Unlearning pathological neuronal synchrony by coordinated reset neuromodulation: treating brain diseases based on synergetic principles

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Unlearning pathological neuronal synchrony with desynchronizing Coordinated Reset (CR) Neuromodulation

- Several brain diseases are characterized by abnormal neuronal synchronization.

- The goal of **Coordinated Reset (CR)** stimulation is to specifically counteract pathological neuronal synchronization by a desynchronization-inducecd unlearning of both pathological connectiviy and synchrony.

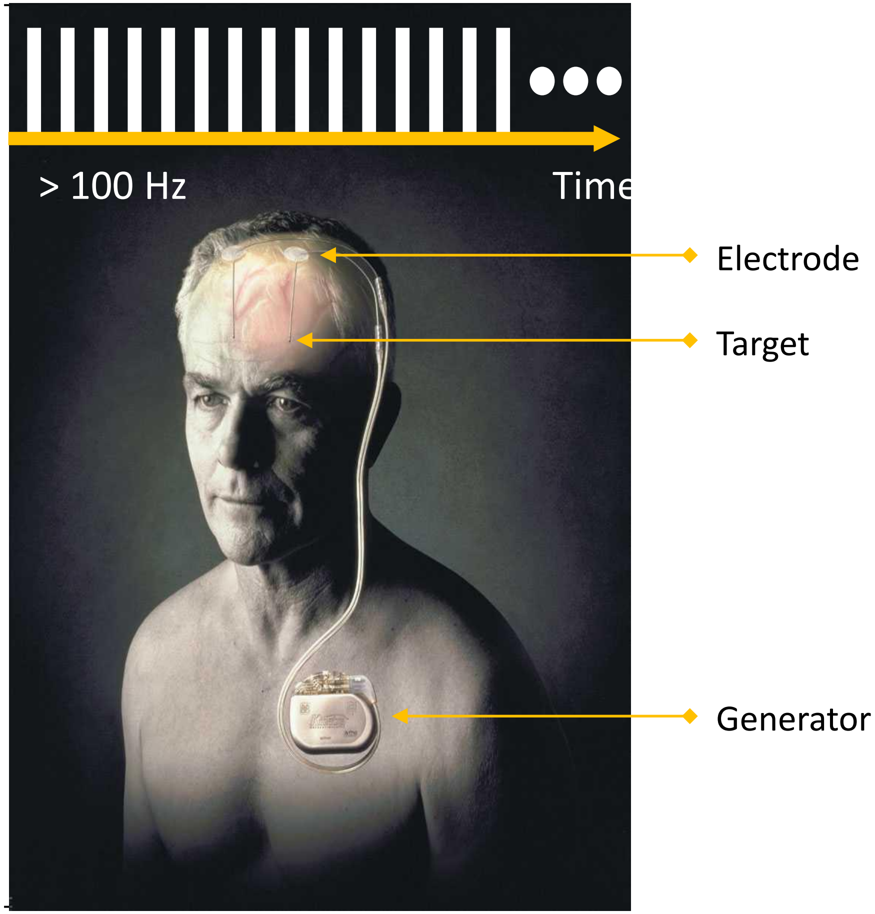
- CR may be applied by means of different stimulation modalities, e.g. direct electrical or indirect sensory stimulation:
  - **Parkinson's** (electrical Coordinated Reset neuromodulation)
  - **Tinnitus** (acoustic Coordinated Reset neuromodulation)

Electrical CR Neuromodulation for Parkinson's

Standard Cardiac Pacemaker = Permanent High-Frequency (HF) Stimulation

High-frequency (HF) brain pacemakers are the **standard therapy form** for patients with severe movement disorders that cannot be treated with medication

- Empirically based
- **Neuronal activity** in the target areas is subjected to **massive alteration** / suppression ("hard" method)
- **Significant side-effects** (such as speech or balance disorders)
- **No long-term therapeutic effects**



Model-based Development of Coordinated Reset

Objectives of Research Work

- To specifically counteract pathological synchronization processes by **desynchronization** Tass: Phase Resetting in Medicine and Biology. Springer 1999

- **To unlearn pathological connectivity** – long-term therapeutic effects Tass & Majtanik, Biol. Cybern. 2006; Tass & Hauptmann, Nonl. Phen. Compl. Sys. 2006; Haupt-mann & Tass, Biosystems 2007; Tass & Hauptmann, Int. J. Psychophysiol. 2007; Maistrenko et al., Phys. Rev. E, 2007; Hauptmann & Tass, J. Neural. Eng. 2009; Tass & Hauptmann, Rest. Neurol. Neurosci. 2009

Mathematical Models of Relevant Brain Areas

Synergetics, Statistical Physics, and Non-linear Dynamics Self-organisation & Plasticity

- Stimulation with Feedback (with / without time delay) Popovych et al. Phys. Rev. Lett 2005; Hauptmann et al. Phys. Rev. E 2007; Pyragas et al. Europhys. Lett. 2007; Omelchenko et al. Phys. Rev. Lett. 2000; Popovych und Tass, Phys.Rev. E 2010
- **Coordinated Reset** (CR) Neuromodulation Tass: Biol. Cybern. 2003; Phys. Rev. E 2003; Prog. Theor. Phys. Supp. 2003

Model – phase oscillator network with spike timing dependent plasticity

coupling **Stimulation via 4 sites**

$$\frac{d\psi_j}{dt} = \omega_j + \underbrace{\frac{1}{N}\sum_{k=1}^{N} K_{kj}(t)\sin(\psi_k - \psi_j)}_{\text{coupling}} + \underbrace{\sum_{\nu=1}^{4} X_\nu(t) S_\nu(\psi_j)\rho_j^{(\nu)}}_{\text{Stimulation via 4 sites}} + \xi_j(t)$$

ω_j = eigenfrequency of jth neuron

$K_{kj}(t)$ = strength of synaptic interaction from neuron $k \rightarrow$ neuron j

$X_\nu(t) = 1$ iff stimulation via site ν is on and 0 else

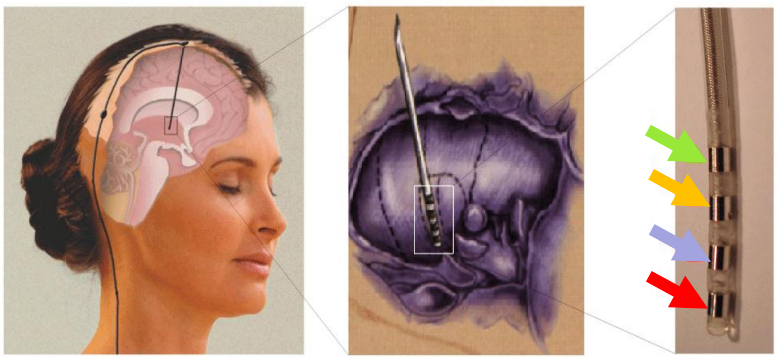
$S_\nu(\psi_j)$ = phase dependent effect of stimulation, e.g. $S_\nu(\psi_j) = I_\nu \cos(\psi_j)$

ξ_j = Gaussian white noise : $\langle \xi_j(t) \rangle = 0$ and $\langle \xi_j(t)\xi_k(t') \rangle = D\delta_{jk}\delta(t - t')$

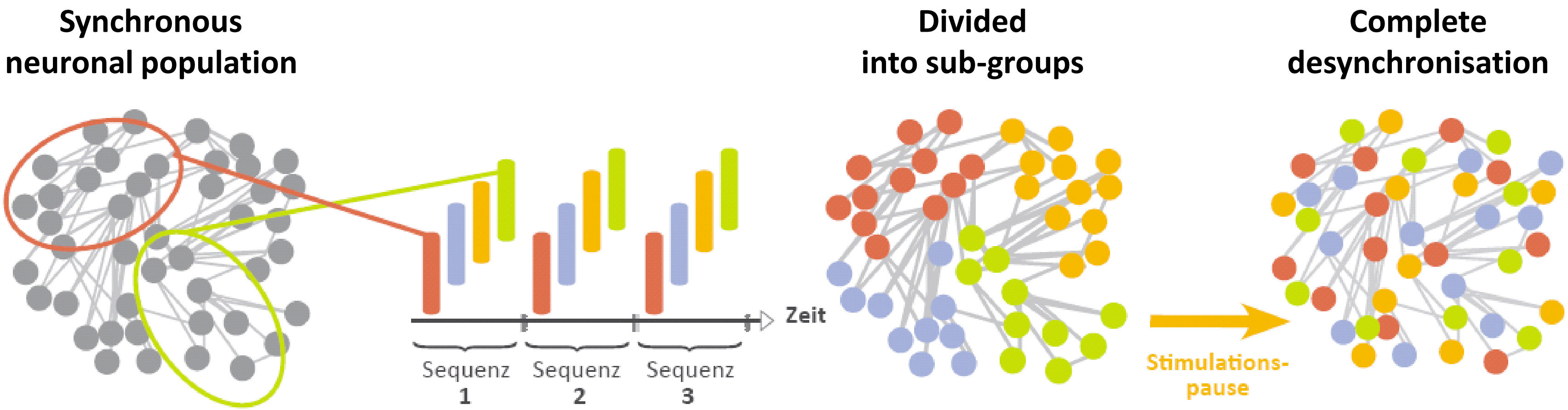
Tass & Majtanik, Biol. Cybern. 2006

Coordinated Reset (CR) Brain Pacemaker

Schematic diagram

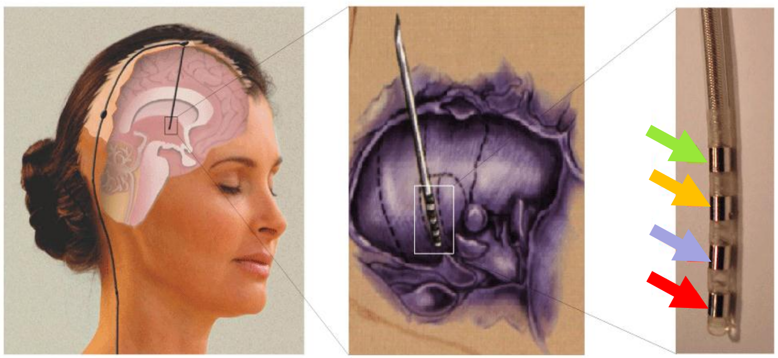


- Neuronal activity is modulated (not suppressed) through targeted impulses
- Enables long-term therapeutic effects



