

# Individual Differences in Adult Human Sleep and Wakefulness: Leitmotif for a Research Agenda

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**Abstract:** This paper reviews the literature on interindividual variability in human sleep parameters, sleepiness, responses to sleep deprivation, and manifestations of sleep disorders. Variability among individuals in sleep/wake biology and behavior is pervasive. The magnitude of such individual differences is often considerable and comparable to the effect sizes of many experimental and clinical interventions. Evidence is accumulating that certain aspects of sleep/wake-related variability—such as sleep duration, daytime sleepiness, and vulnerability to the effects of sleep loss—involve trait characteristics in healthy populations and among sleep-disordered patients. Establishing the trait-specific nature of variability in sleep/wake parameters is a prerequisite for elucidating the corresponding neurophysiologic and/or genetic mechanisms. At present, it remains largely unknown what underlies or predicts sleep/wake-related traits, what relationships these traits may have to each other, and what

functional significance may be associated with specific traits. Scientific studies addressing these issues are warranted, as understanding the basis of trait variability may yield new insights into sleep/wake regulation and sleep pathology. Understanding individual differences in sleep and wakefulness may also have provocative but important implications for health economics and clinical care, as well as for safety, productivity, and general well-being. This paper gives suggestions for a research agenda focusing on individual differences in sleep research and sleep medicine.

**Keywords:** Individual differences, trait variability, genetics, sleep behavior, sleep architecture, sleepiness, waking neurobehavioral functions, sleep deprivation, differential vulnerability, sleep disorders, adult humans  
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## INTRODUCTION

INDICATIONS OF VARIABILITY AMONG INDIVIDUALS, COMMONLY REFERRED TO AS (INTER)INDIVIDUAL DIFFERENCES OR (INTER)INDIVIDUAL VARIABILITY, can be found throughout the literature on sleep research. Such variability results partly from stochastic and/or systematic error—due to variations in state, as well as measurement error and other sources of noise. However, evidence is accumulating for the existence of systematic individual differences in sleep/wake-related variables. Thus far, this systematic variability has been largely overlooked in sleep research and data-analysis approaches. The present paper reviews current knowledge about individual variability in human sleep parameters, sleepiness and responses to sleep deprivation, and manifestations of sleep disorders. The focus is primarily on young adults, as developmental and age-related sources of individual variability\* have recently been reviewed elsewhere.<sup>1-3</sup> While reviewing the available literature, suggestions are pointed out here for a research agenda focusing on individual differences in adults' sleep and wakefulness.

Even though individual differences are considerable in a wide

range of sleep/wake-related variables, as observed throughout the sleep field, not all variability among individuals is stable. For instance, in a field experiment of sleep behavior, variability in observed sleep durations could reflect not only systematic individual differences in biological sleep need, but also unsystematic differences in social or professional demands to stay awake. Environmental factors, measurement error, and various other sources of noise may produce individual differences; however, such variation is state specific and would not be replicable when repeating the investigation (if not also carefully recreating the state-specific circumstances). Studies interested in stable individual differences should focus on replicable (ie, systematic) variability that is robust to variations in state-specific circumstances (eg, sleep history, experimental demand characteristics). If both replicability and robustness can be shown, then the individual variability is referred to as a "trait."

Demonstrating systematic individual differences in a variable of interest requires that there is both large variation between subjects as well as comparatively little variation within subjects upon repeated measurement. Accordingly, individual differences are typically investigated in terms of statistical variance and correlation (see Appendix). Repeated measurements within individuals (or, in the case of twin studies, within monozygotic twin pairs) are critical to establish systematic individual variability. Studies of replicability (eg, validation studies) build on the same principles, even though they capitalize on small variability within subjects rather than large variability between subjects. Evidence of replicability or heritability implies systematic individual variability (see Appendix). For this reason, replicability and heritability studies are included in this review, along with studies focusing on individual differences directly.

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\* While aging is actually a source of intraindividual changes rather than interindividual differences, it becomes a factor of individual variability when subjects of different ages (or, rather, different states of development) are considered.

In the next section, the literature on individual differences in normal sleep is reviewed. The subsequent two sections deal with individual differences resulting from sleep deprivation and individual variations observed in sleep medicine. In the last section, a number of implications of individual variability in sleep and wakefulness are considered, and suggestions for an overall research agenda are provided. Methodologic issues are addressed in the Appendix.

## SLEEP IN HEALTHY ADULTS

Individual differences in the sleep of healthy adults have been investigated for several decades, with relatively coherent bodies of research devoted to sleep duration and sleep timing. Less is known about systematic individual differences in sleep architecture, while individual variability in sleep quality has hardly been studied at all.

### Sleep Duration

When considering normal nighttime sleep, perhaps the most easily observed differences among individuals pertain to sleep timing and sleep duration.<sup>4</sup> In the 1998 to 2002 annual “Sleep in America” polls, the National Sleep Foundation found that among adults (aged 18 years and older, 50% women) in the United States, the average self-reported sleep duration was 6.9 to 7.0 hours on weekdays and 7.5 to 7.8 hours on weekends. There was a wide range of sleep durations—12% to 15% reported sleeping less than 6 hours per day on weekdays and 7% to 10% did so on weekends.<sup>5</sup> In a retrospective self-report study of more than a million probands (aged 30–102 years),<sup>6</sup> sleep duration was distributed approximately normally, with 52.4% of subjects reporting a sleep duration of less than 7.5 hours. In this sample, 19.7% of subjects slept less than 6.5 hours, and 4.0% reported sleeping less than 5.5 hours per night. On the other hand, 9.2% of probands slept 8.5 hours or more, and 3.3% reported sleeping 9.5 hours or more per night. There were only very small differences in sleep duration between men and women in this study. It is not known to what extent these self-reported sleep durations accurately reflected physiologic sleep obtained.

Twin studies have indicated self-reported sleep duration to reflect a heritable trait.<sup>7–9</sup> However, heritability has not been confirmed with polysomnography (PSG).<sup>10</sup> This is important because, in addition to physiologic sleep drive, self-reported sleep duration may be a function of lifestyle (eg, waking up early or staying up late for work despite increased sleepiness), social desirability (eg, wanting to be known as a person who needs less sleep than others), and error in subjective estimates of physiologic sleep. Therefore, ascertaining whether individual differences in objectively measured sleep duration also reflect a trait should be a priority in future research.

Despite the absence of evidence for trait variability in objectively measured sleep duration, “short sleepers” and “long sleepers” have been a topic of research since the 1970s. Early studies investigated personality differences<sup>†</sup> as potential correlates of sleep duration.<sup>11–14</sup> However, the evidence for psychological differences between short sleepers and long sleepers has remained limited and inconclusive.<sup>12–16</sup> More biologically oriented studies have investigated short and long sleepers in terms of sleep physiology and circadian rhythms.<sup>11,17–21</sup> It has been reported that

short sleepers have reduced levels of stage 2 and rapid eye movement (REM) sleep, but similar amounts of slow-wave sleep compared to long sleepers,<sup>11,17</sup> supporting a claim that short and long sleepers do not differ in (non-REM) sleep homeostasis.<sup>22,23</sup>

The most extensive investigations of physiologic mechanisms underlying short and long habitual sleep were undertaken by Aeschbach and colleagues.<sup>21–23</sup> They first documented that delta (ie, slow-wave) activity in the non-REM sleep electroencephalogram (EEG) following a 24-hour extension of wakefulness was more enhanced in long sleepers (defined by them as having a habitual sleep duration greater than 9 hours) than in short sleepers (defined by a habitual sleep duration less than 6 hours).<sup>22</sup> They then showed that theta activity in the waking EEG during 40 hours of wakefulness under constant routine was enhanced in the short sleepers compared to the long sleepers.<sup>23</sup> To the extent that delta activity in the non-REM sleep EEG and theta activity in the waking EEG may be markers of a common underlying sleep homeostatic process,<sup>24</sup> these results could be interpreted<sup>‡</sup> as evidence that short sleepers maintain and tolerate a higher homeostatic sleep pressure during wakefulness than long sleepers.<sup>23</sup>

In a further study,<sup>21</sup> it was found that the nocturnal intervals of melatonin, cortisol, and core body temperature—traditional markers of circadian rhythmicity—were longer in long sleepers than in short sleepers. Assuming that the criteria used to define the nocturnal interval in these variables are biologically meaningful (which remains to be determined), this observation indicates that individual differences in the program of the biological clock may underlie individual variability in habitual sleep duration. The longer sleep duration in the long sleepers was mainly associated with a delayed offset (rather than an advanced onset) of “biological night.” Taken together with the evidence for individual variability in tolerance for homeostatic pressure, this finding suggested that the differences between long and short sleepers in wake-up time would be related to differences in the timing of a circadian signal, whereas the differences in bedtime would be related to individual differences in tolerance for sleep drive.<sup>21</sup> This raises the interesting possibility that there might be at least 4 distinct “extreme” phenotypes: short sleepers who fall asleep early, short sleepers who fall asleep late, long sleepers who fall asleep early, and long sleepers who fall asleep late.

