SOF Analysis Plan Submission Form

Date: 12/13/2011

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Other investigators who will be working on this analysis:
Kristine Yaffe, M.D.
Greg Tranah, Ph.D.
Katie Stone, Ph.D.
Joel Kramer, Psy.D.
Susan Redline
Misti Paudel

Analysis Plan Title: The effect of Circadian Activity Rhythms on performance for a Neuropsychological Test Battery in Older Adult Women.

Data sets to be used: SOF Visit 8 & Visit 9

Primary variables to be used in the analysis: Visit 8 actigraphy data and Visit 9 cognitive data

Does this analysis plan involve a consortium or meta-analysis project? NO
If YES,
1. Does this plan propose to use GWAS data?  □ YES  □ NO
2. Who is the investigator leading the analysis?
   a. If not a SOF investigator, please note the lead investigator’s affiliations.
3. What other cohorts are involved in the consortium or meta-analysis?
4. What are the definitions of the primary phenotypes of interest?
5. Describe any authorship policies of the consortium.

Do you plan to submit an abstract based on these results? NO
If YES, when is the abstract due?

Who will perform the analyses?
□ Coordinating Center
x Other local analyst, please specify: I (Christine M Walsh, Ph.D.) will perform the analyses

Is this the first analysis plan you are submitting to utilize SOF data? YES
If YES, please provide 2-3 sentences about your professional background and research interests. I (Christine M Walsh, Ph.D.) received my PhD in Neuroscience, focusing on the effects of REM sleep manipulation on learning. I am currently a postdoctoral fellow at the Memory & Aging
Center, UCSF and am interested in researching the effects of sleep quality and circadian activity rhythms on cognitive performance in the aging population.

Please attach a 1-2 page description of your analysis plan. Please include the following:

1. Short background/rationale for addressing the research question
2. Brief description of statistical methods
3. Mock tables

E-mail this completed form (as an attachment) to Liezl Concepcion (lconcepcion@sfcc-cpmc.net).
SOF Analysis Proposal

Title: The effect of Circadian Activity Rhythms on performance for a Neuropsychological Test Battery in Older Adult Women.

Christine Walsh
Kristine Yaffe
Greg Tranah
Katie Stone
Joel Kramer
and others…

Introduction:
To date, little research has been done investigating the relationship between cognitive performance and circadian activity rhythm patterns in the aging population. Across later life, there is a progression towards an earlier circadian phase along with a lowering of the circadian amplitude and more fragmented sleep/waking patterns (Czeisler et al., 1992; Duffy et al., 2002; Yoon et al., 2003; Kripke et al., 2005; Buysse et al., 2005). In particular the onset of mild cognitive impairment and dementia is associated with altered circadian rhythms (Satlin et al., 1995; Ancoli-Israel, 1997; Gehrman et al., 2005). More specifically, it has been shown that characteristics of the circadian activity rhythm can predict the occurrence of MCI or dementia in older adult women 5 years later (Tranah et al., in press).

Similar to the change in circadian activity rhythms with age, there is a change in the sleep pattern, with older adults having more disrupted sleep patterns (increased fragmentation and decreased slow wave sleep) as compared with younger adults (Miles & Dement, 1980; Van Cauter et al., 2000). Both subjectively and objectively measured poor sleep is associated with cognitive impairments in older adults (Blackwell et al., 2006; Yaffe et al., 2007; Nebes et al., 2009; Blackwell et al., 2011). Further, this relationship appears to go both ways, as cognitive impairments increased, so did sleep disturbances (Yaffe et al., 2007), and as sleep disturbances increased, the risk of cognitive impairment also increased (Blackwell et al., 2006; Blackwell et al., 2011). It remains unclear, however, whether prior circadian activity rhythms can differentially predict performance on individual cognitive tasks 5 years later.

Thus far, few have attempted a prospective approach to determine predictors of specific cognitive task performance. The field in general has relied on cross-sectional studies to isolate contributing factors to poor cognitive performance. While these are of value, they are unable to intimate cause-effect relationships as prospective studies can. Our research question will help to fill a gap in the literature, allowing us to address whether prior circadian characteristics can predict specific cognitive outcomes using a prospective study approach.

Research question:
Can circadian rhythms predict cognitive performance in older women 5 years later? To address this we will look at the circadian rhythm at Visit 8, and compare it to cognitive performance at Visit 9 in the Study of Osteoporotic Fractures.

**Hypothesis**

We hypothesize that a weaker circadian rhythm or a delayed acrophase will be associated with lower performance on the cognitive tests for women in the study of Study of Osteoporotic Fractures.

**Data:**

Visit 8 actigraphy and sleep data: Total sleep time, Sleep efficiency, Sleep latency, Wake after sleep onset, Bed time, Wake time, Amplitude, Mesor, Pseudo-F statistic, Acrophase and Pittsburgh sleep quality index.

Visit 8 cognitive data: Modified Mini-Mental Status test and Trails-B.

Visit 8 data for covariates: Age, Clinic Site, Race, BMI, Geriatric Depression Scale score, Functional Status (ADL/IADL), Alcohol use, Smoking, Caffeine intake, use of benzodiazepines, antidepressants, other hypnotics, self-reported exercise, self-reported health status, and medical comorbidities.

Visit 9 cognitive data: Modified Mini-Mental Status test, Trails-B, Digit Span, Category & Verbal Fluency, California Verbal Learning (CVLT) and Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)

Visit 9 data for covariates: Age, Clinic Site, Race, BMI, Geriatric Depression Scale score, Functional Status (ADL/IADL), Alcohol use, Smoking, Caffeine intake, use of benzodiazepines, antidepressants, other hypnotics, self-reported exercise, self-reported health status, and medical comorbidities.

**Analytic query:** To identify if characteristics of the circadian activity rhythm measured at Visit 8 can predict cognitive performance observed on Visit 9.

**Analyses**

We will use MMSE and Trails-B at Visit 8 to remove subjects that may have had mild cognitive impairments or dementia at the time of actigraphy. Using a combination of linear and logistic regressions we will determine whether circadian factors can predict cognitive performance at Visit 9. We will covary the data with factors thought to affect the sleep/waking, circadian cycle and cognition such as depression, caffeine intake, etc. To determine if perceived cognitive performance is altered
based on the subject’s prior circadian rhythm, we will regress the actigraphy measures with the IQCODE.

We will look at each cognitive variable individually, and also form a composite score of the cognitive variables, to determine the ability for circadian factors to predict overall cognitive ability. Lastly, we will adjust the data for sleep efficiency and sleep fragmentation, to determine whether the predictability of the circadian rhythm on cognitive performance is independent of sleep-related issues, and purely a circadian factor.

Table 1. Circadian amplitude divided into quartiles compared to cognitive performance

<table>
<thead>
<tr>
<th></th>
<th>Upper quartile</th>
<th>Second quartile</th>
<th>Third quartile</th>
<th>Lowest quartile</th>
<th>p-value</th>
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<tbody>
<tr>
<td>MMSE</td>
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<td>Trails-B</td>
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<td>Digit Span</td>
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<td>Verbal Fluency</td>
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<td>CVLT</td>
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<td>Composite Neuropsych</td>
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<tr>
<td>IQCODE</td>
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</table>

Tables 2 – 4: Similar tables would be made to look at mesor, robustness (pseudo F-stat) and acrophase.

References:


