The Effect of Sleep Fragmentation on Daytime Function

Edward J. Stepanski, Ph.D.

Sleep Disorder Service and Research Center, Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL

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INTRODUCTION

RESEARCHERS SET OUT TO STUDY SLEEP FRAGMENTATION IN AN EFFORT TO INCREASE THE UNDERSTANDING OF BASIC MECHANISMS GOVERNING SLEEP STRUCTURE, as well as to explore a model of the type of sleep abnormalities found in patients with sleep disorders, particularly obstructive sleep apnea (OSA). The goal of the study reprinted here[1] was to establish an operational definition for the level of sleep disruption required to contribute to subsequent daytime sleepiness. Our original intention had been to conduct a study that induced sleep fragmentation in normal sleepers and then evaluate changes in daytime function. However, it was unclear from the literature at the time how much sleep fragmentation was necessary to cause significant changes in the restorative function of the sleep. The best available examples of sleep fragmentation arose from the study of the sleep of patients with OSA. But in these patients, apneas might cause very transient EEG arousals, longer EEG arousals associated with a change in sleep stage, or even awakenings 16 seconds to several minutes in duration. Therefore, our first project studied the relation of six definitions of events that caused sleep fragmentation to subsequent daytime sleepiness in four groups of subjects. It was determined that even the most subtle level of sleep fragmentation, an increase in EEG frequency lasting at least three seconds, in conjunction with increased EMG amplitude, was correlated with increased daytime sleepiness.[1] This definition was similar to the definition of arousals adopted by the ASDA in 1992.[2] The primary difference is that the ASDA definition does not require a change in EMG during non-REM sleep; the EEG change alone is sufficient to score an arousal.

The goal of the present paper is to review the literature on sleep fragmentation since the publication of our 1984 paper. Research aimed at furthering our understanding of the effects of fragmented sleep in humans can be categorized into two general areas: 1) study of the effects of experimentally induced arousals/awakenings in normal sleepers using auditory stimulation, or 2) study of the sleep of patients with sleep disorders that cause sleep fragmentation. Another literature that has emerged concerns the effects of sleep fragmentation on cardiovascular physiology; and this will be reviewed briefly.

Address correspondence to: Edward J. Stepanski, Ph.D., Sleep Disorder Service and Research Center, Rush-Presbyterian-St. Luke's Medical Center, 1653 West Congress Parkway, Chicago, IL 60612; Tel.: (312) 942-5440; Fax: (312) 942-8961; E-mail: estepans@rush.edu

Experimental Sleep Fragmentation in Normal Sleepers

Studies that fragmented sleep in normal sleepers, based on changes in the sleep EEG, and measured some aspect of subsequent waking function are summarized in Table 1. Arousals or awakenings were produced at various rates and on different schedules to vary the intensity of the sleep fragmentation. The assumption underlying sleep fragmentation research is that sleep must be uninterrupted for some minimum period if it is to be restorative. If sleep is interrupted, even by a brief EEG arousal, then the benefit of the period of sleep immediately prior to the arousal is lost. This notion is stated explicitly by Bonnet as the Sleep Continuity Hypothesis to explain the effects of sleep fragmentation on daytime function.[3,4] Once it was clear that fragmented sleep produced daytime sleepiness, many studies of sleep fragmentation produced arousals at various rates to determine the minimum unit of uninterrupted sleep that will contribute to restorative sleep (i.e., reverse the effects of sleepiness). As can be seen in Table 1, arousals were delivered at the rate of once per minute, once per five minutes, once per 10 minutes, etc. in an attempt to answer this question.

