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Effects of an experimentally induced rhinovirus cold on sleep, performance, and daytime alertness

Christopher L. Drake[a],*, Timothy A. Roehrs[a], Heather Royer[a], Gale Koshorek[a],
Ronald B. Turner[b], Thomas Roth[a]

[a]*Sleep Disorders and Research Center, Henry Ford Hospital, 2799 West Grand Boulevard, CFP3, Detroit, MI 48202, USA*
[b]*Department of Pediatrics, Medical University of South Carolina, Charleston, SC, USA*

Abstract

Study objectives: There is accumulating evidence that the common cold produces impairments in psychomotor vigilance. This has led some investigators to hypothesize that such illnesses may also have disruptive effects on sleep. While several self-report studies suggest that viral illness may influence sleep parameters, no studies have assessed polysomnographically recorded sleep following viral infections. **Design:** Parallel control group comparison. **Setting:** Sleep laboratory in a large urban medical center. **Participants:** Twenty-one men and women with susceptibility to the rhinovirus type 23. **Interventions:** Nasal inoculation with rhinovirus type 23. **Measurements:** Polysomnographically recorded sleep for five nights (2300–0700 h) post-viral inoculation. Twice daily (1030 and 1430 h) performance assessment during each experimental day using auditory vigilance and divided attention tasks. A multiple sleep latency test (MSLT) was performed daily for the duration of the study. **Results:** In symptomatic individuals, total sleep time decreased an average of 23 min, consolidated sleep decreased an average of 36 min, and sleep efficiency was reduced by an average of 5% during the active viral period (experimental days/nights 3–5) compared with the incubation period. Psychomotor performance was impaired. These changes were significantly greater than those observed in asymptomatic individuals. **Conclusions:** The common cold can have detrimental effects on sleep and psychomotor performance in symptomatic individuals during the initial active phase of the illness. © 2000 Elsevier Science Inc. All rights reserved.

Keywords: Common cold; Rhinovirus type 23; Sleepiness; Psychomotor performance; Sleep efficiency; Sleep continuity; Multiple sleep latency test (MSLT)

There is increasing evidence that viral infections such as the common cold and influenza impact central nervous system function [2,8,10,11,13,16]. For example, experimentally induced respiratory syncytial viruses or coronavirus colds slowed five-choice reaction time with no effect on a more complex decision task [15]. In another study involving viral inoculation, individuals who became symptomatic showed a performance decrement on a pegboard task involving hand–eye coordination, but not on a visual search/memory task, whereas asymptomatic individuals showed no impairment [16]. Studies have shown that performance impairment may be present during the incubation period of the illness [18] and decrements may remain for several days following symptom remission [14].

A number of studies have found no evidence of performance deficits on certain tasks as a result of minor viral infections [8,12,16,17]. Generally, when impairments are observed, they have been found on simple motor tasks rather than more complex cognitive tasks such as those involving memory, selective attention, or other cortical functions [2,8,14,15].

While minor viral infections appear to selectively impair psychomotor performance, the mediating factor(s) responsible for this impairment are as yet unknown. For instance, the observed impairment may be a direct effect of the viral infection and its accompanying symptomatology (i.e., muscle fatigue, general malaise, headache, etc.), or an indirect effect stemming from a secondary mechanism such as a disruption of sleep–wake activity. Indeed, disruptions in the quality and quantity of sleep and the

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ensuing decrease in daytime alertness have been associated with impaired performance on a variety of psychomotor tasks [6,19,21].

With regard to evidence for viral effects on sleep, two studies have examined the effects of experimentally induced influenza A and B on self-reports of sleep [10]. The results showed that self-reported sleep duration in individuals with subclinical infections and influenza was reduced during the "incubation" period (3 days following inoculation) and increased during the "symptomatic period" (6–8 days post-inoculation). In contrast, following a rhinovirus challenge, individuals reported sleeping longer during both the "incubation" and "symptomatic" periods [10]. Interestingly, there were no differences in any of the studies with regard to reported number of awakenings or sleep quality; however, no electrophysiological recordings were obtained. A more recent study found that viral infections reduced self-reported alertness [11].

Thus, while there is evidence for performance impairment as a result of viral infection, it is unknown what specific sleep disruptions may occur in conjunction with these performance decrements. The present study assessed polysomnographically recorded sleep, daytime sleepiness, and psychomotor performance in individuals with experimentally induced rhinovirus colds in comparison to a control group of asymptomatic individuals also exposed to the virus.