Coordinated Reset (CR) Brain Pacemaker

Schematic diagram



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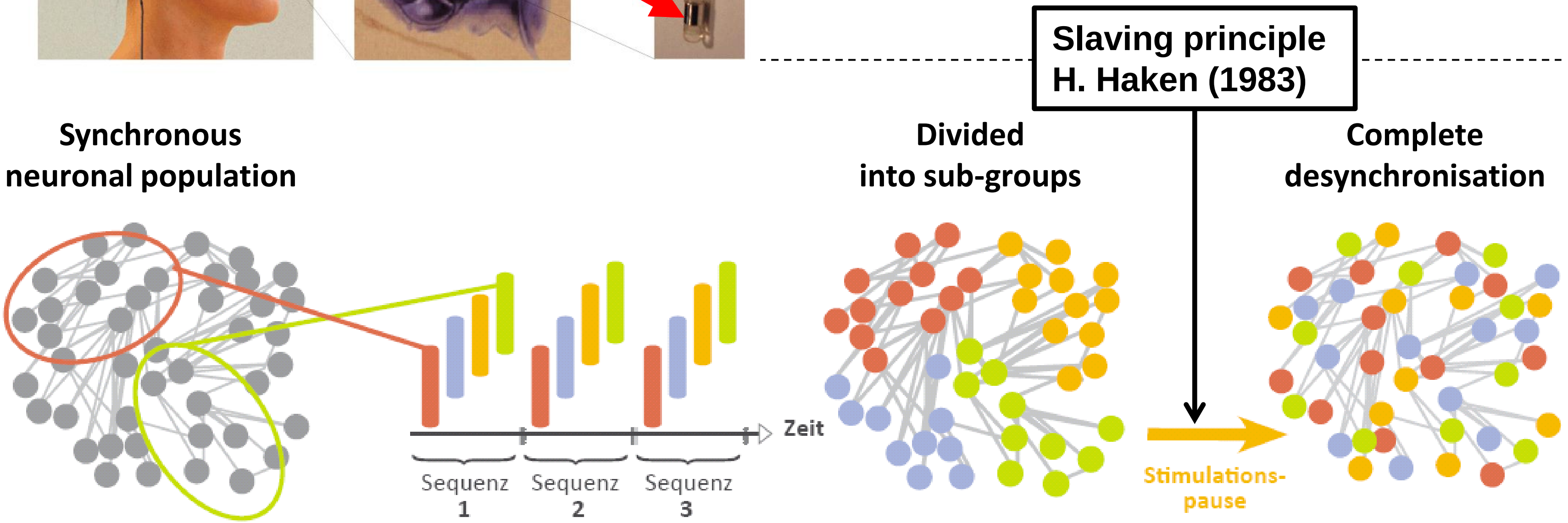
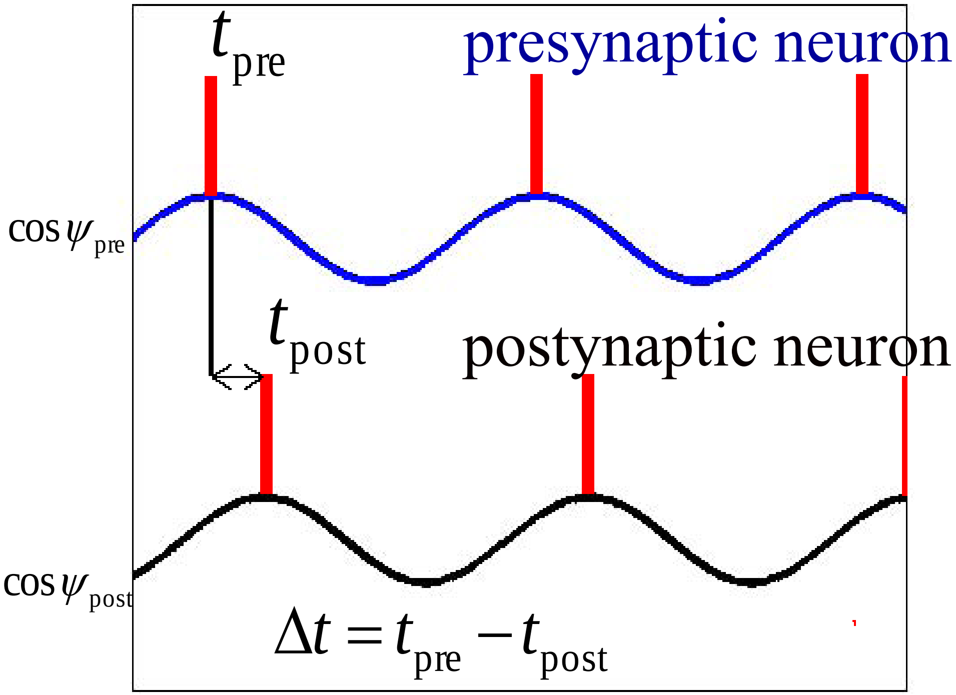
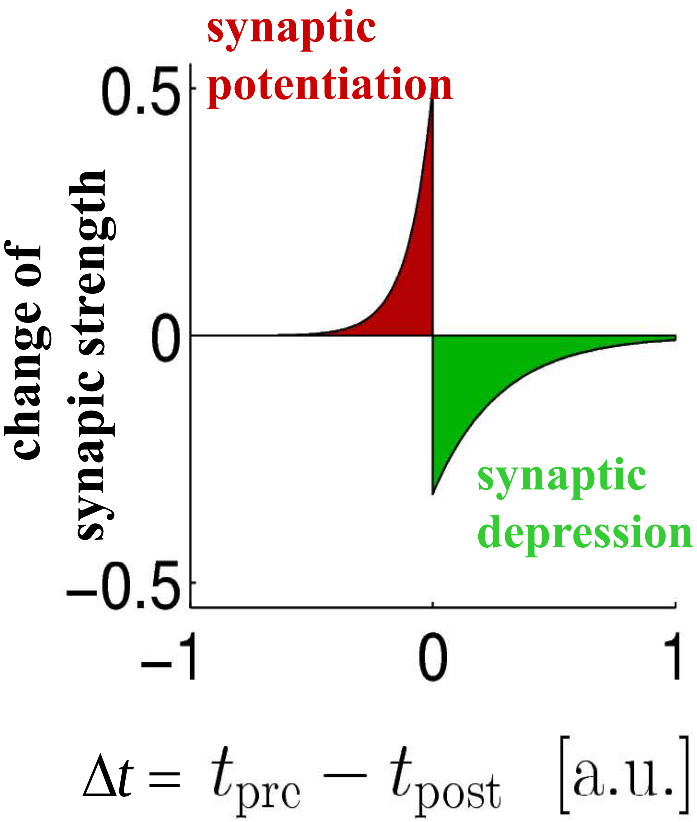
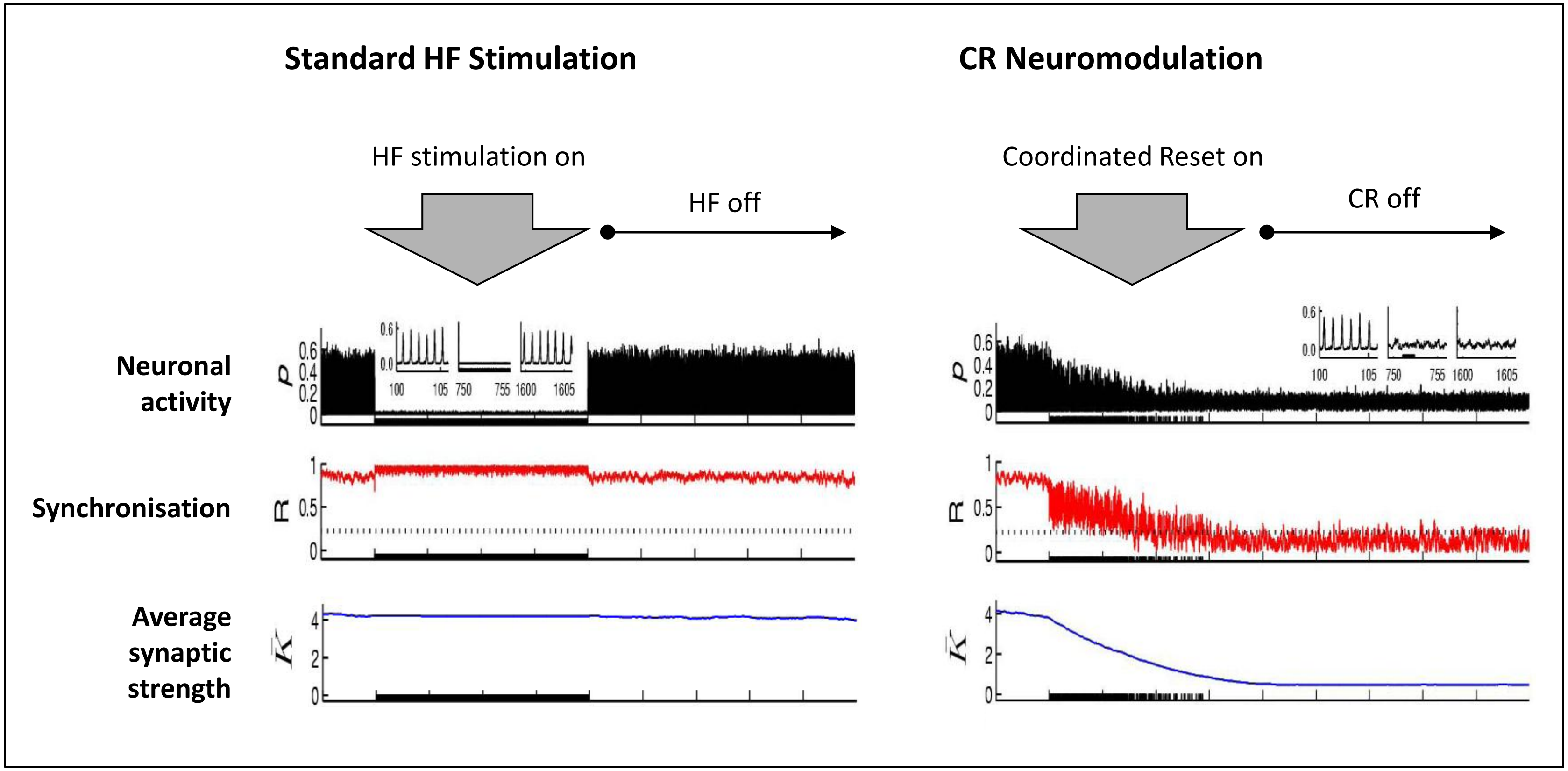


