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**Final Report**
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**"Biomarkers of Sleep-Wake Disturbances in Night Shift Workers"**

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## List of Terms and Abbreviations

**ANW** Asymptomatic Night Workers (controls)

**DLMO** Dim-Light Melatonin Onset, a biomarker of the timing of an individual's characteristic circadian pacemaker

**ERP** Evoked Response Potentials, or Event-Related Potential, an electroencephalographic technique measuring an individual's response to a stimulus, usually auditory. Components of the evoked response potential wave examined in this study include the N1, p3a, p3b, RON (reorienting negativity), and MMN (mismatch negativity).

**ES** Excessive sleepiness

**MSLT** Multiple Sleep Latency Test, the gold standard laboratory measurement for sleepiness and sleep propensity

**PER3** Period 3, a gene linked to the circadian pacemaker and the sleep homeostat

**SWD** Shift Work Disorder

Clinical presentations or "phenotypes" of SWD are noted as follows:
- "**AI**" or "Alert Insomniac" refers to SWD patients who present with insomnia alone. In previous publications this has been noted as **SWD-INS**.
- "**SI**" or "Sleepy Insomniac" refers to SWD patients who present with insomnia and excessive sleepiness. In previous publications this has been noted as **SWD-INS/ES**.

## Abstract

Shift Work Disorder (SWD) is a circadian rhythm disorder diagnosed when shift workers develop excessive sleepiness and/or insomnia that are temporally related to a work schedule that occurs during the physiologic sleep period (e.g., 11 PM to 7 AM five times per week, or 6:30 PM to 6:30 AM three times per week). Findings from laboratory simulations of shift work prior to this study suggested that SWD might be traced to a misalignment between an individual's circadian rhythm and their work-imposed sleep-wake schedule, such that they are forced to be awake during a period of natural sleepiness and attempt to sleep during a period of natural wakefulness. Using salivary melatonin samples collected at frequent and regular intervals, this study demonstrated that asymptomatic (healthy) shift workers have a mean melatonin onset near 5:00 AM, which is highly adaptive to night work. On the other hand, workers meeting criteria for SWD show a mean melatonin onset between 8:00 PM and 11:00 PM, which would be typical and well-adjusted for a day shift worker but is maladaptive for a night shift worker. Accordingly, this project was the first to conclusively link melatonin onset with SWD symptomatology in real night workers.

Other important findings from this project relate to impaired neurophysiologic functioning during night shift hours. Using evoked response potentials, an electroencephalographic technique, reorienting of attention was found to be significantly attenuated in night workers with SWD compared to healthy night-working controls. Many SWD patients also show pathological, even dangerous, levels of sleep propensity during shift hours on the Multiple Sleep Latency Test (MSLT), although recent post-hoc analyses stratifying the sample by symptomatology have clarified that high MSLT scores are variable in their presentation, depending on the symptom profile of the affected worker. Finally, during shift work hours, acute sleep deprivation (like that commonly experienced by shift workers) was shown to decrease behavioral performance in an ERP task.

The findings obtained under this project highlight the magnitude of impairment experienced by night shift workers with SWD. These workers suffer from pathological sleepiness during overnight work hours, disrupted and inadequate sleep during the day (and, in some cases, during the night), and experience neurophysiologic changes due to sleep loss and circadian maladaptation that may lead to serious occupational hazards both to themselves and to the persons with which they interact during the night shift. Since so many night workers are employed in critical positions with grave consequences for error or lapses in judgment (e.g., protective services, transportation, healthcare, and energy), this study reinforces the notion that Shift Work Disorder represents a major occupational risk for public health and public safety.

Fortunately, results from this study also indicate that certain adaptive behaviors are associated with a healthy circadian phase delay and non-pathological sleep and alertness. For example, properly timed light exposure and early-morning "compromised" bedtimes on days off from work were more likely to be found in the asymptomatic group than among workers with SWD. While more research is needed to translate these findings into an intervention trial, our results

provide preliminary evidence that a circadian intervention for Shift Work Disorder may be able to prevent the condition and its deleterious consequences.

## Section One: Concise Report

### Significant Findings

The investigators assert that the training and research goals of this K01 award were successfully achieved. Below is a delineation of the most significant research findings, as they relate to the grant's Specific Aims.

