Of Course Closed Loop Technology Will Provide More Meaningful Improvement vs. Directional Leads In Deep Brain Stimulation!

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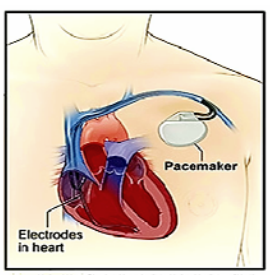
The PROBLEM - DBS currently is an Open-Loop Brain Pacemaker

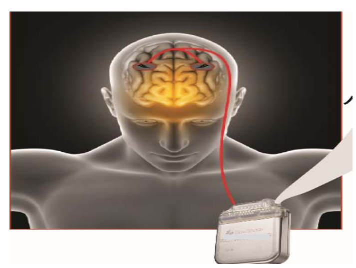
compare to current state of cardiac pacemakers



source: National Heart, Blood and Lung Institute, National Institutes of Health

Cardiac Pacemakers

- Can sense the heart electrical rhythm
- Demand – only activated when the heart rate goes below a threshold
- Sense and learn normal from abnormal rhythms- do not cause other arrhythmias
- Optimized, adaptive and automated stimulation algorithms customized to the patient



Current Open Loop Brain Pacemakers (DBS)

- Only recently can sense the brain electrical rhythms they are modulating
- Cannot sense or respond to specific symptoms (tremor, bradykinesia, gait impairment) nor to activity state (asleep, still, active)
- Cannot respond to medication levels and their influence on brain rhythms
- Continuous, on all the time
- One size fits all parameters

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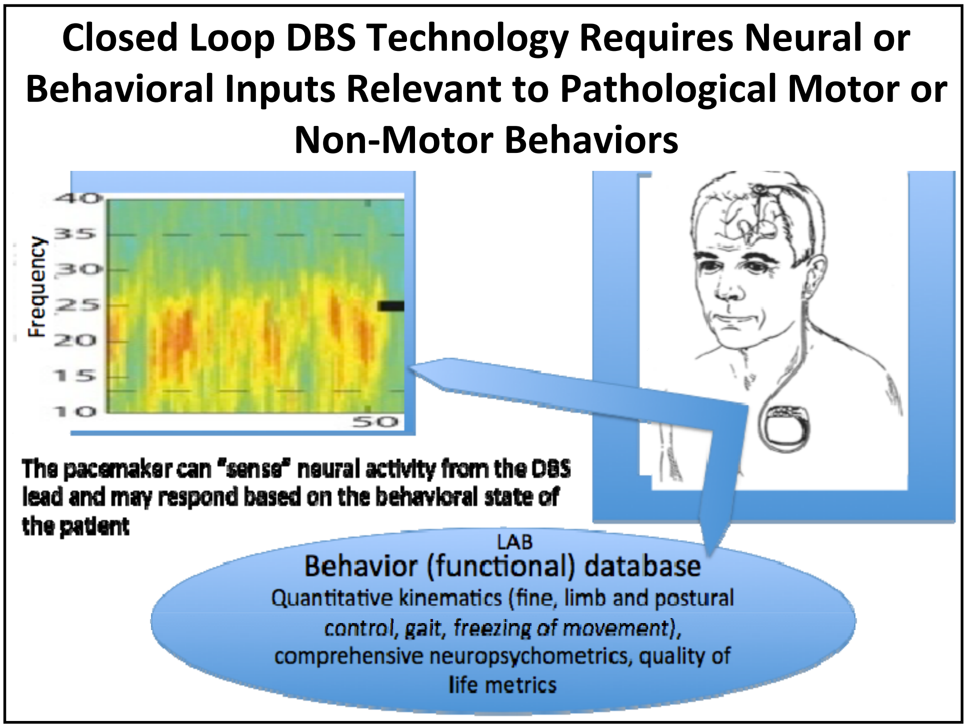
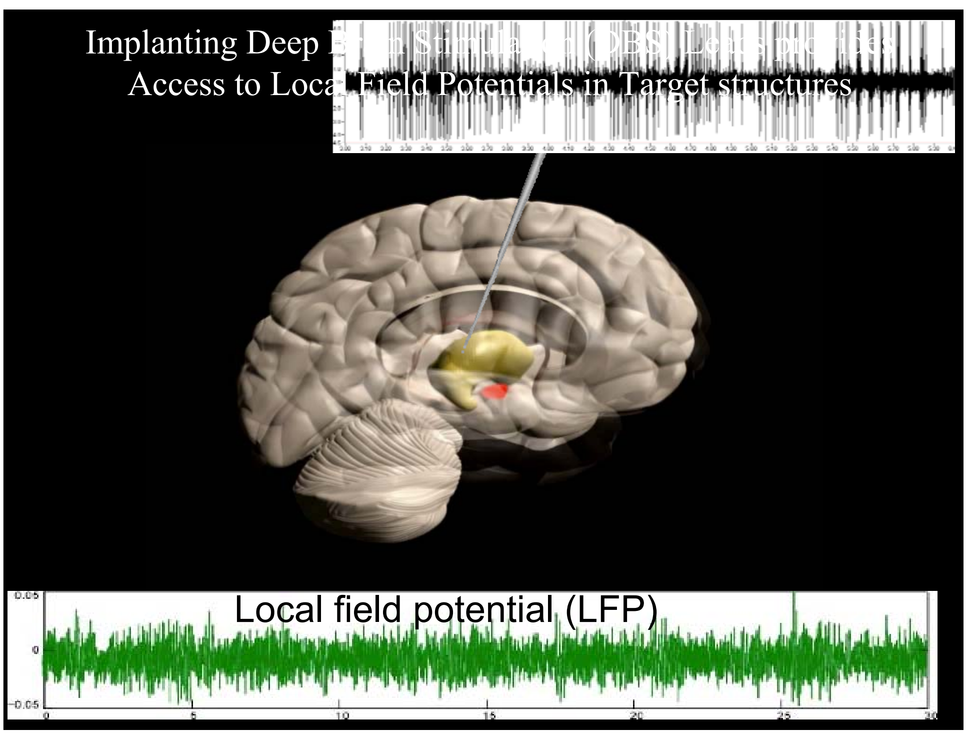

