Using Maths and Physics to Treat Parkinson’s With a Vibrating Glove

Peter A. Tass, MD, PhD
Professor of Neurosurgery
Parkinson’s disease

• Abnormal neuronal synchrony
  Hammond et al., Trends Neurosci. 2007

• Abnormal synaptic connectivity
  McGregor & Nelson, Neuron 2019
Standard permanent high-frequency deep brain stimulation

PD Patient, 48 ys
Parkinson’s disease

High-frequency (> 100Hz) permanent deep brain stimulation:
- no long-lasting therapeutic effects
- may have relevant side effects: DBS-induced movement disorders
- can result in speech deterioration and does not reliably improve gait and other axial symptoms

Computationally based approach to induce long-lasting desynchronization by reshaping network connectivity

- Specifically counteract abnormal neuronal synchrony by desynchronization

- Desynchronization of multistable plastic neural networks → long-lasting desynchronization
  Tass & Majtanik, Biol. Cybern. 2006; Kromer & Tass, PRR 2020
Coordinated Reset Deep Brain Stimulation

Synchronous neuronal population

Divided into sub-groups

Complete desynchronisation

Spike timing-dependent plasticity

A \[ c_{A \rightarrow B} \]

B

time

\[ \Delta t \]


net STDP effect for \( \Delta t \in [\varepsilon, \varepsilon] \) (uniform)


desynchronization-induced reduction of synaptic weights
Standard high-frequency (HF) stimulation vs. CR Stimulation

**Neuronal activity**

- **Standard HF Stimulation**
- **HF stimulation on**
- **HF off**

- **CR Stimulation**
- **Coordinated Reset on**
- **CR off**

**Synchronisation**

**Average synaptic strength**

Tass & Majtanik, Biol. Cybern. 2006
CR stimulation in MPTP monkeys

frequency: 130 Hz,
pulse width: 120 µs
most effective intensity: 0.6 mA ± 0.1 mA

burst = five pulses with
150 Hz intraburst frequency
pulse width: 120 µs
CR stimulation frequency: 7 Hz, fixed
(close to frequency of abnormal oscillations in the STN in MPTP treated non-human primates, Meissner et al. Brain 2005)
CR-DBS (STN) in MPTP monkeys before CR stimulation

Tass, Qin, Hauptmann, Dovero, Bezard, Boraud, Meissner; Annals of Neurology 2012
CR-DBS (STN) in MPTP monkeys after 2h CR stimulation

Tass, Qin, Hauptmann, Dovero, Bezard, Boraud, Meissner; Annals of Neurology 2012
Theoretical prediction: low intensity = DBS-like intensity / 3 is optimal for CR

Experimental cross-over design

- Akinesia was monitored for 90 minutes/day with infrared activity monitors, providing mobility counts every 5 minutes (Bezard et al. Nat. Med. 2003).
- The severity of motor symptoms and dyskinesia were further assessed on a parkinsonian monkey rating scale using videotape recordings of monkeys (Bezard et al. Nat. Med. 2003).

Tass, Qin, Hauptmann, Dovero, Bezard, Boraud, Meissner; Annals of Neurology 2012
Sustained after-effects of CR and standard DBS

Each bar represents the mean of five days of behavioral assessment ± s.e.m. *P<0.05, #P≤0.1

Tass, Qin, Hauptmann, Dovero, Bezard, Boraud, Meissner; Annals of Neurology 2012

intensity: 0.6 mA ± 0.1 mA

intensity: 0.2 mA ± 0.0 mA

intensity: 0.6 mA ± 0.1 mA

AUC = area under curve (mobility count)
Sustained after-effects of CR and standard DBS

intensity: 0.6 mA ± 0.1 mA

Each bar represents the mean of five days of behavioral assessment ± s.e.m.

Tass, Qin, Hauptmann, Dovero, Bezard, Boraud, Meissner; Annals of Neurology 2012

AUC = area under curve (mobility count)

Long-lasting effects confirmed by Wang et al., Brain Stimul. 2015;
Wang et al., Front. Neurol. 2022
Bore et al., Brain Stimul. 2022
Pilot study with unilateral CR-DBS in the STN in externalized patients with Parkinson’s disease

Adamchic et al., Mov. Disord. 2014
Deep brain coordinated reset stimulation

PD patient, 49 ys

Adamchic et al., Mov. Disord. 2014
Long-lasting CR effects - electrophysiology

Significant decrease of LFP beta activity only during the first 12 sec after high-frequency DBS.

Kühn et al., J. Neurosci. 2008

Adamchic et al., Mov. Disord. 2014
Long-lasting and cumulative effects of CR stimulation

6 PD patients (akinetic or equivalence type) without med

**UPDRS III motor score**

**UPDRS subscores 20-26**

Individual normalized beta power (6 patients)  
Individual normalized theta power (4 patients)

**Normalized UPDRS part III motor score vs. reduction of individual beta power (3rd day)**

Subscores 20-26: tremor at rest, action or postural tremor of hands, rigidity, finger taps, hand movements, rapid alternating movements of hands, leg agility

Adamchic et al., Mov. Disord. 2014
Vibrotactile CR stimulation for Parkinson’s therapy – non-invasive approach

Computational prediction: non-invasive CR stimulation

human thalamic somatic sensory nucleus [ventral caudal (Vc)]: vibratory entrainment
Weiss et al., J. Neurophysiol. 2009

Fingertip stimulation
Penfield & Rasmussen 1950
Vibrotactile CR stimulation for the treatment of Parkinson’s disease

C-MF tactors
Engineering Acoustics, Inc.
3 months pilot study
Noisy vibrotactile CR –
acute effects (day 1) vs. cumulative effects (3 months)
off medication (n=6)

Pfeifer et al., Front. Physiol. 2021
Noisy vibrotactile CR – clinical significance

Delta MD-S-UPDRS III

P1  P2  P3  P4  P5  P6

0  -3  -6  -9  -12  -15  -18  -21

Acute Delta 1st Visit
Cumulative Delta 3 Months

Delta UPDRS = UPDRS post vCR – UPDRS pre vCR

-3.25 MCID
Levodopa Equivalent Daily Dose (LEDD)

3 Month Vibrotactile Effects

Pfeifer et al., Front. Physiol. 2021
Noisy vibrotactile CR – EEG analysis: sLORETA high beta power

Sensorimotor Cortex
High Beta Band (21-30) Hz
Relative Power

Baseline

3 Months of vCR Therapy

Pfeifer et al., Front. Physiol. 2021

sLORETA power in somatomotor A region (ROI)
Schaefer et al., Cereb. Cortex 2018
6+ months case series study - Noisy vs. regular vibrotactile CR

A, B: regular vibrotactile CR (no jitter of stimulus timing)
C: noisy vibrotactile CR (23.5% jitter of stimulus timing)

Pfeifer et al., Front. Physiol. 2021
PD diagnosis in 2007

Meds:
20-25 Carbidopa Levodopa
25/100 per day
2 Amantadine per day
2-3 vapes of CBD/THC per day

50 % off time

used a cane; supposed to use a wheel chair
1st day of vibrotactile CR stim
(2x2h/day)

6 (instead of 20-25)
Carbidopa Levodopa
25/100 per day

15 min off time

Pfeifer et al.,
Front. Physiol. 2021
6th day of vibrotactile CR stim (2h/day)

6.5 (instead of 20-25)
Carbidopa Levodopa
25/100 per day

“Worked in my office for the first time in 2 years for 4 hours”
15 min off time

7th day of vibrotactile CR stim (2h/day)

6.0 (instead of 20-25)
Carbidopa Levodopa
25/100 per day

“Worked a full day in my office after 2 years”
15 min off time

8th day of vibrotactile CR stim (2h/day)

6.5 (instead of 20-25)
Carbidopa Levodopa
25/100 per day

“Noticed an improved sense of smell and taste”
10 min off time

Pfeifer et al.,
Front. Physiol. 2021
PD diagnosis at age 27

off meds, prior to vibrotactile treatment

Pfeifer et al., Front. Physiol. 2021
after 6 weeks of vibrotactile noisy CR

Pfeifer et al., Front. Physiol. 2021
1st visit, 1st day morning off meds, before vibrotactile therapy
3-month visit, 1\textsuperscript{st} day morning off meds
after 5 months
After 6 months vCR and 1 month pre-planned pause
Theoretical/computational studies – for DBS

• other plasticity mechanisms, e.g., structural (homeostatic)

• different types of spike-timing-dependent plasticity curves vs. different stimulation patterns
  Kromer & Tass, PRR 2020; Kromer et al., Chaos 2020; Khaledi-Nasab et al., Front Physiol. 2021a, 2021b;

• cortico-basal ganglia-thalamo-cortical loops → propagation
  Kromer, Bokil, Tass (in preparation)

Outlook

• Theoretical/computational studies – for vibrotactile stimulation

• impact on neurodegeneration
Theoretical/computational studies

- desynchronization-induced reduction of synaptic weights

- decoupling stimulation: reduction of synaptic weights without acute desynchronization

- reshaping network topology with, e.g., periodic multichannel stimulation (PMCS)

Outlook

- stimulation-induced metabolic changes
Acknowledgments

Tass lab

Justus A. Kromer
Kristina Pfeiffer
Jessica Kalinova Yankulova
Ellyn Daly
Alexander Cook
Tina Munjal

Stanford Neurology
Leila Montaser Kouhsari
Maya Katz
Kathleen Poston
Adam Fogarty

Stanford Neurosurgery
Summer Han

University of Arkansas

Rohit Dhall
Center for Neurodegenerative Disorders
Department of Neurology
University of Arkansas for Medical Sciences

Funding
Binns family foundation
McGrath family foundation
John A. Blume Foundation
Vaughn Bryson Research Fund
The Anonymous Life Science Fund
Synergic Medical Technologies
Boston Scientific Neuromodulation
NIH, The Parkinson Alliance

Email: ptass@stanford.edu
Thank you!