1. Methods

1.1. Subjects

Twenty-one healthy men and women, aged 18–45 years (mean 27.5 ± 8.13), without sleep complaints, and with no evidence of sleep pathologies on a nocturnal polysomnogram (NPSG) completed the study.

1.2. Screening procedures

A total of 293 individuals were screened for serum neutralizing antibody titers to rhinovirus type 23. One hundred twenty-two individuals with titers of $\leq 1:4$ were selected for further screening. Physical exams, drug use histories, laboratory test results (blood and urine samples for verification of major system functions), and urine drug screens were required to be negative. No individuals who reported a daily caffeine intake of more than 400 mg were included in the study. Individuals who reported significant sleep–wake complaints or unusual sleep habits were excluded from participation.

Each participant received a standard 8-h NPSG screening. Recordings included three electroencephalograms (C_3 or C_4, and O_Z referenced to mastoid), two electrooculograms (EOGs; bilateral horizontal), submental electromyogram (EMG), and electrocardiogram (EKG) activity (V5

lead). Participants were required to have sleep efficiencies >80% with no evidence of significant sleep apnea or periodic leg movements during sleep ($>5 \text{ h}^{-1}$). At screening, participants were tested using a four-nap (0930, 1130, 1330, 1530) clinical version of the multiple sleep latency test (MSLT) that was administered and scored according to standard criteria [5]. Individuals were required to have MSLT latencies between 8 and 14 min to qualify for study participation. All subsequent MSLTs were performed according to standard research criteria [5]. The Institutional Review Board approved all study procedures. All participants provided written informed consent and were paid for their participation.

1.3. Study design

1.3.1. Inoculum source

The rhinovirus type 23 used in this study was originally isolated and typed in a natural cold study at the University of Michigan. The resulting pool was safety tested according to consensus guidelines [7].

1.3.2. Inoculation procedures

At 0800 h on day 1 of the study protocol, participants arrived at the sleep laboratory and received a symptom checklist (see symptom assessment), a nasal wash, and were then inoculated with rhinovirus type 23 using standard procedures [3,7]. Following a nasal wash (5 ml saline), each participant was challenged with virus in two inoculations in the form of nasal drops. Inoculations were given 15 min apart, for a total inoculum of approximately 100 tissue culture infection dose ($TCID_{50}$) of human rhinovirus 23. The procedure was performed with the participant in the supine position and lasted approximately 30 min. Following the inoculation, participants were instructed to refrain from clearing their nasal passages for 1 h. Participants remained in the laboratory for the subsequent 5 days/nights.

1.3.3. Symptom assessment

At 0800 and 2000 h on each experimental day, participants completed a symptom assessment. Participants rated the following eight symptoms — sneezing, runny nose, nasal obstruction, sore throat, cough, headache, malaise, and chilliness — on a scale of 0–4 corresponding to a symptom severity of absent, mild, moderate, severe, or very severe. The daily symptom scores for each symptom were calculated as the mean of the morning and evening assessment. Total symptom score for each symptom was the sum of daily symptom scores across the 5 days of assessment. Each individual was classified as symptomatic or asymptomatic according to Jackson Cold Criteria, which requires a daily symptom score of at least six for the 5 days post-challenge and either the presence of runny nose for at least 3 consecutive days or the subjective impression that they have a cold.

1.3.4. Nocturnal sleep assessment

Polysomnographically recorded sleep (2300–0700 h) was measured during each experimental night [1–5] post-inoculation [9]. Sleep parameters assessed included consolidated sleep (total sleep time excluding non-rapid eye movement [NREM] stage 1 sleep), sleep efficiency, total sleep time, percentage of NREM sleep stages 1, 2, and 3/4, and percentage of rapid eye movement (REM) sleep. All measures were scored according to standard procedures [9].

1.3.5. Performance measures

Participants completed a divided attention task at 1030 and 1430 h on each testing day. This 15-min task required participants to track a moving target across a video screen using a joystick while simultaneously responding with a button press to the appearance of stimuli in the center of the target or periphery of the screen. A total of 52 stimuli were presented at random intervals throughout each task period. Dependent measures for this task were reaction time (in milliseconds) to central and peripheral stimuli and tracking deviations measured in pixels.

