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Evaluation of neurocognitive functioning and MEG low-frequency imaging in patients at high risk for TBI and PTSD

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Abstract:
We combined neuroimaging and clinical interviews to analyze the cognitive inhibitory preformance of 37 United States Marines from the explosive ordinance disposal (EOD) team. Each subject underwent an MRI scan and provided self-report data on traumatic brain injuries (TBI), PTSD symptoms and demographic data. In addition, subjects had an magnetoencephalography (MEG) scan while performing the neurocognitive Go-NoGo task. After comparing the clinical findings (PTSD, TBI, etc) with the neuroimaging (MRI and MEG) and the Go-NoGo performance (commission errors and reaction times), we found the Go stimulus to activate the motor cortex exclusively while the NoGo stimulus activated the dorsolateral prefrontal cortex (DLPFC) and left mediolateral temporal lobe (MLTL) exclusively. We also found statistically significant negative correlations between DLPFC and commission errors (responding to NoGo prompt) and between MLTL and PTSD evaluation score.

Background:
Concussions are a leading cause of sustained physical, cognitive, and emotional impairment in both athletes and military personnel\textsuperscript{1}. A pathological feature is disinhibited brain frontal and temporal lobe function, with impaired attention, memory, judgment, emotional regulation, and decision-making\textsuperscript{2}. Very little is actually known about the mechanism and neural circuits involved, making TBI assessment and treatment difficult\textsuperscript{3}. Currently, there are only a few studies analyzing TBIs using magnetoencephalography (MEG) scans\textsuperscript{4}. In addition to confirming the neural circuitry and functioning seen in other imaging techniques, MEGs allow us to assess the effects of TBIs at different frequency brainwaves (see standard frequencies below).
To obtain objective data on the cognitive performance, specifically inhibitory abilities, the Go-NoGo task is an ideal task. In Go-NoGo tasks using fMRI to visualize activity, results showed that the right inferior prefrontal area is involved in the inhibitory response with multiple targets. The right inferior frontal cortex has also been associated with many other inhibition tasks through various imaging and lesion studies5.

With the novel approach of visualizing the brain activity with the MEG scan, we have more spatial precision than an EEG with anatomical differences having less of an effect on magnetic fields. We also have more temporal precision with data on a milliseconds time scale6,7. Nakata et al have analyzed the MEG cortical rhythm in conjunction with a Go-NoGo task, but did not associated any personal subject data, e.i. TBI/PTSD history or demographics.

Because relatively little is known about the neural changes that occur in TBIs and PTSD, the only accepted management is physician monitoring and avoidance of exposure to further trauma3. In addition, TBIs and PTSD are difficult to objectively diagnose and assess because conventional CT and MRI scans cannot reliably detect the injury. Positive findings for TBIs with MRIs in the study by Huang et al were 8.9% and 20.0% for mild and moderate TBIs, respectively. However, using automatic magnetoencephalography (MEG) low-frequency source imaging, Huang et al showed detection of abnormalities with 87% accuracy in mild TBIs and 100% accuracy in moderate TBIs4. It has been previously documented that these focal low-frequency delta waves found by the MEG imaging are abnormal in normal awake adults4.
In this study, Huang et al. focused solely on whether the MEG could reliably detect a TBI while the brain is in a resting state without analyzing working brain state MEGs. For my current study, the Go-NoGo task provides objective data on cognitive performance, specifically inhibitory abilities, to correlate with the objective MEG scans that will be taken throughout the task as well as the demographic, TBI and PTSD data.

**Materials and Methods:**

In the Go-NoGo task, subjects are instructed to respond to a “Go” stimulus, the letter “K”, and refrain from responding to a “NoGo” stimulus, the letter “X”. The stimuli are presented on a screen in a 3:1 ratio of Go to NoGo stimuli to create a bias towards response. Each stimulus is presented for 5000ms with a random interval period between stimuli anywhere from 550ms to 1450ms. By using an unpredictable target sequence with a stutter, the “jitter”, we ensure that the commission errors are a result of an inhibitory neural mechanism error rather than a sustained attention error12.

Throughout the task, we measure the subject’s reaction rate (RT) to respond to the Go stimulus, commission errors (E) when responding to the NoGo stimulus, and commission error reaction time (ERT). We analyzed the data within subjects so each subject provided its own control.

