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

Institute for Neuroscience and Medicine – Neuromodulation Research Center Jülich, Germany
&
Department of Neuromodulation
University of Cologne, Germany
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-induced unlearning of both pathological connectivity 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**

Benabid et al., Lancet 1991
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


Mathematical Models of Relevant Brain Areas
Synergetics, Statistical Physics, and Non-linear Dynamics
Self-organisation & Plasticity


Model – phase oscillator network with spike timing dependent plasticity

\[ \frac{d\psi_j}{dt} = \omega_j + \frac{1}{N} \sum_{k=1}^{N} K_{kj}(t) \sin(\psi_k - \psi_j) + \sum_{\nu=1}^{4} X_\nu(t) S_\nu(\psi_j) \rho_j^{(\nu)} + \xi_j(t) \]

- \( \omega_j \) = eigenfrequency of \( j \)th neuron
- \( K_{kj}(t) \) = strength of synaptic interaction from neuron \( k \rightarrow j \)
- \( X_\nu(t) = 1 \) iff stimulation via site \( \nu \) is on and 0 else
- \( S_\nu(\psi_j) \) = phase dependent effect of stimulation, e.g. \( S_\nu(\psi_j) = I_\nu \cos(\psi_j) \)
- \( \xi_j \) = 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

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

Schematic diagram

- Synchronous neuronal population
- Divided into sub-groups
- Complete desynchronisation

Coordinated Reset (CR) Brain Pacemaker

Schematic diagram

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

Synchronous neuronal population

Divided into sub-groups

Complete desynchronisation

Slaving principle
H. Haken (1983)

Spike-timing dependent plasticity

\[ \Delta t = t_{\text{pre}} - t_{\text{post}} \]

\[ \cos \psi_{\text{pre}} \]

\[ \cos \psi_{\text{post}} \]

\[ \Delta t = t_{\text{pre}} - t_{\text{post}} \]

Gerstner et al., Nature 1996
Basic differences between high-frequency (HF) stimulation and CR Neuromodulation

Standard HF Stimulation

HF stimulation on

HF off

CR Neuromodulation

Coordinated Reset on

CR off

Neuronal activity

Synchronisation

Average synaptic strength

Tass & Majtanik, Biol. Cybern. 2006
Cumulative effects of CR Neuromodulation

Overview of dynamical process in potential (energy landscape)

1. Stimulation epoch
   - Energy
   - Neuronal activity
   - Synchronisation
   - Average synaptic strength

2. Stimulation epoch
   - Energy
   - Pathological
   - Physiological

Relaxation
   - Energy
   - Pathological
   - Physiological

Pilot study in PD patients with CR stimulation in the STN

First clinical exploration (acute study in externalized PD patients)

- Implantation depth electrode
- Implantation generator
- Portable stimulator
- High-frequency stimulation

CR Stimulation 2x2h/day
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
CR stimulation in MPTP monkeys – theoretical predictions

Tass, Qin, Hauptmann, Dovero, Bezard, Boraud, Meissner; Annals of Neurology 2012
CR stimulation in MPTP monkeys

**Experimental cross-over design**

- CR with low intensity
- CR with "DBS-like intensity"
- Classical DBS

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)

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).
CR stimulation in MPTP monkeys

A

high-frequency stimulation
continuous application

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)

B

coordinated reset neuromodulation

Tass, Qin, Hauptmann, Dovero, Bezard, Boraud, Meissner; Annals of Neurology 2012
CR stimulation in MPTP monkeys

Sustained after-effects of CR and DBS

D. CR with “DBS-like intensity”

E. CR with low intensity

F. Classical 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
Invasive vs. non-invasive CR Neuromodulation

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

Stimulation signals

Stimulation signals

Synaptic interaction
with synaptic plasticity

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: inhibition 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
Treatment of Tinnitus with Acoustic Coordinated Reset (CR) Neuromodulation

Pathological synchronisation in the auditory cortex
Pathological synchronisation in the auditory cortex
Treatment of Tinnitus with Acoustic Coordinated Reset (CR) Neuromodulation

Non-invasive acoustic Coordinated Reset stimulation

Pathological synchronisation in the auditory cortex

Tass & Popovych: Biological Cybernetics (2012)
Acoustic CR Neuromodulation

3 cycles ON stimulation, 2 cycles OFF stimulation
OFF cycles optimize the desynchronizing effect according to computational studies
Acoustic CR Neuromodulation

Synchronous neuronal population

Divided into sub-groups

Complete desynchronisation

Tass & Popovych: Biological Cybernetics (2012)
RESET study: acoustic CR in chronic tinnitus
Overview

• 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)
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

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

Alpha, delta and theta 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

<table>
<thead>
<tr>
<th>Frequency Range</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta 1-4 Hz</td>
<td>Delta waves</td>
</tr>
<tr>
<td>Theta 4-8 Hz</td>
<td>Theta waves</td>
</tr>
<tr>
<td>Alpha 8-12 Hz</td>
<td>Alpha waves</td>
</tr>
<tr>
<td>Beta 12-30 Hz</td>
<td>Beta waves</td>
</tr>
<tr>
<td>Gamma low 30-48 Hz</td>
<td>Gamma waves</td>
</tr>
<tr>
<td>Gamma high 52-90 Hz</td>
<td>Gamma waves</td>
</tr>
</tbody>
</table>

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 calculated 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
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

**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**


- Statistical group analysis (ANOVA)

Silchenko, Adamchic, Hauptmann, Tass: manuscript under review
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)

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

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
- Statistical group analysis (ANOVA)
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
Acknowledgements

**DBS:**

**Human:**
Dept. of Stereotactic and Functional Neurosurgery, Univ. Cologne:

**V. Sturm, M. Maarouf, H. Treuer, D. Lenartz**

Institute of Neuroscience and Medicine:

**H.-J. Freund**

**MPTP:**

Inst. for Neurodenenerative Disorders, CNRS UMR 5293, Bordeaux, France,

Dept. of Neurology, University Hospital Bordeaux, France:

**W. Meissner, T. Boraud, E. Bezard**

Inst. of Laboratory Animal Sciences, China Academy of Medical Sciences, Beijing, China:

**L. Qin**
Acknowledgements

Tinnitus:

- Dr. Tatjana von Stackelberg (Meerbusch)
- Dr. Huber Hermes (Kevelaer)
- Dr. Wilhelm Schütz (Jülich)
- Prof. Dr. Jürgen Alberty (Aachen)

- Prof. Dr. Anita Patteet (ANM)

- Dr. Jan Bart Hak (Universität Groningen), Dr. Gentiana Wenzel (Universität Hannover), Prof. Dr. Dr. Ralf Mösges (Universität Köln)
Acknowledgements

Institute for Neuroscience and Medicine – Neuromodulation, Research Center Juelich:
Christian Hauptmann
Safwan Al-Qadhi
Julia Buhlmann
Judith Coenen
Martin Ebert

Oleksandr Popovych
Borys Lysyansky

Ilya Adamchic
Alexander Silchenko
Norbert Pawelcyzk

Department of Neuromodulation, Univ. Cologne:
Utako Barnikol