Nearly all of these studies of experimental sleep fragmentation found changes in daytime function similar to those found with sleep deprivation. Objective daytime sleepiness was increased following sleep fragmentation, as measured by the MSLT,[6,7,13-16] single nap latencies,[4,5,9-12] and the MWT.[15] Self-reported sleepiness increased as shown by the Stanford Sleepiness Scale[5,9,11,17] and ratings of sleepiness on the Clyde Mood Scale.[9,10,11] The increase in sleepiness was greatest following the one arousal per minute schedule in those studies using that manipulation, and this degree of fragmentation produced sleepiness comparable to total sleep deprivation (on at least some measures) in studies where this comparison was possible.[4,7,8] In one study, arousals at the rate of one per 10 minutes of sleep did not cause any increase in sleepiness when compared to uninterrupted sleep.[7] These results have been used to suggest that segments of sleep must be at least 10 minutes in duration to be restorative.[7,8] However, other studies have failed to find differences in daytime sleepiness associated with different rates or schedules for sleep fragmentation, and the view of the 10-minute requirement for sleep to be restorative remains controversial.[6,16]

Measures of psychomotor performance and cognitive function also demonstrated significant decrements in daytime function following sleep fragmentation. Psychomotor performance and cognitive function were impaired as measured by vigilance testing,[4-6,9-12] simple[3,11] and complex reaction-time,[6] divided attention,[7] Trailmaking,[15] PASAT,[15] Wilkinson's addition test,[5,11] and digit-symbol substitution.[3]

Changes in mood have been detected following sleep fragmentation using the Clyde Mood Scale,[9] the Profile of Mood

Table 1-Studies of experimental sleep fragmentation and daytime impairment in human subjects

Study	Type of Event	Experimental Condition	Subjects	Measure of Daytime Function	Design	Findings
Bonnet (3)	Awakening	1 per min	11 young adults	WA DSST SRT SSS Mood	6 nt protocol: 1-ADAPT 1-BSL 2-FRAG 2-REC	Significant perf decrements after FRAG nts
Bonnet (4)	Awakening	4 conditions: 1) 1 per min 2) 1 per 10 mins 3) 2.5 hrs sleep, then every sleep onset 4) TSD	8 young adults	Perf battery* Single nap latency	1-ADAPT, then 5 nt protocol, repeated x3: 1-BSL 2-FRAG 2-REC	1 per min condition shows impairment equivalent to TSD
Bonnet (5)	Awakening	2 conditions: 1) 1 per 10 mins, and at each onset of SWS 2) 1 per 10 mins, or 1 per 5 mins when not in SWS	12 young adults	Perf battery* Single nap latency SSS	5 nt protocol: 1-ADAPT 1-BSL 2-FRAG 1-REC	Both frag conditions showed significant and equal decreases in performance
Stepanski et al (6)	EEG/EMG arousal	3 conditions: 1) 1 per 5 mins 2) 1 per 10 mins 3) 1 per 5 mins for 4 hrs, then 4 hrs solid sleep	5 young adults	MSLT Auditory vigilance testing, Complex reaction time	3 nt protocol: 1-BSL 2-FRAG	Significant decrease in MSLT after nt 2, no diff in condition
Levine et al (7)	EEG arousal	5 conditions: 1) 1 per min 2) 1 per 3 mins	40 young adults	MSLT	Single 3 hour nap given after night of sleep	1 per min=TSD

		3) 1 per 5 mins 4) no arousals 5) TSD			deprivation	
Downey & Bonnet (8)	Awakening	4 conditions: 1) 1 per min 2) 1 per 10 mins 3) 2.5 hrs solid sleep, then at every SO 4) 64 hrs of TSD	5 young adults	Addition problems upon awakening	5 nt protocol, repeated x4: 1-BSL 2-FRAG 2-REC	FRAG conditions: Perf decrements not predicted by amount of prior SWS
Bonnet (9)	3 levels: Awakening Body turn EEG change	1 per 2 mins	11 young adults	Perf battery* Single nap Mood SSS	1-ADAPT, then 4 nt protocol, repeated x3: 1-BSL, 2-FRAG, 1-REC	All definitions for arousal led to significant daytime impairment
Bonnet (10)	Study #1: Awakening Study #2: Awakening	Study #1: 3 conditions, 1) 10 mins solid sleep, then 20 mins frag (1 per min) 2) 20 mins solid sleep, then 40 mins frag (1 per min) 3) 40 mins solid sleep, then 80 mins frag (1 per min) Study #2: 3 control conditions, 1) 2 mins solid sleep, then 4 FRAG (1 per min)	Study #1: 12 young adults Study #2: 7 young adults	Study #1 & #2: Perf battery* Single nap Mood Study #2: Same as #1	Study #1 & #2: 5 nt protocol: 1-ADAPT 1-BSL 2-FRAG 1-REC	Greatest impairment seen in 1 per 2 min cond; greater decrements seen with decreasing length of segments of uninterrupted sleep

