NEUROLOGICAL APPLICATIONS OF FOCUSED ULTRASOUND

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DISCLOSURE

Three Animals in the Brain
• Chief investigator Pfizer supported study for Tyrosine Kinase Inhibitors for treatment of Alzheimer’s and Parkinsons
• Chief investigator Focused Ultrasound study for delivery of Tyrosine Kinase Inhibitor to hippocampus
• Chief investigator Focused Ultrasound study for delivery of Tyrosine Kinase Inhibitor to Substantia Nigra
• Chief investigator autologous adipose derived stem cell injections for chronic migraine
• Chief investigator microbubble enhanced opening of blood brain barrier with focused ultrasound
• Consultant/collaborator BrainSonix
NEUROLOGICAL APPLICATIONS OF FOCUSED ULTRASOUND

- Ablation
- Sonothrombolysis
- Drug delivery and opening blood brain barrier
- Neuromodulation
FOCUSING SOUND

• Ear of Dionysius, Sicily, 367 B.C.E.
FOCUSING SOUND

- Saint Paul Whispering Gallery, London, 1711
FOCUSING SOUND

- Megaphone
WHAT IS ULTRASOUND?
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Electrical Energy transformed into ultrasound: PIEZOELECTRIC EFFECT

Churchill Livingston, 2009
WHAT IS ULTRASOUND?
WHAT IS ULTRASOUND?

- **Focused with the addition of a lens**
- **Focused by a curved crystal**

**Focal zone**

- The beam width of a focused ultrasound beam varies with depth and is narrowest at the focus. Best lateral resolution is achieved at the focus.

Churchill Livingston, 2009
WHAT IS ULTRASOUND?

Churchill Livingston,
2009
WHAT IS ULTRASOUND?

Churchill Livingston, 2009
WHAT IS ULTRASOUND?
WHAT ARE THE EFFECTS OF ULTRASOUND ON TISSUE?

- MECHANICAL
- THERMAL
- STIMULATION
ULTRASOUND VS. SKULL AND BRAIN

- Reflection: Loss of penetrating waves, chance for reflection with standing waves and excess effects
- Refraction: Loss of precision targeting
- Absorption: Loss of penetrating waves, inadvertent scalp heating
MRI GUIDED FOCUSED ULTRASOUND

Diploe: trabecular layer
(c = 2700 m.s\(^{-1}\))

Outer table
(c = 3000 m.s\(^{-1}\))

Inner table
(c = 3000 m.s\(^{-1}\))
SOLUTIONS TO LIMITATIONS

• Single piezoelectric probe, single lens through acoustic window
• Multiple probe over entire skull with phase correction and monitoring (in MRI scanner)
• Hybrid (in and out of MRI scanner)
SOLUTIONS FOR LIMITATIONS

• Standard Windows through skull
• Individualized Window assessment using MRI/MRA coordinates
• Re evaluation of power and temperature deposition limits
• Phase Correction with CT based data sets
• Accurate/real time temperature and mechanical monitoring
APPLICATIONS

• Ablation, High Intensity Focused Ultrasound; tissue necrosis at center, penumbra of apoptotic effects
• Sonolysis; break up clot, potential for bleeding at frequencies less than one hertz
• drug and particulate delivery; increase blood flow, open tight junctions, possible increased transcellular migration
• Stimulation; release of synaptic vesicles or deformation of post synaptic channels
MRI GUIDED FOCUSED ULTRASOUND WITH MULTIPLE PROBES

Fishman, et al, 2017
MRI GUIDED
FOCUSED
ULTRASOUND
MRI GUIDED FOCUSED ULTRASOUND

Lost Planet, 1953
MRI GUIDED FOCUSED ULTRASOUND

Kyriakou, et al, 2014
MRI GUIDED
FOCUSED
ULTRASOUND

Kyriakou, et al, 2014
Evaluation of a Three-Dimensional MR Acoustic Radiation Force Imaging Pulse Sequence Using a Novel Unbalanced Bipolar Motion Encoding Gradient

Joshua T. de Bever,¹∗ Henrik Odén,² Nick Todd,² Alexis I. Farrer,³ and Dennis L. Parker⁴

