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A further evaluation of the cognitive deficits associated with restless legs syndrome (RLS)

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Abstract

Background and purpose—Restless legs syndrome (RLS) is a common sensorimotor disorder that peaks in severity during the night and comes on with rest. As a result, this condition often results in significant chronic sleep loss, especially for those with severe disease. Chronic partial sleep restriction has been associated with conditions such as depression, anxiety, chronic pain, and decline in cognitive function. Furthermore, studies have found that RLS patients suffer from these conditions more than their unaffected peers. Thus, the morbidity rate associated with RLS has often been attributed to the chronic sleep loss that frequently accompanies this condition. However, no study has specifically compared RLS sufferers to otherwise normal sleep-restricted controls in order to assess disease morbidity independent of its sleep deprivation effects. In this study, we compared the cognitive function of RLS patients who were off treatment to sleep-restricted control subjects.

Subjects and Methods—A novel chronic partial sleep-restriction protocol that utilized a 14-day combined inpatient and outpatient design was implemented in order to test the differences in cognitive functioning between RLS patients and sleep-restricted controls. The brief cognitive battery included instruments assessing general intelligence and global executive function in order to control for baseline cognitive function between the groups, and then the effects of sleep loss were assessed using prefrontal lobe-specific tasks. The final sample consisted of 16 RLS (11 male and 5 female) and 13 sleep-restricted control subjects (7 male and 6 female).

Results—In order to examine the differences in cognitive functioning between sleep-restricted controls and RLS subjects, independent samples *t*-tests were conducted. RLS subjects performed significantly better on both the Letter Fluency ($t = 2.13$, $p < .05$) and Category Fluency ($t = 2.42$, $p < .05$) than sleep-restricted controls.

Conclusions—RLS subjects performed better than the sleep-restricted controls on two tasks that are particularly sensitive to sleep loss. Although previous studies suggest that sleep deprivation may impact the cognitive function of those with RLS, our data suggests that RLS subjects may show a relative degree of sleep loss adaptation. Future investigations that more closely match the sleep loss pattern of RLS subjects to controls are warranted in order to explore these potential traits further.

Keywords

Restless legs syndrome; Cognition; Sleep deprivation; Chronic sleep restriction; Polysomnogram; Pre-frontal cortex; Verbal fluency test; Trail-making test

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Introduction

Restless legs syndrome (RLS) affects approximately 7–10% of the general population living in the United States and Northern Europe(1,2). Individuals with RLS experience a strong urge to move their legs, frequently accompanied by uncomfortable or even painful sensations brought on with rest. These sensations peak in severity at night, often leading to chronic sleep loss. Those with severe disease, may obtain as little as 3–5 hours of sleep per night, amounting to a degree of chronic sleep loss rarely seen in other sleep conditions (3). Illnesses such as depression, anxiety, and chronic pain have been associated with chronic sleep loss and appear to be more prevalent in those with RLS compared to normal controls (4–7).

Cognitive function also appears to be particularly sensitive to sleep loss (4,8–10), but only a few studies have examined cognitive function in the RLS population specifically (11–13). Two studies compared the cognition scores on the medical outcomes (MOS) questionnaire for RLS patients to a normative population and found that RLS patients had significantly lower MOS cognition scores (11,12). We reported the only study that has compared the cognitive performance of RLS patients to normal non-sleep-restricted controls using a cognitive battery designed to minimize artifacts that are produced by decreased ability to maintain attention after sleep loss (13). This short battery was designed to reflect the primary cognitive functions of the prefrontal lobe because of its sensitivity to sleep loss while also attempting to control for the decrease in attention maintenance often associated with sleep deprivation. That study demonstrated that RLS patients had significant cognitive impairment compared to their age-matched controls. The impairment, as expected, involved those cognitive tasks previously shown to be very disrupted by one night's sleep loss. Thus, we postulated that the cognitive deficits seen with RLS resulted from sleep loss.

Aside from the established impact of sleep loss on cognition, perhaps other aspects of the RLS disorder impact cognitive function differently than the deficits seen with sleep loss. If so, documenting this might shed further light on the neurobiology and morbidity of RLS. This is particularly important since clinical reports indicate that RLS patients report less sleepiness than expected for their degree of sleep loss (7) and, in one study, RLS patients did not show any increase in traffic accident rates (14). Thus, RLS appears to have some alerting or arousal features that may potentially reduce the amount of sleepiness expected for this degree of chronic sleep loss. Perhaps this also serves to reduce the cognitive effects of sleep loss. The critical study then becomes comparing the cognitive function of RLS patients to normal controls who are similarly sleep-restricted. The controls should not be sleep-deprived for one night; rather, they should be chronically sleep-restricted in an attempt to similarly match the degree of sleep loss experienced by RLS patients.