		2) 20 mins solid sleep, followed by single awakening 3) 40 mins solid sleep, followed by single awakening				
Bonnet (11)	Awakening	10 mins solid sleep, then 20 mins FRAG (1 per min)	12 young (18-28 yrs) 12 older (55-70 yrs)	Perf battery* Single nap Mood SSS	5 nt protocol: 1-ADAPT, 1-BSL, 2-FRAG, 1-REC	Older subjects were less affected by FRAG
Bonnet et al (12)	EEG arousal	Tones presented after spindles, K-complexes, and REMs	12 young adults	WA Visual vigilance task, POMS Single nap	3 nt protocol: 1-BSL 1-FRAG 1-REC	Significant increase in sleepiness and daytime impairment; and sig. increase in metabolism after FRAG
Roehrs et al (13)	EEG arousal	1 per 2 mins	36 young adults	MSLT Divided attention task	3 nt protocol: 1-BSL 2-FRAG	Significant decrease in MSLT score following both FRAG nts
Phillip et al (14)	EEG arousal	1 per min	8 young adults	MSLT Fingertapping DSST Benton WA	1-BSL 1-FRAG not consecutive nts; counter-balanced	Significant increase in MSLT score; no change in performance
Martin et al (15)	EEG arousal	1 per 2 mins	16 young adults	MSLT MWT Cognitive function** Mood	1-ADAPT 1-BSL 1-ADAPT 1-FRAG	Increased sleepiness on MWT and MSLT. Decreased cognitive function. Decreased mood.
Martin et al (16)	EEG arousal	2 conditions: 1) 1 per 90 secs	16 young adults	MSLT MWT	2 nt protocol, repeated twice:	Both conditions led to increases in sleepiness on

		2) 1 per 30 secs for 30 mins, then solid sleep for 1 hr; repeat this cycle every 90 mins		SSS Cognitive function** Mood	1-ADAPT 1-FRAG	MSLT and MWT, as well as decreased cognitive function
Kingshott et al (17)	EEG arousal	1 per 2 mins	8 young adults	MWT Mood SSS Cognitive function** Evoked potentials	1-ADAPT 1-FRAG 1-ADAPT 1-BSL 2 nt sequences counterbalanced	No change in MWT or P300 latency with FRAG. Decreased P300 amplitude. Increased sleepiness on SSS. Decreased mood with FRAG.

* Battery: Wilkinson's Addition Test, Wilkinson's Vigilance Test, simple reaction time

** Trailmaking A & B, Paced Auditory Serial Addition Test, DSST, Block Design, Steer Clear, Rapid Visual Information Processing

WA: Wilkinson's Addition Test; DSST: Digit Symbol Substitution; POMS: Profile of Mood States; SSS: Stanford Sleepiness Scale; SRT: simple reaction time

States,[12] and the UWIST mood adjective checklist.[15,17] Typical changes in mood following sleep fragmentation are in the direction of increased negative mood characteristics and include subjects feeling less friendly, more depressed, less hedonic, and more tense.

One study evaluated evoked potentials following sleep fragmentation, with the hypothesis that the P300 latencies would be delayed following sleep fragmentation.[17] Although P300 latencies were unchanged, the P300 amplitudes were decreased at six sites. These results offer further evidence of decreased attention following one night of sleep fragmentation.

General Methodological Issues

The methodology used in studies of experimental sleep fragmentation has many similarities, as well as important differences (see Table 1). One feature of sleep fragmentation research that has been used in all studies shown in Table 1 is the use of acoustic stimulation to cause the arousals/awakenings. Tones are presented through headphones to a sleeping subject, beginning at about 40 db, and increased by 5-10 db until an arousal/awakening occurs. In many instances, this approach with ascending tones requires that multiple tones be presented before an arousal occurs, and represents a very demanding protocol for research staff.

