

# CANDIDATE PREDICTORS OF VULNERABILITY TO SLEEP DEPRIVATION

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## INTRODUCTION

Individuals have been documented to vary systematically in their neurobehavioral responses to sleep restriction; such trait-like inter-individual differences in vulnerability to sleep loss have become evident in recent studies with repeated exposure to sleep loss in the same subjects.<sup>(1,2)</sup>

Van Dongen and colleagues<sup>(1)</sup> studied performance impairment from sleep loss in 21 subjects over two identical exposures to 36 hours of sleep deprivation in a controlled laboratory environment. Every 2 hours, subjects underwent a neurobehavioral test battery including 13 performance tasks and self-report assessments of sleepiness. For each subject, averages were computed over the last 24 hours of each 36-hour sleep deprivation period. The intra-class correlation coefficient (ICC), a measure of stable inter-individual variability, ranged from 78.9% to 95.8% across the different outcome measures, which provided strong evidence for substantial trait-like inter-individual differences in vulnerability to sleep loss.

Leproult and colleagues<sup>(2)</sup> studied 8 men in two 27-hour sessions of maintained wakefulness under constant routine. Every hour, subjects were administered a selective attention task, a sustained attention task and a visual analog scale of vigor. It was found that performance deficits were a highly reproducible individual characteristic. Scores of alertness during the first sleep deprivation were reproducible (90% correlation) for a given individual on the second trial, several weeks later. Both Leproult et al.<sup>2</sup> and Van Dongen et al.<sup>1</sup> observed that inter-individual differences in objective performance measures were incongruent with inter-individual differences in subjective assessments.

Here we report on a preliminary investigation to identify psychological, neuroendocrine and physiological predictors for trait-like inter-individual variability in the vulnerability to neurobehavioral deficits from sleep loss.

## METHODS

### Subjects and Procedures

As part of a larger study, 21 healthy subjects (age 29.5±5.3; 9 females) underwent 36 hours of laboratory-based sleep deprivation on two occasions, separated by at least 2 weeks. During the 7 days prior to each deprivation, subjects were required to spend 12 hours time in bed (22:00–10:00) daily. During the subsequent in-laboratory session, subjects underwent a 12-hour baseline sleep period, followed by the 36-hour sleep deprivation period. Core body temperature was recorded rectally at 6-minute intervals throughout this 36-hour sleep deprivation period. After the sleep deprivation, subjects received 12 hours time in bed for recovery sleep.

Every 2 hours during sleep deprivation, subjects completed a 1-hour neurobehavioral test battery which included the Karolinska Sleepiness Scale (administered at the beginning and end of the battery: KSS1 and KSS2), serial addition/subtraction task (SAST), digit symbol substitution task (DSST), word detection task (WDT), repeated acquisition of response sequences task (RARST), and psychomotor vigilance task (PVT). The outcome measures were the subjective sleepiness score for the KSS, the number of correct responses for the DSST, SAST and WDT, the number of acquisitions for the RARST, and the number of lapses (reaction time  $\geq 500$ ms) for the PVT. For each subject, an average was computed over the last 24 hours (i.e., across the circadian cycle) of each sleep deprivation period as well as over the two sleep deprivation periods (as previous analyses had shown that subjects' responses were stable across the two sleep deprivations<sup>1</sup>). This method yielded a single measure of impairment per subject for each outcome variable.

Prior to the experiment, subjects underwent a laboratory adaptation session, during which they were acclimated to sleeping in the laboratory and practiced the neurobehavioral test battery.

#### Predictor Variables

Before the adaptation session, subjects completed 11 questionnaires measuring psychological, stress- and sleep-related characteristics, and underwent a blood screening. The scores on all 46 subscales of the questionnaires were evaluated as candidate predictors of vulnerability to sleep loss. The concentrations of 41 different hormones, cells, enzymes and ions from the blood screening were also used as candidate predictors of inter-individual differences in vulnerability to sleep loss. The circadian phase and amplitude of the core body temperature rhythm, determined by fitting a two-harmonic sinusoidal curve after artifact rejection, were included as candidate predictor variables as well. A final source of candidate predictors involved subjects' demographic information including gender, age, height, weight, body mass index (BMI) and handedness. For statistical analysis, each candidate predictor was grouped into one of eleven domains, as shown in Table 1.

#### Statistical Analysis

First, candidate predictors were analyzed for each domain independently. For every neurobehavioral outcome (e.g., PVT lapses, KSS scores, etc.), all candidate predictor variables in a given domain were entered into a forward stepwise regression analysis against the individual subjects' neurobehavioral deficits from sleep loss. Entry and removal criteria for the stepwise regression were set at 0.05 and 0.10, respectively. For each domain, only the one predictor variable that explained the most variance (if any significant predictor variables emerged) was selected for further analysis, so as to prevent saturation of the final statistical model by inclusion of too many predictors. Then, a cross-domain linear regression analysis was performed using the selected predictors, with the purpose of identifying an overall equation, for each neurobehavioral outcome, that predicted the systematic inter-individual differences in the response to sleep loss.

