Non-invasive Electrical Stimulation for the Central and Peripheral Nervous System

Adam Williamson
Senior Research Team Leader
International Clinical Research Center (ICRC),
St. Anne’s University Hospital and Faculty of Medicine, Masaryk University,
Brno, Czech Republic
Temporal Interference (TI): Epilepsy as a model
  - Preliminary work in rodents and scaling TI to humans
  - Clinical Temporal Interference

Tremor and Parkinson’s disease

Clinical TI of Peripheral nerves
  - Hypoglossal nerve
  - Vagus Nerve

Conclusions
The Problem

1) Antiepileptic Drugs
2) Penetrating Electrodes
3) Resective Surgery
4) Electrical Stimulation
The Problem

1) Antiepileptic Drugs
2) Penetrating Electrodes
3) Resective Surgery
4) Electrical Stimulation

- increase explorable tissue
- decrease resected tissue
The Solution

State-of-the-Art Engineering: non-invasive interferential electric fields

State-of-the-Art Clinical Neuroscience: deep brain implants for seizure identification and control

\[ |f_1 - f_2| \]
The Solution

State-of-the-Art Engineering: non-invasive interferential electric fields

complete focal/position control

State-of-the-Art Clinical Neuroscience: deep brain implants for seizure identification and control

Complete Non-invasive Deep Brain Stimulation in Epilepsy
Temporal Interference (TI) Stimulation
Preliminary Results: **Efficacy**

**A** Standard Transcranial Excitatory Stimulation

- 1250 Hz
- 1200 Hz
- 50 Hz

Δf = 50 Hz

**B** Excitatory Stimulation

- Classic Intracranial
  - f = 50 Hz

- TI
  - TI – 1200 + 1250 Hz
  - TI evoked seizure

- No standard evoked
Preliminary Results: **Efficacy**

A. Standard Transcranial Excitatory Stimulation (HFS)

- Δf = 130 Hz

B. Excitatory Stimulation

A. TI – 1200 + 1250 Hz

- TI evoked seizure
- No standard evoked

C. Inhibitory Stimulation (HFS)

- Pathological Interictal spiking in epileptic mice

Classic Intracranial

f = 130 Hz
Preliminary Results: **Efficacy**

**A**
- 1430 Hz
- 1300 Hz
- 130 Hz

$\Delta f = 130$ Hz

**Standard Transcranial**

**B**

**Excitatory Stimulation**

- TCS 130Hz
- 1mA
- 2mA

**Inhibitory Stimulation (HFS)**

- Rate (IEDs/min)
- Area ($\mu^2$s)
- Duration (s)
- Amplitude ($\mu$V)

**C**

- Deep
- Superficial
Simulations of Standard TI and the EZ

Patient Stimulation with Standard TI of the EZ

TI Results: Suppression of pathological activity rate

TI Results: pathological spike properties are significantly reduced. Seizures very unlikely to propagate with such reduction in pathological activity

Area (µV².s) | Duration (s) | Amplitude (µV)
---|---|---
** | *** | **

Time (mS) | Amplitude envelope (mV)
---|---
0 | 0
5 | 5
10 | 10
15 | 15
20 | 20
500 | 500
1000 | 1000
1500 | 1500
2000 | 2000
2500 | 2500
3000 | 3000
3500 | 3500
4000 | 4000
4500 | 4500
5000 | 5000
5500 | 5500
6000 | 6000
6500 | 6500
7000 | 7000
7500 | 7500
8000 | 8000
8500 | 8500
9000 | 9000
9500 | 9500
10000 | 10000

Amplitude envelope (mV)

Deep

Superficial
Temporal Interference (TI): Epilepsy as a model

- Preliminary work in rodents and scaling TI to humans
- Clinical Temporal Interference

- Tremor and Parkinson’s disease

- Clinical TI of Peripheral nerves
  - Hypoglossal nerve
  - Vagus Nerve

- Conclusions
Temporal Interference Stimulation (TIS) - principle

- Subject specific modelling of e-fields and electrode positions
Temporal Interference Stimulation (TIS) of subthalamic nucleus (STN)
Pilot measurement – 1st patient

Parkinson’s disease patient
- male, 64 years, right-handed
- Disease duration 14 years, dominant side - right
- With freezings, LED = 1385, UPDRS = 41
- Indicated to STN-DBS, Medtronic Percept IPG, Directional Leads B33005

- Externalized leads, LFP recording, medication OFF state
Lead localization

Orange – motor, blue – associative, yellow – limbic part of STN
Temporal Interference Stimulation (TIS)