Arousal Definitions

One key methodological difference affecting the results of these studies is in the criteria used to define the event that is provoked to produce sleep fragmentation. Different operational definitions for arousal/awakening were used in these early studies since a standard definition for an EEG arousal wasn't adopted by the American Sleep Disorders Association until 1992.[2] Bonnet conducted many of the studies on the effects of experimental sleep fragmentation in healthy young adults.[3-5,8-12] In all but one of those studies, subjects were awakened in order to produce sleep fragmentation. In several studies subjects were required to make a behavioral response with each awakening. An awakening provides a standardized event leading to easily recognized breaks in sleep continuity. However, precipitating a full awakening will cause more changes in sleep architecture as compared to a transient EEG arousal. Forced awakenings can also lead to an accumulation of wakefulness over the course of the night as well as greater increases in stage one sleep, and decreased slow-wave and REM sleep. This approach is useful in studies investigating the structure of sleep as it relates to daytime sleepiness, but is less analogous to the abnormalities seen in patients with sleep disorders.

Researchers interested in developing a model of sleep fragmentation aimed at understanding the sleep of patients with OSA were more likely to use EEG arousals, instead of full awakenings, since this is similar to what is seen in the sleep EEGs of OSA patients.[6,7,13-17] These experimental studies, as well as work with patient populations, led the ASDA Task Force to define an EEG arousal as an increase in EEG frequency lasting for at least three seconds.[2] Events in REM sleep also require an increase in EMG amplitude in conjunction with the change in the EEG to be scored as an arousal. This definition has since been widely used in clinical populations, as well as in experimental work, to provide a measure of the degree of sleep fragmentation.

Sleep fragmentation using definitions of arousal that do not include EEG changes has also been shown to produce daytime sleepiness.[18] Presentation of tones sufficient to cause transient increases in blood pressure or heart rate, but not an EEG arousal, caused a significant increase in daytime sleepiness as measured by an MSLT and MWT. Other investigators have shown that tones sufficient to increase blood pressure are also accompanied by increases in EEG frequency that could be detected with spectral analysis, but that did not meet criteria for EEG arousal.[19] There are also several studies that looked at arousals defined by changes in autonomic function that have been performed in patients with OSA, (these are reviewed below). This line of research demonstrates that relying on visual scoring of EEG arousals may miss events that are capable of impacting daytime function. However, it has yet to be shown that measurement of these events provides more robust prediction of daytime sleepiness than is obtained with traditional measures of EEG arousals.

Reliability of Arousal Scoring

The section above considers the validity of various definitions of arousal. That is, what changes in the EEG or EMG are predictive of subsequent daytime impairment, and therefore of practical relevance? However, the arousal definition also impacts the reliability of visual scoring of those events. As the definition of an arousal becomes increasingly subtle, the reliability of visual scoring of that event decreases. For example, it has been suggested that even EEG arousals shorter than the standard three-second minimum may contribute to daytime sleepiness.[20] However, it has been shown that reliability for scoring events shorter than three seconds is poor compared to longer events.[21] The intraclass correlation for spontaneous arousals three seconds or longer is .84, as compared to .37 for arousals 1.5-3 seconds. Raters understandably have a much more difficult time agreeing about identification of arousal events when the duration is less than three seconds. Another example of reliability being affected by the arousal definition concerns inclusion of increased EMG amplitude in addition to the EEG criteria. The reliability coefficients reported in our original study were high, but our most subtle arousal definition consisted of both increased EEG frequency, and an increase in EMG amplitude (1). Drinnan et al suggest that inclusion of EMG criteria increases reliability of scored arousals.[22] They found moderate reliability for scoring of arousals according to the ASDA definition (kappa=.47). However, since reliability was higher for arousals scored in REM sleep (kappa=.52), compared to light non-REM (kappa=.28), and arousals in REM sleep require an increase in EMG, they concluded that inclusion of EMG improves reliability across raters. Smurra et al. scored the studies of 20 patients with OSA using standard ASDA definition, and a definition that included an EMG increase.[23] They found similar reliability between these definitions for scoring arousals, and found a correlation of .98 between the two scores. However, they did note that scoring time was significantly shorter using the definition that included EMG criteria, suggesting that raters found this to be the easier task. It is likely that the lower reliability reported by Drinnan et al. is, in part, related to a specific aspect of the methodology used in that study.[22] They computed agreement across raters from 14 different sleep centers, rather than comparing raters from within a sin-

