The Role of Neurophysiologic Measurements in Clinical Practice: An Ally for Effective DBS Treatment

Alfonso Fasano, MD, PhD, FAAN

Chair in Neuromodulation and Multidisciplinary Care
Professor of Medicine (Neurology) – University of Toronto, Canada
Clinician Investigator – Krembil Research Centre
Co-director surgical program, Movement Disorders Centre
Toronto Western Hospital - UHN

Disclosures

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- Participation in a company sponsored advisory board
  - Abbott, Abbvie, Boston Scientific, Ipsen, Medtronic, Sunovion

Topics

- Introduction to DBS
- Neurophysiology ***before*** DBS
- Neurophysiology ***during*** DBS
- Neurophysiology ***after*** DBS
- Conclusions

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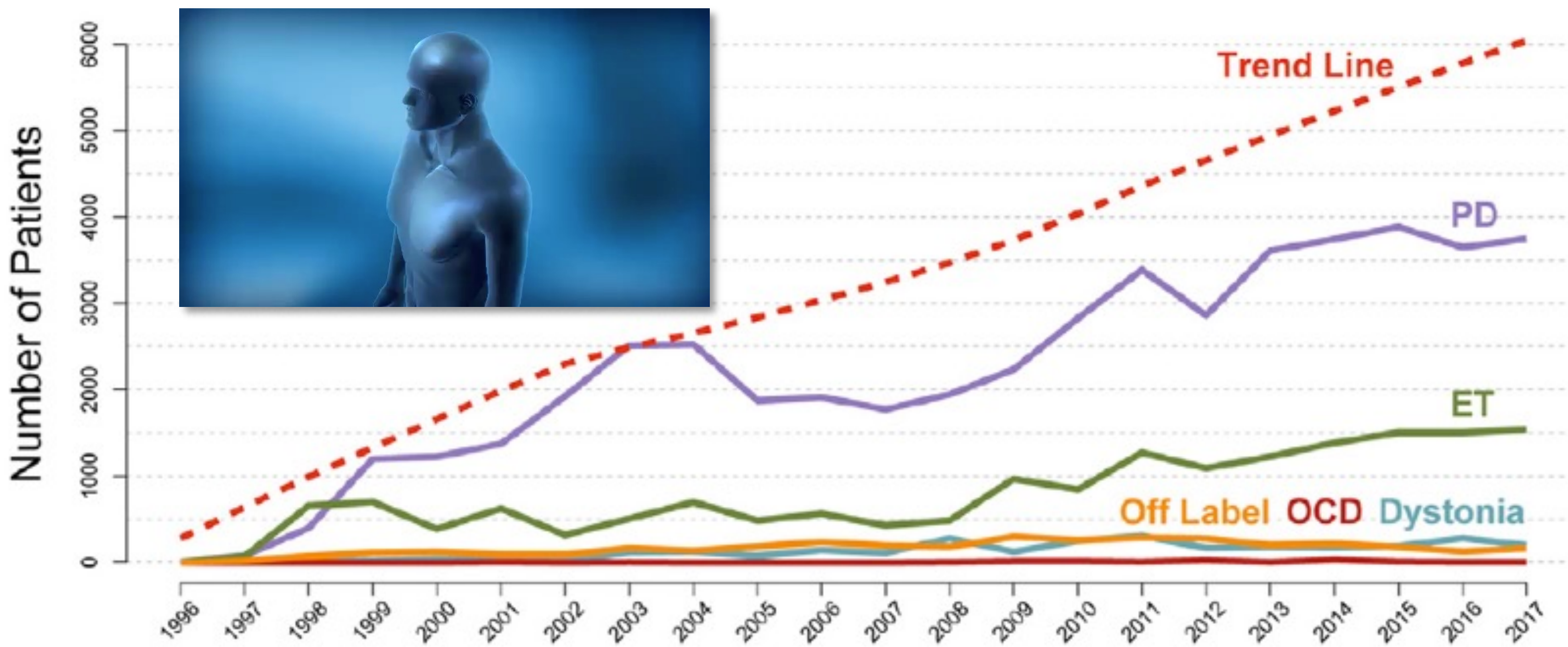
DBS use 1993-2017 (USA)

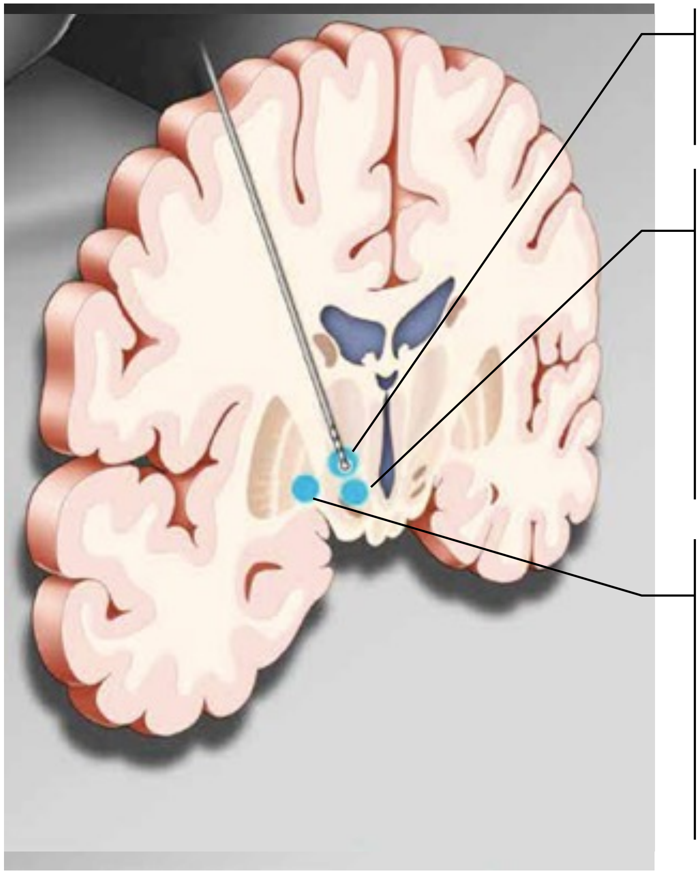


Sarica et al., 2023

Indications and distribution of DBS

- **Parkinson's Disease**
- **Essential Tremor**
- **Dystonia**
- Epilepsy*
- Obsessive Compulsive Disorder*

(Jan 2020)



Thalamus
- Essential Tremor
- Other tremors

Subthalamus
- PD tremor
- PD rigidity
- PD bradykinesia
- PD fluctuations
- Dyskinesias (in PD due to medication reduction)
- Dystonia?

Globus pallidus pars interna
- Dystonia
- PD tremor (*less than STN?*)
- PD rigidity
- PD bradykinesia (*less than STN?*)
- PD fluctuations
- Dyskinesias

Fasano, 2018

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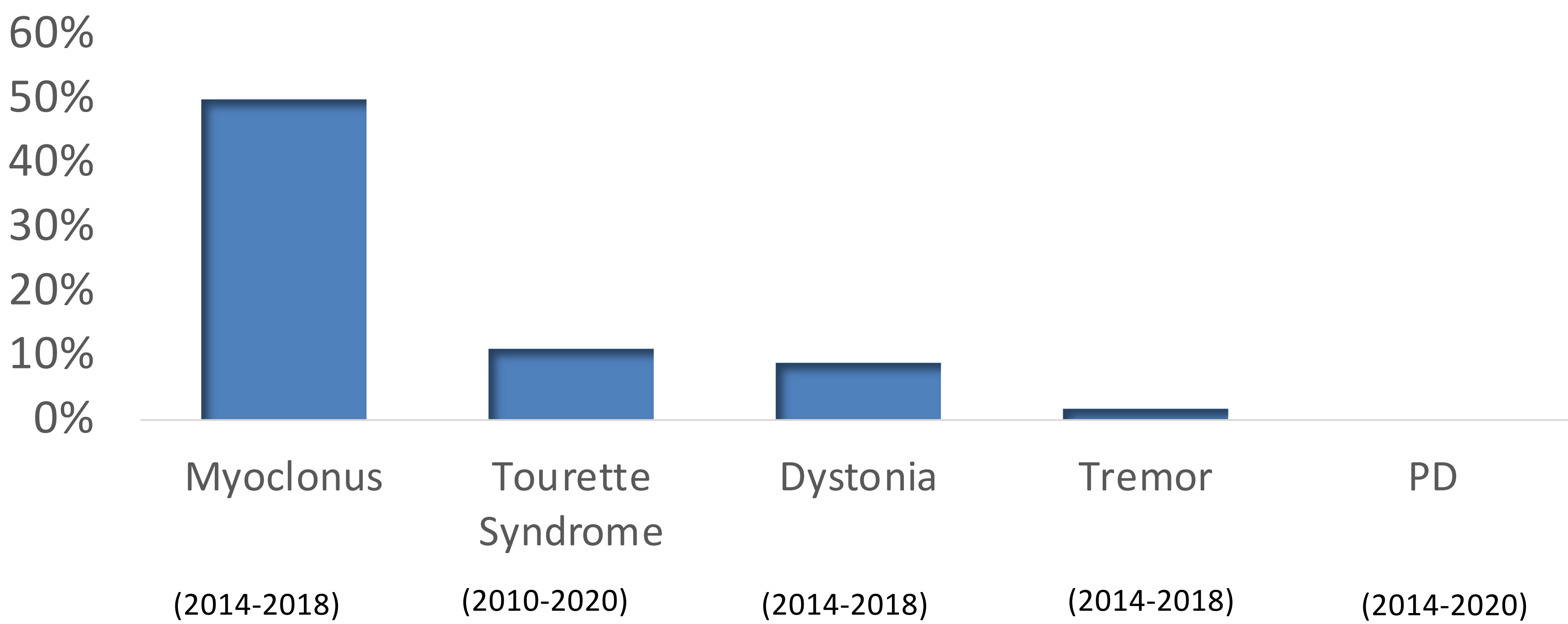
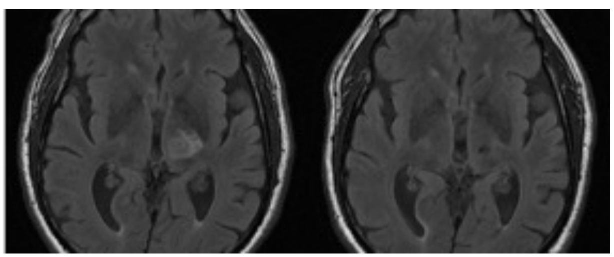
% of FND among DBS referrals at TWH



Gorodetsky et al, 2022

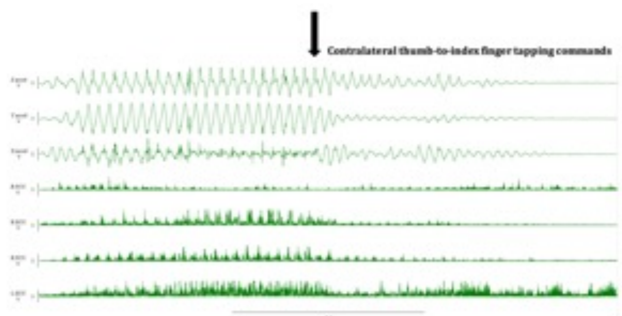
FND after MRgFUS thalamotomy

Before MRgFUS thalamotomy

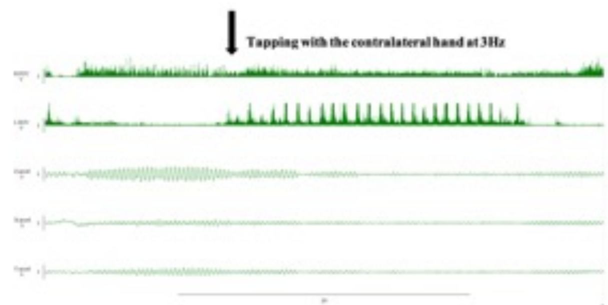


1 day and 6 months after MRgFUS

3 months after MRgFUS

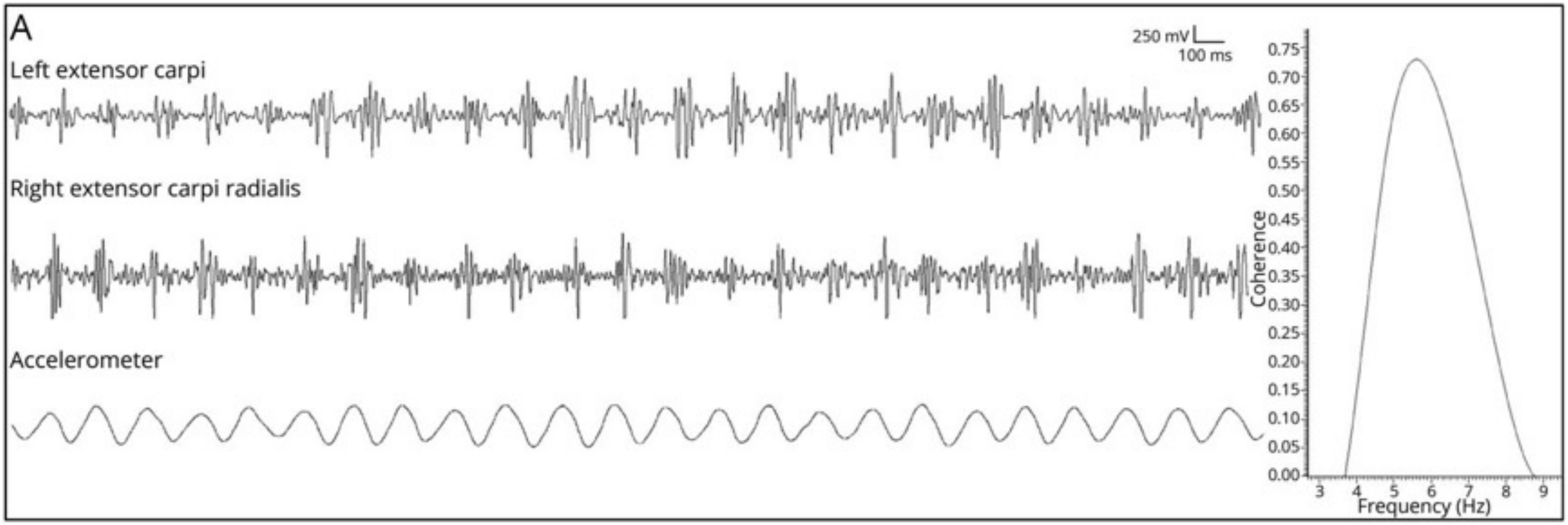


18 months after MRgFUS



AlShimemeri et al. 2022

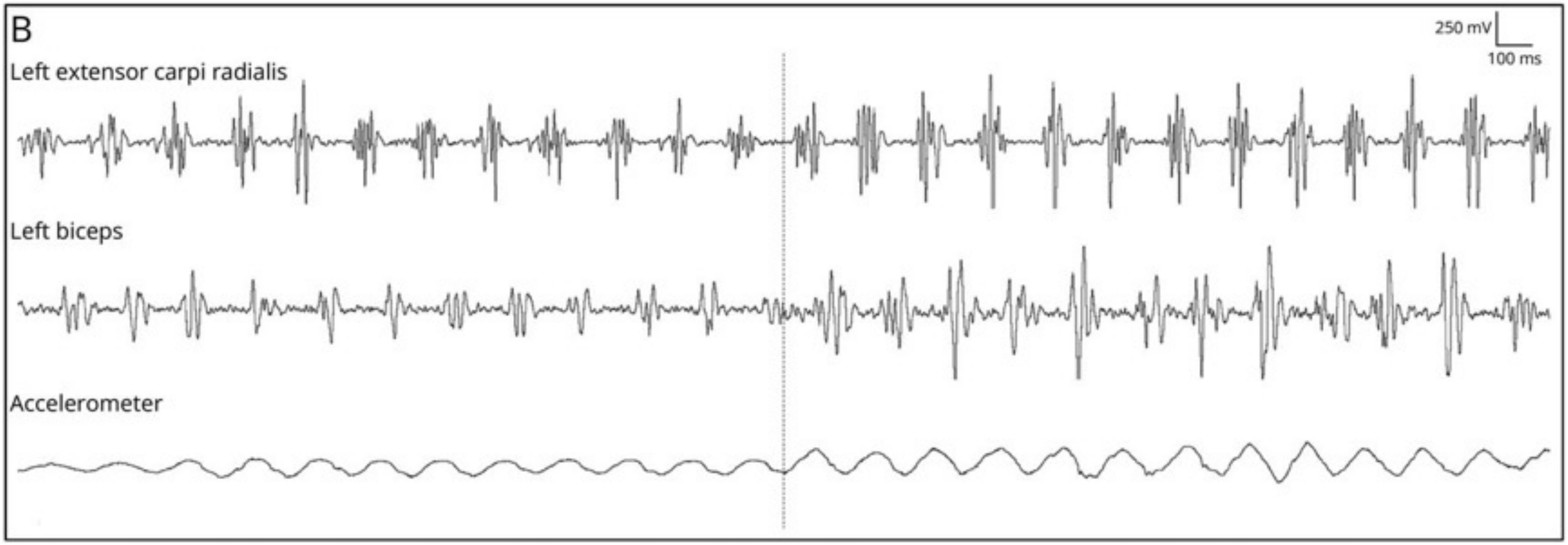
Multichannel surface EMG and accelerometer in a tremor DBS candidate



Coherence analysis exhibiting a high coherence value to 0.75/1 between the extensor muscles (graphic representation on the right side)

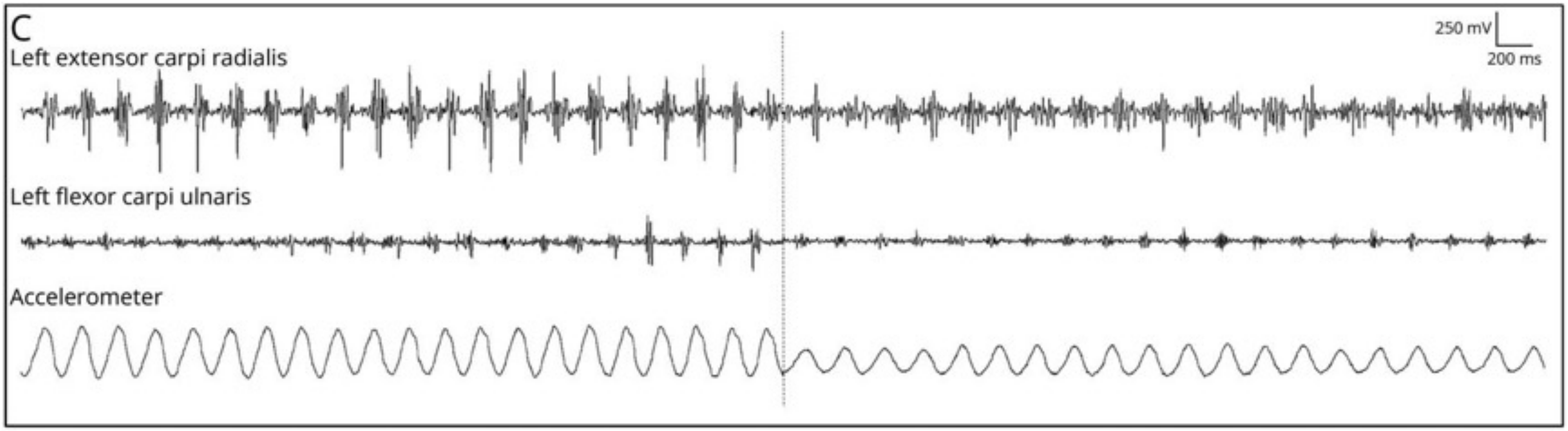
Boogers & Fasano, 2024

Multichannel surface EMG and accelerometer in a tremor DBS candidate



Significant increase in amplitude (right of the dotted line) compared with baseline (left of the dotted line) upon weight-bearing on the left wrist

Multichannel surface EMG and accelerometer in a tremor DBS candidate



Significant reduction in amplitude (right of the dotted line) compared with the baseline (left of the dotted line) during cognitive task of serial 7 subtraction

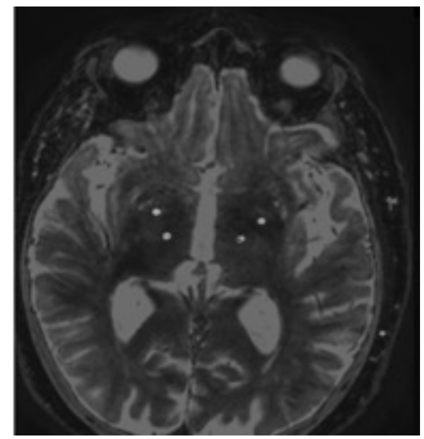
Quantitative Separation of Tremor and Ataxia in Essential Tremor

Agostina Casamento-Moran, PhD,[1] Basma Yacoubi, PhD,[1] Bradley J. Wilkes, PhD,[1]
Christopher W. Hess, MD,[2] Kelly D. Foote, MD,[2] Michael S. Okun, MD,[2]
Aparna Wagle Shukla, MD,[2] David E. Vaillancourt, PhD,[1,2] and Evangelos A. Christou, PhD[1]

Objective: This study addresses an important problem in neurology, distinguishing tremor and ataxia using quantitative methods. Specifically, we aimed to quantitatively separate dysmetria, a cardinal sign of ataxia, from tremor in essential tremor (ET).
Methods: In Experiment 1, we compared 19 participants diagnosed with ET undergoing thalamic deep brain stimulation (DBS; ET_{DBS}) to 19 healthy controls (HC). We quantified tremor during postural tasks using accelerometry and dysmetria with fast, reverse-at-target goal-directed movements. To ensure that endpoint accuracy was unaffected by tremor, we quantified dysmetria in selected trials manifesting a smooth trajectory to the endpoint. Finally, we manipulated tremor amplitude by switching DBS ON and OFF to examine its effect on dysmetria. In Experiment 2, we compared 10 ET participants with 10 HC to determine whether we could identify and distinguish dysmetria from tremor in non-DBS ET.
Results: Three findings suggest that we can quantify dysmetria independently of tremor in ET. First, ET_{DBS} and ET exhibited greater dysmetria than HC and dysmetria did not correlate with tremor ($R^2 < 0.01$). Second, even for trials with tremor-free trajectories to the target, ET exhibited greater dysmetria than HC ($p < 0.01$). Third, activating DBS reduced tremor ($p < 0.01$) but had no effect on dysmetria ($p > 0.2$).
Interpretation: We demonstrate that dysmetria can be quantified independently of tremor using fast, reverse-at-target goal-directed movements. These results have important implications for the understanding of ET and other cerebellar and tremor disorders. Future research should examine the neurophysiological mechanisms underlying each symptom and characterize their independent contribution to disability.