*Specific Aim 1: Determine whether the symptomatic night shift workers have an advanced phase of their circadian pacemaker relative to asymptomatic night workers.*

For this aim, we examined the circadian rhythms of 37 subjects: 11 asymptomatic night workers (ANW) and 26 symptomatic night workers meeting criteria for Shift Work Disorder (SWD). Of these 23 symptomatic night workers, clinical presentation was as follows: 12 presented with insomnia alone, 11 presented with insomnia and excessive sleepiness, and 3 presented with excessive sleepiness alone. For each of these subjects, we calculated dim light melatonin onset (DLMO) from saliva samples collected at regular intervals. DLMO is a commonly used metric of circadian rhythm, as it indicates the point in clock time when an individual's melatonin production begins to increase, signaling the onset of the physiological sleep period. Our results showed that the ANW group indeed has an advanced DLMO (04:54±3.7h) with respect to SWD subjects with insomnia alone (22:45±4.9h) and SWD subjects with insomnia and excessive sleepiness (20:55±4.6h).

*Specific Aim 2. Determine what components of physiologic maladaptation to night work are associated with neurophysiological correlates of impairment in attention and memory processes.*

For this aim, the same number of participants and groups were assessed by event-related brain potentials (ERPs) performed at 1700, 0500 and 1600 hours. Three ERP components relating to attention and memory processes (the P3a, P3b, and RON) were measured and compared across groups and across time-of-day.

More than other ERP components, the RON (re-orienting negativity, an index of reorienting of attention) is sensitive to sleep pressure accumulating during night shift. The most vulnerable group is the SWD group, which was found to be more at risk than the asymptomatic group.

*Specific Aim 2a: Determine whether excessive sleepiness is associated with neurophysiological brain impairment of memory (probed by the Mismatch Negativity (MMN) ERP component) in the frontal cortex of night workers.*

For this aim, the MMN paradigm, with "ignore" and "attend" conditions, was performed in 34 participants during an acute sleep deprivation protocol. In this study we found that the N1 ERP was significantly higher in amplitude in insomnia-only SWD patients as compared to patients with insomnia alongside sleepiness and as compared to asymptomatic group. This finding revealed that the clinical phenotype of SWD presenting insomnia without excessive sleepiness

("alert insomniacs") has similar cortical hyperactivity as was shown in physiological (non-shift-working) insomnia patients across multiple studies.

*Specific Aim 2b: Determine whether an index of neuronal processes involved in allocating attention to novel events (probed by novel P3 ERP) is related to insomnia in night workers.*

As expected, we found that insomnia is associated with a deficit in the network underlying the P3 novel ERP and the P3b ERP, as compared to sleepy insomnia and asymptomatic group.

**Translation of Findings**

This grant supported the first demonstration of differential circadian phase and electrophysiology between asymptomatic night workers and those with Shift Work Disorder. Our results indicate that the consequences of maladaptation to shift work represent major occupational hazards: excessive sleepiness during the overnight shift and significant impairments in attention and memory. These decrements are related to symptomatology as well as circadian phase, and the dramatic difference in melatonin onset (DLMO) between the asymptomatic group and the Shift Work Disorder group suggests that interventions aimed at delaying the circadian clock (i.e., light therapy and exogenous melatonin) are essential for preventing injuries and diseases on the night shift.

**Outcomes and Impact**

*Potential Outcomes:* Our findings not only highlight the magnitude of impairment suffered by poorly adapted night workers, but the comparative normalcy of phase-delayed night workers. In other words, it is possible for night workers to adjust their circadian pacemaker to better align with the sleep-wake demands of night work, and this adjustment is associated with non-pathological scores and results on validated measures of sleepiness, insomnia, and brain functioning.

Accordingly, we recommend that clinicians and employers urge night workers to perform interventions aimed at delaying the circadian clock. Future research is needed to guide best practices for these treatments, as present research, while promising, is limited to interventions performed on simulated night workers in laboratory settings.

*Intermediate Outcomes:* This project has not led to findings, results, or recommendations being used by others to influence practices, legislation, product design, safety management programs or training.

*End Outcomes*: This project has not led to documented reductions in work-related morbidity, mortality, or exposure.