Closed Loop DBS Technology Requires Neural or Behavioral Inputs Relevant to Pathological Motor or Non-Motor Behaviors
Frequency
40
35
30
25
20
15
10
50
The pacemaker can "sense" neural activity from the DBS lead and may respond based on the behavioral state of the patient
LAB
Behavior (functional) database
Quantitative kinematics (fine, limb and postural control, gait, freezing of movement), comprehensive neuropsychometrics, quality of life metrics

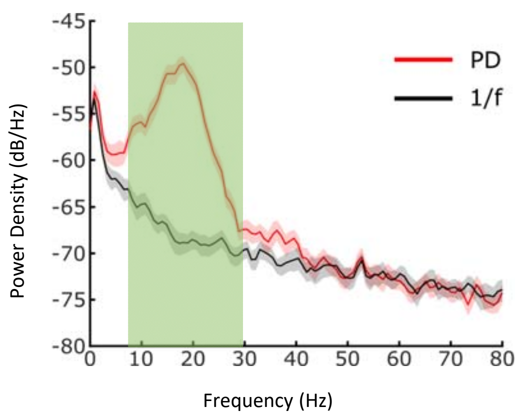

Implanting Deep
Access to Local Field Potentials in Target structures
Local field potential (LFP)

The Role of LFPs in Clinical Practice

- Revealing disorders of neuronal oscillations – **oscillopathies**
    - Clinically relevant to movement disorders
- Guiding electrode (contact) selection for DBS programming
- Using as inputs for closed loop (cl)DBS technologies