ANN NEUROL 2020;88:375–387

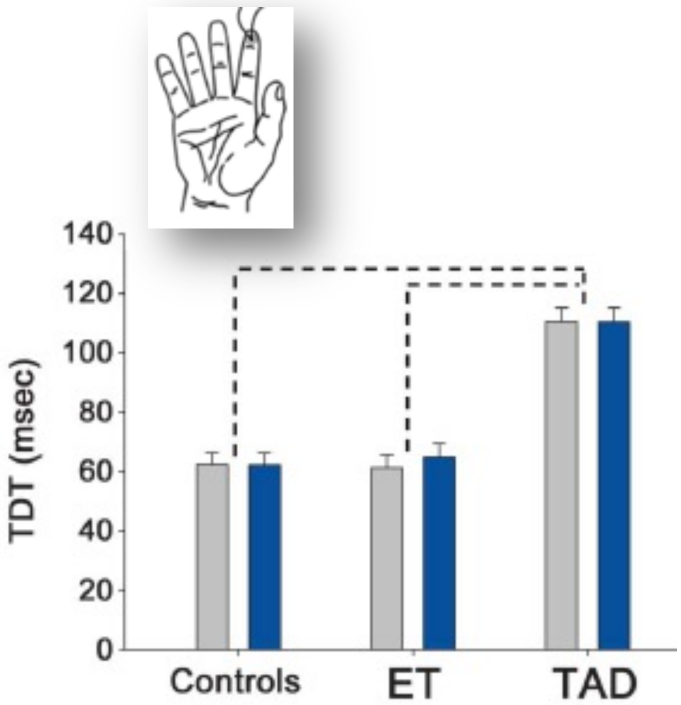
Dystonia as complication of thalamic neurosurgery



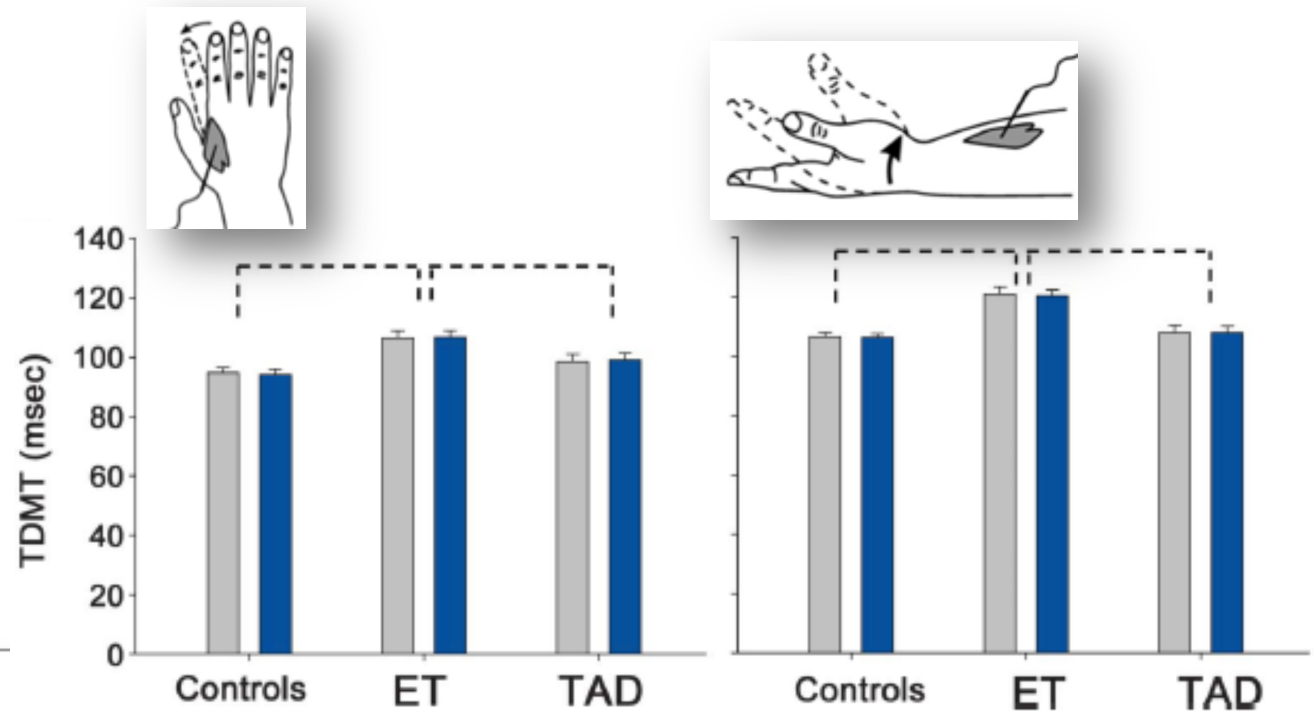
ET – before Vim DBS (ET plus?) Dystonia – after Vim DBS +Gpi DBS

Picillo et al., 2019

Insights from temporal discrimination



Tactile



Movement

Tinazzi, Fasano et al., 2013
Tinazzi, Morgante et al.,2016

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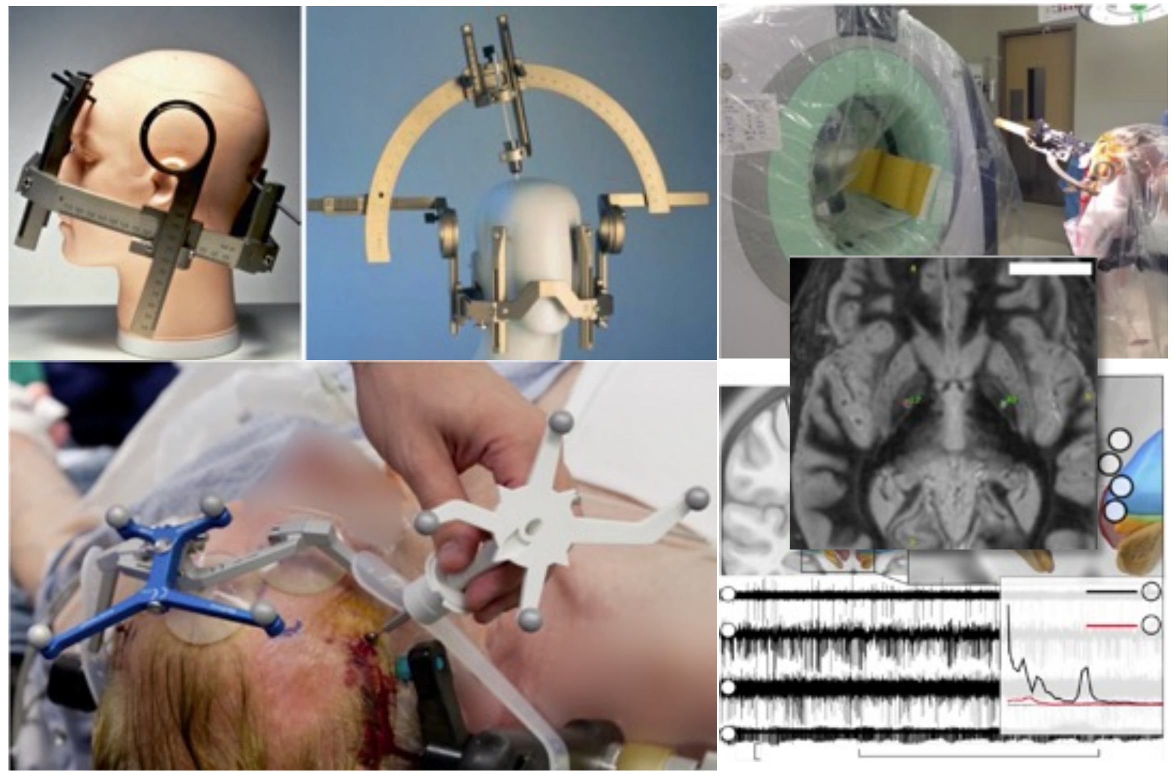
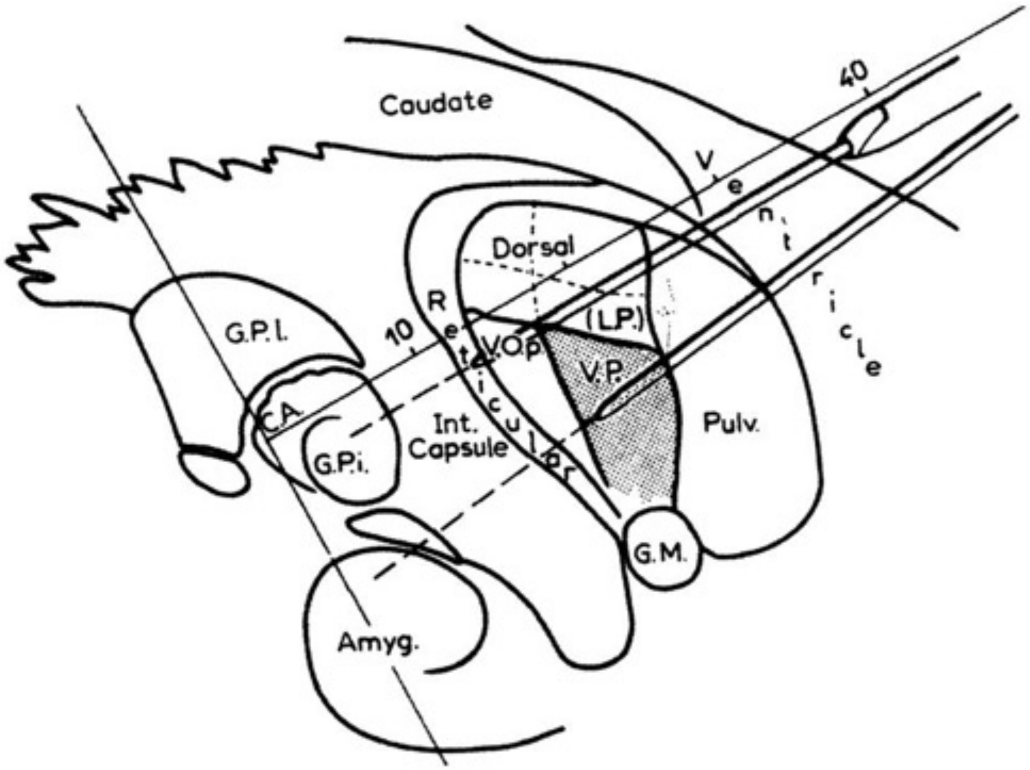
Surgical techniques

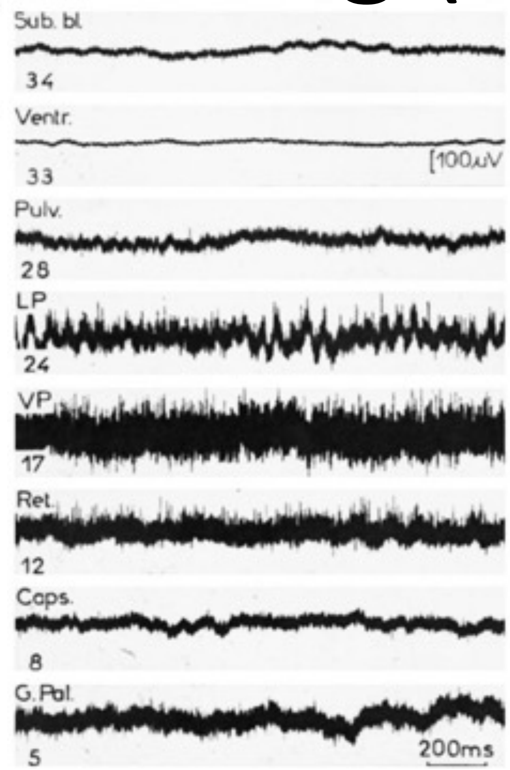
- Targeting
  - Indirect
  - Direct
    - Intra-OP MRI
- Anesthetic techniques
  - Local (awake) followed by GA
  - Asleep-Awake-Asleep
  - Asleep
- **Intra-OP recording, y/n**
- Intra-OP testing, y/n



Fundamentals and Clinics of DBS, 2020 ed. Temel, Leentjens, de Bie, Chabardes, Fasano
Schulder et al., 2023

Micro-electrode recording (MER)

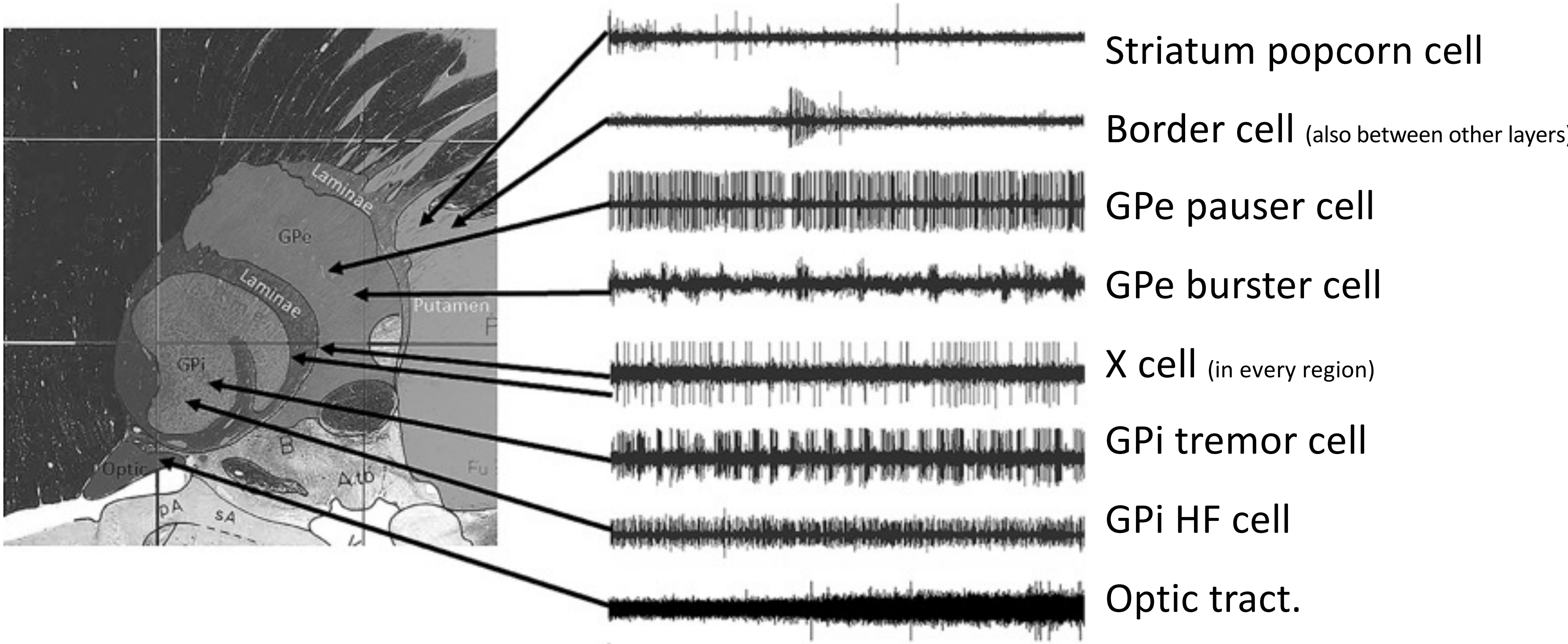




Electrophysiologically defined VIM

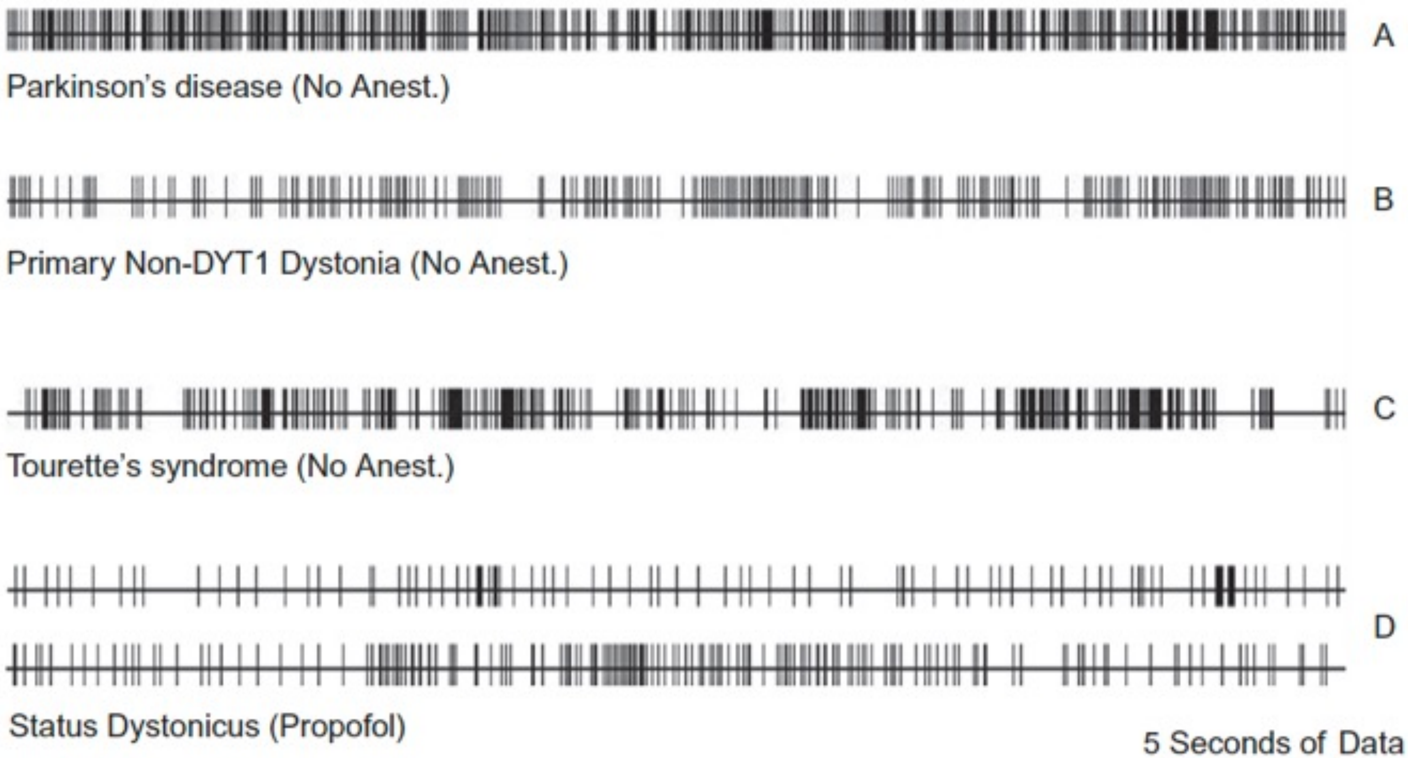
Albe-Fessard et al., 1966

Globus pallidum



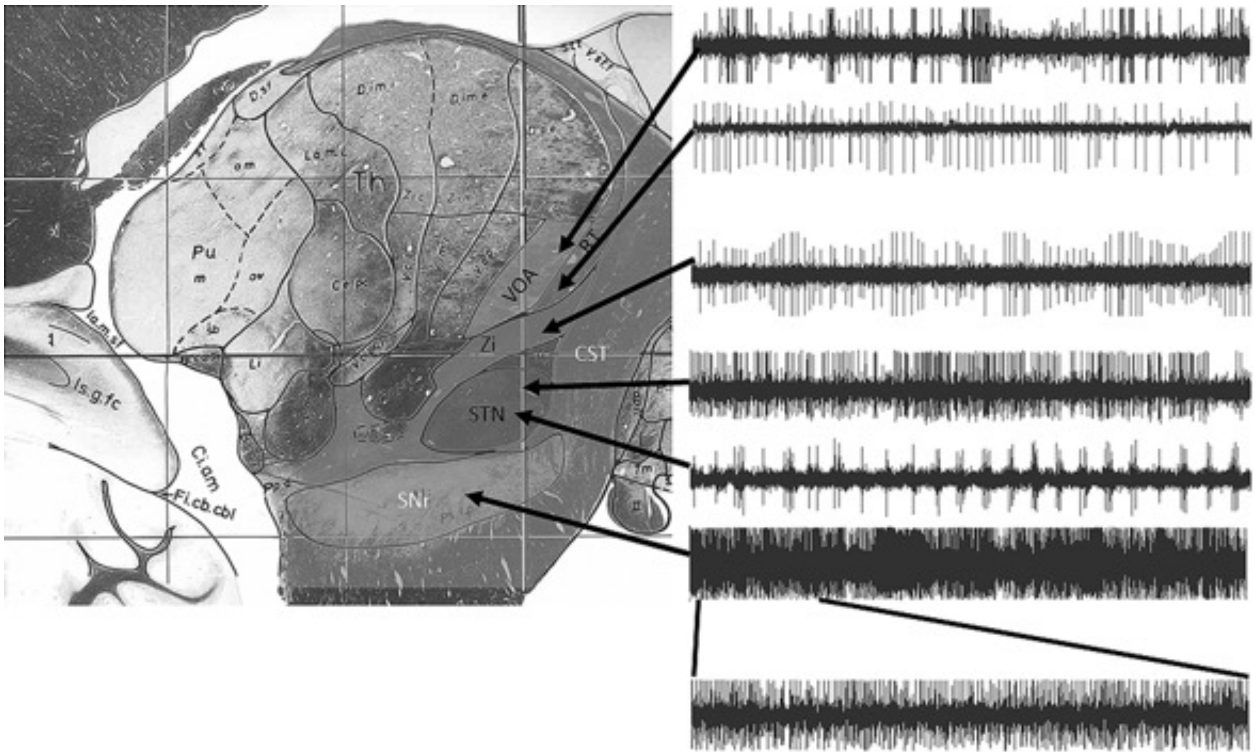
Mod from Tagliati et al., 2002

GPi recordings in different states



Shils et al., 2022

Subthalamus



Mod from Tagliati et al., 2002

Asleep MER

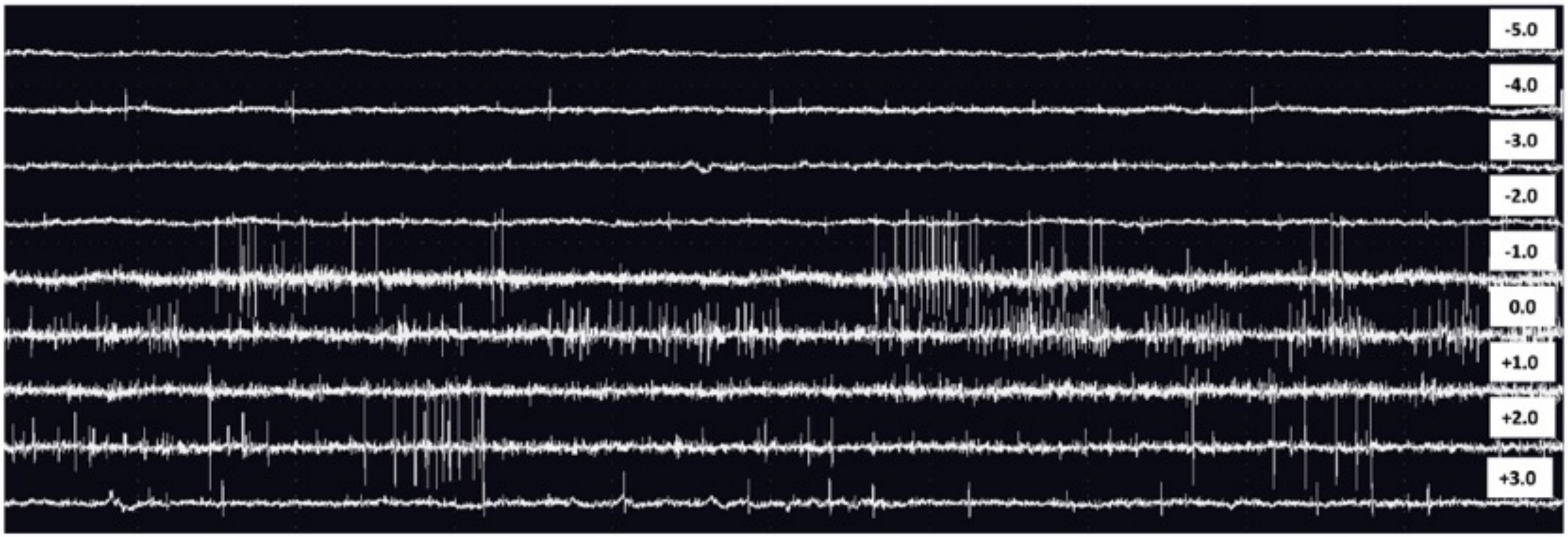
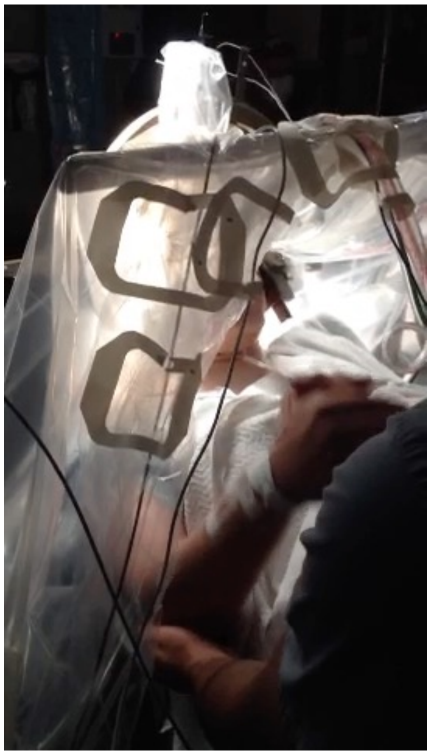


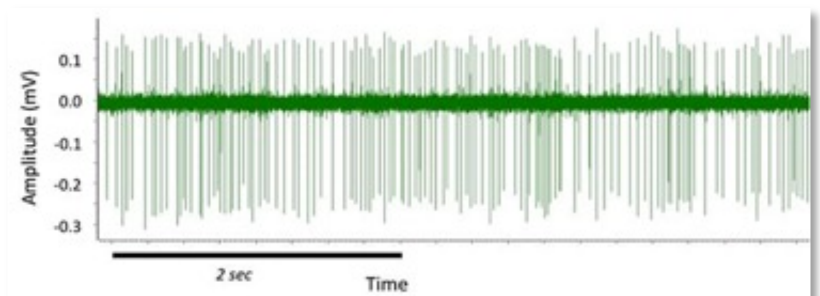
Fig. 1 MER showing the typical STN discharge pattern in 2 PD patients operated under general anesthesia. Implanted depth, 0 *(upper patient)*, +2 mm *(lower patient)*

Izzo et al 2024

Additional testing



- Detection of kinesthetic cells (tactile/proprioceptive stimuli)
  - Gpi: face,arm: ventrolateral; leg: central/dorsomedial
  - STN: not clear distinction
- Detection of other phenomena (e.g. OT firing increases after flashing a light)
- MEP correlates with distance from the IC
- SEP/VEP
- (Clinical assessment)

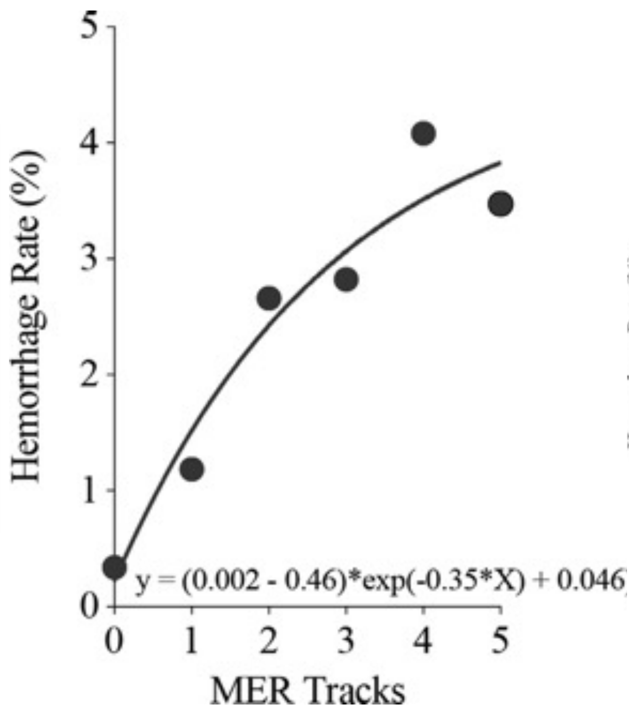


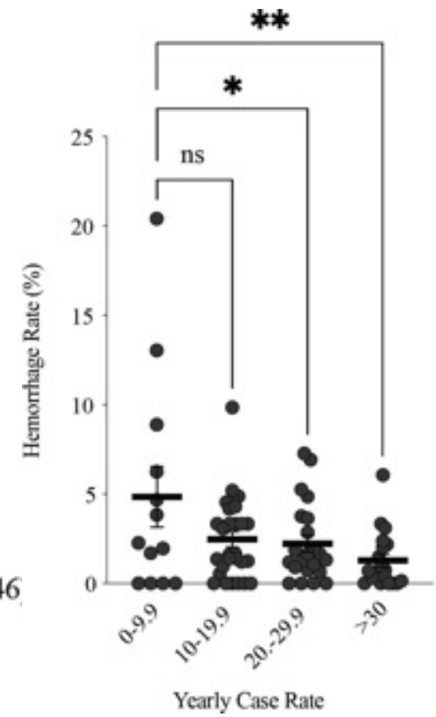
Taha et al., 1996; Vitek et al.,1998
Guridi et al., 1999; Trenado et al 2024

Is MER safe?

The role of n of traces and center volume

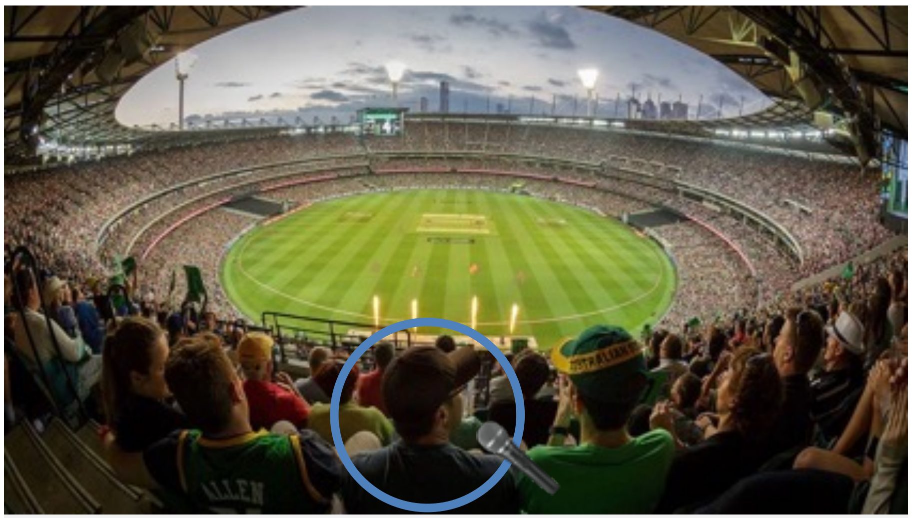
MER Tracks	Number of Studies	Total Patients	Patients with Hemorrhage	Hemorrhage Rate (%)	Odds Ratio	Corrected *P* Value
0 (No MER)	13	293	1	0.34	-	-
1	8	760	9	1.18	3.49	0.299
2	10	489	13	2.66	7.96	0.028
3	15	992	28	2.82	8.47	0.011
4	4	196	8	4.08	12.37	0.009
5	11	984	20	3.47	10.49	0.009





Rasiah et al., 2023

MER vs Local Field Potentials (LFPs)

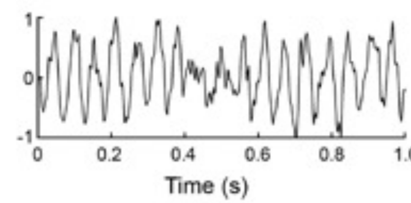


MER:

- Single or multi-unit recordings
- Provides detailed information about neuronal characteristics
- Does not provide a broad picture of how neuronal populations are communicating within a nucleus

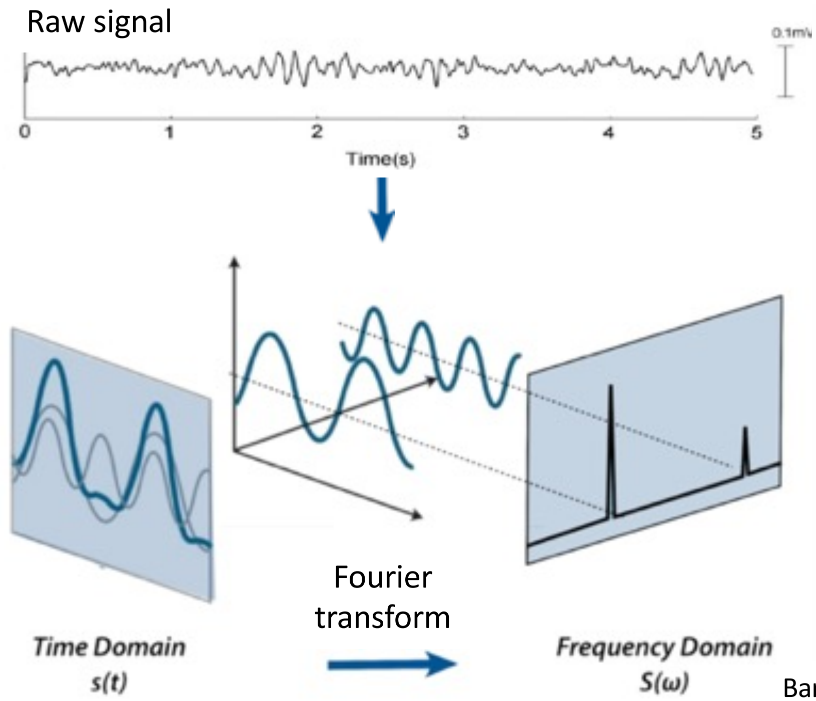
LFP recording:

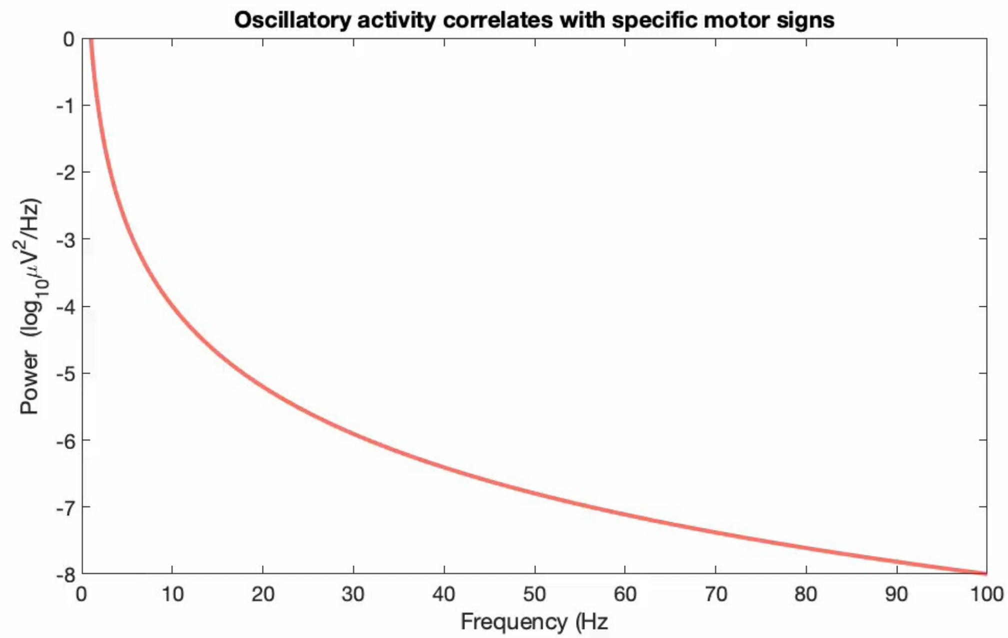
- Recordings from a much larger population of neurons
- Reveals the presence of neural rhythms or synchronised oscillatory activity



Mailing et al., 2018

Local Field Potentials





Band name: **delta theta alpha beta gamma**

Hz: (0-3) (4-7) (8-12)(13-30) (31-200)

Video by Simon Little, MD, PhD, UCSF

Medicine
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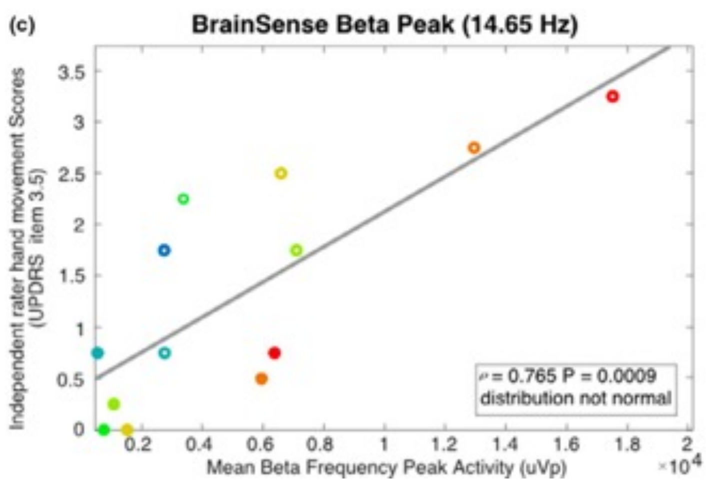
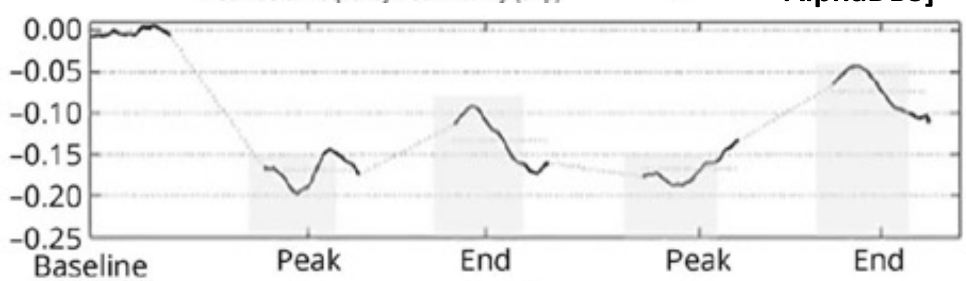
STN β-LFP: what do we know

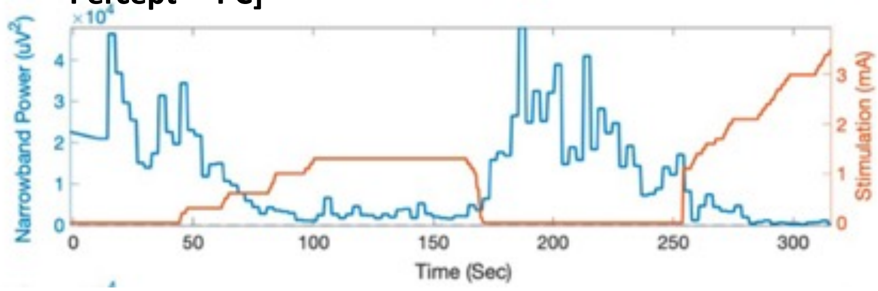


Correlates with contralateral PD severity (no tremor) **[Medtronic Percept^{TM} PC]**

Reduces with L-dopa **[Newronika AlphaDBS]**



Reduces with stimulation amplitude **[Medtronic Percept^{TM} PC]**



LFP power centered at 19.53 Hz integrated across a 5 Hz band and averaged in 3-s intervals

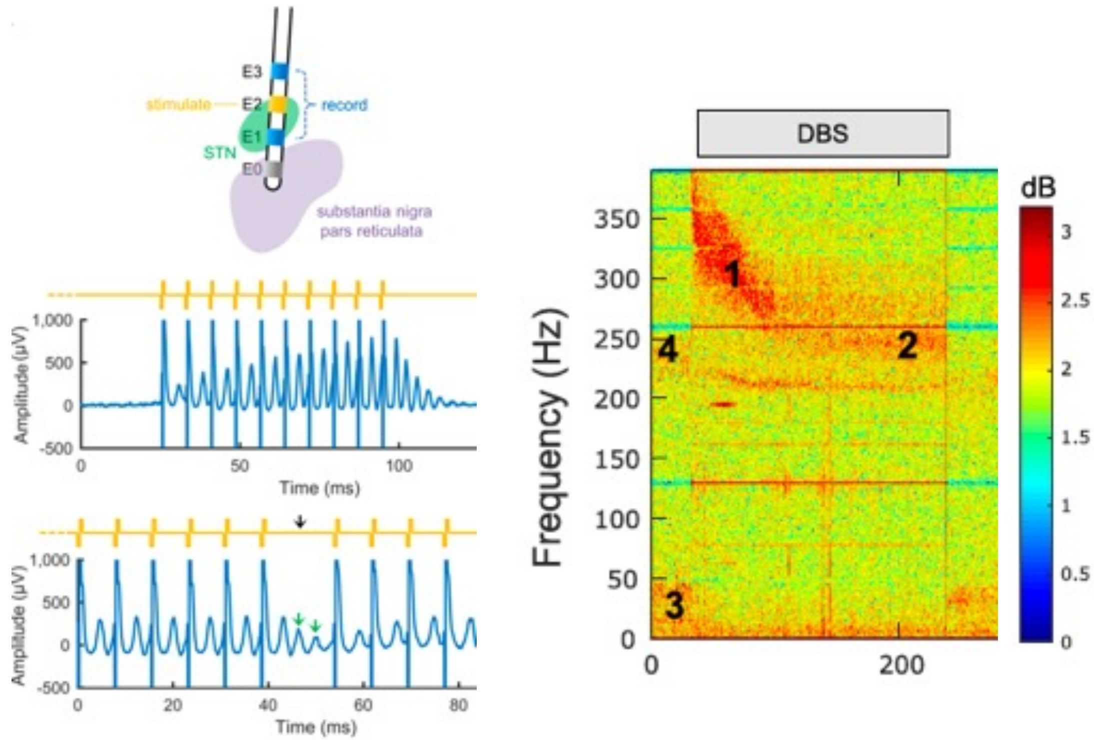
Reduces with DBS **[Medtronic externalized lead]**

Signal may not be present or measurable in all patients.
Clinical benefits of brain sensing have not been established.