## Section Two: Scientific Report

### Background and Specific Aims

More than 7 million Americans work on a night or rotating-shift basis (US Bureau of Labor Statistics, 2005) and their sleep-wake system is challenged by irregular hours for work and sleep. Impaired wakefulness during night work and the commute home can be seriously impaired due to maladaptation to night work[17, 18,19,20, 21]. Insomnia during the daytime sleep episode is also a common feature of night shift work. These sleep-wake disturbances may be due to differences in circadian adaptation [22] to the shift work schedule. Circadian rhythms such as core body temperature, melatonin and sleep/wake regulation are controlled by the biological clock or circadian pacemaker in the suprachiasmatic nuclei of the hypothalamus. The time of melatonin onset in dim light, Dim-light melatonin onset (DLMO), provides the best non-invasive measure available of the timing of the internal circadian clock or circadian phase. Simulated and field studies demonstrated that the phase of the circadian pacemaker can be shifted in response to bright light exposure [23,15,24,25] or to a night work schedule [26,27]. However, there is a large inter-individual variability [28] in the degree of shift of circadian phase (–1 hr to + 9 hrs) in response to a 12 hour shift in sleep-wake schedule across a 14-night simulated night shift study [16]. Larger delays in circadian phase were associated with improved sleep and performance. Epidemiological studies show a subset (10%) of night and rotating-shift workers have clinically significant symptoms of excessive sleepiness (ES) and/or insomnia ,[13, 29]. **However, no studies prior to this have directly evaluated the degree to which maladaptation in actual night workers (e.g., excessive sleepiness and/or insomnia) is related to differences in circadian phase. Our specific aim #1 addressed this gap in the literature by proposing to determine the differences between symptomatic and asymptomatic night workers in terms of the direction and magnitude of circadian phase using DLMO and objective measures of sleep and excessive sleepiness (as biological markers of symptoms).**

In 2005, Saper and colleagues [30] showed that animal performance and alertness are regulated by the biological clock in the suprachiasmatic nuclei in the hypothalamus. In humans, both simulated and field studies in shift workers have revealed that circadian misalignment in shift workers is associated with reduced psychomotor performance [31,32,33, 34,35,36]. It was also shown that subjective sleepiness and the EEG components of physiological sleepiness (4–7 Hz and 8–12 Hz) react to circadian and homeostatic influences in the same way [33]. Based on these and other studies we also know that some individuals clearly have difficulties handling night shift work as compared to others. Many of these individuals probably change to day work but it is not always possible. The major characteristics of these individuals seem to be excessive sleepiness [37] increasing the risk for serious accidents in the workplace including death from critical errors [38]. Prior to our study, neurophysiological brain impairments had not been measured in these individuals, but it was clear that health and safety were affected [39]. This category of individuals was our main target for the proposed study. It is important to determine why this group has a tendency to react differentially to the challenges of night work. **Our specific aim #2 addressed this highly important gap using a comprehensive analysis of multiple measures thought to be related to maladaptation to night work to determine what components of maladaptation**

**are associated with neurophysiological impairment in specific ERP measures of attention and memory processes.**
In our and others previous studies, night shift workers showed sleep onset latency ~5 min [40,] (Gumenyuk et al., 2009). The levels seen in these studies would be interpreted as pathological sleepiness[41], should they be observed during a dayshift. They also fall below the levels seen in connection with, for example, moderate intake of alcohol or hypnotics [42]. There is no doubt that their memory and attention processes will have sleepiness-related brain performance impairments. *However, since it was never measured in night workers with symptoms of excessive sleepiness and/or insomnia, we did not know what degree of impairment is present*.

**In our specific aim 2a, we proposed to measure the memory related brain impairments by the ERP component called "mismatch negativity" (MMN).** It was shown that MMN is an objective physiological measure of sensory memory while awake and during sleep [43, 44, 45]. The biological function of MMN is an automatic change-detection of acoustical changes using a memory-operator. The neurophysiological studies on humans and animals have shown that MMN mainly originates in the auditory cortex, although it receives an important contribution from subcortical areas (especially at the level of the thalamus), as well as frontal areas [46]. All these aspects of the MMN component made it an appropriate tool for our specific aim 2a to determine the excessive sleepiness related brain impairments in night workers (with and without symptoms of insomnia). In our published preliminary study (see preliminary data section) we found that the MMN component is attenuated in symptomatic night workers with respect to asymptomatic. Our preliminary data also demonstrated that subjective sleepiness (ESS) is correlated with the MMN component. Specifically, the frontal subcomponent of MMN was found to be impacted by sleepiness. These converging lines of evidence gave us strong support to continue our investigation of the relation between excessive sleepiness and memory processing in night workers.