Spike-timing dependent plasticity



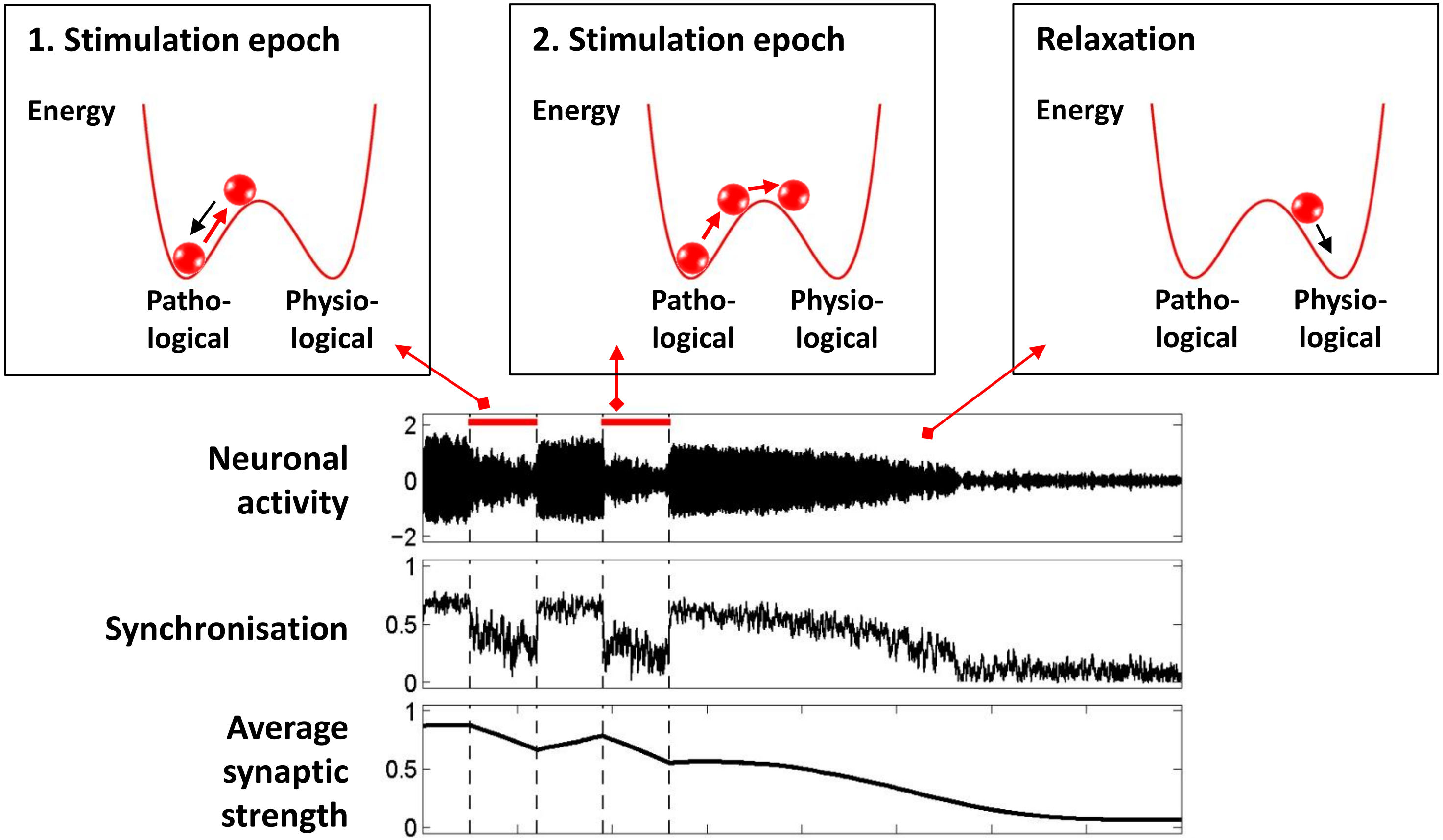


Basic differences between high-frequency (HF) stimulation and CR Neuromodulation



Cumulative effects of CR Neuromodulation

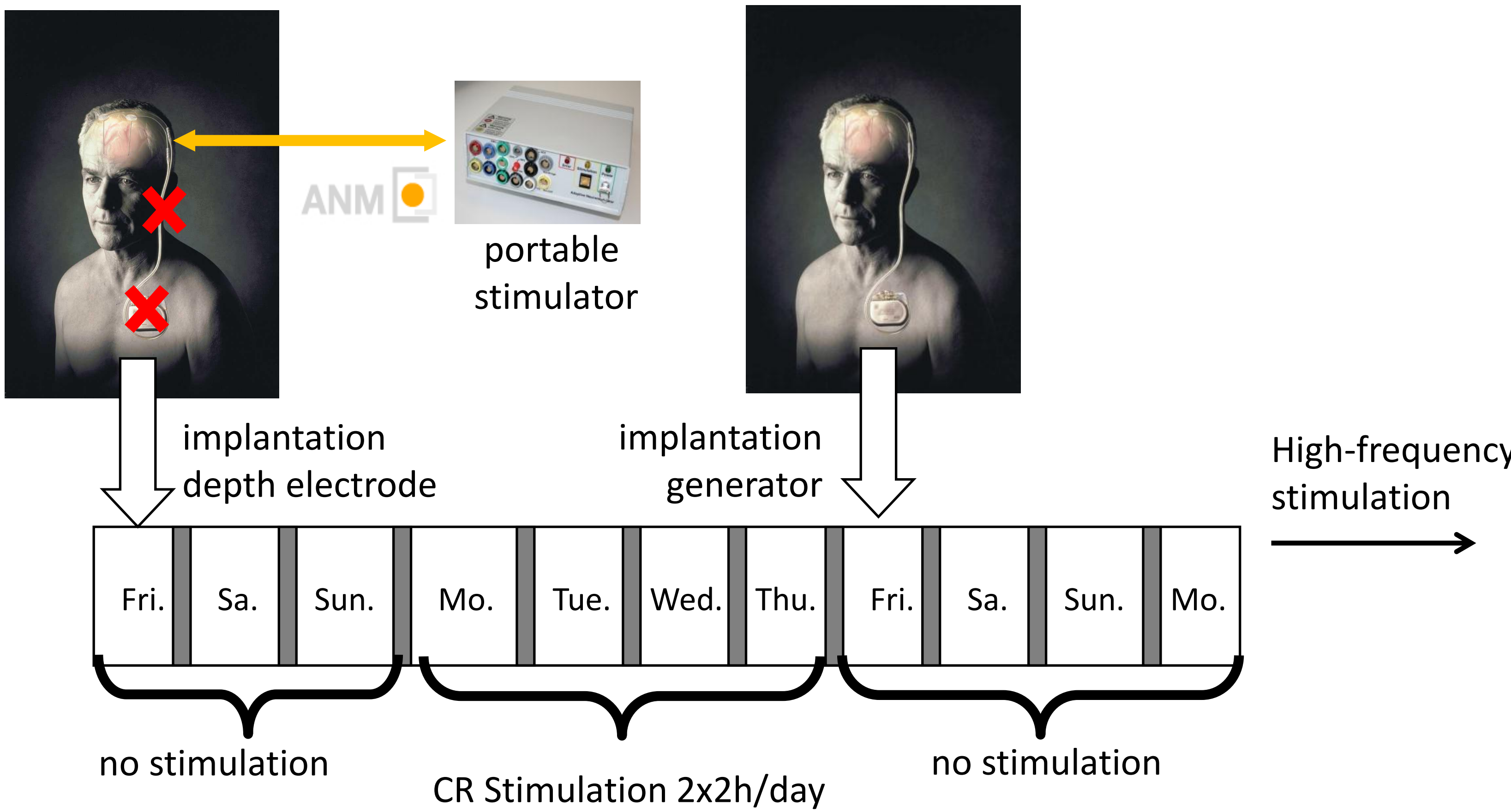
Overview of dynamical process in potential (energy landscape)



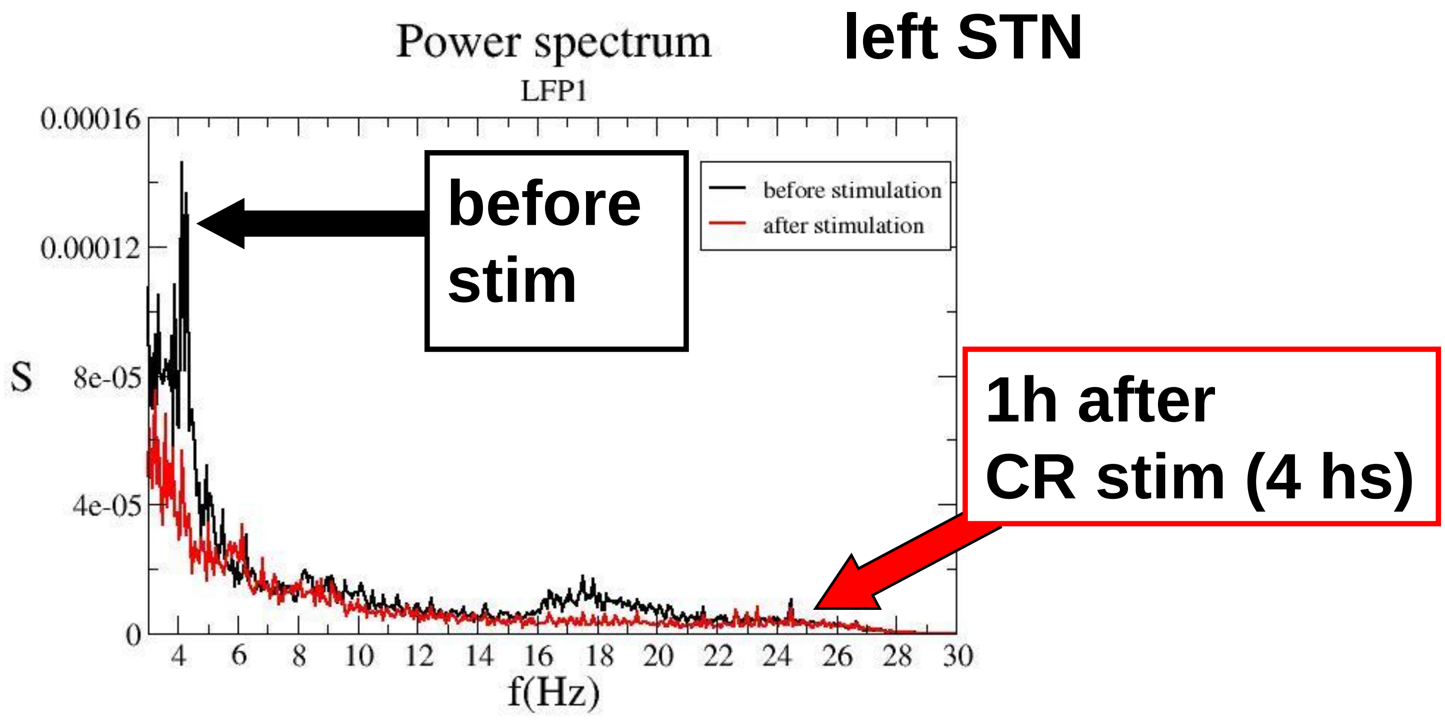
Source: Hauptmann, Tass, J. Neural. Eng., 2009

Pilot study in PD patients with CR stimulation in the STN

First clinical exploration (acute study in externalized PD patients)



Long-lasting CR effects - electrophysiology

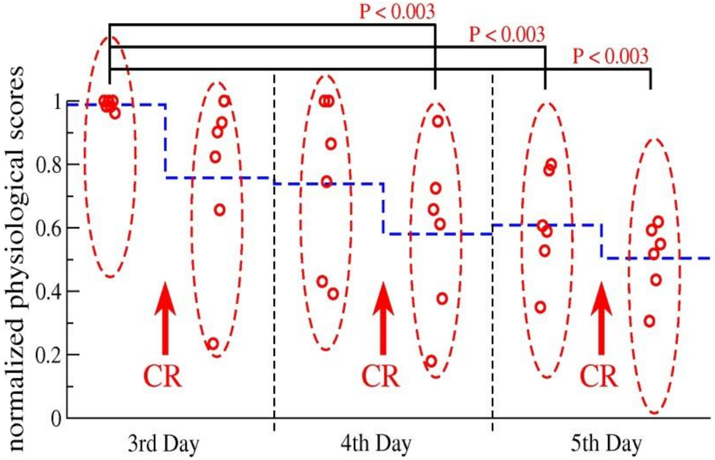


↔ **Significant decrease of LFP beta activity only during the first 12 sec after high-frequency DBS.**

