



## Insomnia in Shift Work Disorder Relates to Occupational and Neurophysiological Impairment

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**Study Objectives:** To determine whether occupational and neurophysiological decrements within shift work disorder (SWD) are differentially related to its two diagnostic symptoms, insomnia and excessive sleepiness.

**Methods:** Thirty-four permanent night workers participated in an overnight lab protocol including a multiple sleep latency test (MSLT) and an event-related brain potential (ERP) task testing auditory target detection (P3a and P3b). At 16:00, each subject completed an Endicott Work Productivity Scale (EWPS), two Insomnia Severity Indices (ISI-Day, ISI-Night), and an Epworth Sleepiness Scale (ESS). Subjects were grouped by ISI and ESS scores into clinical phenotypes. This study compared EWPS and ERP results between alert insomniacs (“AI,” reporting insomnia without sleepiness), sleepy insomniacs (“SI,” reporting both insomnia and sleepiness), and controls.

**Results:** The AI group was most impaired on the EWPS, significantly more impaired than controls ( $25.8 \pm 14.8$  vs.  $12.3 \pm 9.4$ ,  $p < 0.05$ ). SI were not statistically different from controls ( $19.5 \pm 8.7$  vs.  $12.3 \pm 9.4$ ,  $p > 0.05$ ). Compared to controls, AI

showed significantly attenuated P3a response (Fcz, Czp, Cpz, mean difference [MD] 1.62–1.77,  $p < 0.05$ ) and target-detection P3b response (Fcz, Czp, Cpz, MD 1.28–1.64,  $p < 0.05$ ). P3b in SI was not different from controls ( $p > 0.10$ ), and P3a was only different at one electrode site (Cpz, MD 1.43,  $p < 0.01$ ). Neither the MSLT nor the ESS correlated with EWPS scores or ERP (P3a/P3b) amplitudes ( $p > 0.10$ ). However, the mean of the ISI measurements correlated with the EWPS ( $r = 0.409$ ,  $p < 0.01$ ) and the attention-to-novelty P3a ( $r = -0.410$ ,  $p < 0.01$ ).

**Conclusions:** Among shift work disorder patients, insomnia is linked to functional and cognitive impairments. Insomniacs with normal sleepiness showed more severe impairments than insomniacs who also reported excessive sleepiness.

**Keywords:** insomnia, excessive sleepiness, shift work, event-related brain potentials, Insomnia Severity Index, multiple sleep latency test, Epworth Sleepiness Scale, circadian phase, work productivity

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Shift work disorder (SWD) is a circadian rhythm disorder characterized by a chronic mismatch between a shift worker’s sleep-wake schedule and his or her circadian clock.<sup>1–5</sup> Clinically, this mismatch manifests in insomnia and/or excessive sleepiness. Diagnostic criteria for SWD require the presence of one or both of these symptoms, temporally related to a shift work schedule for at least three months, and not better explained by another medical, psychiatric, or sleep disorder.<sup>4</sup>

Many shift workers meeting diagnostic criteria for SWD report sleep difficulties consistent with those reported by patients with an insomnia disorder, while others report excessive sleepiness (either alone or in combination with insomnia symptoms).<sup>3,6</sup> Studies comparing night shift workers with day workers estimate that 44.8% of night workers score greater than 10 on the Epworth Sleepiness Scale (compared to 32.7% of day workers), and 24.7% score greater than 13 (compared to 15.5% of day workers).<sup>6</sup> With regard to insomnia, 18.5% of night workers met DSM-IV criteria for the disorder, while only 8.6% of day workers did.<sup>6</sup> In conducting previous studies on SWD,<sup>1,2,7–9</sup> we have observed that the population of shift workers reporting insomnia can be classified into two phenotypes: those reporting insomnia only, and those reporting insomnia alongside excessive sleepiness. We call

### BRIEF SUMMARY

**Current Knowledge/Study Rationale:** Workplace accidents, lost productivity, and neurophysiologic impairment are known to be associated with night shift work. This study aimed to determine whether these problems are differently related to insomnia and to excessive sleepiness, two hallmark symptoms that are diagnostic of shift work disorder (SWD) but are not reliably comorbid.

**Study Impact:** Our findings suggest that treatments focusing on excessive sleepiness in SWD may not sufficiently improve work-related outcomes, as overnight occupational and neurophysiologic impairment is more strongly correlated to insomnia than it is to sleepiness. Further research is needed to evaluate the impact of insomnia therapies on workplace safety and productivity in patients with SWD.

the corresponding phenotypes “sleepy insomniacs” (SI) and “alert insomniacs” (AI). The phenotype presenting excessive sleepiness *without* insomnia (sleepy non-insomniacs [SN]) appears to be less common and is not considered in this study (see Methods).