**In our specific aim 2b, we proposed to determine the attentional brain impairments related specifically to sleep disturbances using the ERP component called "novelty P3" (nP3).** In the auditory context it has been shown that, against a standard tone background, the unexpected occurrence of a change (e.g. dog barking, or phone ring) results in distraction due to a momentary attention shift (or allocation) which is reflected by the nP3 ERP component [47,48]. It has also been shown that the nP3 is a complex signal that comprises attention, orienting and executive control processes triggered by the unexpected stimulus [48, 2, 3, 49, 50]. Several brain regions are involved in generation of the nP3 component, the most well established are the frontal lobes [51,52], hippocampal formation [52], and anterior cingulate [53,54]. In our preliminary studies prior to grant submission, we found that the nP3 component is correlated with indexes of sleep disturbances (e.g. sleep onset latency and wake after sleep onset). That finding was promising for the evaluation of insomnia symptoms and objective sleep disturbance in night shift workers. We hypothesized that sleep disturbances impacted the neuronal network (particularly the generators of subcortical regions) underlying the nP3 component and that the amplitude of this component would be attenuated in individuals with sleep disturbances.

**Methodology**

Recruitment of participants: A total of 40 subjects were enrolled from the large pool of night workers in industries in and around tri-county metropolitan Detroit.

Inclusion and exclusion criteria. Subjects were men and women ages 25 to 55. They worked a night shift (8-12 hrs of duration) between 8pm and 8am for at least the past 6 months. They worked a minimum of 3 night shifts per week. All participants were free from psychiatric and neurological conditions as determined by clinical evaluation by a physician. All participants must have shown a minimum 5 hours or more time in bed (average from a 2-week sleep diary) of diurnal and/or nocturnal sleep per 24-hrs. All participants were free from CNS acting medication at least 2 weeks prior to the study.

Exclusion for participants (in all groups).

1) Presence of other sleep disorders (based on the Berlin Sleep Questionnaire and Restless Leg Syndrome Quality of Life (RLSQoL) questionnaire and below threshold for other sleep disorders as determined by the global sleep assessment questionnaire), psychiatric, neurological conditions determined by physician assessment or Hamilton Depression Rating Scale.

2) Current pregnancy.

3) Caffeine (>500 mg/day).

4) Individuals who are using beta-blockers, NSAIDs or other drugs known to affect melatonin production.

Three subjects in this study dropped out or were disqualified after providing informed consent to participate.

Measurements and Laboratory Procedure by Specific Aim

*Specific Aim 1***.** Determine whether symptomatic night shift workers have an advanced (i.e., earlier) phase of their circadian pacemaker relative to asymptomatic night workers. Specifically, symptomatic night workers are proposed to have a circadian phase similar to day workers (e.g., non-adapted).

> Protocol: We obtained 51 saliva samples from each participant, collected every 30 min over 25 hrs (under ≤ 10 lux of light). A full 25 hour assessment was deemed necessary as previous studies had shown extreme variations in DLMO circadian phase in shift workers. In this study, we utilized three specially designed rooms located in the circadian suite at the Sleep Center. Subjects were required not to sleep for the 25 hr study (excluding MSLT naps) starting from 1700 and ending at 1800 on the next day. The MSLT (20 min nap) was performed every second hour from 22:30 to 12:30.
>
> The time of DLMO was calculated as follows: sample times and values immediately before and after salivary melatonin levels reached 3pg/ml [55] were selected and calculated using the “TREND function” of Microsoft Excel (for details see Wright et al., 2008).

*Specific Aim 2***.** Determine what specific components of physiologic maladaptation to night work are associated with neurophysiological impairment in attention and memory processes.