Parkinson's disease – the Alpha/Beta Oscillopathy

Exaggerated neuronal oscillations and synchrony in the 8-30 Hz range



Theta	3 – 8 Hz
Alpha	8 – 13 Hz
Beta	13 – 30 Hz

Beta oscillopathy's relevance
- Evident in bilateral sensorimotor network in PD
- Increases with disease progression- greater in more affected STN
- Related to hypokinetic aspects – bradykinesia, rigidity, gait, FOG
- Attenuated during resting tremor
- Attenuated in a dose dependent manne by DBS and dopaminergic medication
- Degree of attenuation is related to degree of improvement in B/R

- High Frequency Oscillations (200-400 Hz, HFO) and beta phase HFO amplitude coupling (PAC)

Bergman 1998, Brown 2001, Cassidy 2002, Levy 2002, Williams 2002, Priori 2004, Kuhn 2006, 2008, 2009, Wingeier 2006, Weinberger 2006, Hammond 2007, Ray 2008, Bronte-Stewart 2009, Eusebio 2011, Whitmer 2012, Quinn 2015, Weiss 2015, Matzner 2016, Blumenfeld 2017, Shreve 2017, Tinkhauser 2017, Anidi 2018, Velisar 2019, Afzal 2019, Ozkurt 2020, Molina 2020

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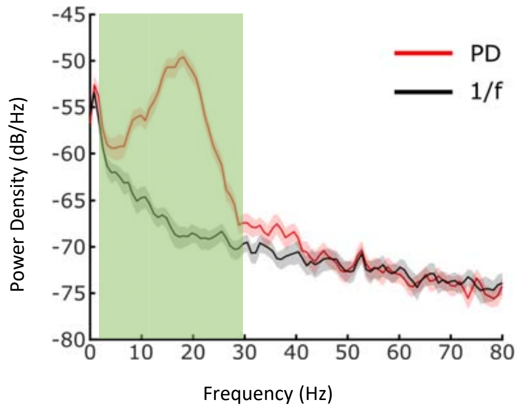
Dystonia – theta-alpha-beta oscillopathy



Theta	3 – 8 Hz
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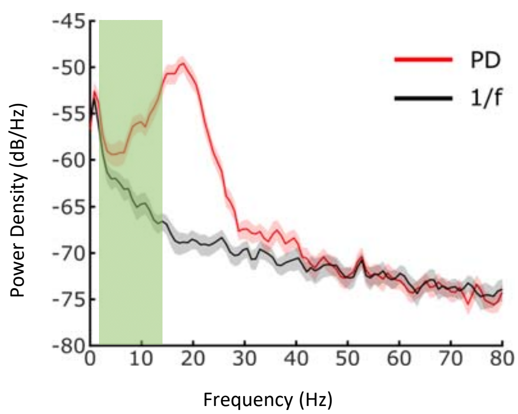
Beta	13 – 30 Hz

Dystonia

3-12 Hz – hyperkinetic
(Liu 2002, 2006, Silberstein 2003, Chen 2006, Foncke 2007, Neumann 2012, Whitmer 2012, Barrow 2014, Huebl 2019)

Beta – hypokinetic
(Weinberger 2012, Whitmer 2012, Huebl 2019, Pina-Fuentes 2019)

Tourettes – theta (beta) oscillopathy



Theta	3 – 8 Hz
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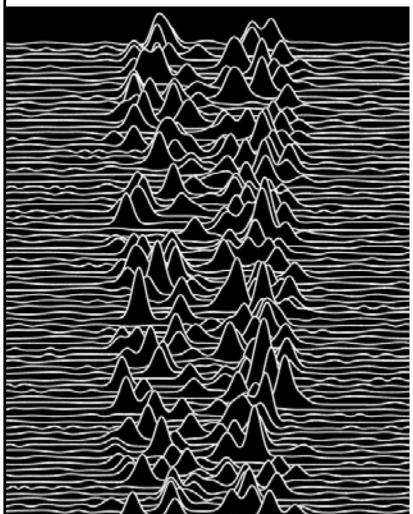
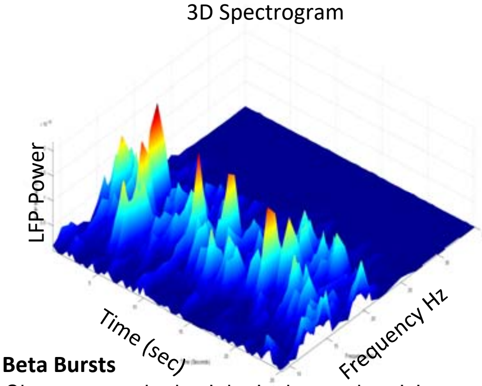
Tourette syndrome