Functional impairments related to sleep deprivation and/or circadian misalignment are common in shift work and represent a major productivity and safety risk.<sup>10–19</sup> However, most research on performance and safety decrements among shift workers has focused on the deleterious effects of

**Table 1**—Sleep diary, sleepiness, and circadian parameters by SWD phenotype.

	CO (n = 11)	AI (n = 12)	SI (n = 11)	p values		
				AI vs. CO	SI vs. CO	AI vs. SI
ISI mean (day and night)	5.18 ± 3.56	13.04 ± 3.93	11.73 ± 5.53	<b>0.000</b>	<b>0.004</b>	0.516
Epworth Sleepiness Scale	7.27 ± 2.33	7.33 ± 1.92	10.73 ± 3.50	0.946	0.013	<b>0.008</b>
Dim-light melatonin onset	05:00 ± 3:31	22:25 ± 5:05	20:33 ± 4:37	<b>0.002</b>	<b>0.000</b>	0.367
Nocturnal MSLT score	8.23 ± 5.22	7.84 ± 5.13	3.12 ± 3.01	0.860	<b>0.011</b>	<b>0.015</b>
Daytime sleep						
Insomnia Severity Index	5.36 ± 3.01	14.67 ± 3.17	14.27 ± 4.82	<b>0.000</b>	<b>0.000</b>	0.818
Bed time	9:03 ± 0:45	10:09 ± 1:59	9:37 ± 2:00	0.102	0.391	0.530
Wake time	15:24 ± 1:34	16:25 ± 2:34	15:13 ± 2:35	0.269	0.847	0.277
Latency to sleep, min	13.73 ± 15.41	34.59 ± 23.53	17.82 ± 9.33	<b>0.021</b>	0.461	<b>0.039</b>
Sleep efficiency	0.96 ± 0.04	0.81 ± 0.17	0.88 ± 0.11	<b>0.013</b>	<b>0.035</b>	0.259
Time in bed, hours)	6.36 ± 1.22	6.44 ± 1.31	5.44 ± 0.88	0.881	0.056	<b>0.045</b>
Total sleep time, hours	6.09 ± 1.11	5.21 ± 1.18	4.78 ± 0.69	0.078	<b>0.003</b>	0.304
Number of awakenings	0.54 ± 0.71	1.55 ± 1.62	1.79 ± 1.81	0.070	<b>0.045</b>	0.741
Wake after onset, min	2.02 ± 2.61	32.43 ± 48.51	16.78 ± 24.53	0.051	0.061	0.347
Nighttime sleep						
Insomnia Severity Index	5.00 ± 4.52	11.42 ± 6.93	9.18 ± 6.74	<b>0.017</b>	0.103	0.443
Bed time	02:35 ± 3:46	20:26 ± 4:48	23:56 ± 2:34	<b>0.003</b>	0.068	<b>0.043</b>
Wake time	11:05 ± 3:32	05:13 ± 6:05	07:04 ± 3:30	<b>0.011</b>	<b>0.014</b>	0.387
Latency to sleep, min	17.74 ± 18.03	42.97 ± 35.59	22.40 ± 22.84	<b>0.049</b>	0.608	0.118
Sleep efficiency	0.93 ± 0.06	0.81 ± 0.13	0.85 ± 0.15	<b>0.009</b>	0.121	0.501
Time in bed, hours	8.48 ± 2.05	7.92 ± 2.12	7.57 ± 1.87	0.527	0.290	0.680
Total sleep time, hours	7.76 ± 2.15	6.75 ± 1.90	6.66 ± 1.58	0.265	0.193	0.903
Number of awakenings	0.80 ± 0.70	1.33 ± 1.42	1.45 ± 1.42	0.277	0.193	0.842
Wake after onset, min	15.62 ± 30.26	63.09 ± 100.94	47.38 ± 73.08	0.149	0.198	0.676

Values presented as mean ± standard deviation. SWD, shift work disorder; CO, controls; AI, alert insomniacs; SI, sleepy insomniacs. Data originally presented in Gumenyuk et al., 2015.<sup>9</sup> Numbers in bold indicate p values below 0.05.

sleepiness,<sup>11,20–29</sup> with less regard to shift-work related insomnia. Indeed, most of our knowledge on insomnia and performance is based upon findings in day workers.<sup>30–36</sup> Given the different treatment paradigms for excessive sleepiness and insomnia (whether circadian-related or psychophysiological), investigation into the potentially different occupational sequelae of these two symptoms remains an important priority for research on shift work and SWD. By considering two different clinical presentations of SWD in comparison with healthy night-working controls, this study aims to determine whether occupational and neurophysiological decrements within shift work disorder are differentially related to insomnia and excessive sleepiness.

In our previous research,<sup>9</sup> we presented evidence of differences in neurophysiological markers, sleepiness, and sleep parameters between the AI and SI phenotypes of SWD. AI patients had increased amplitudes of the N1 ERP, an index of cortical hyperarousal<sup>54</sup>; normal MSLT during night-working hours; and sleep latency and maintenance problems during both diurnal and nocturnal sleep periods (with no statistically different differences in sleep parameters between the sleep periods: see **Table 1**). On the other hand, SI patients showed normal N1 amplitudes, suggesting normal cortical arousal and pathological levels of sleepiness during night shift hours.