In epidemiologic studies, both relatively long and relatively short sleepers (ie, individuals who reported sleeping significantly more or less than approximately 7 hours per day) were found to have increased risk of mortality.<sup>6,25–27</sup> Such findings would suggest that individual differences in sleep duration may mediate morbidity and mortality, but it should be noted that sleep durations in these studies were based on self-report data. Thus, physiologic sleep amounts (as well as night-to-night variability thereof) were not known. Moreover, causality in these studies remained unproven. If a causal relationship can be confirmed, though, then understanding individual differences in sleep duration may have important health implications.

<sup>†</sup> When mentioned in a psychological context, the term “individual differences” is often used as a synonym for personality differences.

<sup>‡</sup> This interpretation is critically dependent on the assumption that the kinetics of the homeostatic pressure for sleep do not differ between long and short sleepers. No statistically significant differences in the time constants for build-up and dissipation of homeostatic pressure were found between long sleepers and short sleepers.<sup>22,23</sup> This finding is not conclusive, however—there may have been little statistical power in the comparisons between the 2 groups, as individual variability in estimated time constants was not properly accounted for (see Appendix).

## Research Needs

- Establish whether individual differences in ad libitum sleep duration, assessed by means of PSG, reflect trait variability
- Verify the hypothesis that the existence of short and long sleepers results from individual differences in tolerance for homeostatic pressure and duration of the biological night
- Examine if there is a causal relationship between objectively measured habitual sleep duration and risk of mortality

## Sleep Timing

The issue of individual variability in sleep timing has been studied mainly in the context of morningness/eveningness (or “chronotype”), which refers to the variation found among people in preferred times for waking activities and sleep (ie, circadian phase preference). The literature on morningness/eveningness has been reviewed elsewhere.<sup>28,29</sup>

Using a constant routine experiment, Kerkhof and Van Dongen<sup>30</sup> demonstrated that morningness/eveningness is associated with individual differences in circadian phase position. The timing of circadian rhythmicity was approximately 2 hours earlier in extreme morning types than in extreme evening types. In a repeated constant-routine study,<sup>31</sup> circadian phase position<sup>31</sup> and circadian amplitude<sup>32</sup> were found to be stable within individuals and robust to seasonal changes, suggesting that individual differences in circadian rhythmicity represent a trait. Recent experimental data have indicated that small but potentially influential differences in the intrinsic period of the circadian pacemaker<sup>33</sup> are correlated with systematic individual differences in circadian phase,<sup>34</sup> but, to date, no study has been reported with a sufficiently large spread in these variables to allow interpretation of the correlation with confidence (see Appendix).

Twin studies of morningness/eveningness questionnaire scores,<sup>35</sup> sleep timing,<sup>8,9</sup> and the circadian rhythm of cortisol<sup>36</sup> have suggested that circadian phase preference is genetically determined. A polymorphism in the human *Clock* gene has been reported to be associated with circadian phase preference,<sup>37</sup> but this finding could not be replicated.<sup>38</sup> Another polymorphism, in the human circadian clock gene *Per3*, has recently been identified as a potential genetic marker for morningness/eveningness.<sup>39</sup> It has not been assessed whether the human circadian clock gene *Per2*, which is associated with familial advanced sleep phase syndrome,<sup>40</sup> may also exhibit a polymorphism related to morningness/eveningness.

Like nocturnal sleep, daytime napping behavior exhibits systematic individual variability.<sup>41-43</sup> Some societies favor napping behavior by way of the siesta.<sup>44</sup> On the other hand, some individuals avoid napping because of susceptibility to sleep inertia—the cognitive performance impairment, grogginess, and pressure to return to sleep immediately after awakening.<sup>45</sup> Genetic factors may play a role, as suggested by greater concordance of napping behavior in monozygotic twin pairs than in dizygotic twin pairs.<sup>8</sup> Nevertheless, to what extent individual differences in napping behavior reflect a trait remains uncertain because social, occupational, and neurophysiologic constraints on napping produce a convoluted picture. Laboratory studies could reveal if napping behavior is mediated by individual differences in sleep regulatory mechanisms.

## Research Needs

- Assess the correlation between differences in the intrinsic period of the circadian pacemaker and differences in the circadian phase position in extreme morning types and evening types
- Expand the search for genes underlying trait individual differences in circadian rhythmicity (amplitude, phase position, intrinsic period, and entrainment properties)
- Establish if endogenous differences in ad libitum napping behavior reflect a trait
- Examine the role of sleep regulatory mechanisms as mediators of individual differences in napping behavior

## Sleep Quality

Self-described normal sleepers show individual variability in perceived sleep quality, with evidence of moderate heritability.<sup>7-9,46</sup> Healthy subjects with high levels of lifestyle regularity have been found to report relatively good sleep quality,<sup>47</sup> which may be attributable to greater synchrony of lifestyle with the circadian modulation of sleep propensity.<sup>48</sup> Determining the social, behavioral, and neurophysiologic factors relevant for sleep quality is important, as self-reported sleep quality is associated with self-reported general well-being.<sup>49</sup> To what extent self evaluations of sleep quality also reflect physiologic sleep parameters is uncertain, however, as it is not clear what quantitatively measurable properties of sleep correspond with self-reported sleep quality. It has been suggested that depth of sleep and sleep continuity may be markers of sleep quality,<sup>50</sup> but further research is needed to establish whether individual differences in those physiologic parameters reliably capture individual differences in self-reported sleep quality and vice versa.

## Research Needs

- Assess the physiologic correlates of individual differences in subjective sleep quality
- Establish if individual differences in objectively measured sleep quality reflect a trait

## Sleep Architecture

Various studies have focused on differences among subjects in PSG features of sleep and on the stability of those differences.<sup>51-56</sup> Collectively, these studies have provided evidence for systematic individual variability—typically not normally distributed among subjects<sup>55</sup>—for REM sleep, REM density, non-REM sleep, slow-wave sleep,<sup>8</sup> sleep spindles, and microarousals. A recent study of ad libitum sleep during 72 hours of constant darkness<sup>57</sup> illustrated the magnitude of individual variability in PSG-determined sleep. Sleep variables for the last 24 hours of constant darkness, expressed as mean  $\pm$  standard deviation in 9 young adults, were 606  $\pm$  89 minutes for total sleep time, 58  $\pm$  30 minutes for stage 1 sleep, 322  $\pm$  70 minutes for stage 2 sleep, 116  $\pm$  64 minutes for slow-wave sleep, and 109  $\pm$  41 minutes for REM sleep. The standard deviations in this particular study directly reflected individual differences, which were clearly sub-

§ Individual variability in the expression of EEG slow waves during sleep has been experienced as problematic when scoring PSG records by standardized criteria.<sup>225</sup> This has led to the common practice of combining stages 3 and 4 as slow-wave sleep and, occasionally, to dropping the amplitude requirement for scoring these stages (particularly in older individuals, who consistently show reduced amplitude of slow waves).



stantial in magnitude.

Systematic individual differences in sleep physiology appear to be considerable relative to various state-related differences. For instance, there is evidence for “use-dependent” effects on aspects of human sleep physiology<sup>58,59</sup> (ie, waking activities influencing subsequent sleep architecture), but these effects appear to be small relative to natural individual variability.<sup>58</sup> In a study of road traffic noise on PSG-determined sleep variables, it was found that idiosyncratic individual differences, together with age differences, had greater overall effects on sleep structure than did experimentally controlled differences in the noise level.<sup>60</sup> Such findings suggest that individual differences in sleep physiology are robust and may, therefore, reflect trait variability.

The trait aspect of PSG-determined sleep architecture has been investigated in a number of twin studies.<sup>10,61-64</sup> The sample sizes of these studies were small, but they consistently showed greater resemblance of sleep architecture between monozygotic twins than between dizygotic twins. Such heritability studies provide evidence that individual differences in sleep structure have a genetic origin, although the specific human genes have yet to be identified. The most extensive PSG research involving twins has been done by Linkowski and coworkers, who conducted a series of studies involving a total of 45 monozygotic and 46 dizygotic twin pairs.<sup>10,63,64</sup> Genetic effects for REM sleep were found to be inconclusive. However, heritability for slow-wave sleep ranged from 50% to 90% and exceeded the degree of genetic influence found for most human traits.