3-12 Hz - prolonged pallidal and thalamic theta bursts associated with tic severity (Neumann 2018)

The Beta Oscillopathy is Dynamic- occurring in Bursts



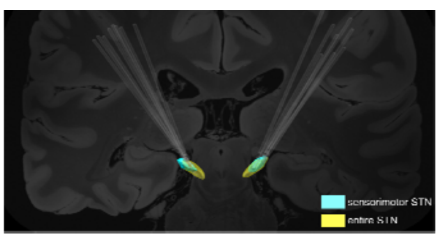


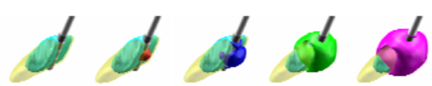
Beta Bursts

- Short - normal, physiological neural activity
- Long- pathological
- Duration related the PD disease severity, gait impairment and FOG
- Duration decreased on medication and ON DBS

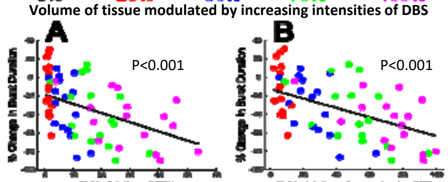
(Murphy and Fetz 1992, Feingold 2015, Tinkhauser 2017, 2018, Anidi 2018, Defains 2018, Torrecillos 2018, Cagnan 2019, Meidahl 2019, Anderson 2020, Kehnemouyi, Wilkins 2020)

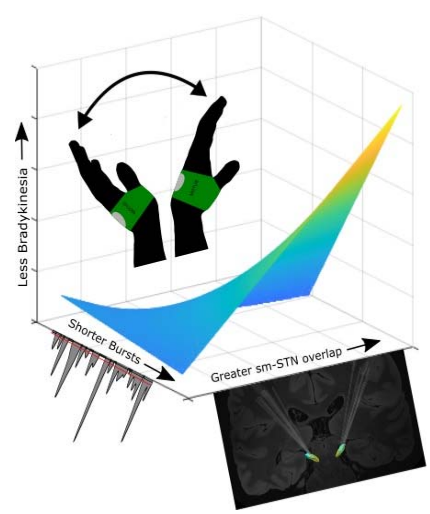
Predicting outcome from lead location and beta oscillopathy using DBS as an Investigative Tool





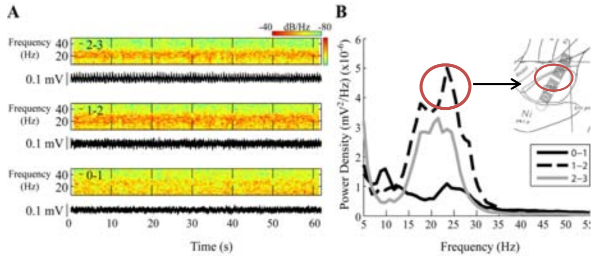
Volume of tissue modulated by increasing intensities of DBS





Kehnemouyi Y, Wilkins K et al. Brain 2020

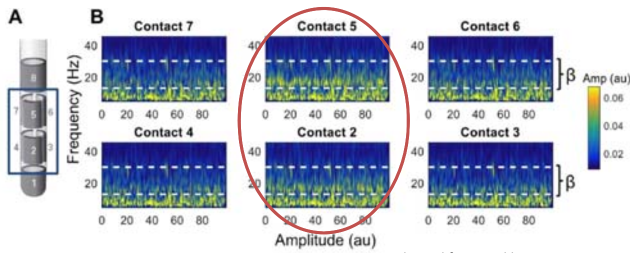
LFPs can be used to guide electrode (contact) selection DBS programming