- Two stimulation pairs on scalp, high frequency carriers
  - $f_1 = 9000 \text{ Hz}$, $f_2 = 9130 \text{ Hz}$, $\Delta f = 130 \text{ Hz}$
  - Stimulation target: position of L1 contact

- LFP recording from externalized leads, $f_s = 25\text{kHz}$, Cz scalp reference, recalculated to bipolar L0L1, L1L2, L2L3 (R0R1, R1R2, R2R3)

Note that magnitude of interference artifact differs across bipolar contacts on lead. It means we are able to focus the stimulation also in subcortical regions.
LFP recording, beta power analysis

- \( fs = 25kHz \), Cz scalp reference, recalculated to bipolar
- analysis of LOL3 signal with focus on beta peak power

Comparison of oscillatory components of power spectrum between baseline, conventional DBS stimulation and non-invasive temporal interference stimulation

- Baseline resting state, 2 minutes, OFF medication
- Rest after DBS, 2 mins of recording immediately after 3 mins of stimulation of L1L2, 130Hz, 90us, 2V
- Rest after TIS, 2 mins of recording immediately after 3 mins of stimulation targeted L1, 130 Hz

Note that beta power peak at 26.5Hz is the highest in baseline condition and falls after DBS or TIS stimulation – evaluated after-effect of stimulation. Between DBS and TIS session was approx. 30 minutes pause.
Temporal Interference Stimulation (TIS) of subthalamic nucleus (STN)
Pilot measurement – 2nd patient

- Parkinson’s disease patient
- male, 53 years, right-handed
- Dominant side - left
- Indicated to STN-DBS, Abbott Infinity IPG, Directional Leads 6172

- Externalized leads, LFP recording, medication OFF state
Lead localization

Orange – motor, blue – associative, yellow – limbic part of STN
Temporal Interference Stimulation (TIS)

- Two stimulation pairs on scalp, high frequency carriers
  - $f_1 = 9000$ Hz, $f_2 = 9130$ Hz, $\Delta f = 130$ Hz
  - Stimulation target: position of R1 contact

- LFP recording from externalized leads, $fs = 25$kHz, Cz scalp reference, recalculated to bipolar L0L1, L1L2, L2L3 (R0R1, R1R2, R2R3)

Note: Unfortunately, no clear difference in envelope amplitude between bipolar contacts
LFP recording, beta power analysis

- \( f_s = 25\, \text{kHz} \), Cz scalp reference, recalculated to bipolar
- analysis of R1R2 signal with focus on beta peak power

Comparison of oscillatory components of power spectrum between baseline, non-invasive temporal interference stimulation and conventional DBS stimulation

- Baseline resting state, 2 minutes, OFF medication
- Rest after TIS, 2 mins of recording immediately after 3 mins of stimulation targeted R1, 130 Hz
- Rest after DBS, 2 mins of recording immediately after 3 mins of stimulation of R1R2, 130Hz, 90us, 2V

Note that beta power peak is the highest in baseline condition and falls after TIS and DBS stimulation – evaluated after-effect of stimulation. Between TIS and DBS session was approx. 20 minutes pause.
Temporal Interference (TI): Epilepsy as a model
  Preliminary work in rodents and scaling TI to humans
  Clinical Temporal Interference
Tremor and Parkinson’s disease
Clinical TI of Peripheral nerves
  Hypoglossal nerve
  Vagus Nerve
Conclusions
Clinical Temporal Interference

Vagus nerve wrapped with clinical stimulation electrodes

Hamdi et al., *Operative Neurosurgery*, 18, 5, 487–495 (2020)
Clinical Temporal Interference

Vagus nerve wrapped with clinical stimulation electrodes

Hamdi et al., *Operative Neurosurgery*, 18, 5, 487–495 (2020)

Vagus Nerve
Phrenic Nerve
Hypoglossal Nerve

transcutaneous TI

implantable stimulator
- **Normal airflow** with no pathological obstruction due to tongue collapse

- Hypoglossal nerve is responsible for tongue tonus
For the 1 Billion people with obstructive sleep apnea (OSA), CPAP is the standard of care. Loud, Uncomfortable, Infection Risk, Massive Recalls, Poor Compliance.
Obstructive Sleep Apnea (OSA)

For the 1 Billion people with obstructive sleep apnea (OSA), CPAP is the standard of care. Loud, Uncomfortable, Infection Risk, Massive Recalls, Poor Compliance.

AIR FLOW

Healthy participant

Obstructive participant

Hypoglossal nerve

Fourth intercostal region

Stimulation lead

Neurostimulator

Sensing lead

Normalized EF

Inspire
Sleep Apnea Innovation
● Hypoglossal nerve stimulation is the standard surgical treatment for OSA

● Non-invasive stimulation is challenging but would avoid surgical procedure and tongue collapse during the night for OSA patients
• With no stimulation, no tongue tonus and protrusion will be induced.