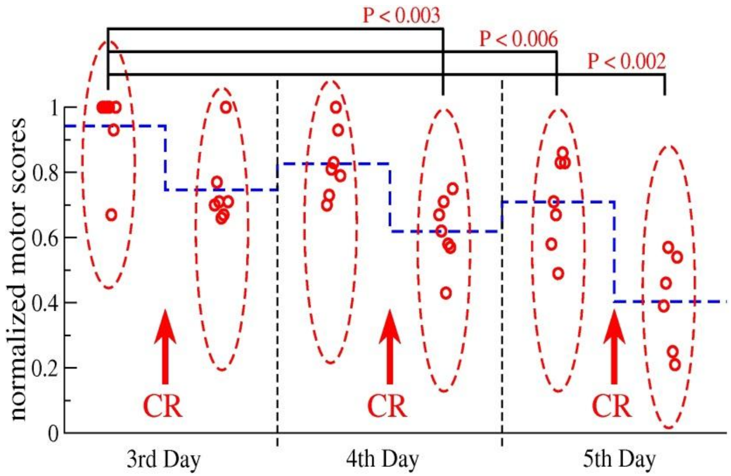
Kühn et al., J. Neurosci. 2008

Long-lasting and cumulative effects of CR stimulation

6 PD patients (akinetic or equivalence type) with constant med

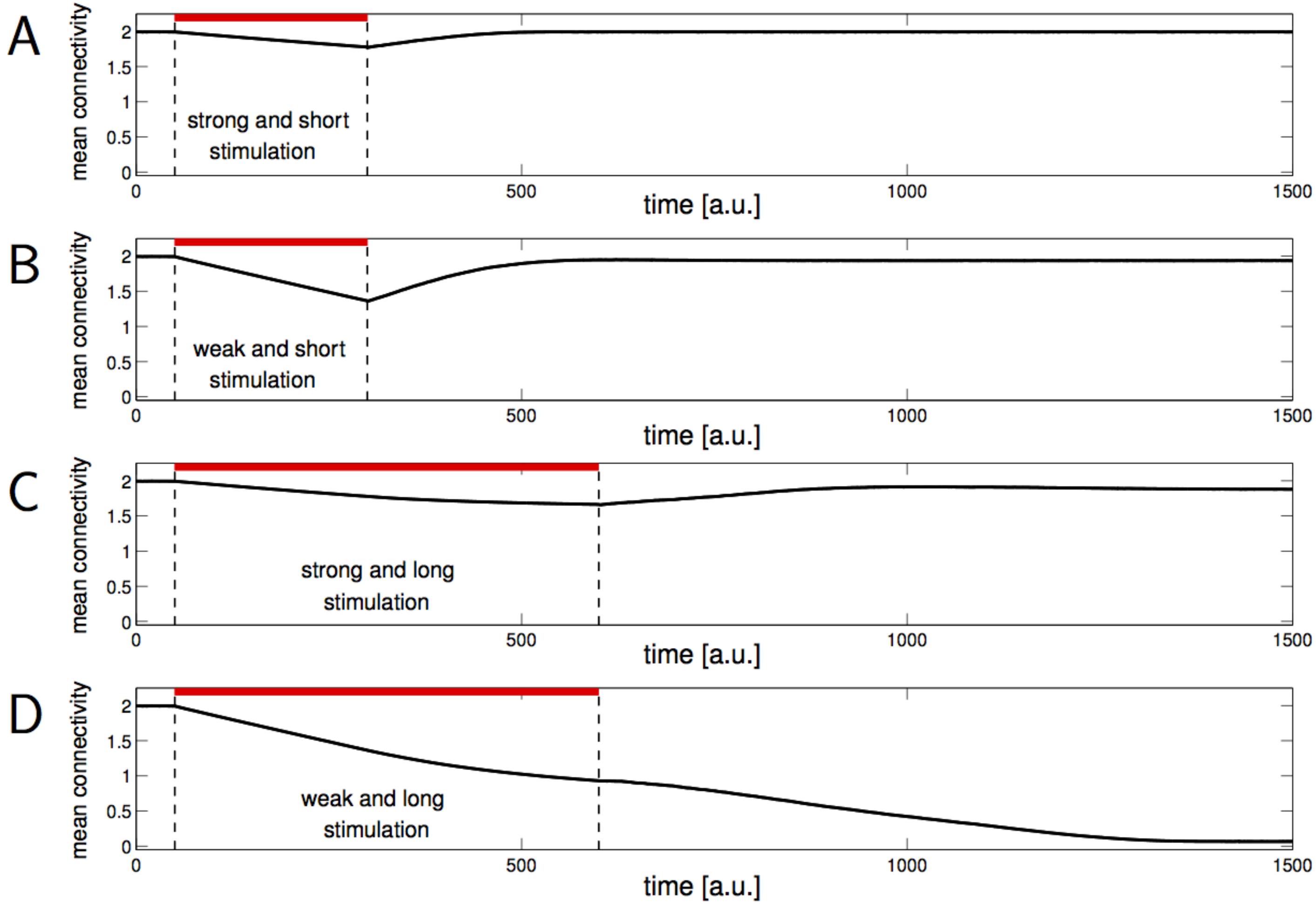


Average normalized individual beta band STN activity



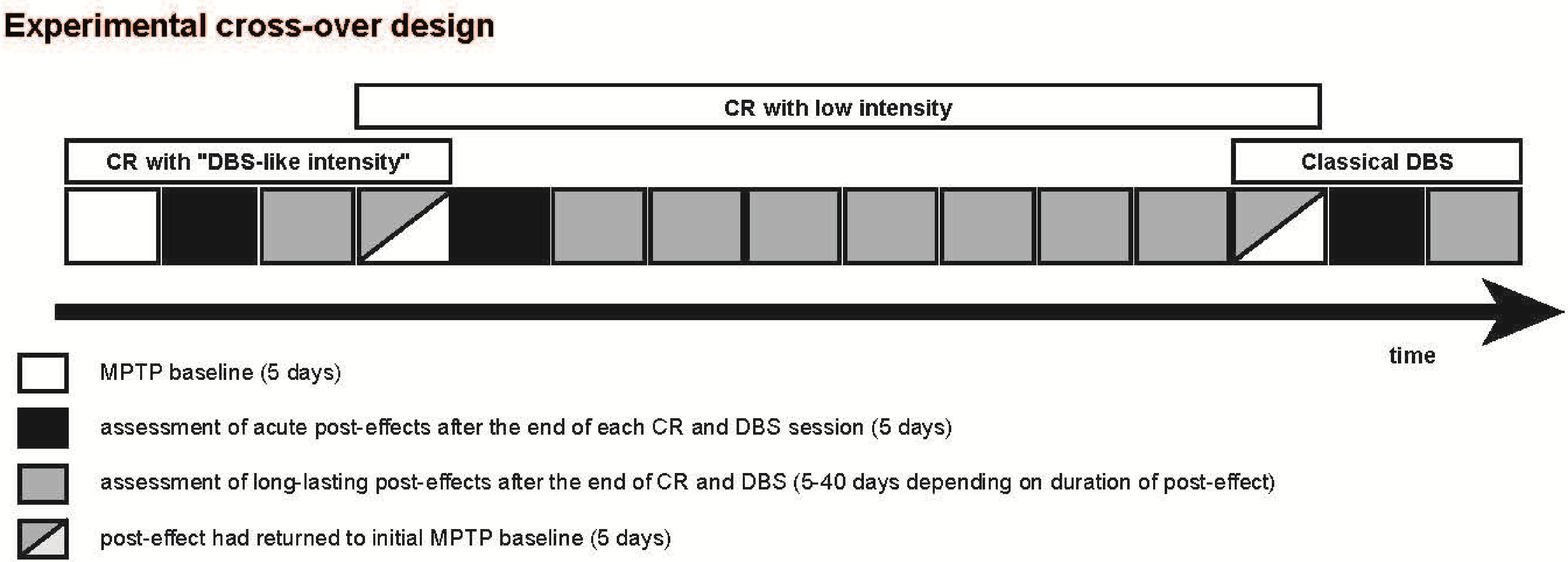
Average normalized Motor scores

CR stimulation in MPTP monkeys – theoretical predictions



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

CR stimulation in MPTP monkeys

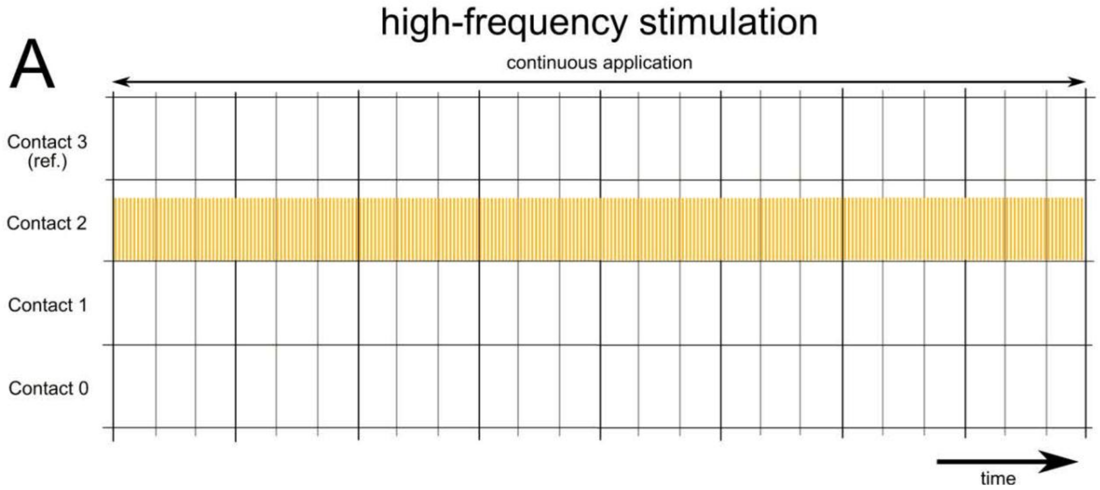


low intensity = DBS-like intensity / 3 (see Lysyansky et al. J. Neural Eng. 2011)

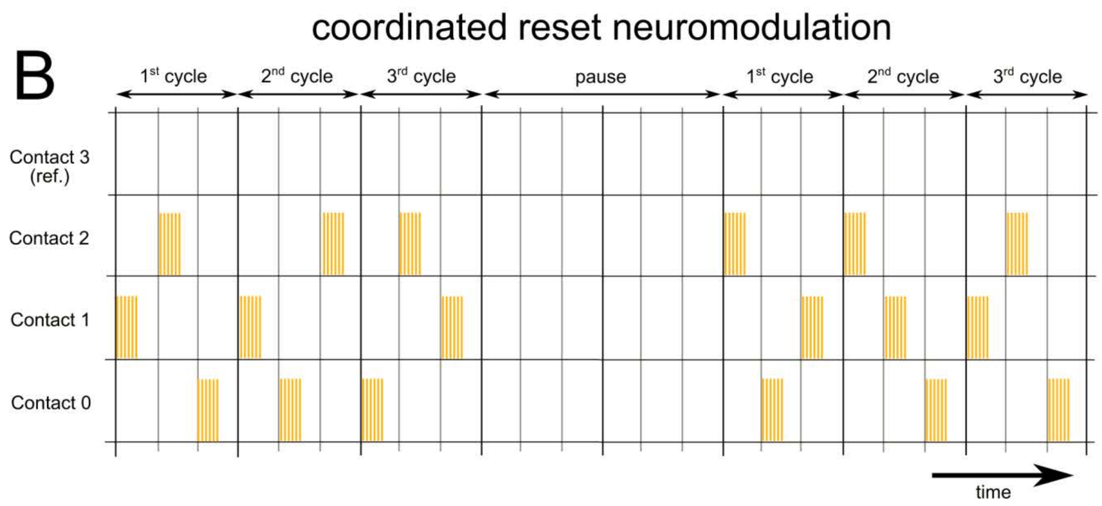
- Akinesia was monitored for 90 minutes/day with infrared activity monitors, providing mobility counts every 5 minutes (Bezard et al. Nat. Med. 2003).
- The severity of motor symptoms and dyskinesia were further assessed on a parkinsonian monkey rating scale using videotape recordings of monkeys (Bezard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

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

CR stimulation in MPTP monkeys



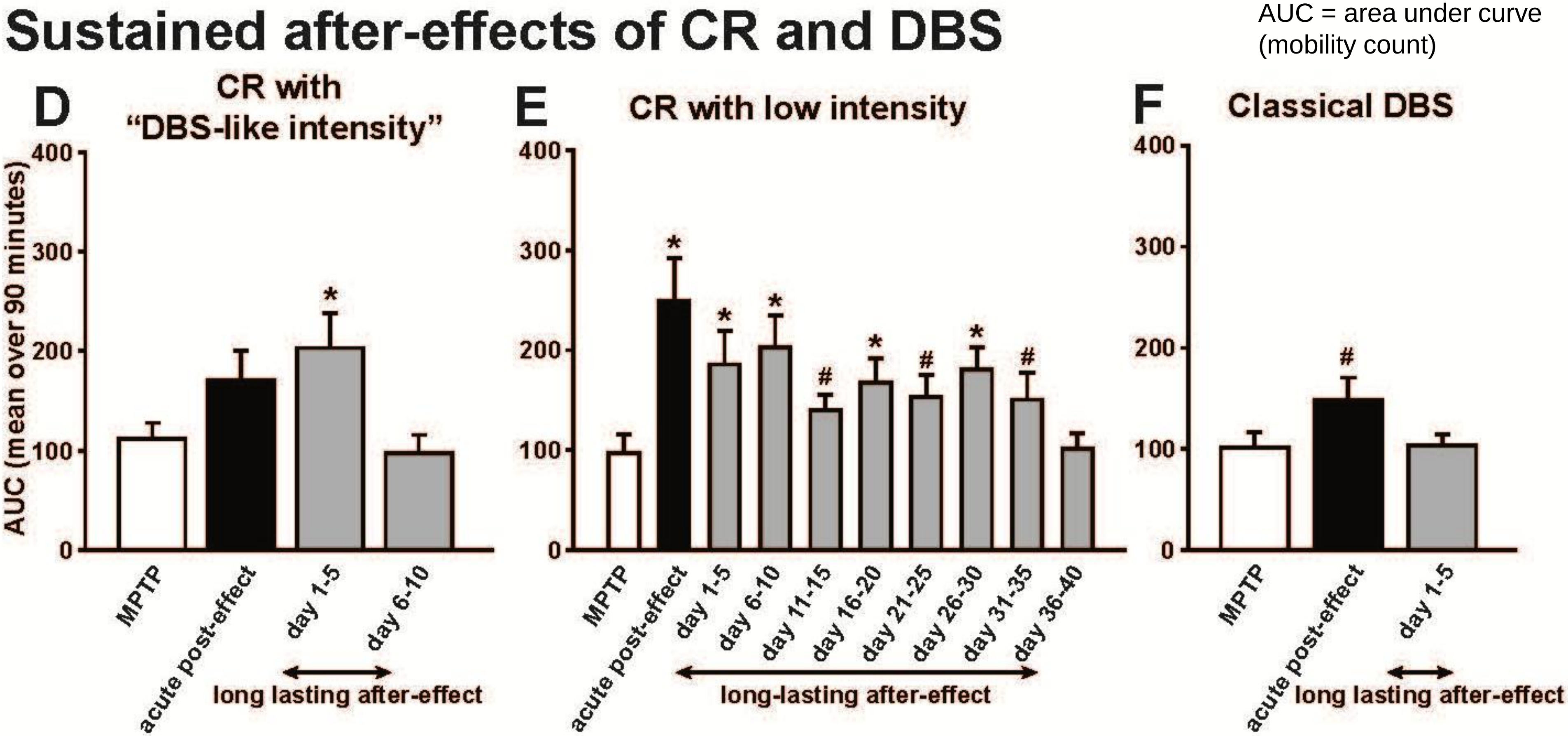
frequency: 130 Hz,
pulse width: 120 µs
most effective intensity: 0.6 mA ± 0.1 mA



each burst contains five pulses with an intraburst frequency of 150 Hz
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 stimulation in MPTP monkeys

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

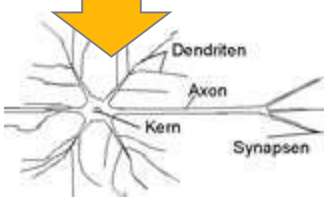
Each bar represents the mean of five days of behavioral assessment ± s.e.m. *P<0.05, #P≤0.1

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

Invasive vs. non-invasive CR Neuromodulation

A

Direct electrical CR stimulation of brain cells in the target area (e.g. brain pacemaker)



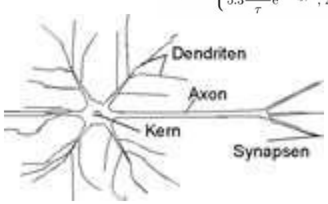
Synaptic interaction

$$\dot{s}_i = \frac{\alpha}{1+\exp(-(v_i+0.1)/0.25)}(1-s_i) - \beta s_i$$

$$S_i(t) = (V_r - v_i(t)) \cdot \frac{1}{N}\sum_{j=1}^{N} c_{ij} s_j(t)$$

with synaptic plasticity

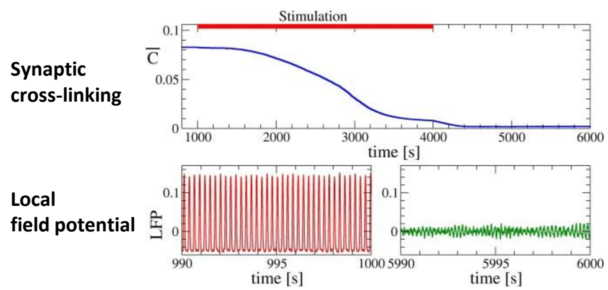
$$\Delta c_{ij} = \gamma \begin{cases} e^{-5\Delta t_{ij}/\tau}, & \Delta t_{ij} \geq 0 \\ 5.3\frac{\Delta t_{ij}}{\tau} e^{4\Delta t_{ij}/\tau}, & \Delta t_{ij} < 0 \end{cases}$$



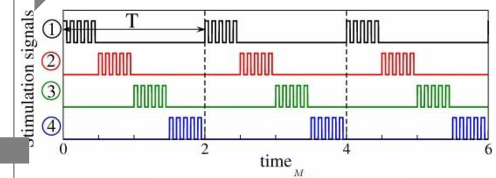
$$\dot{v}_i = \nu(v_i - v_i^3/3 - w_i + y_i + I_i) + S_i(t) + F_i(t)$$

$$\dot{w}_i = \delta(a + v_i - b w_i),$$

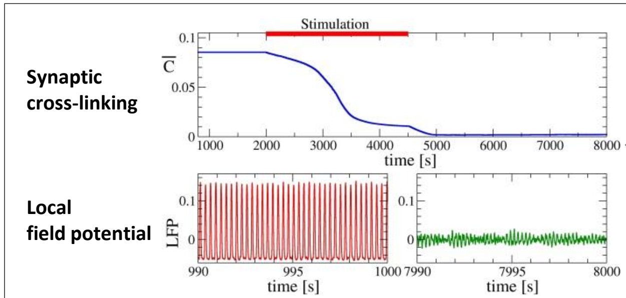
$$\dot{y}_i = \mu(c - v_i - d y_i), \qquad i = 1, \ldots, N,$$



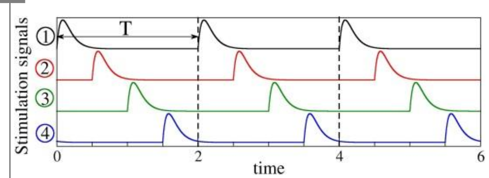
Stimulation signals



$$F_i(t) = (V_r - v_i(t)) \cdot K \sum_{j=1}^{M} D(i,j)\rho_j(t)P(t)$$



Stimulation signals



$$F_i(t) = (V_r - v_i(t)) \cdot K \sum_{j=1}^{M} D(i,j)\Lambda_j(t),$$

$$\Lambda_j(t) = \lambda(t - t_{j,k})e^{-\lambda(t-t_{j,k})}, \quad t_{j,k} \leq t < t_{j,k+1},$$

$t_{j,k}$, $k = 1, 2, \ldots$ – activation times of the jth stimulation site

B

Synaptic CR stimulation of nerve cells via afferent fibres (e.g. brain pacemaker, sensory stimulation)

Tass & Popovych, Biological Cybernetics (2012);
Popovych & Tass , Frontiers in Human Neuroscience (2012)

Acoustic CR Neuromodulation for Tinnitus

Electrophysiological correlate of the tinnitus percept

pathological neuronal synchronization highly related to tinnitus

→ neuronal synchronization emerges immediately or within a few hours after noise trauma in cats
Norena & Eggermont, Hear. Res. 2003

→ tinnitus reduction by suppression of delta band activity and enhancement of alpha band activity by means of neurofeedback (EEG)
Dohrmann et al., RNN 2007 (human)

→ during residual inhibition significantly reduced delta band activity in temporal areas (MEG)
Kahlbrock & Weisz, BMC Biol. 2008 (human)

→ Direct epicortical recordings from the secondary auditory cortex
DeRidder et al., J .Neurosurg. 2011; van der Loo et al., under review

→ acute transient tinnitus within 3-4 h after rock music exposure: bilateral temporary hearing loss + increased gamma band activity in the right auditory cortex (MEG)
Ortmann et al., EJN 2011 (human)

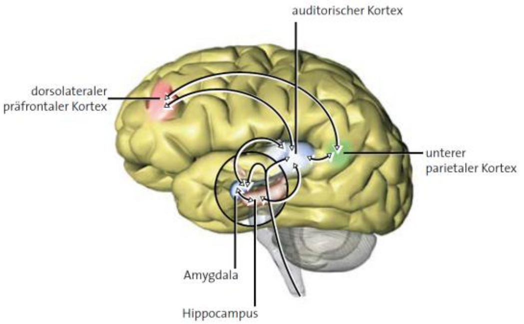
Impact of non-auditory brain areas on tinnitus perception

Limbic and paralimbic structures in and around the subcallosal area:
inhbition of the tinnitus signal at the thalamic gate. Reduction of this inhibition leads to tinnitus.