gle center. Reliability for any sleep parameter will be less when raters from different institutions are compared due to local scoring biases and procedures.

Confounding Factors

A recent paper reviewed and re-analyzed much of the data described above, and proposed a different interpretation.[24] Those authors suggest that the increased daytime sleepiness following the nights of sleep fragmentation is due to changes in total sleep time (TST) and/or changes in sleep architecture (e.g., increased stage one sleep, decreased slow-wave sleep, decreased REM sleep). They point out that stage one sleep may not be as restorative as other sleep stages, and that an increase in stage one sleep, in conjunction with decreased TST, leads to a significant sleep debt. Therefore, the increased daytime sleepiness following sleep fragmentation can be explained as a consequence of partial sleep deprivation.

The possibility that daytime sleepiness was caused by sleep loss or changes in sleep architecture was considered by the investigators who performed the original sleep fragmentation studies, and this is reflected in the design and analysis of these studies.[6,8-10,13] Certainly it is the case that when sleep fragmentation is achieved through awakenings, TST may be decreased by an hour or more.[3,4] Also, there may be markedly increased stage one sleep, and decreased slow-wave and REM sleep. Since increased rates of sleep fragmentation (e.g., one awakening per minute) lead to greater changes in sleep architecture, the effects of these changes in TST and sleep architecture are often confounded with the effects of sleep fragmentation. It is generally true that the higher the number of arousals, the greater the amount of stage one sleep. The high intercorrelations between the number of arousals and percentage of stage one sleep are such that the percentage stage one sleep can be used as an estimate of the degree of sleep fragmentation.

However, studies that use transient arousals generally do not cause decreased TST, and have a smaller impact on sleep stage changes.[6,18] It has been shown that even when there are no significant changes in sleep stage percentages or TST, sleep fragmentation will cause significant increases in daytime sleepiness.[6] Also, when the fragmentation is caused in a way to deliberately reduce SWS vs. leaving SWS intact, subsequent sleepiness is the same.[8] Finally, several studies have shown that causing arousals at the rate of one per minute leads to daytime impairment similar to total sleep deprivation, even though the subject has clearly accumulated hours of non-stage one sleep.[4,8] This point is also illustrated by the sleep and daytime sleepiness of patients with sleep-fragmenting disorders (presented below). In summary, there is sufficient evidence that fragmented sleep does not have the same restorative value as uninterrupted sleep.

Sleep Fragmentation and Daytime Sleepiness in Patients with Sleep Disorders

A major impetus for the study of the effects of sleep fragmentation arose from an attempt to understand clinical sleep disorders. The observation that patients with sleep-disordered breathing would experience severe daytime sleepiness, even after obtaining 8-10 hours of total sleep time, prompted the hypothesis that it was the disruption of sleep that contributed to non-restorative sleep. The competing hypothesis was that hypoxemia was to blame for daytime sleepiness. Differentiating between these hypotheses has been difficult because of the high correlation between sleep fragmentation and hypoxemia in patients with OSA. EEG arousals and episodes of oxygen desaturation are both consequences of obstructive events, and tend to occur with the same frequency, and even contiguously.

Various approaches have been used to evaluate the role of sleep fragmentation vs. hypoxemia in producing daytime sleepiness in patients with OSA. Roehrs et al.[25] performed multiple regression using arousal index and measures of hypoxemia as predictors of MSLT score in 466 patients with OSA. The arousal index was the single best predictor of MSLT score (r=.36), and hypoxemia did not add significantly to the explained variance once arousal index was in the regression model.