These findings led us to evaluate and compare attention-related brain responses (P3a and P3b ERPs), as these provide additional insight into executive dysfunction potentially related to occupational impairment. These neurophysiological measures of brain activity associated with attention and memory are likely affected in people with higher sleep pressure due to either sleep restriction or circadian misalignment. In the current study, conducted within the same sample of night workers as our previous report, we measured the P300 ERP component. This component consists of the P3a and P3b markers, which are associated with involuntary attention switching between target task stimuli and irrelevant distracting stimuli. The P3a has latency around 200–300 ms from deviance onset and a frontocentral scalp distribution. ERP studies in humans with frontal lobe lesions have found that such patients produce a clear diminution of the P3a from a distracting stimulus. Frontal lobe engagement is therefore necessary for P3a generation and mechanisms of attention control.<sup>37</sup> Unlike the P3a, the P3b marker is task relevant and associated with target detection. It is elicited when a subject's attention is focused on a stimulus.<sup>38</sup> The P3b is associated with the process of memory comparison in the context of the previous stimuli, generating a brain potential with a parietal scalp distribution. The initial processing of a new stimulus engages the switching of attention that underlies P3a production, whereas the subsequent memory

comparison engages the operations associated with P3b production. Based on previous research linking wakefulness, level of arousal, and sleep quality to the cognitive P3a and P3b ERP components,<sup>39–43</sup> we expected that SWD patients predominantly suffering from insomnia may show different P3a and P3b markers compared to SWD patients who also experience excessive sleepiness.

We employed evoked response potentials and the Endicott Work Productivity Scale, a validated measure of work performance,<sup>44–46</sup> to assess the functional abilities of night shift workers. The EWPS contains five subscales related to specific attributes of work performance: fatigue, executive function, interpersonal interactions, work efficiency, and counterproductive work behavior. Using groupwise comparisons of these measures between shift workers who present with insomnia, excessive sleepiness, both symptoms, or no symptoms, and using linear regression modeling to compare the symptoms head-to-head, this study aims to test the hypothesis that the two diagnostic symptoms of shift work disorder contribute differentially to occupational functioning and neurophysiology of attention related processes.

## METHODS

This paper presents a secondary analysis from a larger study. Primary results from the MSLT, sleep diary, circadian phase assessment, and ISI and ESS questionnaires were presented in a previous report<sup>9</sup> and are summarized in **Table 1**.

### Subjects

Permanent night workers were recruited from healthcare and industrial settings to participate in an overnight laboratory sleep deprivation study. Subjects were required to have worked exclusively on a night shift for  $\geq 6$  months ( $\geq 3$  night shifts per week, with each shift lasting 8–12 h and occurring between 19:00 and 08:00) and must not have worked a rotating shift or “picked up” daytime shifts during the 6 months preceding the laboratory study. They were required to have low probability for obstructive sleep apnea, restless leg syndrome, narcolepsy, and psychiatric disorders by providing responses in the normal range on the self-completed Berlin Questionnaire and staff-administered Hamilton Depression Scale, as well as in a clinical interview with a sleep medicine physician. Participants who had been diagnosed with insomnia or excessive sleepiness prior to beginning their nighttime work shift were excluded. They were required to be free from head injury, hearing problems, alcohol or substance abuse; must have been nonsmokers; and must not have consumed more than 300 mg of caffeine, on average, per day. Finally, they were required to be free from all CNS-acting medication as well as  $\beta$ -adrenergic blocking agents and other drugs which are known to affect the circadian rhythm, sleep-wake function, or melatonin production. Drugs encountered and disqualified included sertraline, tamoxifen, paroxetine, zolpidem, metoprolol, atenolol, bupropion, alprazolam, venlafaxine, methylphenidate, gabapentin, tramadol, diazepam, triazolam, levocetirizine, buspirone, citalopram, lisdexamfetamine, and trazodone. An exception was made for shift workers with insomnia symptoms who had taken melatonin

or sleep-promoting agents while working nighttime shifts, but had subsequently discontinued medication and had been free of the drug and all potential metabolites for  $\geq 2$  weeks prior to the laboratory study.

Ninety-five night workers initially responded to flyers and online newsletter advertisements. Initial advertisements did not specify symptoms of SWD, while subsequent advertisements recruited night workers experiencing “sleepiness or trouble sleeping during the day,” based on recruitment needs. Of the 95 respondents, 35 (36.8%) were disqualified based on an online survey; 13 (13.7%) did not comply with pre-screening requests to keep a sleep diary or failed to keep a screening appointment; 5 (5.3%) were disqualified at the screening appointment; 3 (3.2%) were eligible but not enrolled; and 1 (1.1%) dropped out following enrollment. Thirty-eight subjects (40.0%) qualified based on inclusion criteria. Excluding one subject released for noncompliance, 37 subjects completed the study (mean age  $35.41 \pm 9.35$  years, 62.2% female).

At the screening appointment, 26 of 37 qualifying subjects (70.2%) were diagnosed with SWD upon a clinical interview with a sleep medicine physician and review of the participant’s screening sleep diary. The remaining 11 (29.7%) were asymptomatic (controls).

### Self-Reported Sleep

For 2 weeks prior to the laboratory study, subjects kept a sleep diary reporting bedtime, wake time, latency to sleep, number of awakenings, use of alcohol and caffeine, and subjective sleep quality.

