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

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
Using neural and/or kinematic signatures of movement disorders to drive adaptive (closed loop) DBS

Closed Loop DBS Technology Requires Neural or Behavioral Inputs Relevant to Pathological Motor or Non-Motor Behaviors

Implanting Deep Brain Stimulation (DBS) leads provides access to local field potentials in target structures.

The pacemaker can "sense" neural activity from the DBS lead and may respond based on the behavioral state of the patient.

Behavior (functional) database
Quantitative kinematics (fine, limb and postural control, gait, freezing of movement), comprehensive neuropsychometrics, quality of life metrics.
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

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

- 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 manner by DBS and dopaminergic medication
- Degree of attenuation is related to degree of improvement in B/R

Dystonia – theta-alpha-beta oscillopathy

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<td>Frequency</td>
<td>3 – 8 Hz</td>
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Dystonia
3-12 Hz – hyperkinetic

Beta – hypokinetic

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Tourettes – theta (beta) oscillopathy

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

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The Beta Oscillopathy is Dynamic- occurring in 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

Beta Bursts


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

(Kehnemouyi Y, Wilkins K et al. Brain 2020)
LFPs can be used to guide electrode (contact) selection DBS programming

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)

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
Closed Loop Technologies - meaningful improvement adapting to medication/dyskinesias

- 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

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(Bronte-Stewart Lab unpublished data)

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

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

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 cIDBS = 51.5% of oDBS (P=0.002)

Malekmohammadi et al. 2016, Cagnan 2017, Herron 2017
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


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

- A. Vrms = 9 deg/s, OFF stimulation, Arhythmicity = 121%
- B. Vrms = 367 deg/s, clinical olDBS, Arhythmicity = 24%
- C. Vrms = 424 deg/s, eNetDBS 60 minutes, Arhythmicity = 12%

**Average Power:**
- B: $2.01 \times 10^{-4}$ W
- C: $0.83 \times 10^{-4}$ W
Superiority of Closed Loop DBS for FOG and Gait Arrhythmicity (sequence effect)

Adapted from Petrucci, Afzal et al. 2020

Hope becomes reality..

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