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

Peter A. Tass, MD, PhD

Professor of Neurosurgery

Stanford MEDICINE | Neurosurgery

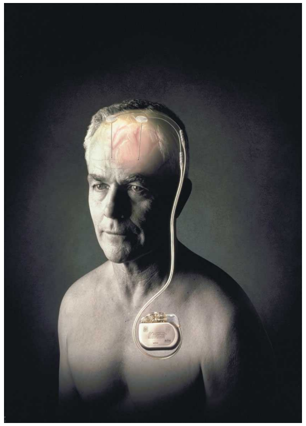
Parkinson‘s disease

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

- Abnormal synaptic connectivity
  McGregor & Nelson, Neuron 2019

Standard permament

high-frequency deep brain stimulation

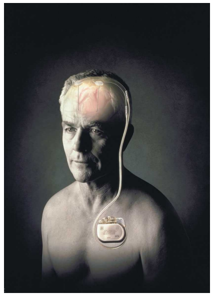


PD Patient, 48 ys

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

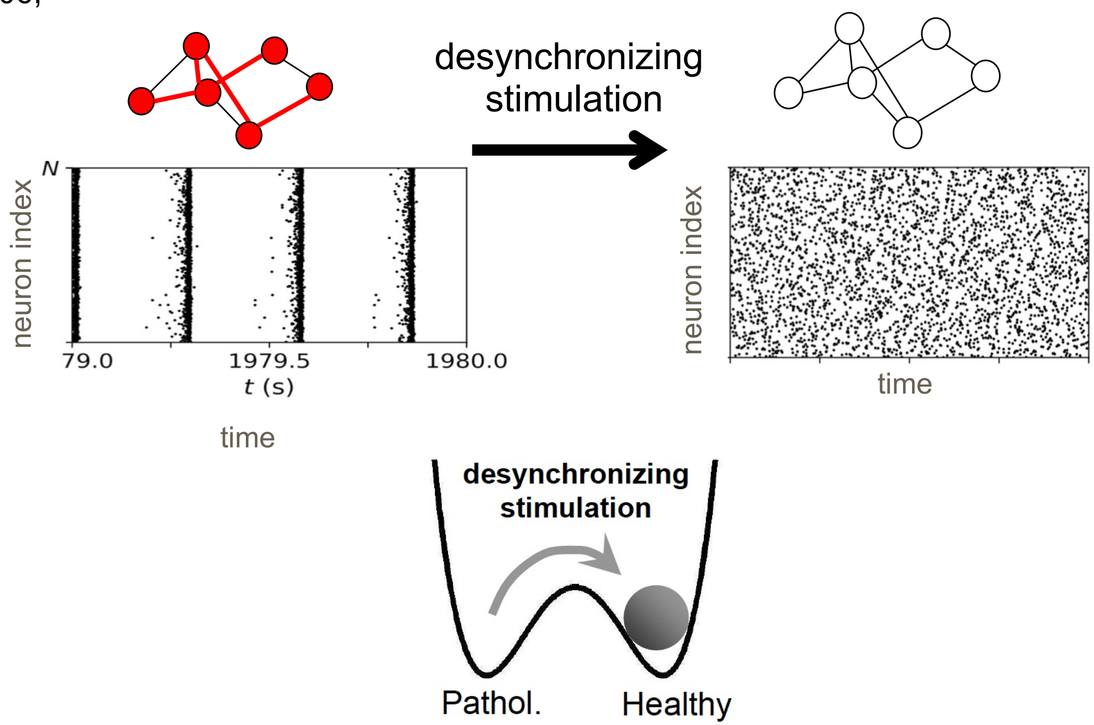
Benabid et al., The Lancet 1991; Baizabal-Carvallo et al Park. Rel. Dis. 2016; Buhmann et al PLoS One 2016; Lozana et al., Nature Rev Neurol 2019



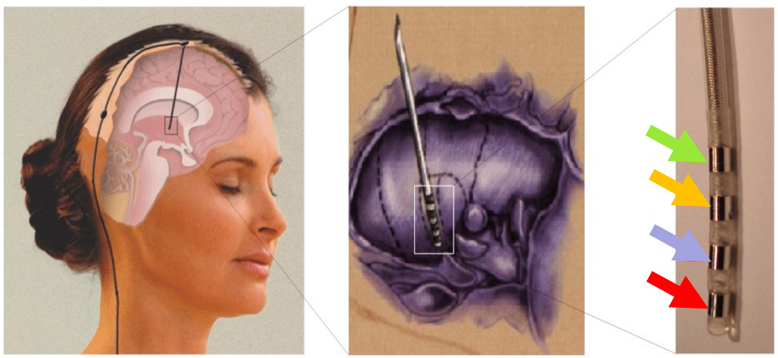
Computationally based approach to induce long-lasting desynchronization by reshaping network connectivity

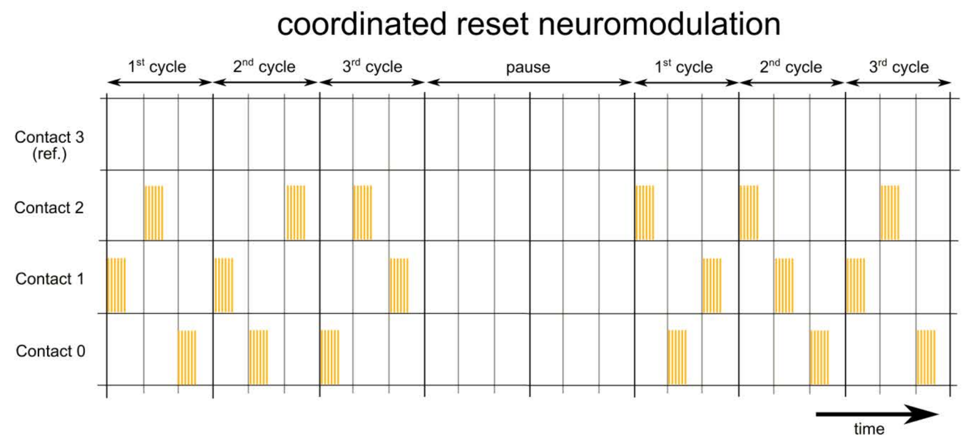
- Specifically counteract abnormal neuronal synchrony by desynchronization
  Tass, Phase Resetting in Medicine and Biology. Springer 1999; Tass, Biol. Cybern. 2003