Adapted from Shreve 2017

The DBS electrode closest to the site of maximal beta band power in the STN had the best outcome if used for neurostimulation

(Zaidel 2010, Yoshida 2010, Ince 2010, Connolly 2015, Horn 2019)



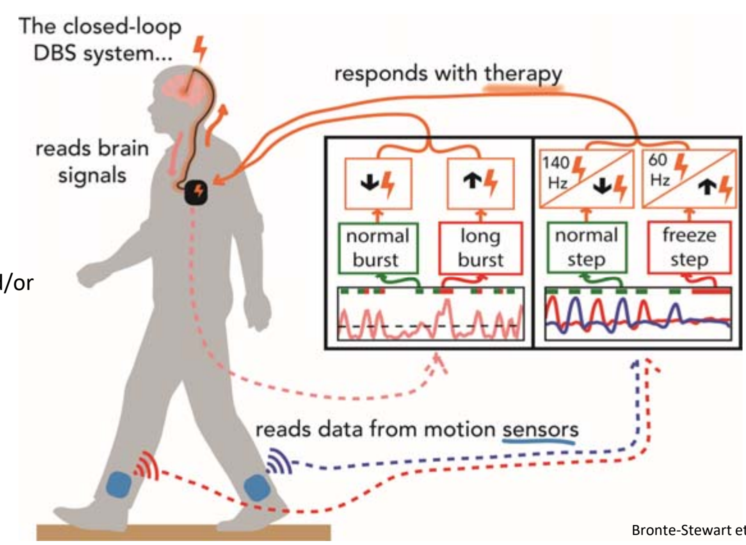
Adapted from Tinkhauser 2018

This was also demonstrated for rigidity using the directional electrodes

(Fernandez-Garcia 2017, Tinkhauser 2018)

Neural and Kinematic Closed Loop DBS Technologies in Movement Disorders

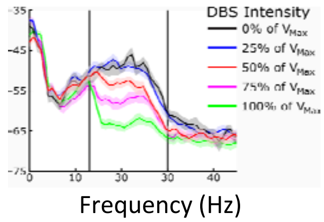
Using relevant neural and/or kinematic signals



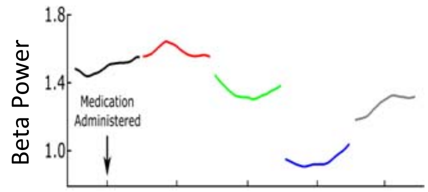
Bronte-Stewart et al 2020

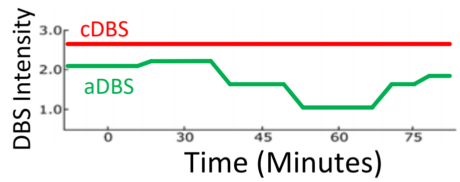
Closed Loop Technologies - meaningful improvement adapting to medication/dyskinesias

STN DBS attenuates beta power in a dose dependent manner
(Eusebio 2011, Whitmer el 2012, Quinn 2015, Velisar 2019, Kehemouyi, Wilkins 2020)



Beta power responds to onset and offset of levodopa dose
(Bronte-Stewart Lab unpublished data)

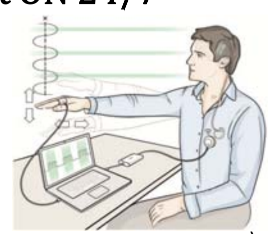




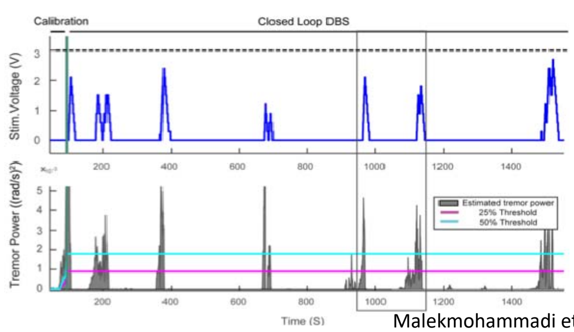
- STN clDBS adapted intensity with onset and offset of medication with ns reduction in dyskinesias (Arlotti 2018)
- STN clDBS responded to cortical gamma oscillopathy (60 – 90 Hz) relevant to dyskinesia (Swann 2018, de Hemptinne 2015)
- ADAPT-PD trial (Medtronic PLC) – primary outcome - on time without dyskinesias