Rauschecker, Leaver & Mühlau: Neuron 66, 2010, 819-826

Tinnitus distress is associated with an increased activity in the amygdala, cingulate cortex and parahippocampus

Vanneste et al., NeuroImage 52 (2010) 470–480



„inflow“ into right and left temporal cortex (presumably corresponding to auditory cortex) positively correlates with tinnitus distress

W. Schlee et al., BMC Biology 7 (2009) 80

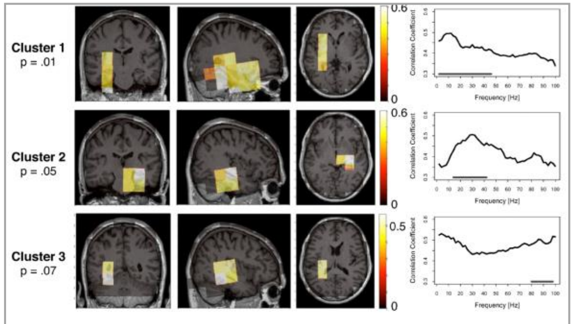
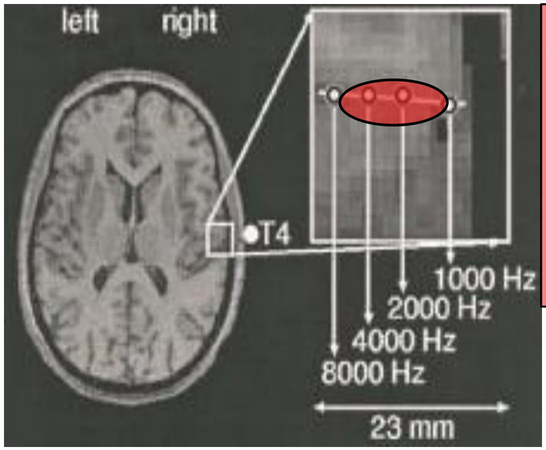


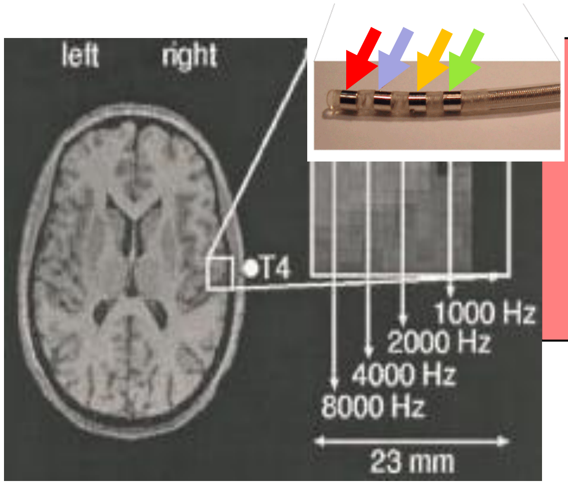
Figure 5
Location and frequency band of the inflow-clusters that correlated with the individual tinnitus distress. The stronger the inflow to the clusters, the stronger the subjective strength of tinnitus distress as assessed with a standard German Questionnaire. The location of the clusters are shown in the coronal, sagittal and horizontal view. The right column displays the significant frequency range of the clusters.

Treatment of Tinnitus with Acoustic Coordinated Reset (CR) Neuromodulation



Pathological synchronisation in the auditory cortex

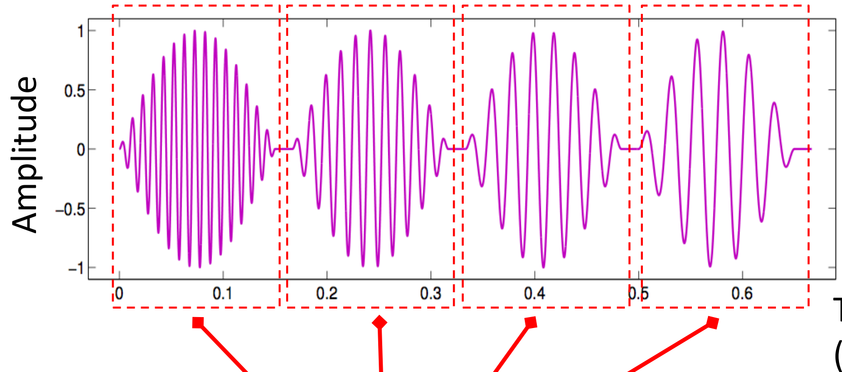
Treatment of Tinnitus with Acoustic Coordinated Reset (CR) Neuromodulation



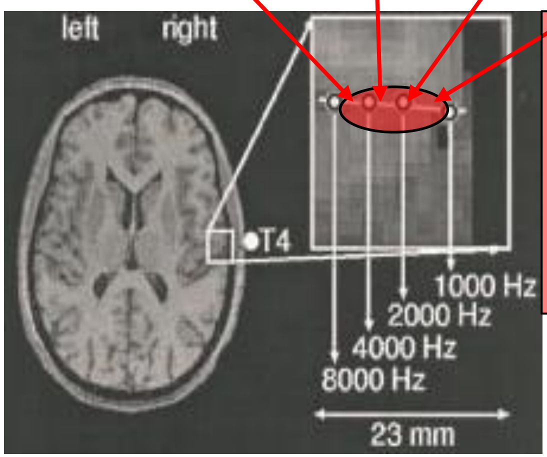
Pathological synchronisation in the auditory cortex

Treatment of Tinnitus with Acoustic Coordinated Reset (CR) Neuromodulation

Acoustic CR® stimulation signal

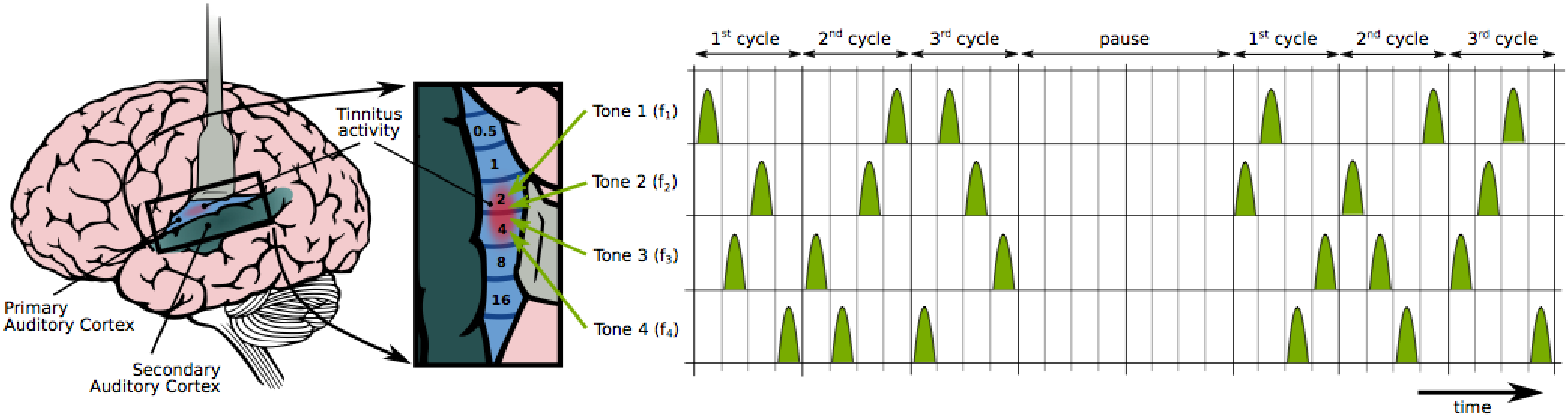


Non-invasive acoustic Coordinated Reset stimulation



Pathological synchronisation in the auditory cortex

Acoustic CR Neuromodulation

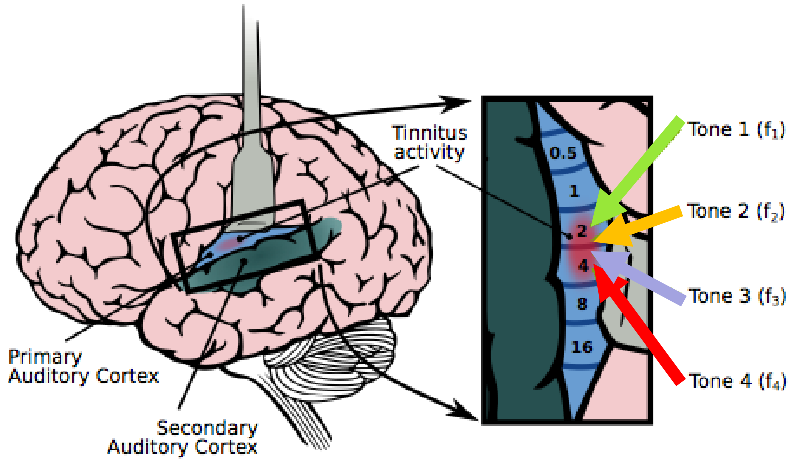


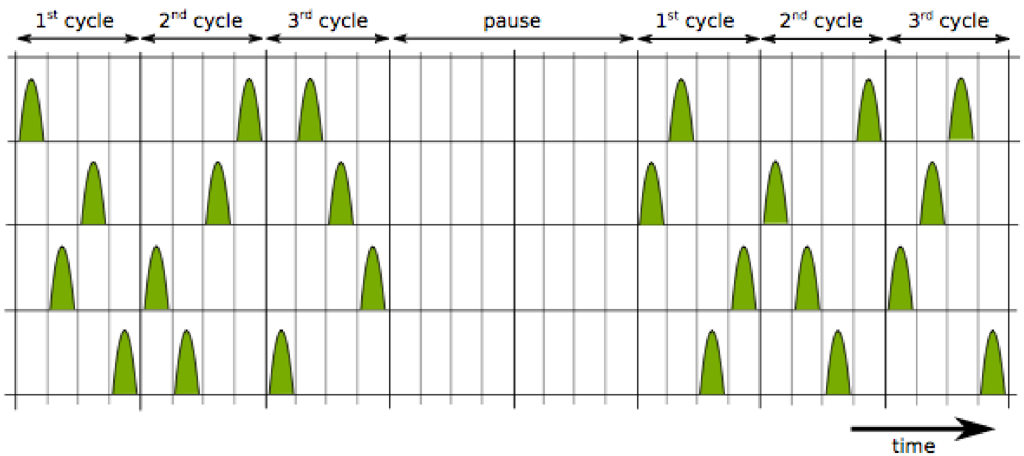
3 cycles ON stimulaton, 2 cycles OFF stimulation