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



Coordinated Reset Deep Brain Stimulation

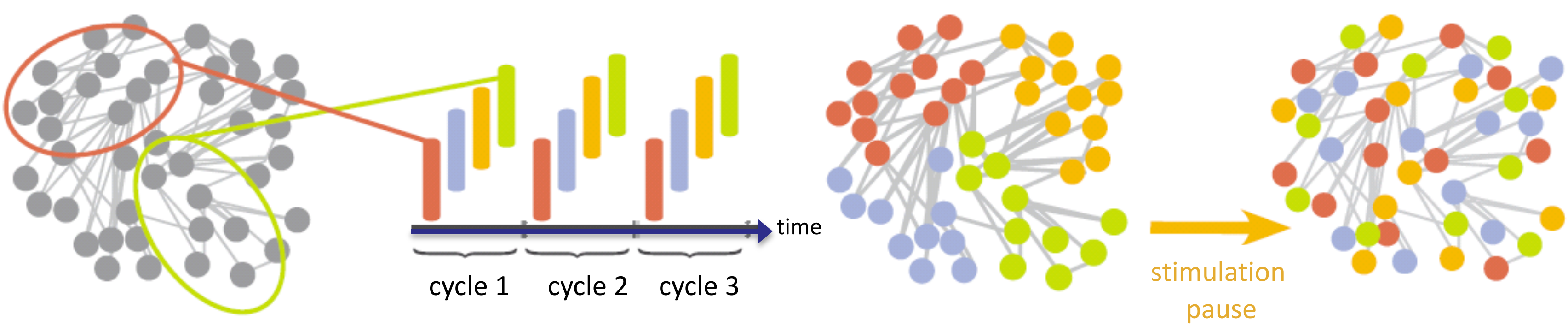




Synchronous neuronal population

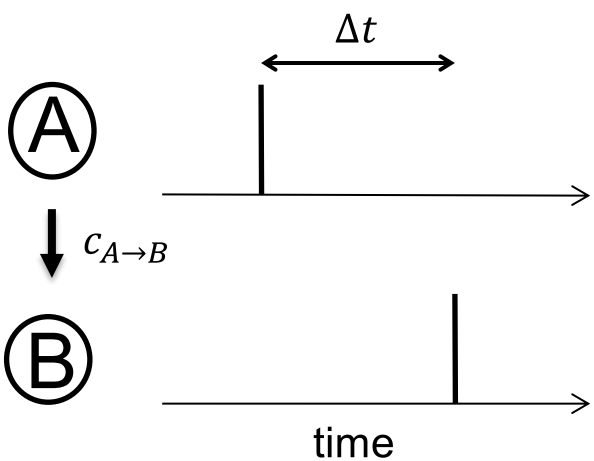
Divided into sub-groups

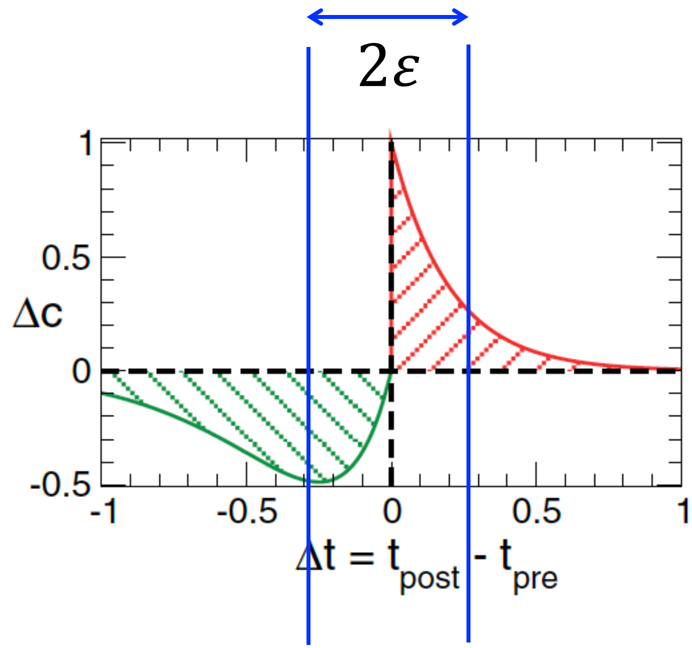
Complete desynchronisation



Tass, Biol. Cybern 2003; Phys. Rev. E 2003; Prog. Theor. Phys. 2003

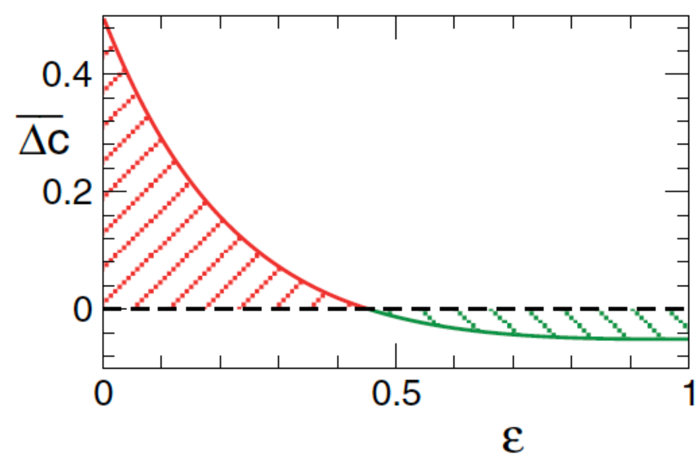
Spike timing-dependent plasticity





Hebb, D.O. (1949). The Organization of Behavior. New York: Wiley & Sons; Gerstner et al., Nature 1996; Markram et al., Science 1997

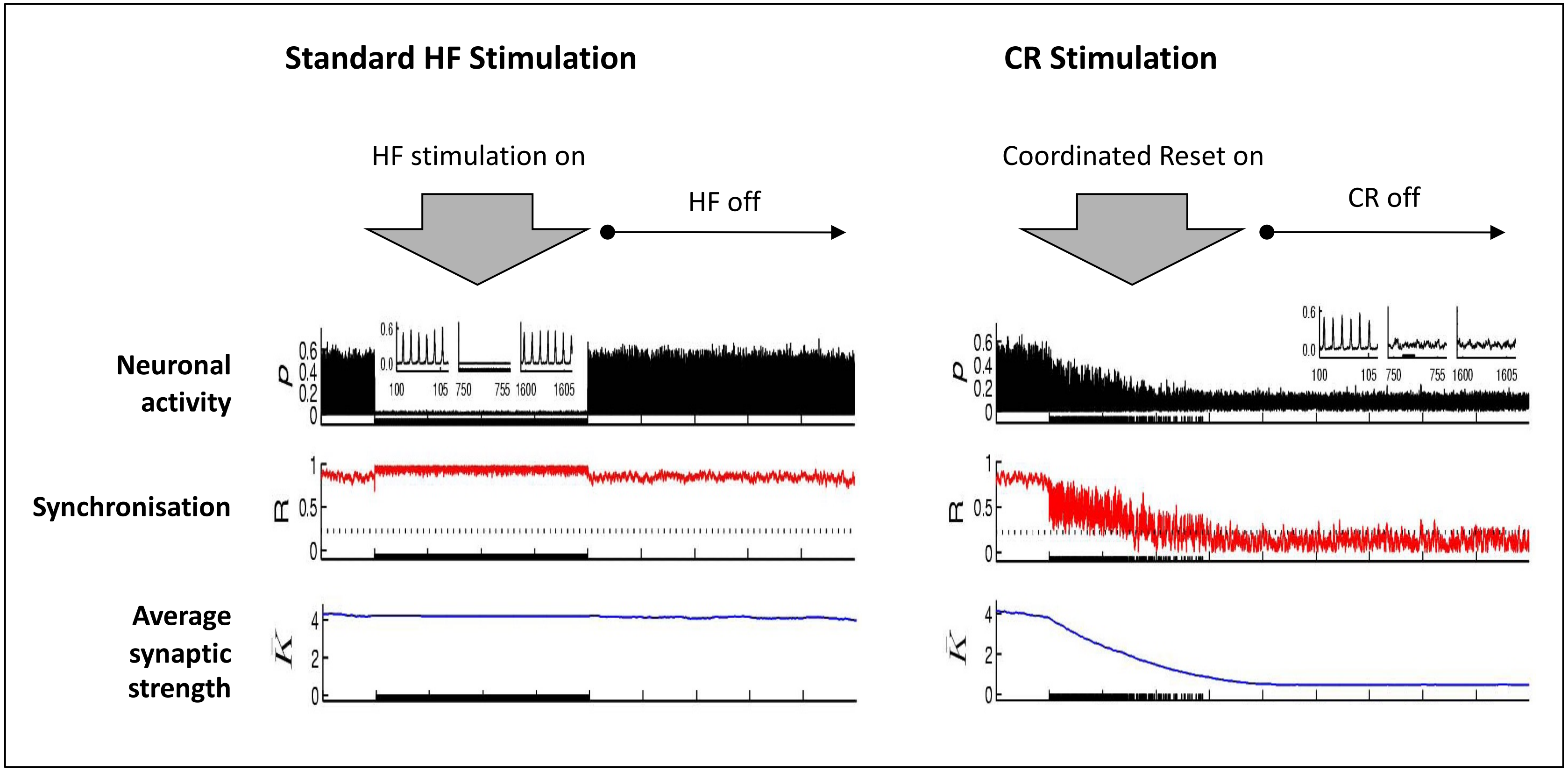
net STDP effect for $\Delta t \in [-\varepsilon, \varepsilon]$ (uniform)



desynchronization-induced reduction of synaptic weights

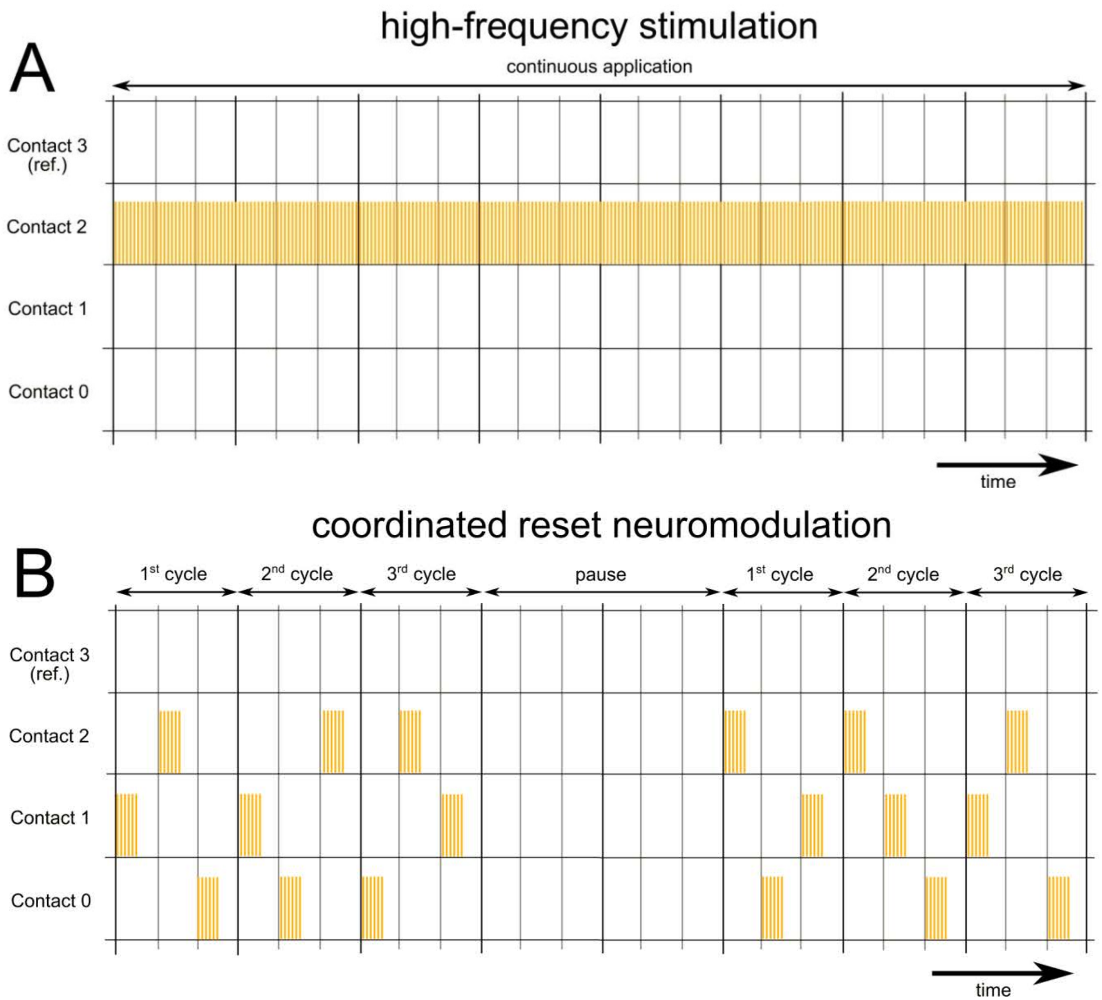
Tass & Majtanik, Biol. Cybern. 2006; Popovych & Tass, Front. Hum. Neurosci. 2012