### Laboratory Procedures

The laboratory study was scheduled to begin on an evening after the subject had worked  $\geq 3$  consecutive night shifts. They were instructed to sleep during the day before coming to the laboratory, as if sleeping before a subsequent night shift. On the study day, they arrived at 16:00 and were housed in a dimly lit ( $< 15$  lux), sound-attenuated private bedroom and bathroom that they would occupy for 25 hours. Participants were aware of clock time. They were not permitted to sleep at any point during their entire experimental session, and were required to remain out of bed except for nap trials during the multiple sleep latency test (see below). Internet access, television, and cellular phone usage were permitted during unscheduled time, and 3 meals were provided at the subject’s request in addition to snacks and water. Meals did not contain foods or drinks known to affect sleep or circadian rhythms such as caffeine, ethanol, milk, bananas, or tomatoes. Subjects were also prohibited from consuming crunchy foods that might injure the gums and permit blood contamination of the saliva samples (see below). Registered polysomnographic technologists and research associates continuously monitored all participants for wakefulness throughout the study.

### Questionnaires

At 18:00, each subject completed an Epworth Sleepiness Scale (ESS), 2 separate Insomnia Severity Index (ISI) questionnaires, and the Endicott Work Productivity Scale (EWPS). Items on the separate ISIs were identical, but both verbal and written instructions prompted subjects to separately evaluate

their diurnal sleep on one questionnaire (ISI-D) and nocturnal sleep on the other (ISI-N).

### Phenotype Classification

Twenty-six subjects with SWD were classified into 3 phenotypes using scores from the ESS and ISI, as well as a diagnostic interview with a sleep medicine physician.<sup>9</sup> Twelve subjects presented pathologic scores ( $\geq 10$ ) on the ISI-D, ISI-N, or both, while scoring in the normal range ( $< 10$ ) on the ESS. These subjects were classified “alert insomniacs” (AI). Within this subgroup, 11 subjects (91.7%) had pathologic scores on the ISI-D and 8 (66.7%) were flagged for pathologic scores on the ISI-N.

Eleven subjects with elevated scores on one or both ISIs as well as the ESS were classified into the sleepy insomniac (SI) group. Within this subgroup, 10 subjects (90.9%) had pathologic scores on the ISI-D, and 4 (36.4%) had pathologic scores on the ISI-N.

Eleven controls showed normal scores on the ESS and both ISIs, corroborating the diagnostic interview at the screening appointment.

Finally, 3 subjects showed pathologic sleepiness (ESS  $\geq 10$ ) but normal scores on both insomnia indices (ISI-D and ISI-N  $< 10$ ). These subjects were classified “sleepy non-insomniacs” (SN). Because of the small number of subjects who met criteria for this group, it was excluded from the analyses.

### Circadian Phase Assessment

Beginning at 17:00, saliva samples were collected at 30-min intervals using a Salivette tube with a cotton insert (Sarstedt Group, Numbrecht, Germany). Prior to 17:00, subjects were instructed on the procedure of saliva collection and the amount of saliva required for each sample. Each sample was weighed to ensure that  $\geq 1$  mL of saliva was provided. Saliva was then extracted from the cotton insert in a frozen centrifuge, and samples were frozen at  $-20^{\circ}\text{C}$  until being shipped over dry ice to SolidPhase, Inc. (Portland, Maine, USA), where they were radio-immunoassayed. The intra-assay precision was 2.6% to 20.1%, with functional sensitivity of 0.9 pg/mL and analytical sensitivity of 0.2 pg/mL.

Dim light melatonin onset (DLMO) is an individual’s characteristic point in clock time marking the onset of elevated melatonin levels that normally coincide with the timing of the sleep period.<sup>47–49</sup> DLMO was calculated as the time that the amplitude of the fitted LOWESS curve for melatonin concentration rose and remained above a subject’s melatonin threshold for at least one hour. The threshold used was the average of the 5 lowest concentrations of melatonin during the 24-h phase assessment, plus 15% of the average of the 5 highest concentrations.

### Objective Sleepiness Assessment

Objective sleepiness was assessed with a nocturnal multiple sleep latency test (MSLT), following standard research protocol. Electrode integrity was checked by physical inspection and electrical biocalibration before each nap. The first 5 naps (22:30 to 06:30) coincided with night shift hours, while the last 3 (08:30 to 12:30) evaluated the effects of acute sleep deprivation. In this report we are presenting the results of a 4-nap

MSLT collected between 22:30 and 04:30, corresponding to night shift hours.

### P3a and P3b Event Related Brain Potential

The typical oddball paradigm was used for an active auditory processing task. This paradigm consists of 4 types of regularly occurring sounds as well as a rare auditory target. Seventy percent of the regular sounds were simple tones (duration = 100 ms, frequency = 800 Hz) and served as a standard; 10% of regular sounds were complex tones (environmental sounds), which served as novel stimuli. Not included in the P3a/P3b analyses presented here are deviant frequency simple tones (10%, duration = 100 ms, frequency = 1,000 Hz) and deviant duration simple tones (10%, duration = 150 ms, frequency = 800 Hz). The irregular target was a high-pitch sound presented rarely (25 sounds across 14 min) and interspersed with all other sounds. Participants were instructed to press the button when they heard a target sound by using their dominant index finger. All sounds were presented through earplugs binaurally at a 75 dB SPL (sound pressure level) with 5 ms rise/fall time. All stimuli were presented at a constant inter-stimulus interval of 800 ms. Each session lasted 7.3 min. A total of 2 sessions with a short inter-session break (2 min) were presented to each subject. The clock time of the task was between 18:00 and 19:00 for each subject, a time in the 24-h cycle that occurs at neither the nadir for well-adjusted night workers nor the nadir for unadjusted night workers.<sup>1,9</sup> It was thus a “neutral zone” in the circadian cycles of our subjects, and timing the ERP in this window permitted the examination of cognitive differences shortly after waking, without the confounding influence of acute sleep deprivation.