The goal of this investigation was to look at the cognitive performance of RLS patients compared to age-matched, sleep-restricted controls (SRCs) in order to independently assess the potential impact of the RLS disease state on cognitive performance. Based on the previously reported clinical findings, we hypothesized that RLS patients would perform better on cognitive tasks, which are sensitive to sleep loss, compared to similarly sleep-restricted age-matched controls.

Most current sleep deprivation research evaluates individuals by using an acute short-term total sleep deprivation design. In contrast, most Americans, especially those with RLS, primarily face the challenge of cumulative chronic sleep loss. Conducting an inpatient chronic sleep loss protocol is often impractical and not feasible due to the extensive resources necessary to carry out this type of research design. Thus, only a limited number of chronic partial sleep restriction studies (≤ 7 hours of sleep nightly for ≥ 6 days) exist in the literature. In this project, we also

set out to develop an innovative approach to conduct a chronic partial sleep restriction protocol that mixed a 12-day outpatient with a final two-day inpatient sleep restriction protocol.

Methods and Materials

Subject Criteria

Data for RLS subjects were generated from a cognitive battery performed on RLS subjects who had previously participated in a larger clinical study. All of the subjects consented to participation in this Institutional Review Board (IRB)-approved protocol. A complete description of the inclusion/exclusion criteria for the RLS cohort has been published previously (13), so specific details regarding the subject criteria, design, and methods will be limited to the sleep-restricted control (SRC) subjects. The cognitive battery was performed on the RLS subjects while off RLS medications and sleep aids for at least 14 days.

SRC subjects over the age of 18 years were screened by self-administered history forms and questionnaires as well as a face-to-face interview by a neurologist with subspecialty training in sleep disorders. SRC subjects were included only if they reported a normal circadian sleep pattern (sleeping between the hours of 9pm–9am) and a minimum sleep duration of 7.5 hours, and were able to comply with the eligibility process (could follow the sleep restriction schedule, wear a small watch-sized activity monitor on their wrist, and keep a log for their sleep and wake behavior). SRC subjects were excluded if they demonstrated any of the following: (1) clinical symptoms of RLS; (2) periodic leg movements ≥ 10 per hour; (3) a significant sleep disorder as determined by clinical history, sleep questionnaires, or evidence of significant sleep apnea as determined by a home apnea monitor (respiratory disturbance index [RDI] ≥ 15) if there was a history of snoring or body mass index (BMI) > 27.5 ; (4) any medical (e.g., chronic pain syndromes) or neurological (e.g., amyotrophic lateral sclerosis [ALS], stroke, multiple sclerosis [MS], hydrocephalus) conditions or chronic medications that are likely to compromise normal sleep; and (5) daytime sleepiness at the time of screening as indicated by the Pittsburgh Sleep Quality Index.

Once the control subjects were approved for appropriate candidacy, they consented and were enrolled in a sleep restriction protocol in order to generate data comparing the cognitive performance of RLS patients to age and gender-matched SRCs. A final sample of 16 RLS (11 male and 5 female) and 13 SRC subjects (7 male and 6 female) were used (see Table 1).

Cognitive Tests: Prefrontal, Parietal, Temporal Lobes

The cognitive assessment included the following tests: Stroop Word Test, the Trail Making Test (both test A and B), the Colored Progressive Matrices Test, Vineland Revision of the Porteus Maze Test, and two forms of the Verbal Fluency Tests (fluency letters, and fluency categories). This battery could be performed in less than 60 minutes and was developed based on the recommended criteria for evaluating neurobehavioral performance during sleep deprivation, which included the following: (1) valid and reliable measure of waking cognition; (2) repeatable; (3) brief; and (4) unaffected by aptitude for those of normal intelligence (13, 15). The colored progressive matrices served as a non-verbal assessment of overall cognitive function providing a crude measurement of general intelligence (16). This ensures that the effects of overall intelligence could be controlled for when interpreting the cognitive performance of the two groups. The Stroop Word Test and Porteus maze target the frontal, parietal, and temporal lobes so they served as assessments of global cognitive function (17, 18). The two Verbal Fluency tests (fluency letter and fluency category) and Trails B of the Trail Making tests were chosen as prefrontal lobe-specific tasks. Because prefrontal lobe function is exquisitely sensitive to sleep loss, the cognitive deficits related to sleep loss tend to be more robust in the prefrontal lobe-specific tasks compared to those tasks targeting global

cortical and executive function (19–21). This battery of tests was used in our prior study showing significant cognitive loss for RLS patients on the prefrontal lobe-specific tasks only (Verbal Fluency and Trails B of the Trail Making Test), suggesting that the RLS subjects demonstrate their earliest impairments on the more sleep-sensitive cognitive tasks (13). Similar to our prior study, we hypothesized that the most robust difference between the two groups would again be demonstrated on the prefrontal lobe-specific tasks with minimal to no differences seen on the other more global cognitive tasks.

