating programming barriers, it democratizes access to advanced DBS data analysis, accelerating research toward clinical implementation of closed-loop neuromodulation.

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P088

Subthalamic–ventrolateral thalamic stimulation with Cartesia HX leads: long-term outcomes in three patients with tremor-dominant Parkinson's disease

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Introduction

Deep brain stimulation (DBS) of the subthalamic region is an established therapy for Parkinson"s disease (PD), yet treatment optimisation continues to advance with newer lead technologies. The introduction of multisegmented directional leads (Cartesia™ X and Cartesia™ HX) provides the opportunity to target multiple interconnected brain structures and personalise stimulation strategies.

Goals

We report the long-term clinical outcomes of three patients with tremor-dominant PD who underwent bilateral implantation of Cartesia HX directional DBS leads. Electrodes were positioned to allow simultaneous modulation of the subthalamic nucleus (STN) and the ventrolateral thalamus.

Materials and Methods

Clinical assessments were performed before surgery (T0) and at 1-year follow-up (T1), including the MDS-UPDRS (Parts I–IV), the Non-Motor Symptoms Scale (NMSS), and the Gait and Falls Questionnaire (GFQ). MDS-UPDRS Part III, PDQ-39, and levodopa equivalent daily dose (LEDD) were collected preoperatively and up to 3 years post-DBS.

Results

At T1, all patients demonstrated a marked reduction in motor symptom severity in the MED-OFF/STIM-ON condition compared with their preoperative MED-OFF state. Improvements in MDS-UPDRS Part III were sustained for up to 3 years. Non-motor symptoms and gait disturbances, as measured by NMSS and GFQ, also showed consistent improvement. Volume of tissue activated (VTA) modelling revealed that stimulation extended beyond the dorsolateral STN to include portions of the zona incerta (ZI) and ventrolateral thalamic nuclei in all cases, suggesting a multimodal network effect contributing to clinical benefit.

Summary

The expanded directional capabilities of the Cartesia HX lead enabled precise shaping of stimulation to engage adjacent therapeutic targets while minimising capsular spread and adverse effects. Although limited by the small sample size, these observations support further systematic evaluation of this lead technology and its potential to individualise DBS therapy based on patient-specific anatomy and symptom profiles.

P089

High definition deep brain stimulation

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Introduction

The standard lead technology for Deep Brain Stimulation (DBS) presents significant limitations with respect to: 1) precise targeting, 2) ability to avoid stimulation of unwanted brain structures owing to its large lead size and associated large volume of tissue activation relative to the complex and highly precise organization of neuronal circuits, 3) danger of microcapillary damage and 4) progressive structural ablation over time. These shortcomings underly the commonly seen adverse side effects of DBS which curtail its therapeutic efficacy, longevity and number of potential clinical indications.

To this end, we have developed a microelectrode-based technology for precise deep brain stimulation comprising a plurality of ultra-thin and flexible microelectrodes that can be spread out in the target tissue as a regular cluster. By selective stimulation of subsets of implanted microelectrodes, highly specific therapeutic effects without noticeable adverse effects have been achieved in animal models of Parkinsons disease and pain (Mohammed et al, 2021; Forni et al 2021).

Materials / Methods

We here evaluate the biocompatibility of the microelectrode technology. A comprehensive series of quantitative immunofluorescence studies of the glial reactions, loss of neurons around the microelectrodes and bleeding were made in acute (1 week), medium (6 weeks) and long term (6 months) implantation time in rats (n=95). In addition, a translational study was made in minipigs (n=4). These tissue effects were compared to those around miniaturized DBS leads in rats and authentic DBS leads in minipigs.

Results

Glial reactions were minimal and neuron density was essentially preserved over a 6 months period. Compared to standard DBS leads, the tissue injury was dramatically smaller. No bleeding in the target region was seen in any animal studied. Very low stimulation intensities sufficed to provoke strong therapeutic effects.

Discussion

The results demonstrate an unprecedented biocompatibility of the novel neurotechnology evaluated, which is a prerequisite for precise brain stimulation.

Conclusions

The novel neurotechnology evaluated is a disruptive advancement in DBS lead technology, capable of producing potent beneficial effects with minimal side effects thus enabling longevity of the therapy.

Learning Objectives

Objective 1: To clarify the relationship between design of implantable neural interfaces and glia reactions. The desired result is an improved understanding of how the design of an implant impact glia reactions around brain implants.

Objective 2: To clarify how the design of implantable electrodes affects the neuronal density in the vicinity of electrode implants. The desired result is a better understanding of how to reduce the risk of neuronal loss.

Objective 3: To clarify the relationship between biocompatibility and limits for stimulation specificity. The desired result is a better understanding of how implant biocompatibility can influence the specificity of brain stimulation.

Acknowledgements

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Closed-loop-neurostimulation

P090

Anatomically continous vs. LFP-guided adaptive deep brain stimulation for Parkinsons disease: Study protocol for a randomized double-blind crossover trial

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Parkinson"s disease (PD) motor symptoms respond well to subthalamic deep brain stimulation (STN-DBS). We now test a newer approach: local field potential–guided, adaptive stimulation (LFP-adaptive-DBS), which modulates current in response to ongoing neuronal activity against an anatomically guided continuous mode (Anatomy-continuous-DBS). In a monocentric, randomized, double-blind crossover study, 30 PD patients will undergo both programs for two weeks each, following an initial optimization phase. For LFP-adaptive-DBS, contacts are chosen using LFP recordings; for Anatomy-continuous-DBS, contacts are selected by individual anatomy targeting the dorsolateral STN. The primary endpoint is patient preference after completion of both periods. Secondary endpoints include motor outcomes, electrophysiological readouts, accelerometry, and questionnaire-based measures covering non-motor symptoms, treatment expectation, and quality of life. As no head-to-head comparison of these strategies exists, the trial is designed to clarify the clinical utility of LFP-adaptive-DBS versus anatomy-informed continuous stimulation and to identify which patients are most likely to benefit from LFP-adaptive-DBS.

P091

Beyond beta rhythms: subthalamic aperiodic broadband power scales with Parkinson's disease severity–a cross-sectional multicentre study

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Question

Parkinson's disease is linked to increased beta rhythms (13–30 Hz) in the subthalamic nucleus, which correlate with motor symptoms. However, findings across studies are inconsistent. Furthermore, the contribution of other frequencies to symptom severity remains underexplored.

Methods

We analysed subthalamic local field potentials from 119 patients with Parkinson's disease (31 female; mean age 60 ± 9 years) across five independent datasets. Power spectra were parametrised and studied in relation to Levodopa administration and the severity of motor symptoms.

Results

Our findings suggest that small sample sizes contributed to the variable correlations between beta power and motor symptoms reported in previous studies. Here, we demonstrate that more than 100 patients are required for stable replication. Aperiodic offset and low gamma (30–45 Hz) oscillations were negatively correlated with motor deficits (?$_{Offset}$=−0.32, ?=4□?−4; ?$_{L□γ}$=−0.21, ?=0.021), whereas low beta oscillations were positively correlated (?$_{L□β}$=0.24, ?=0.010). Combining offset, low beta, and low gamma power (?$_{Lin.reg.(Offset,L□β,L□γ)}$=0.47, ?=1□?−4) explained significantly more variance in symptom severity than low beta alone (*J*-test: ?=2□?−5). Interhemispheric within-patient analyses showed that, unlike beta oscillations, aperiodic broadband power (2–60 Hz)–likely reflecting spiking activity–was increased in the more affected hemisphere (Levodopa off-state: ?=0.015; on-state: ?=0.005).

Conclusions

Spectral features beyond conventional beta rhythms are critical to understanding Parkinson's pathophysiology. Aperiodic broadband power shows potential as a new biomarker for adaptive deep brain stimulation, providing important insights into the relationship between subthalamic hyperactivity and motor symptoms in Parkinson's disease.

P092

Guiding deep brain stimulation contact selection: neural oscillations predict therapeutic windows

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Introduction: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective therapy for Parkinson's disease (PD). However, identifying the optimal stimulation parameters is a complex and time-consuming task. While machine learning is emerging as a tool to aid this process, many approaches rely on imaging or single electrophysiological markers, such as beta power. This may be suboptimal, as a wealth of other neural oscillations may also carry clinically relevant information.

Goals: This study aimed to develop and validate a multivariate machine learning model to predict the therapeutic window of individual electrode contacts. We investigated whether a model integrating electrophysiological features, specifically STN power and STN-cortex coherence across multiple frequency bands, could predict the therapeutic window of a contact and thus provide a data-driven tool to support and accelerate the selection of the optimal contact.

Methods: We analyzed resting-state data from 45 PD patients and validated the model on a separate independent cohort of 8 PD patients. All patients had externalized DBS electrodes, allowing for simultaneous magnetoencephalography (MEG) and local field potential (LFP) recordings from the STN. Data were collected one day after surgery, following an overnight withdrawal from medication. We extracted STN power and STN-cortex coherence features across seven frequency bands (theta, alpha, low-beta, high-beta, low-gamma, high-gamma, and high frequency oscillation). An extreme gradient boosting model was trained to predict the therapeutic window, and its performance was assessed using leave-one-electrode-out (LOEO) cross-validation and testing on the independent cohort.

Results: The model successfully predicted the therapeutic windows. In the main cohort, the LOEO cross-validation showed a significant positive correlation between predicted and actual therapeutic windows ($r = 0.45$, $p < 0.001$). This ability to generalize was confirmed in the independent cohort ($r = 0.30$, $p < 0.01$). Feature importance analysis revealed that the model did not rely on a single marker but on a combination of features, most notably fast subthalamic activity (> 35 Hz) and STN-cortex coherence in several bands. A combined model using both power and coherence features outperformed models trained on either feature set alone. Furthermore, we used the model to rank all contacts of each electrode according to clinical utility. The model's ranking was significantly better than random ranking, demonstrating its potential to find the best contact faster in a clinical setting.

Conclusion: This study demonstrates the feasibility of predicting the therapeutic window of DBS electrode contacts using a multivariate model operating on electrophysiological features. This work provides a foundation for a future decision-support tool that could contribute to a faster semi-automated process for DBS programming.

P093

Long-term evaluation and refinement of adaptive deep brain stimulation in Parkinson's disease

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Introduction: Adaptive deep brain stimulation (aDBS), which adjusts stimulation amplitudes based on neurophysiological feedback, has gained attention as a strategy to address residual motor fluctuations in Parkinson"s disease (PD). Our previously published study demonstrated the short-term feasibility and potential clinical benefits of commercially available Dual Threshold aDBS in eight PD patients. However, long-term effects, optimal programming strategies, and broader clinical applicability remain to be determined.

Goals: This project builds on the published findings by aiming to evaluate long-term outcomes approximately one year after initial aDBS programming, including quality of life and motor function, determine whether patients continue using aDBS in daily clinical practice, further characterize long-term beta dynamics and patient-specific adaptation profiles, and refine programming strategies informed by accumulated clinical experience.

Methods: In the published work, eight PD patients received Dual Threshold aDBS guided by subthalamic beta power. Clinical status and well-being were monitored at home using ecological momentary assessments during two-week periods of continuous DBS (cDBS) and aDBS, with patients unblinded to stimulation mode. Challenges such as biomarker variability, threshold selection, and artifact-related maladaptation were systematically evaluated to derive practical mitigation strategies. The current follow-up protocol includes a comprehensive evaluation approximately one year after aDBS initiation. Alongside validated questionnaires (e.g., PDQ-39), assessments will include motor and non-motor scores, routine local field potential (LFP) recordings using BrainSense streaming both at rest and during quantitative motor tasks such as finger tapping. In addition, we will expand the exploration of single-threshold aDBS to assess its feasibility and potential advantages compared with dual-threshold paradigms.

Results: In the published study, group-level analyses showed a significant improvement in overall well-being during aDBS compared with cDBS ($p = 0.007$) and a trend toward better movement quality ($p = 0.058$). Three of eight patients exhibited significant within-subject improvements, and six elected to remain on aDBS. Subsequent clinical experience has revealed heterogeneous long-term adaptation patterns, emphasizing the importance of individualized thresholding and robust artifact detection. Preliminary observations from routine clinical practice also indicate that simplified single-threshold configurations may be feasible in selected cases, supporting their planned broader evaluation.

Summary: This ongoing project extends our published short-term findings by addressing key knowledge gaps regarding the long-term effectiveness, patient adherence, and practical optimization of aDBS in PD. Through one-year follow-up, expanded physiological measurements, and detailed clinical assessments, we aim to elucidate the durability and real-world applicability of aDBS. These efforts are expected to refine patient selection and guide future implementation of personalized, biomarker-based neuromodulation strategies.

P094

Oscillatory synchronization across spatiotemporal resolutions in the globus pallidus internus contrast Parkinson's disease and dystonia

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Question

Abnormal oscillatory activity in the cortico-basal ganglia-thalamic (CBT) circuit is a frequently implicated physiological feature of Parkinson's disease (PD) and dystonia (DY), both of which are movement disorders treated with high-frequency deep brain stimulation (DBS) of the globus pallidus internus (GPi) despite differing symptom profiles. Hypokinetic symptoms of PD are associated with elevated beta oscillatory power (12-35Hz) while dystonic symptoms are associated with low-frequency oscillations (4-10Hz). This work investigates universal and varying features of oscillatory coupling across spatiotemporal resolutions between disease states, which may inform circuit-informed closed-loop DBS strategies to desynchronize aberrant oscillations by manipulating neural activity at specific phases of the oscillation.

Methods

We analyzed resting-state microelectrode recordings of 22 people with PD (41 hemispheres, 225 locations) and 6 with DY (11 hemispheres, 105 locations) obtained during GPi DBS implantation surgeries. We assess differences in oscillatory power, oscillatory coupling across spatial resolutions (micro-local-field potential, μLFP; single-unit activity, SUA; background activity, BUA) using phase-amplitude coupling and mean-vector length measures, and the temporal evolution of LFP-BUA oscillatory coupling during beta bursts (transient increases in μLFP beta oscillatory amplitude) between conditions.

Results

In contrast with prior literature comparing PD and DY in DBS macroelectrode LFP recordings, μLFP showed minimal differences in oscillatory power across conditions in any evaluated frequency range (theta: 4-8Hz, alpha: 8-12Hz, low-beta: 12-21Hz, high-beta: 21-35Hz, gamma: 35-70Hz). However, oscillatory coupling between the μLFP and BUA, and between the μLFP and SUA, in the beta frequency range was significant in a greater proportion of recordings in PD than in DY. As this was the sole frequency range that exhibited significant differences between PD and DY, subsequent analyses focused on beta oscillatory dynamics. In the subset of recordings that exhibited significant beta oscillatory coupling, the dominant phase of spiking activity at both the single-unit and population level occurred on the rising phase of the μLFP beta oscillation in both conditions. In this same subset, despite a lower baseline degree of synchronization in DY, the temporal profile of μLFP-BUA beta phase synchronization time-locked to the onset of beta bursts exhibited similar dynamics across conditions, rising and falling with the amplitude of the beta burst.

Conclusions

The greater proportion of recordings in PD relative to DY demonstrating significant synaptic-to-spike coupling in the beta frequency range advances the theoretical framework of excess beta synchrony as a characteristic feature of PD. However, the similar rising phase preference relating the μLFP to spiking activity at both the single-unit and population level, as well as similar synchronization dynamics during beta bursts in both conditions, implicates a universal principle of

beta oscillatory coupling in the GPi that persists across disease states. Insights from this analysis may be used to inform therapeutic stimulation strategies to manipulate oscillatory activity in the CBT circuit by stimulating at optimal phases to disturb pathological coupling between synaptic and spiking activity associated with PD.

P095

Towards symptom-specific adaptive deep brain stimulation: Classification of local field potential markers for motor symptom severity in Parkinson's disease

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Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is generally effective in Parkinson"s disease (PD), but its inability to adjust stimulation to fluctuations in symptom severity may result in suboptimal treatment. Adaptive DBS (aDBS) modulates stimulation based on physiomarkers detected from local field potential (LFP) recorded from the STN. Most aDBS approaches rely on the spectral power of beta band oscillations (13-30 Hz), which captures only a portion of symptom variability. Multi-feature strategies may therefore provide more robust feedback signals.

Goals

To develop and evaluate multifeature LFP models that predict motor symptom severity as a basis for individualized aDBS.

Material and methods

LFP signals were recorded from 71 PD patients during multiple MDS-UPDRS-III assessments across stimulation and medication states during the postoperative optimization phase.[1] Task onsets were video-aligned with the LFP recordings to synchronize LFP segments with MDS-UPDRS-III subscores. Scores were binarized into high (2–4) versus low (0–1) scores. LFP signals underwent ECG suppression, filtering (1–100 Hz), artifact rejection (>7 MAD), and selection of 5-s task epochs. Time- and frequency-domain features were derived, including spectral, aperiodic, Hjorth, and burst-related metrics. Spearman correlations assessed feature–symptom associations. Machine learning (ML) classifiers (support vector machine (SVM), random forest (RF), and extreme gradient boosting (XGB)) and a deep learning (DL) classifier (convolutional neural network (CNN)) were trained and validated with nested cross-validation with hyperparameter optimization and bootstrapping, and their performance was evaluated with area under the curve (AUC).

Results

Sixty patients were included (mean±SD age 67±7 years; mean disease duration 11±6 years) with a mean preoperative MDS-UPDRS-III OFF-score of 45±11 points and ON-score of 21±9 points. In total, 402 recordings were analyzed. Beta-related and Hjorth features showed the strongest correlations with non-tremor tasks (ρ -0.28–0.30). Low-frequency (1–4 Hz), aperiodic, and high-gamma features showed minimal associations (ρ 0.00-0.19). Across tasks, ML models achieved poor to moderate discrimination (AUC 0.57–0.77), and highest performance for gait (AUC up to 0.77) and leg movement tasks (AUC up to 0.74). Tremor-related tasks showed consistently lower AUCs. Differences between SVM, RF, and XGB were small. The CNN generally underperformed compared to the classical models.

Summary

Combining multiple LFP features provides informative markers for several motor symptoms, with classical ML models showing the best performance. Gait impairments were the most detectable, whereas predicting tremor remains challenging. The CNN performed worse, likely because short noisy LFP segments offer insufficient structure for DL feature extraction. Overall performance is promising, but not yet sufficient for clinical use. The results suggest that individual physiology imposes constraints on generic models, implying that clinically meaningful aDBS models will likely require subject-specific calibration or training rather than relying solely on group-level models.

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P096

Movement state-dependent subthalamic deep brain stimulation in Parkinson's disease

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In recent years, closed-loop deep brain stimulation approaches have demonstrated that the ongoing state of a patient can be decisive for the stimulation effect. Most of this body of research has focused on the brain activity of a patient as the target state, such as oscillatory power and phase. The motor state of a patient, in this regard, has remained largely unexplored. Inspired by rodent research, we have shown in previous work that subthalamic deep brain stimulation (STN-DBS) counteracted bradykinetic speed decline in Parkinson"s more effectively when applied during fast compared to slow movements [1]. Given these results, we hypothesized that STN-DBS has a stronger anti-bradykinetic effect if applied during movement compared to rest, the movement state with the lowest possible speed.

To test this, we developed a movement state–dependent stimulation paradigm, in which 20 PD patients OFF dopaminergic medication performed 15 burst-like 4-second-long forearm movements, separated by rest periods of the same duration. Exploiting the temporal precision of stimulation control in the externalized DBS state, high-frequency bilateral STN-DBS at clinically effective amplitudes was applied in 4 separate blocks: stimulation during movement periods only, stimulation during rest periods only and continuous stimulation during both periods and no stimulation at all, serving as two control conditions.

Movement peak speed declined less strongly, capturing bradykinetic decline, in the block in which stimulation was applied during movement compared to during rest periods, confirming our hypothesis. Notably, this effect extended to movements following the stimulation period, suggesting plastic, carry-over effects of motor state-dependent DBS. Analysis of the control conditions revealed a stronger anti-bradykinetic effect of continuous compared to no stimulation, confirming the general efficacy of the stimulation. No difference was found between continuously and movement-selective DBS, even though stimulation time was reduced by 50%.

While this investigation employed only short 2-minute experimental blocks, it provides novel group-level evidence that movement-selective STN-DBS might more effectively counteract bradykinesia than rest-selective stimulation. These findings support the further development of movement-triggered DBS approaches to treat slowness of movement in Parkinson"s disease.

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P097

Decoding finely-tuned gamma oscillations in chronic deep brain stimulation for Parkinson's disease

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Question

Finely tuned gamma (FTG)—spontaneous narrowband low-gamma activity or oscillations entrained to half the stimulation frequency—has been associated with ON-medication states and dyskinesia in Parkinson's disease (PD), representing a potential biomarker for adaptive DBS (aDBS) [1,2]. However, the conditions under which FTG emerges and becomes entrained remain unclear due to limited and conflicting evidence [1-4]. The recently proposed Arnold's tongue framework may explain FTG entrainment, but has not been fully validated in PD [5]. This exploratory study aims to clarify the characteristics of spontaneous FTG (sFTG) and entrained FTG (eFTG) in PD patients to help inform future research. Additionally, the relationship between 1:2 entrainment and potential 1:1 entrainment effects is investigated across clinical recordings.