Table 1: Candidate Predictors Categorized By Domain.

<i>Domain</i>	<i>Variables Included</i>
Demographics <sup>1</sup> Stress Variables <sup>1</sup>	gender, age, weight, height, body mass index, handedness conflict/stress questionnaire, Spielberg state-trait anxiety inventory, Penn State worry questionnaire, survey of work styles
Baseline Sleep and Circadian Parameters <sup>1,3</sup>	morningness/eveningness questionnaire, Epworth sleepiness scale, Pittsburgh sleep quality questionnaire, sleep disorders questionnaire, multivariate apnea predictor, amplitude and phase of body temperature
Personality <sup>1</sup>	Marlowe-Crowne social desirability scale, Eysenck personality inventory, Myers-Briggs type indicator, Minnesota multiphasic personality inventory
Immune Parameters <sup>2</sup>	number of white blood cells, % granulocytes, % lymphocytes, % basophils, % mononuclears, % eosinophils
Erythrocyte Make-Up <sup>2</sup>	number of red blood cells, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell distribution width, platelets
Gastrointestinal Indicators <sup>2</sup> Sex Hormones <sup>2</sup>	triglycerides, cholesterol, iron, transferrin luteinizing hormone, follicle stimulating hormone, testosterone
Kidney Function Indicators <sup>2</sup> Enzymes <sup>2</sup>	potassium, chlorine, urea nitrogen, creatinine, calcium, phosphate, uric acid, total protein, albumin, total bilirubin alanine transaminase, aspartate aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase
Miscellaneous <sup>2</sup>	thyroid stimulating hormone, DHEA-sulfate, carbon dioxide

<sup>1</sup>from questionnaires; <sup>2</sup>from blood screen; <sup>3</sup>from core body temperature

## RESULTS

For each neurobehavioral outcome measure, with the exception of the SAST, there were predictor variables that, when combined across domains, explained significant amounts of variance. For the WDT, 68% of the variance could be explained by considering plasma dehydroepiandrosterone-sulfate, plasma total bilirubin, red blood cell distribution width (RDW) and body-mass index (BMI) as predictors. For the RARST, 54% of the variance was explained by (small variation in) the sleep disorders questionnaire (psychiatric sleep disorder subscale), plasma total bilirubin and age. For the DSST, 49% of the variance was explained by plasma hematocrit, plasma creatinine and weight. For the PVT, levels of urea nitrogen and handedness accounted for 12% of the variance. The predictive model that emerged for the first administration of the KSS explained 9% of the variance with testosterone, transferrin and DHEA-sulfate. For the second administration of the KSS, 51% of the variance was explained by considering potassium, transferrin, testosterone and thyroid stimulating hormone (TSH). Table 2 summarizes the results.

Table 2: Significant Predictor Variables for Each Neurobehavioral Outcome.

<i>Neurobehavioral Outcome</i>	<i>Predictor Variables</i>	<i>R<sup>2</sup></i>
KSS1	DHEA-sulfate, transferrin, testosterone	0.09
KSS2	potassium, transferrin, testosterone, TSH	0.51
WDT	DHEA-sulfate, total bilirubin, RDW, BMI	0.68
RARST	total bilirubin, psychiatric sleep disorder subscale, age	0.54
DSST	hematocrit, creatinine, weight	0.49
SAST	—	—
PVT	urea nitrogen, handedness	0.12

*R<sup>2</sup>* stands for explained variance

Since the two administrations of the KSS were highly correlated, the analysis of the first administration was repeated using the candidate predictors originally identified for the second. In this analysis, 63% of the variance was explained.

## **DISCUSSION**

The extent to which inter-individual differences in responses to sleep deprivation could be predicted appeared to vary according to the neurobehavioral outcome considered. For most of the cognitive performance measures, a relatively large percentage of the variance could be explained with selected predictors from the set of candidates evaluated in this study. Predictive power for subjective sleepiness was inconsistent—a considerable amount of variance was accounted for in the second administration of the KSS, while only a small amount of variance was explained in the first administration. This latter result was markedly improved when the predictors identified for the second KSS were applied in the cross-domain regression analysis for the first KSS. This suggests that the present two-stage approach relying on forward stepwise regression to identify domain-specific candidate predictors followed by cross-domain linear regression on the selected candidates may leave promising candidate predictors unidentified. Other methods of dimensionality reduction like principal components analysis or computer-intensive model selection methods such as the bootstrap should be considered in further research.

Candidate predictors grouped under the domains of immune parameters (from blood screen), gastrointestinal indicators (from blood screen), enzymes (from blood screen), personality (from questionnaires), and stress variables (from questionnaires) proved to be least predictive, yielding no significant predictors in stepwise forward regression for any of the neurobehavioral outcomes. Surprisingly, the generally most predictive domain for inter-individual differences in vulnerability to sleep deprivation was the kidney function domain (including levels of potassium, urea nitrogen, creatinine, and total bilirubin). The extent to which these variables stay predictive of vulnerability to sleep loss across different subject samples remains to be established.

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