• During an OSA event, the direct stimulation of the hypoglossal nerve will prevent tongue collapse.
- **Unilateral** nerve stimulation only induces a **partial lateral** tongue protrusion.

- The stimulation amplitude needed to induce a tongue tonus with unilateral TI is high and induce tingling on the skin.
- **Bilateral** nerve stimulation induces a **complete central tongue protrusion**.

- **Diminution** of stimulation **amplitude** of about 40%, reducing tingling sensation for a **same stimulation output**.
- **Crossed TI design** for optimal hypoglossal nerve targeting

- **High-frequency carriers** to reduce tingling sensation on the skin when applying the bTI stimulation

- **Bilateral TI** with both hypoglossal nerve stimulation at $\Delta f = 50$Hz
Left side

Right side

\begin{align*}
f_1 &= 5000 \text{Hz} \\
f_2 &= 5050 \text{Hz} \\
f_3 &= 6050 \text{Hz} \\
f_4 &= 6000 \text{Hz}
\end{align*}

\begin{align*}
T_{ILS} &= 50 \text{Hz} \\
T_{IRS} &= 50 \text{Hz}
\end{align*}

\text{bTI = 50Hz, 0.5s ON / 2s OFF}
**O₂ saturation** is a direct readout of apneas and hypopneas

**Apnea Hypopnea Index (AHI)** is calculated overnight and a low AHI is correlated with a good sleep

![Graph showing overnight polysomnography](image)

Overnight polysomnogram

**bTi** stimulation efficiently **decreases** the number of **apneas** during the night and **reduces** overnight **AHI** (~60% reduction in women)

**High sex dependency**, men hypoglossal nerves are more difficult to depolarize using electrical stimulation
Device downsizing

FDA designation “Breakthrough Device”

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has received the above submission requesting designation as a Breakthrough Device. The proposed indications for use includes "The treatment of adult patients with a BMI ≥35 with moderate to severe OSA (AHI 15-50) who fail or do not tolerate PAP/oral appliances." We are pleased to inform you that your device and proposed indication for use meet the criteria and have been granted designation as a Breakthrough Device.

Please refer to the FDA guidance document entitled "Breakthrough Devices Program", for more information regarding the program, available at https://www.fda.gov/media/108135/download.

We recommend you review the FDA guidance document for the Breakthrough Devices Program referenced above for the available mechanisms for obtaining feedback from the Agency on device development for designated breakthrough devices. When submitting any new requests, please reference Q230334. Any new submission should be provided as an eCopy, it should include the FDA reference number for this submission, and should be submitted to the following address:

- Of the 760 devices given Breakthrough Designation since the program started in 2015, only 7 have been under the ENT category and 0 for Sleep.
Temporal Interference (TI): Epilepsy as a model

Preliminary work in rodents and scaling TI to humans

Clinical Temporal Interference

Tremor and Parkinson’s disease

Clinical TI of Peripheral nerves

Hypoglossal nerve

Vagus Nerve

Conclusions
Vagus nerve stimulation (VNS) is an alternative treatment in pharmacoresistant epilepsy.
Vagus nerve stimulation (VNS) is an alternative treatment in pharmacoresistant epilepsy.
Vagus nerve stimulation (VNS) is an alternative treatment in pharmacoresistant epilepsy.
Vagus nerve wrapped with clinical stimulation electrodes

Hamdi et al., *Operative Neurosurgery*, 18, 5, 487–495 (2020)
Hamdi et al., *Operative Neurosurgery*, 18, 5, 487–495 (2020)

Vagus nerve wrapped with clinical stimulation electrodes

implantable VNS
Arrangements of electrodes are placed on the skin above the vagus nerve and implant.
Arrangements of electrodes are placed on the skin above the vagus nerve and implant.

Battery replacement

1) Incision to remove old stimulator

Hamdi et al., *Operative Neurosurgery*, 18, 5, 487–495 (2020)
Arrangements of electrodes are placed on the skin above the vagus nerve and implant.

Battery replacement

1) Incision to remove old stimulator

2) Battery replacement allows direct access to electrodes on the vagus

Hamdi et al., *Operative Neurosurgery*, 18, 5, 487–495 (2020)
Arrangements of electrodes are placed on the skin above the vagus nerve and implant.

Battery replacement

1) Incision to remove old stimulator

2) Battery replacement allows direct access to electrodes on the vagus

Connections from electrodes on the skin to our TI and transcutaneous stimulation...