Methods

Local field potentials recorded from the subthalamic nucleus (STN) with SenSight™ leads and Percept™ neurostimulators were retrospectively analyzed using a structured set of clinically relevant questions. FTG was defined as narrowband (≤10Hz) activity between 40-125Hz. FTG unrelated to stimulation frequency was considered to be sFTG, whereas eFTG was centered at half the stimulation frequency (1:2) or potentially at the stimulation frequency (1:1).

Results

Among 67 patients (134 STN), sFTG occurred in 24 STN (18%), and eFTG (1:2 and potential 1:1) in 35 STN (26%). All FTG subtypes were found ON-medication or stun-effect related (sFTG 96%; eFTG 77%) but independent of dyskinesia (sFTG 48%; eFTG 40%). Stimulation amplitude was changed by ≥1.5 mA in 28 STN with eFTG (80%). After beta activity diminished in these STN, eFTG appeared either directly (13 STN) or after transitioning through sFTG (15 STN). Once present, 1:2 entrainment appeared alone (14 STN) or alternated with potential 1:1 effects (14 STN). Consistent with the Arnold's tongue framework, 1:2 entrainment weakened at higher stimulation amplitudes and was inversely related to potential 1:1 entrainment effects.

Stimulation artifacts were observed ipsilaterally and contralaterally at the stimulation frequency during 125 Hz stimulation, but no sFTG, 1:2, or 1:1 activity occurred in the contralateral (unstimulated) hemisphere, supporting the physiological origin of these FTG subtypes. Subharmonic artifacts occurred at half the stimulation frequency in 12 STN (9%; all stimulated at 180Hz). In 3 STN (2%; also 180Hz), half-frequency activity could not be clearly classified as 1:2 entrainment or artifact. No subharmonic artifacts occurred during 125Hz stimulation.

Conclusion

This study provides clinical evidence for potential 1:1 entrainment and confirms its interaction with 1:2 entrainment, consistent with the Arnold's tongue framework. FTG expression—spontaneous or 1:2/1:1 entrained—is shaped by DBS and clinical state yet can occur independently of dyskinesia. These findings inform future research by highlighting the need to clarify the interplay between beta activity, sFTG, and 1:2/1:1 entrainment to advance combined physiomarkers for personalized (a)DBS. However, the selective occurrence of FTG and the presence of potential subharmonic artifacts underscore the need for a cautious, tailored approach.

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P098

Adaptive deep brain stimulation for Parkinson's disease in clinical practice: initial experiences

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Introduction: In Parkinson's disease (PD), the local field potential (LFP) spectral power of beta oscillations (13-30 Hz) within the subthalamic nucleus (STN) is linked to contralateral motor symptom severity.[1] Beta power can act as a physiomarker to guide adaptive deep brain stimulation (aDBS), which adjusts stimulation in real-time using closed-loop control. aDBS may alleviate levodopa-related adverse effects or stimulation-induced adverse effects of continuous DBS (cDBS), and it may address insufficient efficacy during OFF states.[2] Recently, aDBS has become available in a care-as-usual setting.

Goals: To describe our approach for patient selection and aDBS programming and to present the outcomes of the first PD cases treated with aDBS in our center.

Materials & Methods: Sixteen patients with insufficient effect or adverse effects after cDBS titration were selected for receiving aDBS. The physiomarker to inform the aDBS algorithm was determined by finding the frequency showing the largest levodopa-induced decrease in LFP power within the low beta range (12-20 Hz). After establishing quantitative correlations between longitudinal physiomarker recordings and patient-reported symptom documentation, aDBS was initially activated on dual-threshold mode in one or both hemispheres. If necessary, aDBS was optimized using a standardized workflow until the desired clinical outcome was reached or no more improvement could be expected. Outcomes were determined using the Clinical Global Impression of Improvement (CGI-I) scale.

Results: Indications for aDBS were stimulation-induced dysarthria (n=11), dyskinesia (n=5), bradykinesia/rigidity (n=6), gait impairment (n=5), freezing of gait (n=4), tremor (n=3), dystonia (n=1), and stimulation-induced postural instability (n=1). Multiple indications could apply for one patient. At follow-up (median 66 [IQR 51-112] days after activation), eight patients were treated with dual-threshold mode, three with single-threshold mode and three had returned to cDBS treatment because no improvement was seen (n=2), or because sufficient clinical improvement was reached (CGI-I 3) despite the algorithm stimulating only at the upper stimulation limit and thus effectively delivering cDBS (n=1). Ten of the patients who remained on aDBS (81%) improved minimally (CGI-I 3) and three (19%) showed much improvement (CGI-I 2). The presence of a physiomarker which is both responsive to in-clinic levodopa administration and related to patient-reported diary data seemed to contribute most to clinical improvement.

Summary: We describe sixteen patients of whom all but three improved after aDBS, with three patients even showing much improvement. This case series shows that aDBS is a feasible and promising treatment for PD patients with an unmet clinical need after cDBS treatment.

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P099

Closed-loop neuromodulation for post-traumatic stress disorder: clinical trial outcomes

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Introduction

After witnessing a life-threatening event, individuals can develop post-traumatic stress disorder (PTSD) characterized by vivid memories and nightmares. In severe cases, the interplay between the medial prefrontal cortex (mPFC), the basolateral amygdala (BLA) and the hippocampus sets the stage for an inability to extinguish fear. In particular, coupling of theta and gamma oscillations between the mPFC and the BLA are thought to mediate transitions between fear and safety states. We describe a strategy applying neuromodulation to this circuitry to facilitate extinction and treat PTSD.

Goals

We aim to evaluate the feasibility of closed-loop neuromodulation of the BLA in 6 patients suffering from treatment-resistant PTSD (trPTSD). In each case, we evaluated the safety, efficacy and target engagement after stimulation initiation.

Materials & Methods

Six (6) patients suffering from trPTSD were enrolled in the trial and underwent the placement of bilateral BLA electrodes connected to the responsive NeuroStimulation (RNS) implant (Neuropace). The patients underwent in-laboratory exposure sessions during live ECoG recordings to identify neurophysiological biomarkers of fear and PTSD symptoms. Monthly psychological assessments were completed that included the clinician administered PTSD scale (CAPS) as the primary clinical outcome measure.

Results

Four (4) patients are in remission or near remission with improvement in CAPS from baseline of 86%, 55%, 74% and 82%. One patient has experienced a modest improvement of 30% and we continue to make programming adjustments. The last patient only started receiving stimulation recently. We programed the RNS device to detect and stimulate based on an increase in theta range frequency in the BLA. Responsiveness to therapy was generally characterized by a reduction in theta power and of the theta/gamma ratio within the BLA.

Summary

We found that closed-loop neuromodulation of the BLA was well tolerated. One patient suffered from a delayed small cerebral hemorrhage without lasting neurological deficit. We found the therapy response rate encouraging in this small but highly treatment-resistant group. Our neurophysiological findings in relation to clinical state appear consistent with preclinical data describing transitions between fear and extinction. We feel that further clinical study looking into the effectiveness of the treatment is warranted.

P100

Neural decoding from deep brain electrodes to supportclosed loop therapies inpatients with Parkinson's disease

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Despite impressive advances in neuromodulation therapies for Parkinson"s disease (PD), a majority of patients with advanced PD develop disturbances of gait and balance, including postural instability, festination, or freezing of gait, that are refractory to existing treatments. These deficits lead to frequent falls and increase comorbid conditions. Closed-loop stimulation therapies of brain and spinal cord have the potential to better address locomotor abnormalities. However, the delivery of stimulation must be tuned online to the fluctuating state of patients, as well as to task- and context-related constraints encountered in daily life. Such closed-loop therapies are contingent on biomarkers that inform about locomotor activities and deficits in real-time.

Here, we aimed to leverage the neural sensing capabilities of last-generation neurostimulators for deep brain stimulation to (i) identify neural biomarkers that underlie locomotor function and dysfunction in the subthalamic nucleus of PD patients, (ii) characterize changes in these biomarkers under different therapeutic conditions (medication, DBS), and (ii) prototype a modular decoding framework that is able to robustly predict locomotor states and deficits despite fluctuations and real-life constraints.

We recorded 35 participants with advanced PD implanted with DBS, and we thoroughly characterized the changes induced by LDopa and DBS on gait biomarkers, across a variety of locomotor tasks of daily life. We found distinct modulations in low-beta, high-beta and Gamma bands that encoded locomotor states such as sitting, standing and walking. Gait encoding across these frequency bands responded differently to DBS and LDopa, which hindered the performance of a single neural decoder across different therapeutic conditions. We leveraged these observations to design a modular framework that automatically selects among two neural decoders in real-time, based on condition-specific neural correlates. This modular framework robustly coped with therapy-related fluctuations. Considering the large number of patients treated worldwide with DBS implants, as well as the capabilities of newest commercial stimulators, our work pave the way for the possibility of controlling the stimulation in closed-loop neuromodulation therapies that address gait deficits in everyday life conditions.

P101

Parkinson's disease therapies differentially modulate leg motor encoding and sensory feedback across basal ganglia nuclei

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Parkinson's disease (PD) leads to a spectrum of locomotor deficits, including gait abnormalities, balan-ce disturbances, and episodes of freezing of gait. These impairments remain insufficiently managed by standard therapies, including dopamine replacement therapy (L-DOPA) and subthalamic nucleus (STN) deep brain stimulation (DBS). In some cases, STN DBS may even exacerbate locomotor deficits. As a result, gait disturbances markedly reduce mobility, independence, and quality of life. Because L-DOPA and STN DBS can exert distinct and sometimes opposing effects on gait and balance, elucidating how each therapy modulates gait-related circuit dynamics in PD is critical to understanding the patho-physiology of locomotor impairments and to guiding therapeutic optimization.

Here, we investigated how L-DOPA and STN DBS modulate voluntary leg motor encoding and leg movement-related sensory feedback across a comprehensive battery of locomotor tasks. We recorded neurophysiological activity from the motor STN (mSTN) in 35 individuals with PD under each thera-peutic condition. For comparison, we examined associative STN (aSTN) activity in two individuals with obsessive-compulsive disorder (OCD) who performed the same tasks, as well as ventralis intermedius thalamic (VIM) activity in one individual treated for essential tremor (ET). We observed distinct modulations in the motor STN (mSTN) within the low-beta, high-beta, and gamma frequency bands, which differentially encoded voluntary leg movements and movement-related sensory feedback. Although these frequency bands were conserved across nuclei, their modulation patterns in the associative STN (aSTN) and ventralis intermedius thalamus (VIM) differed, indicating that motor and sensory information is encoded differently across basal ganglia and thalamic circuits. Encoding remained preserved under both L-DOPA and STN DBS, yet each therapy imposed distinct spectral alterations.

Understanding these therapy-dependent modulations opens the door to more robust decoding and targeting of locomotor activities across multiple nuclei. Our observations provide a framework for developing closed-loop neuromodulation strategies that address gait and balance impairments while adapting to the complex and fluctuating dynamics of everyday life.

P102

Disentangling the phenomenology of entrained gamma in the subthalamic nucleus of Parkinson's disease patients OFF medication

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Background: Recently, adaptive Deep Brain Stimulation (aDBS) that adjusts stimulation amplitude based on power in the beta band has entered clinical routine. Another promising biomarker is entrained gamma, an activity that occurs exactly at half the stimulation frequency and is thought to fluctuate with dopamine levels and indicate a good ON state. Currently, entrained gamma is conceptualized as entrainment of preexisting Finely Tuned Gamma (FTG) oscillations, that can occur after intake of dopaminergic medication, by stimulation. Here, we investigate the phenomenology of entrained gamma activity in 34 subthalamic nuclei (STNs) of patients with Parkinson"s disease (PD) who were withdrawn from dopaminergic medication.

Methods: All patients were recorded using the Percept PC device in conjunction with SenSight electrodes three months after surgery. Dopaminergic medication was withdrawn at least 12 hours prior to the recordings. Recordings were obtained in the "BrainSense Streaming" mode that allows for concurrent stimulation and local field potential (LFP) acquisition. The two middle electrode levels are segmented into three subcontacts. A monopolar review was conducted at each directional contact and the respective ring contact in a randomized order and a pronation-supination task was used to assess motor performance at each amplitude. Importantly, the recording configuration remained constant while stimulating at different contacts on one level, with the ring contacts above and below the stimulated contact used for sensing. Data were downloaded for offline analysis and a FOOOF (fitting oscillations & one over f) algorithm was used to detect entrained gamma activity.

Results: 18 patients (34 STNs) were included. Preexisting medication induced FTG was not observed in any recording. However, we observed entrained gamma activity at 112 out of 224 stimulated contacts, in 31 out of 34 STNs, in 17 out of 18 patients. The probability to induce entrained gamma increased with higher stimulation amplitudes. Stimulation using directional contacts was more likely to induce entrained gamma. In some cases, entrained gamma was absent during rest but emerged during movement at the same stimulation amplitude (33/224 contacts, 16/34 STNs, 11/18 patients). In general, motor activity increased the power of entrained activity on the group level (power increase over 33% in 43/224 contacts, 19/34 STNs, 14/18 patients). In 15 STNs entrained gamma activity was more pronounced during stimulation at specific segmented contacts compared to others, even though similar stimulation amplitudes were used. We localized the entrained gamma sweetspot to a subregion in the STN that is distinct from the beta suppression sweetspot obtained from the same dataset. Finally, presence of entrained gamma activity was associated with 33.5% higher movement velocity (GLMM, ß = 0.289, t = 2.223, p = 0.0266).

Conclusions: Entrained gamma can be elicited in the majority of subthalamic nuclei of PD patients off medication, in the absence of preexisting FTG oscillations. This activity can be

modulated by movement and is related to stimulation of a defined subregion in the STN and increased movement velocity. Our research further characterizes entrained gamma activity in the STN and underlines the importance of a thorough understanding of neural biomarkers for treatment optimization.

P103

Activity-dependent DBS controlled by neural signatures of gait alleviates locomotor deficits in people with Parkinson's disease

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Advanced Parkinson's disease (PD) leads to a spectrum of locomotor deficits, including heterogeneous gait abnormalities and freezing of gait (FOG) that remain poorly managed by standard treatments. Unlike cardinal motor symptoms, conventional deep brain stimulation (DBS) often displays variable and sometimes detrimental efficacy for locomotor deficits. As a result, a majority of individuals with advanced PD experience progressive loss of mobility, increased risk of falls, and long-term care dependency. Locomotor deficits exhibit episodic and context-dependent behaviors, emerging during demanding tasks or when multitasking. These deficits are further exacerbated by fatigue, stress, or unexpected attentional shifts. Continuous DBS (cDBS) protocols are thus suboptimal to address this episodic nature, which may explain their inconsistent clinical efficacy. Instead, approaches that dynamically adjust stimulation in real time, aligned with the onset of gait disturbances, may more effectively prevent freezing, asymmetry, and initiation difficulties.

Here, we present preliminary results from the ADAP-GAIT clinical trial (NCT06791902), in which we evaluate the safety and preliminary efficacy of aDBS therapies aligned to locomotor states to better address gait impairments. We enrolled three participants with advanced PD, chronically implanted with a Percept PC (Medtronic, USA) in the subthalamic nucleus (STN), and exhibiting disabling gait disorders despite optimized DBS settings. For each participant, we first identified the most bothersome gait deficits and mapped how changes in DBS amplitudes influence cardinal versus locomotor deficits. The optimal stimulation amplitudes to address each set of impairments were defined through clinical evaluation (MDS UPDRS-III). Then, we leveraged a neural decoding algorithm to identify the best personalised STN neural signatures that capture the encoding of locomotor activities (i.e., sitting, standing, walking, or avoiding obstacles) across changing DBS amplitudes, separately for high and low L-DOPA states. Optimal spectral features typically differed between medication states. These neural biomarkers were then selected to close the loop and automatically adapt the delivery of DBS (up- or down-regulation of stimulation amplitude) in real time, based on the ongoing locomotor activity.

Two participants with predominantly unilateral gait impairments exhibited improved locomotor performance and increased gait fluidity with gait-targeted aDBS compared to standard-of-care cDBS, as assessed by kinematic and electromyographic patterns moving towards those of healthy controls. One of these participants also experienced FOG when low in L-DOPA, along with a third participant whose primary gait deficit was FOG; in both, aDBS markedly reduced FOG episodes with respect to cDBS. Despite the heterogeneous locomotor deficits shown by the participants, activity-dependent DBS reliably delivered the optimal stimulation based on the locomotor states

and effectively alleviated locomotor deficits both in well-controlled laboratory settings and in out-of-laboratory conditions. Participants' subjective reports confirmed these quantifications. These findings demonstrate the feasibility and therapeutic potential of activity-dependent DBS aligned to locomotor states for treating disabling gait impairments in PD. Ongoing recruitment will assess the generalizability of these results in a larger cohort.

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Spatial propagation of movement-related synchronisation in the subthalamic nucleus predicts Parkinsonian Motor states

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Movement-related gamma activity (>60 Hz) in cortico–basal ganglia networks reflects prokinetic synchronization. In the cortex these dynamics shift spatially across topographically organized networks that facilitates fine-tuning behavior. It is unclear, whether a similar spatial propagation occurs in the basal ganglia and how it relates to motor function. Here we recorded LFPs from the STN of 46 PD patients (77 hemispheres) at rest and during a simple cued hand movement task and investigated the spatial properties of basal ganglia oscillations. LFPs have been decomposed into the following sub-bands: high-gamma [60-90 Hz], fast-gamma [110-140 Hz], slow-HFO [200-300 Hz] and fast-HFO [300-400 Hz]. Each sub-band displayed spatially distinct hotspots within the STN that propagate predominantly along the inferior–superior axis. While both HG and FG hotspots transiently occupy the associative sub-region of the STN, both SHFO and FHFO remain largely confined to the motor STN. These distinct spatial and spectral trajectories suggest that specific functional roles are exhibited across bands that synchronize during motion. Moreover, since both magnitude of synchronization and spatial propagation are temporally unrelated, we suggest that the latter represents a separate dimension in motor encoding. Importantly, spatial propagation in frequencies > 110 Hz was inversely correlated with dopamine-related motor improvement and could represent compensatory mechanisms following neurodegeneration. These insights into the spatial dynamics of basal ganglia oscillations open new avenues for spectro-behavioral research, clinical translation in motor and neuropsychiatric disorders and spatially-informed DBS strategies.

P105

Towards optimal motor state prediction for adaptive neuromodulation in Parkinson's disease

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Introduction

Adaptive deep brain stimulation adjusts stimulation parameters in real time based on feedback signals that reflect symptom type and severity. In Parkinson's disease, neurophysiological biomarkers such as subthalamic beta- and entrained gamma-band activity have been used in closed-loop algorithms as they have been associated with hypo- and hyperkinetic states, respectively. However, it remains unclear whether individual signal features reliably predict an optimal clinical state across effective stimulation amplitudes and medication conditions. Robust symptom-state prediction may therefore benefit from integrating multiple signal features, enabling improved adaptation of stimulation parameters.

Goals

To develop a model that uses features derived from subthalamic local field potentials to predict periods of good motor performance without troublesome dyskinesia at effective stimulation amplitudes, generalizing across medication conditions.

Materials & Methods

We included 22 patients with Parkinson's disease who were implanted with a sensing-enabled neurostimulator. Local field potentials were recorded while patients were in the OFF-medication state and continuously during a standardized levodopa challenge until they transitioned into the ON state. During repeated blocks within the levodopa challenge, stimulation amplitude was increased stepwise around the clinically defined effective amplitude. Motor performance and dyskinesia severity were evaluated across various stimulation amplitudes and medication states. At this stage of the analysis, band-power features were extracted and correlated to medication intake, stimulation intensity, motor performance and dyskinesia severity to establish the basis for predictive modeling.

Results

Beta power reliably differentiated between OFF and ON medication and stimulation states, respectively, and correlated with differences in motor performance across these states. However, within the stimulation-ON condition at clinically effective amplitudes, the association between beta power and motor performance was markedly reduced. In contrast, entrained gamma activity varied around clinically effective stimulation amplitudes, while its relationship to medication state was less consistent.

Summary

Our preliminary results suggest that single band-power features may not fully capture fluctuations in motor performance and dyskinesia severity at clinically effective stimulation amplitudes. Because reliable symptom state estimation is a prerequisite for personalized stimulation parameter adaptation, we aim to integrate multiple biomarkers to enable more accurate tracking of symptom states during ongoing deep brain stimulation.

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Deployment of adaptive deep brain stimulation in practice: insights, innovations, and implementation challenges in Parkinson disease

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Objective: To identify challenges, solutions, and clinical practices in the use of adaptive deep brain stimulation (aDBS) for Parkinson disease (PD).

Background: Recently approved aDBS technology allows for real-time, closed-loop adjustment of DBS stimulation amplitude using beta frequency local field potential (LFP) power as a control mechanism. aDBS provides similar on-time to continuous DBS, and is often preferred by patients over continuous DBS. However, aDBS is complex to program and many uncertainties exist about how best to use this technology in clinical practice.

Methods: We report a single center experience with aDBS programming in a cohort of PD patients. Patients were seen by one of six movement disorder neurologists experienced in DBS programming. Clinician were surveyed to ascertain trends in aDBS programming.

Results: A total of 43 patients (13 female) were seen for aDBS programming between March and August 2025. aDBS could not be configured in a total of 7 patients due to artifact in LFP signals (2), lack of clear frequency of interest (2), and optimal contacts being incompatible with aDBS (3). Nine patients had fewer than two visits at the time of data collection and were excluded from analysis. Symptoms targeted for improvement with aDBS by clinicians included dyskinesia (11), motor fluctuations (8), gait disturbance (8), speech (6), rigidity or bradykinesia (5), or tremor (5). The mean (SD) number of visits required until aDBS was either considered optimized or could not be configured was 3.4 (1.5).