Standard high-frequency (HF) stimulation vs. CR Stimulation



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)

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

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

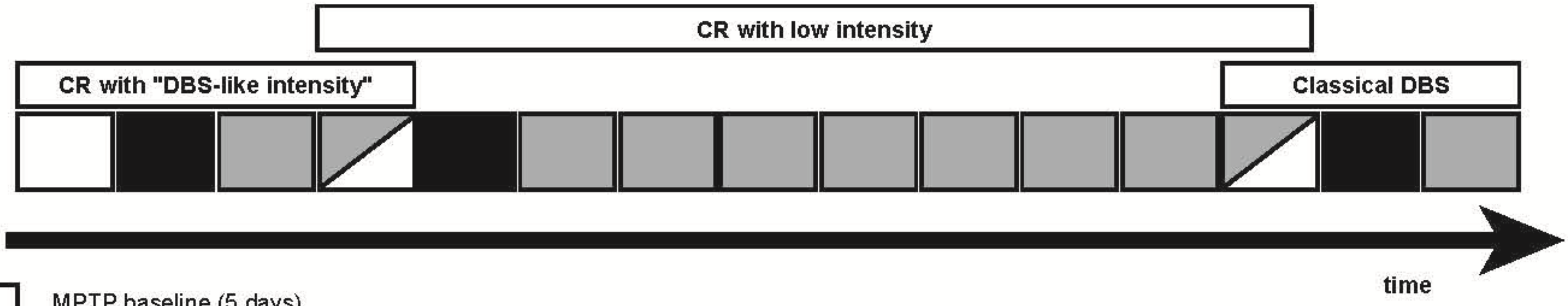
Tass, Qin, Hauptmann, Dovero, Bezard, Boraud, Meissner; Annals of Neurology 2012

CR deep brain stimulation in MPTP monkeys

Theoretical prediction: low intensity = DBS-like intensity / 3 is optimal for CR

Lysyansky et al. J. Neural Eng. 2011

Experimental cross-over design



MPTP baseline (5 days)

assessment of acute post-effects after the end of each CR and DBS session (5 days)

assessment of long-lasting post-effects after the end of CR and DBS (5-40 days depending on duration of post-effect)

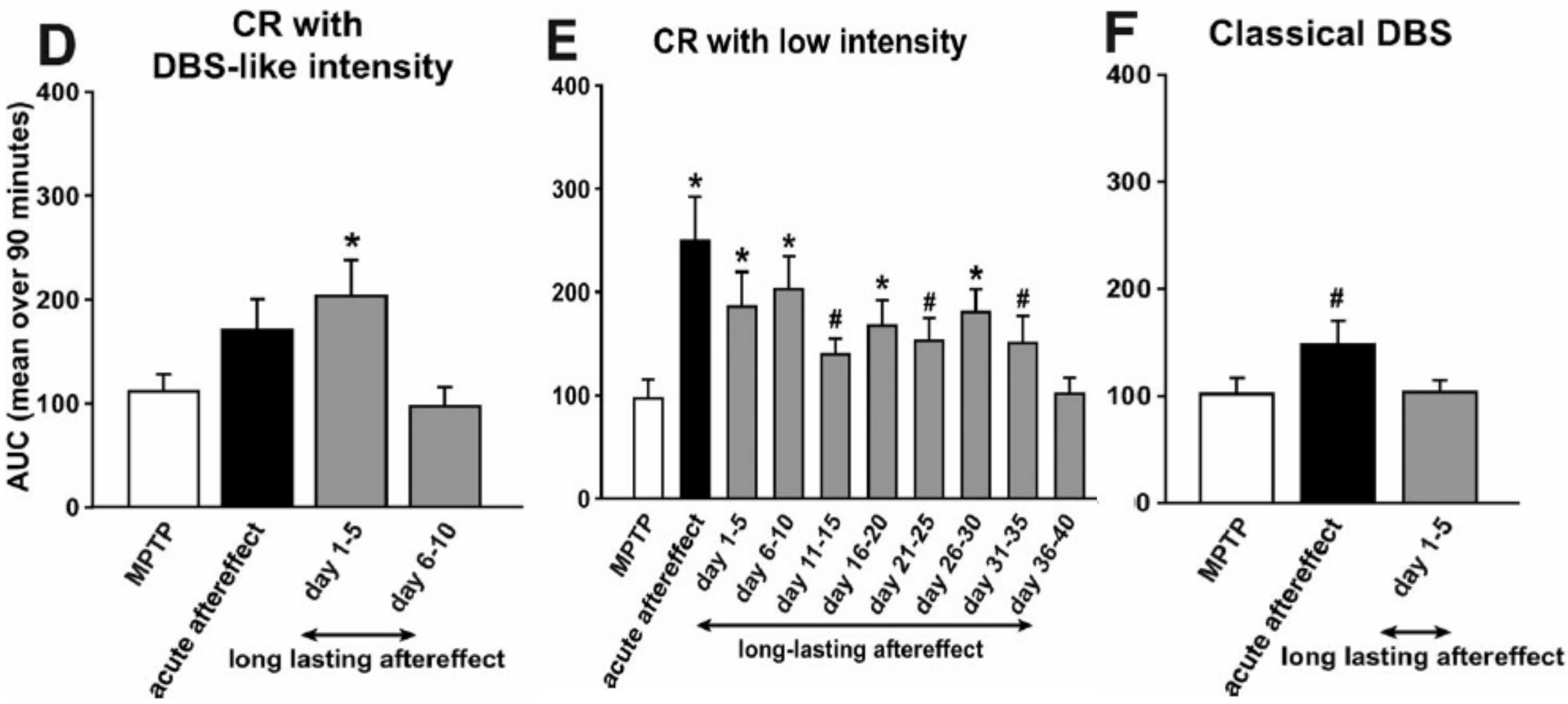
post-effect had returned to initial MPTP baseline (5 days)

- 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

AUC = area under curve (mobility count)



intensity: 0.6 mA ± 0.1 mA

intensity: 0.2 mA ± 0.0 mA

intensity: 0.6 mA ± 0.1 mA

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

Sustained after-effects of CR and standard DBS

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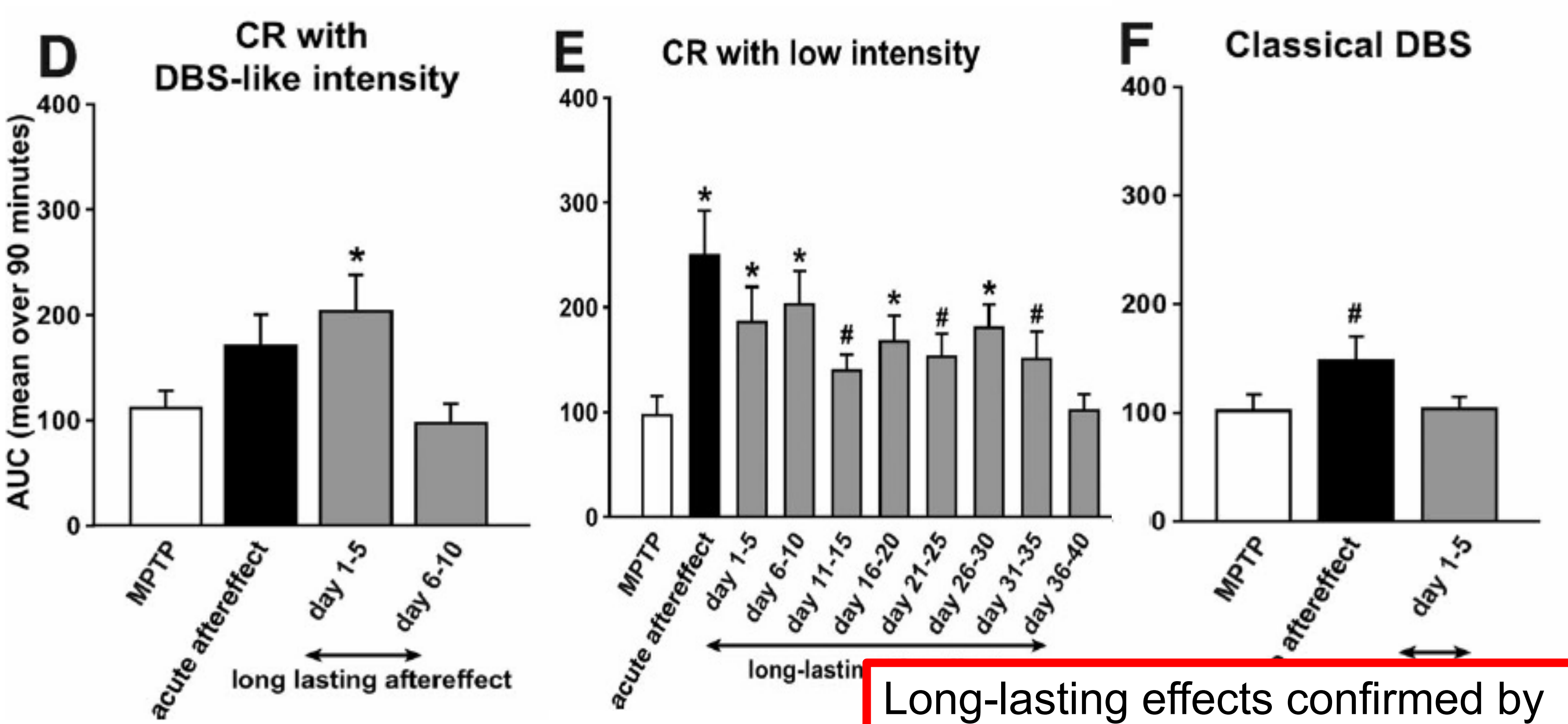