### EEG Recording and ERP Data Analysis

EEG data was recorded via a 32-channel EEG cap (10-20 system, Easy Cap, Gilching, Germany) and an ASA system (ANT, the Netherlands). Electrooculogram (EOG) was recorded by 2 electrodes at the left and right canthus and 2 electrodes above and below the left eye of the subject. Impedances were kept  $< 10$  kilo $\Omega$ , and a band-pass filter was set from 0.1 to 100 Hz. The sampling rate was 1,024 Hz.

Data were analyzed off-line using Brain Vision Analyzer software (Brain Products GmbH, Gilching, Germany). ERP data were separately analyzed for each sound type. Each segment began 100 ms prior to the stimulus onset and continued for 700 ms after the stimulus onset. A band-pass filter from 0.1 to 30 Hz was applied to segmented data. Segments in which the EEG or EOG exceeded  $\pm 75$  microvolts were excluded from the average. ERPs in response to standard and novel stimuli were averaged separately. Baseline correction (100 ms pre-stimulus interval) was applied to the averaged data. On average,  $\geq 300$  trials for the standard tone and  $\geq 100$  trials for the novel sounds were included for each subject.

To evaluate ERP data, the obligatory auditory N1 waveform was identified as the largest negative wave at latency 80 to 130 ms from sound onset in each individual grand average corresponding to each type of stimulus (standard and novel). The difference wave between ERPs to novel minus ERPs to standard was computed for each participant and then averaged per group. The peak amplitude and latency of the P3a and P3b of

**Table 2**—Endicott Work Productivity Scale scores and subscores by SWD phenotype.

Item	CO	AI	SI	p values	
				AI vs. CO	SI vs. CO
Total score	12.27 (9.41)	25.67 (14.84)	19.55 (8.69)	<b>0.018</b>	0.064
Executive functioning	2.82 (2.64)	5.83 (4.26)	4.91 (2.07)	0.057	0.052
Interpersonal interactions	3.09 (2.21)	5.67 (5.40)	4.09 (3.05)	0.156	0.389
Fatigue	3.36 (2.66)	6.33 (3.11)	4.82 (1.72)	<b>0.023</b>	0.143
Work efficiency	1.91 (2.26)	4.75 (3.31)	3.91 (2.55)	<b>0.027</b>	0.065
Counterproductive work behaviors	1.09 (1.64)	2.17 (1.80)	1.81 (2.18)	0.150	0.387

Values presented as mean (standard deviation). All p values (AI vs. SI) were nonsignificant ( $p > 0.10$ ). SWD, shift work disorder; CO, controls; AI, alert insomniacs; SI, sleepy insomniacs. Numbers in bold indicate p values below 0.05.

the difference wave were measured within an 200–300 ms and 400–600 ms time window from sound onset at the FCz and Cpz electrodes, as these are typically shown in studies to present the largest amplitude for P3a (FCz, frontal) and P3b (CPz, parietal) ERP components.

### Statistical Analyses

Groupwise comparisons between strata of shift workers presenting different combinations of symptoms (AI and SI) and presenting no symptoms at all (controls) were performed. These phenotypic differences were analyzed using two-tailed Student's *t*-tests. Pearson bivariate correlations and linear regression modeling were also used, within the full sample, to clarify the differential contributions of SWD symptoms to variance in EWPS and ERP findings. All statistical comparisons of the P3a and P3b to novel sounds involved computing difference waves (amplitudes in response to novel sounds minus amplitudes to the standard tone). The time windows for mean amplitude comparisons were selected based on the peak amplitude of each brain response at FCz (frontal) and CPz (parietal) electrodes.

## RESULTS

### Endicott Work Productivity Scale

Night-working controls presented the lowest scores on the EWPS ( $12.27 \pm 9.41$ ), indicating the lowest level of occupational impairment. Subjects presenting insomnia alongside excessive sleepiness showed higher levels of impairment than controls ( $19.55 \pm 8.69$ ,  $p = 0.06$ ), and SWD subjects only reporting insomnia had the greatest degree of impairment ( $25.67 \pm 14.84$ ,  $p < 0.05$  vs. controls).

Summary data of the EWPS aggregate scores and subscales are presented in **Table 2**. An interesting and significant difference emerged on the fatigue subscale of the EWPS (items such as losing interest, becoming reckless, and falling asleep at work), with AI subjects reporting higher levels of fatigue than controls ( $6.3 \pm 3.1$  vs.  $3.4 \pm 2.62$ ,  $p < 0.05$  vs. controls). Paradoxically, SI subjects showed *lower* scores on the fatigue subscale than insomnia-only subjects, not significantly different from controls ( $4.82 \pm 1.72$ ,  $p > 0.10$ ). This suggests that the EWPS may be sensitive to the distinction between fatigue and sleepiness. Compared to controls, AI subjects also reported

higher levels of impairment in work efficiency (items such as working slowly, having to repeat tasks, and daydreaming): AI subjects scored  $4.75 \pm 3.31$  compared to  $1.91 \pm 2.26$  in controls ( $p < 0.05$ ). SI subjects were not statistically different from controls on any of the EWPS subscales.