Closed Loop Technologies - meaningful improvement demand based - not ON 24/7

clDBS driven by power or phase of resting or action tremor using Bluetooth enabled Smartwatch or accelerometer



(Adapted from Cagnan 2017)



closed loop DBS driven by resting tremor was on for only 11% of time that clinical continuous open loop DBS would have been ON.

Average time ON clDBS = 51.5% of olDBS (P=0.002)

Malekmohammadi et al. 2016, Cagnan 2017, Herron 2017

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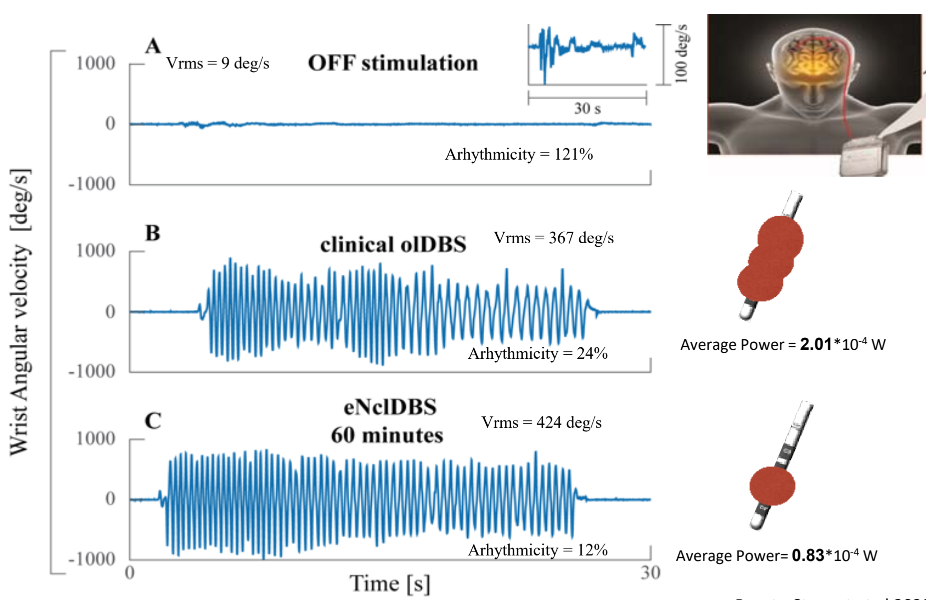
Closed Loop Technology – Evidence for Meaningful Improvement for DBS

- clDBS driven by beta power is safe and efficacious for tremor and bradykinesia in PD (external and embedded systems) and was superior to olDBS in one study (Little 2013)
- clDBS is more efficient- uses less total electrical energy delivered (TEED) than olDBS
- clDBS did not worsen speech whereas open loop DBS did
- Demand based clDBS for tremor driven by either resting tremor intensity or the phase of action tremor significantly reduced tremor and used on average 50-70% less TEED than olDBS
- clDBS is efficacious for ET driven by cortical beta desynchronization with arm movement

Behavioral: tremor: Malekmohammadi 2016, Cagnan 2017,
Neural: Little 2013, 2015, 2016, Rosa 2015, 2017, Pina-Fuentes 2017, 2019,2020, Arlotti 2018, Swann 2018, Velisar 2019, Afzal 2019, Bronte-Stewart 2020, Petrucci 2020, Ferlegger 2020, Opri 2020

Superiority of fully embedded closed loop DBS for progressive bradykinesia (sequence effect)



