Repetitive Transcranial Magnetic Stimulation in Generalized Anxiety Disorder

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http://www.semel.ucla.edu/adc/index.htm
Low Frequency Transcranial Magnetic Stimulation using fMRI activation in Anxiety Disorders.

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Prevalence of Generalized Anxiety Disorder (GAD):

As per NIMH data:

- Approximately 6.8 million American adults, or about 3.1 percent of people age 18 and over, have GAD in a given year.

- A lifetime risk of developing GAD is as high as 4-7%.
Causes and Mechanism

- Combination of genetic and environmental causes. (metabolic, medications, substance abuse, organic cause)

- Abnormalities in the neurotransmitters and their receptors

- Failure of GABA receptors in the limbic system to bind with GABA

- Increased Norepinephrine activity in the Locus ceruleus and decreased Serotonin activity are hypothesized

- GAD increases mortality (suicide, cardiac arrhythmias, hypertension)

- High co-morbidity is seen with depression, substance abuse, panic disorders etc.
Social and Economic Impact of GAD

- **Social impairment**
  - Major studies show GAD impairment is comparable to that of pure major depression

- **Work productivity**
  - GAD is associated with significant loss of workplace productivity
  - Average yearly indirect workplace cost is $4 billion

Cost to healthcare: 42-44 Billion $ (comparable with Stroke and Heart conditions)
Treatment of GAD

Combination of Psychotherapy and medications works best
PHARMACOLOGICAL:

- SSRIs are the drug of choice (sertraline, fluoxetine, fluvoxamine, paroxetine, citalopram, escitalopram)
- Benzodiazepines as adjunct for short term use (lorazepam, clonazepam, diazepam, diazepamoxide)
- SNRI (venlafaxine)
- TCAs (imipramine, clomipramine)
- MAOIs (phenelzine)
- Anti-anxiety drugs (buspirone)
- Beta-blockers (propranolol)
NON-PHARMACOLOGICAL:

- Psychotherapy: CBT (Exposure)
- Neurosurgery: Severe cases (to decrease mortality by suicide): cingulotomy, subcaudate tractotomy, capsulotomy, and limbic leucotomy

OTHER INVESTIGATIONAL:

- Herbal (Rhodiola)
- Repeated transcranial magnetic stimulation (rTMS)
- Deep brain stimulation (DBS)
- Vagal nerve stimulation (VNS)
- Yoga, meditation, relaxation techniques
rTMS

- Superficial magnetic stimulation of brain

- Low Frequency (1-10 Hertz) slows down and High Frequency (15 and up) activates brain activity

- Non-invasive, painless form of stimulating the cerebral cortex and affecting the electrical activity in the brain

- It has been successfully implemented for treatment of seizures, treatment resistant depression and PTSD

- Safety of the procedure has been documented in multiple studies
TMS Set-up
rTMS

- Magnetic pulses
- Electrical impulses
- Activation of brain cells
Only a few studies have been done on r TMS for GAD. (studies show hyperactivity of prefrontal and temporal cortex) Furthermore, none of the studies done used neuro-imaging prior to treatment to select target areas in the cortex.

Basis of our study: Low frequency r TMS should slow down these hyperactive areas in the brain.
Prospective randomized trial of 3 weeks duration based in NPI and Brain Mapping center, UCLA

First study to use neuro-imaging for targeting the TMS
Goal of the study

- To conduct low frequency rTMS (1 Hz) in patients with DSM-IV diagnosis of GAD
- To use fMRI data obtained during cognitive activation using risk taking videogames to randomize patients into two treatment groups
  a) standard prefrontal treatment location
  b) treatment of the area of highest activity on fMRI
Recruitment

- 10 Subjects aged 18 to 65 meeting DSM-IV criteria for GAD with no additional comorbidity, not taking any psychotropic medications and not having any metallic implants in the body will be recruited.

- Screening is done on Visit 1 by rating scales such as MINI, Hamilton Anxiety rating scale, HAM-D, UCLA-4D Anxiety rating scale, Self-efficiency scale and a general physical examination.

- HAM-D scores > 14 are excluded.
Study Design and Method

- All eligible subjects undergo a functional MRI to help locate the exact positioning of the TMS coil.

- The subjects are asked to play a gambling game and are told that they will lose their $50 (visit 1 compensation) if they don’t win and gain $100 if they win.

- It is not revealed that the game is designed and manipulated to provoke anxiety by never letting them win.
r TMS is performed twice a week for next 3 weeks (6 sessions)

- The motor threshold is determined for each subject by eliciting motor evoked potentials (MEPs) in the first dorsal interosseus muscle of the dominant hand.
- This procedure uses computer software to co-register the location of the subject’s head in real space with his/her head on a structural MRI scan.
- Repetitive TMS (at 1Hz and 90% of the motor threshold) is delivered for 15 minutes

- Subjects are evaluated twice during the 6 sessions by HAM-A, HAM-D, SES, UCLA-4D and a general Side-effect checklist
Side-effects of the procedure include:

- Headache, discomfort (tylenol)
- Seizures (highly unlikely with low freq.)
- Hearing loss (earplugs, headphones during MRI)
- Claustrophobia during MRI (headphones)
The primary variable will be a score on HARS.

Secondary variables will be scores on UCLA-4D Anxiety Scales subscales.

The response will be judged as the 35% decrease in main variables scores.

Repeated measures ANCOVAs with contrast to baseline will be used to determine the effect.

Significance level of 0.05 in two-tail test will be used.
• Siemens image files will be converted in Analyze files and processed with FSL. (http://www.fmrib.ox.ac.uk/fsl)

• Motion Correction in f MRI will be done using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Linear Image Registration Tool (MCFLIRT)

• We will consider the results positive if the response in either group exceeds 50%.
Limitations

- We believe that this is a pilot study and statistical significance may not be achieved with the small sample size unless the difference between the treatment groups is very pronounced.

However, the pilot study will provide preliminary data that may be used for the report as well as for the power calculation for a larger study provided the results of pilot are positive.
Choosing the target areas for the rTMS treatment is a complex matter.

Currently true synchronization of modern brain imaging techniques with rTMS is impossible even though some promising work in that direction is ongoing.
Assessing long term effectiveness

Phone call 1 month after the study is over

We plan to include follow-up in the larger study
Papers


How the brain works.