Blumenfeld et al., 2017
Arlotti et al., 2018
Cummins et al, 2021
Feldmann et al., 2021

Evoked resonant neural activity (ERNA)

- Evoked potential characterized by high-frequency (200–500 Hz), begins ~4 ms after the DBS pulse for at least 10 ms
- In STN and GPI, in PD, dystonia, MSA
  - Not in VIM in ET
  - Signal might arise from the reciprocal connection between STN and Gpe
- Candidate biomarker for lead placement and DBS programming
  - contacts with larger ERNA with better therapeutic effect
  - Preserved under GA
  - Modulated by sleep stages



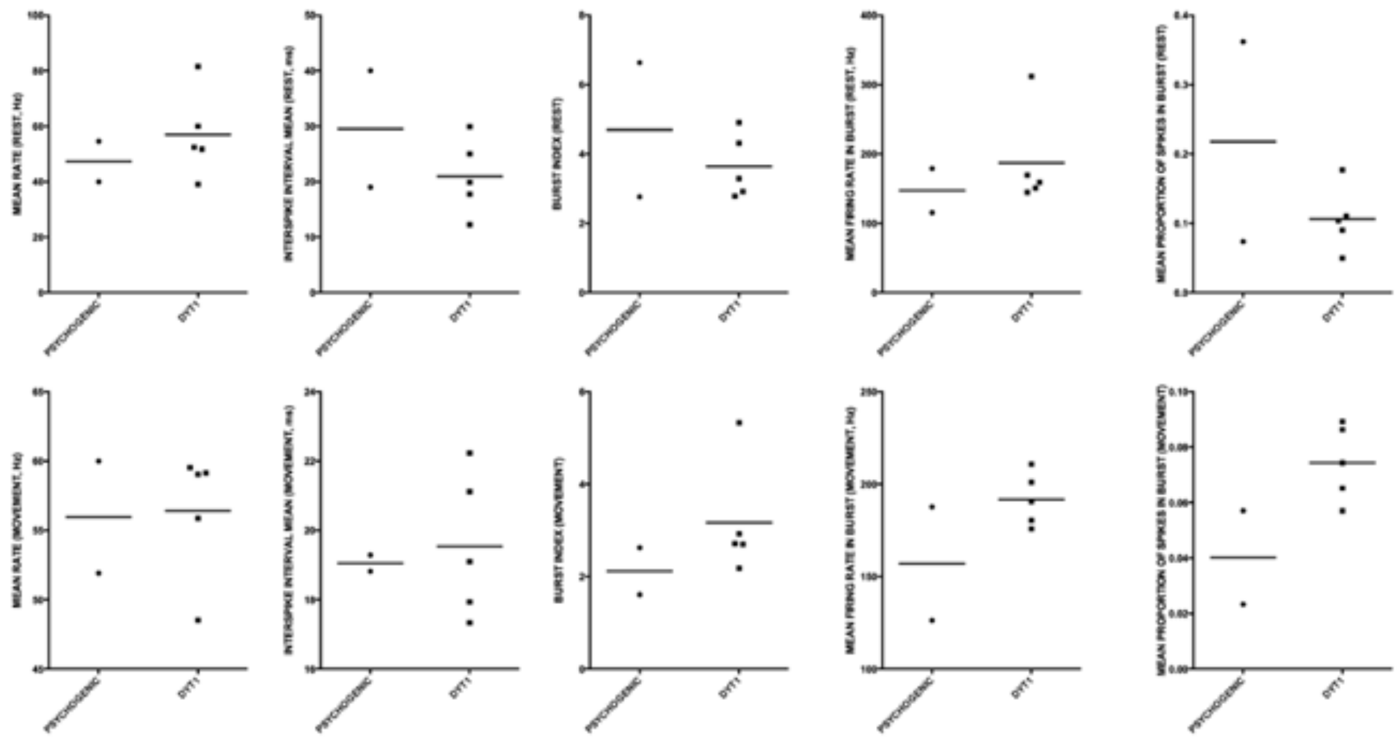
Sinclair et al, 2019; Wiest et al, 2020, 2022
Xu et al 2022; Johnson et al, 2023

Thalamus in n=1 functional dystonia

- Firing rates and thalamic reorganization
  - functional = ’organic’ dystonia
- Signal-to-noise ratio in Vop
  - ’organic’ dystonia > functional > pain patients
- Cells responding to movements in Vim
  - functional > ‘organic’ dystonia
- Thalamic neuronal activity ‘*may drive movement for both, whether it is a consequence of dystonic movements or a risk factor for the development of these movements*’

Kobayashi et al., 2011

GPi in functional dystonia versus DYT-1



Ramos et al., 2015

Nothing new…

Cortical and Spinal Abnormalities in Psychogenic Dystonia

Alberto J. Espay, MD,[1–3] Francesca Morgante, MD,[1,2] Jamie Purzner, HBSc,[1,2] Carolyn A. Gunraj, MHSc,[1,2] Anthony E. Lang, MD, FRCPC,[1,2] and Robert Chen, MBBChir, MSc, FRCPC[1,2]

Objective: The pathophysiology of psychogenic dystonia has not been examined, but a growing body of literature suggests that abnormal sensory input from repetitive movements can lead to plastic cortical changes. Reduced cortical and spinal inhibition is well documented in organic dystonia. We tested the hypothesis that aberrant sensory input associated with abnormal posture may cause similar abnormalities by testing patients with psychogenic dystonia.
Methods: We assessed cortical and spinal inhibitory circuits and cortical activity associated with voluntary movement in 10 patients with clinically definite psychogenic dystonia, 8 patients with organic dystonia, and 12 age-matched healthy control subjects.
Results: Three measures of cortical inhibition, resting short- and long-interval intracortical inhibition and cortical silent period, were reduced in both psychogenic dystonia and organic dystonia. Cutaneous silent period mediated by spinal circuitries was increased in psychogenic and organic dystonia. Forearm spinal reciprocal inhibition was reduced in psychogenic dystonia.
Interpretation: Psychogenic and organic dystonia share similar physiological abnormalities. Previous findings of abnormal cortical and spinal excitability in organic dystonia may, in part, be a consequence rather than a cause of dystonia. Alternatively, these findings may represent endophenotypic abnormalities that predispose to both types of dystonia.

Ann Neurol 2006;59:825–834

Test	Organic Dystonia	Psychogenic Dystonia
SICI-rest[a]	↓	↓
SICI-active	↓	↓
ICF-rest	↔	↔
ICF-active	↔	↔
LICI-rest[b]	↓	↓
LICI-active	↔	↔
SP	↓	↓
CuSP	↑	↑
RI-1[c]	↓	↓
RI-2[c]	↔	↓
RI-3	↔	↔
BP[d]	↑	↔

- BP: Bereitschaftspotential (amplitude of the premovement cortical potential)
- RI-(1-3): inhibitory phases (1-3) of the reciprocal inhibition of the H reflex

Espay et al., 2006

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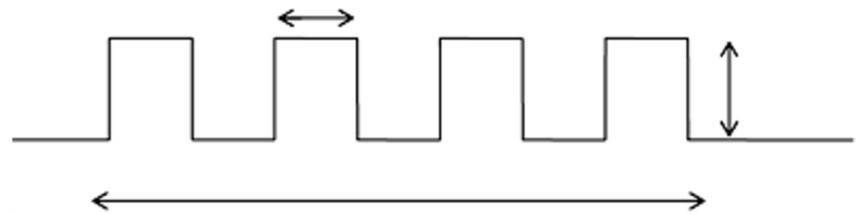
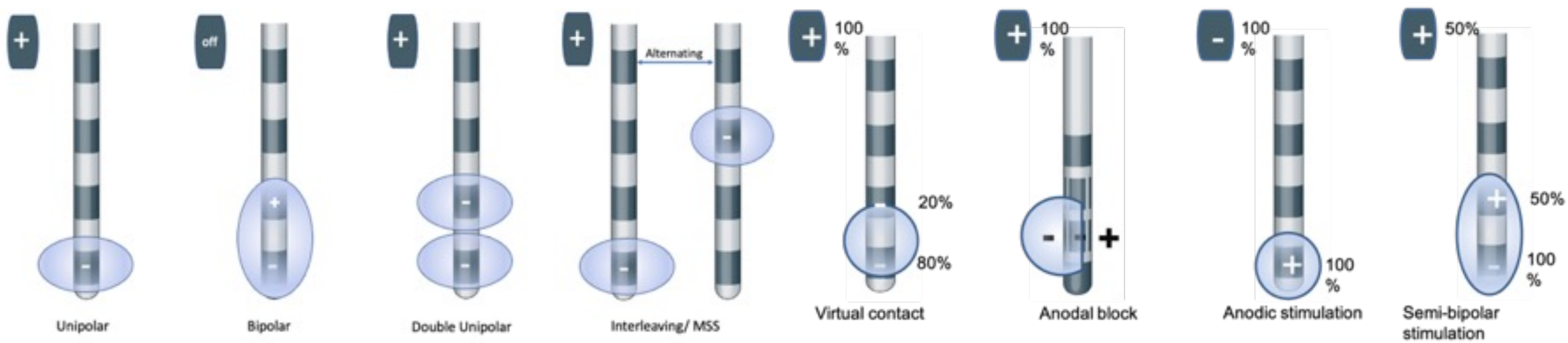
Stimulating parameters

- Amplitude (Volt) | Pulse width (mcsec) |Frequency (Hz)



- Configurations:



Paff et al, 2020
Gorodetsky & Fasano, 2021

DBS programming approaches

Current standard of care

- Pure clinical algorithms (e.g., monopolar review)
- Clinical algorithms informed by hierarchical contact selection imbedded in the DBS programming software

Based on biomarkers

- Kinematics (e.g., accelerometers)
- Metabolic brain changes measured with functional MRI
- LFP-based programming (including supervised closed-loop DBS)

Algorithm-driven online optimization

- Closed-loop based on kinematics (e.g., tremor)

Based on neuroimaging

- Qualitative VTA-based
- Quantitative algorithm-based

Implementing automation in deep brain stimulation: has the time come?

DBS=deep brain stimulation. LFP=local field potential. VTA=volume of tissue activated.

Bonizzato & Fasano, 2023

When and why

			LFP of interest, 5Hz window (Set-up)	*LFP agnostic, ~0-100Hz window*
Stim OFF (also ON for streaming)	During clinic visit		BrainSense™ Streaming	BrainSense™ Survey
		Purpose	Visualize patient LFP signal changes in real-time	A utility for identifying the existence of LFP signal on all contact pairs
		Clinical value	Observe real-time physiologic response during stimulation parameter adjustments	LFP and system integrity check
Stim ON (also with 0mA)	Between clinic visits		BrainSense™ Timeline	BrainSense™ Events
		Purpose	Display events and chronically-recorded LFP data in calendar format	Capture patient-triggered, customizable events stored on device
		Clinical value	Observe what your patient actually experiences outside of the clinic	Generate a Timeline diary of events with corresponding LFP data

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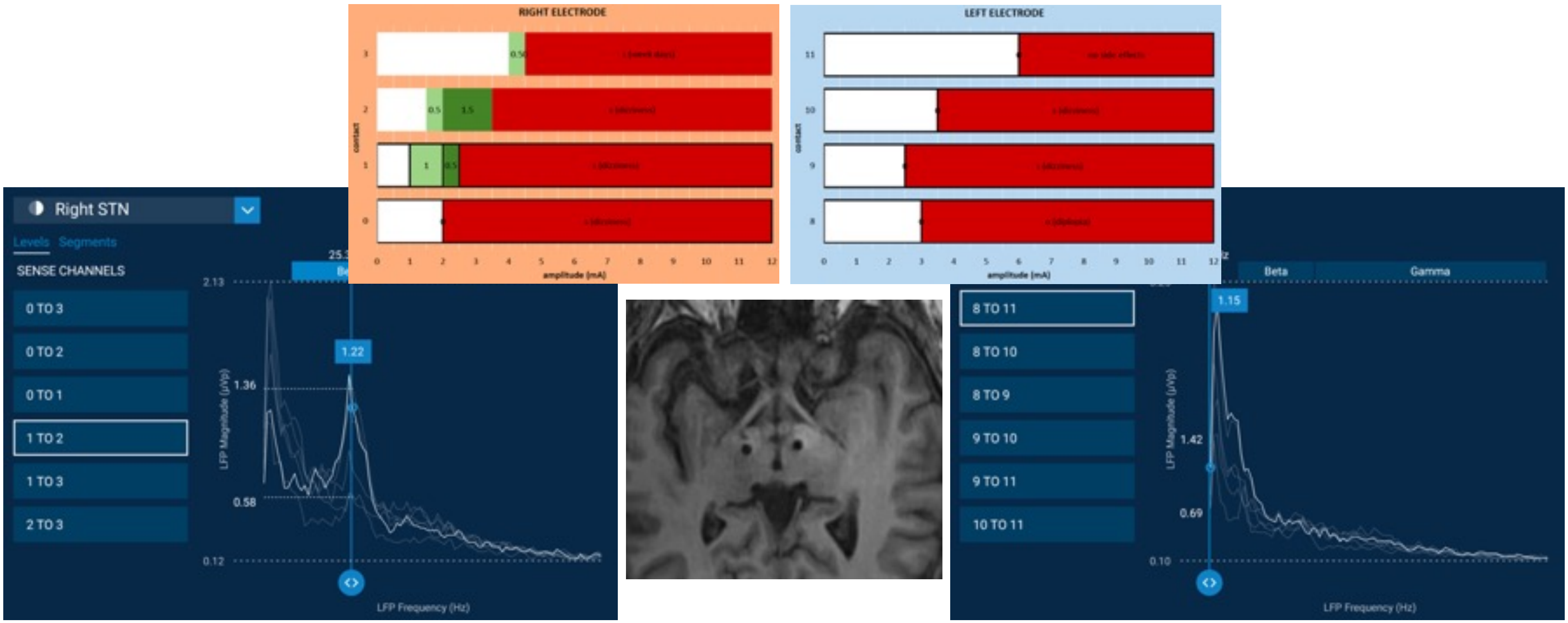
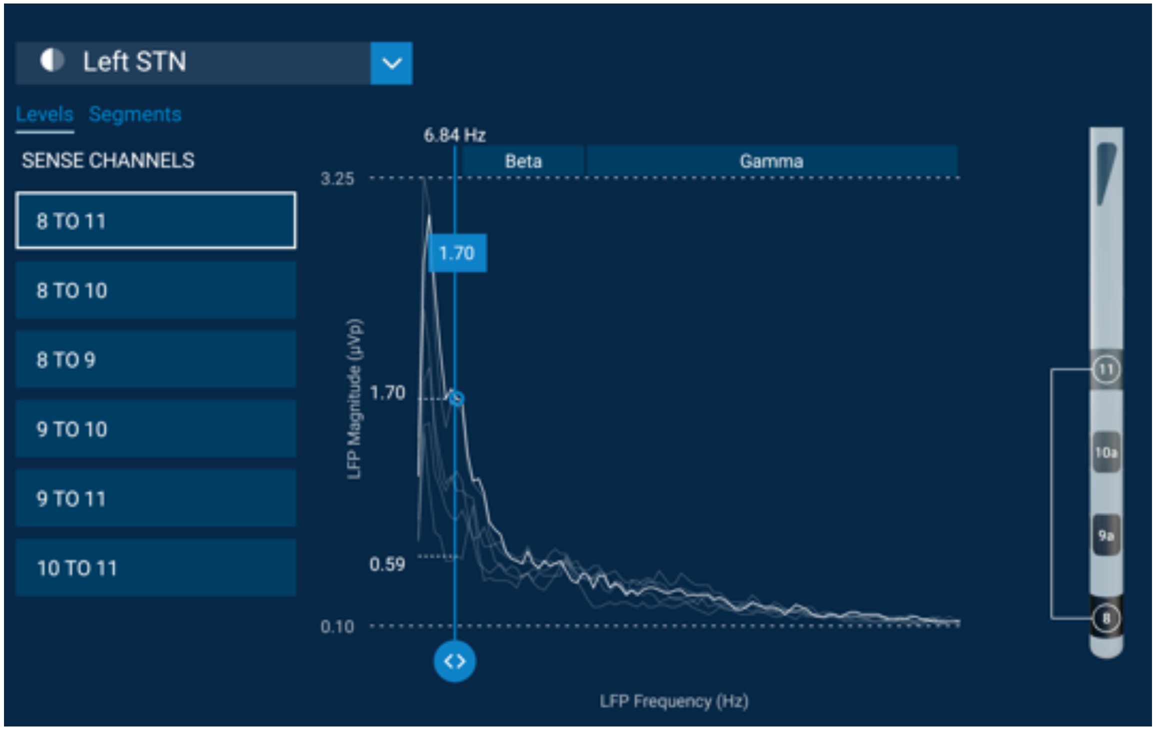
LFP and electrode’s placement

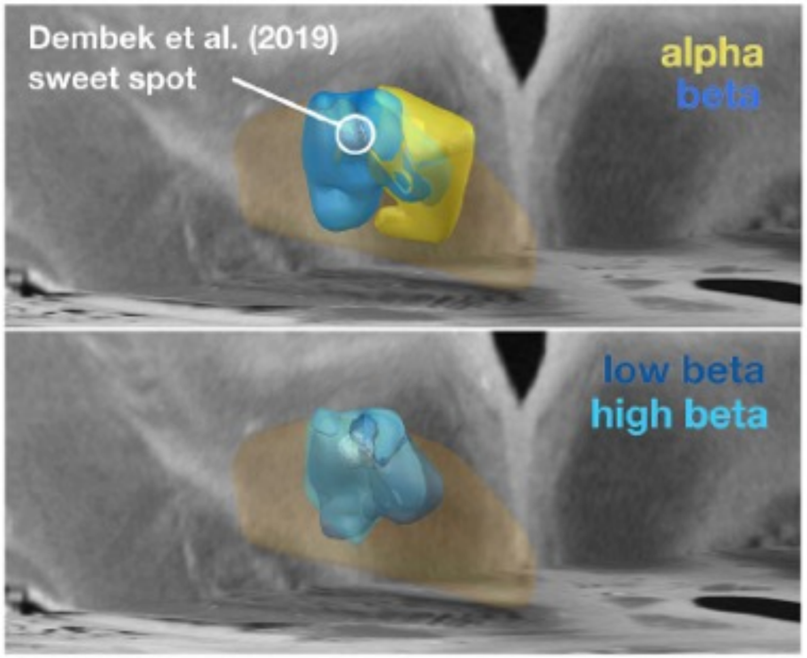


Courtesy of Dr. A. Boogers

Same patient, misplaced side



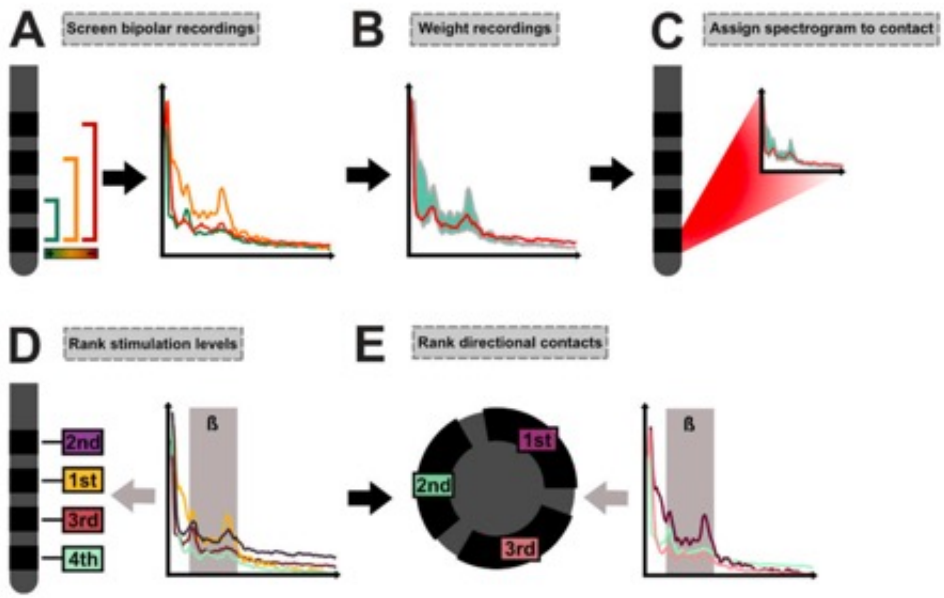
Volumetric map of max. peaks (hemispheres)



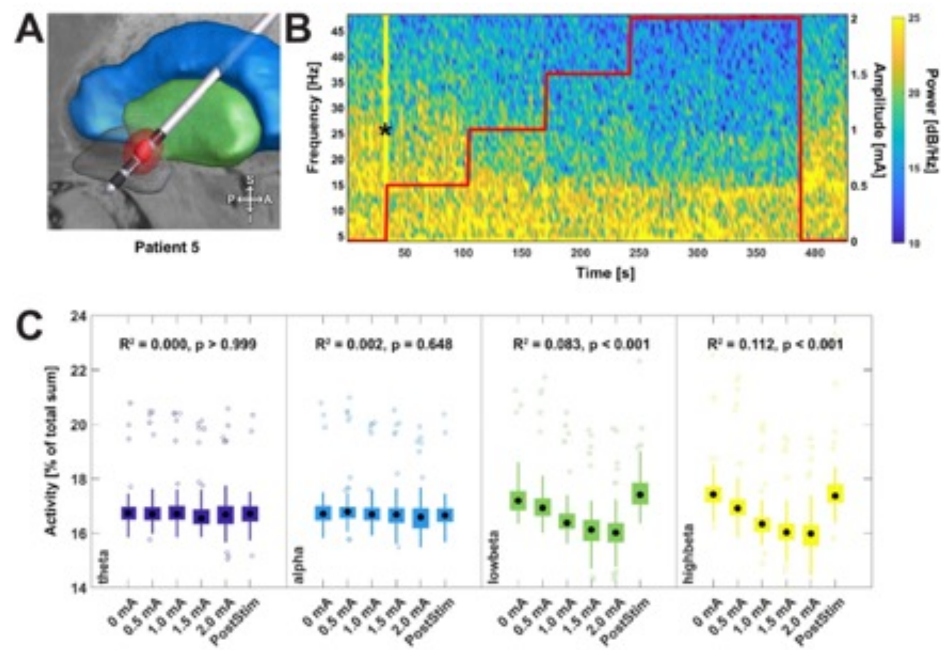
Darcy et al. 2022

LFPs to inform programming?