### Event-Related Potentials (P3a and P3b)

At the FCz, CZp, and CPz electrodes, alert insomniacs showed significantly attenuated P3a responses (mean difference 1.62–1.77,  $p < 0.05$ ) and target-detection P3b responses (mean difference 1.28–1.64,  $p < 0.05$ ) relative to controls (see **Figure 1A**). P3b in SI was not different from controls ( $p > 0.10$ ), and P3a was only different at one electrode (CPz), mean difference 1.43,  $p < 0.01$ . **Figure 1B** illustrates the topographical scalp distribution of the P3a and P3b brain responses to the novel sounds.

### Correlations to Insomnia and Sleepiness Metrics

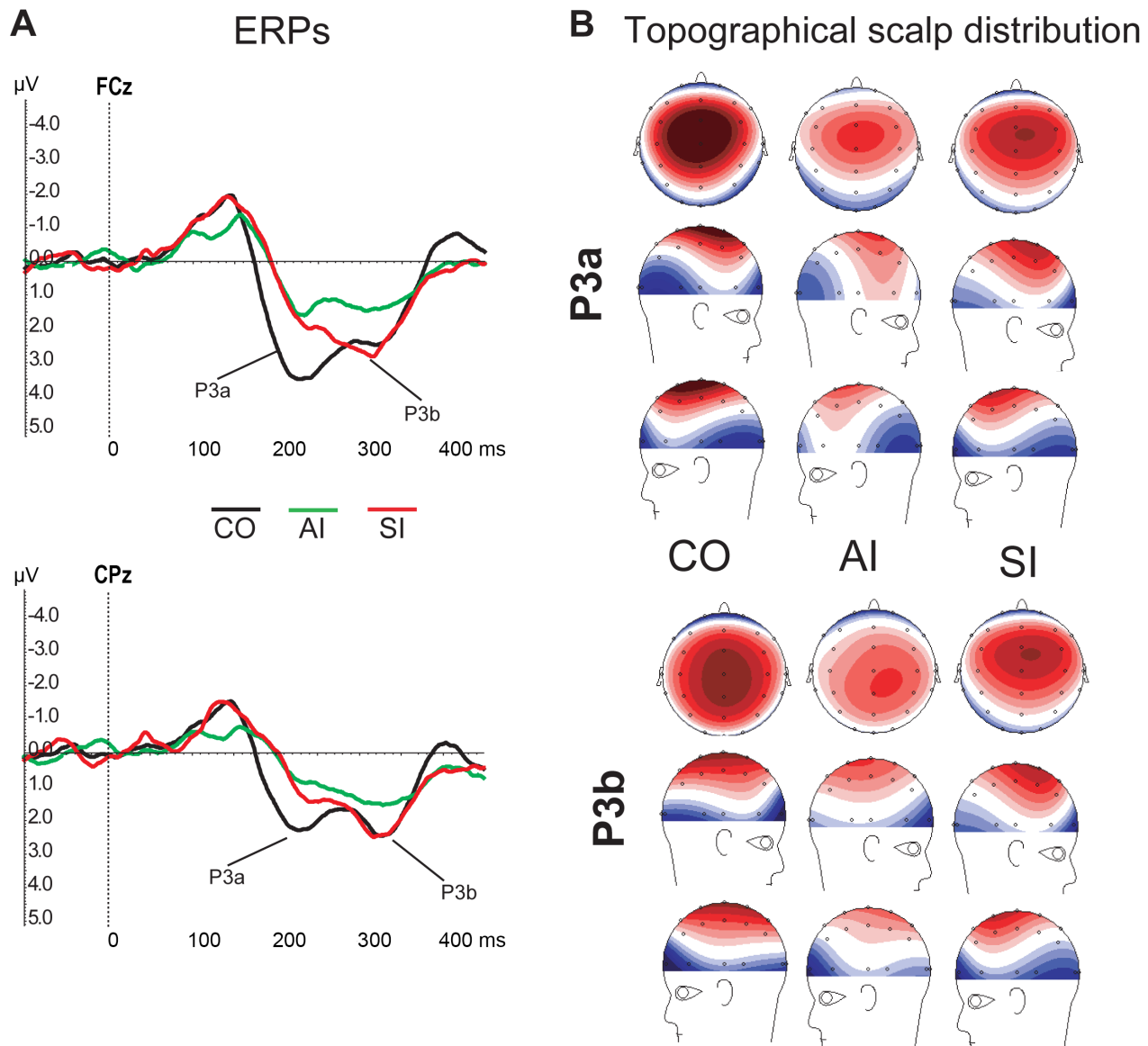
Primary results from the MSLT, sleep diary, circadian phase assessment, and ISI and ESS questionnaires were presented in a previous report<sup>9</sup> and are summarized in **Table 1**. Neither measure of sleepiness (MSLT or ESS) correlated with EWPS scores or ERP amplitudes ( $p > 0.10$ ). However, the mean of the 2 ISI measures correlated with the EWPS ( $r = 0.409$ ,  $p < 0.01$ ) and the attention-to-novelty P3a ( $r = -0.410$ ,  $p < 0.01$ ). This suggests that insomnia in SWD is a strong predictor of occupational and neurophysiological impairment, compared to reports and objective measures of sleepiness.