At 1045 and 1445 h, participants performed a 40-min auditory vigilance task. For this task, participants were instructed to respond to a series of tones by pressing a button every time an individual tone deviated from a "standard" tone. The task consisted of four 10-min blocks with 15 deviate tones generated per block. Standard tone duration was 250 ms and deviate tone duration was 450 ms. Interstimulus interval was randomized throughout each 10-min block. If no response was detected within a 2-s window following the stimuli presentation, the trial was coded as a lapse. The dependent measures for the auditory vigilance task were reaction time in milliseconds and number of lapses. All participants were trained on each task at screening in order to minimize the possibility of practice effects.

1.3.6. Mood and subjective sleepiness

Participants completed the Profile of Mood States (POMS) at 0730, 1000, 1200, 1400, 1600, and 1800 h throughout each of the experimental days. Participants rated their subjective sleepiness, sleep quality, sleep latency, number of awakenings, time awake after sleep onset, and total sleep time upon awakening.

1.3.7. Analyses

An "incubation period" was operationally defined to include experimental days/nights 1 and 2 following viral inoculation as this time period was prior to symptom development. An "active viral period" was defined to include days/nights 3–5 as this period was marked by the presence of symptoms in affected individuals. Mixed two-factor (Group × Period) analysis of variance (ANOVA) with repeated measures (Period) was performed to assess significant differences between symptomatic and asymptomatic

Table 1
Mean total symptom score for days 1–5 for asymptomatic and symptomatic individuals

	Runny nose	Sneezing	Nasal obstruction	Sore throat	Cough	Headache	Malaise	Chilliness	Total symptom score
Asymptomatic group									
1	0	0	0	0.17	0	0.08	0	0.08	0.33
2	0	0	1.50	0	0	0	0	0	1.5
3	0	0	0	0	0	1	0	0	1
4	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0
7	1	0.5	1.25	0	0	0	0	0.50	3.25
8	0	0	0.5	0	0.50	0	0	4.57	5.57
9	0	0	0	0	0	0	0	0	0
10	0	0	0	0.50	0	4	0	0	4.5
11	1	1.50	0	0	0	0	0	0	2.5
12	2	0.50	1.25	0.50	0	0.50	0	0.50	5.25
13	0	1.50	0.5	1.50	0	0	0	0.50	4
14	1	0	1	0	0	0	0	1	3
Total	0.36	0.29	0.43	0.19	0.04	0.40	0.00	0.51	2.22
Symptomatic group									
1	2.50	1	0.50	1	4.25	1.50	0	0	10.75
2	7	4.50	5	2.50	1.50	3	3.50	2	29
3	3	3.50	5	5	4.50	4	3	6	34
4	0.50	1	1.50	3	0	2.50	1.50	1.50	11.5
5	1	1.50	3.50	0.50	1	0	0	0	7.5
6	2	0	0	4	0	0.50	0	0	6.5
7	4	3.50	7	3.50	0	2.50	4.50	1	26
Total	2.86	2.14	3.21	2.79	1.61	2.00	1.79	1.50	17.9

Scores for each symptom represent the total symptom score across the 5 days of the study.

Table 2
Polysomongraphic sleep parameters for asymptomatic and symptomatic groups during the incubation and active viral period

	Asymptomatic ($n = 14$)		Symptomatic ($n = 7$)	
	Incubation	Active viral	Incubation	Active viral
Sleep efficiency measures				
Total sleep time (min) **	437.7 (22.3)	431.4 (18.6)	440.2 (35.2)	416.9 (38.7)
Sleep efficiency (%) **	91.9 (4.7)	89.9 (3.9)	91.7 (7.4)	86.9 (8.1)
Consolidated sleep (min) ***	381.2 (42.2)	386.5 (34.1)	406.9 (37.8)	371.1 (43.4)
Consolidated sleep efficiency (%) ***	79.4 (8.8)	80.5 (7.1)	84.8 (7.9)	77.3 (9.0)
Latency to stage 1 (min)	23.0 (28.2)	26.2 (12.1)	11.0 (4.9)	20.1 (9.8)
Latency to persistent sleep (min)	28.9 (39.3)	39.3 (18.5)	14.5 (7.3)	24.7 (14.0)
Entries into wake	21.5 (11.9)	19.2 (7.1)	18.9 (5.6)	20.8 (5.3)
Sleep stage measures				
Percent stage 1 *	15.3 (11.0)	13.5 (10.7)	7.6 (2.3)	10.1 (5.2)
Percent stage 2	57.7 (7.6)	53.4 (14.4)	53.7 (11.5)	51.8 (10.9)
Percent stage 3/4	14.1 (6.9)	16.8 (7.6)	15.3 (8.6)	17.2 (11.8)
Percent REM	19.4 (2.4)	19.4 (2.8)	19.1 (3.7)	20.3 (4.2)
Latency to REM (min)	94.2 (32.6)	75.4 (19.8)	92.1 (34.5)	82.4 (18.2)

Data are means ($\pm$ SD).