Protocol: In the lab on the study night, participants performed a battery of ERP tasks three times (18:00, 05:00, and 14:00). This study consisted of two tasks:

*MMN task (Specific Aim 2a).* The oddball paradigm consisted of 2 types of sounds (simple tone=standard [100 ms], duration deviant sound=deviant [simple tone + 50 ms]) which were used for MMN brain response elicitation. Duration deviance was chosen since it was shown that the processing of sound duration eliciting the MMN is less attenuated by sleep than is frequency deviance in normal subjects [56]. A total of 550 trials were presented per session via earplugs, and each session lasted 7.3 min. A total of 4 sessions with a short intersession break (2 min) were presented to each subject. The EEG was recorded using a 64-EEG channel cap (Easy Cap, Gilching, Germany). Impedance was kept at less than 10 kΩ. The band-pass filter of the ASA amplifier was set from 0.1 to 100 Hz and the sampling rate was at 1024 Hz.

ERP data was analyzed using Brain Vision Analyzer software (Brain Products GmbH, Gilching, Germany). All statistical comparisons of MMN involved computing difference waves (ERPs in response to duration sounds minus ERPs to the standard tone). The time windows for mean amplitude comparisons were selected based on the peak amplitude of the MMN component. The mean amplitude of MMN to duration sounds was measured within the 220-260 ms time window. In order to validate the presence of the MMN, the mean amplitudes measured at the frontal (F3, Fz, F4) and central electrodes (C3, Cz, C4) were compared against zero using a *t*-test. The between-group differences and scalp distribution of the MMN components were statistically compared with three-way ANOVAs including the following factors (Group (ES vs. INS vs. ES/INS vs. AWN), Frontality (frontal electrodes F3, Fz, and F4 vs. central electrodes C3, Cz and C4 vs. parietal electrodes P3, Pz and P4), and Laterality (left-hemisphere electrodes F3, C3 and P3 vs. midline electrodes Fz, Cz, and Pz vs. right-hemisphere electrodes F4, C4, and P4).

*For the nP3 task (Specific Aim 2b):* the auditory distraction paradigm was applied (for details of the task please see our published studies[2, 3]). The mean amplitude for the nP3 was measured around the peak (within 250-300 ms) and the appropriate time window was determined for each subject. The scalp distributions of the nP3 were statistically analyzed after voltage normalization [57].

**Results and Discussion**

The most significant results from this study, as published in several manuscripts and presented at academic conferences, are summarized in this section.

1) **Asymptomatic night workers show a Dim Light Melatonin Onset significantly later than night workers with Shift Work Disorder[60, 61, 62]**. This finding has been presented in several manuscripts over the course of the grant; the largest and most recent sample shows a mean DLMO of  this suggests that the symptoms experienced by SWD patients can be at least partially traced to a misalignment between the endogenous circadian rhythm and the individual's sleep-wake schedule. It also suggests that some shift workers do shift their circadian rhythm without formal intervention, since the mean DLMO of

(04:54±3.7h) in the ANW control group, versus 22:45±4.9h among SWD subjects experiencing insomnia alone and 20:55±4.6h in SWD subjects experiencing insomnia and excessive sleepiness (p<.05 between either SWD group and controls; p n/s between SWD groups).

2) **Attenuation of light during the morning hours and later bedtimes on days off were found frequently in the asymptomatic group, but less frequently in SWD patients[60].** Light exposure was tracked by an actigraph. SWD patients were exposed to more light in the morning hours (05:00-11:00) than the ANW group: 798±398 lux vs. 180±120 lux, respectively, p<.05). Regarding bedtimes, 5 of 5 ANW shift workers had bedtimes later than midnight on days off, while only 1 of 5 SWD shift worker had the same adaptive behavior, as measured by sleep diary. These results indicate that light-based and behavioral adaptations to shift work that serve to delay the circadian clock are associated with non-pathological sleep and sleepiness.

**3) Some SWD patients show significantly higher levels of sleepiness than those seen in healthy night-working controls[60,61,62].** Like circadian phase, this result has been presented in several manuscripts. The largest and most recent sample shows a mean MSLT score for healthy controls at 8.14±3.58 minutes. SWD patients with insomnia alone showed an MSLT of 7.85±5.13 minutes (p n/s from controls) while SWD patients with insomnia and excessive sleepiness had significantly lower MSLT scores: 3.12±3.01 minutes (p<.01 vs. controls and vs. insomnia-only patients).