Procedures

After completing the screening and consent process, 13 eligible control candidates participated in a 14-day sleep restriction protocol in an attempt to simulate the chronic sleep loss routinely experienced by the RLS group. In our original study, the RLS subjects often reported receiving little to no sleep for the first 1–4 nights of their 14-day medication washout period. The SRC protocol involved two phases: in the first phase, subjects restricted their sleep to a maximum of six hours nightly, with no daytime naps, as an outpatient for 12 days. Compliance was monitored using daily sleep-wake logs, body position, and wrist-activity monitors were worn continuously except while showering. If the sleep log, body position monitor or actigraphy suggested >20% non-compliance with the sleep restriction guidelines over the course of 12 days, then the subject was disqualified from the study. Subjects were contacted daily to ensure their safety and were offered transportation if they reported pathological levels of sleepiness on the Epworth sleepiness scale (score ≥ 11 out of 24). Due to the inherent safety issues of an outpatient chronic partial sleep-restriction protocol, the IRB on research in human subjects (IRB) would not permit subjects to be restricted to less than six hours of sleep while at home. Subjects spent nights 13 and 14 (phase 2) in the Johns Hopkins General Clinic Research Center (GCRC) as inpatients where their sleep could be restricted to five hours nightly. During the inpatient phase, subjects underwent a protocol similar to that for the RLS patients, including nightly polysomnograms (PSGs) and a cognitive battery on the morning of discharge (day 15).

Statistical Analyses

The differences in cognitive performance between the RLS subjects and SRC subjects were measured using independent samples *t*-tests with 95% confidence interval limits.

Results

The demographics for each group presented in Table 1 show no significant difference in age or gender between SRCs and RLS subjects. Furthermore, there were no significant differences in total sleep time (TST) between RLS subjects and SRC subjects. However, during the second night's PSG, RLS subjects showed significantly less sleep efficiency (mean $\pm$ standard deviation [SD], 83.4 $\pm$ 8.3) than SRCs (mean $\pm$ SD, 98.3 $\pm$ 2.6), ($t = 6.10$, $p = 0.00$).

RLS subjects were less likely (7:9) to have post-high school education than SRC controls (1:12, $\chi^2 = 4.67$, $p = 0.03$). However, there were no significant differences in general intelligence between SRC and RLS subjects based on their performance on the colored progressive matrices task (see Table 2). The measures of global cognitive function (The Stroop test and Porteus maze) and one of the measures of prefrontal lobe functioning (Trails B of the Trail Making task) similarly showed no significant differences in performance between the two groups. There were, however, significant differences between the groups on both of the Verbal Fluency tests. The test for word with set first letter (sum of responses for the letters F, A, and S) showed more correct words produced for RLS patients than SRCs (mean $\pm$ SD, 39.9 $\pm$ 8.2) (mean $\pm$ SD, 32.9 $\pm$ 9.1, respectively = 2.13, $p < .05$). Furthermore, when the total words named from the categories Fruits, Animals, and Vegetables were summed, RLS patients also named

significantly more words (mean $\pm$ SD, 42.1 ± 8.8) than did SRCs (mean $\pm$ SD, 35.2 ± 5.7 , $t = 2.42$, $p < .05$).

Discussion

We set out to compare the cognitive performance of untreated RLS subjects with marked sleep loss to that of chronic SRCs. In order to conduct this comparison, we developed a chronic partial sleep-restriction protocol that partially matched the sleep loss experienced by the RLS patients. Since these patients were withdrawn from their RLS medications for at least 14 days prior to performing the cognitive battery, we sought to match their sleep restriction period in a group of controls in order to compare their cognitive performances. Our novel protocol using a combined inpatient and outpatient design to produce sleep deprivation provided us a control group with sleep loss closer in character to that experienced by RLS patients.

Although RLS subjects often report minimal subjective sleepiness despite significant chronic sleep loss, our previously reported study comparing the cognitive performance of RLS subjects to normal non-sleep-restricted controls showed that RLS subjects performed significantly worse on the cognitive tasks sensitive to sleep loss (13). However, in this study, when we compared the performance of RLS subjects to SRC subjects, the RLS subjects performed statistically better than their SRC counterparts on tasks sensitive to sleep loss. Our investigation is the first to compare the cognitive performance of RLS subjects to normal SRCs. Although sleep deprivation impacts the cognitive function of those with RLS compared to normal non-sleep-restricted controls, our data suggests that RLS subjects may show a relative degree of sleep loss adaptation with less impairment than observed for controls with nearly equivalent sleep loss.