Conclusion: aDBS requires multiple programming sessions and a high level of expertise to program successfully. We present several key lessons learned and sample clinical workflows for aDBS optimization.

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Investigating chronic beta power in the context of continuous and adaptive deep brain stimulation in the STN of Parkinson's patients

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Background/Introduction: Chronic sensing enabled deep brain stimulation (DBS) systems provide unprecedented opportunities to characterise neural dynamics in naturalistic settings. However, the interpretation of local field potential (LFP) signals used to drive adaptive DBS (aDBS) algorithms remains complex, as measured beta band activity may reflect a composite of oscillatory activity, aperiodic background fluctuations, and artifacts.

Objective/Goal: This ongoing study aims to decompose the components underlying chronic beta band (13–30 Hz) recordings in the subthalamic nucleus (STN) to better understand the drivers of the activity changes measured by the implantable pulse generator (IPG) during aDBS. Specifically, we investigate the relative contributions of oscillatory dynamics, aperiodic (1/f) activity, and artifact contamination (particularly ECG) to the beta power signals used for stimulation amplitude modulation.

Methods: We analysed chronic STN LFPs from 23 Parkinson"s disease patients implanted with Percept sensing-enabled DBS systems. Each patient contributed recordings during cDBS and aDBS phases, enabling direct comparison of stimulation strategies and their differential effects on beta power dynamics and suppression. Data included: BrainSense Timeline beta power (5 Hz bands, sampled every 10 min), patient-triggered full-spectrum snapshots (0–100 Hz), and extended BrainSense Streaming sessions (up to 16 h) for diurnal assessment. Event snapshots were programmed to capture LFP recordings during defined clinical states: medication intake, motor state extremes (hypokinetic and hyperkinetic), and pain related presentations. Periodic and aperiodic components were separated using FOOOF and the effects of ECG contamination and movement-related artifacts on beta detection and aDBS performance were systematically evaluated.

Preliminary Findings: Data from approximately 150 recording sessions have been collected and are currently under analysis. Charactersitics of beta dynamics in subjects who have chosen to revert to cDBS will be presented and compared to subjects who stayed on aDBS. Preliminary observations suggest variability in beta band signal composition. Initial inspection indicates potential contributions from movement related artifacts, ECG contamination, and long-term activity trends independent of oscillatory dynamics.

Summary/Significance: By characterizing the oscillatory, aperiodic, and artifact components of chronic beta recordings through multi scale monitoring of snapshot and continuous recordings, this work clarifies the factors that contribute to changes in IPG measured activity within the clinician selected frequency range. Understanding these signal components is important for refining closed loop stimulation algorithms and for interpreting fluctuations in LFP power that guide therapeutic adjustments in real world settings.

P108

Decoding of medication states in individualized subthalamic local field potentials: a few-shot adaptation approach

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Introduction

Patients with Parkinson"s disease (PD) experience significant medication fluctuations, highlighting the need for a medication-aware adaptive deep brain stimulation (aDBS) strategy [1]. Although medication state decoding from subthalamic nucleus (STN) local field potentials (LFPs) has shown promising results [2], most studies have relied on patient-specific models, which suffer from cold-start in new patients and overfitting on limited labeled data, while naïve group models risk averaging out individualized biomarkers. This study investigated whether a group-pretrained STN-LFP medication state decoder was able to adapt to new patients with a few patient-specific samples, thereby combining group-level information with individualized performance.

Goals

This study explored whether a group-pretrained medication decoder, fine-tuned with few samples, could match or surpass individual model for STN-LFP medication state classification.

Materials & Methods

LFPs were collected from 19 PD patients with STN-DBS implantation under both Med ON/OFF states. A convolutional neural network (CNN) was trained on raw STN-LFPs to classify medication state. Using the CNN, we trained individual models within-subject and group models in a leave-one-subject-out scheme. For the Group-CNN+FT strategy, the CNN was first pre-trained on pooled data and then further fine-tuned with k labeled samples (k = 2–128, length = 2s) from the held-out subject. A conventional feature-based support vector machine (SVM) model was additionally used as a baseline model.

Results

The proposed Group-CNN+FT strategy leveraged group-level information to achieve medication state classification performance that closed to, and in many patients higher than, that of patient-specific models. The replication of prior findings showed that the baseline Group-SVM models (~63.6% balanced accuracy) performed worse than Individual-SVM models (~75.8%, $p<0.001$). In contrast, the non-fine-tuned Group-CNN model (~72.1±2.9%) already approached the individual baseline. When adapting Group-CNN+FT, the performance improved significantly: in 16/19 subjects (~84%), using only few samples (k≈16), Group-CNN+Ft (~87.7%) achieved performance comparable to the Individual model (~88.0%). In 8/19 subjects, Group-CNN+Ft even exceeded the Individual model. For subjects with poor individual performance (~49.4%), the group-pretrained model improved accuracy by ~26.0%, indicating a significant benefit gained from group-level information. However, in three patients Group-CNN+FT remained below the individual model, suggesting the need for further adaptation strategies.

Summary

The Group-CNN+FT strategy achieved performance comparable to Individual models in 84% of subjects and significantly improved outcomes for patients with limited data or poor individual performance. By providing a robust initial model and requiring only minimal patient-specific data, this framework reduced the cold-start and overfitting risk for new patients, underscoring the potential of deep learning for robust, personalized aDBS.

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P109

Real-time closed-loop DBS using internal model control for evoked potential amplitude regulation

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Introduction: Closed-loop DBS (clDBS) involves real-time adjustment of stimulation based on a feedback signal that reflects the current neural or clinical state of the patient. Beta oscillations (13–30 Hz) are the most widely studied biomarker for clDBS in Parkinson's disease. However, the utility of beta oscillations may be limited since these signals are potently suppressed during DBS. Evoked resonant neural activity (ERNA) is a stimulation-induced signature of indirect pathway engagement within the subthalamic–globus pallidus externus (STN–GPe) network. ERNA correlates with medication state, sleep, stimulation parameters, targeting, and clinical outcomes, suggesting its potential as a biomarker for continuous clDBS.

Question: How does ERNA amplitude relate to stimulation intensity, and can this relationship be used to develop a continuous closed-loop controller that dynamically adjusts stimulation to maintain a target ERNA amplitude?

Methods: Experiments were conducted during awake microelectrode mapping procedures. For closed-loop control design, stimulation dose–responses were obtained by delivering 100 Hz stimulation to the STN at intensities ranging from 10–130 μA. The generation of this dose-response curve revealed a stable and predictable input-output relationship and led to the identification of the suitable operational range of 50-120 μA for the prospective closed loop controller. To this end, we utilized Nikiforov's internal-model-based control framework for linear time-invariant systems to design an internal model controller (IMC). The feedback controller computes the required stimulation intensity from the tracking error and the internal model state, enabling compensation for deviations from the reference and ensuring zero steady-state error. The dose–response data were used for plant identification via least-squares fitting and for subsequent controller design and simulation, ensuring that the resulting control law satisfied the desired specifications and hardware limitations. The IMC controller was then evaluated in three patients, whose plant model was identified immediately prior to closed-loop testing, and controller performance metrics were quantified offline following each closed-loop run.

Results: The control objective was to maintain ERNA amplitude at specified target levels relative to baseline set at 110 μA to maximize ERNA amplitude. Across all target levels, closed-loop control kept ERNA amplitude within ~17% of the target, with ~1.3 s convergence time. Rise and settling times were 0.7 s and 3.3 s, respectively, indicating acceptable reference tracking. These results suggest that an IMC approach could compensate for unmodeled effects, without requiring an explicit real-time estimate of the underlying biological mechanisms (e.g., the specific fiber populations recruited by stimulation). Furthermore, this approach enables acceptable reference tracking under a patient-specific approximation of the ERNA response.

Conclusions: ERNA remains measurable under stimulation, maintains a consistent and monotonic input–output relationship with stimulation intensity, and exhibits stable dynamics that can be modelled and regulated in real time. Thus, ERNA has potential to address the limitations of beta power, which becomes decoupled from the underlying clinical state when stimulation is ON. Together, these findings position ERNA as a possible biomarker for continuous clDBS.

P110

Beta in the match: how subthalamic oscillations are modulated by engagement in sport events

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Introduction. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a mainstay treatment for advanced Parkinson's disease (PD). Currently available adaptive DBS (aDBS) systems modulate stimulation in real time based on the amplitude of STN local field potentials (LFPs) monitored within a patient-specific frequency range (P-range). Since the STN integrates motor, cognitive, and limbic information, its activity may encode not only motor but also non-motor processes, including emotional experiences. However, the relationship between real-life emotional states and chronically recorded STN activity remains unknown.

Goals. To investigate the temporal dynamics of STN P-range during emotional engagement induced by live sports viewing in aDBS-treated PD patients.

Materials & Methods. We enrolled eight PD patients implanted with the AlphaDBS device (Newronika, Italy) and chronically treated with aDBS. STN LFPs amplitude (nV/√Hz) was recorded bilaterally in a patient-specific alpha-beta P-range (8-23 Hz) at 1-min resolution. Each patient watched one or more tennis and soccer live matches at home. Post-viewing interviews classified each viewing episode as engaged (N=15) or neutral (N=13) and engaged viewings (EVs) were further subdivided into intervals of higher versus lower engagement. On a finer temporal scale, key-events (1-min resolution) were retrieved from sports newspapers and validated through video recordings of the matches. Each EV was compared with its own baseline day (BD, different hours of the same day) and with control periods (CP, same hours on subsequent days). EV signals were decomposed into a trend component (30-min sliding mean) and a detrended component. First and second derivatives of the trend were obtained via Savitzky-Golay filtering to identify changes. Associations between key events and detrended extrema (maxima/minima) within ±1 min or detrended event-to-point distance were tested using permutation testing (10K iterations). Per-match/hemisphere comparisons used Mann-Whitney U with Benjamini-Hochberg FDR correction. Population-level analysis used Wilcoxon signed-rank. Effect size was estimated with Cohen"s d.

Results. During EV, median P-range amplitude was significantly higher than BD (left: $p<0.05$, $d=0.71$; right: $p<0.01$, $d=0.73$) and CP (left: $p<0.05$, $d=0.71$; right: $p<0.01$, $d=0.47$). No significant difference emerged for neutral viewing conditions.

Higher-engagement intervals showed significantly larger trend derivatives than lower-engagement intervals in the left STN (first derivative: $p<0.001$, $d=0.80$; second derivative: $p<0.005$, $d=1.09$), and a greater proportion of time spent above the 75th percentile (first: 33±12% vs 21±5%, $p<0.05$; second: 36±9% vs 23±2%, $p<0.005$).

In six tennis viewings from one patient, key-event times were significantly associated with detrended P-range maxima/minima in the left STN ($p<0.05$, $d=1.94$). Event-to-point distance showed no significant association.

Summary. We showed that STN alpha-beta oscillations vary systematically with emotional engagement across multiple temporal scales. These findings support the idea that, in real-life

contexts, the STN encodes rich emotional information beyond its established motor functions, opening new possibilities for more personalized DBS approaches in neurological disorders.

P111

A wearable platform for daily-life monitoring of neural and motor gait biomarkers in Parkinson's disease

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A majority of individuals with advanced Parkinson"s disease develop severe gait and balance deficits that significantly restrict mobility, independence, and quality of life. Despite impressive technological advances, gait impairments remain poorly understood and notoriously hard to treat. Most attempts to characterize gait deficits or to identify neural biomarkers of gait dysfunction have been confined to well-controlled, sophisticated laboratory settings. However, such environments fail to capture many critical contextual factors that exacerbate gait deficits in real-world conditions, such as stress, fatigue, or unexpected distractions and environmental constraints. Replicating these unpredictable conditions in laboratory settings remains a significant challenge.

To address this, we developed a wearable neuromonitoring platform integrating (i) smart, sensorized shoes with embedded microchips running A.I. algorithms for online gait quality assessment, along with (ii) wireless recordings of local field potentials from chronically implanted electrodes for deep brain stimulation. This platform enables continuous monitoring of motor and neural biomarkers of gait function and dysfunction across activities of daily life. 13 participants with advanced Parkinson"s disease were monitored during a comprehensive set of out-of-laboratory locomotor tasks, both in the ON and OFF medication conditions. Our platform allowed to assess gait quality, quantify modulations in response to medication, fatigue, and context-specific demands, and to map the underlying neural correlates. This neuromonitoring platform offers valuable possibilities for refining neuromodulation protocols and supporting closed-loop therapies for gait impairments in real-life conditions.

P112

Sleep-wake modulation of subthalamic activity in patients with Parkinson's disease and conventional or adaptive deep brain stimulation

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Introduction: The biomarker currently used for adaptive deep brain stimulation (aDBS) in Parkinson's disease (PD) is the power of subthalamic local field potentials (STN-LFP) in the beta band (12–30 Hz). Because STN beta power decreases during sleep, aDBS has the potential to automatically reduce stimulation amplitude at night, preventing overstimulation and associated side effects. However, evidence on how closed-loop stimulation affects circadian neural dynamics remains limited. In particular, the differential impact of conventional DBS (cDBS) versus aDBS on STN-LFP across awake and asleep states is virtually unexplored. Elucidating these effects is essential for refining and optimizing future aDBS algorithms.

Goal: To investigate the impact of cDBS and aDBS on periodic and aperiodic components of STN-LFP spectra associated with the sleep-wake cycle.

Materials & Methods: We recruited ten PD patients who were blindly treated with cDBS and aDBS for two weeks in each mode. In aDBS, the stimulation amplitude was linearly adjusted every minute between two clinically defined limits, according to the STN-LFP amplitude within a patient-specific beta frequency range. Medications were kept constant. Patients were evaluated with the MDS-UPDRS-III scale before entering the study (baseline) in Stim-off/Meds-off condition (i.e., with DBS switched off and overnight withdrawal of dopaminergic drugs), and at the end of each two-week period in Stim-on/Meds-on condition (i.e., under the ongoing stimulation mode and the usual medical treatment). Clinical improvement in the two stimulation modes was defined as the percentual change with respect to baseline. STN-LFP spectra were continuously recorded with a 10-minute resolution and decomposed into their aperiodic and periodic components. We assessed the influence of circadian state (awake/asleep as determined from patient diaries) and stimulation mode (cDBS/aDBS) on the aperiodic spectral offset, knee, and slope and on the amplitude of oscillatory activity within a 5 Hz window centered on the individual beta peak. Statistical analyses were performed using two-way ANOVA and the Wilcoxon signed-rank test.

Results: cDBS and aDBS modes provided significant and similar clinical improvement with respect to baseline (MDS-UPDRS-III %change as average [range]: cDBS, 59.1 [20.7 – 97.7], and aDBS, 59.9 [23.5 – 88.4]). Beta peak frequency remained stable across states and modes for all patients. Both offset and beta peak amplitude were significantly larger in awake compared to asleep state, with no influence of stimulation mode (delta awake-asleep in cDBS and aDBS: offset (a.u.): 0.8 [-0.3 – 2.6] and 0.7 [-0.4 – 2.3]; peak amplitude (nV): 0.2 [-0.6 – 0.8] and 0.3 [-0.1 – 1.1]).

Summary: Our findings suggest that beta amplitude suppression during sleep is independent of the stimulation mode, likely reflecting the reduction of akinetic-rigid symptoms during sleep. Importantly, alongside beta suppression, the offset of the aperiodic spectral component also showed a marked decrease during sleep, underscoring its potential as a complementary

biomarker for sleep-targeted aDBS. These results highlight the need for future aDBS designs to account for the influence of aperiodic activity on biomarker computation, particularly when adapting stimulation across the sleep/wake cycle.

P113

Neuronal signatures of motor symptom severity in Parkinson's disease extracted from subthalamic nucleus local field potential recordings

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Introduction - Adaptive deep brain stimulation (aDBS) for Parkinson"s disease (PD) aims to improve treatment efficacy by adjusting stimulation amplitude based on a neurophysiological feedback signal, or physiomarker, corresponding to the patient"s clinical state. While beta band (13–30 Hz) spectral power from local field potential (LFP) recordings using DBS electrodes is the best-characterized physiomarker to-date, correlation values with PD motor symptom severity are relatively low.

Goals - To explore whether explained variance in PD motor symptom severity can be increased by combining spectral information from multiple frequencies in the LFP signal.

Materials & Methods - We applied canonical correlation analysis (CCA) to the full power spectral density (1–100 Hz) of LFP recordings from 67 patients with PD, receiving DBS of the subthalamic nucleus, alongside scores on clustered and individual items of the Movement Disorders Society Unified Parkinson's Disease Rating Scale part III (UPDRS-III). Recordings were performed under varying medication and stimulation conditions.

Results - CCA redundancy indices quantified that over 20% of variance in UPDRS-III scores was explained by a linear combination of power from frequencies across the spectrum, compared to ~10% by beta power alone. Beta frequencies contributed most strongly to total UPDRS-III scores and indicated a positive correlation, with slightly stronger contributions of low-beta (~13–25 Hz) than high-beta (~26–35 Hz) ranges. Low frequency (<10 Hz) and finely-tuned gamma activity at half the stimulation frequency (62–63 Hz) contributed with a negative sign to the total UPDRS-III scores. A clear double beta peak was observed in the canonical loadings of the frequency spectra associated with bradykinesia, while rigidity was mostly associated with low-beta power. Canonical loadings for the correlation with tremor showed a less distinctive spectral pattern. CCA analyses performed separately for contralateral and ipsilateral UPDRS-III scores demonstrated highly similar spectral patterns, potentially due to the strong correlations found between individuals" left and right UPDRS-III hemibody scores.

Summary - Overall, CCA results revealed both overlapping as well as distinctive spectral patterns across symptoms and body sides. This is indicative of shared neural mechanisms underlying motor symptom expression, yet also suggests the potential for identifying "neuronal signatures" of specific PD motor symptoms. Inverse contributions from low-frequency and finely-tuned gamma activity at half the stimulation frequency demonstrated the added value of a broader spectral physiomarker.

P114

Deep learning for motor state classification using chronic local field potentials in Parkinson's disease

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Introduction: Recent advances in implantable neurostimulators for deep brain stimulation (DBS) in Parkinson"s disease (PD) now enable adaptive strategies (aDBS) that automatically adjust stimulation parameters based on neural biomarkers. Accurate and reliable identification of motor states through long-term monitoring of neural dynamics in real-world conditions is essential for discovering robust biomarkers of symptoms and therapeutic response, and ultimately for advancing the development of increasingly effective neurostimulation strategies.

Goals: In this study, we present a multimodal classification framework that extracts time-frequency features from subthalamic nucleus local field potentials (STN-LFPs) to predict motor states.

Materials & Methods: Thirteen patients with PD (2 women, aged 45-74 years) and implanted with the AlphaDBS device (Newronika SpA, Milan, Italy) were tested at home for two weeks in conventional DBS (cDBS; fixed stimulation parameters) and two weeks in adaptive DBS (aDBS; stimulation current modulated by a linear proportional algorithm based on LFP beta-power fluctuations). The device enabled 24/7 recordings of LFPs (one beta power value per minute and one power spectrum 5-35Hz every 10 min). During the study, patients completed the Hauser diary, reporting their motor state and sleep every 30 min. LFP data (4,440 hours total) were labeled using the diaries into three motor states: ON (including with/without dyskinesia), OFF, and SLEEP. Feature extraction was performed from the beta (13-30Hz) power and the full spectrum (5-35 Hz) power, and included mean, standard deviation (STD), root mean square (RMS), peak-to-peak (PTP) amplitude, energy of the beta signal, spectral power in other bands, Hjort parameters, complexity, and Continuous Wavelet Transform (CWT) using Morlet wavelets to estimate time-frequency dynamics. Dimensionality reduction using principal component analysis (PCA) preserved 95% of variance while reducing computational complexity. Multiple machine learning and deep learning classifiers were then evaluated.

Results: Among the models tested, the multilayer perceptron (MLP) classifier trained on time–frequency features achieved the highest F1-score across all thirteen patients (F1 = 93.1%). However, its generalization was limited, as performance in the leave-one-patient-out test was markedly lower (F1 = 30%).

Summary: These findings demonstrate that time–frequency representations enable motor state classification and support the development of continuous, patient-tailored aDBS systems for real-life applications, which must still be customized for each patient.

P115

Randomized controlled trial comparing adaptive versus continuous subthalamic nucleus deep brain stimulation in Parkinson's disease. Closed loop optimization of deep brain stimulation effect in Parkinson's disease (CLOSE-PD study)

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Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a well-established treatment for motor fluctuations in Parkinson"s disease (PD). To date, stimulation amplitude is applied in a continuous manner and must be manually titrated to exert its desired effect, a process frequently limited by stimulation-induced side effects such as dysarthria and dyskinesia or insufficient stimulation. Closed-loop, adaptive DBS (aDBS) could possibly offer more effective control of motor symptoms and a reduction in side effects compared to continuous DBS (cDBS). Adaptive DBS dynamically adjusts stimulation on the basis of local field potentials (LFP) in the beta (13-30 Hz) frequency range, a physiological marker of bradykinesia and rigidity in PD. A recent, unblinded study suggested improved clinical outcomes of aDBS compared to cDBS1.

Goals

To evaluate whether STN-aDBS is more efficacious than STN-cDBS for the treatment of motor fluctuations in PD.