### Linear Modeling

**Table 3** presents the results of 2 linear regression models using the ISI, ESS, and MSLT to predict EWPS scores and ERP amplitudes. The P3a marker at the CPz electrode was the only ERP amplitude impaired in both the AI and SI groups, and was thus selected as the ERP outcome variable for linear modeling. In Models 1a and 1b, the mean of 2 ISIs is the only significant predictor of EWPS score and P3a amplitude. We interpret this as further evidence that insomnia is a stronger predictor of occupational and neurophysiological impairment than sleepiness.

To determine if circadian phase is a factor in the ERP or EWPS assessments, dim-light melatonin onset (DLMO) was added to the other predictive variables in Model 2a and Model 2b. DLMO does not change the significance level or substantially affect the standardized effect size of the ISI on EWPS

Figure 1



(A) Illustration of ERP difference waveforms corresponding to each group at FCz and CPz electrodes. (B) Topographical scalp distribution of P3a (200–240 ms) and P3b (340–380 ms) activities evaluated in each group. Positive voltage is colored red, negative voltage is colored blue, and white color corresponds to zero. CO, controls; AI, alert insomniacs; SI, sleepy insomniacs

scores, although it does reduce the significance of the ISI in predicting P3a amplitudes. Results from this analysis confirm that a mean of the 2 ISI assessments is a robust predictor of occupational and neurophysiological functioning, such that higher levels of reported insomnia are linked to higher levels of occupational impairment as well as attenuated (impaired) ERP amplitudes.

### Relationship between EWPS Scores and ERP Amplitudes

Total EWPS scores were correlated with the P3a, an attention-to-novelty response (Cpz,  $r = -0.344$ ,  $p < 0.05$ ). The fatigue subscale was also correlated to the P3a response (Cpz,  $r = -0.523$ ,  $p < 0.01$ ), as was the executive function subscale

(difficulty concentrating, organizing work, and forgetting information; CPz,  $r = -0.343$ ,  $p < 0.05$ ). Three subscales measuring interpersonal interactions, work efficiency, and counterproductive work behavior did not significantly relate to the P3a, and none of the EWPS scores related to P3b (target detection) amplitudes. These results suggest that lower EWPS scores in night workers with insomnia are more likely related to the attentional network (P3a) and less related to the memory-updating network (P3b).

### DISCUSSION

The primary result of the present study is that insomnia is strongly linked to functional and cognitive impairments

**Table 3**—Linear regression models predicting Endicott Work Productivity Scale scores and P3a amplitude.

	EWPS Score (n = 34)					CPz P3a Amplitude (n = 34)			
	B	$\beta$	SE	p		B	$\beta$	SE	p
<b>Model 1a</b>					<b>Model 1b</b>				
Constant	9.70	—	7.38	0.199	Constant	2.33	—	0.91	0.015
ISI Mean	<b>0.849</b>	<b>0.390</b>	<b>0.374</b>	<b>0.031</b>	ISI Mean	<b>-0.094</b>	<b>-0.362</b>	<b>0.046</b>	<b>0.048</b>
ESS	-0.049	-0.012	0.697	0.944	ESS	-0.013	-0.028	0.085	0.879
MSLT	0.295	0.123	0.418	0.486	MSLT	-0.013	-0.044	0.051	0.808
		R <sup>2</sup> = 0.180					R <sup>2</sup> = 0.141		
<b>Model 2a</b>					<b>Model 2b</b>				
Constant	2.82	—	13.33	0.834	Constant	1.75	—	1.64	0.296
ISI Mean	<b>0.946</b>	<b>0.435</b>	<b>0.409</b>	<b>0.028</b>	ISI Mean	-0.086	-0.330	0.050	0.098
ESS	-0.016	-0.004	0.706	0.982	ESS	-0.010	-0.022	0.087	0.906
MSLT	0.126	0.053	0.502	0.804	MSLT	-0.027	-0.094	0.062	0.666
DLMO	0.280	0.132	0.450	0.538	DLMO	0.024	0.094	0.055	0.670
		R <sup>2</sup> = 0.190					R <sup>2</sup> = 0.147		

Models 1a and 2a present coefficients, standardized coefficients, standard errors and significance levels from a linear regression of three predictors on (a) scores from the Endicott Work Productivity Scale and (b) P3a amplitudes from the CPz electrode. Numbers in bold indicate regression coefficients, standardized coefficients, standard errors, and p values for independent variables found to be statistically significant in the model ( $p < 0.05$ ). Models 2a and 2b present coefficients, standardized coefficients, standard errors, and significance levels from a linear regression of four predictors on (a) scores from the Endicott Work Productivity Scale and (b) P3a amplitudes from the CPz electrode. Models 2a and 2b account for DLMO in addition to the predictors included in Models 1a and 1b. EWPS, Endicott Work Productivity Scale; SE, standard error; ISI, Insomnia Severity Index; ESS, Epworth Sleepiness Scale; MSLT, multiple sleep latency test; DLMO, dim-light melatonin onset.

in shift workers, while sleepiness appears to make a smaller contribution. Insomniacs without excessive sleepiness showed more severe impairments than insomniacs who report excessive sleepiness. Finally, linear modeling and correlation analyses indicate that the ISI is a more robust predictor of functional sequelae than the MSLT or the ESS.