DETEC algorithm



Low-beta suppression



Strelow et al., 2022, 2023

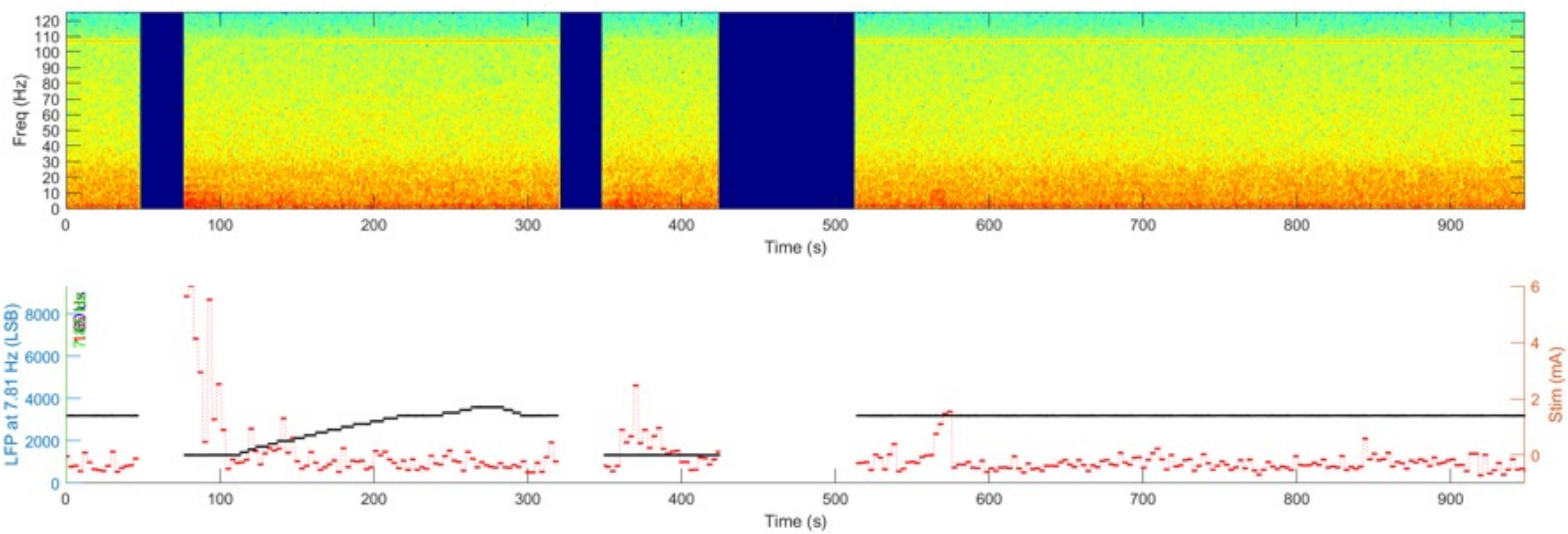
Brain sense: rest vs action tremor

Activating 2 contacts

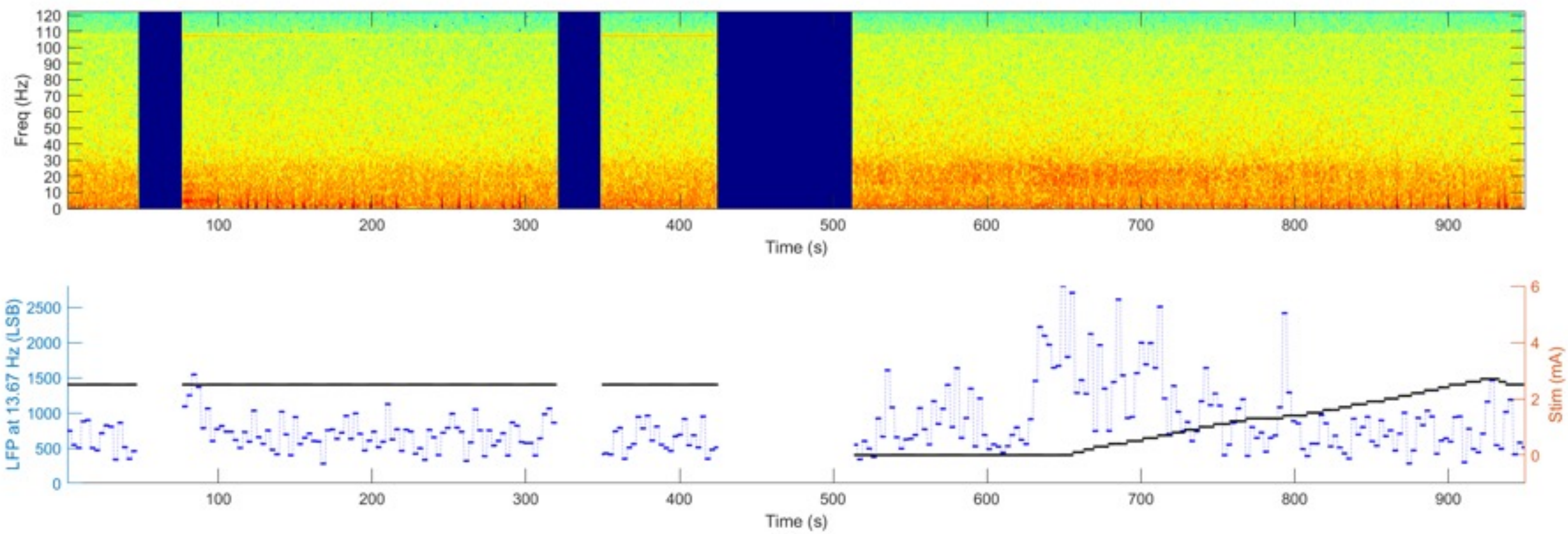
When and why

			LFP of interest, 5Hz window (Set-up)	*LFP agnostic, ~0-100Hz window*
Stim OFF (also ON for streaming)	During clinic visit		BrainSense™ Streaming	BrainSense™ Survey
		Purpose	Visualize patient LFP signal changes in real-time	A utility for identifying the existence of LFP signal on all contact pairs
		Clinical value	Observe real-time physiologic response during stimulation parameter adjustments	LFP and system integrity check
Stim ON (also with 0mA)	Between clinic visits		BrainSense™ Timeline	BrainSense™ Events
		Purpose	Display events and chronically-recorded LFP data in calendar format	Capture patient-triggered, customizable events stored on device
		Clinical value	Observe what your patient actually experiences outside of the clinic	Generate a Timeline diary of events with corresponding LFP data

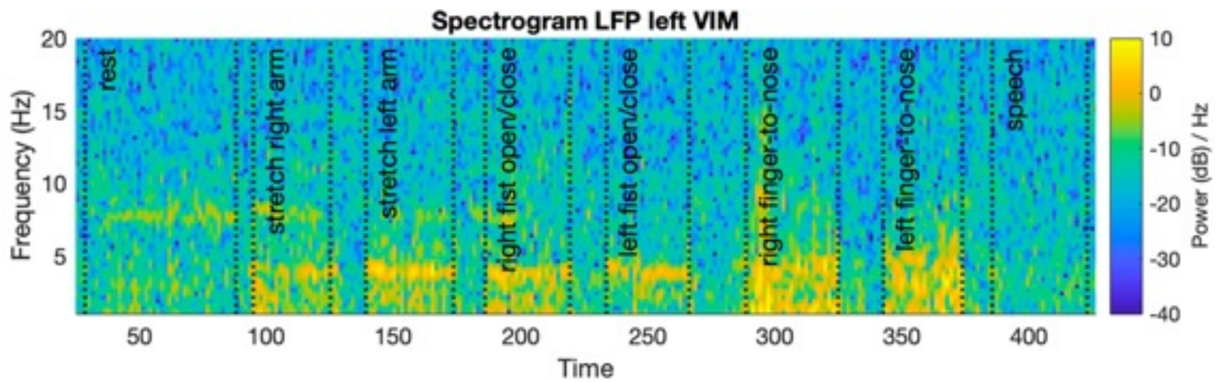
Right STN streaming @7.81 Hz

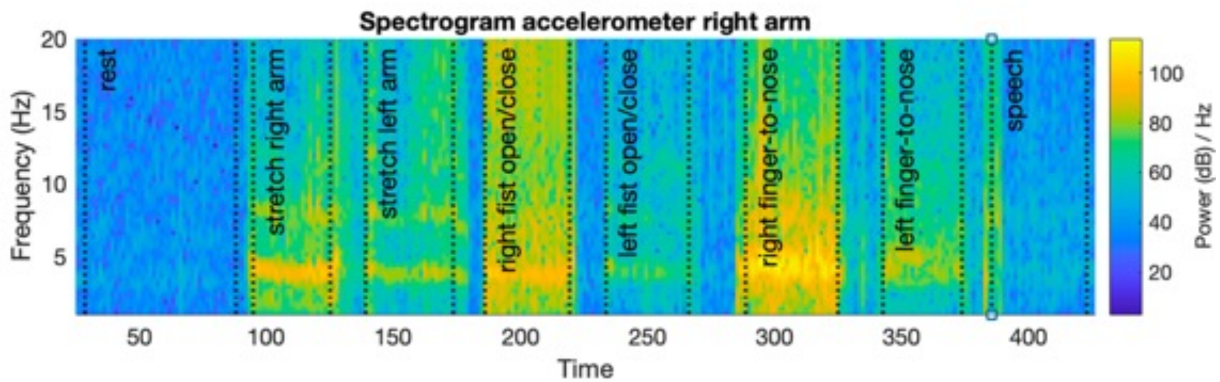


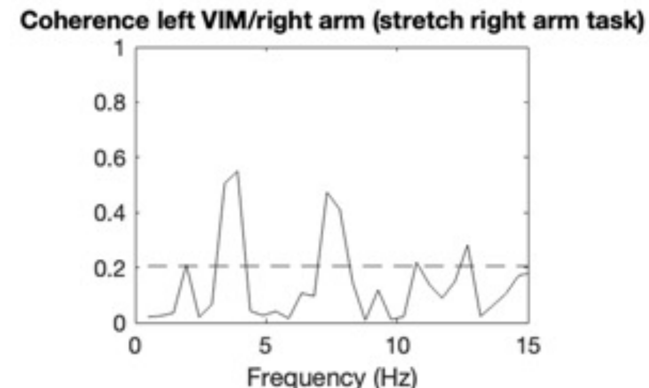
Left STN streaming @13.67 Hz

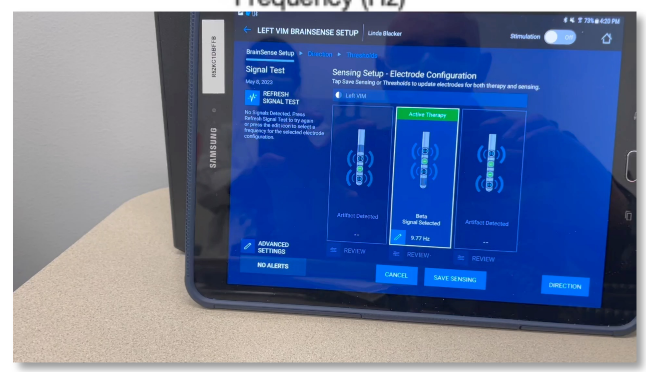


Not just beta: tremor recording in Vim









Buijink et al., 2022

Streaming during a seizure

When and why

			LFP of interest, 5Hz window (Set-up)	*LFP agnostic, ~0-100Hz window*
Stim OFF (also ON for streaming)	During clinic visit		BrainSense™ Streaming	BrainSense™ Survey
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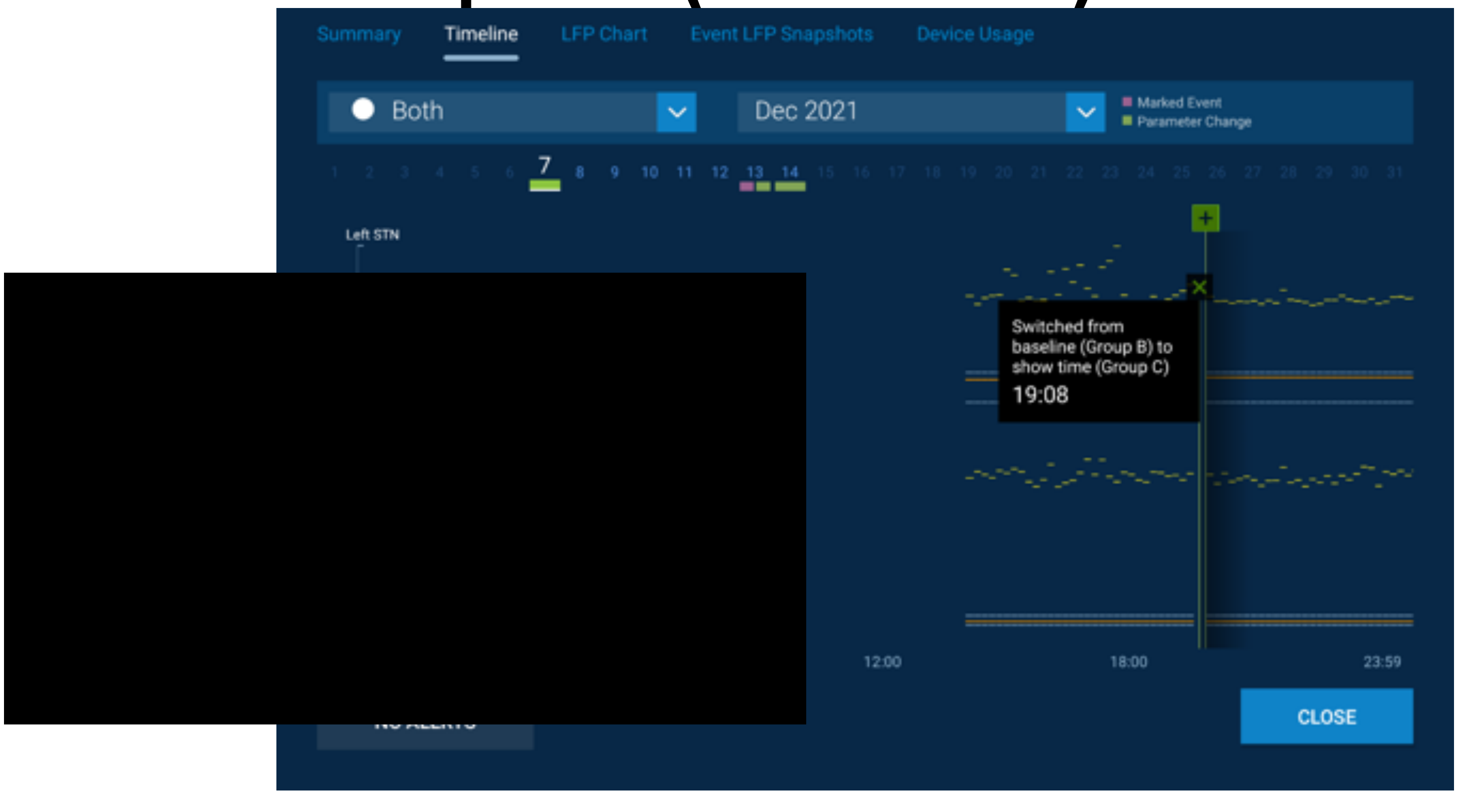
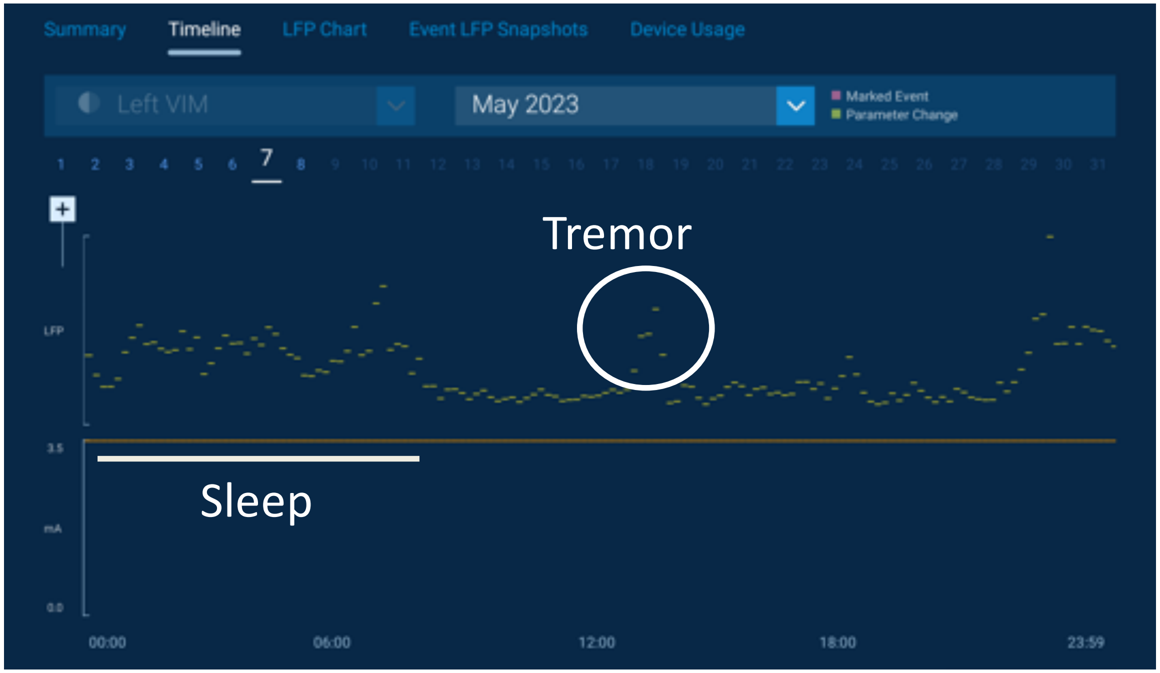
Beta after lesional effect is gone