Sleep efficiency = sleep time/bed time $\times$ 100; Consolidated sleep = min non-stage 1 sleep; Consolidated sleep efficiency = Consolidated sleep/bed time $\times$ 100; Latency to persistent sleep = min to the first epoch of 10 continuous min of sleep; Latency to stage 1 = minutes to the first epoch of stage 1; Entries into wake = number of shifts from any sleep stage to an epoch of wake; Incubation = nights 1–2; Active viral = nights 3–5.

* $p \leq 0.1$.

** $p \leq 0.05$.

*** $p \leq 0.01$.

groups across incubation and active viral periods. Log transformations were performed for variables that were not normally distributed. Alpha criterion for statistical significance was set at $p < 0.05$.

2. Results

2.1. Study population

Of the 21 participants, seven met Jackson Cold Criteria based on self-reported symptoms while 14 remained asymptomatic. Individual symptom profiles are listed in Table 1.

As might be expected based on the method of constructing the two groups, there was a significantly greater difference in total daily symptom score between experimental days 2 and 3 for the symptomatic group compared with the asymptomatic group ($F_{1,19} = 5.38$, $p = 0.04$), indicating a separation between the last day of the incubation period and the first day of the active viral period. In addition, participants in the symptomatic group reported a significant increase in feeling ill during the active viral period while the asymptomatic group reported no such increase ($F_{1,19} = 11.77$, $p = 0.003$).

2.2. Polysomnographic sleep

Mean values for nocturnal sleep parameters during incubation and active viral periods for each group are presented in Table 2. A significant interaction between

Group and Period in minutes of consolidated sleep ($F_{1,19} = 10.75$, $p = 0.004$) indicated a significantly greater decline in minutes of consolidated sleep for the symptomatic group (Fig. 1). A Group $\times$ Period interaction for sleep efficiency ($F_{1,19} = 4.31$, $p = 0.05$) indicated a significantly greater decline in sleep efficiency in the symptomatic group compared with the asymptomatic group from incubation to active viral period (Fig. 2). In addition, for the symptomatic group, there was a tendency for decreased percentage of stage 1 NREM sleep ($F_{1,19} = 3.18$, $p = 0.09$) from incubation to active viral periods.

2.3. Self-reports of sleep parameters and mood

Means for each of the subjective sleep parameters can be found in Table 3. For "ease of falling asleep", a
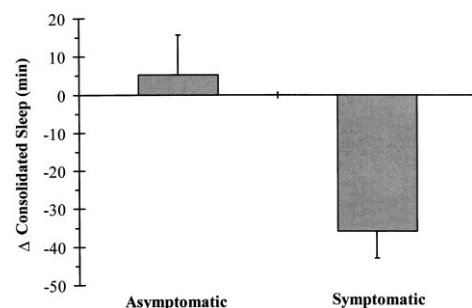

Fig. 1. Mean change ($\pm$ SEM) in consolidated sleep from incubation to active viral periods in asymptomatic and symptomatic groups.
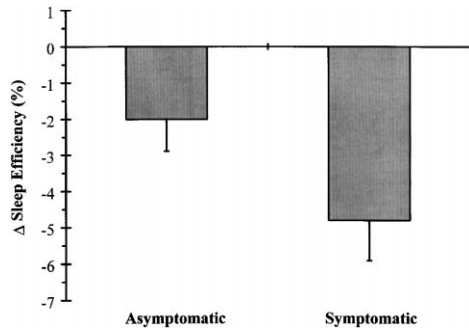
Fig. 2. Mean change ($\pm$ SEM) in sleep efficiency from incubation to active viral periods in asymptomatic and symptomatic groups.