To what extent individual differences in sleep parameters such as EEG slow waves may be due to functionally irrelevant factors (eg, skull characteristics, electrode impedance) has not been firmly established. Nevertheless, clues regarding the functional significance of natural individual differences in sleep architecture may be sought in correlates of these differences. Slow-wave sleep and growth hormone secretion are associated, and this association extends to individual differences.<sup>65</sup> Results have differed regarding a possible correlation in humans between body size and REM sleep.<sup>66,67</sup> Personality traits do not seem to predict sleep structure.<sup>68</sup>

The fact that considerable individual differences in sleep architecture have not yet been associated with clearly interpretable correlates in human neurophysiology and behavior presents a critical challenge for hypotheses about the functions of sleep. In this regard, it is noteworthy that the number of orthogonal components of individual variability (ie, facets of sleep that may vary independently among subjects) is limited by the total sleep time available for the expression of the different sleep stages.<sup>55</sup> Assessing which components of sleep can vary independently may be a useful strategy to inform the debate about which parts of sleep are important for possible functions of sleep, such as memory consolidation.<sup>69</sup>

### **Research Needs**

- Assess which components of sleep physiology may independently vary among subjects
- Investigate the functional significance of trait individual differences in sleep architecture

### **Individual Differences by Sex and Ethnicity**

Remarkably little systematic research has been done with regard to sex- and ethnicity-related differences in sleep, and a

comprehensive database of systematic differences and similarities between males and females and among different ethnic groups with regard to sleep parameters is not available. Various funding agencies in the United States and other parts of the world now require research study samples to be balanced in sex distribution and to have representation among multiple ethnic categories, which may help to fill this gap. The available literature on sex differences is not discussed here but has been reviewed in two recent papers.<sup>70,71</sup>

A handful of studies,<sup>72-75</sup> of which most were based in California (United States),<sup>72-74</sup> investigated differences by ethnicity for PSG-determined sleep variables. Overall, differences among ethnic groups were marginal. However, PSG recordings showed about half as much slow-wave sleep in Blacks<sup>72-74</sup> (particularly males<sup>72</sup>) and American Indians<sup>75</sup> as in other ethnic groups. Partly due to the fact that evaluations of ethnic differences often involve secondary analysis of data originally recorded for other purposes, it is unclear to what extent such findings reflect differences in genetic background or in sociocultural environment (or both).

Sex and ethnic differences in sleep architecture have been described in patients with depression,<sup>70,76-78</sup> and the possibility should be considered that there is a relationship between variability in sleep architecture and susceptibility to psychiatric disorders as a function of sex<sup>70</sup> and ethnicity.<sup>72</sup> To investigate this, it would be useful to study the functional significance of sex and ethnic differences in sleep.

### **Research Needs**

- Establish a comprehensive database of systematic sleep differences by sex and ethnicity
- Examine the functional significance of sex- and ethnicity-related differences in sleep

### **SLEEPINESS AND SLEEP DEPRIVATION**

Individual variability in waking neurobehavioral functions of healthy adults has attracted considerable scientific interest, both under normal conditions and during sleep deprivation. However, the relationship between individual differences in waking functions and individual differences in sleep physiology has hardly been examined.

### **Sleepiness/Alertness**

Since sleepiness can play an important role in the quality of life, individual differences in sleepiness are of considerable interest. In a series of studies extending the seminal work of Carskadon and Dement,<sup>79</sup> Roth, Roehrs, and colleagues compared sleepy subjects with alert ones.<sup>80-86</sup> To define sleepiness/alertness, they utilized the natural variability in average sleep latencies on the Multiple Sleep Latency Test (MSLT),<sup>87,88</sup> for which they found high test-retest reliability.<sup>89</sup> In a group of 176 healthy normals, it was observed that MSLT scores (ie, average sleep latencies) were normally distributed, with a mean score of 11.1 minutes. The most extreme 20% of subjects on either side of the distribution had MSLT scores of 6 minutes or less and 16 minutes or more—these were called “sleepy” and “alert” subjects, respectively.

Subsequent studies have yielded a variety of experimental results concerning daytime cognitive performance,<sup>81</sup> sleep laten-

cy and sleep efficiency in nocturnal PSG,<sup>81</sup> auditory awakening thresholds,<sup>86</sup> sleep efficiency after a 4-hour advance of the nocturnal sleep period<sup>84</sup> and following sleep extension for 14 days,<sup>85</sup> and MSLT scores after a sedative alcohol challenge<sup>82</sup> and following sleep extension for 6 days.<sup>80</sup> All findings appeared to be consistent with the hypothesis that sleepy subjects were chronically sleep deprived,<sup>90</sup> so that the difference between sleepy and alert subjects would lie in a (potentially state-specific) difference in sleep history. It was argued that, since in each experiment, sleepy subjects showed signs of sleep deprivation, they did not fulfill their daily need for sleep. Assuming that there were no systematic differences in habitual sleep duration (and morningness/eveningness<sup>91</sup>) between sleepy and alert subjects, it would follow that sleepy individuals have a greater need for sleep than do alert individuals—providing indirect evidence for systematic individual differences in biological sleep need.<sup>90</sup>

Lavie and coworkers<sup>92</sup> defined sleepy and alert subjects, which they designated “somnotypes,” by their characteristic sleep-propensity patterns. To study the 24-hour time course of sleep propensity, they employed an ultrashort 7-minute sleep/13-minute wake alternation paradigm. Eight subjects underwent the ultrashort sleep/wake cycle protocol twice, for 2 days on each occasion, with instructions to either attempt or resist sleep. The 24-hour sleep-propensity patterns were highly characteristic for the individual subjects, both across the 2 days for each condition and between the sleep-attempt and sleep-resist conditions. Subjects displaying greater daytime sleep propensities also showed shorter sleep latencies and higher sleep efficiencies in baseline nocturnal sleep recordings,<sup>92</sup> which is consistent with observations by Roth and colleagues.<sup>90</sup> In contrast with the latter, however, Lavie and coworkers interpreted their findings as evidence that sleep propensity may be partially determined by individual variability in sleep/wake organization instead of individual differences in sleep need.<sup>92</sup>

There may be alternative explanations for the observed individual differences in sleep latency and sleep propensity. For instance, these differences may reflect systematic individual variability in the effects of laboratory-based recording procedures (eg, anxiety about PSG measurement). Furthermore, individual differences in sleepability (ie, ability to fall asleep easily), unrelated to sleepiness, have been suggested.<sup>93,94</sup> De Valck and Cluydts<sup>95</sup> have proposed the concept of “trait sleepiness” as a composite of sleep need, sleepability, and other individual difference factors. This idea may be supported by the finding of a hereditary component to self-reported overall alertness<sup>9</sup> independent of self-reported sleep timing and duration. Nevertheless, the issue of why sleepy and alert individuals exist is bound to be complex,<sup>96,97</sup> and more research is needed to unambiguously distinguish the different factors potentially underlying systematic individual differences in sleepiness/alertness (see also the section below on differential vulnerability to sleep loss).

Features of the waking EEG have been used as physiologic markers of sleepiness and alertness.<sup>98-100</sup> Although often ignored in the context of sleep research, individual differences in the spontaneous (non-sleep-deprived) waking EEG have been documented repeatedly. These individual differences have been found to be highly replicable<sup>101,102</sup> (though not as much when considering spatio-temporal distributions rather than just temporal profiles<sup>103</sup>) and remarkably heritable.<sup>102,104</sup> It remains to be determined to what extent trait variability in the waking EEG may be related to physiologic

sleepiness—in addition to individual differences in the (functional) neuroanatomy of the brain<sup>105,106</sup> and other sources of variance.

## Research Needs

- Distinguish the different factors potentially underlying systematic individual differences in sleepiness, such as individual differences in basal sleep need, sleepability, and sleep/wake regulation
- Assess the relationship of trait individual variability in the spontaneous waking EEG to systematic individual differences in sleepiness/alertness

## Differential Vulnerability to Sleep Loss

Laboratory studies have revealed that individuals differ in the magnitude of sleepiness and cognitive performance impairment during sleep deprivation—by as much as an order of magnitude—and that this individual variability is highly replicable over repeated exposures to sleep deprivation.<sup>32,107-109</sup> In the most extensive and most quantitative of these studies,<sup>32</sup> subjects were exposed 3 times to 36 hours of sleep deprivation while state variance was carefully minimized. Intraclass correlation coefficients (see Appendix) were found to range from 0.68 to 0.92, indicating that up to 92% of the variance in cognitive deficits and subjective sleepiness was explained by systematic variability among individuals. Although there were baseline differences among subjects in cognitive performance capability (eg, due to differences in aptitude<sup>110</sup> or cognitive style<sup>111</sup>), individual variability in 10 out of 13 different neurobehavioral responses to sleep deprivation remained significant after controlling for these baseline differences.<sup>32</sup>

The study also showed that the individual differences in impairment from sleep loss were robust to experimental manipulation of sleep history.<sup>32</sup> This was operationalized as restricting sleep to 6 hours time in bed—as contrasted with 12 hours time in bed—for each of the 7 days prior to laboratory sleep deprivation. This intervention resulted in an effective sleep reduction of 4.1 hours per day on average, and it had a measurable adverse effect on subjects’ functioning during subsequent total sleep deprivation. However, the magnitude of this effect was less than 10% of the full range of systematic individual variability. Thus, individual differences in neurobehavioral deficits from sleep loss were demonstrated to constitute trait differential vulnerability.<sup>32,112</sup> We suggest that, based on the Greek word *trotos* for vulnerability, and in line with the terms “chronotype” and “somnotype,” this phenotype may be referred to as “trototype.”

In the study, the ranking of subjects from least to most vulnerable was not the same for every neurobehavioral response to sleep deprivation.<sup>32</sup> Individual differences in the 13 neurobehavioral variables measured in the study clustered on 3 orthogonal dimensions: self-evaluation of sleepiness and mood, cognitive processing capability, and sustained attention performance.\*\* Similarly, individual differences in self-reported vigor and individual differences in attention performance were dissociated during sleep deprivation in another study, which involved repeated exposure to a 27-hour constant routine.<sup>108</sup> It needs to be explored whether other categories of outcome variables, such as sleepiness measured with the MSLT, may entail additional orthogonal

\*\* It has not been ruled out that the durations of the various neurobehavioral tasks could play a role in the way objective performance measures clustered on different dimensions.

dimensions of individual variability during sleep deprivation.