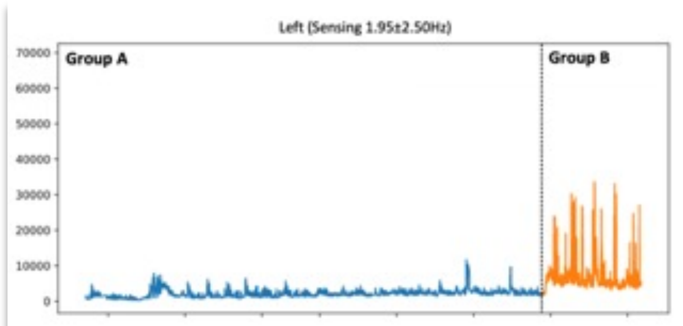
Alpha (tremor) in PD

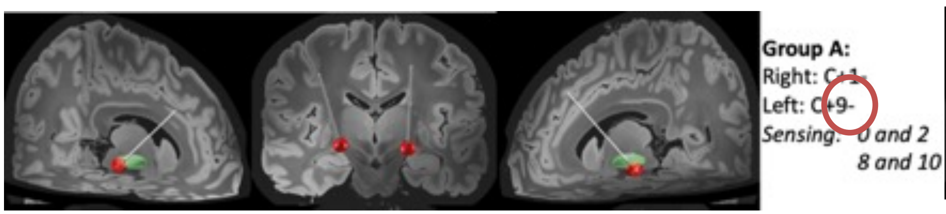


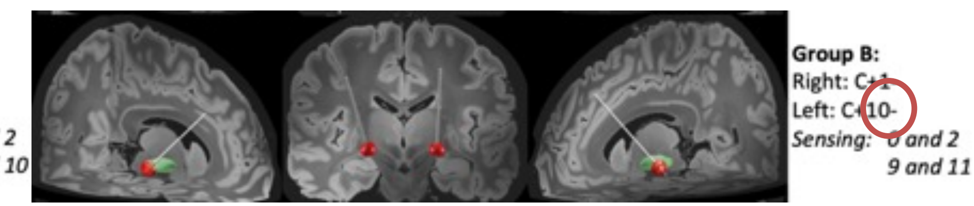
Timeline in ET (VIM)



LFP in status dystonicus

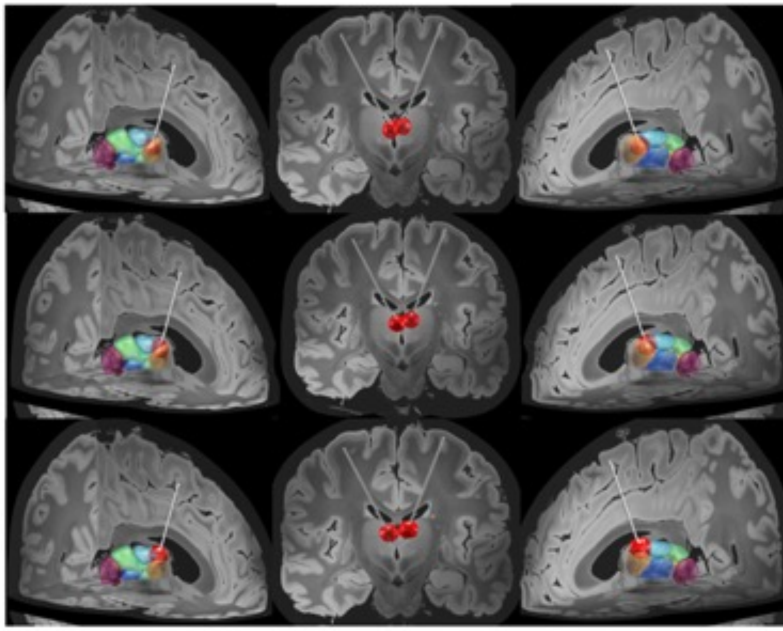


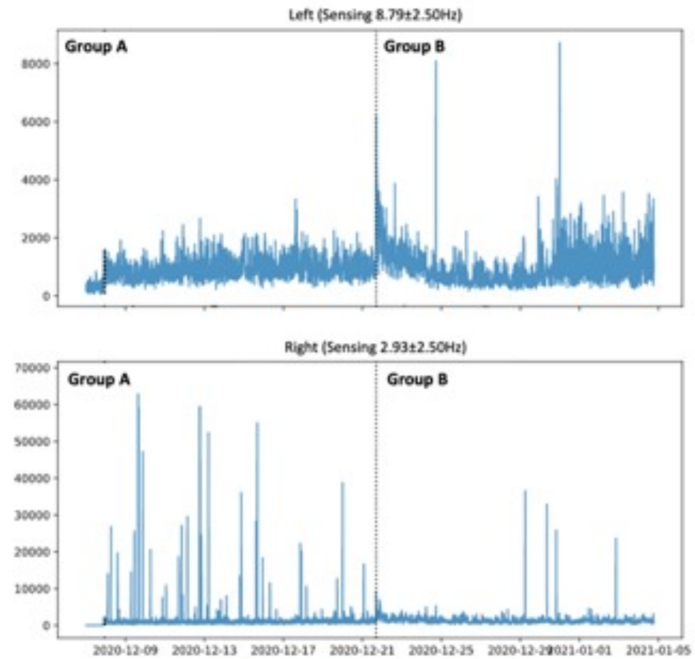




Fasano et al, 2021

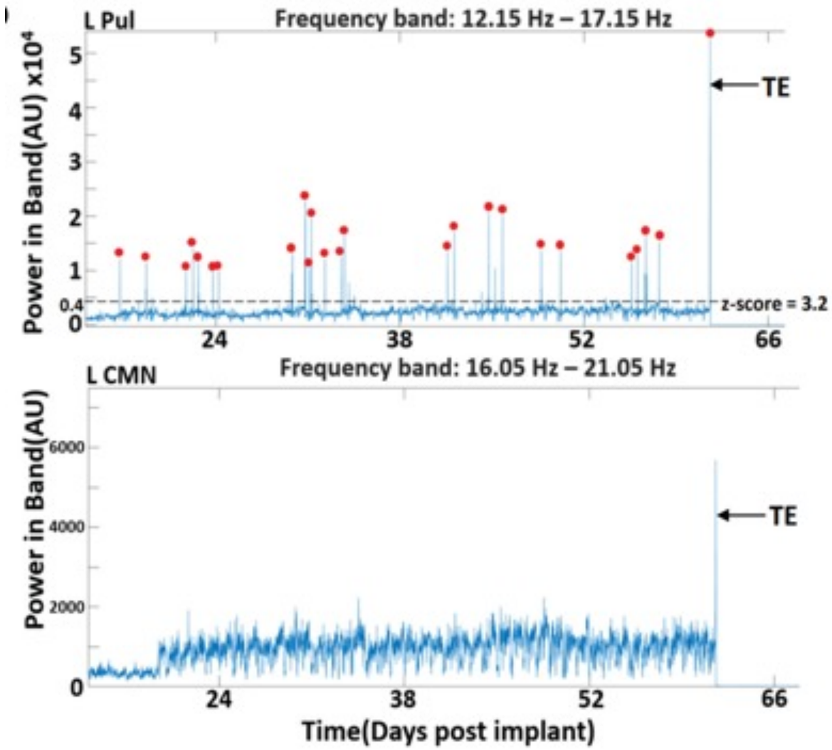
LFP-based programming (epilepsy)





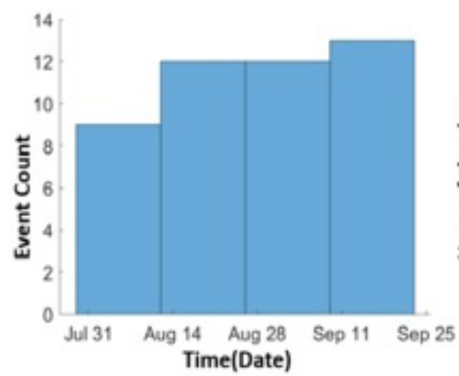
Fasano et al, 2021

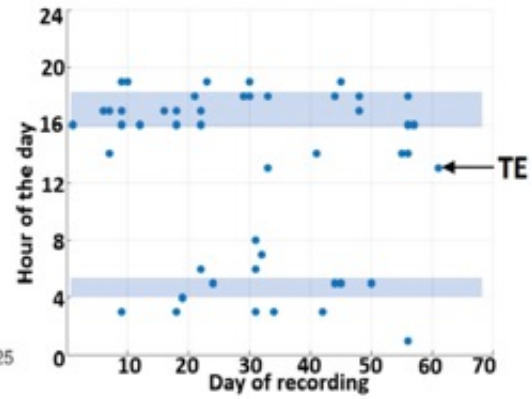
Timeline in SUDEP



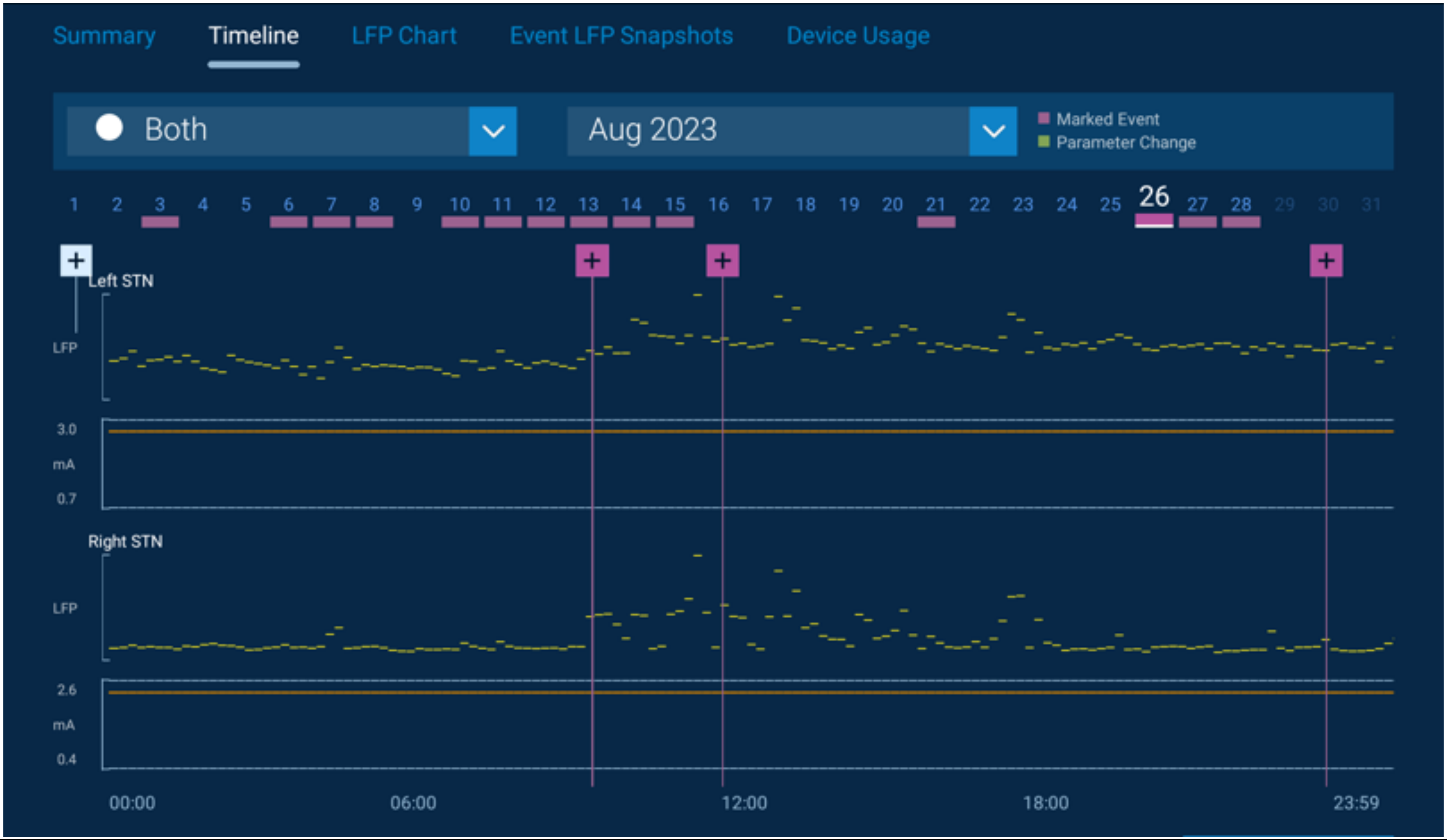
57-year-old man with intractable multifocal epilepsy secondary to cortical dysplasia and encephalomalacia resulting from severe traumatic brain injury

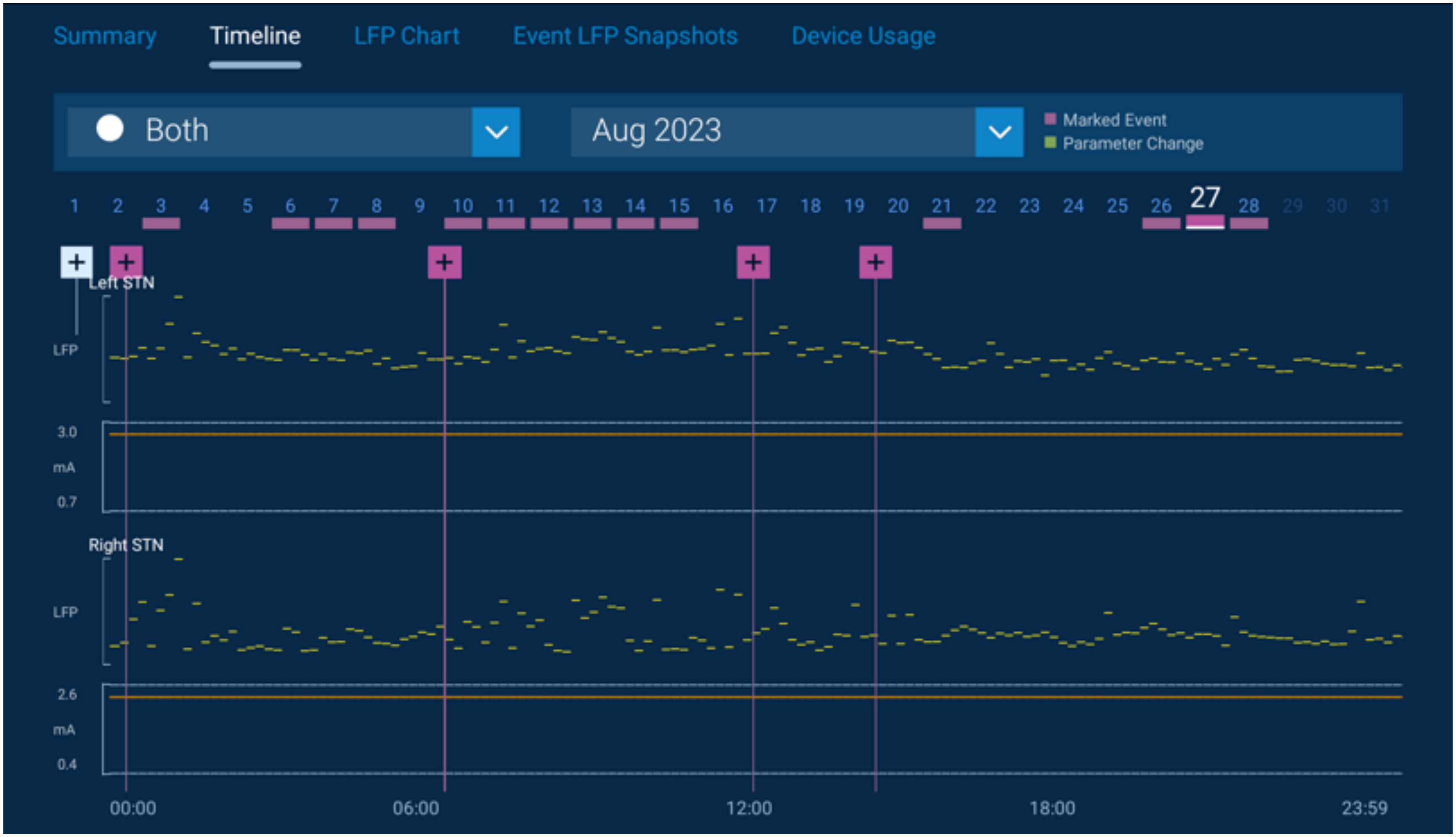
Left Pulvinar/Left CM DBS with Percept





Suresh et al., 2024


Summary
Timeline
LFP Chart
Event LFP Snapshots
Device Usage
Both
Aug 2023
Marked Event
Parameter Change
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31
Left STN
LFP
3.0
mA
0.7
Right STN
LFP
2.6
mA
0.4
00:00
06:00
12:00
18:00
23:59



Summary
Timeline
LFP Chart
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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31
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23:59

When and why

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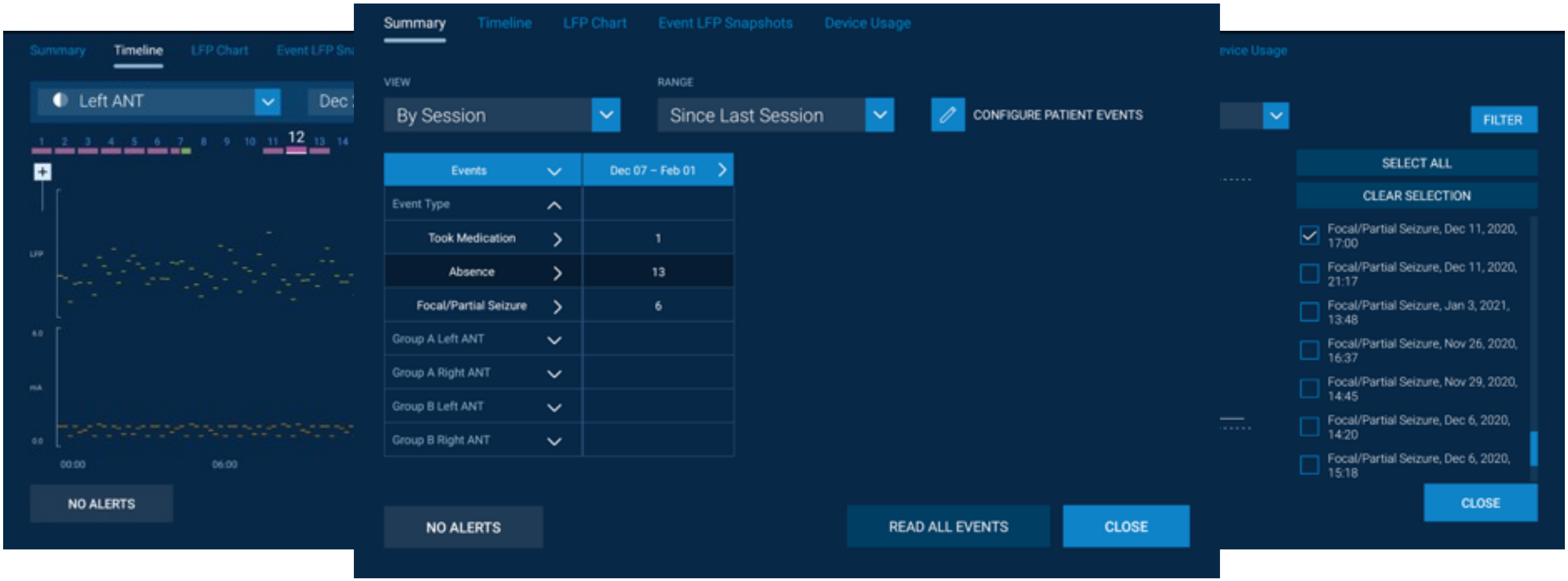
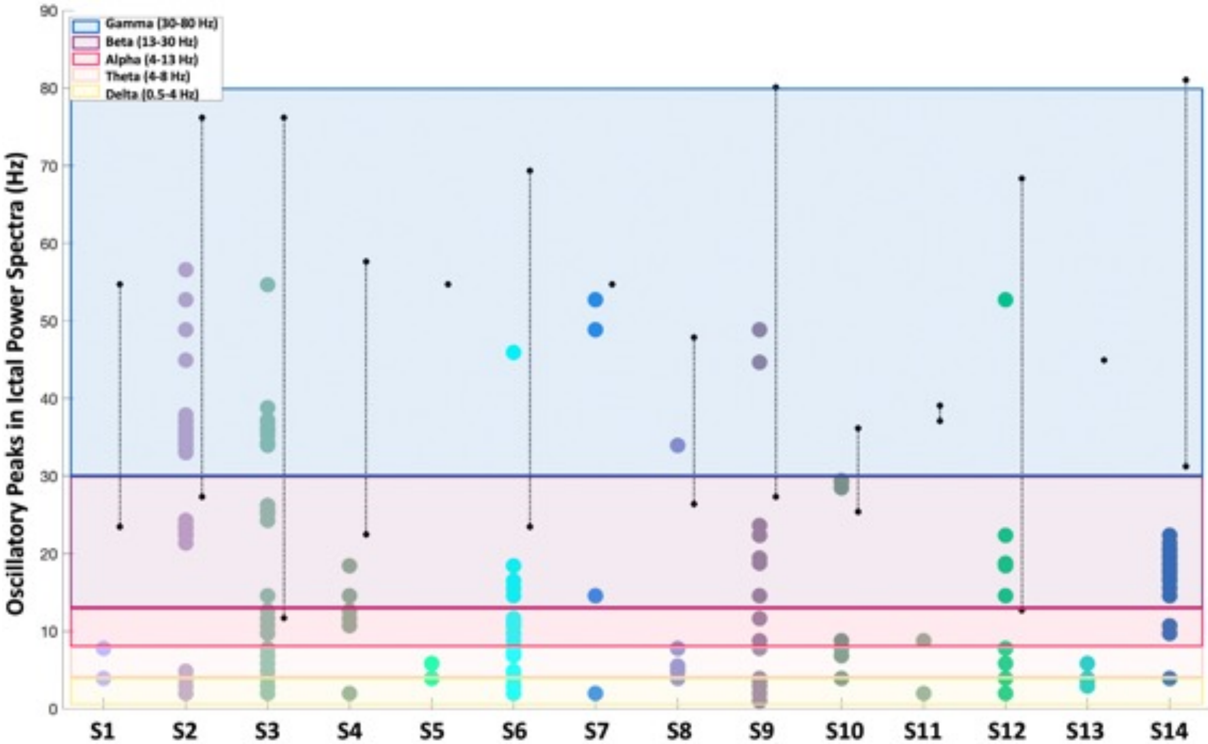
Utility of events recording in epilepsy