intensity: 0.6 mA ± 0.1 mA

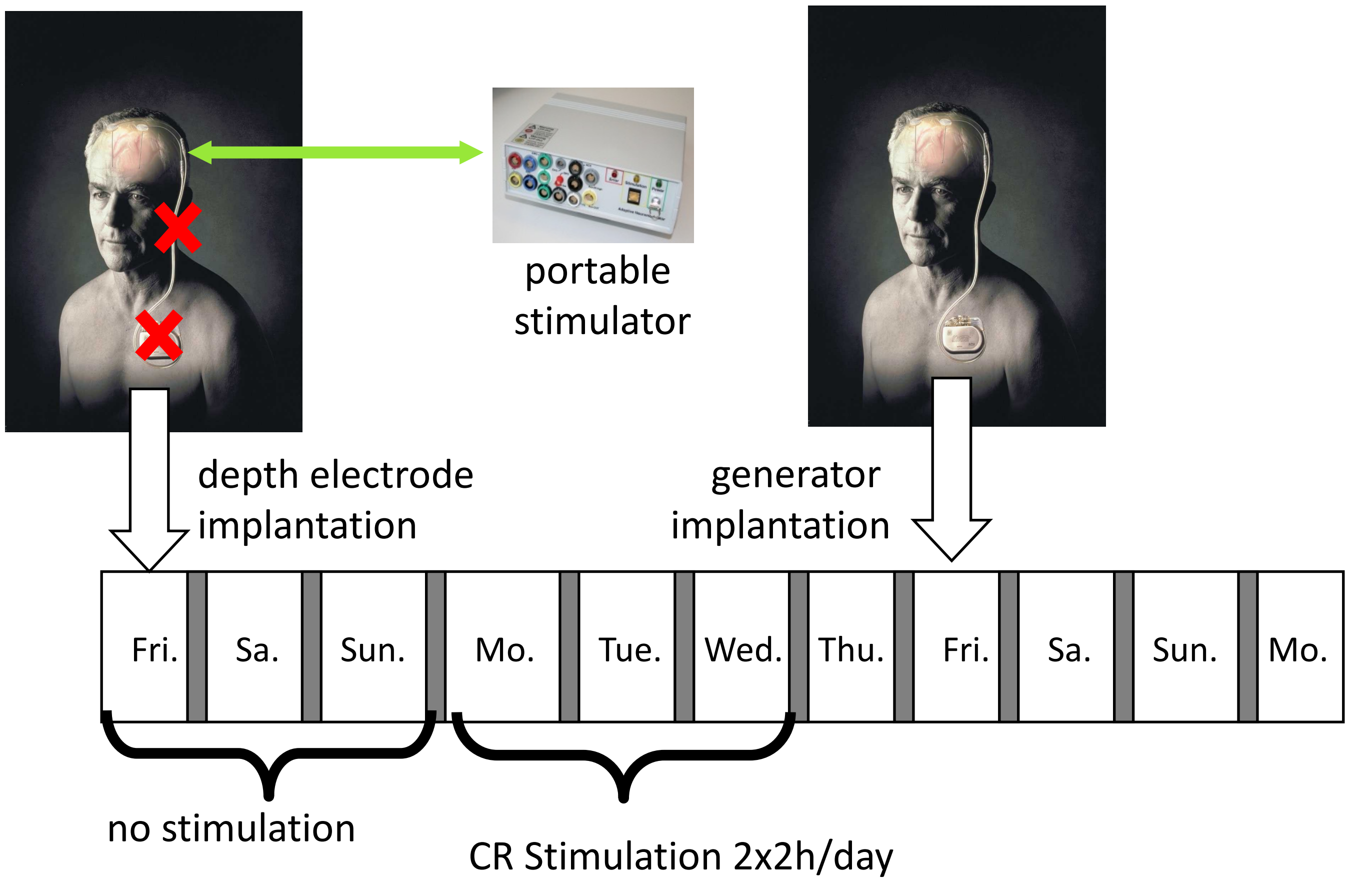
intensity: 0.2 mA ±

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

Tass, Qin, Hauptmann, Dovero, Bezard, Boraud, Meissner; Annal

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



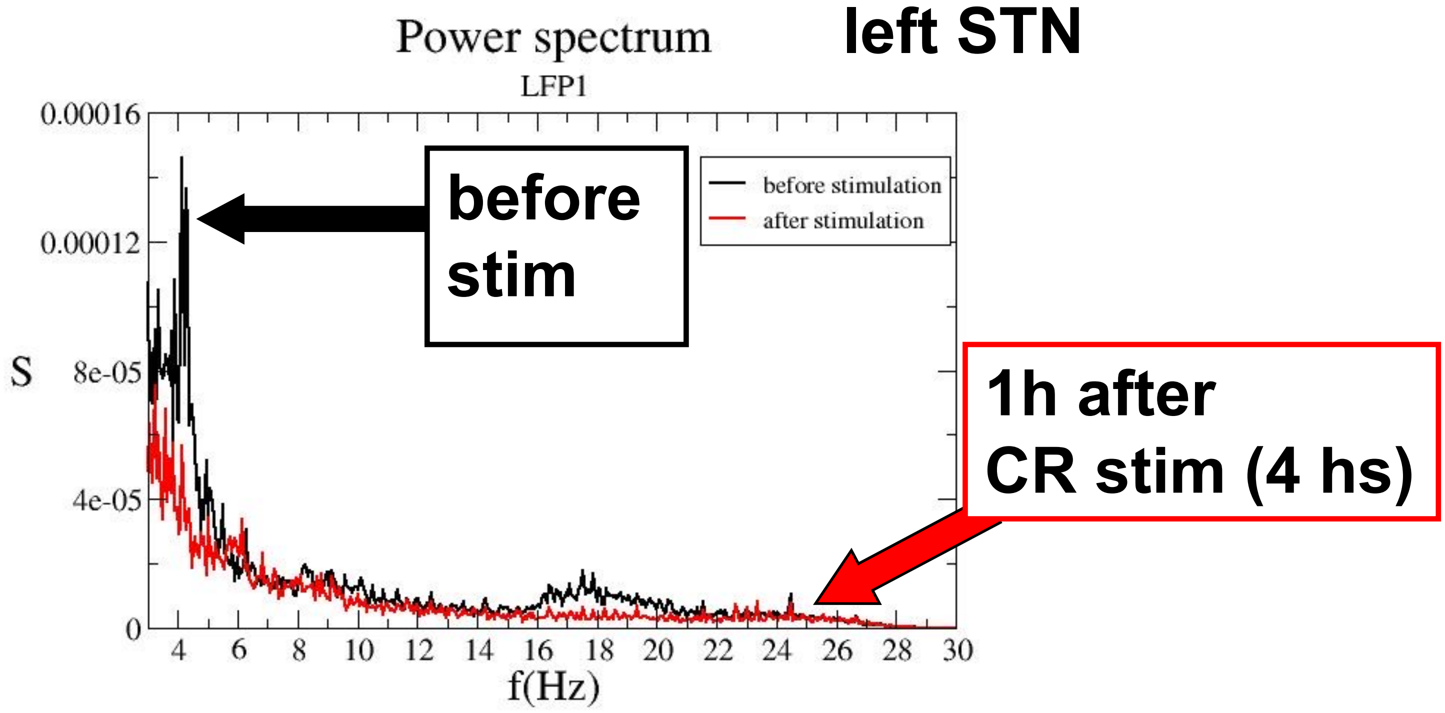
Adamchic et al., Mov. Disord. 2014

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.**

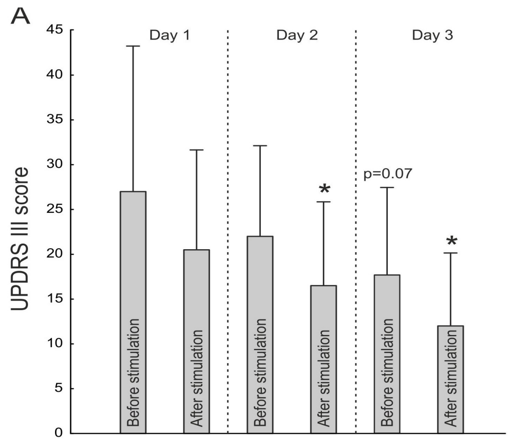
Kühn et al., J. Neurosci. 2008

Adamchic et al., Mov. Disord. 2014

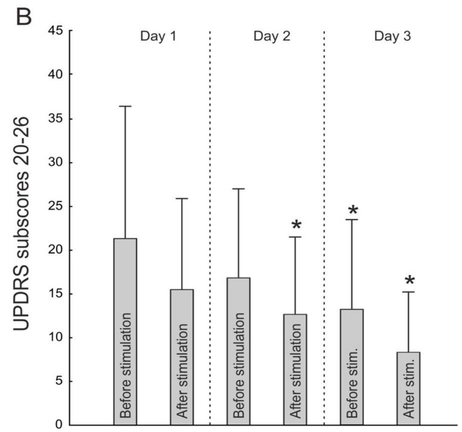
Long-lasting and cumulative effects of CR stimulation

6 PD patients (akinetic or equivalence type) without med

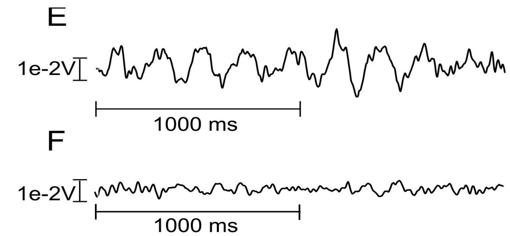
UPDRS III motor score

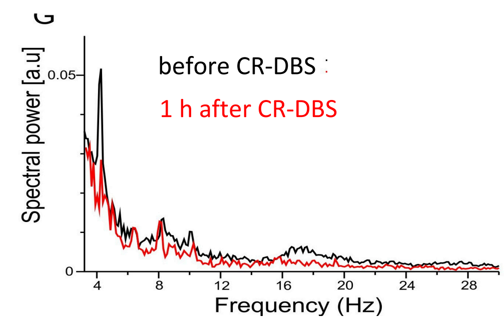


UPDRS subscores 20-26

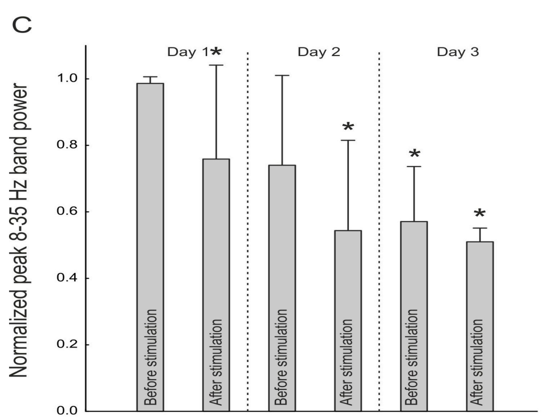


raw LFP

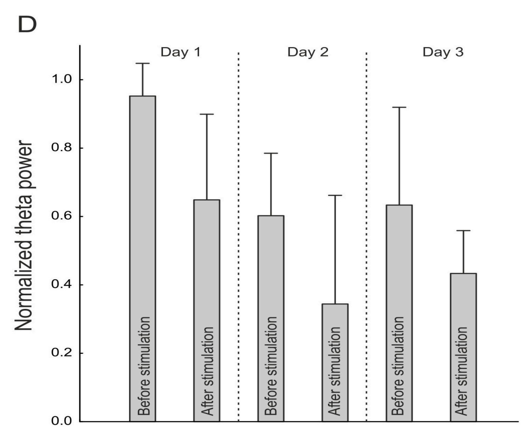




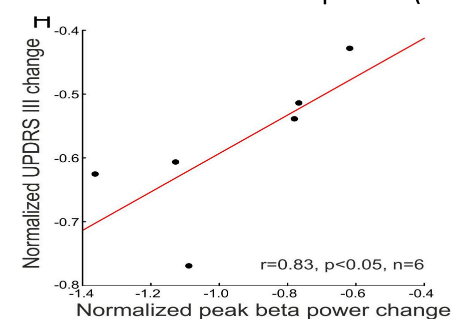
Individual normalized beta power (6 patients)



Individual normalized theta power (4 patients)



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



Subsores 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

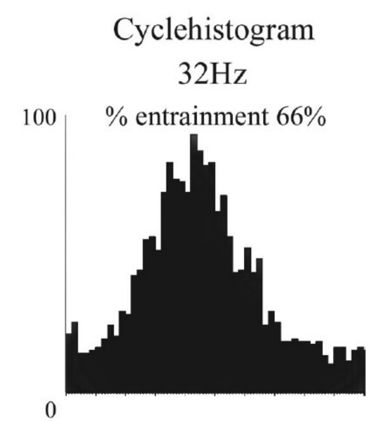
Vibrotactile CR stimulation for Parkinson‘s therapy – non-invasive approach

Computational prediction: non-invasive CR stimulation

Tass & Popovych, Biol. Cybern. 2012; Popovych & Tass , Front. Hum. Neurosci. 2012; Pfeifer et al., Front. Physiol. 2021

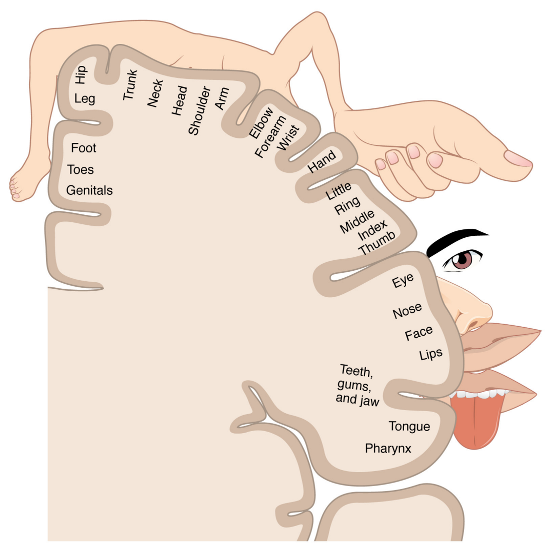
human thalamic somatic sensory nucleus [ventral caudal (Vc)]: vibratory entrainment

Weiss et al., J. Neurophysiol. 2009



Fingertip stimulation

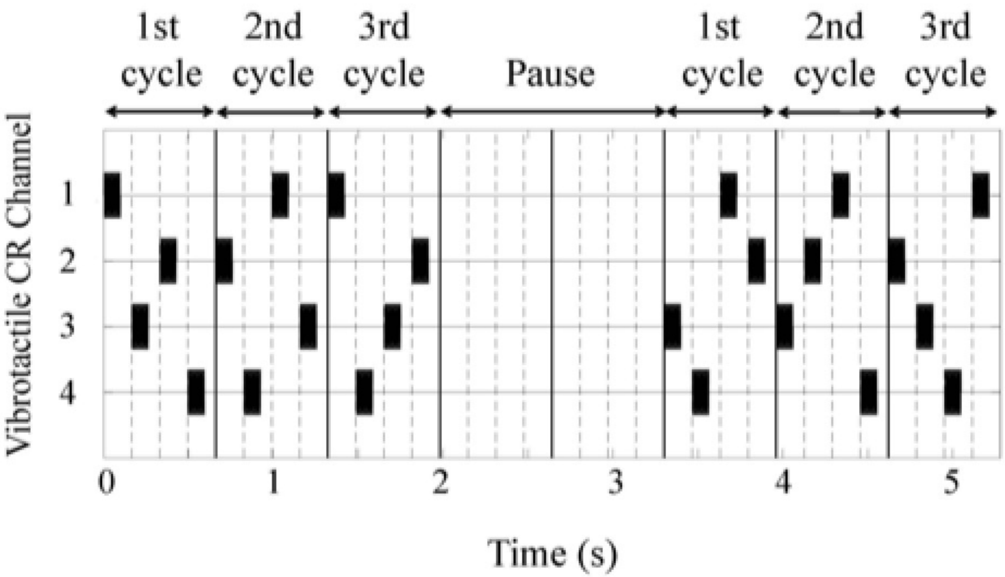
Penfield & Rasmussen 1950



Tass, Cureus, 2017

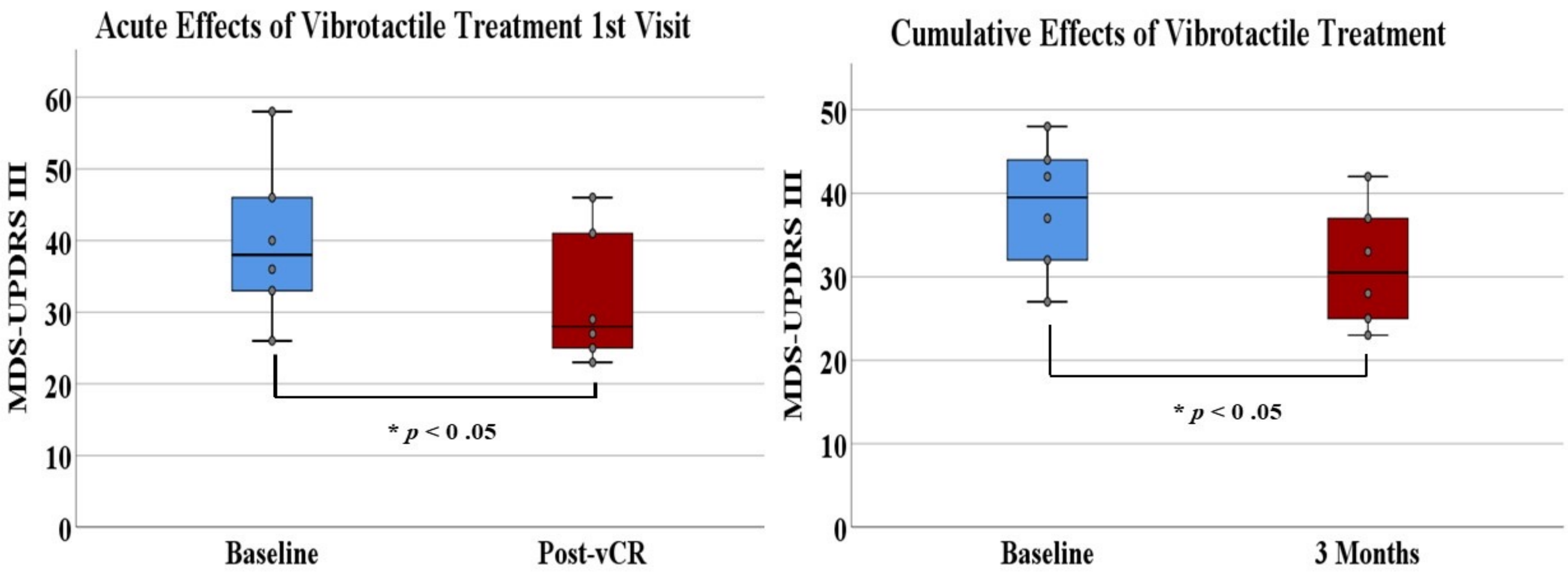
Vibrotactile CR stimulation for the treatment of Parkinson's disease

C-MF tactors
Engineering Acoustics, Inc.