Materials & methods

This study is a prospective, multicenter, randomized, double-blind, controlled trial (RCT) with a parallel-group design for a direct comparison between aDBS and cDBS. Participant enrollment will take place at three hospitals in the Netherlands and one in Belgium. The research cohort will consist of 130 patients with idiopathic PD who will have bilateral STN-DBS implanted with a PerceptTM PC/RC neurostimulator (Medtronic Inc., Minneapolis, MN, USA). Participants will be randomized to be treated with aDBS or conventional cDBS and will be blinded for the treatment allocation. The participants will be evaluated by a blinded assessor at six months of follow-up. The primary outcome is the change from baseline to six-month follow-up in daily mean ON time without troublesome dyskinesia using the PD Home diary, in the aDBS group compared to the cDBS group. Secondary outcomes are the between-group difference in the change from baseline to six-month follow-up in motor symptom severity, motor complications, dopaminergic medication usage, sleep disturbances and quality of sleep, mood, apathy status, level of physical disability (ALDS), cognitive function (MoCA) and disease-specific quality of life (PDQ-39). Additional secondary

outcomes will be stimulation parameters (e.g., energy consumption, stimulation amplitudes, average stimulation fraction), LFP characteristics, participant"s degree of experienced burden of the treatment, participant"s degree of satisfaction and the assessor"s ease of programming.

Results

Participant enrollment is expected to start in February 2026. This study will provide important insights into the potential benefits of STN-aDBS versus conventional STN-cDBS and will be crucial to evaluate the potential implementation of STN-aDBS in standard clinical care in PD.

Summary

This study is a prospective, multicenter, double-blind RCT to evaluate whether STN-aDBS is more efficacious than STN-cDBS in PD. The trial is registered at ClinicalTrials.gov (NCT06909045).

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P116

Chronic adaptive deep brain stimulation in Parkinson's disease: ADAPT-START findings and programming principles

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Introduction

Deep brain stimulation (DBS) is an established treatment for advanced Parkinson"s disease (PD), but conventional DBS (cDBS) may provide suboptimal symptom control and can induce stimulation-related adverse effects. Adaptive DBS (aDBS), which dynamically adjusts stimulation amplitude in response to subthalamic beta-band activity, offers the potential for more personalized therapy. However, applicability in clinical practice, programming demands, and clinical benefit are still only partially defined.

Goals

We aimed to: (1) assess the feasibility of implementing dual threshold aDBS in routine clinical follow-up of PD patients with chronic cDBS and a Medtronic Percept neurostimulator; (2) describe reasons for ineligibility or delayed programming; and (3) report motor and gait outcomes, as well as patient preference, for chronic aDBS compared with cDBS.

Materials & Methods

Between January and April 2025, we offered the opportunity to test aDBS with the dual threshold algorithm to 20 PD patients with chronic cDBS and a Percept device. We recruited patients with stable cDBS treatment for a minimum of four months. To facilitate implementation in routine clinical practice, aDBS setup was limited to three visits, with one supplementary visit allowed when necessary. Motor symptom severity and gait were assessed in the chronic cDBS condition and after one month of aDBS using unblinded MDS-UPDRS III and the Freezing of Gait Questionnaire (FOG-Q).

Results

Of the 20 screened patients, nine (45%) were eligible and tested the aDBS mode. The reasons for exclusion were signal artifacts or absence of a clear alpha–beta peak (three patients), cDBS settings not compatible with aDBS (three patients), and psychiatric comorbidities (one patient). In four recently implanted patients, the electrode identifier tool indicated an alternative active contact configuration to the one previously used, prompting the evaluation of a new cDBS setting. By July 2025, five of the nine eligible patients had transitioned to chronic aDBS, one reverted to cDBS by personal preference, and three remained in the optimization phase due to variability of the alpha–beta peak over time (one patient) and difficulties in optimizing stimulation parameters (two patients). Three patients completed the aDBS setup within the three scheduled programming visits, whereas two required one supplementary visit. In the five patients receiving chronic aDBS, the median MDS-UPDRS III score was 15 (range 6-18) in aDBS/Meds-OFF, representing a 35% greater motor improvement compared with their cDBS settings (cDBS/Meds-OFF: 23 (range 10-

29)). The median FOG-Q score was 3 (range 2-8) in aDBS, corresponding to a 40% reduction with respect to the cDBS/Meds-OFF condition (FOG-Q score: 5 (range 1-7)).

Summary

In this small clinical cohort, among optimized patients, all but one preferred aDBS over cDBS, reporting clinically meaningful motor improvement and a consistent trend toward gait benefits. Technical limitations in sensing and programming demands still restrict the broader implementation of aDBS, underscoring the need for optimized algorithms and larger controlled studies.

P117

Gait kinematics meet brain oscillations: toward new biomarkers for deep brain stimulation in Parkinson's disease

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Parkinson"s disease (PD) is one of the most common neurodegenerative disorders, and abnormal neural oscillations within cortico–basal ganglia–thalamo–cortical circuits are central to its pathophysiology [1]. Oscillatory activity in specific EEG and local field potential (LFP) frequencies correlates with motor symptoms such as bradykinesia, and beta-band activity in subthalamic LFPs has been used as a relatively stationary biomarker for adaptive deep brain stimulation (aDBS) [2]. However, the neural underpinnings of gait impairment in PD and their relationship to neural activity remain poorly understood [3].

We simultaneously recorded kinematic data from optical motion capture and cortical activity from EEG during 6 minutes of figure-of-eight overground walking in 10 patients with PD and 10 age-matched healthy controls (HC). LFPs were recorded from the DBS electrode in the hemisphere contralateral to the symptom-dominant side. EEG analysis focused on motor-cortical electrodes (Cz, C1, C2, C3, C4). Gait was quantified using 37 parameters spanning seven domains, including spatial parameters, rhythm, variability, asymmetry, margin of stability, foot clearance, and arm/hand coordination. EEG and LFP power were computed in three frequency bands: low beta (12–20 Hz), high beta (20–30 Hz), and gamma (30–45 Hz), and across four gait-cycle phases: initial double support (IDS), final double support (FDS), left single support (LLS), and right single support (RLS).

Patients with PD were clustered into two subgroups using anchored k-means based on their similarity to HC across all gait features, forming groups with milder versus more pronounced gait deficits. Independent t-tests with false discovery rate (FDR) correction were used to identify gait parameters differing significantly between subgroups. These parameters were then correlated with gait-phase- and frequency-specific EEG and LFP power using Spearman"s rank correlation with FDR correction.

Six patients were classified as more impaired relative to HC, and four as closer to HC. Six gait parameters, walking speed, stance time asymmetry, cadence variability, stance time variability, stride length, and step length, emerged as markers of gait impairment. Step length ($\rho = 0.69$, FDR-corrected $p = 0.04$) and stride length ($\rho = 0.68$, FDR-corrected $p = 0.04$) were positively associated with gamma-band EEG power during IDS. No gait parameter showed a significant association with gait-phase–averaged LFP power in any frequency band.

The positive association between cortical gamma power during IDS and step/stride length may indicate that patients who can generate larger steps rely more on cortical resources to support weight transfer, compensating for reduced automaticity of basal ganglia control. Step length, stride length, and cortical gamma activity may therefore represent exploratory neural and gait markers of gait control in PD and could motivate future work on their relevance for aDBS personalization.

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P118

A fully open-source closed-loop neuromodulation platform for real-time phase- and amplitude-based stimulation

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Background: Closed-loop neuromodulation based on real-time neural signal processing has strong potential to improve experimental and therapeutic brain stimulation. In previous work, we introduced an open-hardware platform for phase-locked stimulation with real-time processing, validated using artificial benchmarks and experimental data [1]. However, dependence on external software environments limited portability, real-time parameter adjustment, and experimental flexibility, particularly during in vivo studies. Fully open, self-contained solutions combining real-time processing, intuitive control, and robustness remain limited.

Objective: To present an evolved version of our system implementing a fully open-source closed-loop neuromodulation platform that integrates open hardware and open software, enabling flexible real-time control and improved usability during in vivo experiments.

Methods: The system is implemented on an Arduino Nano 33 BLE Sense and features a redesigned software architecture. Real-time signal processing and closed-loop control are programmed directly using the Arduino IDE, while a Python-based graphical user interface (GUI) provides experimental control. The GUI enables: (1) online reprogramming of closed-loop parameters during ongoing processing, (2) real-time visualization of the power spectral density (PSD) to select frequencies of interest, (3) monitoring of phase-locking quality, and (4) stimulation based on signal amplitude independently of phase. The platform operates as a fully self-contained solution without proprietary software. Performance was assessed using artificial benchmarks and validated in freely moving animals using the 6-hydroxydopamine (6-OHDA) model of Parkinson"s disease.

Results: The updated system achieved performance comparable to the previous implementation for stimulation frequencies up to 100 Hz. In vivo experiments demonstrated stable operation in freely moving conditions, with reliable real-time phase and amplitude tracking. Compared to the earlier version, the platform offers improved versatility, more precise control of real-time processing parameters, and enhanced experimental operability. Removing external software dependencies facilitated faster parameter tuning and greater robustness during in vivo experiments.

Conclusion: This work presents a fully open-source, portable closed-loop neuromodulation platform integrating embedded real-time processing with an intuitive Python-based interface. The system improves flexibility, control, and usability during in vivo experiments, supporting reproducible neuromodulation research and lowering the barrier for deploying closed-loop stimulation paradigms in freely moving animal models.

P119

Months-long real-world profiling of chronic adaptive DBS

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Question: Chronic sensing from implanted DBS systems offers a unique window into long-term beta-band LFP dynamics, yet it is unclear how these signals relate to the *way* adaptive DBS (aDBS) operates over months in routine care. We aimed to (i) characterise the stability and temporal structure of chronic beta sensing, and (ii) test whether distinct aDBS operating regimes differ in LFP behaviour or represent primarily different controller modes.

Methods: We retrospectively analysed Medtronic Percept PC chronic sensing data in a single-centre cohort using a within-hemisphere comparison of adaptive versus conventional (nonadaptive) stimulation under a unified programming SOP. The dataset comprised 27 patients (54 hemispheres) with 966,664 samples at native 10-min resolution (mean follow-up 4.4 months). We quantified biomarker drift, modelled circadian structure, and examined residual dynamics after de-seasonalisation. Adaptive behaviour was captured by the Adaptive Variability Index (AVI), reflecting controller activity within the programmed therapeutic corridor. We identified operational regimes of aDBS via unsupervised clustering of amplitude time series (two-regime solution) and, separately, residual LFP "microstates" (six-cluster solution). We then tested mode/microstate–amplitude coupling and assessed changes following threshold adjustments (n=284 events) and energy expenditure (TEED).

Results: Chronic beta sensing was stable over months (drift −0.22%/month; 95% CI crossing zero). Circadian modelling explained 96.8% of LFP variance, while residuals retained structured dynamics (lag-1 ACF≈0.38; half-life ~40–50 min; slightly "pink" spectrum), indicating physiologically meaningful fluctuations beyond measurement noise. aDBS behaviour was heterogeneous by AVI (minimal 21%, moderate 46%, active 24%, high 9%). Importantly, amplitude dynamics segregated into two robust operating regimes: a **static** regime with long plateaus and minimal controller engagement, and a **modulating** regime with frequent updates (bootstrap ARI=0.578). These regimes did **not** map onto residual LFP microstates: microstates neither distinguished adaptive vs conventional stimulation nor predicted amplitude (Δ amplitude ≈0.007 mA; p=0.62; LFP–amplitude r<0.01). After threshold adjustments, controller behaviour stabilised gradually over weeks, with improved corridor containment (+6–7 percentage points from 7→14→28 days) and reduced amplitude variability. aDBS achieved therapeutic equivalence on mean LFP and mean amplitude while reducing TEED by 17%.

Conclusions: In real-world practice, chronic sensing shows a highly predictable circadian beta structure with stable long-term biomarker levels and structured residual dynamics. aDBS does not appear to continuously track residual LFP states; instead, it operates in two distinct controller modes—quiet/static versus engaged/modulating—consistent with corridor-based, event-triggered control. These operating regimes help reconcile heterogeneous adaptive behaviour with preserved average therapeutic state and meaningful energy savings.

P120

Long-term subthalamic interhemispheric coupling in Parkinson's disease during conventional and adaptive deep brain stimulation

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Introduction: In Parkinson"s disease (PD), adaptive deep brain stimulation (aDBS) of the subthalamic nucleus (STN) holds the promise to enhance clinical benefits and reduce side effects of conventional DBS (cDBS). In single drive mode (SD-aDBS), stimulation of both hemispheres is modulated based on the local field potentials (LFP) recorded from one side. This makes interhemispheric coupling a key determinant for ensuring appropriate stimulation. To date, interhemispheric coupling of the STN has been investigated only in acute settings and in the absence of active stimulation.

Goals: To investigate the effect of chronic cDBS and SD-aDBS on subthalamic interhemispheric coupling in PD patients.

Materials & Methods: We recruited twelve PD patients who were blindly treated with the AlphaDBS device (Newronika) in either cDBS or SD-aDBS for two consecutive weeks in each mode, with medications unchanged. In SD-aDBS, a "linear proportional algorithm" adjusted stimulation amplitude every minute, between two clinically defined limits, based on STN-LFP amplitude within a patient-specific beta frequency range. Patients were evaluated using MDS-UPDRS-III at enrollment (in stim-OFF/meds-OFF, after overnight withdrawal of dopaminergic drugs), and at the end of each two-week treatment period (stim-ON/meds-ON). Clinical improvement was defined as percentual change of MDS-UPDRS-III score relative to enrollment. Patients also completed the Hauser diary, from which ON-time and OFF-time percentages during the awake time were calculated. STN-LFP spectra were continuously recorded (10-minutes resolution) and decomposed into aperiodic and periodic components. Interhemispheric coupling was assessed using Pearson"s correlation (r^2) across four spectral features: the offset and slope of the aperiodic component, and the amplitude of oscillatory activity in the low-beta (12–20Hz) and high-beta (21–30Hz) bands. Statistical comparisons used the Wilcoxon signed-rank test (p=0.05), and correlations (r) were performed between interhemispheric r^2 values and MDS-UPDRS-III scores and ON-time and OFF-time percentages.

Results: cDBS and SD-aDBS yielded comparable clinical improvement (MDS-UPDRS-III % change, mean [range]: 59.1 [20.7–97.7] vs 58.0 [23.5–88.4]), with Hauser diary ON-time of 72% [22–100] and 83% [40–100], and OFF-time of 28% [0–78] and 17% [0–60], respectively. Notably, 10 of 12 patients blindly preferred SD-aDBS. Interhemispheric coupling (r^2) was significant for all features in most patients under both stimulation modes. Low-beta interhemispheric coupling was significantly higher during cDBS than SD-aDBS (cDBS r^2: 0.34 [0.06–0.73]; SD-aDBS r^2: 0.19 [0.01–0.53]), and in SD-aDBS, low-beta interhemispheric r^2 positively correlated with the percentage of OFF-time (r: 0.69).

Summary: We showed that chronic cDBS and SD-aDBS using a linear proportional algorithm differentially modulate subthalamic interhemispheric coupling, with SD-aDBS producing a greater reduction. This effect may represent a key mechanism underlying the additional clinical benefit associated with this stimulation mode, as reflected by patient preference and home monitoring. Notably, conventional clinical rating scales may be insufficient to capture incremental improvements achieved by highly effective DBS treatments.

P121

Volatility of local field potentials reduce after introduction of adaptive deep brain stimulation: secondary analysis of the ADAPT-PD clinical trial

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Adaptive deep brain stimulation (aDBS) modulates stimulation parameters in real time based on physiological feedback and has emerged as a promising strategy for personalized treatment of Parkinson"s disease (PD). In this secondary analysis of the ADAPT-PD clinical trial, we examined whether aDBS alters the temporal variability of beta-band local field potentials (LFPs) relative to conventional continuous DBS (cDBS). Chronic LFP recordings were analyzed in five individuals with PD (nine hemispheres) implanted with the Medtronic Percept™ PC system. Volatility metrics were derived from beta-band power recorded during awake periods and compared between cDBS baseline and subsequent aDBS phases. Across patients, aDBS was associated with sustained reductions in amplitude-based LFP volatility metrics, including standard deviation, mean absolute deviation, and root mean square coefficients of variation. Electrophysiological changes coincided with increased patient-reported "ON" time without dyskinesia and improvements in motor performance as assessed by UPDRS-III scores. Higher-order spectral-temporal measures showed more heterogeneous, hemisphere-specific modulation, suggesting selective rather than global suppression of neural dynamics. Collectively, these findings support LFP volatility as a candidate electrophysiological biomarker of aDBS-related network modulation. Incorporating volatility-based metrics into closed-loop neuromodulation frameworks may provide an additional dimension for optimizing stimulation parameters and tailoring therapy to individual neural dynamics in Parkinson"s disease.

P122

Circadian and multi-day dynamics of LFP beta band power in a cohort of people with Parkinson's disease and chronic closed-loop deep brain stimulation

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Question: Adaptive deep brain stimulation (aDBS) leverages beta oscillations (13–35 Hz) in the subthalamic nucleus (STN) as a feedback signal that correlates with motor symptoms in Parkinson"s Disease (PD). The Medtronic Percept aDBS system uses fixed, clinician-defined thresholds to drive stimulation delivery. However, beta power explains a limited portion of symptom variance, shows context dependence, and its long-term variability has been increasingly characterized. These factors could cause a dissociation between preset thresholds and the patient's actual neurophysiological status, leading to under- or overstimulation. This study reports our clinical experiences with a cohort of patients with dual-threshold chronic aDBS and characterizes circadian and multi-day variability in beta power.

Methods: We prospectively enrolled 12 patients with Parkinson's disease (mean age at diagnosis: 53.0 ± 10.2 years; age at surgery: 62.2 ± 8.4 years) who underwent bilateral STN-DBS (Medtronic Percept RC, directional segmented leads). Anatomical reconstructions using the Lead DBS v3.2 toolbox confirmed consistent electrode placement in the dorsolateral STN. All patients demonstrated robust levodopa responsiveness (preoperative MDS-UPDRS-III improvement: -49.85 ± 18.69%). The mean duration from surgery until aDBS initiation was 1.7 ± 1.2 years. The mean sensing frequency was set at 19.51 ± 3.16 Hz. Continuously stored average beta power and stimulation amplitudes in 10-minute bins were exported for analysis of long-term beta signal variability.

Results: Bilateral sensing was active in 9 participants (unilateral in 3). Over the observation period, aDBS was active for 75.19 ± 32.88% of the time. The algorithm maintained the local field potential (LFP) within target thresholds for 61.99 ± 22.01% of the recording duration, using an amplitude modulation range of 1.14 ± 0.75 mA. The mean delivered amplitude during aDBS was slightly lower than the cDBS baseline (-0.17 ± 0.3 mA). Regarding clinical management, the Levodopa Equivalent Daily Dose (LEDD) had decreased by 58.01 ± 17.49% following the initial surgery but remained stable during the cDBS-to-aDBS transition. The clinical experience was heterogeneous: while seven patients reported stable or improved global impression (PGIC), one reported worsening, and three returned to cDBS due to dissatisfaction. Analysis of chronic LFP beta-power logs revealed distinct circadian patterns and multi-day variability. These changes suggest that fixed LFP thresholds may intermittently drift out of the optimal therapeutic window.

Conclusions: Chronic closed-loop neurostimulation is feasible and reduces the total electrical energy delivered to the brain. We observed heterogeneous clinical outcomes. While a majority preferred aDBS, 25% returned to cDBS, underscoring the complexity of parameter optimization and the need for repeated tuning. Circadian and multi-day variability, as well as long-term evolution of beta power, have been documented and may depend on behavioral states and activity levels. While standard clinical aDBS protocols typically use fixed thresholds, adaptive thresholding approaches have been experimentally demonstrated. Our findings from a chronic aDBS cohort are consistent with these observations and support a clinical role for circadian-aware or time-varying thresholds in routine aDBS care to maintain therapeutic efficacy over longer periods.

P123

Evoked response signatures guide deep brain stimulation programming

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Deep brain stimulation parameter selection currently follows a time-consuming trial-and-error process. Stimulation-evoked cortical potentials might guide parameter selection but this concept has not yet been tested and mounting *wet* EEG systems is too time-consuming to scale in outpatient clinic settings.

Here, we test the utility of a novel method that leverages the *spatial pattern* of stimulation-evoked potentials using a *dry* EEG setup to identify optimal deep brain stimulation settings in a cohort of 29 patients with Parkinson"s disease (n = 58 hemispheres). Generalizability to the context of contact selection was assessed using a prospective cohort of 11 patients recorded using the same *dry* EEG setup (n = 22 hemispheres).

Cortical responses evoked by a total of 57,503 stimulation pulses at 58 subthalamic stimulation sites in 29 patients (10 female, median [IQR] age, 61 [43-70] years) were included in the discovery data set. We created a model of optimal evoked potential topography. Similarities of individual response patterns to this model were able to estimate significant amounts of variance in empirical UPDRS-III improvements (10-fold-crossvalidation: r, 0.49, $P < .001$). Finally, we tested whether the model was capable of selecting the optimal contact in a validation cohort of 11 patients (4 female, median [IQR] age, 63 [51-69] years). This process correctly identified the top- and second-ranked stimulation contact with a probability of 86% and 90% respectively and performed significantly better than random contact selection ($P < .05$).