Individual differences in responses to sleep loss have been observed not only during acute total sleep deprivation, but also under conditions of chronic sleep restriction, both with<sup>113</sup> and without<sup>114</sup> full laboratory control. Van Dongen and colleagues found that a regression model with systematic individual variability accounted for 83% of the variance in progressive changes of psychomotor vigilance performance across 14 days of sleep restricted to 4 hours, 6 hours, or 8 hours per day in the laboratory.<sup>113</sup> Without the individual variability, the regression model explained only 22% of the variance. This result underlines the considerable magnitude of individual variability in impairment from sleep loss for cognitive measures. Individual differences in responses to sleep deprivation have also been noticed in aspects of physical performance.<sup>115,116</sup> This latter topic has remained almost entirely unexplored in sleep research, however, and studies are needed to assess if individual differences in physical performance deficits during sleep deprivation represent a trait.

The identification of predictors for vulnerability to sleep loss would have important biological implications and would also yield significant advantages for safety and productivity in settings in which sleep deprivation is an issue.<sup>117</sup> To date, a handful of studies have considered a diversity of candidate predictor variables,<sup>32,108,116,118-121</sup> but no strong evidence for reliable predictors has yet emerged. A systematic, wide-ranging exploration of candidate predictors for vulnerability to sleep loss is warranted. Furthermore, it would be useful to investigate if individual differences in vulnerability to sleep loss covary with individual differences in basal sleep need and/or baseline sleepiness/alertness. This could clarify if individual differences in vulnerability to sleep loss are involved in the existence of naturally sleepy and alert individuals.

### **Research Needs**

- Investigate whether individual differences in physical performance deficits during sleep deprivation represent a trait
- Establish the multiplicity (or singularity) of independent dimensions of systematic individual variability in neurobehavioral responses to sleep deprivation
- Quantify the extent to which individual differences in vulnerability to sleep loss, individual differences in sleep need, and individual differences in baseline sleepiness/alertness covary
- Identify predictors of vulnerability to impairment from sleep loss

### **Relationship between Wakefulness and Sleep**

Not much is known about individual differences in the architecture of recovery sleep following sleep deprivation. Finelli and colleagues<sup>122</sup> observed that the spectral power distribution of the non-REM EEG during recovery sleep after 40 hours of sleep deprivation differed markedly among subjects (across multiple electrode locations), but, within each subject, the power distribution was very similar to that observed during baseline sleep. The magnitude of individual variability appeared to exceed the magnitude of the effect of sleep deprivation on the non-REM sleep EEG. Furthermore, there was a systematic relationship of delta power in subjects' non-REM sleep EEG (change from baseline to recovery) with theta power in their waking EEG during the 40

hours of wakefulness, suggesting that the individual differences in the waking and sleep EEG reflected a single underlying process. It has been hypothesized that this process is concerned with homeostatic sleep regulation.<sup>24</sup> Whether or not this is correct, it seems important to pinpoint the functional significance of these remarkably consistent individual differences.

Two studies have reported individual differences in the context of selective REM sleep deprivation and subsequent recovery sleep.<sup>123,124</sup> In one study, involving 3 nights of REM sleep deprivation, it was reported that individuals differed in the number of awakenings (ranging from 17 to 69) necessary to deprive them of REM sleep.<sup>123</sup> The more often subjects needed to be awakened, the more their recovery sleep consisted of a mixture of REM and stage 2 sleep. Among the 10 subjects in the study, 3 different patterns of responses to REM sleep deprivation were distinguished.<sup>123</sup> In the other study, recovery sleep following partial differential REM sleep deprivation displayed fairly substantial individual differences in REM rebound, and the increase in the percentage of REM sleep was stable across 2 recordings made for each individual.<sup>124</sup> REM-rebound rates did not show any significant covariation with baseline REM amounts or with the decrease of REM in the partial deprivation nights, but did correlate with personality characteristics. The interpretation of these findings remains unclear.

### **Research Needs**

- Examine the functional significance of the consistent individual differences in the waking EEG during sleep deprivation and the sleep EEG during the preceding baseline night and the following recovery night
- Clarify the interpretation of individual variability in REM-rebound patterns during and after selective REM sleep deprivation

### **SLEEP DISORDERS**

The literature on individual differences in the context of sleep disorders is scattered, lacking breadth, depth, and coherence in many areas. What little information is available has been organized here in 6 broad categories: sleep disturbance, excessive daytime sleepiness (EDS), sleep apnea, narcolepsy, parasomnias, and insomnia.

#### **Sleep Disturbance**

According to the National Sleep Foundation's 1999 omnibus "Sleep in America" poll, 62% of adults in the United States reported experiencing a sleep problem a few nights a week or more during the year before.<sup>125</sup> In the 2002 "Sleep in America" poll, 27% of respondents categorized their sleep quality as fair or poor.<sup>5</sup> Thus, subjective sleep problems seem to be widespread. Twin studies have indicated that subjective sleep problems have some genetic mediation,<sup>126,127</sup> while they appear to be independent of habitual sleep duration and daytime napping.<sup>8,127</sup> These findings point to the existence of trait-specific vulnerability to subjective sleep disturbance. Identifying predictors for this vulnerability may have useful medical and economic implications. A sample of same-sex twin pairs in Australia yielded personality (neuroticism and extraversion) and liability to symptoms of anxiety and depression as candidate predictor variables.<sup>127</sup> Ethnicity has also been investigated as a predictor of subjective sleep problems,<sup>128,129</sup> but results have been inconsistent.



In a study of experimental sleep disturbance, Bonnet and Arand<sup>130</sup> showed that variability among normal sleepers in PSG-assessed sleep efficiency in a hospital environment was fairly consistent across an adaptation night and 2 intervention nights with sleep phase advances of 3 and 6 hours, although the individual variability was diminished in baseline nights that followed the adaptation night (due to adaptation to the study procedures and, possibly, as a result of regression to the mean). Subjects with the lowest sleep efficiency on the adaptation night also had the greatest reduction in sleep efficiency when their sleep was advanced by 6 hours and—in a subset of subjects who underwent an additional condition—when they were given caffeine just before bedtime. The same subjects exhibited shorter sleep latencies on the MSLT<sup>131,132</sup> following the sleep period that was advanced by 6 hours, but displayed longer sleep latencies on the MSLT following the night with caffeine.<sup>130</sup> Despite these inconsistent effects on objective daytime sleepiness, the study results indicated systematic individual differences in responsiveness to sleep disturbance.

Drake and colleagues<sup>133</sup> developed a questionnaire to measure stress-related vulnerability to sleep disturbance. They found that individuals scoring higher on the questionnaire had relatively lower sleep efficiency on a first night of laboratory PSG, but also displayed longer sleep latencies on the MSLT during the following day. These elevated daytime sleep latencies (despite significantly disturbed prior sleep) were interpreted as evidence of physiologic hyperarousal in the individuals reporting high stress-related vulnerability to sleep disturbance.<sup>133</sup> The questionnaire developed by Drake et al<sup>133</sup> may effectively predict the differential responsiveness to sleep disturbance exposed by the study of Bonnet and Arand,<sup>130</sup> but further experiments would be needed to determine this.

### **Research Need**

- Identify predictors of vulnerability to sleep disturbance

### **Excessive Daytime Sleepiness**

Excessive daytime sleepiness (EDS) is a symptom of various sleep disorders. Individual variability in EDS has been found to moderately reflect genetic susceptibility—in a study of World War II veteran twin pairs,<sup>134</sup> the heritability estimate for EDS scores on the Epworth Sleepiness Scale<sup>135</sup> was 38%. Obesity—by itself a heritable trait<sup>136,137</sup>—was found to correlate positively with EDS.<sup>134</sup> A study of monozygotic twin pairs discordant for obesity found relatively moderate obesity to be associated with disruption of the physiologic structure of sleep in the absence of snoring or breathing disturbances.<sup>138</sup> However, obesity is also a risk factor for sleep-disordered breathing, for which genetic predisposition has been described as well.<sup>139</sup> These observations sketch a complex picture of trait-specific EDS, suggesting that individual differences in susceptibility to EDS reflect genetic patterns that will be challenging to unravel.

### **Research Need**

- Investigate which independent factors contribute to trait EDS

### **Sleep Apnea**

Unexplained differences in EDS have been observed among sleep apnea patients with equivalent degrees of disease severity.<sup>140-142</sup> There is a documented poor relationship between the apnea-hypopnea index (AHI), a primary measure of sleep apnea severity, and EDS.<sup>143,144</sup> To some extent, this may be an artifact of misestimation of disease severity due to night-to-night variability in respiratory disturbance<sup>145,146</sup> or the result of individual variabilities in obesity, comorbidities, or medication use. Ethnicity may contribute as well<sup>147,148</sup> but may not be independent of other factors.<sup>149</sup> Because apnea induces sleep fragmentation, leading to sleep loss, individual differences in EDS among patients with similar disease severity may also reflect differential vulnerability to the effects of sleep loss (see the earlier section on this topic). Research is needed to disentangle these underlying factors.