4) **Acute sleep deprivation impairs behavioral performance and the P3a evoked response potential in night workers[61].** Correct responses to visual stimuli following nondistracting sounds in the ERP task decreased from 86% at T1 to 76% at T2 and 73% at T3. Likewise, the IP3a amplitude showed a significant decrease at T2 and T3 across groups ($F(2,52)=44.94$; P<.001). More generally, sleep diary total sleep time was negatively correlated with RON amplitude at the Fz electrode ($r=-0.45$, p<.01), such that night workers with less sleep time had lower RON amplitude than workers who slept more.

**5) Reorienting of attention is significant impaired in SWD patients when compared to healthy night working controls[61].** The SWD group showed a significantly lower amplitude of the RON marker in an ERP task (p<.004), although after 25 hours of wakefulness, both groups showed a similar RON amplitude.

**6) The insomnia-only phenotype of SWD resembles an insomnia disorder per se (on top of a circadian rhythm disorder) and may require different clinical management[62].** The insomnia-only phenotype shows normal MSLT scores but elevated N1 amplitudes on an ERP task, indicating cortical hyperarousal consistent with non-shift-working insomniacs. SWD patients with insomnia and sleepiness show pathologically low MSLT scores but normal N1 amplitudes. The two presentations do not significantly differ in circadian phase. The insomnia-only group shows longer sleep latencies and lower sleep efficiency compared to controls during daytime and nighttime sleep on a sleep diary. On the other hand, SWD patients with both insomnia and sleepiness differ

from controls in many nocturnal sleep parameters but differences during diurnal sleep periods were smaller and not statistically significant. Finally, 9 of 10 shift workers reporting sleepiness in a post-hoc genetic substudy were found to carry the long tandem repeat of the Period 3 gene, while 4 of 14 shift workers without excessive sleepiness carried the long allele. Taken together, these results suggest that the sleepy insomnia phenotype (as it is described in the second 2014 manuscript in SLEEP) is comprehensively explained by circadian misalignment, while the alert insomnia phenotype resembles an insomnia disorder precipitated by shift work.

**Conclusions**

Taken together, the findings obtained under this project highlight the magnitude of impairment experienced by night shift workers with Shift Work Disorder. These workers suffer from pathological sleepiness during overnight work hours, disrupted and inadequate sleep during the day (and, in some cases, during the night), and experience neurophysiologic changes due to sleep loss and circadian maladaptation that may lead to serious occupational hazards both to themselves and to the persons with which they interact during the night shift. Since so many night workers are employed in critical positions with grave consequences for error or lapses in judgment (e.g., protective services, transportation, healthcare, and energy), we feel that Shift Work Disorder represents a major occupational risk for public health and public safety.

Fortunately, results from this study also indicate that certain adaptive behaviors are associated with circadian phase delay and non-pathological sleep and alertness among shift workers. For example, properly timed light exposure and adaptive, “compromised” bedtimes on days off from work were more likely to be found in the asymptomatic group. While more research is clearly needed to translate these findings into an intervention trial, our results do provide strong preliminary evidence that a circadian intervention for Shift Work Disorder may be able to prevent the condition (and its deleterious consequences).

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## Inclusion Enrollment Report

| PART A. TOTAL ENROLLMENT REPORT: Number of Subjects Enrolled to Date (Cumulative) by Ethnicity and Race | | | | |
|---|---|---|---|---|
| **Ethnic Category** | **Females** | **Males** | **Sex/Gender Unknown or Not Reported** | **Total** |
| Hispanic or Latino | 0 | 1 | 0 | 1 ** |
| Not Hispanic or Latino | 23 | 16 | 0 | 39 |
| Unknown (individuals not reporting ethnicity) | 0 | 0 | 0 | 0 |
| **Ethnic Category: Total of All Subjects*** | 23 | 17 | 0 | 40 * |
| **Racial Categories** | | | | |
| American Indian/Alaska Native | 0 | 0 | 0 | 0 |
| Asian | 0 | 3 | 0 | 3 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 | 0 |
| Black or African American | 17 | 6 | 0 | 23 |
| White | 6 | 6 | 0 | 12 |
| More Than One Race | 0 | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 2 | **0** | 2 |
| **Racial Categories: Total of All Subjects*** | 23 | 17 | 0 | 40 * |