The findings in this study indicate that cortical response patterns evoked by subthalamic stimulation relate to outcomes and could be used for identifying the optimal contact in clinical care settings.

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Kinematic discriminative component a new biomarker to measure Parkinson's disease severity

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Objective. To develop and validate a video-based biomarker for Parkinson's disease (PD) that provides a low-dimensional, interpretable, and clinically relevant measure of motor severity sensitive to medication, DBS treatment and disease evolution.

Background. The clinical assessment of Parkinson's disease motor severity relies heavily on rating scales like the Unified Parkinson's Disease Rating Scale (UPDRS), which are known to be subjective and suffer from inter-rater variability. This subjectivity creates a critical need for objective, data-driven biomarkers. While recent machine learning approaches using video have attempted to automate UPDRS scoring, they are often trained using these same subjective clinical scores as target labels. Consequently, such models inherit the inherent biases of the clinicians who provided the original ratings, failing to produce a truly objective measure. There remains a need for a biomarker derived directly from kinematic data—independent of subjective labels—that can provide a low-dimensional and interpretable readout of the disease state.

Methods. We analyzed video kinematics from a cohort of PD patients and healthy controls performing finger tapping and hand grasping tasks. Participants with PD were assessed in both "ON" and "OFF" medication states, as well as DBS "ON" and "OFF". A machine learning classifier was trained to distinguish between PD and healthy states based on kinematic data. Using explainable AI techniques, we identified a single, stable latent dimension—the Kinematic Discriminative Component (KDC)—that was causally responsible for the classifier's output. We evaluated the KDC's consistency across two different tasks: finger tapping and hand grasping, its sensitivity to medication and Deep Brain Stimulation (DBS), and its ability to predict dopamine transporter (DAT) imaging status in a held-out cohort of individuals with uncertain parkinsonism. Longitudinal data was used as well to assess the KDC's capacity to forecast the disease evolution.

Results. The classifier accurately distinguished PD patients from healthy controls, and the underlying KDC was robustly identified across both finger tapping and hand grasping tasks. Progression along this single dimension corresponded to coordinated changes in interpretable kinematic features. As illustrated in the latent space scatter plot, the KDC provides a clear separation between the two groups. The KDC demonstrated a significant shift towards a healthier state with both medication and DBS. Furthermore, longitudinal analysis showed that changes in the KDC can capture the disease progression.

Conclusions. We have developed a novel, video-derived biomarker, the KDC, which offers a low-dimensional and interpretable measure of Parkinsonian motor severity. Its consistency across tasks, sensitivity to therapeutic interventions, and predictive validity for diagnostic purposes suggest its potential to enhance patient management and augment bedside assessment, enable remote monitoring, and provide a sensitive, objective endpoint for trials and precision neurology.

P125

EEG-based estimation of directional DBS lead orientation

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Introduction: Directional DBS leads enable current steering to optimise treatment, but this benefit depends on knowing the precise orientation of the lead"s segmented contacts. At present, orientation is obtained using postoperative CT or rotational fluoroscopy, methods that add cost, time, and radiation exposure. A novel method using magnetoencephalography (MEG) was recently suggested, but MEG is expensive and not easily available in the clinic.

Goals: We aimed to test whether short, high-sampling EEG recordings of DBS artefacts combined with individualised forward modelling can recover the postoperative orientation of segmented GPi leads with clinically useful accuracy.

Methods: Following successful testing of the feasibility of the proposed approach in an EEG phantom, we recorded a 29-channel EEG at 100 kHz in a 54-year-old male with cervical dystonia who had bilateral GPi Boston Scientific Vercise Directed DBS leads. We sequentially tested each of the three pairs of bipolar segments (A–B+, B–C+, C–A+) in the lower ring, separately for each hemisphere, providing continuous 130-Hz stimulation. Stimulation-locked epochs were high-pass filtered at 120 Hz, aligned using an auxiliary ECG/artefact channel, and averaged to obtain scalp topographies. A subject-specific three-layer boundary element EEG forward model (BEM) informed by contact locations from LeadDBS was used to predict expected artefact patterns for different lead orientations. A current dipole at the active ring was rotated 0–360 degrees to simulate scalp potentials. For each stimulation montage, Pearson correlations between measured and simulated maps were computed across angles; peak correlations were combined across montages and projected once to the AC--PC plane to estimate lead orientation.

Results: The measured scalp maps closely matched the BEM predictions and reproduced the expected approximately 120-degree spacing of the pairs of horizontal segments. EEG-derived orientations differed from CT/MRI by 8 degrees for the right and 15 degrees for the left GPi lead.

Conclusions: EEG-based correlation of DBS artifact topographies with biophysical forward models can estimate the orientation of a directional GPi lead within approx 10-15 degrees of imaging, offering a rapid radiation-free complement to CT or fluoroscopy for postoperative verification of lead orientation. We will next test the possibility of achieving the same accuracy with fewer channels and a lower sampling rate, with the eventual aim of designing an easy-to-use system to aid DBS programming.

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Interactive oscillatory normative connectomes with ConnectoMEG toolbox

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Pathological brain oscillations are a hallmark of Parkinson"s disease (PD), dystonia, epilepsy, and other neurological disorders. These rhythmic activities act as indicators of brain health and can predict the outcomes of circuit-based therapies such as deep brain stimulation. Oscillatory dynamics can be represented through normative connectomes, which are brain wiring diagrams that enable comparisons across structural, functional, and genetic brain profiles. Although many such profiles are publicly available, the lack of an open-source oscillatory profile has remained a significant limitation. To overcome this, we developed ConnectoMEG, an open-source toolbox that generates oscillatory normative connectomes from magnetoencephalography (MEG) and integrates them with genetic expression data.

Using standardized preprocessing pipelines, we constructed cortical connectomes from MEG recordings across three repositories: the Human Connectome Project (n=57), Cam-CAN (n=647), and the Open MEG Archive (n=114 + n=47 with PD). Whole-cortex coherence, the imaginary component of coherence, and time-reversed corrected Granger causality were computed across six frequency bands to produce normative connectomes. These were further mapped on publicly available genetic expression profiles from the Allen Brain Institute.

The novelty of this work is that the ConnectoMEG toolbox allows for the integration of oscillatory brain patterns with structural, functional, or genetic findings through multi-cohort open-source normative connectomes, sparking biomechanistic hypotheses about neuromodulation effects.

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DBSsync: an open-source toolbox for synchronization of chronic data from DBS electrodes with multimodal external data to investigate new biomarkers

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Introduction: Implanted deep brain stimulation (DBS) devices are now capable of chronically recording activity from intracranial brain areas. Reliable paradigms for temporally precise synchronization of intracranial recordings with external data are needed to use this novel technology for research purposes and extend the possibilities of analyzing multimodal datasets. With the innovative approach of adaptive deep brain stimulation now clinically available, multimodal characterization of neural biomarkers becomes of utmost importance to define optimal feedback signals for adaptive brain stimulation and allow for better fine-tuning of stimulation parameters.

Goals: Our aim was to develop an open-source Python toolbox with a graphical user interface to easily synchronize intracranial DBS recordings with multimodal external sensor data.

Materials and methods: DBS pulses were delivered to induce artifacts allowing the synchronization of intracranial and external data in 25 Parkinson"s disease patients with implanted sensing-enabled neurostimulators over 35 recording sessions. Synchronization pulses were detected in the external recordings using a bipolar electrode placed close to the neurostimulator. This bipolar electrode was recorded through a digital amplifier recording accelerometer and electroencephalography data. For other data modalities tested, Lab Streaming Layer was used to perform online synchronization of all external data with the bipolar electrode before using DBSsync to synchronize it with the intracranial data. Our toolbox also includes a preprocessing pipeline to remove cardiac artifacts from intracranial recordings and corrects small inaccuracies in the sampling frequency of DBS devices.

Results: We were able to synchronize all recording sessions using DBSsync. The alignment of endogenous cardiac artifacts was used to validate the synchronization in a subset of sessions yielding a deviation in time precision of 8 milliseconds. Cardiac artifacts could then be removed from the recordings using our custom-made pipeline.

Summary: DBSsync provides reliable and precise synchronization between intracranial and external recordings and can be used to expand research protocols using chronic recordings from sensing-enabled neurostimulators in parallel with diverse externally acquired data.

P128

Automated symptom scoring for objective deep brain stimulation programming in Parkinson's disease: a proof-of-concept study

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Introduction

Deep Brain Stimulation (DBS) to treat Parkinson"s Disease (PD) depends on subjective clinical assessment to facilitate parameter selection, which introduces significant variability. This study evaluates a data-driven approach that combines wearable sensing and algorithmic guided programming to provide continuously graded, objective symptom assessment to steer an automated search of DBS settings.

Methods

Study participants (n = 10) chronically treated with DBS for PD tested the system under conditions to mimic those of an initial programming appointment. A sensor-driven machine-learning algorithm (Serg One, SERG Technologies Limited, UK) was used to rate bradykinesia, tremor, and rigidity symptoms. The sensor scores served to compute the subsequent DBS settings using StimSearch™ (Boston Scientific, USA), an algorithm-guided programmer (AgP).

Results

The sensor derived scores successfully assessed changes in the participant"s motor symptoms resulting from DBS parameter changes, enabling the AgP to function as intended. During AgP programming, Pearson"s correlation between Serg One and clinician scores were 0.82 for rigidity, 0.74 for tremor, and 0.59 for bradykinesia. Both the standard of care DBS programs and the AgP programs significantly and similarly improved motor symptoms compared to the off-medication and off-stimulation baseline (a 43.9 inter-quartile range (IQR) 33.2|63.4% and 43.0 IQR 15.7|57.2% reduction in total score of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III, respectively). The AgP sessions for both hemispheres were completed under a median of 1.18 IQR 0.7|1.46 hours.

Summary

Automated, sensor based programming is comparable to clinician programming and may offer a more precise and consistent alternative to traditional methods, demonstrating potential for improving the efficiency of DBS programming.

P129

Imaging-informed brain network simulations predict personalized DBS response

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Introduction: Deep Brain Stimulation (DBS) is a successful symptom-relieving treatment for Parkinson"s disease (PD). However, the introduction of advanced directional DBS electrodes significantly expands the programming parameter space, rendering the traditional trial-and-error approach for DBS optimization impractical and demonstrating the need for computational tools. Our recently developed DBS model using The Virtual Brain simulation tool was able to reproduce biologically plausible multiscale DBS effects in PD, though a link with clinical outcome data was still missing.

Methods: In the current work, we extended our virtual DBS model toward higher resolution for the stimulus input, incorporating streamlines around the electrode and the electric field calculation. The region-based whole-brain simulations were set up with The Virtual Brain applying the generic two-dimensional oscillator as neural mass model and an averaged connectome from the Human Connectome Project S1200 release as underlying structural network. We simulated DBS of N=14 PD patients with available empirical data on monopolar ring and directional contact activations of N=392 different electrode settings (in total over all patients, with varying amplitudes between 0 and 3mA) of the "SenSight" electrode with corresponding motor task outcome. The motor task involved maximum-velocity pronation-supination movements of the lower arm, with the movement velocity recorded using a handlebar-like hand-held device. To predict the motor task outcome for each individual setting, we fitted a linear model based on the first three principal components of the N=392 time-averaged DBS-evoked simulated responses.

Results: The whole-brain simulations are now sensitive to the exact three-dimensional location of the activated contact and the tested amplitude. Our prediction model based on the simulated or so-called *sweet dynamics* demonstrated a correlation between predicted and empirically observed motor task improvements due to DBS of $r=0.386$ ($p<0.0001$) in a leave-one-setting-out cross-validation. Benchmarking revealed a trend toward better predictions with our *sweet dynamics* than imaging-based static methods such as the sweet spot ($r=0.16$, $p<0.05$) and sweet streamline ($r=0.26$, $p<0.0001$) approaches. Furthermore, our model outperforms the traditional trial-and-error method in predicting optimal clinical settings for individual patients, e.g. achieving an over 60% likelihood of identifying the optimal contact within the first two suggested contacts compared to a 25% likelihood for the trial-and-error method.

Conclusions: We identified the *sweet dynamics* that show improved motor task outcome for individual electrode settings of PD patients. These simulated DBS-evoked responses can be used to find the optimal electrode settings via a novel network-dynamics-based computational method. In the future, the developed framework can be used to prospectively optimize the electrode placement and settings *in silico* in individual patients, showcasing the potential benefit of whole-brain simulations for improving clinical routine.

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Clinical and anatomical evidence of dual VIM–PSA stimulation in essential tremor: comparative analysis of three targets with VTA overlap maps

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Introduction

Deep brain stimulation (DBS) of the ventral intermediate nucleus (VIM) and the posterior subthalamic area (PSA) are well-established targets for refractory essential tremor. The possibility of modulating both regions within a single trajectory may broaden the therapeutic window and optimize symptom control in selected patient profiles. This study compares the clinical and anatomical outcomes of VIM, PSA, and dual VIM–PSA stimulation.

Methods

Twenty-six consecutive patients with essential tremor underwent bilateral DBS using the Vercise™ Genus system and linear octopolar electrodes. Patients were classified according to the active contact location into VIM (n=16), PSA (n=2), and dual VIM–PSA (n=8). Clinical evolution was assessed using the Fahn–Tolosa–Marin (FTM) scale at baseline and at optimal programming. A "good responder" was defined as ≥50% improvement. Comparisons were performed using Fisher"s exact test and Firth-penalized logistic regression adjusted for baseline FTM. The volume of tissue activated (VTA) was generated using GUIDE XT® and subsequently visualized in Quentry® to obtain qualitative overlap maps for each target.

Results

FTM scores significantly decreased from 51.7±18.9 to 16.3±10.4 ($p<0.001$), with 80.8% (21/26) classified as good responders. All three targets showed comparable clinical improvements. The initial Fisher test yielded $p=0.050$, not reaching statistical significance. Numerical differences were observed in responder rates (VIM: 93.8%; PSA: 100%; Dual VIM–PSA: 50.0%). These differences disappeared after adjusting for baseline FTM using logistic regression, indicating no relevant differences between targets regarding the likelihood of poor response. VTA maps demonstrated a dorsal stimulation pattern for VIM and a ventromedial pattern for PSA, while dual stimulation showed areas of overlap consistent with combined modulation.

Conclusions

DBS provides robust clinical improvement in essential tremor. Dual VIM–PSA stimulation represents a safe and potentially valuable strategy for personalized therapy, allowing modulation of complementary regions within the tremor circuit. Furthermore, the use of electrodes with sufficient span enables effective dual targeting by covering both targets within a single trajectory. The integration of clinical outcomes and VTA mapping supports the usefulness of this approach within individualized DBS programming.

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Identifying wearable-based features of bradykinesia in PD: correlation of subjective and objective measures in naturalistic multimodal monitoring

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Background:

The naturalistic monitoring of motor fluctuations is a key challenge in the management of Parkinson"s disease (PD). Conventional clinical assessments provide only brief snapshots of motor function, lack ecological validity, and fail to reflect real-world motor behavior during daily life. Continuous and naturalistic home monitoring could provide more ecologically valid insights and support personalized therapy adjustments.

Objective:

This study aims to combine wrist-worn accelerometer sensors with ecological momentary assessments (EMAs) to identify and validate accelerometer-derived features that correlate with bradykinesia. The overarching goal is to detect fluctuations in bradykinesia during sessions with different effective deep brain stimulation (DBS).

Methods:

Thirty-five patients with PD will participate in four two-week measurement blocks: (1) before DBS surgery, (2) 2 months after surgery (before stimulation optimization), (3) 3 months after surgery (after optimization), and (4) 12 months after surgery in a stable clinical setting. During each block, participants continuously wear a wrist-worn cardio watch recording triaxial accelerometry. In parallel, EMA questionnaires are delivered six times daily at pseudorandomized intervals, assessing motor and non-motor symptoms and contextual factors. For post-surgical blocks, local field potential (LFP) data are collected. Accelerometer data will undergo kinematic analyses comprising human activity recognition and the derivation of bradykinesia-related features across temporal and spectral domains, aligned with patient-reported EMA assessments. Patient-reported EMA measures of bradykinesia will serve as labels to train multivariate models aimed at capturing fluctuations in bradykinesia both within and across recording sessions.

Results:

16 patients (30 sessions) were included and completed a total of 1166 EMA assessments (mean completion rate: 0.43 ± 0.22) and collected on average 16.64 h ± 5.40 h hours of acc-data per day. Preliminary analyses demonstrated consistent human activity recognition and correlations between accelerometer-derived bradykinetic features and self-reported symptom severity are conducted to assess the ecological validity of wearable-based motor monitoring in PD

Conclusion:

Naturalistic home monitoring using wearable sensors and EMA is feasible and may capture motor fluctuations under real-world conditions. Preliminary findings suggest that EMA-reported bradykinesia changes align with UPDRS-based assessments, and integrating EMA with passive accelerometry may provide ecologically valid monitoring of motor fluctuations in PD. This combined approach could ultimately support individualized therapy adjustments and remote disease tracking.

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Interpretable video-based machine learning for objective assessment of Parkinsonian severity across medication and DBS states

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Introduction

Accurate, scalable quantification of motor severity in Parkinson"s disease (PD) is essential for monitoring progression and optimizing medication and deep brain stimulation (DBS) therapy. Current rating scales such as the MDS-UPDRS are subjective, time-consuming, and insensitive to subtle fluctuations, while existing digital approaches are limited by small sample sizes, narrow task coverage, and lack of treatment-state diversity.

Goals

We aimed to develop a robust, interpretable, and device-agnostic machine-learning framework for automated PD motor severity assessment using standardized clinical videos acquired across four treatment conditions, including medication and DBS states.

Materials & Methods

We analyzed 1313 standardized motor evaluations collected from 634 PD patients under Medoff_preop, Medon_preop, Medoff_DBSon, and Medon_DBSon conditions. Human pose estimation was applied to video recordings of seven MDS-UPDRS tasks to extract anatomical trajectories. From these, 202 movement variables (MovVars) representing frequency, amplitude, entropy, timing, symmetry, gait speed, and freezing-related features were computed. After preprocessing (missing-data filtering, bilateral aggregation, KNN imputation), LASSO was used to select stable features. Nine machine-learning classifiers—spanning linear, kernel-based, tree-based, and boosting models—were trained using group-wise cross-validation to ensure patient-level separation. Model interpretability was examined using SHAP values, and latent feature organization was assessed using multidimensional scaling (MDS).

Results

Binary classification (mild vs. moderate–severe) showed strong performance across most models, with SVM and LR achieving the highest AUCs (0.8796 and 0.8779) and RF yielding the best accuracy (0.7872 ± 0.0089). In the three-class task (mild, moderate, severe), SVM again achieved the top AUC (0.8439), while RF and XGBoost provided the highest accuracies (~0.70). LR demonstrated consistently strong and well-calibrated performance across both tasks. SHAP analysis revealed that early-stage severity was dominated by fine-motor features such as finger tapping frequency and temporal entropy, whereas gait- and balance-related features contributed more strongly in advanced disease. Low-dimensional projections demonstrated a structured progression from mild to severe cases, indicating that LASSO-selected movement features ptured meaningful clinical severity gradients.

Summary

We present a scalable, interpretable machine-learning framework for video-based PD motor severity assessment across medication and DBS states. The workflow achieves high discriminative performance, clinically meaningful feature attribution, and a robust latent severity structure. These findings highlight the potential of computer-vision-based motor quantification as a digital innovation to support objective, accessible, and treatment-aware PD evaluation in real-world clinical workflows.

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Remote deep brain stimulation programming for Parkinson's disease: a prospective, randomized, controlled, multicentre, open-label, non-inferiority trial

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Background Deep brain stimulation (DBS) is an established therapy for advanced Parkinson"s disease (PD), but long-term benefit depends on expert programming, which usually requires in-person visits to specialised centres. Remote DBS programming could improve access while maintaining treatment quality, yet prospective, controlled evidence comparing remote with in-person programming is scarce.

Methods We conducted a prospective, multicenter, randomized, controlled, open-label, non-inferiority trial at DBS centers across Germany. Patients with idiopathic PD requiring DBS programming were randomly assigned (1:1) to receive either standard in-person DBS programming (standard of care [SoC]) or remote DBS programming via a secure telemedicine platform. The primary endpoint was the Movement Disorder Society–Unified Parkinson"s Disease Rating Scale (MDS-UPDRS) Part III score in the medication-on/stimulation-on state at 3 months. The non-inferiority margin was 5 points. Secondary outcomes included changes in MDS-UPDRS total score and subscales, Hoehn and Yahr stage, quality of life (Parkinson"s Disease Questionnaire-39), cognition (Montreal Cognitive Assessment [MoCA]), mood (Beck Depression Inventory II), levodopa equivalent daily dose (LEDD), number of programming sessions, and adverse events. Analyses were performed in the per-protocol population. This trial is registered with ClinicalTrials.gov (NCT05193825).