A study by Colt et al.[26] attempted to separate out the causes of sleepiness in OSA patients with an experimental protocol. They studied seven patients with OSA under three conditions: at baseline (fragmentation and hypoxemia), on optimal CPAP pressure (no fragmentation or hypoxemia), and on CPAP with episodic exposure to 100% nitrogen (no fragmentation, regular episodes of hypoxemia). They found that in both experimental conditions, sleepiness was improved compared to baseline. Therefore, they concluded that hypoxemia, by itself, is not a cause of daytime sleepiness.

Arousal Definitions in OSA Patients

Various definitions for arousals in patients with OSA have been studied. Interest in this has arisen because of recognition that the arousal index often has only modest correlation with measures of daytime sleepiness in these patients.[27] Martin et al. scored the studies of 63 patients with OSA using four definitions of arousals and correlated the arousal indices with an MSLT.[20] The types of arousals were: 1) standard ASDA arousals, 2) ASDA definition, but shortened to 1.5 second as the minimum duration, 3) increased EEG frequency but with increased EMG amplitude, and 4) full awakening according to standard Rechtshaffen and Kales criteria.[28] One interesting result was that it was found that more apneas/hypopneas terminated with the short (1.5 sec) arousals than with the traditional >3-second arousals. However, all three definitions of micro-arousals were equally correlated with daytime sleepiness. So there was no incremental benefit to scoring the shorter arousals with respect to predicting severity of daytime sleepiness.

A new direction in the definition of arousals concerns use of measures of autonomic activity rather than the traditional EEG measures.[19] Such arousals have been called "sub-cortical" arousals. This has led to the suggestion that even more subtle events than are identified with traditional EEG definitions may contribute to sleep fragmentation. Rees et al.[29] note that blood pressure increases occurred at the end of every apnea, while EEG arousal only occurred following 72% of the apneic episodes. This finding demonstrates that autonomic arousals occur more frequently than the traditionally scored EEG arousals, but the clinical significance of the autonomic arousals is unknown. As described above, induction of autonomic arousals in normal sleepers is followed by a modest increase in daytime sleepiness (8.0 vs. 6.2 mins on MSLT; ref #18). However, this effect may not be noticeable in the context of OSA, given the massive sleep

fragmentation present.

Pitson and Stradling[30] correlated EEG arousals and autonomic arousals with daytime sleepiness in patients undergoing polysomnography for suspected OSA. They found that changes in blood pressure predicted sleepiness better than heart rate changes, suggesting that not all autonomic changes are equivalent in their effect on the restorative value of sleep. Also, the blood pressure changes were no better, but no worse, than EEG arousals in predicting daytime sleepiness. One shortcoming to this study is that the measure of sleepiness used was a subjective measure, the Epworth Sleepiness Scale. Since an objective measure like the MSLT provides a more direct reflection of physiological state, one would expect that the MSLT would allow for more precise insight into mechanisms that produce physiological sleepiness.

Sforza et al. examined the studies of 10 patients with untreated RLS/PLMD.[31] They found that 99% of PLMS were associated with a shortened R-R interval, but only 34% were associated with a standard EEG arousal. These data fit with other studies that find a hierarchy to arousal phenomenon.[29] Changes in autonomic measures can occur without EEG changes; however, when changes in EEG are seen, there are always autonomic changes.

An additional innovation in the assessment of sleep fragmentation is to conduct computerized analysis of the EEG signal, rather than to rely on visual scoring of EEG changes. Bennett et al.[32] scored EEG arousals according to standard criteria and using a 1.5 second duration criterion, as well as autonomic arousals, and movement arousals in 41 patients ranging from non-snorers to severe OSA patients. Additionally, they analyzed the EEG signal with autoregressive modeling to yield two measures of sleep fragmentation. All measures of sleep fragmentation correlated significantly with the ESS score at baseline, as well as with the change in ESS once the patients were treated with nasal CPAP. So, while the autonomic measure and the computerized EEG measures showed a high correlation with sleepiness, they did not clearly add new information to that obtained with traditional measures of daytime sleepiness. Once again, a potential weakness of this study is reliance on the ESS as the measure of sleepiness.