### **Research Need**

- Investigate which independent factors contribute to individual differences in EDS among sleep apnea patients with equivalent degrees of disease severity

### **Narcolepsy**

Narcolepsy exhibits a wide range of individual variability in symptomatology (even among monozygotic twins<sup>150</sup>). Most narcoleptic patients experience cataplexy,<sup>151</sup> but the frequency of cataplectic episodes ranges from a few instances per year to several times per day. Hypnagogic hallucinations may occur in 28% to 82% of cases diagnosed with narcolepsy, and rates of sleep paralysis may range between 27% and 80%.<sup>152</sup> Only up to 50% of narcoleptic patients show the full spectrum of classic symptoms: EDS, cataplexy, hypnagogic hallucinations, and sleep paralysis. Evidence has suggested that ethnicity is not an important modulator of the individual differences in narcoleptic symptomatology.<sup>153</sup>

In a twin study of self-reported narcoleptic symptoms, from 35% (men) to 39% (women) of trait variance was attributable to genetic effects.<sup>154</sup> Nevertheless, while familial cases have been reported frequently, narcolepsy appears not to be a simple genetic disorder, and only up to 31% of monozygotic twins show concordance for narcolepsy.<sup>155</sup> There is a strong association between the expression of narcolepsy and the HLA gene DQB1\*0602,<sup>155</sup> but false positives and false negatives exist (even in discordant monozygotic twin pairs<sup>156</sup>). Since individual differences in this primary sleep disorder are so prevalent, investigating their origin could serve to better characterize the underlying pathology. Such research may also help to explain why healthy individuals may occasionally experience sleep-onset REM episodes, as well as hypnagogic hallucinations and sleep paralysis<sup>157</sup>—symptoms normally associated with narcolepsy.

### **Research Need**

- Investigate the origin of individual differences in the symptomatology of narcolepsy

### **Parasomnias**

Individual variability in overt behaviors during sleep has been scarcely studied. One sleep study of healthy men, recorded by

videotaping on 2 consecutive nights, documented that sleeping positions varied from subject to subject, while similar positions (and similar frequencies of rolling over) occurred within subjects over the 2 nights.<sup>158</sup> Thus, there appeared to be systematic individual differences in normal sleep behaviors. Individual differences in abnormal sleep behaviors such as sleepwalking, sleep talking, sleep terrors, bruxism (grinding teeth), and enuresis (bed-wetting) have been studied primarily for the assessment of heritability and genetic factors. Notable progress has been made with regard to enuresis. The heritability characteristics of enuresis have been well established, with about 70% of trait variance in children found to be attributable to genetic effects.<sup>159</sup> Moreover, linkages to chromosomal loci have been shown (although the specific genes and their functions remain unknown). For other parasomnias, most of the available evidence is based on self-report studies in twin cohorts, as reviewed by Hublin and Kaprio.<sup>159</sup> The data suggest moderate (35%–55%) genetic liability for these disorders, with significant probabilities of co-occurrence.

Very little is currently known about individual variability in nightmares. While in nonclinical populations the self-reported nightmare frequency has been found to differ among subjects,<sup>160,161</sup> state measures of stress and anxiety explain much of the variability. This would suggest that nightmare frequency may not represent a trait by itself. On the other hand, a population-based twin study yielded evidence for a moderate role of genetic effects in self-reported frequency of nightmares.<sup>162</sup> Self-report studies of nightmare frequency, however, like all retrospective studies, are likely to be affected by reporting errors and bias—which may depend on the severity of the nightmares. In this respect, it may be of relevance that surveys of healthy individuals have shown only dream-recall frequency but not dream content to be a relatively stable individual characteristic.<sup>163–165</sup>

While much emphasis has been placed on genetic aspects of the various parasomnias per se, virtually no attention has been paid to individual differences in the manifestation of symptoms. As in narcolepsy, investigating the origin of individual variability in symptom expression could serve to better characterize the underlying pathology and, ultimately, help to identify the genetic mediators.

### **Research Needs**

- Investigate the origin of individual differences in the symptomatology of the various parasomnias
- Establish whether individual differences in the occurrence of nightmares reflect a trait

### **Insomnia**

There appears to be relatively little temporal stability among insomniacs in the diagnosis of different subtypes of insomnia (sleep onset insomnia, sleep maintenance insomnia, early morning awakening).<sup>166</sup> Nevertheless, in patients complaining of insomnia, systematic individual differences of time in bed and total sleep time have been found over a week of nightly recording, using both sleep logs and PSG.<sup>167</sup> Such individual differences constitute a confounding factor in the evaluation of treatment efficacy, as those subjects showing the greatest effects of insomnia would be expected to benefit most from treatment.<sup>168</sup> This is particularly relevant in studies employing subjects without

insomnia complaints for the purpose of evaluating potentially sleep-improving treatments (eg, exercise, melatonin administration). The interpretation of the results from such studies is problematic because considerable portions of the study samples should have exhibited relatively high sleep efficiency to begin with, leaving little room for benefit from treatment.

Youngstedt framed this issue in terms of an inherent negative correlation between baseline levels and responses to treatment.<sup>168</sup> In a meta-analysis, he found that individual differences in baseline levels explained approximately 60% of the variance in changes in sleep latency, total sleep time, and wakefulness after sleep onset induced by treatment with hypnotics. Baseline levels actually appeared to be more predictive of sleep improvement than did hypnotic dose. Appropriate statistical methods are available to deal with this issue,<sup>109,169–172</sup> and it may be worthwhile to reanalyze the available studies to better evaluate the potential of different treatment options for insomnia.

### **Research Need**

- Examine pretreatment individual differences in the evaluation of the efficacy of insomnia treatments

### **IMPLICATIONS**

The previous sections reviewed the individual variability observed in a number of variables relevant to sleep research and sleep medicine. In this last section, the implications of such variability are discussed from some different perspectives. The section concludes with suggestions for an integrated research agenda.

### **Trait Individual Differences**

Individual variability in sleep/wake-related variables is by itself of interest as a focus of scientific inquiry. However, research focusing on individual variability per se first requires careful phenotyping of the population. Thus, evidence must be provided that the individual differences are substantial (distinguishable), replicable (stable), and robust<sup>32</sup>—ie, reflect a trait or phenotype. Typically, this means repeating the same experiment in the same individuals in order to assess stability<sup>109,117</sup> and demonstrating that the individual differences persist in the face of a relevant experimental challenge in order to ascertain robustness.<sup>32</sup> It may also be crucial to establish sample inclusion and exclusion criteria that reduce systematic state-specific variability (eg, exclusion of subjects who work shifts so as to limit systematic state-dependent circadian variations).<sup>109</sup>

Following the identification of a clearly defined phenotype, heritability can be investigated (eg, by means of twin or segregation studies), and ultimately the search for underlying genes can commence. Modern techniques such as forward genetics (eg, mutagenesis, quantitative trait loci analysis) and reverse genetics (eg, transgenics, knock-outs) have proven useful for the identification of genes related to phenotypes.<sup>173</sup> Considerable progress in gene identification has already been made in studies with specially bred animals with clearly distinct phenotypes.<sup>174,175</sup> In humans, however, phenotypes cannot be generated this way. Thus, the need remains to determine to what extent individual differences occurring naturally among humans are trait specific. This requires rigorous experimental control and appropriate statistical methodology (see Appendix) in studies designed specifically to establish trait variability.



Human studies of the replicability and robustness of individual differences in objectively measured variables are listed in Table 1 (sleep and circadian rhythms in healthy adults and sleep-disordered patients) and Table 2 (sleepiness and sleep deprivation in healthy adults). It is noteworthy that most of these studies had small sample sizes, and the majority of them involved male subjects only. Findings from studies based on self-report data, which typically employed larger samples with mixed sex, are not included in the tables because the reliability of self-report data cannot be ascertained due to the effects of contextual factors (eg, demand characteristics, scale interpretation, report bias).

Tables 1 and 2 reveal that among objectively measured sleep/wake-related variables, the only ones for which trait variability (ie, both replicability and robustness) has been demonstrated experimentally are MSLT-defined sleepiness/alertness (see Zwyghuizen-Doorenbos et al<sup>89</sup> for replicability and Roth et al<sup>90</sup> for robustness) and vulnerability to neurobehavioral impairment from sleep loss (see Van Dongen et al<sup>32</sup>). In twin studies, aspects of sleep structure (see Webb and Campbell<sup>62</sup> and

Linkowski et al<sup>63,64</sup>) have displayed genetic control—from which trait variability may be inferred as well—but the results of these studies turned out to be inconsistent. All in all, trait individual differences in human sleep research and sleep medicine have been severely understudied.

Sample selection is an issue to consider when investigating individual differences; by definition, heterogeneous samples show greater differences among subjects than do more homogeneous samples. Thus far, little is known about the extent to which different populations (eg, healthy young adults, healthy older adults, males or females, patients with sleep problems, patients with severe apnea, ethnically diverse populations, volunteers for laboratory experiments, etc.) vary in degree of heterogeneity with regard to sleep/wake variables. In certain occupational settings, such as night and shift work, self-selection processes may result in populations that are predominantly resistant to sleep loss and/or circadian misalignment (or perceive themselves as such)—but this possibility has not been tested with empirical data.