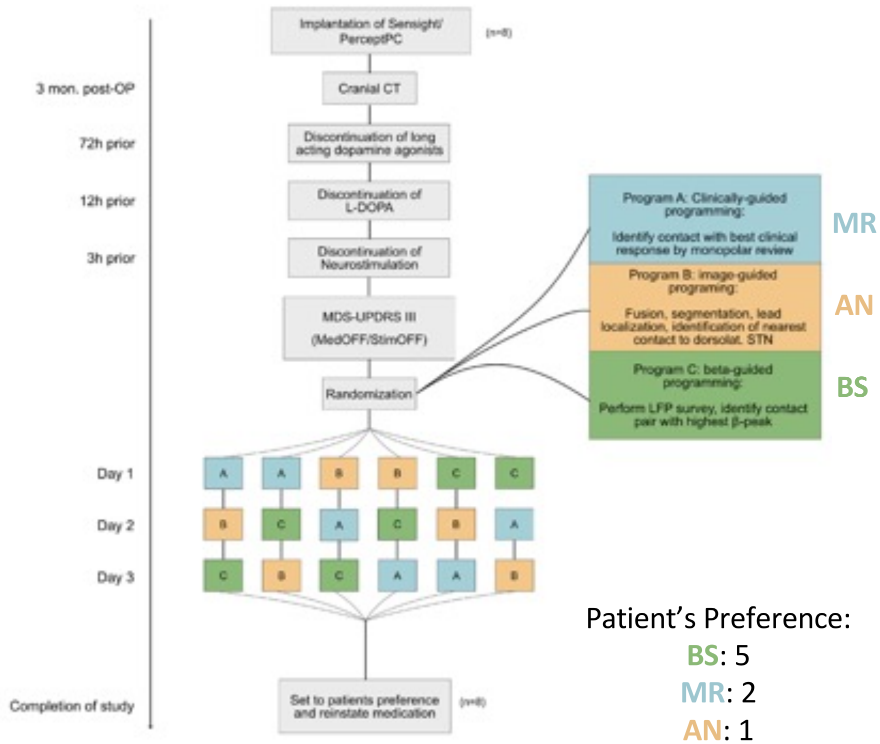
222 events in 12 ANT/2 CM DBS

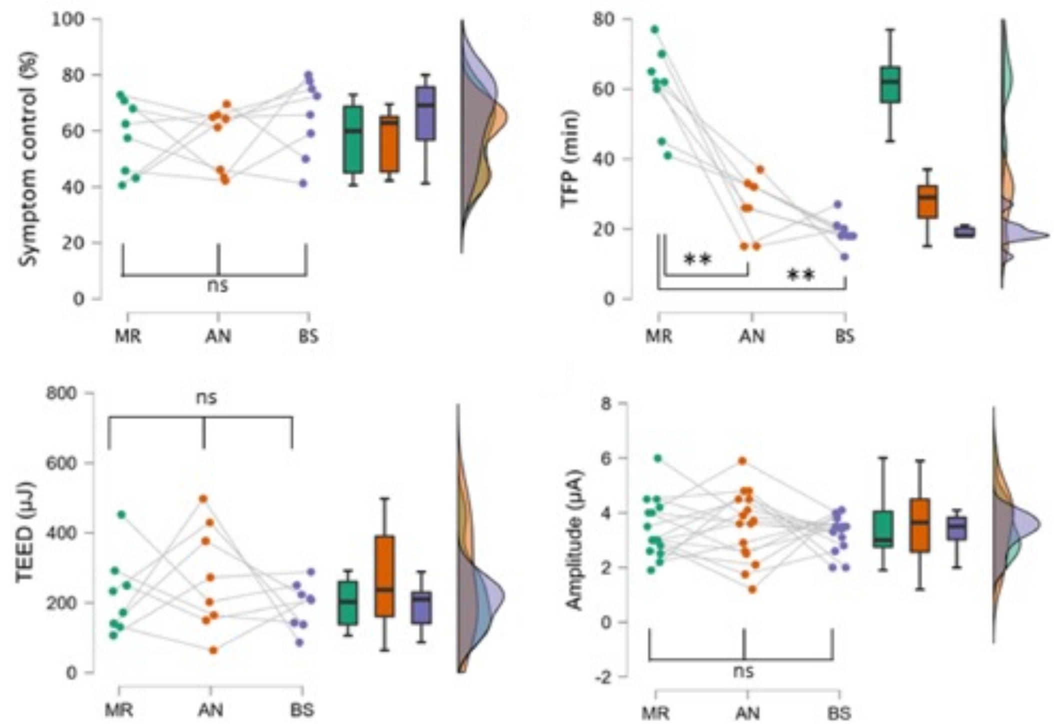


- LFPs present during seizures in all 14 patients (in 91.2 ±3.5% of events)
- Peaks occurred unilaterally in 74.2± 8.1% events
- In generalized epilepsy treated with CM: bilateral in 66.7±4.2%

Yang et al., 2023

Clinical, sensing or neuroimaging?



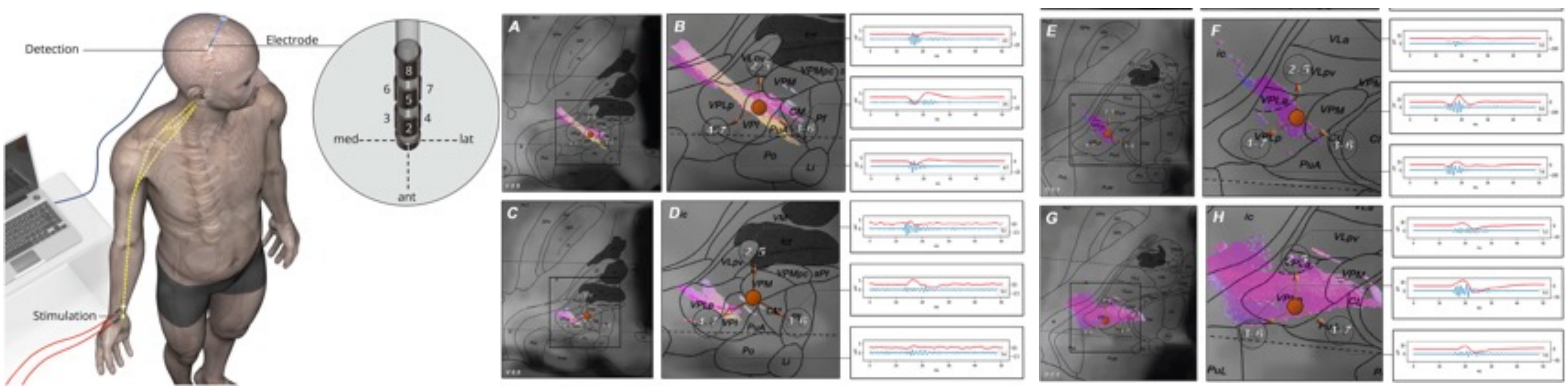


Patient's Preference:
BS: 5
MR: 2
AN: 1

Binder et al., 2023

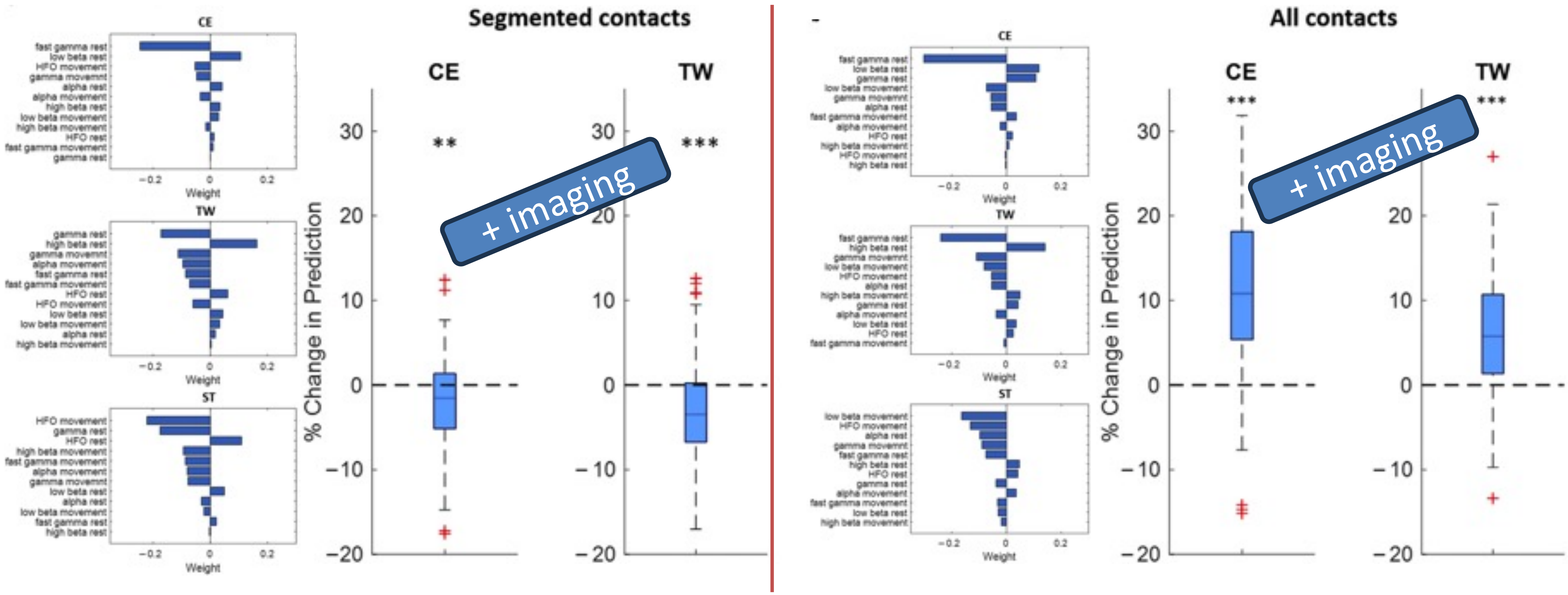
SEP in thalamic DBS for pain

- No correlation with atlas-based anatomical position and fiber-tracking of the medial lemniscus.
- Correlated with the segment of lowest threshold for paraesthesia



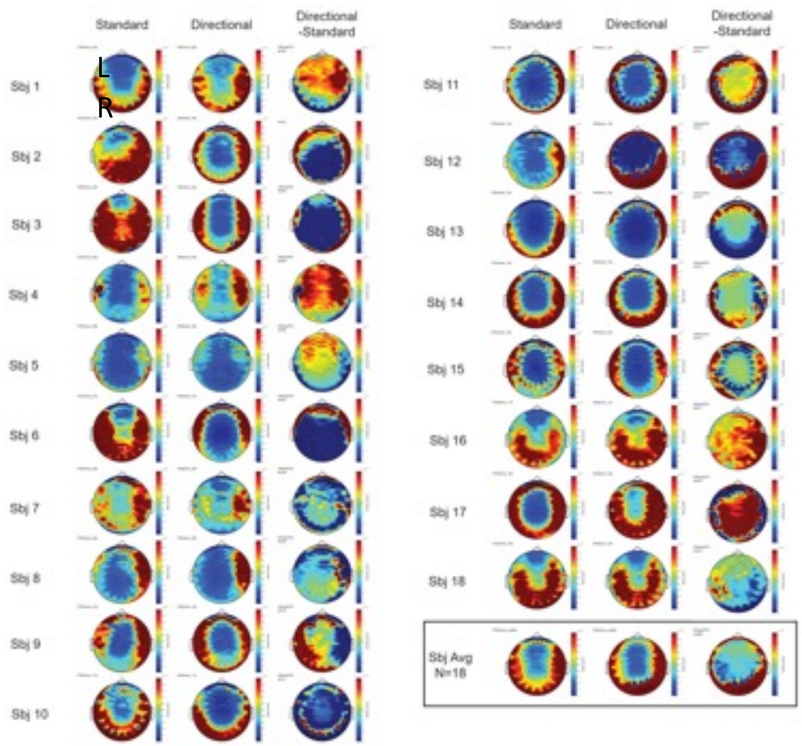
Nowacki et al., 2023

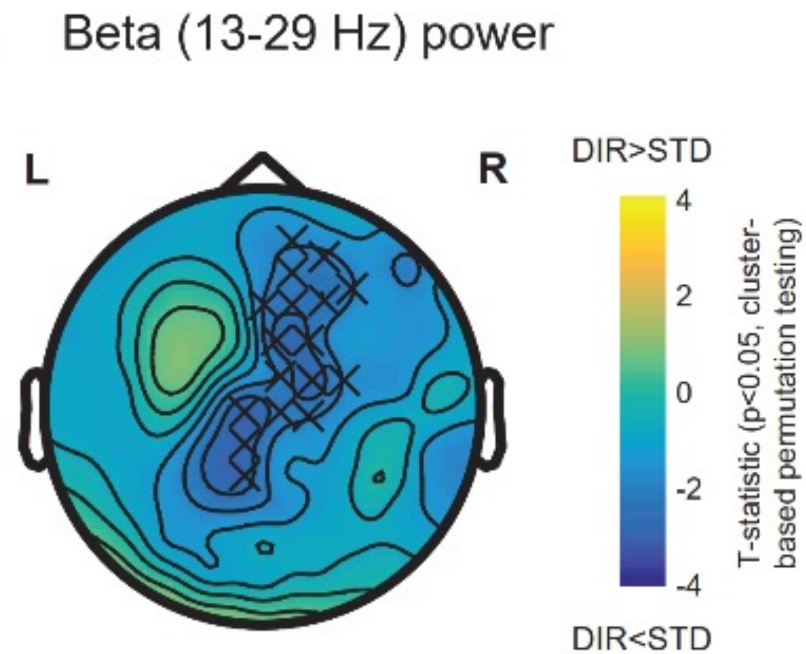
Integrating sensing and imaging



CE: clinical efficacy, ST: side-effect threshold, TW: Therapeutic window

Cortical beta with directional DBS

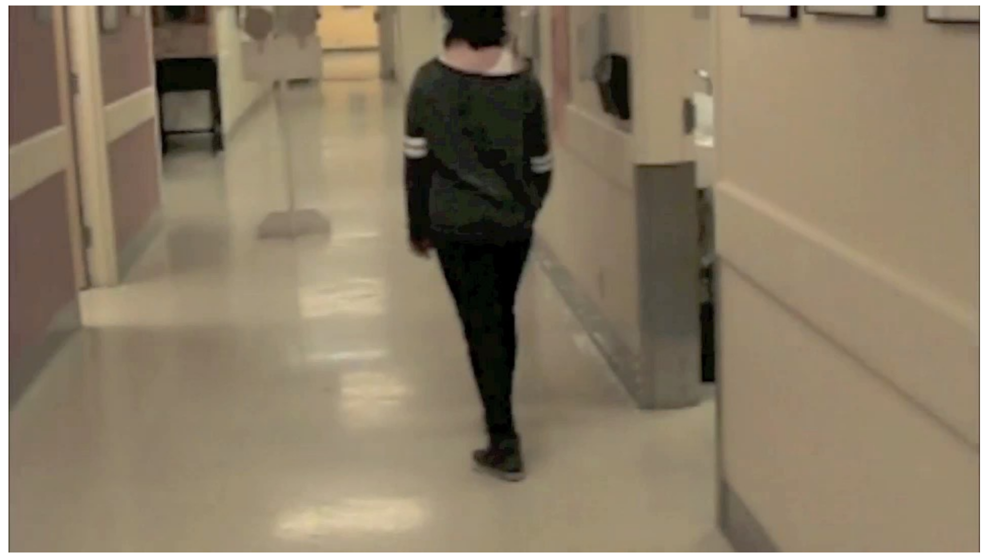




Courtesy of Irene E. Harmsen

Gpi DBS in a CP patient

Baseline
BFMDRS severity/disability scores: 24.5/8

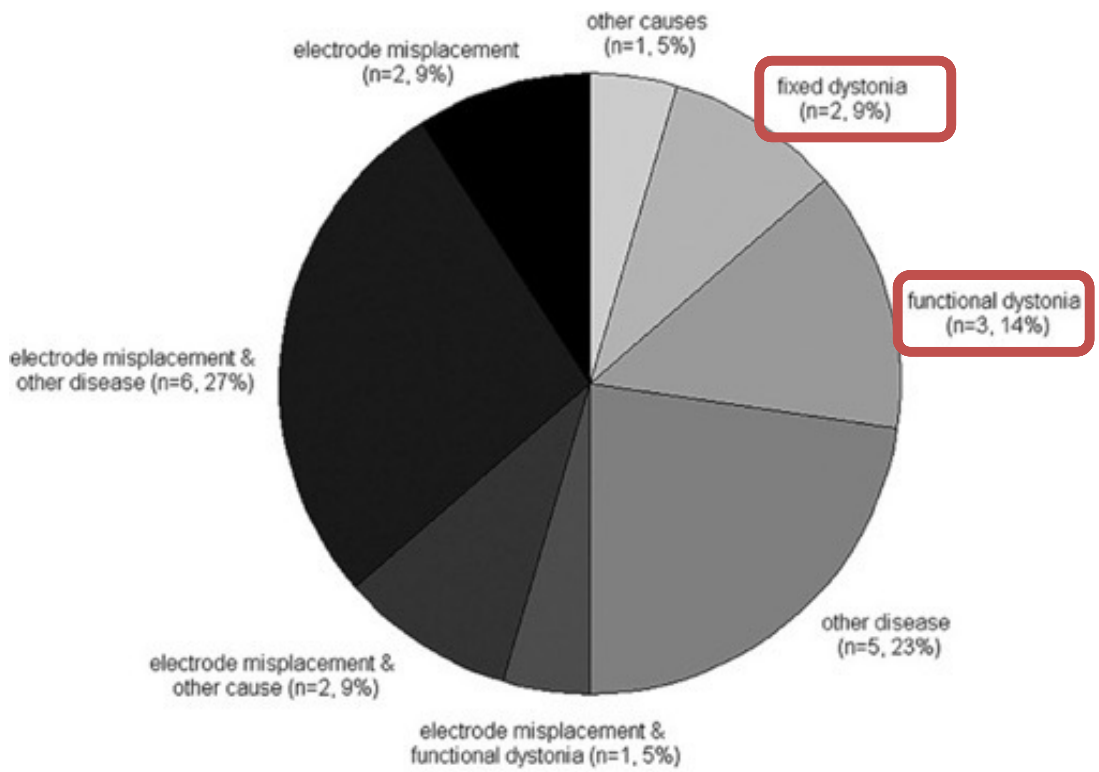


1 year after DBS
BFMDRS severity/disability scores: 11.5/5

New signs after 2 years

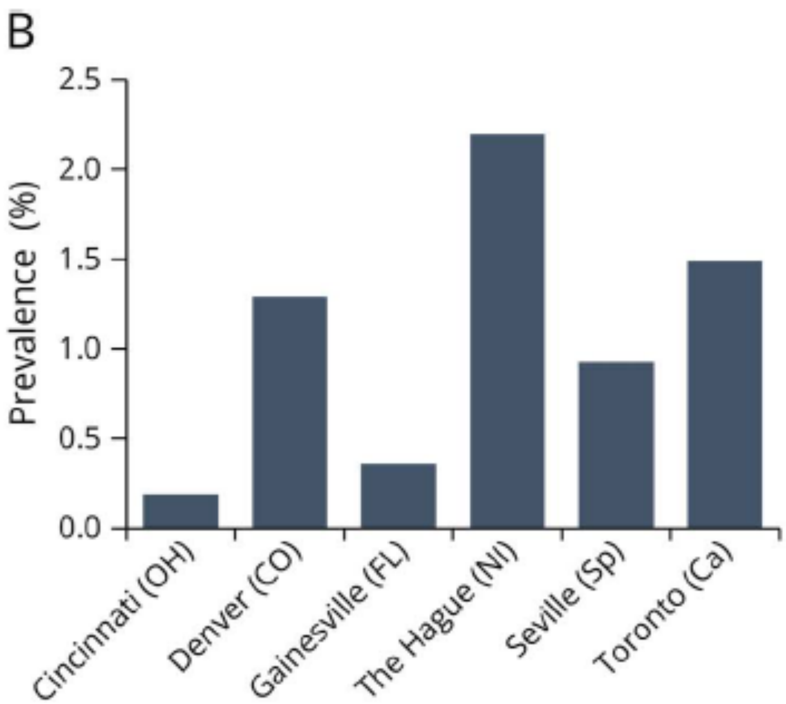
22 patients with <30% improvement at 6 months

GPI DBS failure in ‘isolated’ dystonia



Pauls et al., 2017

FND *after* DBS



CLINICAL/SCIENTIFIC NOTES

Functional movement disorders arising after successful deep brain stimulation

David P. Breen, MBChB, PhD, Mohammad Rohani, MD, Elena Moro, MD, PhD, Helen S. Mayberg, MD, Mateusz Zurowski, MD, MSc, Andres M. Lozano, MD, PhD, and Alfonso Fasano, MD, PhD