| PART B. HISPANIC ENROLLMENT REPORT: Number of Hispanics or Latinos Enrolled to Date (Cumulative) | | | | |
|---|---|---|---|---|
| **Racial Categories** | **Females** | **Males** | **Sex/Gender Unknown or Not Reported** | **Total** |
| American Indian or Alaska Native | 0 | 0 | 0 | 0 |
| Asian | **0** | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 | **0** |
| Black or African American | 0 | 0 | 0 | 0 |
| White | 0 | 0 | 0 | 0 |
| More Than One Race | 0 | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 1 | 0 | 1 |
| **Racial Categories: Total of Hispanics or Latinos**** | 0 | 1 | 0 | 1 ** |

* These totals must agree.
** These totals must agree.

## Publications

### Manuscripts in Refereed Journals

Gumenyuk V, Roth T, Korzyukov O, Jefferson C, Bowyer S, Drake CL: [2011] Habitual Short Sleep Impacts Frontal Switch Mechanism in Attention to Novelty. SLEEP 34:1659-1670.

Babajani-Feremi A, Gumenyuk V, Roth T, Drake CL, Soltanian-Zadeh H: [2012] Connectivity Analysis of Novelty Process in Habitual Short Sleepers. Neuroimage 63:1001-1010.

Gumenyuk V, Roth T, Drake CL: [2012] Circadian Phase, Sleepiness, and Light Exposure Assessment in Night Workers With and Without Shift Work Disorder. Chronobiol Int 29:928-936.

Gumenyuk V, Korzyukov O, Roth T, Bowyer SM, Drake CL: [2013] Sleep Extension Normalizes ERP of Waking Auditory Sensory Gating in Healthy Habitually Short Sleeping Individuals. PlOS One 8:e59007.

Roehrs T, Gumenyuk V, Drake C, Roth T: [2014] Physiological Correlates of Insomnia. In press, Curr Top Behav Neurosci.

Gumenyuk V, Howard R, Roth T, Korzyukov O, Drake CL: [2014] Sleep Loss, Circadian Mismatch, and Abnormalities in Reorienting of Attention in Night Workers with Shift Work Disorder. SLEEP 37:545-556.

Gumenyuk V, Belcher R, Drake CL, Roth T: [2014] Differential Sleep, Sleepiness, and Electrophysiology in the Insomnia Phenotypes of Shift Work Disorder. In press, SLEEP.

### Proceedings and Presentations

Gumenyuk V, Roth T, Jefferson C, and Drake C: [2011] Electrophysiological Evidence of Impact on Auditory Pre-Attentive Brain Mechanism in Habitual Short Sleepers: Study I. Abstract Supplement of the 2011 Meeting of the Associated Professional Sleep Societies, Minneapolis, Minnesota, June 11-15, 2011.

Gumenyuk V, Roth T, Jefferson C, and Drake C: [2011] Electrophysiological Evidence of Improvement of the Brain Mechanism of Auditory Pre-Attentive processing in Habitual Short Sleepers after Sleep Extension: Study II. Abstract Supplement of the 2011 Meeting of the Associated Professional Sleep Societies, Minneapolis, Minnesota, June 11-15, 2011.

Babajani-Feremi A, Gumenyuk V, Jefferson C, Roth T, Drake CL, Soltanian-Zadeh H [2011]: Study of chronic short sleep using brain connectivity analysis of EEG data. Abstracts of the 8$^{th}$ Annual Research Symposium of Henry Ford Health System, Detroit, Michigan, May 12-13, 2011.

Drake C, Gumenyuk V, Jefferson C and Roth T: [2011] Circadian Phase Differences in Patients with Shift Work Disorder relative to Asymptomatic Shift Workers. Abstract Supplement of the 2011 Meeting of the Associated Professional Sleep Societies, Minneapolis, Minnesota, June 11-15, 2011.