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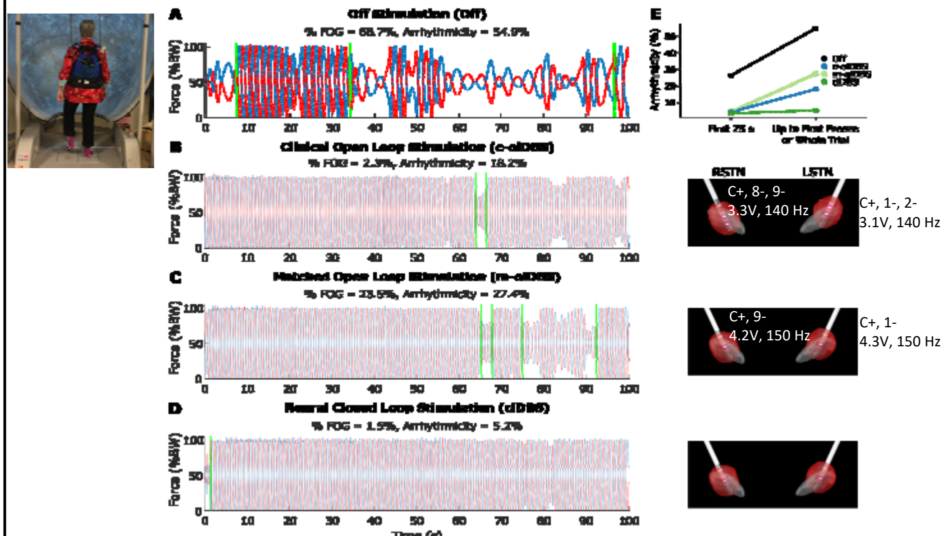
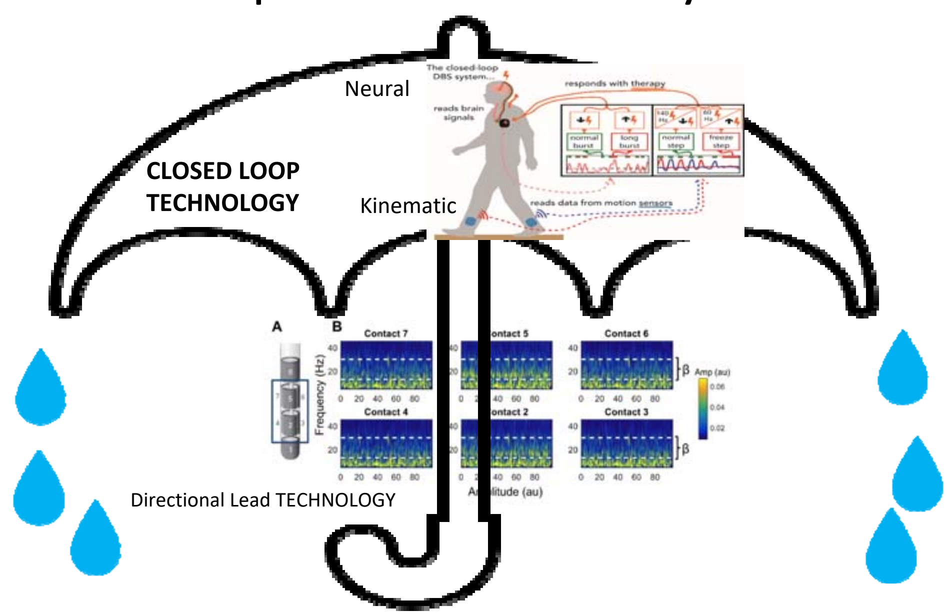
Superiority of Closed Loop DBS for FOG and Gait Arrhythmicity (sequence effect)



Adapted from Petrucci, Afzal et al. 2020

Hope becomes reality..



Thank You

to the people with Parkinson's disease who have volunteered many hours of their time and energy, and without whom none of this research would be possible

Changing lives for the ***Beta***

The Stanford Human Motor Control and Neuromodulation L

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BRAIN INITIATIVE

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SPRING

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