Findings Between March 2022, and Dec 2024, 54 patients were screened and 52 enrolled and randomly assigned to SoC (n=26) or remote (n=26). Four patients in the remote group were excluded after randomization, leaving 26 in the SoC group and 22 in the remote group for analysis. At 3 months, MDS-UPDRS Part III improved by a median of −23·0 points (IQR −15·0 to −34·3) in the SoC group and −20·5 (−10·0 to −30·0) in the remote group (between-group difference not significant; p=0·3618). The unpaired median difference between the SoC and Remote group was -2.5 [95.0% CI -9.0, 2.0] meeting the prespecified criterion for non-inferiority. Total MDS-UPDRS, Hoehn and Yahr stage, and PDQ-39 improvements were comparable between groups. Cognitive outcomes favored remote programming, with a significant improvement in MoCA scores (between-group difference in change; p=0·0332). LEDD reduction was greater in the SoC group (−525 mg [230–705]) than in the remote group (−244 mg [61–576]; p=0·015). Other secondary endpoints, including BDI-II, Ardouin scale, and adverse events, did not differ significantly. Serious adverse events occurred in three (11·5%) patients in the SoC group and four (15·3%) in the remote group. No deaths occurred. Exploratory subgroup analyses suggested that younger patients (<60 years) and those with preserved cognition (MoCA ≥25) derived greater benefit from remote programming.

Interpretation Remote DBS programming was non-inferior to in-person programming for motor improvement at 3 months, with comparable safety and patient-reported outcomes. Cognitive outcomes were more favorable with remote programming, and exploratory analyses suggest particular benefit in younger patients with intact cognition. These findings support the integration of remote programming into clinical practice to expand access to expert DBS care.

Funding This trial was supported by Abbott Medical Inc.

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Digital measurement of ocular microtremor in Parkinson's disease: analytical and clinical validation

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INTRODUCTION: Ocular microtremor (OMT) has been shown to have a mean frequency range of 70 - 90 Hertz (Hz) in healthy adults. Previous research suggests OMT is reduced in neurological diseases such as in people with Parkinson"s Disease (PD), therefore, OMT represents a potential objective digital biomarker for diagnosing and monitoring neurological conditions, including response to interventions (e.g., Deep Brain Stimulation - DBS). Historically, OMT has been measured invasively using lengthy protocols. The iTremor ONE device is a novel method for measuring OMT quickly, comfortably, and non-invasively. This pilot study examined the analytical and clinical validation of OMT measurement via the iTremor ONE device in PD.

METHODS: A total of 34 PD and 31 age matched controls participated in this study. Measures of motor function and OMT frequency (Hz) were assessed. For analytical validation, 22 PwPD completed a test re-test assessment of OMT frequency, with assessments one week apart. Interclass correlation coefficients (ICC) were used to assess test-retest reliability. For clinical validation, ROC curve and AUC was used to assess diagnostic ability of OMT in PwPD (n=22) vs. controls. 24 PD were also tested 12 hours "OFF" their dopaminergic medication. Correlations were explored between OMT frequency and the clinical rating scales.

RESULTS: The iTremor ONE reliably measured OMT in PD. OMT frequency (Hz) had excellent agreement in test-retest reliability for the right, left and both eyes (ICC >0.9). OMT had excellent (AUC >0.7) discriminative ability in differentiating between PD and controls. No substantial change was seen in OMT frequency or MDS-UPDRS in response to dopaminergic medication in PD.

CONCLUSION: The iTremor One Device reliably measured OMT in PwPD and OMT was associated with selective aspects of PD disease severity. The present study found no difference in OMT frequency in response to dopaminergic medication, therefore future work should explore the relationship between OMT and other neurotransmitters involved in PD e.g. acetylcholine This is the first study of its kind to investigate OMT as a marker/monitor for PD with non-invasive technology that can be used within the clinic, laboratory, and home settings. Identifying OMT as a potential biomarker for PD, could support clinicians in their assessments (e.g., pre and post DBS) and enable better provision of care to patients allowing improved disease monitoring.

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Delineating therapeutic and non-therapeutic neural signatures of deep brain stimulation

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Background: Local field potential (LFP) recordings can optimize deep brain stimulation (DBS) by providing real-time, objective information on neuronal activity to guide programming adjustments. Yet, despite various hardware filters, the neural recordings contain both non-therapeutic effects of stimulation, i.e., artefacts, and therapeutic neural responses. This makes it difficult to distinguish neural features that predict therapeutic benefit from those that merely detect stimulation presence. Without objective methods to identify which neural dimensions track symptom improvement, clinical programming remains reliant on time-intensive trial-and-error approaches.

Approach: We applied Generative Causal Explanations (GCE), a machine learning framework that partitions the latent space of a variational autoencoder (VAE) – a generative model - into separate dimensions that either maximize or minimize mutual information with classifier predictions. We hypothesized that therapeutic and non-therapeutic effects of stimulation represent distinct neural mechanisms captured by different latent dimensions and this information-theoretic partitioning approach can delineate their mechanisms.

Methods: We analyzed bilateral LFP recordings from 9 Parkinson's patients during ON (125Hz, 110Hz, 85Hz, 55Hz) and OFF stimulation, extracting 70 features (spectral band features, partial directed coherence, nonlinear dynamics measures, phase-amplitude coupling). We trained a classifier that distinguishes ON- and OFF-stimulation LFP recordings and then implemented GCE: we looked for the optimal $K \in \{1,2,3\}$ classifier-dependent dimensions (maximizing mutual information with the pre-trained stimulation classifier) and $L \in \{2,3,4,5,6\}$ classifier-independent dimensions (constrained to be independent of classifier outputs). The VAE configuration that both maximised information flow to the classifier and reconstruction loss was chosen. Latent representations were then correlated with UPDRS III, rigidity, bradykinesia, and tremor.

Results: Systematic optimization identified K=1, L=5 as optimal. The single classifier-dependent dimension showed no correlation with clinical outcomes ($|\rho|<0.19$, $p>0.08$), validating that it detects stimulation occurrence without encoding therapeutic benefit. In contrast, combined auxiliary dimensions 1+2 strongly predicted clinical improvement across multiple measures: total UPDRS (Spearman $\rho=0.580$, $p=0.0002$), rigidity ($\rho=0.610$, $p<0.0001$), and bradykinesia ($\rho=0.390$, $p=0.019$), but not tremor ($\rho=0.236$, $p=0.164$). These correlations remained significant across Pearson, Spearman, and Kendall methods, demonstrating robustness to statistical assumptions.

Significance: To our knowledge, this work establishes the first application of information-theoretic representation learning to identify therapeutic biomarkers, independent of non-therapeutic stimulation effects, from LFP recordings during active DBS. By demonstrating that (1) detection and therapy are separable neural processes and (2) latent representations predict clinical outcomes, and (3) distinct symptoms map to different encoding schemes, we provide a path toward LFP-driven DBS optimization.

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Deep learning gait profiling in Parkinson's disease patients under different treatments

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Introduction: The effectiveness of Deep Brain Stimulation (DBS) differs among individuals, and its impact on gait and balance continues to be an area of active investigation. Identifying gait-related characteristics that reflect DBS-specific responses is essential for optimizing therapeutic strategies and improving patient outcomes.

Goals: To distinguish gait patterns in Parkinson"s Disease (PD) patients with medical or DBS treatment and healthy controls, by using wearable sensor systems and deep learning (DL) approaches.

Methods: Three groups of participants were enrolled in the Movement Disorders Clinics from two hospitals in Greece (University General Hospital of Heraklion and the University General Hospital of Patras). Group A were healthy controls, Group B were PD patients treated with bilateral DBS of the subthalamic nucleus (STN), and Group C were PD patients under dopaminergic substitution therapies (non-DBS). The participants executed a segment of the Smart-Insole Gait Assessment Protocol [1], wearing a validated sensor insole system generating 18 distinct special and temporal gait features. PD patients (Hoehn & Yahr stages 1-4) underwent standard clinical assessments including Part III MDS- MDS-UPDRS. In the current analysis clinical and pressure-sensor data were used from the ON medication condition. Digital gate features were further analysed using novel deep learning techniques. A Conditional Deep Convolutional Generative Adversarial Network (DC-GAN) was utilized for data augmentation, and a Vision Transformer (ViT) using recurrence plots (RPs), to differentiate gait patterns between the 3 groups. Participant"s characteristics are described as median (interquartile range, IR) scores.

Results: 44 healthy controls (10 females) with median age 53.0 (21) years were recruited in the current study. Among the PD patients, 13 have undergone STN-DBS (5 female) with median age 63.73 (5.36) years and median disease duration 16.0 (11.5), and 154 comprised the non-DBS group (53 females) with mean age 67.5 (14.3) and disease duration 6.7 (6.7) years. Assessment of the synthetic dataset through several performance metrics indicates a significant resemblance between the actual and DC-GAN created data. For multi-class classification (comparing all 3 groups), the ViT model with attention-based feature fusion achieved the highest accuracy, (94.58%), while cross-attention mechanisms exhibited enhanced performance in binary tasks (comparing the groups in pairs). Interestingly, performance metrics decreased for A (controls) vs. B (DBS) group classification, with lower precision and recall rates. This pattern may suggest partial gait normalization in DBS-treated patients, though standard clinical assessments reveal higher MDS-UPDRS-III ON scores in DBS (median 33, IR 23) compared to non-DBS patients (median 28, IR 18), including gait specific items.

Summary: The integration of wearable gait data and deep learning provides novel insights into how DBS and pharmacological therapy shape motor performance in PD. These findings

underscore the value of objective, data-oriented methods in complementing clinical assessments and advancing personalized care.

Chatzaki C, Skaramagkas V, Kefalopoulou Z, et al. *"Can Gait Features Help in Differentiating Parkinson"s Disease Medication States and Severity Levels? A Machine Learning Approach"*. Sensors 2022, 22, 9937.

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Multimodal remote health data collection as a precision tool for optimizing DBS in Parkinson's disease

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Question: Deep brain stimulation (DBS) is an effective therapeutic intervention for Parkinson's disease (PD), yet the optimization of stimulation parameters remains a critical challenge. Individual variability in symptom presentation, medication response, and disease progression necessitates personalized approaches to parameter selection and adjustment. How can continuous, multimodal remote monitoring of motor and non-motor symptoms in patients' real-world environments enhance the precision and efficacy of DBS treatment?

Methods: We present Spica, an integrated multimodal health data collection platform designed for continuous remote monitoring of PD patients before and after DBS surgery. The platform comprises three core components: (1) a flexible ecosystem of wearable sensors including activity trackers, cardiowatches, mobile electroencephalography (EEG), electrocardiography (ECG) belts, smart rings, and motion sensors, enabling collection of heart rate variability (HRV), heart rate, ECG, EEG, accelerometry, gyroscopic data, sleep patterns, and activity levels; (2) a mobile application with integrated ecological momentary assessment (EMA) questionnaires administered on a pre-scheduled basis to capture subjective symptom severity and patient experiences in real-time; and (3) a gamified motor assessment suite comprising six evidence-based game protocols (Finger Tapping, Spiral Tremor, Connect the Dots, Pinch-and-Zoom, Device Motion & Balance, and Reaction Time tasks) that extract quantitative biomarkers of motor function from smartphone sensors, including bradykinesia indices, tremor characteristics, fine motor planning, bimanual dexterity, postural sway, gait parameters, and cognitive-motor integration. All data are encrypted and transmitted to a secure clinical dashboard accessible to clinicians and scientists, enabling real-time patient monitoring and remote communication. A patient engagement interface visualizes data collection metrics and study participation to optimize adherence.

Results: The platform has been deployed in clinical settings at Charité Hospital and Düsseldorf University Hospital for ongoing data collection from PD patients undergoing DBS treatment. Clinical and research teams have utilized EMA and sensor data to track medication effects, motor symptom fluctuations, and the real-world impact of stimulation parameter adjustments in patients' daily environments. The continuous, objective nature of the collected data—including passive physiological monitoring and active gamified assessments—provides granular temporal resolution of symptom dynamics that conventional clinic-based assessments cannot capture.

Conclusions: Spica represents a paradigm shift in DBS optimization, enabling clinicians and researchers to monitor the chronic effectiveness of stimulation in real-world contexts and to make data-informed decisions about personalized parameter adjustment. By capturing multimodal biomarkers of motor and non-motor symptom severity continuously and longitudinally, this platform facilitates precision medicine approaches to DBS and supports more adaptive, individualized treatment strategies for Parkinson's disease. The integration of wearable sensors, subjective symptom assessment, and objective gamified motor tasks provides a comprehensive, patient-centric framework for enhancing both clinical outcomes and scientific understanding of DBS effectiveness in Parkinson's disease.

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Objective identification of Parkinsonian ON/OFF states from chronic STN LFPs via convolutional neural networks

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Background: Continuous and objective identification of motor ON/OFF fluctuations remains a major unmet need in Parkinson"s disease (PD). While beta-band activity in the subthalamic nucleus (STN) is a robust correlate of motor impairment, a strictly beta-centric view may miss relevant information embedded across broader frequency ranges. Chronic LFP recordings from implantable devices offer an opportunity to move toward integrative, data-driven state estimation.

Objective: To evaluate whether a convolutional neural network (CNN) can reliably discriminate dopaminergic ON and OFF states from chronic STN LFPs integrating spectral information across the full 1–40 Hz range, under strict patient-wise validation.

Methods: From 79 PD patients with implanted DBS systems, 46 met clinical and signal-quality criteria. Ninety-three recording sessions with reliable ON/OFF labels (based on time since levodopa intake) were analyzed. Artifact-contaminated, ambiguous, or corrupted segments were excluded. Signals were filtered (1-40 Hz), converted to spectral representations, normalized per session, and segmented into 5-second windows across multiple bipolar channels. A compact CNN was trained using patient-grouped cross-validation. Window-level predictions were aggregated at the session level. Balanced accuracy, sensitivity, specificity, AUC, clustered bootstrap, and patient-level permutation testing were used for statistical evaluation.

Results: The final dataset comprised 5,965 windows (OFF=3,574; ON=2,391). Mean cross-validation performance showed a balanced accuracy of 0.761±0.081, sensitivity of 0.871, specificity of 0.651, and AUC of 0.813. On the pooled test set, balanced accuracy was 0.742 and AUC 0.792. Bootstrap analysis confirmed robust performance (balanced accuracy 0.742, 95% CI 0.671–0.819), and permutation testing demonstrated performance significantly above chance (p=0.00050). Sensitivity consistently exceeded specificity, suggesting more stable identification of dopaminergic ON states and greater physiological heterogeneity during OFF.

Conclusion: CNN-based, integrative analysis of chronic STN LFPs enables robust discrimination of ON/OFF motor states beyond traditional beta-band markers. Rather than replacing established physiological signatures, this data-driven approach complements them by capturing distributed spectral patterns that better reflect global brain state. These findings support the development of operational, implantable biomarkers for objective monitoring of motor fluctuations and provide a translational foundation for next-generation adaptive DBS based on real-time state estimation.

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Translational approaches in DBS

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Deep brain stimulation of the medial geniculate body for refractory tinnitus: a feasibility study

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Background

Tinnitus disorder, can lead to impaired quality of life and psychological suffering, especially when refractory to standard care. Deep brain stimulation (DBS) of the medial geniculate body (MGB) is a potential treatment for severe tinnitus by attenuation of pathological neuronal activity in the central auditory pathway. The aim of this pilot study is to assess the safety and feasibility of bilateral MGB DBS in patients with refractory tinnitus disorder.

Methods

This double-blind 2 × 2 cross-over study was conducted at Maastricht University Medical Centre, Maastricht, the Netherlands. Included patients had treatment refractory, severe and chronic tinnitus without an anatomical cause. Patients with bilateral MGB DBS were randomised to ON-OFF or OFF-ON as stimulation order for two cross-over phases. Primary outcome consisted of safety and feasibility. Secondary outcome on tinnitus severity, psychiatric and cognitive functioning and quality of life was assessed at screening, after both cross-over phases and at one-year follow-up.

Results

Four patients were included. No irreversible stimulation-induced side effects occurred. Surgical-related side effects were transient and resolved within two weeks. All patients experienced DBS as an acceptable treatment. Three of four patients showed improvement of tinnitus on the Tinnitus Functional Index. In the non-responder electrodes had the largest distance from the centre of the MGB.

Conclusions

This study shows that bilateral MGB DBS is safe and feasible for patients with refractory tinnitus. Findings suggest a potential of clinically meaningful reduction in tinnitus burden. However, effectiveness needs to be evaluated in a follow-up study.

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Unravelling the mechanisms of pallidal DBS in dystonia: a network perspective

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Introduction

Deep brain stimulation (DBS) of the entopeduncular nucleus (EPN; rodent GPi) is highly effective in dystonia, yet its mechanisms remain poorly understood. In the dtsz hamster, we investigated effects of pallidal DBS from synapse to system, integrating striatal physiology, intrinsic excitability, cortical–thalamic dynamics, cerebellar activity, immediate early gene responses, and extracellular matrix (ECM) regulation.

Aim

We sought to define acute and chronic actions of pallidal DBS on cortico-striatal transmission and intrinsic MSN excitability, clarify cholinergic modulation, establish network effects in thalamus, cortex and cerebellum, assess cerebellar c-Fos expression, and explore ECM involvement.

Methods

Male dtsz hamsters received short- and long-term EPN DBS with clinically relevant parameters. Cortico-striatal slices were studied by whole-cell recordings from MSNs, measuring miniature and spontaneous EPSCs, firing responses, sodium channel dependence, and cholinergic modulation. Network effects were probed by thalamic and cortical plasticity measures, cerebellar activity mapping, and c-Fos immunohistochemistry in cerebellar nuclei. ECM profiling focused on brevican expression before and after DBS.

Results

Acute synaptic de-weighting. Short-term DBS reduced cortico-striatal excitatory drive, with prolonged inter-event intervals and lower EPSC frequencies, while amplitudes were preserved, consistent with presynaptic dampening. The TTX-sensitive component of sEPSCs was preferentially affected. *Intrinsic excitability shifts with time.* Short-term DBS enhanced MSN firing to depolarisation, whereas long-term stimulation decreased intrinsic excitability without further synaptic depression, suggesting an adaptive reconfiguration from synaptic to intrinsic mechanisms. *Cholinergic modulation adapts.* Acetylcholine increased mEPSC frequency more after short-term than after long-term DBS, indicating that initial cholinergic gain diminishes with chronic stimulation. *Network-wide normalisation.* Pallidal DBS modulated spike patterns and plasticity in thalamus and cortex, and normalised aberrant cerebellar activity, highlighting widespread restorative effects. *Immediate early gene responses.* c-Fos immunoreactivity in cerebellar nuclei was altered after short-term DBS, consistent with downstream cerebellar engagement. *Extracellular matrix context.* Brevican expression analysis suggested ECM involvement as a structural correlate of the observed adaptations.

Conclusion

Our findings suggest a temporally staged mechanism of pallidal DBS in dystonia. An early phase is characterised by synaptic de-weighting of cortico-striatal inputs, enhanced MSN responsiveness, and cholinergic gain; with continued stimulation, adaptations shift towards reduced intrinsic striatal excitability and attenuated cholinergic effects. Network-level functional signatures in thalamus, cortex and cerebellum progressively normalise, while cerebellar c-Fos changes and ECM regulation provide demonstrate persistent structural changes. Thus, pallidal

DBS does not act locally alone, but re-balances the distributed motor network through adaptive interactions between synaptic, intrinsic and circuit-level processes.

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Deep brain stimulation of the medial preoptic nucleus evokes hypothermia and protects the ischemic mouse brain

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Therapeutic hypothermia at 32-34 °C during or after cerebral ischaemia is neuroprotective. However, peripheral cold sensor-triggered hypothermia is ineffective and evokes vigorous counteractive shivering thermogenesis, as well as complications that are difficult to tolerate in awake patients. Here, we show in mice that deep brain stimulation (DBS) of warm-sensitive neurones (WSNs) in the medial preoptic nucleus (MPN) produces tolerable hypothermia. In contrast to surface cooling-evoked hypothermia, DBS mice exhibit a torpor-like state without the counteractive shivering response. Like hypothermia evoked by chemogenetic activation of WSNs, DBS in freely moving mice elicits a rapid lowering of core body temperature to 32-34 °C, which confers significant brain protection and preserves motor function. Mechanistically, activation of WSNs contributes to DBS-evoked hypothermia. Inhibition of WSNs prevents DBS-evoked hypothermia. Maintaining the core body temperature at normothermia during DBS abolishes DBS-mediated brain protection. Thus, the MPN is a DBS target to evoke tolerable therapeutic hypothermia for stroke treatment.

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Predicting safe day-0/1 discharge after DBS for Parkinsons disease: derivation of a clinical index

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Introduction

Deep brain stimulation (DBS) is standard care for advanced Parkinson's disease (PD), yet postoperative length of stay (LOS) varies from same-day to multi-day across centers. Validated, DBS-specific criteria that identify candidates for safe early discharge are lacking. We aimed to derive and internally validate a "Same-Day DBS Discharge Index" for PD.

Methods

We conducted a single-center retrospective study using a standardized registry and electronic health record abstraction instrument co-developed with neurosurgery and movement-disorder neurology. Candidate predictors captured demographics; PD severity (MDS-UPDRS III OFF/ON); comorbidity and ASA class; operative details (target, microelectrode-recording passes); and immediate postoperative signals (IV opioid use in morphine-milligram equivalents [MME], first-day neurological exam, early imaging), plus disposition and 30-day utilization. Modeling uses multivariable logistic regression and classification-and-regression trees to derive a point-based index; performance is assessed with AUC, calibration, reclassification, and decision-curve analyses.

Results

Among PD cases accrued to date (n=26; median age 65.5 [IQR 63.5-69.0]; 42% female; targets: GPi 50%, STN 46%), LOS was available for 25 patients (median 1.0 day). Twenty of 25 (80%) were discharged on postoperative day <=1. No early-discharge patients (0/20) were readmitted within 30 days vs 2/5 (40%) among those with LOS > 1. Early-discharge patients had lower IV opioid requirements (median 11.6 vs 61.3 MME) and were more likely to have a normal first-day neurological examination (90% vs 33%). These signals align with planned index components and support feasibility of standardized early-discharge pathways.