Group $\times$ Period interaction indicated that in the symptomatic group, there was a significant decrease in ease of falling asleep compared with the asymptomatic group ($F_{1,19} = 4.20$, $p = 0.05$). A Group $\times$ Period interaction ($F_{1,19} = 3.96$, $p = 0.06$) for sleep latency indicated that there was a tendency for the symptomatic group to report a greater increase in sleep latency from incubation to the active viral period. With regard to sleep quality, the Group $\times$ Period interaction approached significance ($F_{1,19} = 3.35$, $p = 0.08$) and indicated a tendency for the

symptomatic group to report that sleep quality decreased while the asymptomatic group reported an increase in sleep quality. No significant differences were found between groups on any of the POMS scales from incubation to active viral periods.

2.4. Psychomotor performance

Means and standard deviations for the performance measures are presented in Table 4. A Group $\times$ Period interaction ($F_{1,19} = 5.29$, $p = 0.03$) for mean reaction time on the auditory vigilance task indicated a slowing of reaction time from incubation to active viral period in the symptomatic group while reaction time remained similar for the asymptomatic group (see Fig. 3). No significant differences were found on the divided attention task.

2.5. Daytime alertness

During the incubation period, mean sleep latency on the MSLT was 7.56 ± 4.02 and 7.32 ± 4.11 for asymptomatic and symptomatic groups, respectively. During the active viral period, mean MSLT latency was 7.84 ± 3.64 and 8.75 ± 2.79 for asymptomatic and symptomatic groups,

Table 3

Self-reports of sleep parameters for asymptomatic and symptomatic groups during the incubation and active viral period

Sleep parameter	Asymptomatic ($n = 14$)		Symptomatic ($n = 7$)	
	Incubation	Active viral	Incubation	Active viral
Have you felt ill at all today/now? [a],***	2.00 (0)	1.95 (0.12)	1.79 (0.39)	1.38 (0.41)
How long after bedtime did you fall asleep? (min) *	30.3 (33.4)	25.5 (16.2)	27.5 (15.9)	48.3 (36.6)
How many times did you wake up during the night?	2.5 (1.2)	2.3 (1.1)	3.3 (2.7)	2.7 (2.1)
Did you have difficulty falling back asleep? [a]	1.92 (0.20)	1.78 (0.27)	1.75 (0.38)	1.86 (0.22)
How much time did you spend awake after falling asleep for the night? (min)	30.6 (36.3)	18.7 (17.7)	24.0 (34.2)	19.0 (20.7)
How many hours did you sleep last night? (h)	7.2 (0.92)	7.3 (0.45)	7.2 (0.60)	6.9 (0.86)
How would you describe your sleep last night (quality)? [b],*	2.71 (0.87)	2.52 (0.65)	2.86 (0.80)	3.10 (0.54)
How easy was it for you to fall asleep last night? [c],**	43.2 (28.5)	38.7 (20.0)	44.7 (28.7)	63.0 (25.4)
How would you evaluate the refreshing quality of sleep? [b]	2.57 (0.87)	2.43 (0.70)	3.14 (0.48)	3.19 (0.47)

Data are means ($\pm$ SD).
[a] Responses represented as yes = 1, no = 2.
[b] Responses represented as excellent = 1, very good = 2, fair = 3, poor = 4.
[c] The 100 mm analog scale with "very easy" at the left (0) and "not at all easy" at the right (100).
* $p \leq 0.1$.
** $p = 0.05$.
*** $p \leq 0.01$ (symptomatic group, incubation vs. active viral periods).

Table 4

Performance measures for asymptomatic and symptomatic groups during the incubation and active viral period

Performance task	Asymptomatic		Symptomatic	
	Incubation	Active viral	Incubation	Active viral
Vigilance reaction time *	683 (254)	661 (261)	629 (239)	751 (252)
DAT tracking deviations	23.0 (8.0)	31.9 (30.2)	18.3 (3.9)	18.3 (4.3)
DAT reaction time	552 (150)	595 (210)	530 (130)	564 (140)
DAT peripheral reaction time	545 (160)	582 (210)	497 (110)	528 (110)

Data are means ($\pm$ SD); DAT = Divided Attention Task; tracking deviations are average CRT pixels from the target; reaction times are in milliseconds.
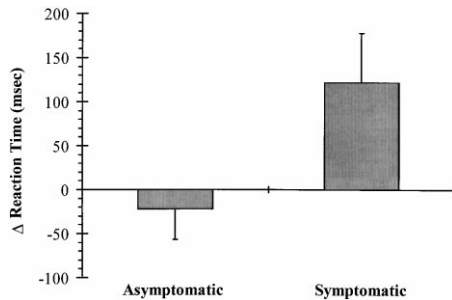* $p < 0.05$ (symptomatic group, incubation vs. active viral period).

