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Homeostatic and Circadian Abnormalities in Sleep and Arousal in Gulf War Syndrome

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This research study is early in the data collection phase. The most significant finding in this study during the research period is that a subject in the active arm (extreme day fatigue) did demonstrate sleeping a sufficient amount of night sleep on 2 continuous nights, while still endorsing fatigue. The subject showed no clinically scored (by standard clinical assessment rules) slow wave sleep, which may be thought of as restorative sleep. That data is currently being assessed with more detailed techniques (as planned) to look at slow wave activity and other parameters.

Dense array EEG, temperature, melatonin, vigilance
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**Introduction**

This research project assesses sleep and wake parameters in veterans of the first Gulf War who have fatigue and other symptoms compared to veterans who do not have fatigue. It utilizes novel assessment of brain waves with high density EEG, which allows for high spatial and temporal resolution to provide a window into how sleep is regulated at the global and local level. This will allow us to determine how specific sleep pattern activity is altered in veterans with fatigue. Beyond the typical overnight polysomnography, this assessment includes objective wave analysis of slow wave characteristics, origin and propagation. Circadian rhythm will also be assessed, including temperature and salivary melatonin measures, as well as salivary cortisol levels. Vigilance at various points will be tested with a psychomotor vigilance test, and there is an optional genetic testing part of the study to assess many polymorphisms that have been associated with other fatiguing conditions and symptoms.

**Body**

In the Statement of Work, we anticipated about 10-12 months to complete the review, obtain regulatory approval, as well as obtain tools, devices and other equipment (salivary storage tubes, freezer space, hard drive space, temperature probes…). This did get completed in the summer of 2011.

Recruitment began in the later summer 2011 and we have successfully completed one research subject through the study. We have 2 others who meet qualifications on initial screening who would like to participate in the winter/spring 2012. We are continuing to recruit subjects at this point.

Data has been collected including core, peripheral and distal body temperature, two nights of dense array EEG, multiple symptom scales involving fatigue, pain, and other symptoms, cortisol samples to be able to note diurnal changes, as well as morning cortisol rise from natural wake. We also have collected melatonin samples in a low light environment to be able to assess dim light melatonin onset. Psychomotor vigilance task (PVT) data has been collected at various points in the day in concert with subjective fatigue and sleepiness data.

The EEG data has shown that a subject with much day fatigue does still get technically a sufficient number of hours of sleep at night (which is consistent with what is clinically expressed—of extreme fatigue despite adequate night sleep time). This then points more to the specific quality of that sleep. The cortisol and melatonin samples will be collected and analyzed in a batch once collected, so there is not yet data from these.

The EEG data is in the processing/analysis stage. This data, from a subject with fatigue shows little to not technically scored clinical slow wave sleep, by standard sleep lab scoring rules. This is not unexpected. We are in the process of more detailed analysis. This will include developing a topography plot of the sleep slow waves across the entire scalp (one below is an example). Comparisons will be made between those with fatigue and control subjects. Power spectral analysis of the frequency of waves across the night, as well as comparison from each of the sleep cycles through the night will be made. Graphs will be drawn similar to below. These demonstrate, on a scalp picture (nose tot the top of picture), the various powers of multiple bins of slow wave activity (all delta
range sleep). In addition to comparing all night overall findings, similar pictures may be drawn with a time frame advance across the night.

The power spectral analysis will generate graphs as below, comparing waves from the beginning of the night to waves later in the night (as indicators of meeting the homeostatic sleep needs). In typical sleep, this is much stronger earlier in the night and markedly diminishes later in the night. With the X axis as time moving across the night (coincident with the clinical sleep hyponogram below it of standard clinical scoring), the Y axis represents power of slow wave activity, stronger earlier in the night and less strong later.
Shown as separate cycles across the night, this will look like the below figure. The 1-4 numbers indicate data from each sleep cycle across the night (the 1\textsuperscript{st}, 2\textsuperscript{nd}, 3\textsuperscript{rd}, 4\textsuperscript{th}...).
This will also allow us to look at the frequencies across the entire night from each lead, such as below.

(Y)-power (X)-frequency (hz)

PVT (psychomotor vigilance task) data is collected at multiple points in the study with subjective fatigue responses, and includes the following from one of our trials, over a 10 minute duration, demonstrating minimal worsening over the 10 minutes at a time when expressing feeling relatively more energetic. We will compare from various times, with levels of fatigue and between subjects when more data is available.
Our temperature measurements include core, distal and peripheral. The below is part of data from our distal temperature probe, shown for about 12 hours across the night in this figure. Fluctuations are noted, and will be correlated with sleep stages/cycles.

Key Research Accomplishments
Initial collection of data

Reportable Outcomes
Reportable outcomes have not yet occurred. We are currently early in the data collection phase.

Conclusion
At this early stage of data collection, substantial conclusions would be premature. However, we have shown that a subject who served in the first Gulf War who has noted extreme fatigue since that time
does express fatigue despite sufficient night sleep time, but with less slow wave sleep than is typically seen. This finding offers some potential areas of future targeted treatments. Other potential contributors will continue to be assessed when they are analyzed (batched), such as melatonin and cortisol.

References
none

Appendices
none