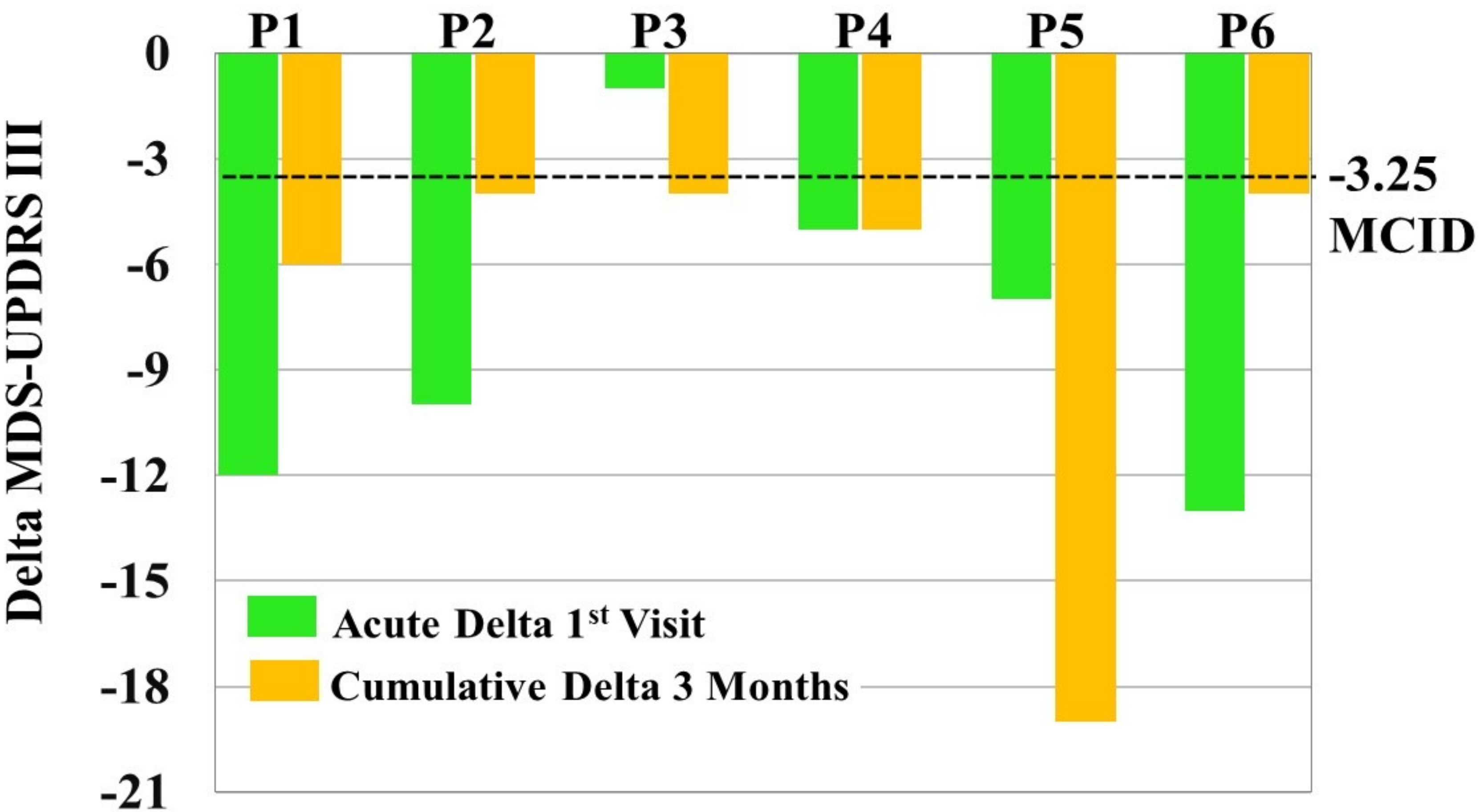
Tass, Cureus, 2017; Pfeifer et al. Front. Physiol. 2021; Syrkin-Nikolau et al., Mov Disord. 2018; Tass, Neural Regen Res, 2021

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

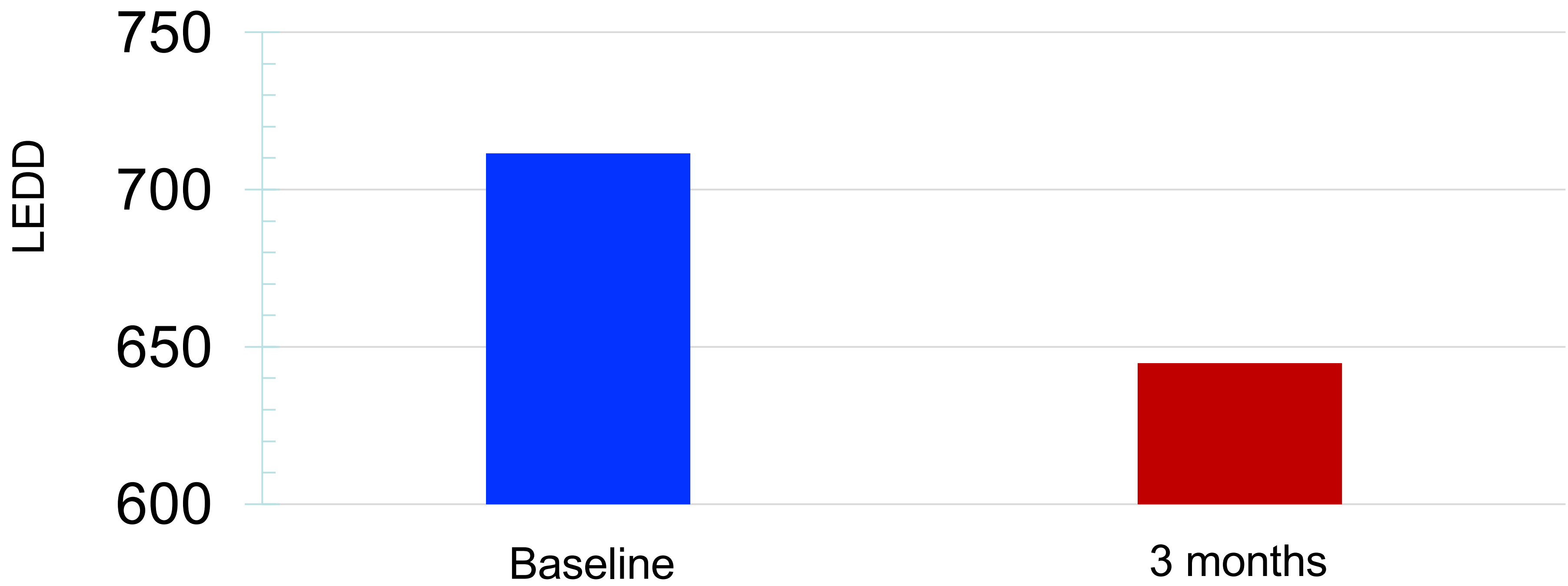
Noisy vibrotactile CR – clinical significance