We have previously reported that there are etiological differences between the two insomnia phenotypes seen in SWD.<sup>9</sup> It was concluded from this study that alert insomniacs (not suffering from excessive sleepiness) were likely to have a preexisting insomnia vulnerability, which evolved into an insomnia disorder in response to the circadian challenge of shift work. In contrast, the SI phenotype primarily had difficulty sleeping when required to sleep at an inappropriate circadian time (i.e., during the day). This was supported by diary data indicating that SWD patients with insomnia alone have disturbed sleep during both nocturnal and diurnal sleep periods, and ERP data showing an N1 response comparable to that seen in day-working individuals with an insomnia disorder. On the other hand, SWD patients reporting both insomnia and excessive sleepiness slept well on days off (i.e., reverting to nocturnal sleep) and showed normal N1 responses. Importantly, these sleep and ERP differences were not attributable to inter-individual differences in the circadian clock, as both groups showed comparable circadian misalignment (DLMO).

The results of the present study extend these findings into the occupational domain and emphasize the real-world stakes of clinical treatment for SWD. First, neurophysiologically, we report that the N1 marker is not the only difference between the two insomnia phenotypes of SWD: the attentional and target-detection markers P3a and P3b are also more impaired in the AI group. Second, we report that these neurophysiological impairments in alert insomniacs have practical and serious

consequences for the workplace, as indicated by significantly elevated P3a and P3b responses and a strong, positive correlation between the EWPS and these ERP amplitudes. Comparing predictors of these impairments head-to-head, we found that the neurophysiological and occupational deficits within the context of SWD were not significantly related to circadian phase or degree of sleepiness, but instead to the severity of their insomnia.

This finding is novel in the context of shift work disorder, where many treatment protocols (e.g., stimulants) and occupational policies (e.g., duty hour restrictions) target the deleterious effects of excessive sleepiness rather than insomnia. On the other hand, it is unremarkable in the context of insomnia research, where multimodal evidence has examined functional and cognitive impairments in insomnia, with mixed findings, for decades (for a review, see Krystal<sup>55</sup>). One recent study of neurobehavioral impairments in day-working insomniacs determined that impairments stem from neurobiological differences between insomniacs and non-insomniacs, not from sleepiness related to reduced sleep time in insomnia<sup>56</sup>—a day worker finding consistent with our observations in shift workers. While our understanding of the exact neurological underpinnings of insomnia is still growing, it appears that neurophysiologic differences in insomniacs are linked to executive and occupational impairment. Our data suggest that these impairment-related neurological attributes are found in the AI phenotype of SWD, but not in the SI phenotype or in healthy night-working controls.

Another interesting result is that while the AI group had lower sleepiness on the ESS (by definition) as well as on the MSLT, they reported significantly greater fatigue. Many patients report sleepiness and fatigue interchangeably, but this paper provides clear evidence that while sleepiness is associated

with MSLT latency, fatigue is not. To the clinician it is critical to differentiate between these two symptoms. These data suggest that, at least among shift workers, the treatment for fatigue is not to enhance alertness but rather to treat insomnia.

We had previously speculated that the treatment of insomnia in these two populations is different, with the SI phenotype needing a circadian readjustment and the AI group needing both circadian readjustment as well as treatment directly aimed at insomnia per se (e.g., CBT-I). The occupational productivity results described here are an additional call for the importance of aggressively treating this symptom, as work productivity and safety may improve in response to insomnia treatment.

This study has a few notable limitations. First, while the timing for our ERP task (18:00–19:00) was carefully selected to occur outside of the circadian nadir for our subjects, intergroup neurophysiologic differences might be different in this time window than during typical night-shift hours. While our study presents evidence of ERP impairment immediately after waking from a diurnal sleep period, future projects may consider collecting ERP data overnight. Second, our occupational impairment findings are limited to self-report. Research on occupational errors in natural environments is an important next direction for SWD, and intervention trials for SWD treatments should consider measuring work productivity and safety alongside the traditional clinical symptoms. Third, the small number of cases within each diagnostic subgroup required us to perform linear regression models within the entire sample instead of separately by group.

This study is part of a larger laboratory protocol, and general limitations to that project are described in a previous report.<sup>9</sup> Summarized, the major limitations are the exclusion of shift workers who consumed large amounts of caffeine, smoked, had high pretest probability for sleep apnea or psychiatric conditions, or used hypnotics or other medications likely to affect the sleep-wake cycle. While these exclusions limit the generalizability of our findings to a true shift-working population, we feel that they reduced the influence of confounding factors in our investigation and were essential to the study's integrity. Finally, our study did not include an objective measure of sleep (e.g., PSG), and the laboratory protocol was only carried out once for each subject.

In conclusion, shift work disorder patients reporting insomnia *without* excessive sleepiness show greater work impairment and attentional impairment on ERP measures than patients reporting sleepiness and insomnia together. The degree of daytime impairment does not relate to degree of daytime sleepiness, but rather to the degree of insomnia and ERP impairment. These results reaffirm that insomnia within SWD demands clinical attention, as it is linked to productivity and neurophysiological impairments with serious consequences for safety and occupational health.

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