Modulating Brain Circuits with Ultrasound

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Neuromodulation

• Dysfunction of brain circuitries are a responsible for many neurological diseases [1]
• Identifying how different regions of the brain interact remains a difficult research goal
  – Casual relationships between circuits
• Method of investigating circuits
  – Manipulate circuitry (in excitatory or inhibitory directions) and correlate changes in behavior or other readouts

US overcomes limitations of other methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Invasiveness</th>
<th>Spatial selectivity</th>
<th>Excite/Inhibit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transcranial magnetic</td>
<td>😊</td>
<td>😞</td>
<td>😊</td>
</tr>
<tr>
<td>Transcranial electrode</td>
<td>😞</td>
<td>😞</td>
<td>😊</td>
</tr>
<tr>
<td>Direct electrode</td>
<td>😞</td>
<td>😊</td>
<td>😊</td>
</tr>
<tr>
<td>Deep brain stimulation</td>
<td>😞</td>
<td>😊</td>
<td>😊</td>
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<tr>
<td>Ultrasound</td>
<td>😊</td>
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</tbody>
</table>
Timeline of FUS Neuromod.

- Suppressed VEP in cats (1958)
- Suppression of reflexes in spinal cord (cats) (1962)
- Differential touch, pain (humans) (1978)
- Evoked auditory sensations (human basilar artery) (1993)
- Suppression of evoked spiking and enhanced dendritic field potential (hippocampal slices) (1993, 1998)
- Motor stimulation and suppression of induced seizure (mice) (2010)
- Resurgence of interest with at least 50 papers and various patents filed (2010-2016)
- Suppression of chemically-induced epilepsy (rats) (1964)
Possible underlying mechanisms
Combined neuromodulation and imaging

Ultrasound neuromodulation

Perform under MR guidance

Couple to functional MRI

Network-level imaging with focal neuromodulation
Scale: size and complexity

• Brain size
  – Wavelengths on the order of 1 mm with 100s of cycles
  – Standing waves increase pressure [1,2]

• Circuits increase in complexity

Modulating FEF with FUS

• Apply ultrasound to frontal eye field (FEF) during task
  – Measure gaze behavior, event-related potentials
    • Saccade response time (SRT), accuracy, EEG
    • Slowing of saccades has been observed previously [1]
  – Expectations stimulating FEF
    • Eliciting saccadic eye movement

Modulating FEF with FUS

- Study design
  - Two monkeys studied (H and G)
    - 7 sessions with 10-minute blocks alternating between US on and off
    - ~125 trials in block and 800 in session

<table>
<thead>
<tr>
<th>Group</th>
<th>Low</th>
<th>High</th>
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<tbody>
<tr>
<td>Session</td>
<td>500 kHz</td>
<td>500 kHz</td>
</tr>
<tr>
<td></td>
<td>250 μsec</td>
<td>250 μsec</td>
</tr>
<tr>
<td></td>
<td>2 kHz</td>
<td>2 kHz</td>
</tr>
<tr>
<td></td>
<td>250 kPa</td>
<td>425 kPa</td>
</tr>
<tr>
<td></td>
<td>300 msec</td>
<td>300 msec</td>
</tr>
</tbody>
</table>

Single Trial

- Ready time (500 ms)
- Response time
- Sonicate (300 ms, 425 kPa)

- F: 500 kHz
- PD: 250 μsec
- PRF: 2 kHz
- PNP: 250 kPa
- TD: 300 msec

- ΔV

Single Trial

- Ready time (500 ms)
- Response time
- Sonicate (300 ms, 425 kPa)
Pulses are within diagnostic limits

Minimum inter-pulse time allowed was 2 sec => Maximum duty factor possible 7.5%

<table>
<thead>
<tr>
<th></th>
<th>Neuromod</th>
<th>FDA Guidelines [1]</th>
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<tbody>
<tr>
<td>Ispta.3 [mW/cm²]</td>
<td>530</td>
<td>720</td>
</tr>
<tr>
<td>MI</td>
<td>0.6</td>
<td>1.9</td>
</tr>
<tr>
<td>Isppa.3 [W/cm²]</td>
<td>7</td>
<td>190</td>
</tr>
</tbody>
</table>
Beam localization
Spatially selective modulation

Eccentricity [°]  SRT_{ON} - SRT_{OFF} [msec]

- 20  0  10  20  45  90

G

H

425 kPa
250 kPa
Intensity dependent modulation of ERP

Zinke et al. SfN 2016

Normalized EEG signal is baseline corrected by subtracting the mean signal in the 250 ms before FUS onset.
Combined neuromodulation and imaging

Ultrasound neuromodulation → Perform under MR guidance → Couple to functional MRI

Network-level imaging with focal neuromodulation

Magnitude Image
Displacement at Focus

Phantom
Focus

TRANSDUCER

Thermal overlay
Mouse

FUS off
FUS on

5μV
100ms
Integrating into MRI
High quality images

Surface coil
Image-guidance for placing probe

Mechanisms visible with MRI
Tracking heat with MRI

Mechanisms visible with MRI
Displacement at safe pressures

Phantom - Intensity vs Displacement at the Focus

Normalized Cross Correlation
Bayes Estimator
Imaging radiation force in phantom

Gel phantom (3% agarose, 2% fiber, 2% n-propanol)

Transducer
Array-based ultrasound
Aberration Correction

- Pressure wave without skull
- Wave with skull and no correction
- Phase-corrected wave

Axial Distance [mm]
Pressure [MPa]
Time reversal implemented in simulations

Native focus

Skull present, no applied delays

Skull present, time reversal delays applied
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Magnitude Image
Displacement at Focus

Phantom
Focus
Transducer

Thermal overlay
Mouse
Transducer

FUS off
FUS on

$\pm 10$ mm
$\pm 10$ μm
Acoustic coupling + shimming

Transducer coupling cone
Surface coil

Parts adjoined for combined imaging and neuromodulation
EPI in presence of ultrasound

No ultrasound

Water-filled

Gd-doped cone

Fomblin-filled
FUS Stimulation

Tactile stimulation (D2&D3) Run 1

Tactile stimulation (D2&D3) Run 2

FUS

P<0.001 (corrected)

Tactile/FUS

30 sec on 30 sec off

.......... x7

posterior

anterior

t value

3

9
Combined neuromodulation and imaging

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Network-level imaging with focal neuromodulation
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