Conclusion

Early, safe discharge after PD DBS appears feasible in a majority of carefully selected patients at our center, with simple peri-operative features—particularly low immediate opioid need and a normal early exam—strongly associated with readiness. A compact, PD-specific index integrating these features could standardize discharge, reduce LOS, and maintain safety; next steps are completion of internal validation and prospective testing.

Keywords

Deep Brain Stimulation; Parkinson"s Disease; Same-Day Discharge; Predictive Index

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Deep brain stimulation in the mesencephalic locomotor region of the rat induces-frequency-dependent behaviours beyond locomotion

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Introduction: Deep brain stimulation (DBS) in the mesencephalic locomotor region (MLR) has been explored for treating gait disturbances in Parkinson's disease (PD). Yet clinical studies report limited benefit of low-frequency DBS in two MLR subregions — the pedunculopontine nucleus (PPN) and cuneiform nucleus (CnF) — and instead note anxiety or other side effects. In contrast, our previous work in rat models indicated that high-frequency DBS of the CnF, but not the PPN can improve gait performance under disease conditions.

Goals: To better understand the neurobiology underlying DBS for retuning of gait, we categorized behavioural responses to MLR-DBS in healthy rats. Because DBS evoked not only locomotor but also defensive responses, we further examined whether the MLR engages higher-order motor pathways and defensive circuits.

Materials & Methods: Rats received low- (20–60 Hz) or high-frequency (80–130 Hz) DBS in the MLR while behaviour was recorded in an inverted open field. Behaviour was quantified using DeepLabCut and machine-learning–based classifiers. Neuronal activation was assessed via cFOS expression in MLR subregions close to the stimulation electrode. To map connectivity, we generated new anterograde and retrograde AAV tracers targeting CnF projection neurons. These vectors express a myristoylated GFP and a nuclear tdTomato under a CamkII(1.3) promoter, enabling identification of neuronal cell bodies and their corresponding axonal fibres.

Results: On the observational level, high-frequency CnF-DBS, but not low-frequency stimulation, elicited acute behavioural responses. High-frequency DBS triggered locomotor activation followed by distinct behavioural states, including running, tail rattling, rearing, and freezing. Unsupervised behavioural analysis revealed that high-frequency stimulation produces amplitude-dependent effects, shifting from naturalistic walking at lower amplitudes to predominantly induced hyperlocomotion (running) at higher amplitudes. In contrast, low-frequency stimulation at higher amplitudes promoted global behavioural transitions toward an immobile state. These findings highlight bradykinesia-like effects of low-frequency DBS, which were corroborated by semi-supervised and kinematic analyses of DBS-induced behaviour.

At the cellular level, high-frequency DBS — but not low-frequency — triggered robust cFOS expression within 90 minutes in both the CnF and PPN. Anterograde tracing revealed strong ascending CnF projections to the substantia nigra pars compacta, subthalamic nucleus (STN), several thalamic nuclei, and the central amygdala (CeA). Retrograde tracing confirmed direct CnF inputs to the STN and CeA.

Summary: Our findings show that DBS in the MLR controls a broader repertoire of behaviours than locomotion alone. Through its ascending projections to motor and defensive circuits, the CnF appears to integrate locomotor and threat-related behaviours. We are now using chemogenetic approaches to determine whether these DBS-induced effects are mediated by a specific glutamatergic CnF projection-neuron subtype.

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Neural architecture of the midbrain periaqueductal gray: Novel target for DBS surgical treatment of neurogenic autonomic disorders

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Background

One "stop shop" for treatment of neurogenic autonomic dysreflexia could be DBS induced therapeutic neuromodulation of the midbrain periaqueductal gray (PAG). The PAG is a critical relay of the limbic brain and maintains strong connections to the autonomic and pain control circuits located in the caudal brainstem and spinal cord. Through these projections the PAG controls the neural circuits that regulate breathing, vocalization, cardiovascular function, bladder function and pain. However, DBS of PAG for treatment of isolated dysautonomia should be assessed with caution due to multiple activations and/or spread of the stimulation effect (via DBS) inducing a wide range of effects that cannot be easily controlled in the clinical setting.

Question

For this reason the neural architecture, circuit physiology/pharmacology and autonomic topography within the PAG needs to be thoroughly investigated. Understanding of properties such as inhibition and disinhibition within the PAG, amplitude and temporal sensitivity of its neurons and chronaxie of its circuits would enable segregation of microcircuits that handle specific autonomic and motor components and consequently selective design and application of DBS. This would require fundamental investigation of the PAG neurophysiology in the animal model.

Methods

Our research mapped the PAG stereotactically in the rat in vivo. Detailed electrophysiological characteristics of neurons such as burst frequency & adaptation, power & amplitude density, threshold activation constants, inter-spike intervals and the topography of neuronal circuit function was investigated.

Conclusion

The PAG was found to be predominantly quiescent in the resting state. Silent PAG cells could be activated by iontophoresis of DL Homocysteic acid (DLH) an excitatory amino acid glutamate agonist. Cells made to fire in this manner ceased activity when either DLH ejection was terminated or by co-iontophoresis of muscimol (GABA agonist). Spontaneously active cells were very few, restricted to the dorsal PAG region and these cells recorded extracellularly typically fired in a slow and irregular pattern. Activation of either behavioral and/or autonomic interventions caused immediate activation of PAG neurons mainly in the lateral and ventrolateral PAG. In such instances, lateral and ventrolateral PAG cells showed two distinct types of activity patterns; 1) single spike firing and 2) burst firing, The cells fired both tonically and phasically when correlated with specific autonomic output such as the diaphragm EMG. Predominantly the non-bursting PAG neurons had a near normal distribution around 200 to 250 msec, while burst-firing cells typically showing a bimodal distribution. The functional implications of PAG neuronal activity are thus discussed in terms of descending motor and autonomic control and effective translation for application of DBS in the treatment of PAG pathology and neurogenic autonomic disease.

Declaration

This work was wholly undertaken in the previous laboratories of HHS-GH at University of Sydney, University of Queensland and University of Groningen with respective institutional ethics approvals. HHS and GH conceived and designed the projects, performed the experiments, analysed primary data and made figure illustrations. SG provided critical inputs on neuromodulation concepts. GH curated and approved the final data/figure representation in this presentation/poster.

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Chronic subthalamic deep brain stimulation induces cortico-striatal plasticity in the A53T α-synuclein rat model of Parkinson's disease

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Objective:
Subthalamic deep brain stimulation (STN-DBS) is an established treatment for alleviating motor dysfunction in Parkinson"s disease (PD). Early and continuous STN-DBS have been shown to slow motor progression in PD patients, suggesting that DBS can induce long-term network plasticity that contributes to motor protection. However, the mechanisms underlying these plastic effects remain poorly understood.

Methods:
This study employed a progressive, human-mimicking PD rat model (AAV1/2-A53T-α-synuclein rats) to investigate brain-wide functional and plastic changes, as well as behavioral outcomes, following 21 days of continuous high-frequency STN-DBS (A53T stim-ON) compared with sham stimulation (A53T stim-OFF). A sham-stimulated empty-vector control group (EV stim-OFF) was also included. Motor function was assessed using the single pellet reaching task at baseline, week 3 (pre DBS/sham-DBS), and week 6 following DBS or sham DBS. An additional behavioral assessment after a 24-h washout time was conducted in the A53T stim-ON group. 18F-fluorodeoxyglucose positron emission tomography and CT imaging were conducted at week 6 to quantify whole-brain glucose uptake and confirm electrode placement, respectively. To examine stimulation-induced plastic metabolic effects, the FDG-PET scan for A53T stim-ON rats was performed after a 48-h washout period.

Results:
Animals with confirmed electrode–STN intersection were included in the post analyses. Preliminary results show that chronic STN-DBS improved single pellet reaching task performance in A53T rats, with motor benefits persisting after the 24-h washout. STN-DBS increased glucose metabolism in the ipsilateral primary/secondary motor cortex and the ipsilateral striatum (lateral part) compared with sham-stimulated A53T rats (A53T stim-ON, n = 4; A53T stim-OFF, n = 5; SPM: independent-sample t-test, $p < 0.05$; FWE-corrected, $p < 0.05$). Notably, glucose metabolism in the ipsilateral motor cortex correlated positively with motor performance ($r = 0.7577$, $p < 0.01$) and $GFAP^+$ astrocyte expression ($r = 0.8240$, $p < 0.01$).

Conclusion:
These preliminary findings suggest that chronic STN-DBS induces plasticity in cortico-striatal circuitry in the A53T rats. The associated cortical hypermetabolism and astrocyte activation may contribute to the motor protective effects of long-term STN-DBS.

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Cortical stimulation and subthalamic response: A bidirectional framework for dopamine-dependent network dynamics in Parkinson's disease

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The cortico–subthalamic hyperdirect pathway provides a fast and anatomically privileged route for cortical influence over basal ganglia processing and is recognized as a key target for deep brain stimulation (DBS) in Parkinson"s disease (PD). To delineate the physiological motifs governing cortico–subthalamic communication and their modulation by dopamine, we obtained simultaneous externalized electrocorticography (ECoG) and subthalamic nucleus (STN) local field potential recordings in 15 patients undergoing DBS implantation. Bidirectional mapping was performed, delivering cortical stimulation while recording from the STN, and STN stimulation while recording from the cortex.

Cortical stimulation elicited a sequence of short- and long-latency STN responses, with the earliest component emerging at 2.6 ± 0.7 ms, followed by responses at 10.1 ± 1.9 ms, 23.9 ± 3.4 ms, 38.9 ± 3.5 ms and 79.9 ± 8.9 ms. Short-latency components were conserved across both antidromic and orthodromic stimulation directions, establishing their origin within the hyperdirect pathway. Long-latency STN responses were selectively amplified in the dopamine-depleted state, indicating increased subthalamic susceptibility to cortical drive under hypodopaminergic conditions. Dopamine, however, did not modulate cortical responses to STN stimulation.

These findings reveal an asymmetric dopaminergic influence on cortico–subthalamic signalling, whereby dopamine preferentially shapes subthalamic, but not cortical, responsiveness to hyperdirect input. By refining the physiological framework for basal ganglia–cortical interactions in PD, this work motivates a shift from oscillation- to network response–based interventions that leverage intrinsic neural dynamics.

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Differential effects of entopeduncular versus cerebellar stimulation on motor pathology in a DYT-TOR1A rat model

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Dystonia is a movement disorder characterized by involuntary muscle contractions that compromise movement and posture control. DYT-TOR1A dystonia, caused by a mutation in the TOR1A gene, is the most common monogenic form of the disease. It shows incomplete penetrance, suggesting that environmental factors such as repeated limb overuse contribute to symptom manifestation. Although deep brain stimulation (DBS) of the globus pallidus internus (GPi) can alleviate symptoms in many patients, responses vary, and alternative targets such as the cerebellar dentate nucleus (DN) have been explored. To investigate how stimulation of different network nodes influences dystonia motor dysfunction, we exposed a rat model expressing the human mutant TOR1A gene to a right-forelimb overuse paradigm involving repeated lever pressing. DBS electrodes were implanted into either the entopeduncular nucleus (EP; the rodent analogue of the GPi) or the DN. Animals performed three weeks of the overuse task without stimulation, followed by two weeks of high-frequency DBS. The lever pressing behaviour of the animals was characterized with DeepLabCut and an automated kinematic analysis pipeline. Preliminary analyses revealed that EP-implanted animals failed to develop the aberrant lever-press trajectories typically observed in non-implanted mutants. EP stimulation itself did not further alter performance. This suggests that electrode implantation in the EP, potentially through a lesion-related mechanism, may disrupt the emergence of dystonic motor patterns. In contrast, DN-implanted rats developed motor abnormalities and DN stimulation did not shift their trajectories toward control-like values. Overall, these findings highlight the importance of basal ganglia output pathways—specifically the EP/GPi—in shaping dystonic motor expression in the DYT-TOR1A model. Moreover, the absence of behavioural rescue with DN-DBS indicates that high-frequency deep cerebellar stimulation is insufficient to normalize the overuse-induced motor deficits in this context.

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Evaluating ^{18}F-DTBZ-PET as an early marker of dopaminergic terminal abnormality in A53T-α-synuclein Parkinson's disease rat model

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Background:
Vesicular monoamine transporter type 2 (VMAT2) PET is increasingly recognized as a reliable biomarker for Parkinson's disease (PD) progression. Current VMAT2-PET studies focus on the phase after motor onset and during follow-up, leaving it unclear whether VMAT2 PET can detect early dopaminergic terminal dysfunction prior to overt neurodegeneration or severe motor deficits.

Methods:
We established a VMAT2 PET imaging pipeline using the tracer 18F-DTBZ in rats. A progressive AAV1/2-A53T-α-synuclein PD rat model was used, consisting of two cohorts—6 weeks (A53T-6W) and 3 weeks (A53T-3W) post A53T virus injection, with each a corresponding empty-vector control group (EV-6W and EV-3W). Rats in the 6-week cohort received longitudinal evaluation of motor performance using the cylinder test at baseline, week 3, and week 6. In the 3-week cohort, the rats were assessed for both motor and non-motor behaviors using the cylinder and open-field tests at baseline and week 3. The rats in the A53T-6W cohort underwent [18F]9-fluoropropyl-(+)-dihydrotetrabenazine (18F-DTBZ) positron emission tomography (PET) to assess dopaminergic function. To investigate DTBZ uptake-related pathological changes, VMAT2 glycosylation states and tyrosine hydroxylase (TH) levels in the striatum were quantified using western blot.

Results:
A53T-6W rats displayed significant forelimb asymmetry at week 6, accompanied by pronounced loss of striatal dopaminergic fibers. DTBZ uptake in the ipsilateral striatum was markedly reduced and strongly correlated with both glycosylated and non-glycosylated VMAT2, as well as TH expression. In contrast, neither A53T-6W nor A53T-3W rats exhibited significant motor asymmetry versus their control groups at week 3. However, A53T-3W rats showed a clear non-motor behavior at this timepoint. Notably, both glycosylated and non-glycosylated VMAT2 levels were already reduced in the ipsilateral striatum at week 3, even though dopaminergic fiber degeneration remained minimal.

Conclusion:
These findings suggest that the reduced DTBZ uptake aligns with the alterations in both glycosylated and non-glycosylated VMAT2 expression in A53T rats at 6 weeks after viral injection. The presence of VMAT2 non-glycosylation and glycosylation deficits in A53T-3W rats—prior to severe terminal loss—supports further investigation into the sensitivity of 18F-DTBZ PET for detecting pre-/mild-degenerative dopaminergic dysfunction in early-stage PD.

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Deep Brain Stimulation decreases neuropathology and immune cell reactivity in a mouse model of Parkinson's disease

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Introduction: The pathognomonic feature of Parkinson's disease (PD) is the accumulation of aggregated α-synuclein within the substantia nigra pars compacta (SNpc). Studies in both PD patients and animal models of PD have demonstrated that these aggregates can trigger T cell infiltration into the SNpc. These T-cells respond directly to α-synuclein peptides by secreting pro-inflammatory cytokines such as IFN-γ. This neuroinflammatory response may contribute to neurodegeneration in the SNpc, which underlies the motor dysfunction characteristic of PD. Identifying interventions that dampen this a-synuclein immune response may address the unmet need of a disease modifying therapy for PD Deep brain stimulation (DBS) is an established intervention for symptomatic management in PD patients. Recent studies show that, when applied to the subthalamic nucleus (STN) in rodent models, DBS can confer neuroprotective effects in the SNpc. However, whether DBS-mediated neuroprotection occurs via modulation of α-synuclein pathology remains unresolved. Understanding the mechanism of DBS-induced neuroprotection is essential for developing disease-modifying therapies for PD.

Goals: The goal of this study was to investigate whether DBS attenuates SNpc dopaminergic neurodegeneration by modulating α-synuclein pathology.

Materials & Methods: We use a well-characterized PD mouse model in which wild-type (WT) mice received stereotactic injections of an adeno-associated virus serotype 1/2 (AAV1/2) expressing human mutant α-synuclein (A53T) into the SN. Two weeks post-injection, electrodes were implanted into the subthalamic nucleus (STN) for continuous DBS over 12-14 days. At six weeks post-injection, the brains, spleens were harvested. We evaluated TH^+ neurons, immune cells, and pathologic α-synuclein by immunohistochemistry (IHC) and immunofluorescence (IF). Splenocytes were isolated and co-cultured with α-synuclein peptides for 2 weeks. In order to measure their reactivity to the α-synuclein peptides, the levels of pro-inflammatory cytokine IFN-γ released by these immune cells were evaluated via Elispot. The open field and cylinder tests were also used to assess motor impairment.

Results: In the SNpc, IF analysis revealed that DBS decreases A53T-induced TH^+ dopaminergic neurodegeneration. T-cell infiltration and α-synuclein aggregation were significantly reduced in the SNpc after DBS. Furthermore, the elevated immune cell reactivity to α-synuclein peptides in the A53T PD mouse model decreased after DBS.

Summary: These findings suggest that DBS may exert neuroprotective effects in PD model mice through modulation of α-synuclein aggregation and immune cell reactivity, providing insights into its potential as a disease-modifying therapy in PD.

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From neural signatures of gait interruptions to phase-locked stimulation in Parkinson's disease

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Gait deficits present an unresolved therapeutic challenge in Parkinson's Disease. At the behavioural level, symptoms exhibit heterogeneity, including bradykinesia and hypokinesia during cyclical limb movements, and sudden, involuntary interruptions in the gait sequence, known as freezing of gait. The neural activities driving these various deficits remain largely unknown. We investigated the neural correlates of gait sequence interruptions with deep neurobehavioral phenotyping. In a rodent Parkinson"s disease model, our approach revealed that gait, akinesia, and stationary movements occupy distinct regions in a low-dimensional embedding space. Among the predominant features separating the states, Hjorth complexity and mobility modulated at akinesia onset. Additionally, we validated our findings in two Parkinson's patients with freezing of gait, where neural features in STN recordings partially reflected the results in rodents. Finally, we explored a closed-loop paradigm locked to a specific phase of ongoing oscillations to deliver timely stimulations. This set-up allows us to explore modulate modulation of pathological biomarkers.

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Dual mechanisms of neuroprotection in Parkinson's disease: deep brain stimulation and physical exercise

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Background:

Parkinson"s disease (PD) is a progressive neurodegenerative disease mainly characterized by motor impairment and dopaminergic neurodegeneration along with neuroinflammation. Deep brain stimulation (DBS) is an established intervention for controlling motor symptoms, yet its effect on neuroprotection remains uncertain and not well understood. Also, regular physical exercise is known to exert neuroprotective effects. But how DBS and physical activity influence each other, and how each independently potentially modulates neuroinflammatory pathways, is still opaque. In this study, we employed a recently self-developed and commercially available standardized wireless DBS (wDBS) system for mice together with a machine-learning-based gait analysis pipeline.

Objective:

We investigated potential neuroprotective effects of wDBS in a unilateral mouse model of Parkinson's disease (AAV1/2-αSYN-A53T) and compared them with those achieved through physical exercise. We further evaluated whether combining DBS with physical exercise results in additive or synergistic neuroprotective benefits.

Methods:

Unilateral wireless DBS (wDBS) electrodes were implanted into mice that received an AAV1/2-αSYN-A53T (hαSYN) injection in the right substantia nigra (SN) earlier. Treatment groups were as follows: wDBS (for 2 weeks), a forced treadmill training regimen (FTT) (for 5 weeks), or both overlapping, with appropriate sham controls. After week 6 the neuroprotective properties of the interventional protocols were evaluated by dopaminergic neuron count in the SN, gait analysis, and analysis of the innate and adaptive immune cell populations employing histology and FACS.

Results:

Both wDBS and FTT led to dopaminergic neuroprotection in all hαSYN mice and neuroprotection translated into a functional benefit most pronounced in hαSYN-FTT (± wDBS) mice. Innate immune activation in the histological analysis was reduced in all treated hαSYN mice if the whole SN was analyzed. Further, histological T cell analysis in the striatum revealed a significantly reduced invasion in treated hαSYN mice. FACS analysis of the blood, however, suggests restauration of distinct regulatory T cell populations in wDBS (± FTT), namely CD8+CD122+CD69+ which could be interpreted as "active" regulatory CD8+ cells and CD4+CD25+FoxP3+ (regulatory CD4+ cells) in FTT (± wDBS) mice. In sum, we observed potentially differential effects of both therapies on regulatory T cell populations – however these changes did not translate into additional dopaminergic neuroprotection suggesting a ceiling effect in our experimental setup.

Conclusions:

Our experimental results suggest independent neuroprotective properties of wDBS and FTT - potentially by influencing the neuroinflammatory milieu. While both interventions were associated with downregulation of innate immune responses, they showed divergent patterns in the restoration of regulatory T-cell subpopulations. At his stage the immune alterations represent potential mediators of neuroprotection, but causality remains uncertain. Overall, our findings indicate that DBS and physical exercise may serve as complementary interventions that not only alleviate symptom burden but also influence disease progression possibly by their distinct effects on neuroinflammation.