In the outpatient phase of our sleep restriction protocol, we could only restrict the control subject's sleep to six hours a night for safety reasons. Some of our RLS patients with severe disease were obtaining as little as 3–5 hours of sleep nightly and many endured significant sleep fragmentation, which was not true for the control subjects, so our control subjects may have actually had less sleep loss than the RLS subjects. This could explain the reason behind the non-significant differences in performance on the Trails B of the Trail Making task between the two groups. Even if the RLS subjects were operating under a greater sleep debt than the controls, they still performed better on the two Verbal Fluency tasks than the sleep-restricted control, suggesting that RLS may in some way reduce the sleep loss effects on cognition. Aside from the relatively mild amount of reported sleepiness often demonstrated in RLS individuals (13,22), additional support for some RLS reduction of sleep loss effects comes from a study that reported high somatic complaints on the Beck Depression Scale in RLS patients but did not find significantly high scores on the items associated with cognitive symptoms (23).

It is important to emphasize that although the RLS patients had fairly severe sleep loss after discontinuing their treatment when entering this study, most were on RLS treatment prior to the study and we have no indication that they were experiencing significant sleep loss prior to entering the study. Although the amount of sleep deprivation may have been slightly worse in the RLS group, the 14-day sleep restriction duration was the same for the sleep-restricted controls and RLS patients. Any adaptation to the effects of sleep loss demonstrated by the RLS group was accordingly based on a similar duration of sleep restriction exposure for the two groups. Thus, the reduced effects of sleep loss on cognitive function may reflect another aspect of the disease process that involves an enhanced level of physiologic alertness.

Conclusion

This is the first study to compare the cognitive function of RLS subjects to controls who had significant sleep loss. While RLS patients perform worse than normal controls, as was reported previously, they actually performed better than the chronic sleep-restricted controls on the prefrontal cognitive tests. Our findings suggest that RLS may be associated with an enhanced physiologic level of alertness that may help to compensate for significant sleep loss. Perhaps this potential expression of compensatory alertness may not only reduce the cognitive deficits from sleep loss but also the actual physiological sleepiness. Thus, RLS patients despite severe chronic sleep loss, do not commonly report problems falling asleep at inappropriate times such as when driving a vehicle. Exploring the mechanism behind this enhanced level of physiologic alertness may further elucidate the pathophysiology of RLS.

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Table 1

Characteristics of the Study Sample

	Sample Size	Age (<i>M</i> , <i>SD</i>)	Age Range	Gender (F:M)	Education level (high school; post- high school)	Mean total sleep time (mins) ± SD	Mean sleep efficiency ± SD
Sleep-Deprived Control	13	59.6 (9.38)	45–77	6:7	1:12	295.4 ± 7.9	98.3 ± 2.6
RLS	16	64.0 (10.3) <i>t</i> = 1.19 <i>p</i> = 0.25	46–80	5:11 χ^2 = 0.68 <i>p</i> = 0.41	7:9 χ^2 = 4.67 <i>p</i> = 0.03	309.3 ± 82.4 <i>t</i> = 0.61, <i>p</i> = 0.55	83.4 ± 8.3 <i>t</i> = 6.10 <i>p</i> = 0.000

Table 2

Cognitive test scores (averages and standard deviation [SD]) for RLS and sleep-deprived control subjects and *t*-test statistic comparing the groups

Tests	RLS	Sleep-deprived Control	RLS vs. sleep-deprived Controls	
	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)	<i>t</i>	<i>p</i>
<i>Stroop</i>				
Color Time	76.7 (18.1)	65.8 (20.0)	1.53	0.14
Color Word Time	143.6 (49.3)	114.4 (44.5)	1.64	0.11
Interference	62.7 (39.7)	48.6 (30.4)	1.05	0.30
<i>Porteus Mazes</i>				
Completion Time	71.4 (44.3)	108.7 (238.9)	0.60	0.56
<i>Colored Progressive Matrices</i>				
Number completed	32.1 (2.9)	31.9 (3.8)	0.17	0.86
<i>Verbal Fluency</i>				
Letter Fluency	39.9 (8.2)	32.9 (9.1)	2.13*	0.04
Category Fluency	42.1 (8.8)	35.2 (5.7)	2.42*	0.02
Trail B	98.7 (54.4)	73.5 (29.4)	1.49	0.15

*
p < .05