Connections from electrodes on the vagus to our recording equipment...
Arrangements of electrodes are placed on the skin above the vagus nerve and implant.

Hamdi et al., *Operative Neurosurgery*, 18, 5, 487–495 (2020)

**Battery replacement**

1) Incision to remove old stimulator

2) Battery replacement allows direct access to electrodes on the vagus

New stimulator is replaced when we finish.
New stimulator is replaced when we finish
Vagus nerve

- Microregulator Pulse Generator
- Wireless Charger
- iPad App

**Implant**
- Along the vagus nerve

**Charge**
- A few minutes each week

**Prescribe**
- HCP prescribes therapy delivery through iPad app

1. Microregulator electrically stimulates vagus nerve
2. Signals through vagus and splanic nerve trigger reduction in activation of T cells and macrophages in spleen
3. Reduced production of systemic inflammation mediators
   - Reduced activation of circulating immune cells
4. Decreased inflammation
   - Decreased joint damage
   - Reduction in joint pain
● Vagus nerve

- Microregulator electrically stimulates vagus nerve
- Signals through vagus and splenic nerve trigger reduction in activation of T cells and macrophages in spleen
- Reduced production of systemic inflammation mediators
- Reduced activation of circulating immune cells
- Decreased inflammation
- Decreased joint damage
- Reduction in joint pain

**SETPOINT MEDICAL**

**Implant**
- Along the vagus nerve

**Charge**
- A few minutes each week

**Prescribe**
- HCP prescribes therapy delivery through iPod app

[Image of human brain and nervous system]
Vagus Nerve

Normalized Electric Field (V/m)

15-20s stim time

f₁ = 9000Hz

f₂ = 9050Hz

TI_{center cross} = 50Hz

Heart-rate

100 pulses/min

50 pulses/min

% decrease of heart-rate

VNS TI (n=5)

Stimulation ON

**

% decrease of heart-rate

STIM OFF STIM ON
Temporal Interference (TI): Epilepsy as a model

- Preliminary work in rodents and scaling TI to humans
- Clinical Temporal Interference

Tremor and Parkinson’s disease

- Clinical TI of Peripheral nerves
  - Hypoglossal nerve
  - Vagus Nerve

Conclusions
State-of-the-Art Clinical Neuroscience: deep brain implants for seizure identification and control

State-of-the-Art Engineering: non-invasive interferential electric fields

envelope = |f1 - f2|
Complete Non-invasive Deep Brain Stimulation in Epilepsy

State-of-the-Art Engineering: non-invasive interferential electric fields

envelope = |f1 - f2| Δf

State-of-the-Art Clinical Neuroscience: deep brain implants for seizure identification and control
Děkuji za pozornost
<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td><strong>Stim</strong></td>
<td><strong>Stim</strong></td>
</tr>
<tr>
<td><strong>PostStim (20min)</strong></td>
<td><strong>PostStim (20min)</strong></td>
</tr>
<tr>
<td><strong>PostStim (24h)</strong></td>
<td><strong>PostStim (24h)</strong></td>
</tr>
</tbody>
</table>

Spike rate per minute

- **Patient 1**: (n.s. 0.65) *** (0.02)
- **Patient 2**: (n.s. 0.37) *** (0.009)
Preliminary Results: **Focality**

Standard TI

---

20 cm
A) TI, 2 waves = 1 envelope...

![Diagram showing the envelope of two waves with frequencies 1975 Hz and 2025 Hz, resulting in an envelope frequency of 50 Hz.](image)
A) TI, 2 waves = 1 envelope...

B) mTI, but two envelopes = 1 large envelope
A) TI, 2 waves = 1 envelope...

B) mTI, but two envelopes = 1 large envelope

large envelope reduced to original envelope = increase in focality
A) TI, 2 waves = 1 envelope...

B) mTI, but two envelopes = 1 large envelope

large envelope reduced to original envelope = increase in focality
Preliminary Results: **Focality**

**Standard TI**

(1 envelope)

\[ f_1 \]

**mTI**

(multiple envelopes)

\[ f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8 \]
Preliminary Results: **Focality**

Standard TI vs mTI: Patent EP 21306447 - DEEP BRAIN STIMULATION SYSTEM
Focality in NHPs
Target: superior colliculus
Target: superior colliculus

sim4Life
SC

stimulation envelope

100 Hz envelopes

evoked spike

saccades

Recording electrode

Superior colliculus

16 recording sites in the region
A “burst of envelopes”

- Sham ON
- Sham OFF
- Octopole-100 Hz ON
- Octopole-100 Hz OFF
- Stimulation train