**Table 1**—Peer-Reviewed Articles Discussing Trait Aspects of Individual Differences in Objective Assessments of Human Sleep-Related Characteristics, in Healthy Adults and Patients With Sleep Disorders\*

Reference	Description
Azumi et al (1982) <sup>54</sup>	Individual variability in the temporal pattern of automatically scored sleep spindles was stable over seven consecutive night recordings (10 male subjects)
Bonnet & Arand (2003) <sup>130</sup>	Individual variability in sleep efficiency seen during an adaptation night was enhanced when sleep was advanced by 3 or 6 hours (17 male and 33 female subjects) or caffeine was administered just before bedtime (subset of 35 subjects), which suggested systematic individual differences in responsiveness to sleep disturbance
Gaillard & Blois (1981) <sup>53</sup>	Individual variability in the density of automatically scored sleep spindles was stable over 2 nighttime recordings (5 male and 5 female subjects)
Kubota et al (2003) <sup>158</sup>	Sleeping positions and roll-over frequencies showed systematic individual variability across two consecutive nights of laboratory videotaping (19 male subjects)
Linkowski et al (1989) <sup>63</sup>	Significant portions of variance in stage 2, stage 4, and slow-wave sleep as well as REM density appeared to be genetically determined, suggesting trait variability in aspects of sleep structure (14 MZ and 12 DZ male twin pairs)
Linkowski et al (1991) <sup>64</sup>	Significant portions of variance in stage 2, stage 4, and slow-wave sleep as well as intermittent wakefulness—but neither REM sleep nor REM density—appeared to be genetically determined, suggesting trait variability in aspects of sleep structure (11 MZ and 15 DZ male twin pairs)
Linkowski et al (1993) <sup>36</sup>	Genetic control was shown for the timing of the nocturnal minimum of plasma cortisol, suggesting trait variability in circadian phase (11 MZ and 10 DZ male twin pairs)
Merica & Gaillard (1985) <sup>55</sup>	Stability was observed for a number of sleep parameters, in particular stage 4 (but not stage 3) sleep, over multiple PSG recordings in the same individuals across different studies (147 subjects; sex distribution not reported)
Modell et al (2002) <sup>192</sup>	Healthy subjects with high genetic risk for affective disorders displayed stability in sleep parameters, including elevated REM density compared to controls, across 2 PSG recordings separated by 3.5 years on average (14 male and 12 female high-risk probands, and 15 male and 20 female controls)
Numberger Jr. et al (1983) <sup>204</sup>	MZ twins exhibited substantial concordance for sensitivity to REM sleep induction by the cholinergic agonist arecoline, suggesting (but not demonstrating) trait variability in the cholinergic regulation of REM sleep (1 male and 6 female MZ twin pairs; no DZ twin pairs)
Sato et al (1993) <sup>60</sup>	Idiosyncratic individual differences had greater influence on sleep structure than did sleeping in a noisy area (facing a main road) versus a quiet area, suggesting that individual differences in sleep structure may be robust (7 male and 1 female subjects)
Silverstein & Levy (1976) <sup>52</sup>	Individual variability in the distribution of automatically scored sleep spindles was stable over three consecutive night recordings (6 male subjects)
Van Dongen et al (1998) <sup>31</sup>	The circadian phase of core body temperature and urinary cortisol was stable across 5 exposures to a 24-hour constant routine at 3-month intervals (6 male subjects)
Webb & Campbell (1983) <sup>62</sup>	When sleeping as long as possible, MZ twin pairs displayed greater correlations for sleep efficiency, intermittent wakefulness, sleep latency, REM sleep, and sleep-stage changes than did DZ twin pairs, suggesting trait variability in these sleep parameters (7 male and 7 female MZ twin pairs; 2 male, 9 female and 3 mixed DZ twin pairs)

\*Findings on sex differences are not included. REM refers to rapid eye movement; MZ, monozygotic; DZ, dizygotic; PSG, polysomnography.

## Research Needs

- Conduct studies to further assess trait individual differences in human sleep and wakefulness
- Compare the heterogeneity of different populations with regard to the trait-specific aspects of sleep and waking functions

## Statistical Analysis of Individual Variability as a Research Outcome

Even when individual variability is not the primary focus of a research study, it should be dealt with properly in the process of data analysis.<sup>109,169,171</sup> Individual differences may well make up the larger part of the variance in the overall data set of any given sleep research project; this alone would justify a methodologic approach handling individual variability properly. Traditional statistical analysis techniques that do not account for individual differences (eg, repeated-measures analysis of variance, multiple regression analysis) mix systematic between-subjects variance with error variance, which can lead to unreliable claims about standard errors and statistical significance or nonsignificance.<sup>169</sup> To some degree, this problem may be mitigated by strict inclusion and exclusion criteria to select homogeneous samples (although this tends to raise questions of generalizability). On the other hand, excellent methods for parameter estimation and statistical inference are now available to deal with systematic individual differences if more than one measurement per subject is available for the same variable (eg, mixed-effects analysis of variance, mixed-effects regression analysis; see Appendix). As an additional benefit, these methods provide estimates of the magnitude of systematic individual variability. Thus, while data analy-

sis may be slightly more complicated when taking into account individual differences, doing so is scientifically more precise and often worth the effort in terms of knowledge gained.

Information about systematic individual differences may be helpful in interpreting study findings and testing research hypotheses. For instance, such information may help to elucidate the reasons why sleep is needed. After all, whatever functions of sleep can be hypothesized, variability should be expected in the execution of those functions in concert with observed variability in the parameters of the proposed mechanisms. As a case in point, it would be reasonable to maintain that sleep plays a pivotal role in consolidating memories<sup>176–178</sup> if it were found that natural individual variations in sleep physiology are associated with congruent individual variations in memory consolidation. As such, variability among subjects may provide a critical test for the memory consolidation hypothesis.

## Research Needs

- Routinely apply statistical methodology dealing properly with individual differences in studies involving repeated measurements
- Employ information about systematic individual variability as a test criterion for hypotheses in sleep research

## Mathematical Modeling

Individual differences represent an important<sup>179</sup> but unresolved issue for mathematical models of sleep regulation and waking functions. Benoit and colleagues<sup>17</sup> pointed out that, “A certain

**Table 2**—Peer-Reviewed Articles Discussing Trait Aspects of Individual Differences in Objective Measurements of Sleepiness and the Effects of Sleep Deprivation in Healthy Adult Humans\*

Reference	Description
Finelli et al (2001) <sup>122</sup>	The power spectrum of the non-REM EEG during recovery sleep after 40 hours of sleep deprivation differed among subjects, but the recovery spectrum resembled the baseline spectrum within subjects and the effect of sleep deprivation was relatively small, suggesting that the non-REM EEG may reflect a trait (8 male subjects)
Lavie & Zvuluni (1992) <sup>92</sup>	Subjects' temporal profiles of sleep propensity showed high stability across 2 exposures to a 48-hour ultrashort sleep/wake alternation paradigm while either attempting or resisting sleep, suggesting that sleep propensity reflects a trait (8 male subjects)
Leproult et al (2003) <sup>108</sup>	Subjects' attention performance decrements, melatonin profiles, and plasma glucose concentrations were stable across 2 exposures to a 27-hour constant routine with intravenous glucose infusion (8 male subjects)
Morgan Jr. et al (1980) <sup>107</sup>	Individual differences in performance decrements on a multiple-task performance battery were stable across 4 exposures to 36 to 44 hours of sleep deprivation with continuous work (8 male subjects)
Nakazawa et al (1975) <sup>124</sup>	The REM rebound in recovery sleep following partial differential REM sleep deprivation showed systematic individual differences across 2 repetitions of the experiment (14 male subjects)
Roth et al (1997) <sup>90</sup>	Individual differences in sleepiness and alertness, as defined by the MSLT, were robust to a variety of experimental challenges (review of a number of peer-reviewed articles)
Van Dongen et al (2003) <sup>113</sup>	Subjects displayed systematic individual differences in performance decrements on a number of cognitive tasks across 88 hours of total sleep deprivation or 14 days with sleep restricted to 4, 6, or 8 hours time in bed per day (42 male and 6 female subjects)
Van Dongen et al (2004) <sup>109</sup>	Individual differences in psychomotor vigilance performance decrements were stable across 2 exposures to 40 hours of sleep deprivation with different degrees of environmental stimulation, suggesting that differential vulnerability to sleep loss reflects a trait (8 male and 1 female subjects)
Van Dongen et al (2004) <sup>32</sup>	Individual differences in performance decrements on a number of cognitive tasks were stable across 3 exposures to 36 hours of sleep deprivation, independent of individual differences in baseline performance, and robust to experimental manipulation of sleep history—which demonstrated that differential vulnerability to sleep loss reflects a trait (12 male and 9 female subjects)
Zwyghuizen-Doorenbos et al (1988) <sup>89</sup>	Sleepiness, as measured with the MSLT, showed high test-retest reliability (ie, stability) independent of the interval (4–14 months) between measurements (14 male subjects)

\*REM refers to rapid eye movement; EEG, electroencephalogram; MSLT, Multiple Sleep Latency Test.

degree of contradiction appears between inter-individual variability and the ability to predict one's sleep pattern based on the temporal circumstances." A 2004 special supplement of the journal *Aviation, Space, and Environmental Medicine* was devoted entirely to the state of the art of mathematical modeling of waking functions, and again the issue of individual differences was brought up.<sup>180</sup> Recent progress in temporal modeling techniques<sup>181</sup> will facilitate new developments in this area, but much remains to be done before mathematical models can accurately describe and predict individual differences.