Fig. 3. Mean change (±SEM) in reaction time (auditory vigilance) from incubation to active viral periods in asymptomatic and symptomatic groups.

respectively. Results did not achieve statistical significance. In addition, an exploratory analysis of correlations between symptoms and sleep parameters yielded only one significant positive correlation ($r = 0.8$) between MSLT latency and "cough".

3. Discussion

The present study is the first to provide evidence that an experimentally induced variant of the common cold (rhinovirus type 23) significantly disrupts nocturnal sleep in symptomatic individuals. Specifically, total sleep time was reduced an average of 23 min/night and consolidated sleep was reduced by an average of 36 min/night during the active phase of the illness. It should be emphasized that while these reductions would not be considered substantial when experienced on an acute and intermittent basis, a significant sleep debt may accumulate following lengthy bouts of illness. Although no previous data are available regarding polysomnographically recorded sleep during cold illnesses, these results are in accord with previous findings that have demonstrated decreased psychomotor performance in individuals with experimentally induced colds [2,8,10,14,15].

Regarding self-report measures of sleep, symptomatic individuals perceived a decrease in the ease of falling asleep with little change in other parameters. Although items specifically related to ease of falling asleep were not assessed in previous studies, total sleep time has been reported to increase during the active phase of the illness [10]. However, self-reports of sleep parameters must be interpreted with caution as they are often uncorrelated with objective findings and such measures may be unduly affected by the general malaise and fatigue often accompanying even minor illnesses.

The present study replicates and extends previous investigations that have found impairment in psychomotor performance in symptomatic individuals following experimentally induced colds [2,8,14–16]. However, one study has shown that performance impairments can be present in subclinically infected individuals who are not experiencing significant symptoms [15]. This apparent incongruity in findings may be related to differences in task sensitivity as several of the performance measures in the present study were unaffected by the rhinovirus challenge. Specifically, lengthy monotonous tasks (i.e., simple reaction time, auditory vigilance) may be more sensitive to the effects of minor reductions in sleep duration while more complex tasks requiring multiple response modalities and increased cognitive effort may be less sensitive to these effects due to their inherent "activating" nature. That is, certain tasks may themselves be activating and thereby "mask" sleepiness that may otherwise have been detected. In one study, impairment was detected in asymptomatic individuals on a five-choice reaction time task but not on a more complex detection task [15]. Similarly, in the present study, impairments were detected on a minimally complex vigilance task but not on a more complex divided attention task. Although it appears unlikely, it may be argued that an even more sensitive task may have enabled detection of impairments in asymptomatic individuals in the present study. Additional studies using a wider range of cognitive tasks are necessary before more definitive conclusions can be made.

Although viral inoculation had no effect on daytime sleepiness, additional studies are needed to determine if effects would be seen with continued assessment beyond the 5-day post-inoculation period used in the present study. This possibility seems plausible given the decreases in consolidated sleep observed along with findings from previous research indicating that cumulative sleep loss of even a few hours nightly can have detrimental effects on alertness and performance [4,6].

The purpose of this study was to determine the effect of viral infections on performance, sleep, and daytime alertness. While previous findings of performance impairment were replicated, the effects on sleep were modest, and no effect on daytime sleepiness was found. Thus, while lack of sleep cannot be ruled out as a mediator of the performance impairment, it is unlikely given the absence of an effect on daytime sleepiness. The correlation between "cough" and MSLT latency suggests another possible explanation that the symptoms themselves may have inhibited sleep onset on the MSLT. While this is not likely given the lack of consistent relationships between sleep latency on the MSLT and symptomatology, the tendency for symptomatic individuals to report increased nocturnal sleep latencies suggests that this possibility cannot be eliminated. Longer studies that evaluate more severe viral infections may show effects on daytime sleepiness.

As experimentally induced colds produce illness comparable to that of natural colds, the present results show that the common cold can have detrimental effects on sleep and psychomotor performance in symptomatic individuals. These findings have potentially important implications as the annual incidence of the common cold is between three and five per individual [20], the duration of such illnesses can be up to 10–12 days [1], and the mild severity of such

illness does not necessarily prevent one from working or carrying out other critical activities (e.g., driving). Further detailed studies are required to determine the exact duration of sleep and performance impairments and whether such effects are modified by variations in the amount of prior sleep or level of basal sleepiness.

Acknowledgments

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