Focused-Ultrasound Mediated Blood-Brain Barrier Disruption

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Blood-brain barrier (BBB)
- Physical and functional barrier that restricts passage of substances from the blood to the brain
- The primary hurdle to the use of drugs in the central nervous system
  - Prevents passage of most small molecule agents and all large molecule agents
- Methods developed to bypass the BBB are invasive, non-targeted and/or require the development of new drugs

BBB disruption with focused ultrasound
- Low-power, pulsed exposures
- Combined with ultrasound contrast agent (Optison, Definity)
- Temporary (~hours), localized, non-invasive

Mechanical interaction between US, microbubbles, and vessel walls results in:
- Transient disassembly of tight junction proteins
- Stimulation of active transport

At higher exposure levels, inertial cavitation occurs, leading to vessel damage

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Hynynen et al., Neuroimage 2004
**BBB disruption with focused ultrasound**

Small animal studies:
- Reliably induce BBB disruption without tissue damage
- Deliver a range of molecules to the brain, including therapeutics
- Improve outcomes in animal disease models

_Glioma, Alzheimer’s_

![Trypan Blue + Anti-α4 antibodies](image)

_Nathan McDannold, PLoS One 2008_

**Enhanced delivery of Herceptin to breast cancer brain metastases model**

- Human breast cancer cells (BT474) injected in the brain of nu/nu rats
- Six weekly treatments with BBBD + Herceptin (690 kHz)

_EJ Park et al. (in preparation)_

**Transcranial MRgFUS (ExAblate 4000, InSightec, Haifa Israel)**

_Glioma feasibility study_

*Image courtesy InSightec*_

_EJ Park et al. (in preparation)_

(Duration: 2/5 minutes)
Safety study in monkeys

- ExAblate 4000 low-frequency MRgFUS system (InSightec, Haifa, Israel)
- 1024-element phased array transducer, 30 cm hemisphere, 220 kHz
  - Designed for ablation
- 3T MRI (GE Healthcare)

Methods

- Seven rhesus macaques, 5-12 kg
  - #3 sonicated 2x over 2 weeks
  - #4 sonicated 13x over 3+ months
  - #5-7 sonicated 5x over 5-9 weeks
    - Same targets sonicated multiple times
- Definity microbubbles
- 0.2-10W (100-700 kPa)
- 10 ms bursts
- Both bolus injection and infusion were tested
  - Establish constant bubble concentration for acoustic emission monitoring
- 185 different sonication targets

BBBD and damage thresholds (grey matter structures)

- Summary results from 185 targets in 7 animals

<table>
<thead>
<tr>
<th>Probability (%)</th>
<th>kPa</th>
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<tbody>
<tr>
<td>50% probability for BBBD:</td>
<td>149 kPa (95% CI: 125-163 kPa)</td>
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<tr>
<td>50% probability for T2*:</td>
<td>300 kPa (95% CI: 278-341 kPa)</td>
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Acoustic emission monitoring

- No BBB disruption
- BBB disruption
- BBB disruption + petechiae
BBBD depends on location as well as pressure amplitude
- Skull effects
- Blood flow/volume; bubble concentration
- Local differences in vasculature?

Results

1.5W (273 kPa)

2W (315 kPa)

1.5W (273 kPa)

Sonications

- One location per sonication (N=34)
- 1 Hz PRF

- Nine locations per sonication via beam steering (N=75)
- New location every 120-400 ms
- 0.25-1.1 Hz PRF at each location

Volumetric sonication

1W (223 kPa) sonication, no damage

T1W FSE + Magnevist (0.2 mmol/kg)
TR/TE=500/14 ms, ETL 4
256x256, 12cm FOV, 3mm slice

Volumetric sonication

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Volumetric sonication

T1W FSE + Magnevist (0.2 mmol/kg)
TR/TE=500/14 ms, ETL 4
256x256, 12cm FOV, 3mm slice

1W (223 kPa) sonication, no damage

Large molecule contrast agent
Ablavar (bound to Albumin)

Small molecule contrast agent
Magnevist

Volumetric sonication: Singulate Cortex

T1W FSE + Magnevist (0.2 mmol/kg)
TR/TE=500/14 ms, ETL 4
256x256, 12cm FOV, 3mm slice

1W (223 kPa) sonication, no damage
**BBBD in grey vs. white matter**

- No contrast enhancement in white matter
- ...but Trypan blue leakage evident

**Histology:** Cingulate Cortex @ ~2h
- BBBD 9x over 7 months
- Stain: Nissl

**Histology:** Cingulate Cortex @ 2h
- BBBD 9x over 7 months
- Stain: H&E

Erythrocyte extravasation (petechia)
Histology: Cingulate Cortex @ 2h
BBBD 9x over 7 months
Stain: Nissl

Histology: White matter @ 2h
BBBD 9x over 7 months
Silver stain

Histology: Putamen @ 6 months
Stain: Nissl

Histology: Putamen @ 6 months
Stain: Nissl

Hemosiderin

Hemosiderin (< 5 µm)
Overexposure: T2*

3D T2*W Gradient echo
TR/TE=33/19 ms, FA=15°
256x256, 12cm FOV, 1mm slice

Functional testing

Monkeys 5-7

- 5 BBBD sessions in visual system
  - Lateral Geniculate Nucleus (LGN)
  - Primary visual cortex

- Pre- and post-FUS functional testing:
  - Ability to remember 26 different symbols
  - Ability to see and recognize the symbols
  - Visual acuity
  - Motor skill

Functional tests

Conclusions

- BBBD is showing some success in animal disease models, even with large-molecule drugs
- BBBD feasible in primates with a clinical device without histological or functional damage
- Effects were contained to the targeted region
- Contrast enhancement not seen in white matter, only gray matter
  - BBBD detected with Trypan Blue
- Improved treatment planning, monitoring, evaluation desired
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