Incorporation of trait individual differences in mathematical models of sleep regulation and waking functions by a priori adjustment of model parameters on the basis of biobehavioral markers (biosignature) would represent a major step forward. The relevant model parameters may involve at least the following factors of sleep/wake regulation: baseline waking functioning, basal sleep need, vulnerability to sleep loss, recovery rate during sleep (after sleep loss), circadian amplitude, circadian phase position, and circadian adaptation rate (following a phase shift). While markers of circadian amplitude and phase position are available (eg, from plasma melatonin or core body temperature), and measuring baseline waking functions may be relatively straightforward, no a priori markers of basal sleep need, vulnerability to sleep loss, recovery rate during sleep, and circadian adaptation rate have been established.

### **Research Needs**

- Develop mathematical models of sleep-regulation and waking functions that can accurately deal with individual differences
- Identify biomarkers of trait individual differences relevant to mathematical models of sleep regulation and waking functions

### **Occupational Settings**

In today's 24-hour society, night and shift-work schedules are common, but not everyone is equally capable of adjusting to these schedules. The extent to which individual-difference factors such as vulnerability to sleep loss, circadian phase preference, and age—and their various interactions—may be predictive of adjustment to and tolerance for night and shift work is reviewed in other papers.<sup>182,183</sup> Research on the factors underlying individual variability in tolerance for night and shift work has been hampered by poor control over secondary sources of variance (eg, social support, coping strategies, activities during time off, self-selection processes).<sup>182,184</sup> Similar difficulties have been encountered in field studies of individual differences in adjustment to time zone changes among flight crew.<sup>185</sup> However, having the capability to predict who is most (or least) vulnerable to the deleterious effects of sleep loss and circadian misalignment, as associated with shift work and travel across time zones, would be valuable for the mitigation of occupational risk. In safety-sensitive operations like the trucking industry, a relatively small portion of individuals may account for the bulk of the risk posed by occupational fatigue.<sup>186</sup> Considering the enormous cost to society of fatigue-related accidents,<sup>187–189</sup> therefore, the research needed to find reliable methods for identifying those individuals who are most at risk will be worth the investment.

It is not reasonable to rely solely on people's self-evaluations of performance impairment to prevent occupational accidents because there is a demonstrated mismatch between subjective

estimates of sleepiness and actual cognitive performance.<sup>32,108,109</sup> Instead, fitness-for-duty tests are sometimes used to evaluate readiness to perform. However, fitness-for-duty tests are subject to individual differences that may not covary with the individual differences in capabilities required for the task at hand. Performance and safety are also controlled by means of rules and regulations (eg, for hours of work), but the existence of substantial individual differences makes it difficult to set reasonable limits on sleep deprivation and other fatiguing factors that would sustain acceptable levels of performance in all individuals.<sup>190,191</sup> In this regard, it should be realized that the 24-hour society could as well create opportunities for individuals who are least affected by sleep loss and circadian misalignment. Although potentially controversial as a medicolegal subject, there remains a need to find reliable methods for the identification of individuals who are most or least at risk of impairment.

### **Research Needs**

- Strengthen research on tolerance for night and shift work by distinguishing trait-specific individual differences from secondary sources of variance
- Find reliable methods for identifying individuals who are most or least at risk of performance impairment in specific occupational settings

### **Clinical Relevance**

There is some evidence that individual differences in sleep architecture may be associated with differential vulnerabilities to clinical disorders.<sup>192,193</sup> It has been found that subjects with a high genetic risk for affective disorders show increased REM density compared to controls, and that this characteristic is stable over time.<sup>192</sup> Likewise, it has been observed that, in monozygotic twin pairs discordant for chronic fatigue syndrome, the discordance may be related to a small difference in the percentage of REM sleep.<sup>193</sup> Variations in sleep and wakefulness have also been suggested to be linked bidirectionally to self-medication with pharmacologically active substances.<sup>194</sup> For example, in cocaine abusers, abstinence leads to an initial state of severe daytime sleepiness, which may lead to a relapse to cocaine use as a means of self-medication to overcome the sleepiness.<sup>194</sup> Similarly, the use of caffeine to maintain wakefulness<sup>195–197</sup> or to overcome sleep inertia<sup>198</sup> may partly explain individual differences in caffeine consumption.<sup>199</sup> Personality factors may be relevant in this regard,<sup>200</sup> as may individual susceptibility to sleep disturbance from caffeine.<sup>201</sup> New discoveries in human pharmacogenomic research may shed more light on these latter issues.

Systematic individual variability in sleep architecture among both clinical and healthy populations presents a challenge for sleep medicine, in that such variability can have a profound effect on the sensitivity and specificity of diagnostic tests based on sleep/wake parameters. As a case in point, the range of sleep efficiencies of diagnosed insomniacs overlaps considerably with the range found in normal control subjects.<sup>167,168,202</sup> This implies high probabilities for false positives and false negatives when diagnoses rely on PSG (as is the case with the *International Classification of Sleep Disorders* criteria for psychophysiologic and idiopathic insomnia<sup>203</sup>). It needs to be verified if diagnostic strategies relying on multiple measures result in greater conver-



gent validity—rather than merely showing the confounding effects of multiple dimensions of individual variability.

Clinical issues also arise from individual variability in the effectiveness of treatments for sleep disorders. In the case of pharmacologic therapy, for instance, systematic individual differences may exist in efficacy,<sup>204</sup> half-life,<sup>205</sup> side effects, toxicity, and treatment adherence. Variability in the effects of pharmacologic agents is well illustrated by caffeine, for which the half-life has been reported to vary among individuals from 2.5 to 10 hours (depending also on dose).<sup>206</sup> This considerable variation remains partly unexplained but is mediated by population variabilities in age and body mass; food intake, cigarette smoking and various drug interactions; and menstrual phase, oral contraceptive use, and pregnancy in women.<sup>207</sup> Sleep (disorders) research can benefit substantially from the pharmacokinetic literature, which provides a rich source of information on individual variability<sup>205</sup> and is at the forefront with regard to applicable statistical methodology (see Appendix).

Finally, individual variabilities in sleep and wakefulness have important implications for general clinical care. The regular routine of the typical hospital environment is at odds with the considerable individual differences in natural sleep timing and duration. In critically ill patients, timing the clinical care in accordance with individual needs could result in substantive improvements in patient outcomes.<sup>208</sup> The central theme is that sleep-related individual differences play a role at all stages of the clinical process, from symptoms and diagnoses to treatment and care. Therefore, broad investigations of individual differences are warranted “from bench to bedside.”

### Research Needs

- Study the effects of systematic individual differences on the sensitivity and specificity of diagnostic strategies in sleep medicine
- Investigate individual differences in the effectiveness of treatments for sleep disorders
- Examine the benefits of individualized timing of clinical care

### Suggestions for an Integrated Research Agenda

As reviewed in this paper, individual differences have been recognized in many aspects of sleep research and sleep medicine. However, they have often been overlooked or ignored, as studies primarily focused on population averages. Individual variabilities in sleep and wakefulness remain understudied scientifically and are rarely considered conceptually (eg, in theories and models) or practically (eg, in diagnostic nosologies and interventions). Yet, differences among people are the norm rather than the exception. In the previous sections, therefore, research needs regarding individual differences have been pointed out across a broad range of sleep-related topics. The following list presents some common themes among these research needs—proposed here as an integrated research agenda focusing on individual differences in adult human sleep and wakefulness.

*a. Assess whether individual differences observed in sleep/wake-related variables reflect trait individual variability, and compare the magnitude of trait individual variability among different populations.* Only a few of the many variables for which individual differences appear to be relevant have been studied in

terms of replicability and robustness (see Tables 1 and 2), and trait variability has only been demonstrated completely for MSLT-defined sleepiness/alertness<sup>89,90</sup> and vulnerability to neurobehavioral impairment from sleep deprivation<sup>32</sup> (see above). Quantitative comparisons of the magnitude of trait variability among different populations have essentially not been performed at all. Studies are needed to establish a solid foundation for individual differences research in the sleep field.

*b. Examine possible relationships/independencies among different dimensions of individual variability.* To give an example, the relationships—if any—among individual variabilities in MSLT-defined sleepiness, waking EEG characteristics, vulnerability to sleep loss, and basal sleep need have been scarcely explored. Studies are needed to reduce the multiplicity of potential individual difference factors in sleep research and sleep medicine to make dealing with individual differences more practicable.

*c. Search for markers or biomarkers of trait individual differences in sleep/wake-related variables and for underlying genes.* This kind of research can accelerate cost-effective identification of phenotypes and may have many practical outcomes—such as identification of individuals who are predisposed to certain sleep disorders, resistant to specific medical treatments, at risk due to occupational fatigue, etc.