OFF cycles optimize the desynchronizing effect according to computational studies

(Tass, Biol. Cybern. 2003; Hauptmann & Tass, J. Neural Eng. 2009; Lysyansky et al., J. Neural Eng. 2011)

Acoustic CR Neuromodulation

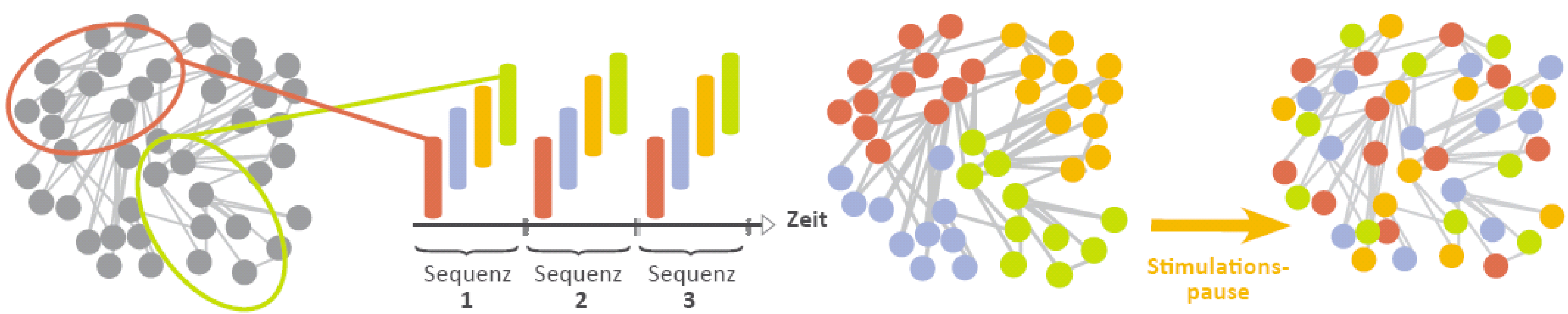




Synchronous neuronal population

Divided into sub-groups

Complete desynchronisation



RESET study: acoustic CR in chronic tinnitus

Overview

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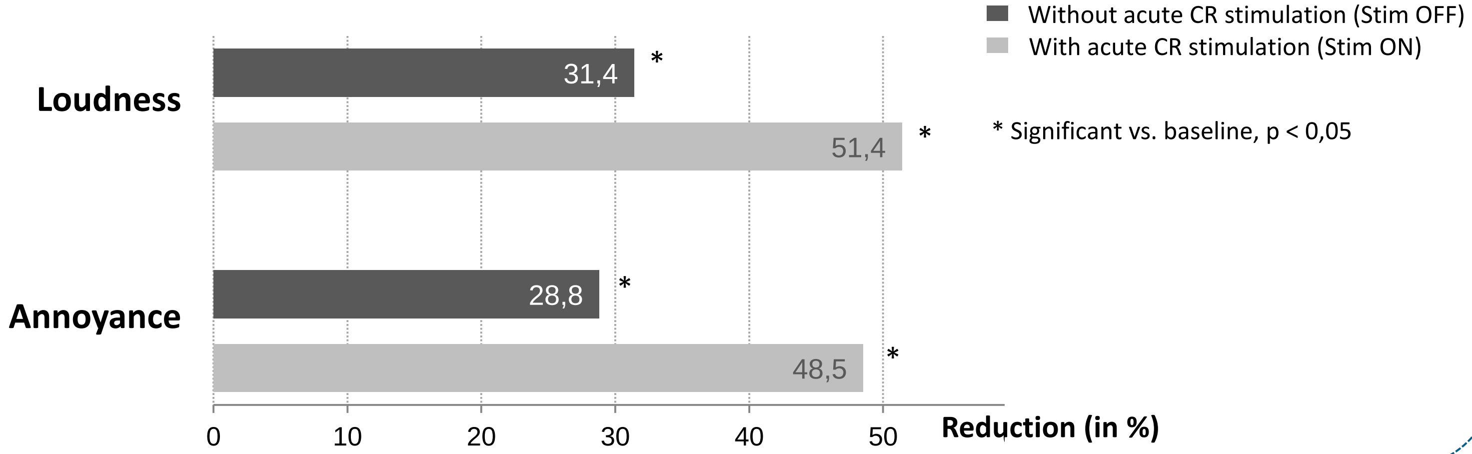
- Prospective, randomized, single blind, placebo-controlled trial in 63 patients with chronic tonal subjective
- Acoustic coordinated reset (CR) neuromodulation used to specifically counteract tinnitus by means of desynchronization of tinnitus related neuronal synchrony
- CR treatment was safe and well-tolerated and resulted in a significant decrease of symptoms, as measured by VAS and TQ scores
- After 10 months: 75 % of the patients are either “winner” (decrease of more than 15 pts in the TQ) or “responder” (decrease of 6-14 pts in TQ)

Reduction in VAS scores after 12 weeks of CR treatment



Improvement of life quality

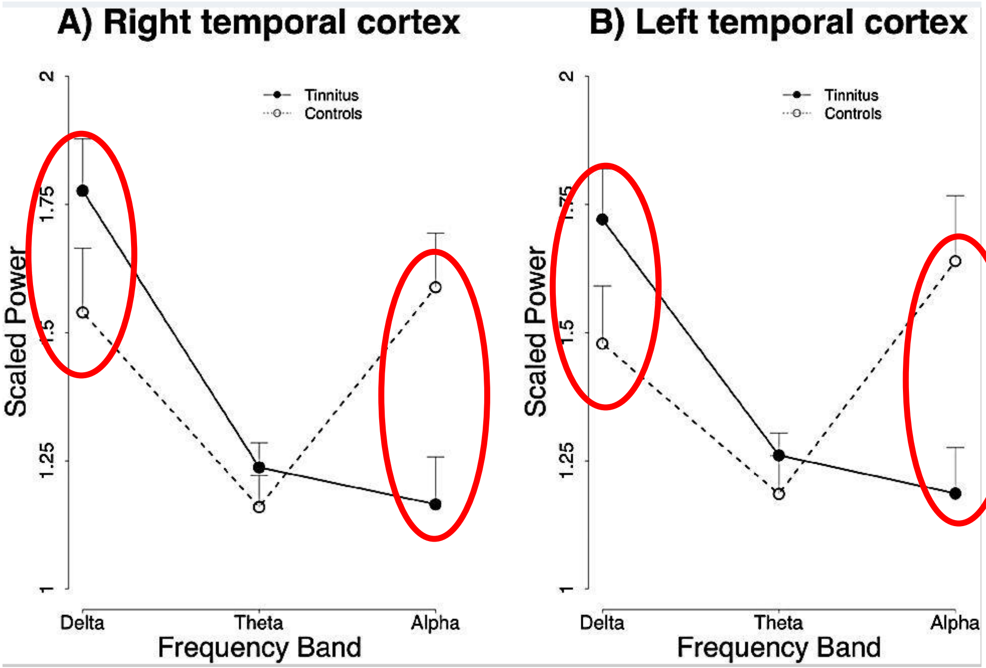
After 3 months: 73 % improve by at least one Tinnitus questionnaire (TQ, total: 84 points) severity group

After 10 months: 75 % are either winner (decrease of more than 15 in the TQ) or responder (decrease of 6-14 in TQ)

According to VAS (Adamchic et al., Am. J. Audiol 2012) and TQ (Adamchic et al., HQLO 2012) evaluation studies (re the Minimal Clinically important Difference, King 2011)
CR-induced improvements of VAS and TQ scores are not only statistically significant, but also clinically significant.

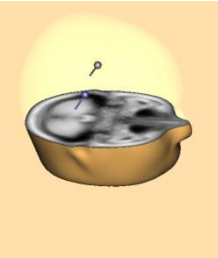
Pathological Change in the MEG of Tinnitus Patients

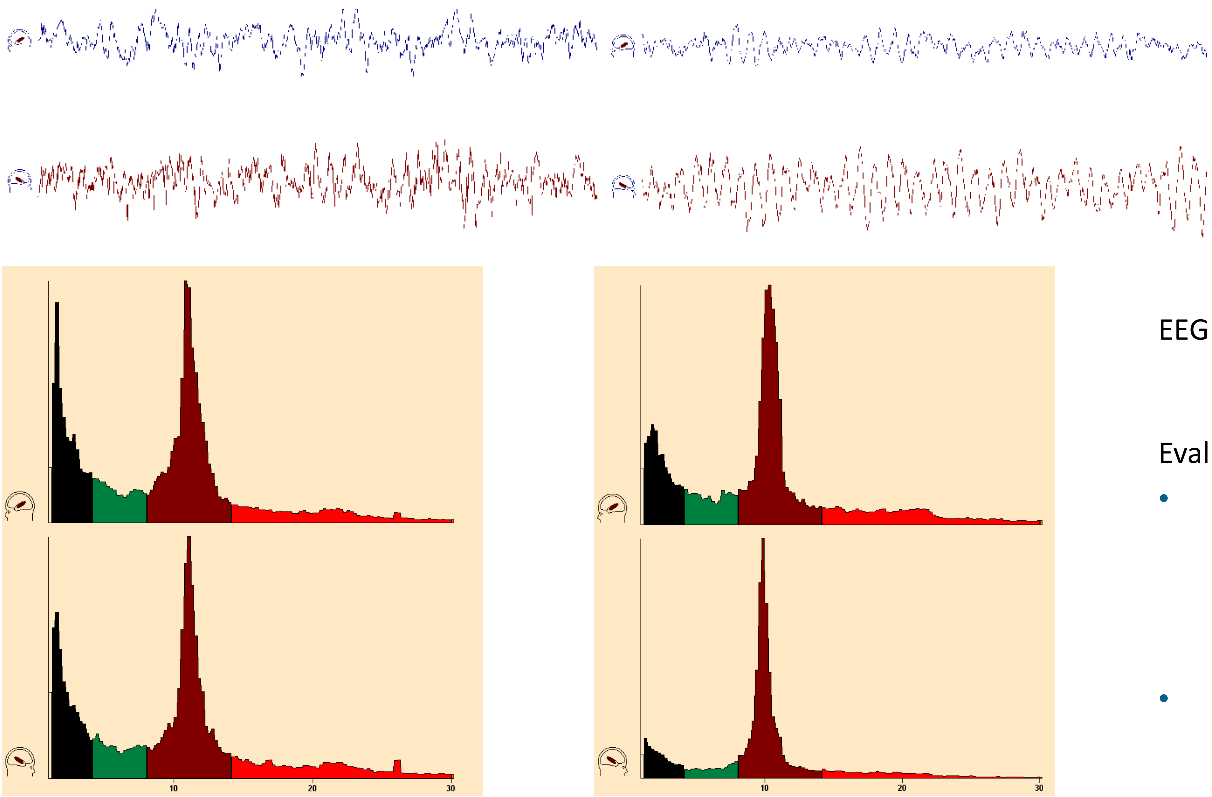
Alpha, delta and theta band activity



- Tinnitus patients show significant changes in comparison to the healthy control group
  - Reduction in alpha band activity
  - Increase in delta band activity