One final innovative approach to the measurement of sleep fragmentation is to measure the number of episodes of sleep according to the duration of the inter-arousal intervals. That is, according to Bonnet's Sleep Continuity Hypothesis, it is not the arousal per se that causes sleepiness, but the fact that sleep has been interfered with in a way that interrupts the restorative process. Therefore, it is not the number of arousals that matter most; it is the degree to which episodes of consolidated sleep are not long enough that leads to increased sleepiness. The studies with experimental sleep fragmentation allow for precise measurement of the periodicity of the arousals, and the intervals of consolidated sleep are carefully controlled (see review above and Table 1). These studies do show that arousals at the rate of one per minute lead to greater sleepiness than one per 10 minutes. However, in studies of patients with OSA, the intervals between arousals will vary. In these patients, the total number of arousals (or arousal index) may not be the best measure of sleepiness. Instead, quantifying the number of intervals of restorative sleep may be better. Aldrich[33] tested this possibility by measuring the number of episodes of sleep that did not include stage one sleep or wakefulness lasting a minimum of two minutes, three minutes, five minutes, 10 minutes and 20 minutes in 123 patients with OSA. The number of intervals lasting two minutes or longer correlated better than intervals five minutes and longer with sleepiness, suggesting that even episodes of sleep two minutes in duration have the ability to provide restoration. Obviously this approach is labor intensive and only feasible with online analysis of sleep.

Cardiovascular Consequences of Arousals

Transient EEG arousals have been shown to be associated with a number of other physiological events that are likely to have clinical significance, especially in the context of OSA. In particular, the surge in sympathetic activity associated with arousals from sleep impact the cardiovascular system, in addition to the central nervous system effects described previously. It is beyond the scope of this paper to review this literature in detail, but a brief overview will be provided. This line of research begins with a classic study by Phillipson et al.[34] showing that experimental sleep fragmentation in dogs produces daytime sleepiness. Additionally, they found that sleep fragmentation produced an attenuated response to hypercapnia and hypoxia during sleep. As an aside, this study is also noteworthy in that it first uses the term 'sleep fragmentation' consistent with its currently accepted meaning. This canine model continues to yield important information about the effects of arousal from sleep on blood pressure[35] and ventilation.[36]

Investigators have also identified physiological consequences of sleep fragmentation in humans. In non-apneic subjects, sleep fragmentation has been shown to increase upper-airway collapsibility,[37] and to increase waking diastolic blood pressure.[38] Studies have shown that the cause of the sharp increase in arterial blood pressure that occurs with resolution of obstructive respiratory events during sleep is due to the arousal event, as opposed to hypoxemia.[19,39] It has also been suggested that the sleep fragmentation associated with primary snoring may cause hypertension.[40]

SUMMARY

It is clear from this literature that fragmented sleep is less restorative than consolidated sleep, and leads to sleepiness-related daytime impairment. The optimal approach to the quantification of sleep fragmentation continues to be debated. Modest and erratic correlations between measures of sleepiness and traditional measures of EEG arousals have pushed investigators to try and find more sensitive measures of sleep fragmentation. Simply correlating various measures of sleep fragmentation with a measure of sleepiness has significant limitations. Since sleep fragmentation is not the only factor affecting daytime sleepiness, these correlations can be misleading. For example, a subject with severely fragmented sleep will show elevated sleepiness during the day. However, the overall correlation may be reduced because lack of fragmented sleep does not guarantee that the level of sleepiness will be low. Multivariate statistical modeling is needed to account for sources of variance simultaneously in the prediction of daytime sleepiness. In this way it may be possible to identify the optimal definition of sleep fragmentation. More studies are needed that evaluate "sub-cortical" arousals, EEG arousals, and daytime function simultaneously. Ideally, clarification of these measurement issues will lead to an improved under-

standing of sleep structure and the mechanism through which sleep fragmentation impacts daytime function.

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