Delta UPDRS = UPDRS post vCR – UPDRS pre vCR

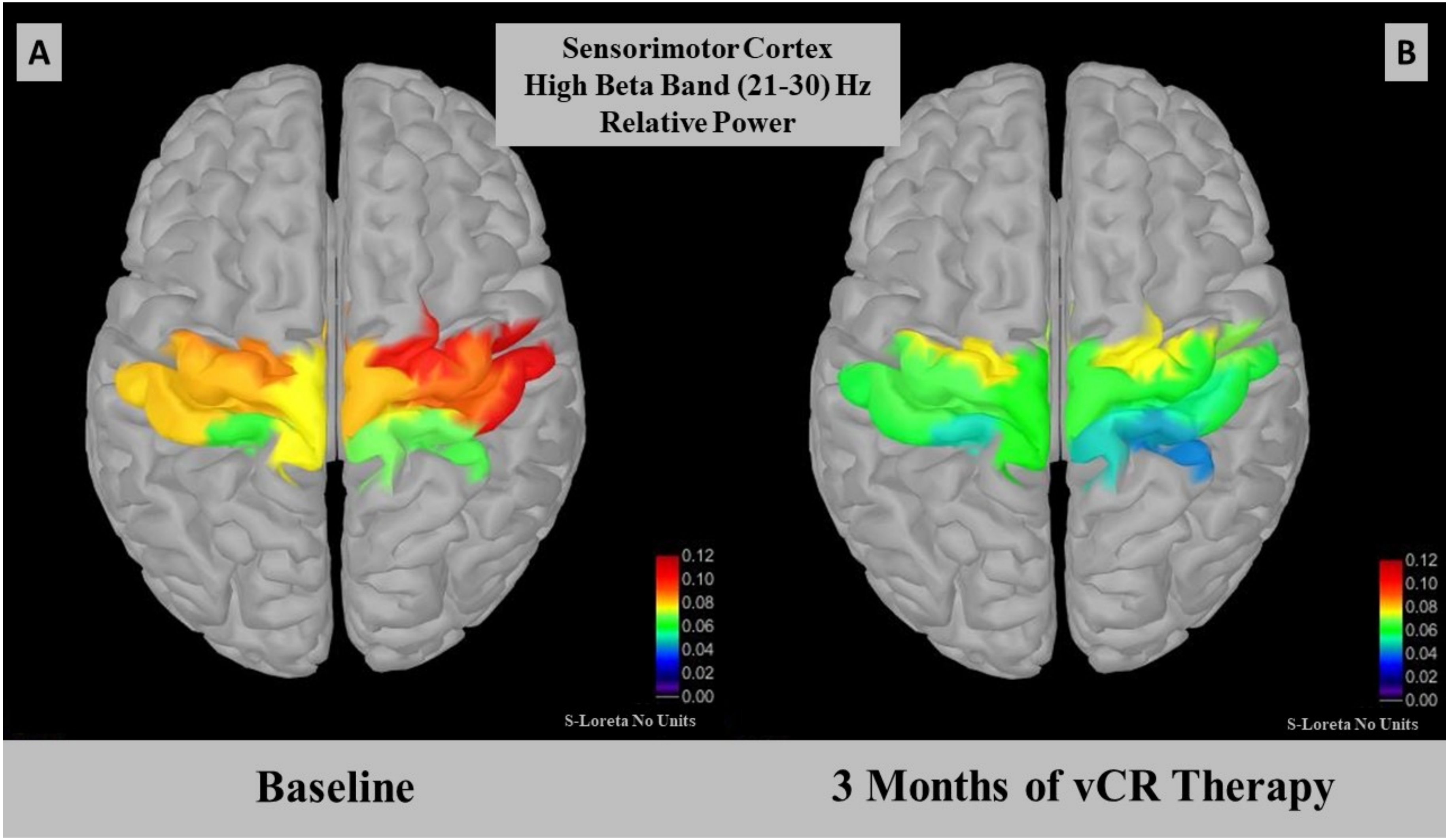
Pfeifer et al., Front. Physiol. 2021

Levodopa Equivalent Daily Dose (LEDD)
3 Month Vibrotactile Effects



Pfeifer et al., Front. Physiol. 2021

Noisy vibrotactile CR – EEG analysis: sLORETA high beta power

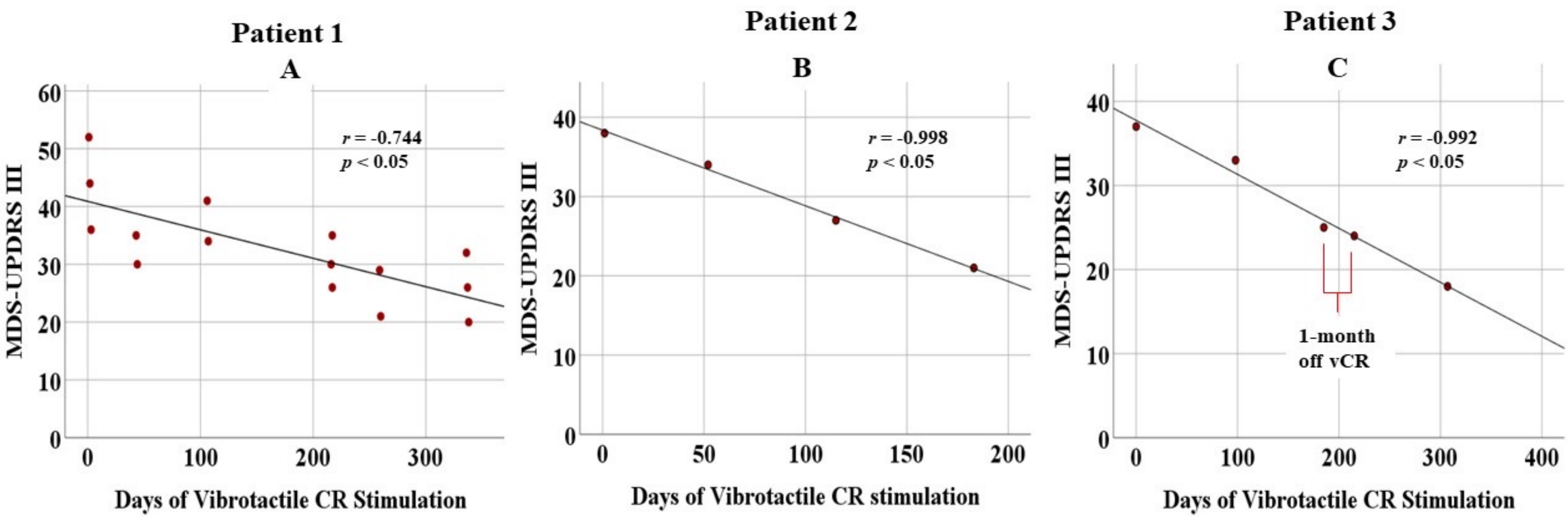


Pfeifer et al., Front. Physiol. 2021

sLORETA power in somatomotor A region (ROI)