*d. Investigate the functional significance of trait individual differences in sleep/wake-related variables.* Even though there is evidence regarding the functional correlates of, say, variability in sleep architecture *within* individuals (eg, more slow-wave sleep would be associated with greater sleep homeostatic recovery), the functional significance of systematic variability *between* individuals has remained largely undetermined. The scientific and clinical implications of research aiming to fill this gap could be considerable.

*e. Study the mechanisms underlying trait individual differences in normal sleep, disordered sleep, and treatment efficacy.* The research agenda proposed here would not be complete without a call for basic scientific studies to understand the very phenomenon of individual variability in sleep, sleep regulation, and sleep pathology. Research on the mechanisms underlying trait individual variability, which can benefit from new developments in measurement techniques like neuroimaging, will inform the further development of conceptual and mathematical models of sleep/wake regulation and may provide new criteria to evaluate hypotheses about the mechanisms and functions of sleep and the etiology of sleep disorders.

If properly exploited, the natural variability among humans in numerous aspects of sleep and wakefulness may yield a large amount of scientifically and clinically relevant information. Study designs and statistical approaches suitable for conducting investigations in this emerging area of sleep research have already been developed (see Appendix). Thus, investigations of individual differences can become a productive part of sleep research and sleep medicine and may ultimately help to elucidate the mysteries of sleep.

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This Appendix provides a brief overview of methodology relevant to the study of individual differences. There is a well-developed literature on data analysis in the context of individual variability. For the present purposes, information has been drawn from literature in the fields of psychology,<sup>209</sup> pharmacology,<sup>205</sup> and biomedical statistics.<sup>171</sup>

Analysis techniques concerned with individual differences aim to distinguish different sources of variability—ie, variance components—in the data at hand.<sup>210</sup> In the simplest case, there are 2 distinct variance components: within-subjects variance and between-subjects variance. Within-subjects variance typically reflects changes within individuals over time due to experimental interventions and noise. Within-subjects variance may also include changes within individuals due to neurobiological variation (eg, circadian rhythmicity, learning curves, reactivity to context, effects of aging), apparent changes due to measurement problems (eg, EEG amplifier drift), and other variability over time. Between-subjects variance reflects individual differences not accounted for by variability within subjects; that is, it reflects systematic individual differences over time. Between-subjects variance also may include systematic state differences among individuals that persist over time (eg, consistent differences in caffeine consumption or physical exercise pattern). In order for estimates of between-subjects variance to reliably approximate true endogenous variability (ie, trait variability) among subjects, consistent state differences should be minimized (for instance, by using a laboratory to control environmental factors).<sup>109</sup>

In studies involving only a single measurement per individual, between-subjects variance and within-subjects variance cannot be separated. For studies with repeated measurements (at least 2) per subject, however, various methods are available (in statistical computer software) to distinguish between-subjects variance from within-subjects variance. The easiest to apply is the *standard two-stage* approach: in the first stage, each subject is analyzed separately so as to deal with within-subjects variance; in the second stage, the results of the first stage are used to consider between-subjects variance. More sophisticated approaches include *mixed-effects* analysis of variance (ANOVA) and *mixed-effects* regression analysis, which distinguish within-subjects variance from between-subjects variance in a single step (see Van Dongen et al<sup>210</sup> for a tutorial). A recent comparison between the standard two-stage approach and two variations of the mixed-effects approach found that results were similar,<sup>109</sup> but the standard two-stage approach could be considerably less accurate under specific conditions.<sup>181</sup> Both techniques are superior, however, to simply lumping all the data together and analyzing them as if there were only 1 “average” individual (*naive pooling* approach).<sup>169,171</sup>

The magnitude of individual variability can be expressed with the between-subjects standard deviation, which is the square root of the between-subjects variance. (It should not be confused with standard error, which is a measure of statistical precision, not individual variability.) A statistically valid measure for quantifying the stability of individual differences over repeated measurements is the intraclass correlation coefficient (ICC).<sup>6</sup> The ICC is defined as the between-subjects variance divided by the sum of the between-subjects variance and the within-subjects variance<sup>109</sup> and reflects the correlation between successive measurements on the same subject.<sup>210</sup> The ICC can range from zero to one, with values close to zero signifying relatively large within-subjects variance and comparatively small between-subjects variance, and values close to one signifying the opposite. It follows that the ICC is large when individual differences are considerable (ie, large between-subjects variance) and stable within subjects (ie, small within-subjects variance). In other words, the ICC is a measure of systematic variability between subjects. However, the ICC can also be interpreted as a measure of stability within subjects (across repeated measurements). As such, *interindividual* variability and *intraindividual* stability are related concepts—as formalized in generalizability theory.<sup>167,211</sup>

The ICC should not be interpreted solely on the basis of statistical significance, for statistical significance only reveals whether the ICC is discernibly different from zero. After statistical significance has been established, the actual value of the ICC should drive the interpretation. It is also worth noting that even if nothing else changes, the value of the ICC varies for populations with different amounts of between-subjects vari-

ance (different degrees of heterogeneity).<sup>212</sup> As a consequence, comparing ICC values between studies is only appropriate if the between-subjects variance does not differ significantly between the different samples. It is recommended, therefore, that the values of between-subjects and within-subjects variance be reported along with the value of the ICC.<sup>109</sup>

In the literature, systematic differences between individuals and stabilities within individuals have been analyzed by means of linear correlation analysis (Pearson's  $r$ ), but this approach is suboptimal (eg, it is insensitive to changes across measurements in the between-subjects mean) and less flexible.<sup>109</sup> Correlation statistics only implicitly recognize the partitioning of total variance into between-subjects variance and within-subjects variance, but they are similarly affected by population heterogeneity. It is critically important to ascertain that the variables from which a correlation coefficient is calculated each show large variability relative to measurement uncertainty (or some other minimal quantity of relevance); otherwise, spurious results could be obtained. The statistical significance of correlation coefficients is primarily a function of sample size<sup>213</sup>—as with the ICC, the actual value of the correlation coefficient should drive the interpretation. Correlation coefficients obtained from small samples are biased; adjusted correlation coefficients are available in various statistical software packages. There are additional issues to consider when calculating the correlation coefficient between two variables with repeated measurements—see the tutorials by Bland and Altman<sup>214–216</sup> and the work of Lin.<sup>217</sup>

The concepts of variability and stability also form a basis for twin studies, albeit that repeated measurements within subjects (ie, across time) are replaced by repeated measurements within twin pairs (ie, across twins). The crux of a twin study is that genetically determined variables will replicate more precisely within monozygotic (MZ) twin pairs (because of the identical genetic profile) than within dizygotic (DZ) twin pairs. One way to assess the importance of genetic background for a particular variable is to compute a heritability estimate.<sup>218</sup> This involves determining the between-twin-pairs variance (as the equivalent of between-subjects variance) and the within-twin-pairs variance (as the equivalent of within-subjects variance) to calculate the ICC, separately for the MZ twin pairs ( $ICC_{MZ}$ ) and the DZ twin pairs ( $ICC_{DZ}$ ). The heritability estimate is then computed as  $h^2 = 2 (ICC_{MZ} - ICC_{DZ})$ . The use of the ICC underlines the importance of having variability among twin pairs for the variable in question. In fact, the results of twin studies depend on trait variability—and vice versa, trait variability may be inferred from the results of twin studies.

Just like systematic state differences among individuals that remain constant over time confound estimates of trait variance (see above), so does common environment (cohabitation) confound estimates of heritability.<sup>219</sup> In fact, twin studies are more powerful at detecting effects of familial background than of genotype.<sup>220</sup> It is possible to control for cohabitation effects by exclusively studying twins living apart or by adjusting for cohabitation during statistical analysis (which still requires at least some pairs of twins living apart). Much more has been written on the topic (eg, with regard to interactions between genetic susceptibility and environmental or developmental influences); readers should refer to the literature for further information.<sup>221–224</sup>

For studies with repeated measurements in which individual differences are not of primary interest, statistical analysis techniques that take individual variability into account (such as mixed-effects ANOVA and mixed-effects regression analysis) are often still preferable over traditional analysis techniques that cannot handle individual variability (eg, repeated-measures ANOVA and multiple regression analysis). The reason is that these latter methods confound error variance with between-subjects variance, resulting in unreliable standard errors and evaluations of statistical significance.<sup>169</sup> For example, unnecessarily large standard errors have been encountered in traditional analyses of time constants for the two-process model of sleep regulation,<sup>23</sup> due to confounding individual variability. To overcome this problem, nonlinear mixed-effects regression analysis could be employed. This would enhance statistical power, and yield an estimate of the magnitude of individual differences in the time constants as well.



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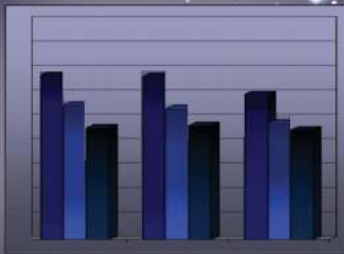
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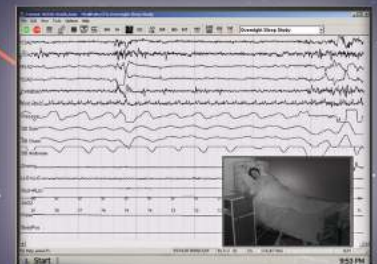
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