Correspondence
Dr. Breen
dpbreen1@gmail.com

Neurology® 2018;0:1-2. doi:10.1212/WNL.0000000000005530

REVIEW

Functional Movement Disorders and Deep Brain Stimulation

A Review

Alexandra Boogers, MD, PhD, and Alfonso Fasano, MD, PhD, FAAN

Neurology: Clinical Practice 2024;00:e200367. doi:10.1212/CPJ.0000000000200367

Marsili et al. 2023

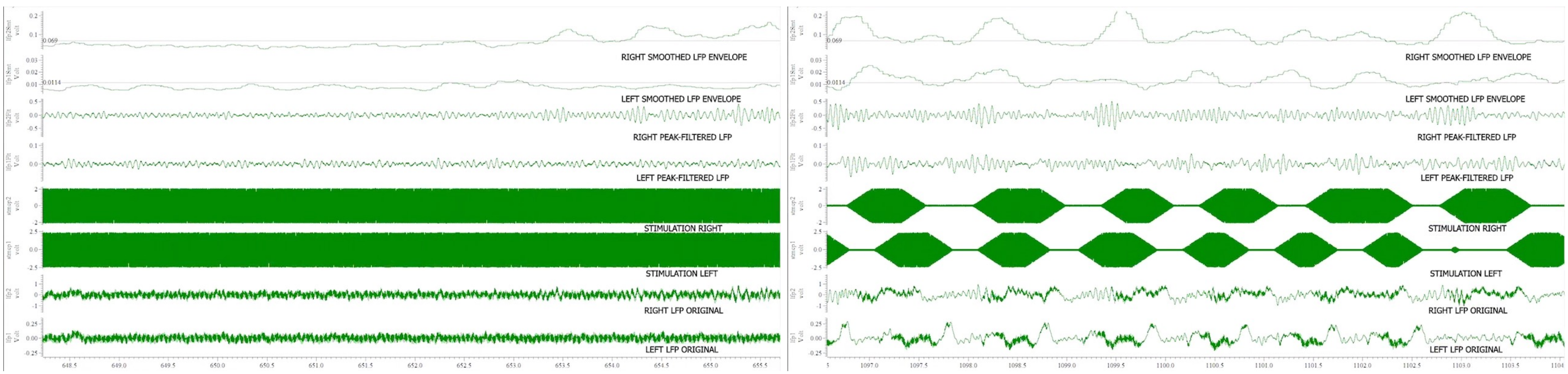
Topics

- Introduction to DBS
- Neurophysiology ***before*** DBS
- Neurophysiology ***during*** DBS
- Neurophysiology ***after*** DBS
- Conclusions

Conclusions

- DBS is being increasingly used and technology is getting complex
- Neurophysiology before DBS is mainly used to rule out functional cases and/or predict the outcome of surgery
- Neurophysiology during DBS is less utilized (still useful in research) as direct targeting is getting better
- Neurophysiology after DBS is being used more and has immediate new applications, e.g. adaptive DBS.

cDBS vs aDBS (single threshold)



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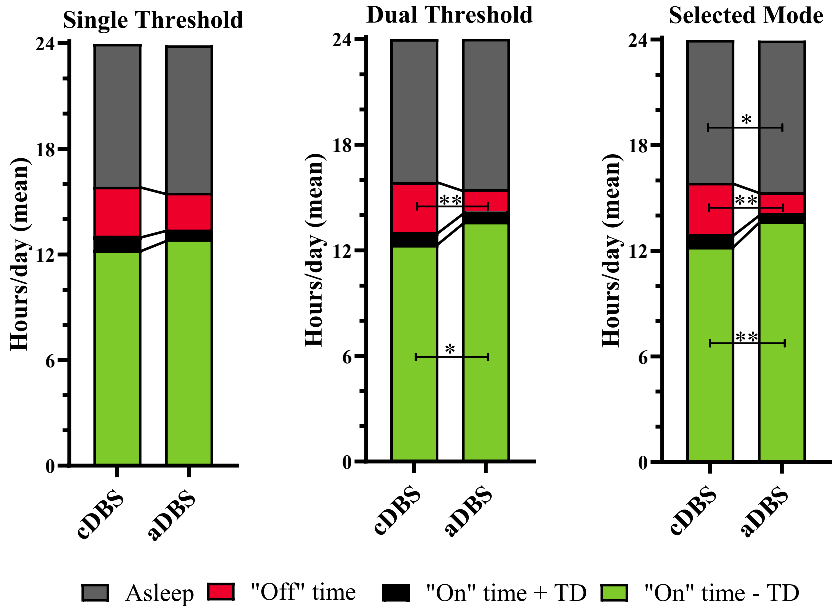
Piña-Fuentes et al., 2020

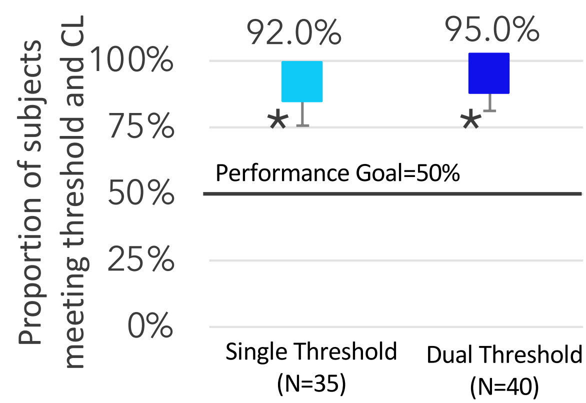
Single- vs. Dual-threshold

ADAPT-PD: motor diaries



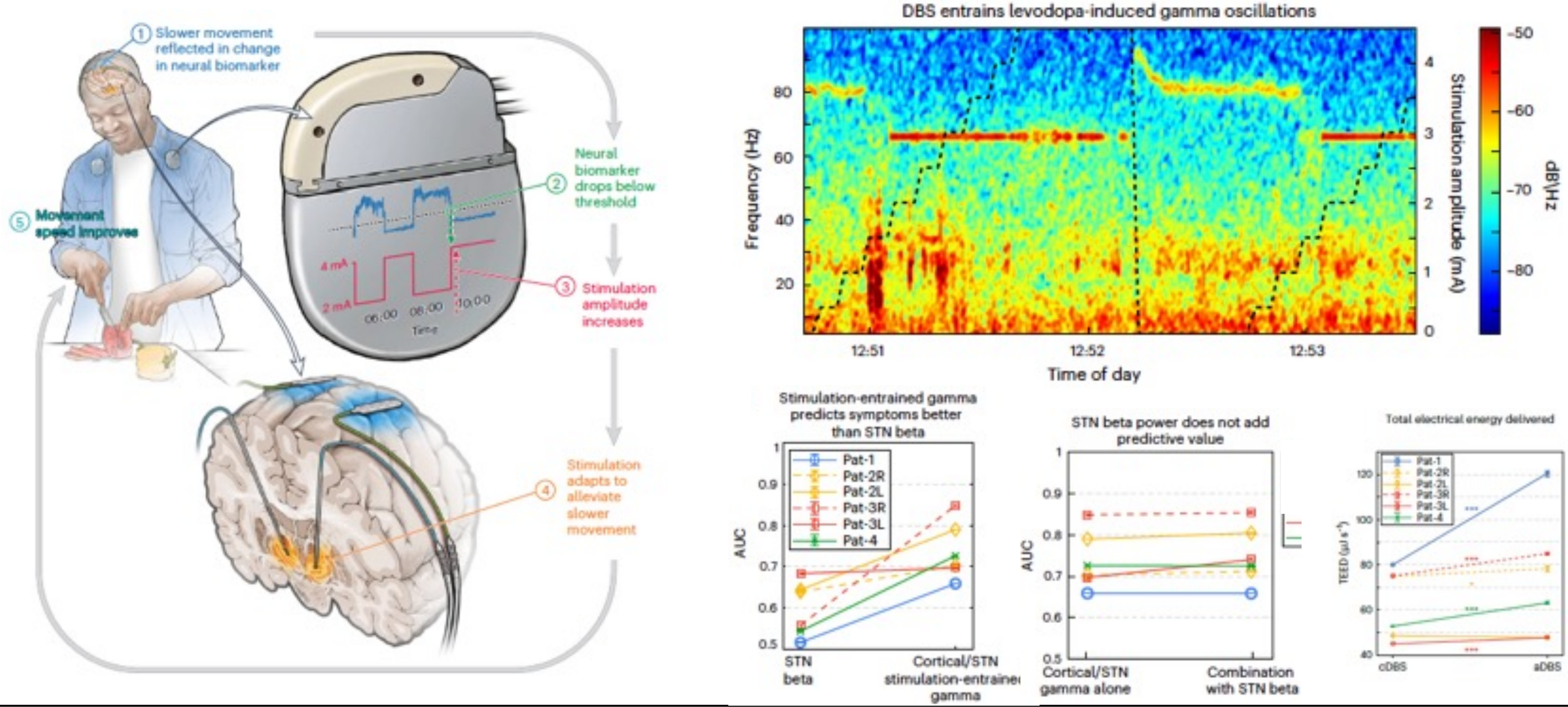
TD = troublesome dyskinesia, * = P<0.025, ** = P<0.01

Primary endpoint: On time w/o troublesome dyskinesia > performance goal of 50%



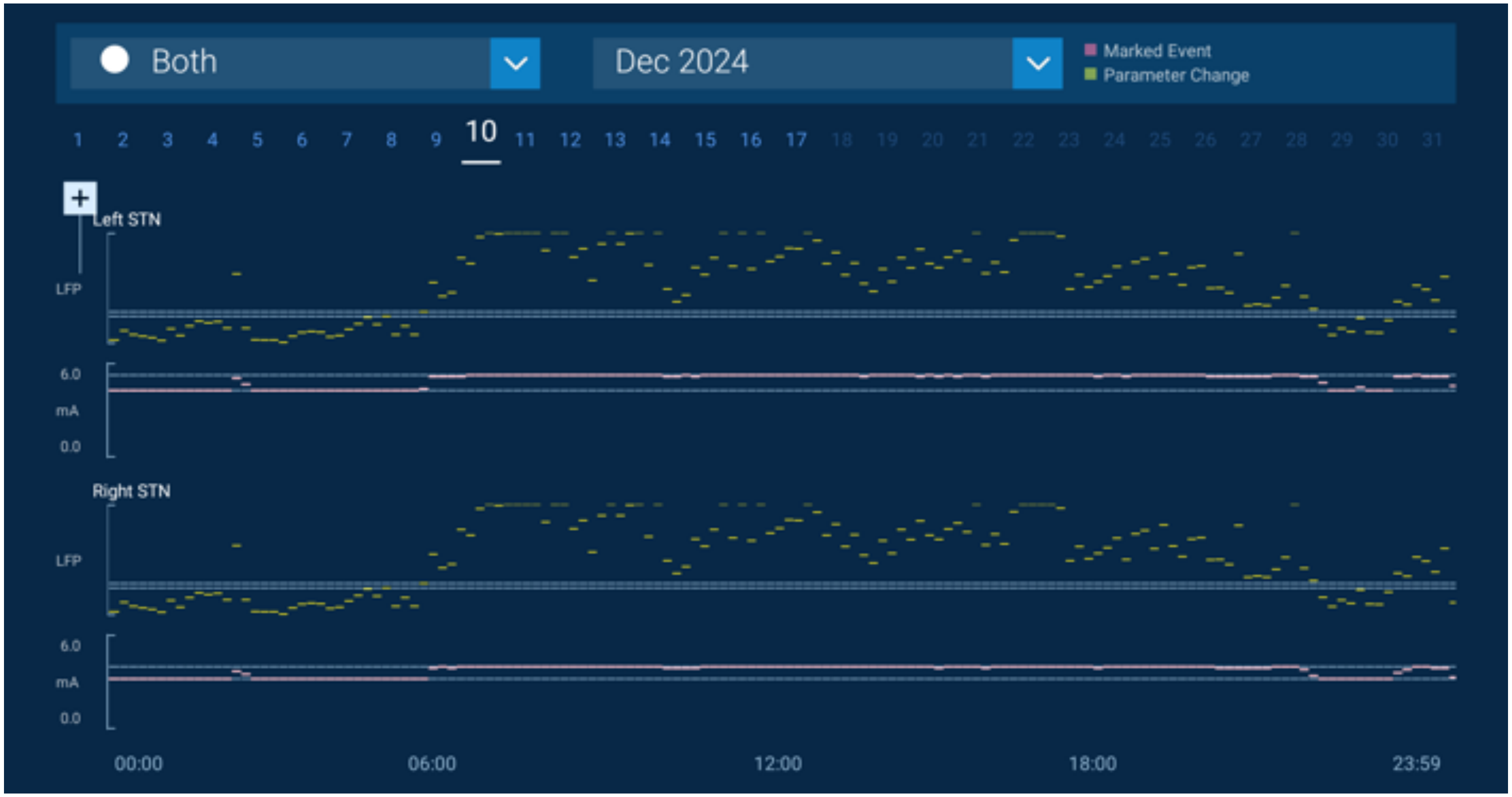
*statistically significant, P<0.0125

Inverse Single Threshold: db RCT

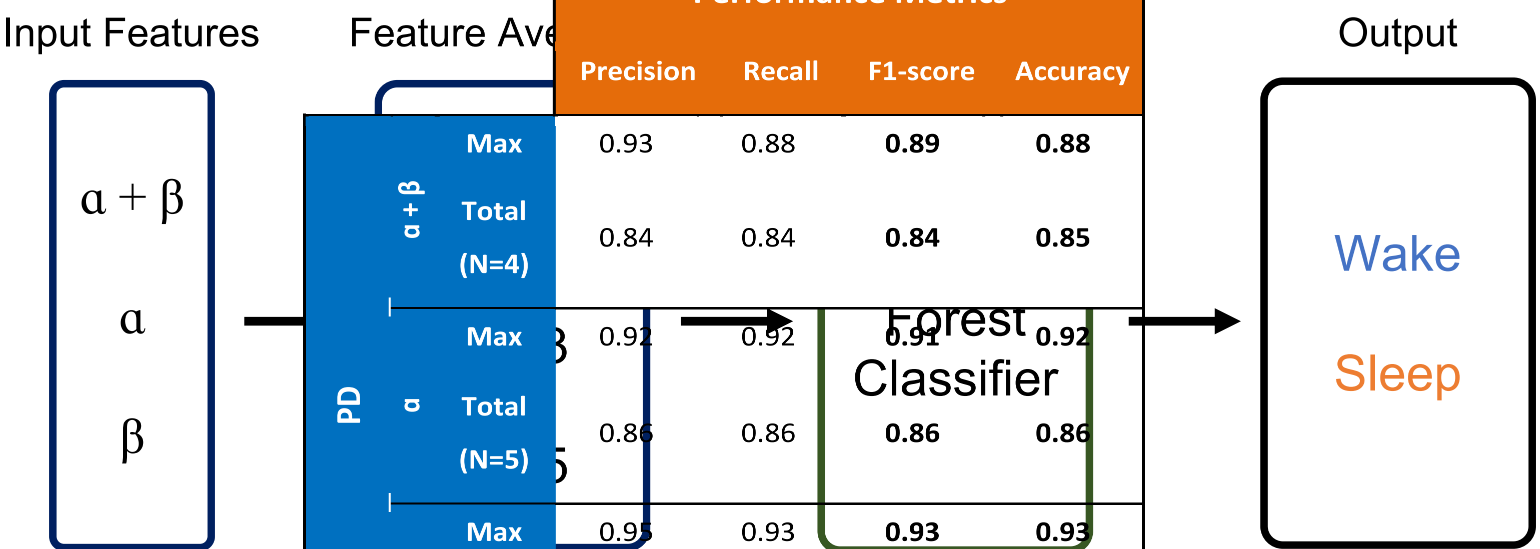


Oehrn, Cernera, Hammer et al., 2024

The issue of nocturnal biomarkers

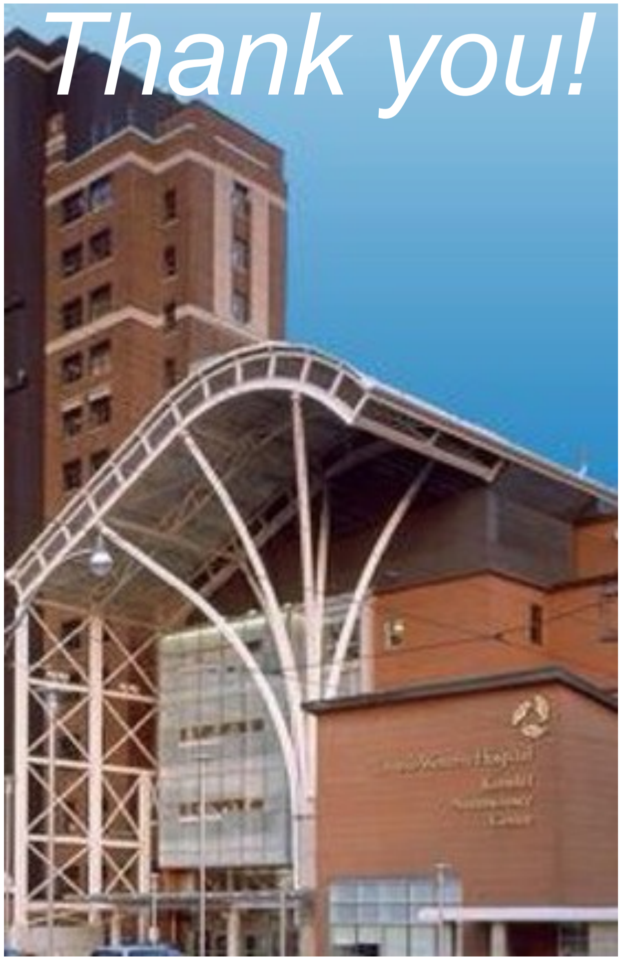


LFPs and machine learning (ML) to predict sleep

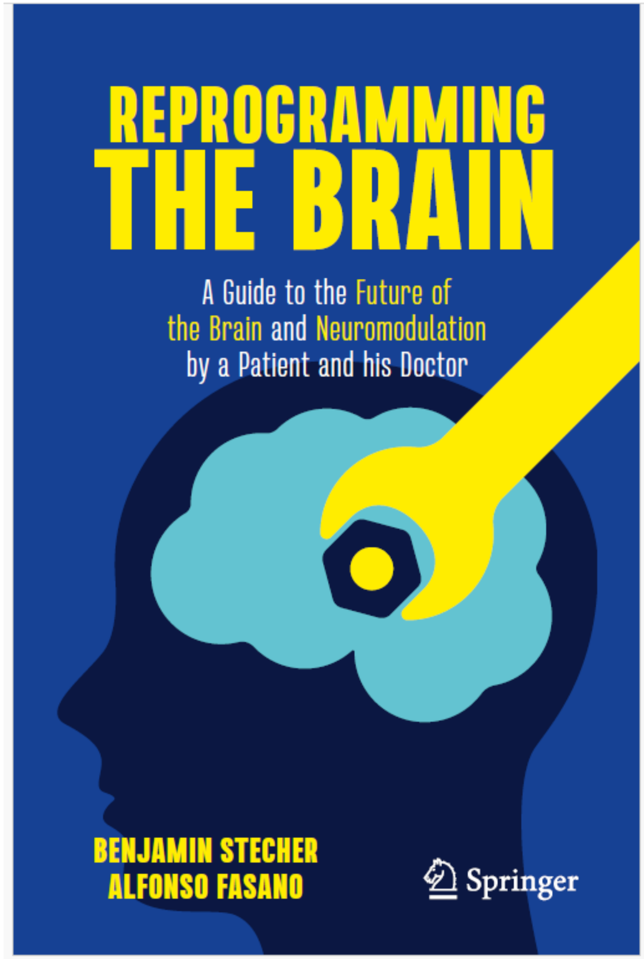


			Performance Metrics			
			Precision	Recall	F1-score	Accuracy
PD	α + β	Max	0.93	0.88	**0.89**	**0.88**
		Total (N=4)	0.84	0.84	**0.84**	**0.85**
	α	Max	0.92	0.92	**0.91**	**0.92**
		Total (N=5)	0.86	0.86	**0.86**	**0.86**
	β	Max	0.95	0.93	**0.93**	**0.93**
		Total (N=4)	0.86	0.85	**0.86**	**0.85**

Balachandar et al., 2024



- Tony Lang
- Carolina Gorodetsky
- DBS team at TWH
  - Dr. Renato Puppi Munhoz
  - Taline Naranian
  - Alejandro Valencia
  - Han Park
  - Howard Chow
  - Cecilia Miraldo
  - Mara Ryan
  - ***Fellows/Students***
- Study coordinator
  - Sara Naghdlou
  - Yu-Yan Poon
- Gait Lab
  - Gianluca Sorrento
- Neurosurgery
  - George Ibrahim
  - Sunel Kalia
  - Andres Lozano
- Neurophysiologists
  - Luka Milosevic
- Neuroimaging
  - Dr. Alex Boutet
  - Jurgen Germann
- Psychiatrists
  - Mateusz Zurowski
- Neuropsychologists
  - Melanie Cohn
  - Marta Statucka



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@DrAlfonsoFasano alfonso.fasano@uhn.ca