Schaefer et al., Cereb. Cortext 2018

6+ months case series study -
Noisy vs. regular vibrotactile CR



off meds scores

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

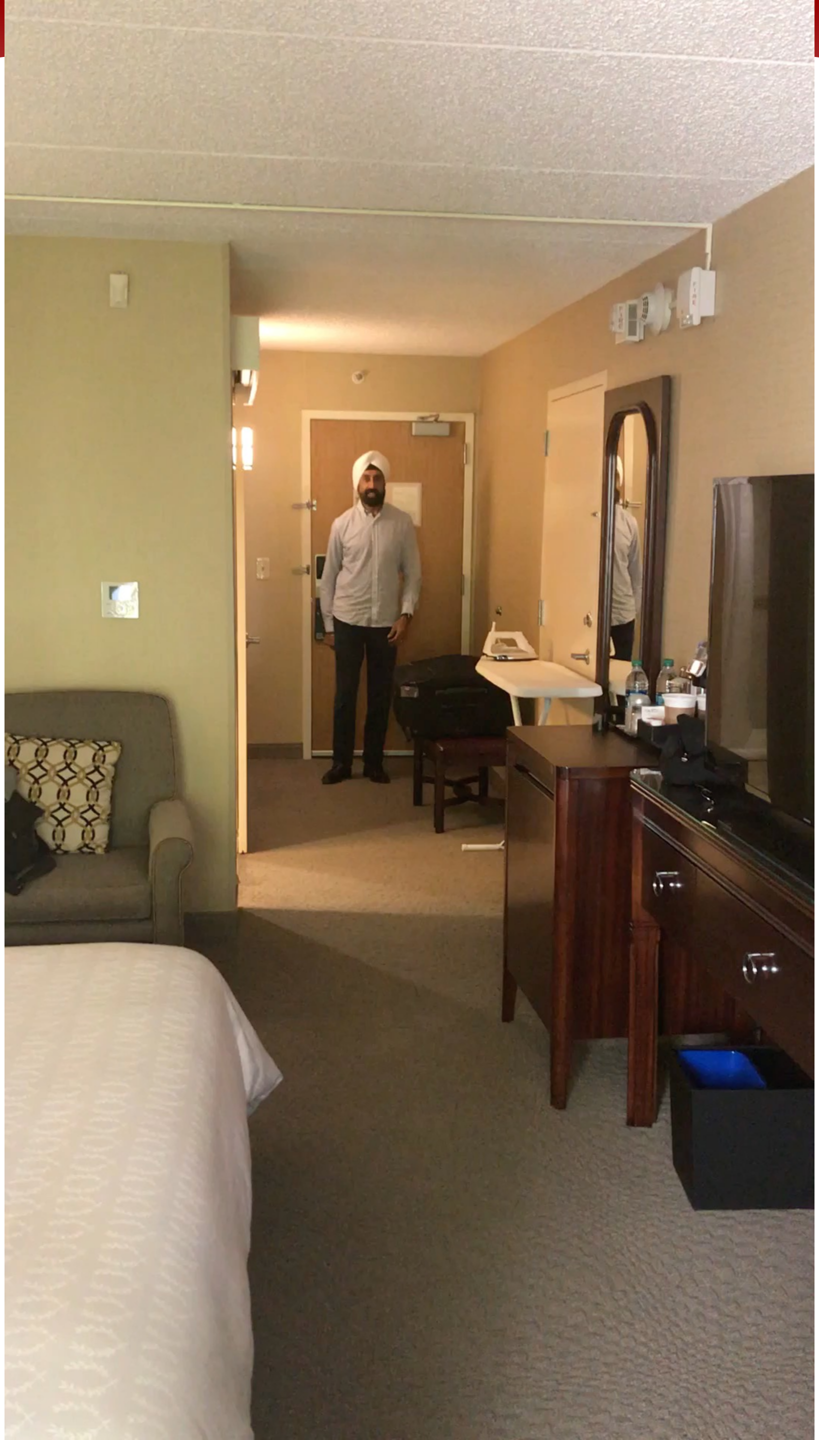
PD diagnosis in 2007

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

Pfeifer et al.,
Front. Physiol. 2021



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

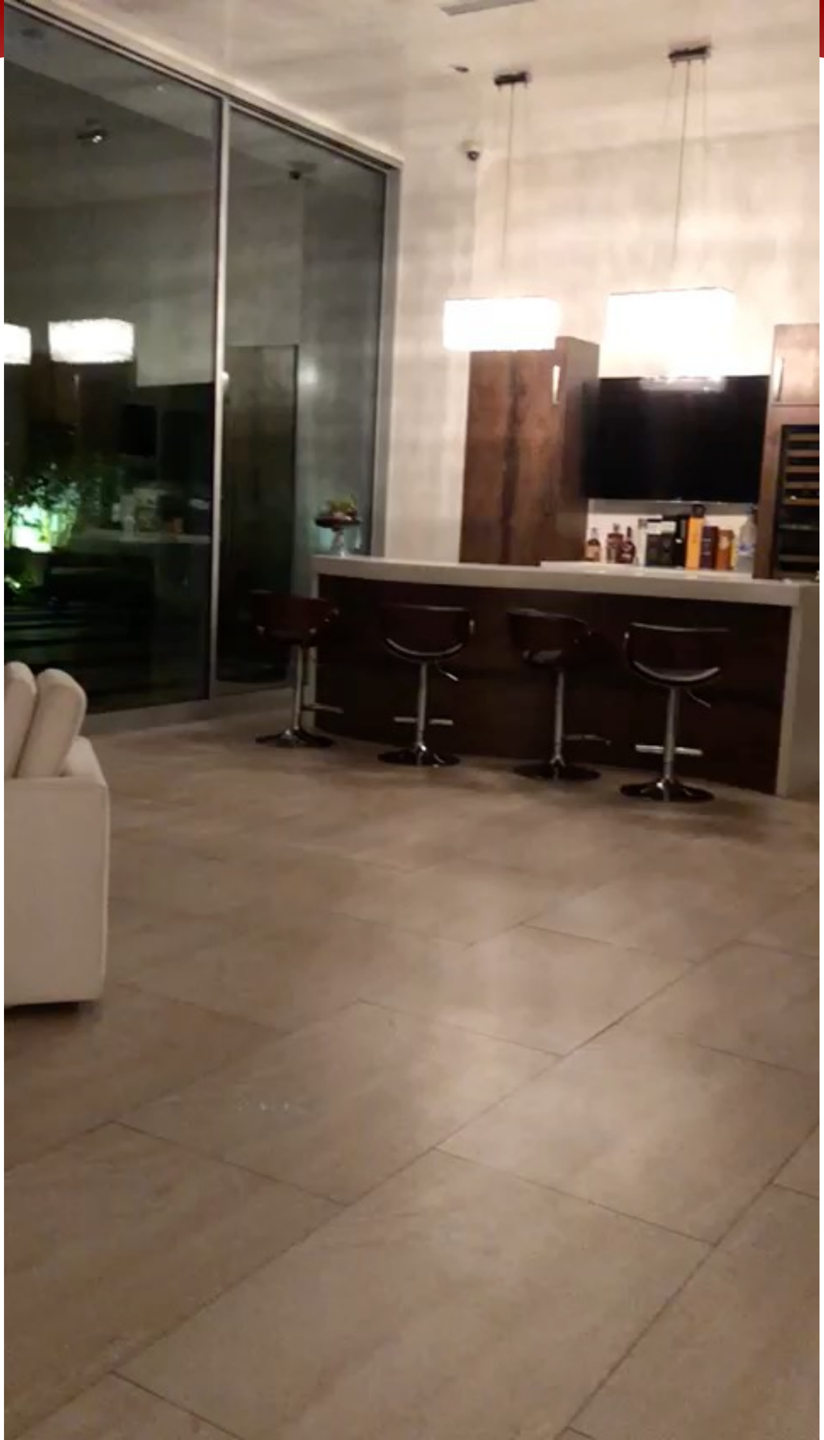
"Worked in my office for the first time in 2 years for 4 hours"

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

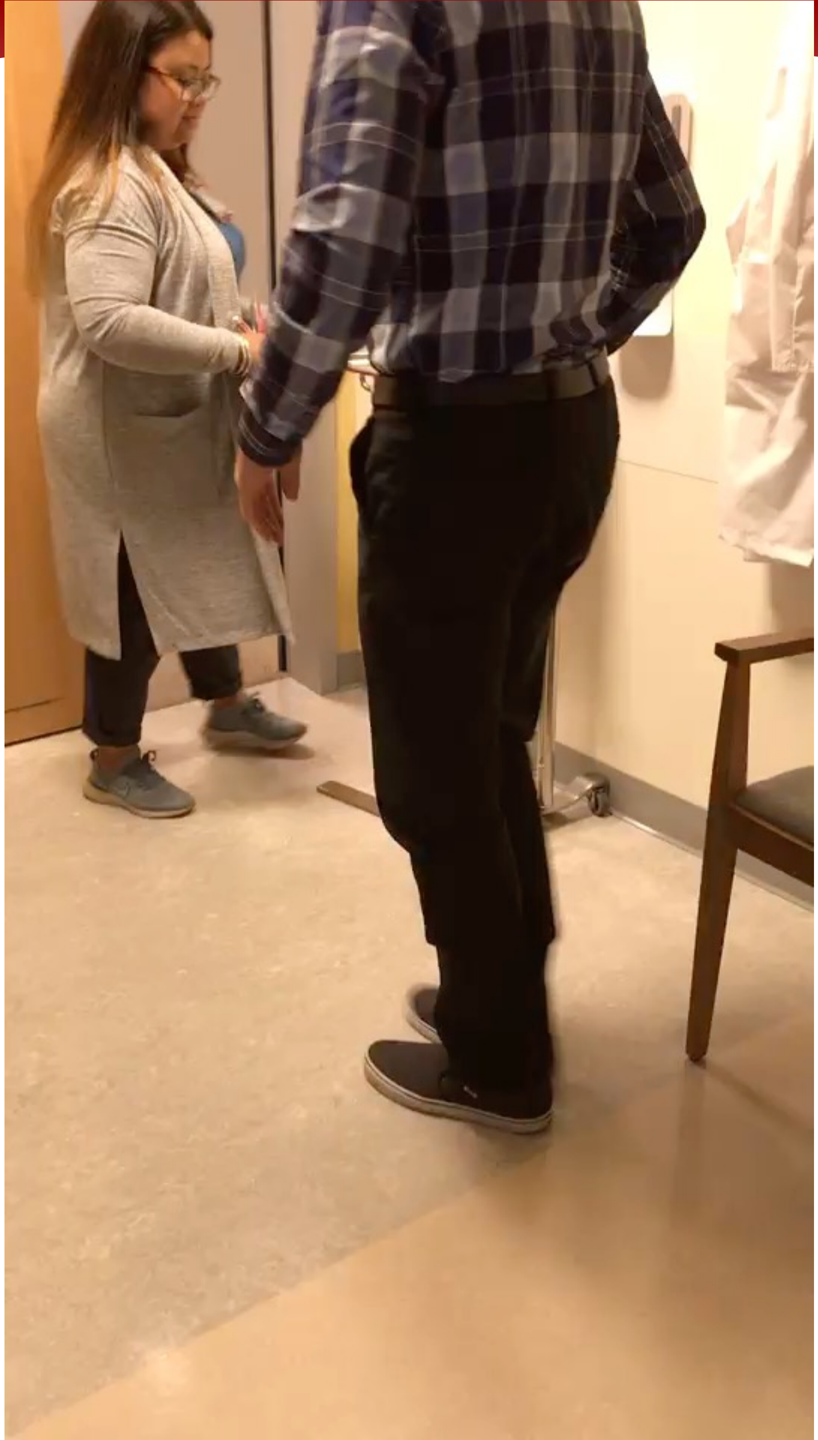
PD diagnosis
at age 27

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

Pfeifer et al., Front. Physiol. 2021

3-month visit, 1st day morning off meds

Pfeifer et al., Front. Physiol. 2021

after 5months

Pfeifer et al., Front. Physiol. 2021

After 6 months
vCR and 1 month
pre-planned pause

Pfeifer et al., Front. Physiol. 2021

Theoretical/computational studies – for DBS

- other plasticity mechanisms, e.g., structural (homeostatic)
  Manos, Diaz, Tass: Front. Physiol. (2021); Chauhan, Khaledi-Nasab, Neiman, Tass: Sci Rep. (2022)

- 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; Khaledi-Nasab et al. Front. Netw. Physiol. (2022)

- 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
  Tass & Majtanik: Biol. Cybern. 2006; Hauptmann & Tass: J. Neural Eng. 2009; Popovych & Tass: Front. Human Neurosci. 2012; Manos, Zeitler, Tass: PLoS Comput. Biol. 2018

- decoupling stimulation: reduction of synaptic weights without acute desynchronization
  Kromer & Tass: Phys. Rev. Research 2020; Khaledi-Nasab, Kromer, Tass: Front. Physiol. 2021

- reshaping network topology with, e.g., periodic multichannel stimulation (PMCS)
  Kromer & Tass: PLoS Biol. Comput. (under review)

Outlook

- stimulation-induced metabolic changes

Acknowledgments

Tass lab

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Email: ptass@stanford.edu

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