MRI-ARFI Acoustic Radiation Force Imaging
MRI GUIDED FOCUSED ULTRASOUND

Wintermark, et al, 2014
MRI GUIDED
FOCUSED
ULTRASOUND

**Acute effects**

**Central zone**
- Protein denaturation and aggregation
- Damage of cellular and nuclear membranes
- Halted metabolism
- Vascular collapse and hemorrhage

**Peripheral zone**
- Hypothenasia
  - Unheated tissue
  - Heated tissue
- Halted/impaired metabolism

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A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor

W. Jeffrey Elias, M.D., Nir Lipsman, M.D., Ph.D., William G. Ondo, M.D., Pejman Ghanouni, M.D., Ph.D., Young G. Kim, M.D., Ph.D., Wonhee Lee, M.D., Ph.D., Michael Schwartz, M.D., Kullervo Hynynen, Ph.D., Andres M. Lozano, M.D., Binit B. Shah, M.D., Diane Huss, D.P.T., N.C.S., Robert F. Dallapiazza, M.D., Ph.D., Ryder Gwinn, M.D., Jennifer Witt, M.D., Susie Ro, M.D., Howard M. Eisenberg, M.D., Ph.D., Paul S. Fishman, M.D., Ph.D., Dheeraj Gandhi, M.D., M.B., B.S., Casey H. Halpern, M.D., Rosalind Chuang, M.D., Kim Butts Pauly, Ph.D., Travis S. Tierney, M.D., Ph.D., Michael T. Hayes, M.D., G. Rees Cosgrove, M.D., Toshio Yamaguchi, M.D., Ph.D., Keiichi Abe, M.D., Takaomi Taira, M.D., Ph.D., and Jin W. Chang, M.D., Ph.D.
MRI GUIDED FOCUSED ULTRASOUND

ELIAS, et al,
NEJM, 2016
MRI GUIDED FOCUSED ULTRASOUND FOR ESSENTIAL TREMOR

- Variable response effect and durability
- Substantial side effect rate particularly if done bilaterally
- Very expensive and demanding of resources
- Uncertain target localization from functional standpoint
- Limited to central brain targets
- Competes with DBS
First noninvasive thermal ablation of a brain tumor with MR-guided focused ultrasound.

Coluccia D¹, Fandino J¹, Schwyzer L¹, O’Gorman R², Remonda L³, Anon J³, Martin E², Werner B².
MRI GUIDED FOCUSED ULTRASOUND

COLUCCIA, et al, 2014
MRI GUIDED FOCUSED ULTRASOUND FOR TUMOR ABLATION

• Unable to treat larger tumors
• Able to target tumors limited to central/thalamic regions
• Competes with Laser, radiation and other modalities
FOCUSED ULTRASOUND FOR SONOLYSIS

- Thrombus sonolysis
  - Safe and effective at frequencies greater than 1 megahertz
  - Hemorrhage at frequencies less than 1 megahertz due to greater energy, penetrance and standing waves
- Amyloid plaque lysis
MRI GUIDED FOCUSED ULTRASOUND FOR DELIVERING MOLECULAR AGENTS, NANOPARTICLE AND CELLULAR AGENTS

• Open blood brain barrier, facilitate trans endothelial migration
• Interaction of mechanical power, penetration effects with lower frequencies
• Enhanced effects with microbubbles
• Greater sized particles, cells require lower frequency (penetration) and power with resultant bleed risk
FOCUSED ULTRASOUND
OPENING OF BLOOD BRAIN BARRIER
Alternative strategy to forceful opening of BBB with high intensity ultrasound; instead use pulsed low intensity ultrasound (LIFUP) aimed at hippocampus for Alzheimer’s disease

Intrinsic or extrinsic neural stimulation would normally result in sufficient NVC

In Alzheimer’s there is loss of coupling; with neural activation there is insufficient blood flow

Insufficient blood flow is likely trigger of inflammatory cascade

Stem cells home to inflammatory cytokines with trans endothelial migration
MRI GUIDED
FOCUSED
ULTRASOUND
FOR STIMULATION

Non-Invasive Ultrasonic Thalamic Stimulation in Disorders of Consciousness after Severe Brain Injury: A First-in-Man Report