Evaluation of EEG Data in the RESET Study





EEG recordings of _all_ study patients over 12 weeks

Evaluation:

- Surface EEG transformed into Brain Source Activity in accordance with "Source Montage Model according to BESA"
- Primary auditory cortex (ACI) was modelled with an equivalent dipole in Brodmann area 41
- Fast Fourier Transform (FFT) on artefact-free sources

Significant changes of oscillatory brain activity

after 12 weeks of treatment with acoustic CR neuromodulation

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Delta
1-4 Hz

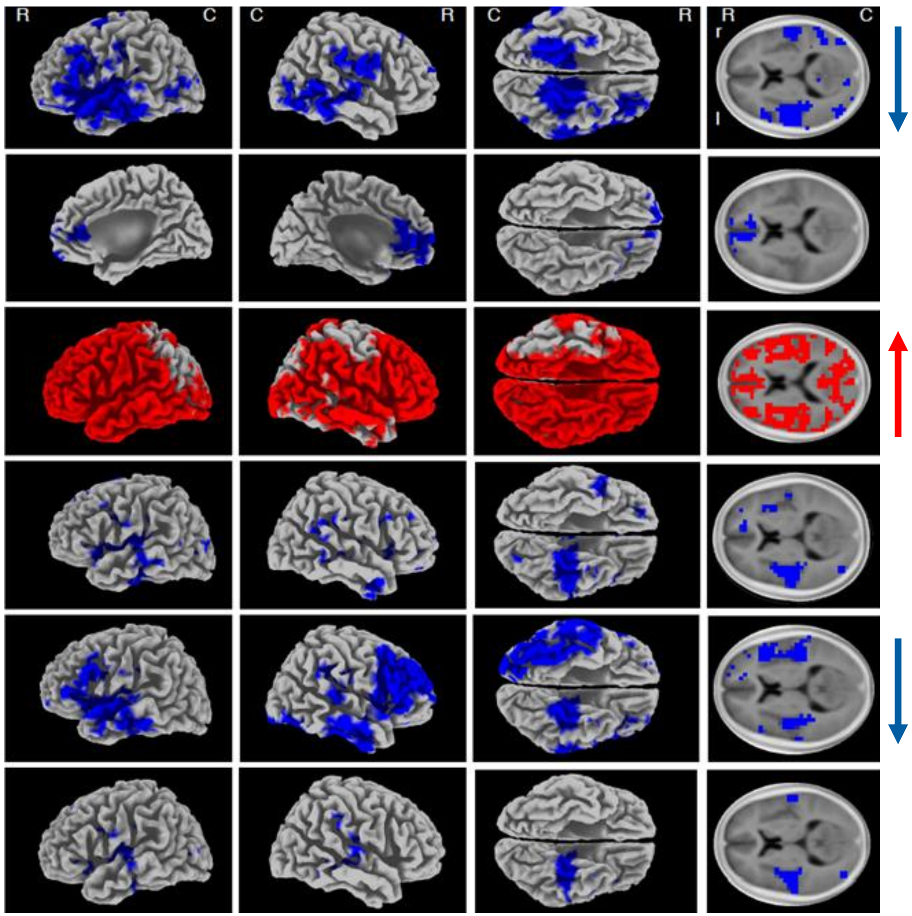
Theta
4-8 Hz

Alpha
8-12 Hz

Beta
12-30 Hz

Gamma low
30-48 Hz

Gamma high
52-90Hz



3D mapping of treatment induced changes in oscillatory EEG activity *(baseline compared to 12 weeks, off-stimulation)*

- To increase signal-to-noise ratio 12 patients with bilateral tinnitus were selected using the reliable-change-index (RCI) (Jacobson & Truax 1991) applied to improvements of TQ scores
- Inverse solutions were caculated with sLORETA (Pascual-Marqui 1999; Pascual-Marqui et al. 1994) restricted to cortical gray matter according to the digitized probability atlas (Brain Imaging Center, Montreal Neurological Institute) with a spatial resolution of 5 mm (6239 voxels).
- statistical analysis of sLORETA maps with the statistical non-parametric mapping (SnPM) (Nichols and Holmes, 2002)

blue = significant decrease, $p < 0.05$
red = significant increase, $p < 0.05$

Tass, Adamchic, Freund, von Stackelberg, Hauptmann: Restorative Neurology and Neuroscience (2012)

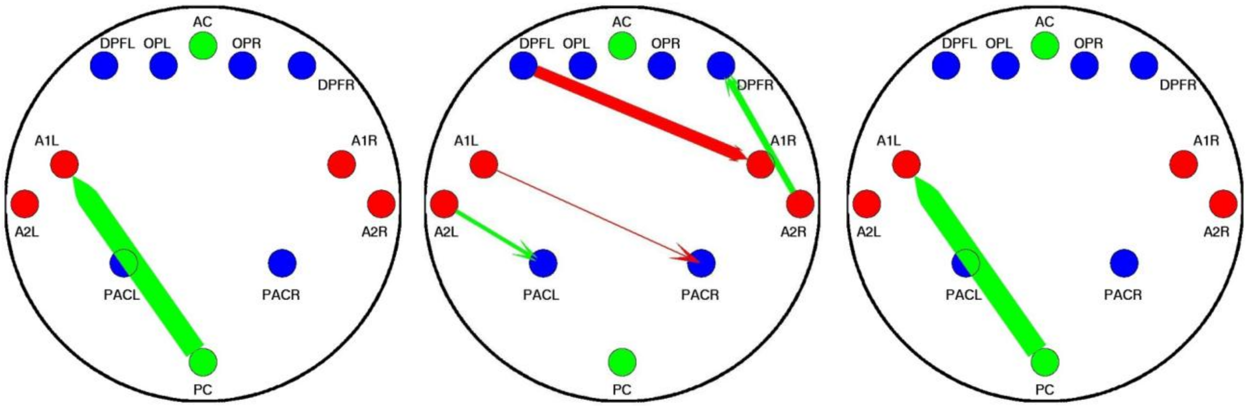
Acoustic CR counteracts imbalance of interactions

of brain areas in patients with subjective chronic tonal tinnitus

Effect of 12 weeks CR® therapy on interactions in the network of brain areas in patients with bilateral tinnitus responding to CR® therapy

Analysis of **effective connectivity in different frequency bands**

Gamma band (45 – 60 Hz)	**Alpha band** (8 – 13 Hz)	**Delta band** (1 – 3 Hz)



Decrease of strength of interaction

Increase of strength of interaction

Connectivity matrices

- Surface EEG was transformed into brain source activity by means of "source montage model" (BESA) in all brain areas associated with tinnitus according to literature
- Analysis of functional connectivity: empirical mode decomposition + partial directed coherence (Silchenko et al., J. Neurosci. Meth. 2010) → Connectivity matrix
- Statistical group analysis (ANOVA)

A1L	primary auditory cortex, left
A1R	primary auditory cortex, right
A2L	secondary auditory cortex, left
A2R	secondary auditory cortex, right
AC	anterior cingulum
PC	posterior cingulum
OFR	orbito-frontal cortex, right
OFL	orbito-frontal cortex, left
DPFL	dorsolateral-prefrontal cortex, left
DPFR	dorsolateral-prefrontal cortex, right
PACL	parietal cortex, left
PACR	parietal cortex, right

Silchenko, Adamchic, Hauptmann, Tass: manuscript under review

Acoustic CR counteracts imbalance of interactions

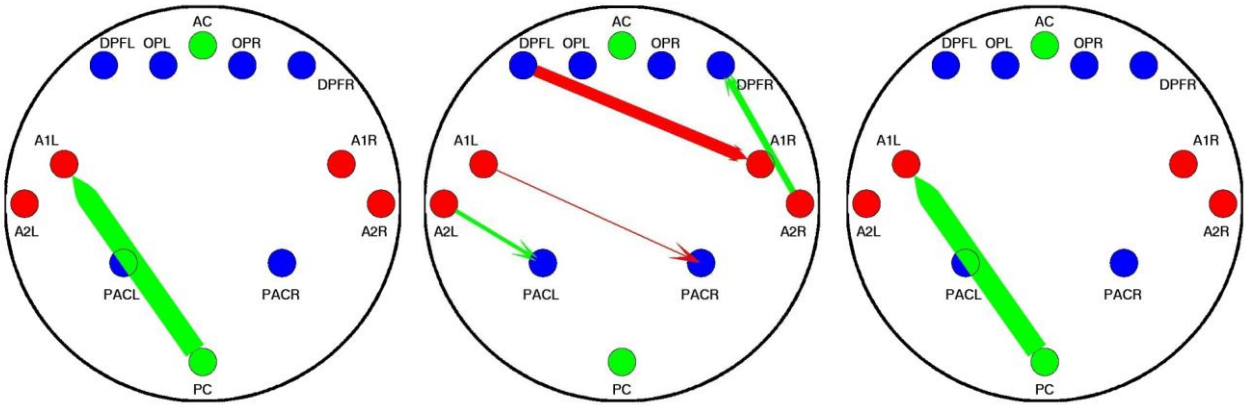
of brain areas in patients with subjective chronic tonal tinnitus

JÜLICH
FORSCHUNGSZENTRUM

Effect of 12 weeks CR® therapy on interactions in the network of brain areas in patients with bilateral tinnitus responding to CR® therapy

Analysis of **effective connectivity in different frequency bands**

Gamma band (45 – 60 Hz) | **Alpha band** (8 – 13 Hz) | **Delta band** (1 – 3 Hz)



Connectivity matrices

- Surface EEG was transformed into brain source activity by means of "source montage model" (BESA) in all brain areas associated with tinnitus according to literature
- Analysis of functional connectivity: empirical mode decomposition + partial directed coherence (Silchenko et al., J. Neurosci. Meth. 2010) → Connectivity matrix
- Statistical group analysis (ANOVA)

Dynamic causal modelling (Moran et al. Neuroimage 2009):

- Reduction of the bi-directional excitatory interaction between A1 and the posterior cingulate area in both delta and gamma bands
- Increase of a bi-directional inhibitory coupling between A1 and DPFC in the alpha band

A1L	primary auditory cortex, left
A1R	primary auditory cortex, right
A2L	secondary auditory cortex, left
A2R	secondary auditory cortex, right
AC	anterior cingulum
PC	posterior cingulum
OFR	orbito-frontal cortex, right
OFL	orbito-frontal cortex, left
DPFL	dorsolateral-prefrontal cortex, left
DPFR	dorsolateral-prefrontal cortex, right
PACL	parietal cortex, left
PACR	parietal cortex, right

Clinical trials and further development of acoustic CR neuromodulation

- RESET study (63 patients)
- CE mark & FDA approval, in Europe approx. 3000 patients (return rate < 15 %)
- RESET Real Life study in Germany (200 patients) (no placebo control): interim results confirm results of RESET study
- RESET2 study (100 patients): London + Nottingham
- RESET3 study (> 200 patients): Jülich + Cologne (Prof. von Wedel) + Bern (Prof. Kompis) + Regensburg (PD Langguth) + Antwerp (Prof. de Ridder)
  EEG calibration (PoC) + clinical trial

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