Nejad-Davarani S., Gumenyuk V, Bagher-Ebadian H., Peltier S, Budaj J, Drake CL, Noll D., Jiang Q., and Chopp M: [2013] Comparison of the Functional Brain Connectivity Network in Night Shift Workers With and Without Shift Work Disorder: A Resting State fMRI Analysis. Abstract Supplement of the 2011 Meeting of the International Society for Magnetic Resonance in Medicine, Salt Lake City, Utah, April 20-26, 2013.

Gumenyuk V, Howard R, Roth T, Roehrs TA, Drake CL: [2013] Insomnia in Shift Work Disorder (SWD) Associated with Cortical Excitability: An ERP Study Prior to a Night Shift. Abstract Supplement of the 2013 Meeting of the Associated Professional Sleep Societies, Baltimore, Maryland, June 1-5, 2013.

Gumenyuk V, Howard R, Roth T, Roehrs TA, Drake CL: [2013] Cortical Excitability in Night Workers with Insomnia Is Attenuated Following a Night Shift: An ERP Study. Abstract Supplement of the 2013 Meeting of the Associated Professional Sleep Societies, Baltimore, Maryland, June 1-5, 2013.

Drake CL. Howard R , Levin AM., Roth T., Gumenyuk V: [2013] PER3 Polymorphism Predicts Sleepiness and Circadian Phase in Shift Workers. Abstract Supplement of the 2013 Meeting of the Associated Professional Sleep Societies, Baltimore, Maryland, June 1-5, 2013.

Howard R, Drake CL, Roth T, Gumenyuk V: [2013] Sensitivity of a Brief Questionnaire to Circadian Phase in Night Workers. Abstract Supplement of the 2013 Meeting of the Associated Professional Sleep Societies, Baltimore, Maryland, June 1-5, 2013.

Howard R., Gumenyuk V., Roth T., Gable M., Drake CL: [2013] Armodafinil Improves Creativity Performance on the Remote Associates Test in Night Workers with Shift Work Disorder. Abstract Supplement of the 2013 Meeting of the Associated Professional Sleep Societies, Baltimore, Maryland, June 1-5, 2013.

Gumenyuk V, Belcher R, Roth T, Bazan L, LaRose C, Drake CL: [2014] Attentional Brain Responses in Night Shift Workers are Sensitive to Occupational Impairment. Abstract Supplement of the 2014 Meeting of the Associated Professional Sleep Societies, Minneapolis, Minnesota, May 31-June 4, 2014.

Roth T, Belcher R, Drake CL, Mengel HJ, Koshorek GL, Gable M, Gumenyuk V: [2014] Differential Sleep Disturbances in Two Phenotypes of Shift Work Disorder. Abstract Supplement of the 2014 Meeting of the Associated Professional Sleep Societies, Minneapolis, Minnesota, May 31-June 4, 2014.

Gumenyuk V, Belcher R, Drake CL, Spear L, Roth T: [2014] Cortical Arousal is Present in Alert Insomniacs but Absent in Sleepy Insomniacs within Shift Work Disorder. Abstract Supplement of the 2014 Meeting of the Associated Professional Sleep Societies, Minneapolis, Minnesota, May 31-June 4, 2014.

Belcher R, Roth T, Drake CL, Mengel HJ, Bazan L, Gumenyuk V: [2014] Separated Insomnia Severity Index (ISI) Distinguishes Two Phenotypes of Shift Work Disorder. Abstract Supplement of the 2014 Meeting of the Associated Professional Sleep Societies, Minneapolis, Minnesota, May 31-June 4, 2014.

Belcher R, Roth T, Gumenyuk V, Mengel HJ, Philport J, Drake CL: [2014] Occupational and Neurophysiological Deficits in Shift Work Disorder Relate to Insomnia, Not Sleepiness. Abstract Supplement of the 2014 Meeting of the Associated Professional Sleep Societies, Minneapolis, Minnesota, May 31-June 4, 2014.

## Inclusion of Gender and Minority Study Subjects

Subjects meeting eligibility criteria were included in this study regardless of sex, race or ethnicity. These demographic variables were not expected to affect or to influence any of the dependent measures of the study.

## Inclusion of Children

Children were not included in this study.

## Materials Available for Other Investigators

No research materials, DNA probes, animal models, protocols, software or other information resulted from this study or could be used by other investigators.