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Restoring stereotaxic accuracy in a novel mouse model of Parkinson's disease

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Precise stereotaxic targeting is essential for preclinical deep brain stimulation (DBS), yet transgenic models can deviate substantially from the anatomical assumptions of wild-type atlases. We found that mice with dopaminergic-neuron–specific mitochondrial complex I deficiency (MCI-PD)1, a progressive and clinically relevant model of Parkinson"s disease, exhibit pronounced non-isotropic cranial and brain dysmorphology. These deformations caused systematic mistargeting of DBS structures such as the subthalamic nucleus (STN) when using standard wild-type coordinates.

To restore targeting accuracy, we generated a **genotype-specific stereotaxic atlas** by integrating high-resolution 50-µm MRI of the brain with matched micro-CT skull imaging in a unified registration framework. Morphometric analyses across 760 annotated regions revealed axis- and region-dependent deformations, confirming that simple proportional scaling from wild-type anatomy is invalid for this model. Using atlas-derived coordinates, we achieved **precise STN targeting**, validated by retrograde tracing and accurate placement of DBS electrodes producing robust improvements in motor performance, demonstrating functional relevance and confirming stereotaxic precision.

This **open-access atlas and codebase** provide a practical solution for achieving reproducible neuromodulation in the MCI-PD model and offer a generalizable framework for building genotype-specific atlases in other transgenic lines. By correcting targeting errors at their source, this resource enhances the reliability of preclinical DBS studies and supports mechanistic investigations in progressive models of Parkinson"s disease.

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Alternative technologies for targeted neuromodulation

P154

Neural signatures of non-invasive deep brain stimulation via transcranial ultrasound

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Transcranial ultrasound stimulation (TUS) is a novel, non-invasive neuromodulation technique with the unique ability to reach deep brain structures with high spatial resolution. Alternative non-invasive technologies that can selectively engage subcortical circuits are of considerable interest as potential complements or substitutes for deep brain stimulation (DBS). While preclinical studies have demonstrated both excitatory and inhibitory effects of TUS depending on dose, target location, and brain state, the electrophysiological signatures of TUS in deep human structures remain poorly characterized.

The goal of this work was to evaluate the safety, feasibility, and the electrophysiological and behavioral effects of TUS applied to the human motor network (basal ganglia and M1).

We combined TUS with local field potential (LFP) recordings from chronically implanted DBS electrodes in patients with Parkinson"s disease. In two parallel studies, LFPs were recorded from the globus pallidus internus (GPi) and the subthalamic nucleus (STN) using Percept PC systems (Darmani et al., 2025; Sarica et al., under review). In one cohort (n = 10), theta-burst TUS (tbTUS) and 10 Hz TUS were applied to the GPi, with simultaneous GPi LFP recordings. In a second cohort (n = 17), patients received tbTUS targeting the GPi, motor cortex, or occipital cortex under randomized, blinded conditions, with STN LFPs recorded during and after stimulation. All sonications were guided by MRI-based targeting and supported by ex vivo and pilot safety testing, as well as individualized simulations to account for skull-related aberrations and distortions, ensuring compliance with international safety standards.

In the first cohort, tbTUS increased GPi theta power during stimulation, whereas 10 Hz TUS enhanced beta power, with effects persisting for up to forty minutes post-sonication (Darmani et al., 2025). In the second cohort, GPi tbTUS enhanced STN beta activity, while motor cortex tbTUS suppressed beta power and reduced beta burst duration—effects consistent with excitatory and inhibitory profiles described in preclinical and prior clinical studies (Sarica et al., under review).

In summary, this work demonstrates that TUS can safely and selectively modulate basal ganglia activity in humans in a frequency- and target-dependent manner. The combination of individualized ultrasound delivery and chronic LFP recordings provides a powerful translational framework for investigating neuromodulation in vivo. These studies highlight TUS as a promising candidate technology for next-generation targeted neuromodulation.

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P155

Clinical efficacy of a novel deep brain stimulation system with 16-contact directional leads for the treatment of Parkinson's disease

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Question

Can a novel deep brain stimulation (DBS) system with 16-contact directional leads and multiple independent current control provide sustained improvements in motor function, quality of life, and medication reduction in patients with Parkinson"s disease (PD)?

Methods

This prospective, multicenter, open-label clinical trial (NCT#04577651) evaluated the efficacy and safety of two 16-contact directional DBS lead configurations (Cartesia X/HX, Boston Scientific) connected to a multiple independent current control neurostimulator (Vercise Genus, Boston Scientific). Forty-nine subjects with PD were implanted across 10 centers. The primary endpoint was change in motor symptoms, measured by the Movement Disorder Society–Unified Parkinson"s Disease Rating Scale Part III (MDS-UPDRS III, meds OFF), from baseline to 12 weeks post-activation. Secondary endpoints included changes in Parkinson"s Disease Questionnaire (PDQ-39) domains, levodopa equivalent daily dose (LEDD), and adverse event reporting. DBS programming was performed according to each clinician"s standard of care, and patients were followed through two years.

Results

Baseline cohort characteristics included mean age 62.5 years, mean disease duration 11.7 years, and mean MDS-UPDRS III score 47.9. At 12 weeks, motor function improved by 20 points (41%) on MDS-UPDRS III ($p<0.0001$). This benefit was sustained at one year (21-point improvement) and two years (22-point improvement). Antiparkinsonian medication use decreased by up to 37% at 26 weeks and remained reduced through year 2 ($p<0.001$). Quality of life, assessed by PDQ-39, demonstrated significant improvements across multiple domains, including mobility, activities of daily living, bodily discomfort, and stigma, with benefits maintained through two years. Safety outcomes were consistent with established DBS practice, with no unexpected adverse events reported. The expanded 16-contact design enabled multi-level stimulation and precise current steering, supporting individualized programming strategies.

Conclusion

This study demonstrates that 16-contact directional DBS leads combined with a multiple independent current control neurostimulator are safe and effective for the treatment of PD. Patients experienced sustained improvements in motor function, quality of life, and reduced reliance on antiparkinsonian medications over two years. The novel lead design extends the span of directional contacts, enabling more precise current steering and multi-level stimulation, thereby broadening the therapeutic window and minimizing side effects. These findings highlight the clinical utility of next-generation DBS systems in delivering durable, patient-tailored therapy for Parkinson"s disease.

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Dopamine and cortical facilitation during rTMS in patients with Parkinson's disease

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Cortical excitation-inhibition balance is critical for motor learning and control but is altered in patients with Parkinson"s disease (PD). Transcranial magnetic stimulation (TMS) of the primary motor cortex (M1) enables probing of cortical excitatory states via motor evoked potentials (MEP). Moreover, cortical facilitation can be assessed through repeated stimulation and resulting MEP modulation, thought to reflect short-term plasticity. Here, we examined whether dopamine influences this facilitatory capacity in patients with PD.

We applied suprathreshold M1 rTMS to eight PD patients during dopaminergic medication OFF and ON sessions, delivering trains of 25 stimuli at 5 Hz and 1 Hz. MEPs were recorded with a 32-channel high-density electromyography (hdEMG) electrode to capture both amplitude and spatial muscle activation patterns. Simultaneously, 32-channel electroencephalography (EEG) was recorded and an additional stimulation sequence of 100 stimuli with variable interstimulus intervals (ISI) of 1.5-2.5 seconds was applied to explore event-related cortical potentials and oscillations. Motor state was evaluated prior to each session with the UPDRS-III.

MEP facilitation was observed during 5 Hz rTMS trains in both medication states but the amplitude increase was approximately doubled ON compared to OFF dopaminergic medication (medOFF: +2.5% per pulse, $p<0.01$; medON: +5.2% per pulse, $p<0.01$). In contrast, 1 Hz rTMS had no measurable impact in either condition while MEP amplitudes were significantly larger in the ON state (+51.3%, $p<0.01$).

These findings demonstrate an important influence of dopamine on cortical facilitation. Combining MEP amplitudes with hdEMG"s spatial resolution and event-related EEG characteristics allows us to gain insights into the dynamics of the underlying motor circuitry. Ultimately, this approach could deepen our understanding of dopamine"s role in cortical balance and plasticity and its impact on the clinical presentation of PD.

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Unraveling brain-heart coupling breakdown in Parkinson's disease: a multi-modal investigation

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Parkinson's disease (PD) is a neural systems disorder that extends beyond the motor system, involving multi-organ interactions. Emerging evidence highlights an altered brain-heart interaction, but the pathophysiological mechanism remains unclear. In particular, the interplay between basal ganglia and cortical physiology in supporting brain-heart synchrony in PD patients has not been elucidated. To address this gap, we investigated the large-scale network disruptions in brain-heart coupling and their potential relevance to clinical manifestations. We analyzed simultaneous resting-state electrocardiography (ECG), electrocorticography (ECoG), and local field potentials (LFP) from 20 PD patients undergoing deep brain stimulation (DBS) surgery, both ON and OFF dopaminergic therapy. The R-peaks from the QRS complex (ventricular depolarization) were subjected to a peak detection algorithm. To investigate neural processing of cardiac activity, heart evoked potentials (HEPs) were obtained by averaging neural signal epochs extracted from -200 ms to 1000 ms time-locked to each R-peak. Our preliminary analyses revealed cortical and subcortical neural responses time-locked to the R-peak, with prominent activity emerging around 300-500 ms post-heartbeat. Notably, dopaminergic medication enhanced subcortical HEPs, suggesting a partial restoration of brain-heart coupling by medication. Furthermore, during dopaminergic medication OFF periods, heart rate variability measures showed significant correlation with electrophysiological markers of subcorticex-heart synchrony (HEP peak amplitude and latency), and clinical motor scores. This suggests that in the medication OFF state, impaired cardiac autonomic regulation, as reflected by reduced heart rate variability, is associated with altered subcortical neural processing of cardiac signals and worsened motor symptoms. These preliminary findings suggest that dopaminergic medication modulates brain-heart synchrony in PD, warranting further analyses of connectivity and network dynamics to deepen our understanding of the complex brain-heart interactions in PD.

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Investigating cortico-striatal plasticity and motor overflow in dystonia using transcranial temporal interference brain stimulation

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Dystonia presents with a loss of normal motor control, where involuntary muscle contractions generate distorted or repetitive movement patterns. Despite a known genetic component of the disease, certain genetic forms like DYT-TOR1A dystonia have a low penetrance, with only around 30 % of carriers developing symptoms. These findings have led to the "second hit hypothesis", which proposes that genetic predisposition interacts with environmental triggers leading to the development of dystonic symptoms. One suspected mechanism underlying this transition from vulnerability to manifestation is maladaptive plasticity within the cortico-striatal network.

Our aim is to elucidate the role of this maladaptive cortico-striatal plasticity in the development of dystonia across both rodent models and human subjects. In both approaches, we will study the kinematics of different groups and modulate plasticity through non-invasive temporal interference (TI) stimulation of the striatum. This modulation will span from a presumably plasticity-enhancing (intermittent theta-burst stimulation – iTBS) to a plasticity-diminishing (continuous theta-burst stimulation – cTBS) protocol as well as a control stimulation.

In mice, we employ a DYT-TOR1A model that is asymptomatic in its naïve state, but has previously been shown to be vulnerable to motor circuit perturbation in form of a peripheral nerve injury. Here, we aim to induce dystonia-like features through forelimb overuse in a lever press task and study the central motor circuit changes through behavioural tests, forelimb electromyography (EMG), TI modulation and neural recordings via in vivo calcium imaging.

In humans, this study investigates the role of striatal plasticity in the emergence of task-unrelated muscle activity (motor overflow) during a figure-of-eight writing task. Participants with focal hand dystonia, non-manifesting carriers with the DYT-TOR1A gene mutation and healthy controls will be studied. Participants will engage in a figure-of-eight writing task while the striatal plasticity state will be modulated with TI stimulation in a within-session, randomized, double-blind, controlled design. We will implement the same stimulation approach as in the animal model. Task-unrelated motor activity will be quantified using multi-channel EMG and joint EMG-kinematic spectral analyses.

We expect the forelimb overuse task to induce a dystonia-like phenotype in mice and to identify stimulation conditions that rescue or exacerbate symptoms. In humans, we anticipate that individuals with dystonia show greater task-unrelated motor activity compared to non-manifesting carriers, who in turn will exceed healthy controls. Furthermore, we predict that iTBS will amplify task-unrelated muscle activity, whereas cTBS will suppress this activity. Findings may elucidate how maladaptive cortico-striatal plasticity contributes to the development of dystonic motor symptoms and inform targeted neuromodulation strategies in future.

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Local and network-level determinants of dopaminergic restoration after human AADC gene therapy

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Introduction: Intracerebral gene therapy for aromatic L-amino acid decarboxylase (AADC) deficiency has transformed a fatal neurotransmitter disorder into a treatable condition, yet the anatomical and network principles governing therapeutic efficacy remain unknown. Leveraging the largest AADC gene-therapy cohort to date, we sought to uncover how viral vector topology, molecular substrate, and network connectivity shape dopaminergic recovery and clinical outcome in the human brain.

Methods: Forty-six patients underwent bilateral AAV2-hAADC infusions into midbrain dopaminergic nuclei. Gadolinium-enhanced volumes of distribution were segmented, normalized, and intersected with probabilistic atlases. Homovanillic acid (HVA) and 3-O-methyldopa (3-OMD) were quantified as biochemical markers of dopaminergic restoration. We mapped spatial correlations between dose and metabolite change, quantified region-specific effects, modeled predictors of clinical outcome, and correlated off-target spread with side effects. Transcriptomic and tractography analyses were used to identify molecular and circuit-level determinants of therapeutic and adverse responses.

Results: All patients demonstrated increased HVA, whereas 3-OMD changes were variable. HVA gain scaled with total vector dose ($R=0.48$, $p<0.01$), but not infusion volume. Probabilistic mapping identified the strongest dose-response correlation in substantia nigra, pars compacta (SNc) and ventral tegmental area (VTA). Effective dose to either nucleus independently predicted HVA increase ($R=0.44$, $p<0.01$ SNc, $R=0.41$, $p=0.01$ VTA, $R=0.47$, $p<0.01$ combined), and modeling of isoboles revealed an additive effect across both structures. Overlap with AADC expression patterns derived from the Allen Human Brain Atlas correlated with HVA change ($R=0.53$, $p<0.01$), exceeding correlations for all other genes, establishing a substrate-specific biomarker for dopaminergic restoration. Correlation between effective dose and clinical outcome as measured using the gross motor function measure (GMFM) was weak, suggesting that biochemical recovery alone does not fully dictate functional improvement. Multiple-regression and mixed-effects models incorporating effective dosage, dose-independent dopaminergic restoration, age, and sex significantly improved explanatory power ($R^2=0.42$, $p=0.01$), and leave-one-out cross-validation yielded a robust correlation between predicted and observed GMFM change ($R=0.38$, $p=0.04$). Structural-connectivity analysis revealed that vectors aligned with nigrostriatal and mesocortical pathways could transduce distant regions, identifying potential network hubs for future large-scale gene delivery.

Conclusion: This study establishes a methodological framework for spatially resolved, network-informed analysis of intracerebral gene therapy. By integrating gene-expression maps, connectomic architecture, biochemical restoration, and validated predictors of clinical outcome, we move beyond empirical targeting toward data-driven, precision delivery of therapeutic genes. The partial dissociation between dopamine restoration and motor improvement highlights a multilevel mechanism in which local transduction provides necessary biochemical recovery, while patient-specific and network-level factors determine functional gains. While validated here in AADC deficiency, this paradigm generalizes to other molecular targets, offering a scalable roadmap for circuit-level design of next-generation gene therapies.

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Closed-loop epidural electrical stimulation of the Lumbosacral spinal cord to address gait impairments and fluctuations in advanced Parkinson's disease

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Despite significant progress in neuromodulation therapies for Parkinson"s disease (PD), many patients with advanced PD continue to experience debilitating gait and balance impairments—including postural instability, festination, and freezing of gait—that remain unresponsive to existing treatments. In the STIMO-PARKINSON trial (NCT04956770), we previously demonstrated that epidural electrical stimulation (EES) of the lumbosacral spinal cord improved these symptoms in a patient with advanced PD. Building on these findings, we initiated the SPARKL clinical trial (NCT06295614), enrolling six individuals with severe gait and balance deficits.

A major challenge in treating these impairments is managing the variability of motor symptoms, which fluctuate with medication, fatigue, stress, and environmental factors. To address this, we developed a wearable monitoring platform using smart sensorized shoes capable of AI-driven gait analysis. This platform enables continuous, real-time tracking of motor biomarkers in daily-life settings. By integrating EES with this wearable system, we implemented a closed-loop neuromodulation approach that dynamically adjusts stimulation parameters in response to real-time gait data. Tested in three participants, the system demonstrated strong usability outside the laboratory and effectively compensated for fatigue-related gait deterioration. These findings support the potential of adaptive EES as a personalized therapy for gait and balance disorders in Parkinson's disease.

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Wireless self-propelling micro-robots for deep brain navigation and electrode implantation

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Introduction and goal

Current deep brain stimulation (DBS) electrode implantation relies on rigid, several-millimeter-diameter probes that must be inserted along straight trajectories from the cortical surface to deep subcortical targets. Although these approaches are clinically effective, they require the creation of large burr holes and the advancement of stiff electrodes through functional brain tissues. This increases surgical risk and can create tissue deformation along the insertion path. Recent attempts to reduce invasiveness, including steerable needles, fluid-driven catheters, and flexible electrode delivery systems, offer meaningful improvements. However, these systems have limitations, including restricted steerability in soft tissues. Here, for the first time, we report a magnetically-actuated, self-propelling helical micro-robot that is minimally invasive and capable of navigating through brain tissues for DBS lead placement.

Methods

The micro-robot is fabricated by two-photon lithography, incorporates a diametric magnetic moment that enables wireless control under an external rotating magnetic field. The helical architecture converts rotation to forward propulsion, enabling fully steerable 3D navigation in *ex vivo* porcine brain tissues. A cargo-carrying mechanism allows the robot to transport DBS lead wires without rotation, thereby preventing wire twisting during motion.

Results

The micro-robot transports 30 µm-diameter copper wires through brain phantoms and *ex vivo* brain tissues. It achieves continuous penetration distances of several centimeters along defined trajectories. The robot can follow curved paths, allowing it to avoid functionally important regions of the brain during navigation, which is not possible with rigid electrodes. Histological analysis along the robot"s path shows that tissue disruption remains confined to a diameter of 700µm, which is substantially smaller than the conventional DBS electrodes.

Conclusions

This study demonstrates the first magnetically-controlled wireless micro-robot that enables minimally-invasive, steerable DBS lead placement in *ex vivo* porcine brain. This technology provides a foundation for a safer electrode implantation and a more precise neuromodulation.

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Anodic deep brain stimulation for troubleshooting in Parkinson´s disease: a retrospektive study of the long-term motor outcome

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1. Introduction

Deep brain stimulation (DBS) is a cornerstone therapy for patients with Parkinson"s disease (PD) experiencing motor fluctuations refractory to medical treatment and is conventionally delivered using high-frequency, charge-balanced cathodic stimulation. However, a subset of patients shows suboptimal benefit or stimulation-induced adverse effects despite extensive programming optimization. Anodic DBS has emerged as a potential nonconventional programming strategy, but data on its long-term efficacy in PD remain limited.

2. Goals

To evaluate long-term motor outcomes of anodic DBS compared with cathodic DBS in PD patients undergoing reprogramming for troubleshooting.

3. Methods

We conducted a retrospective cohort study of PD patients who underwent DBS surgery at the University Hospital of Würzburg between 2011 and 2023. Twenty-one patients initially treated with cathodic stimulation and subsequently trialed on anodic stimulation were identified. Motor outcomes were assessed using UPDRS part III scores in the preoperative off-medication state, preoperative best-medication-on state (levodopa challenge), and postoperative best medication on/stimulation on state under both stimulation polarities. To minimise confounding by disease progression, analyses were restricted to a one-year window for each stimulation mode. Levodopa equivalent daily dose (LEDD) was compared between stimulation conditions. Lead localisation was investigated using Brain Lab tool.

4. Results

Anodic stimulation was initiated due to insufficient efficacy of cathodic DBS (≈60%) or stimulation-induced side effects (≈40%). Approximately 50% of patients discontinued anodic stimulation within the first month because of lack or loss of benefit. Among patients maintaining anodic stimulation for at least one year, UPDRS III scores under anodic DBS were comparable to the preoperative best-medication-on state ($p = 0.483$). In contrast, motor outcomes under cathodic DBS were significantly inferior to the preoperative best-medication-on condition ($p = 0.018$). Direct comparison between stimulation polarities in the best medication on/stimulation on condition revealed a significant difference favoring anodic stimulation ($p = 0.027$). Both stimulation modes significantly improved motor outcomes compared with the preoperative off-medication state. LEDD did not differ significantly between stimulation conditions, rather a tendency to LEDD reduction was shown under anodic stimulation. Most (90%) of the electrodes for which anodic DBS was initiated were localised off-target.

5. Summary

Anodic stimulation appears to be a valid alternative in patients with suboptimal response or adverse effects under cathodic stimulation mode. Anodic stimulation provided better motor symptoms control in this patient cohort with a tendency to a reduction in dopaminergic therapy.

Despite its clinical benefits, long-term maintenance of anodic therapy is limited, with notable discontinuation rate within one year. These findings suggest the need for individualized DBS programming and further research to better understand the polarity-specific mechanisms. Prospective, adequately powered studies are needed to confirm these observations and refine patient selection.

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