MEG data were acquired during the entire Go-No-Go task with an Elekta/Neuromag whole-head MEG system (VectorView) with 204 gradiometers and 102 magnetometers in a magnetically shielded room (IMEDCO-AG, Switzerland). EOG electrodes were used to detect eye blinks and eye movements. Data were recorded at 1000 Hz, with signal averaging on each visual stimulus presentation (X or K) with 500 ms pre-stimulus and 1500 ms post-stimulus epochs. Data were subsequently processed and re-averaged by MaxFilter to remove environment noise. A BEM mesh of 5-mm size for the subject was generated from the inner-skull surface using a set of T1-weighted MRI images taken on a 1.5 T MRI scanner. Registration of MRI and MEG was performed using data obtained from the Polhemus Isotrak system prior to MEG scanning. Source reconstructions of averaged Go and No Go trials for each subject was performed using the FAST-Vestal approach. An evenly spaced grid (5 mm spacing) with ample coverage of the brain volume was used to model the source-space. RMS amplitude per grid point was then computed for each reconstruction and saved in a 3-D Nifty format file. The RMS reconstructions were then smoothed for each subject.

RMS reconstructions per condition were transformed to MNI 152 space using FLIRT registration (FSL). Average volumes of each condition over all subjects were computed to visualize group activations. Significant condition differences in this common brain space between Go and No-Go were then computed using a non-parametric paired statistical approach. The randomize routine (threshold-free clustering) in FSL was used with 2000 iterations to generate corrected p-values with age as a covariant. Furthermore, statistically differential activation during Go
and No-Go conditions were correlated (voxel-by-voxel across subjects) with measurements of GNG performance, demographic data, and neuropsychological testing for PTSD and TBI (GNG reaction time, GNG comission errors, education, CAPS, number of prior TBIs). Uncorrected p-values obtained from correlational analysis were then FDR-corrected to correct for multiple-comparisons.

Data collection for our 37 patients (MEGs and symptom evaluations) began June 17th, 2013 and ended July 16th, 2013. Analysis of the MEGs, neurocognitive assessments and clinical interviews began June 21, 2013 and ended August 17th, 2013. To carry out this project we used the UCSD Radiology Imaging Lab.

**Results:**

After running the 37 subjects’ data through FastVestal and MCBF, we found various statistically significant correlations.

In the stimulus 2 (NoGo) minus stimulus 1 (Go), we found significantly increased (p < 0.05) activity in the gamma and alpha frequency brainwaves. The most noticeable gamma activations were in the left occipital fusiform gyrus, supramarginal gyrus and dorsolateral prefrontal cortex (dlpFC).

![Figure 2: Gamma band activations in the left occipital fusiform gyrus correspond to increased visual processing during NoGo stimuli.](image)

![Figure 3: Gamma band activations in the left supramarginal gyrus correspond to the attention network during NoGo stimuli.](image)
Additionally, we found an increase in activity in the alpha frequency brainwaves in the left sensory-motor area.

Discussion:
It is important to delineate the exact functional neurologic deficits found with TBI and PTSD to determine the risk of allowing military personnel to return to action too soon. This is especially true for positions such as EOD where blasts are prevalent and extreme concentration and mental awareness are essential for job execution and survival. With the results from our study, we analyzed the brain activity data at different frequencies, allowing us to view brain functioning, specifically inhibition, in a new light.

The gamma wave activations we observed correspond to the increase in higher brain functioning during the NoGo condition, supporting the findings of previous literature⁹,¹⁰. The three most significant increases in gamma waves occurred in the left occipital fusiform gyrus, supramarginal gyrus, left DLPFC. These areas are heavily involved in the processing pathway of visual information (left occipital fusiform gyrus to supramarginal gyrus to left DLPFC). The function of this pathway is to perform higher order visual differentiation allowing activation of the attention network activation, which in the case of the NoGo condition is ultimately used to inhibit the motor response. While these pathways have been highlighted in many other imaging studies, this study uniquely isolates significantly increased activation to the gamma frequency, a feature possible only in MEG and EEG and not in fMRI.
We found increased activity in the alpha wave activations in the left sensory-motor area. Since alpha waves are associated with the basal mu rhythm, which predominates with decreases in active brain functioning\(^\text{11}\), the presence of increased alpha rhythm in the left sensory-motor cortex reflects the decrease in cortical activity over motor regions in the NoGo condition. This finding is consistent with the specifics of the task, in which motor activation is only desired during the Go condition.

These structure-function relationships of the brain may be useful to predict concussion risk, monitor recovery, and predict functional deficits based on the structural sites of injury. Furthermore, they elucidate the brain’s use of various frequency bands for functional activation and inhibition in cortical pathways. In the future, these data will be used as baseline data for the secondary similar assessment of the same 37 EOD members that will occur in approximately 18 months. This initial assessment of the pre-deployment measures will be compared against post-deployment to allow for better comparison of neurophysiological changes from TBIs and PTSD.

References: