pii: jc-17-00138 http://dx.doi.org/10.5664/jcsm.6720

JCSM
Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Psychomotor Vigilance Test and Its Association With Daytime Sleepiness and Inflammation in Sleep Apnea: Clinical Implications

Yun Li, MD[1,2]; Alexandros Vgontzas, MD[1]; Ilia Kritikou, MD[1]; Julio Fernandez-Mendoza, PhD[1]; Maria Basta, MD[1]; Slobodanka Pejovic, MD[1]; Jordan Gaines, PhD[1]; Edward O. Bixler, PhD[1]

[1]Sleep Research and Treatment Center, Department of Psychiatry, Pennsylvania State University College of Medicine, Hershey, Pennsylvania; [2]Mental Health Center, Shantou University Medical College, China

Study Objectives: Excessive daytime sleepiness (EDS) is a key symptom of obstructive sleep apnea (OSA). The Psychomotor Vigilance Task (PVT) has been suggested as an objective easy-to-use, inexpensive alternative to the Multiple Sleep Latency Test (MSLT) to measure EDS. In patients with OSA, physiological sleepiness, but not subjective EDS (Epworth Sleepiness Scale [ESS]), has been associated with increased levels of the sleep- inducing proinflammatory cytokine interleukin-6 (IL-6). The goal of this study was to assess the association of PVT with objectively measured sleepiness (MSLT) and subjectively measured sleepiness (ESS) and IL-6 levels in patients with OSA.

Methods: We studied 58 untreated patients with OSA who underwent an 8-hour in-laboratory polysomnography for 4 consecutive nights. MSLT, PVT, and 24-hour serial profiles of IL-6 were assessed on the fourth day. PVT variables included number of lapses, mean reciprocal of the fastest 10% and slowest 10% reaction times, and median of 1/reaction time. ESS was assessed on day 1 of the study.

Results: Higher ESS scores were significantly associated with greater number of lapses (β = .34, *P* = .02) and lower values of 1/RT (β = −.36, *P* = .01) and slowest 10% RTs (β = −.30, *P* = .04). No significant association was observed between PVT and MSLT, nor PVT and IL-6 levels.

Conclusions: Our findings suggest that PVT is associated with subjectively assessed daytime sleepiness, but not with physiological sleepiness nor IL-6 levels in patients with OSA. It appears that ESS and PVT may be useful in predicting risks associated with impaired performance, such as traffic accidents, in patients with OSA.

Keywords: daytime sleepiness, objective daytime sleepiness, Psychomotor Vigilance Task, sleep apnea, subjective daytime sleepiness

Citation: Li Y, Vgontzas A, Kritikou I, Fernandez-Mendoza J, Basta M, Pejovic S, Gaines J, Bixler EO. Psychomotor vigilance test and its association with daytime sleepiness and inflammation in sleep apnea: clinical implications. *J Clin Sleep Med.* 2017;13(9):1049–1056.

INTRODUCTION

Excessive daytime sleepiness (EDS) is one of the most common complaints of patients with obstructive sleep apnea (OSA) and an important criterion for diagnosis and treatment of OSA.[1] The prevalence of EDS in OSA is 16% to 22%[2–5] in epidemiologic samples, and is the most common complaint in clinical samples.[6]

We have previously shown that EDS measured by the Multiple Sleep Latency Test (MSLT) in patients with OSA is associated with increased levels of the proinflammatory cytokine interleukin-6 (IL-6); however, EDS measured by the Epworth Sleepiness Scale (ESS) is not.[7] These findings suggest that objective EDS compared to subjective EDS is a stronger predictor of OSA severity in terms of cardiometabolic risk. However, given that the MSLT is rather costly, impractical, and must be conducted in a sleep laboratory, there is a need to develop simpler, less expensive tests for measuring objective daytime sleepiness in patients with sleep apnea.

The Psychomotor Vigilance Task (PVT) is widely used in assessing behavioral alertness and sustained attention related to sleepiness induced through sleep deprivation and/or associated with sleep disorders, such as OSA.[8–15] It has been shown that sleepiness, as a result of chronic sleep restriction or total sleep deprivation, is associated in a dose-response manner with impaired PVT performance.[13] Dinges and colleagues reported that sleep restriction to 4 to 5 hours per night for 1 week resulted in significantly elevated subjective daytime sleepiness (as measured by the Stanford Sleepiness Scale) and progressive deterioration of PVT performance across the days of restricted sleep.[10] Furthermore, impaired PVT performance was correlated closely with lower MSLT sleep latency.[10] In contrast,

BRIEF SUMMARY

Current Knowledge/Study Rationale: Daytime sleepiness is a key symptom in patients with OSA; however, determining the best method of assessing excessive daytime sleepiness (EDS) in terms of its clinical utility and ease of use is currently an open issue.

Study Impact: In this study, we demonstrate that Psychomotor Vigilance Task correlates best with subjectively measured EDS (via Epworth Sleepiness Scale) but not objectively measured EDS (via Multiple Sleep Latency Test) nor peripheral levels of IL-6. It appears that the Epworth Sleepiness Scale is a good predictor of impaired performance and associated risks, such as traffic accidents, in patients with OSA, but not of cardiometabolic risk, as assessed by inflammation. Thus, it is possible that subjective and objective EDS reflect different central nervous system processes with different underlying mechanisms.

Franzen and colleagues suggested that PVT performance decrement did not correlate with objective (measured by MSLT and spontaneous oscillations in pupil diameter) or subjective (measured by visual analog scale) sleepiness in totally sleep-deprived individuals.[16]

PVT has also been used as a sensitive method to assess the attentional capability of patients with OSA. Most studies have shown that patients with OSA have worse PVT performance as compared to controls,[12,17–19] and that the impairment correlates significantly with the severity of OSA (ie, apnea-hypopnea index [AHI] correlates with number of lapses).[19] Sforza and colleagues reported that in patients with OSA, objectively measured daytime sleepiness via the Maintenance of Wakefulness Test (MWT) is associated with slower reaction time in PVT, whereas subjectively assessed daytime sleepiness measured by ESS is associated with increased numbers of lapses.[12] Furthermore, PVT performance has been used to assess the efficacy of therapeutic interventions, such as the use of modafinil to reduce residual sleepiness in patients with OSA treated with continuous positive airway pressure.[20]

Only one study has examined simultaneously the association between MSLT, ESS, and PVT performance in OSA. In a community-based sample study, Kim et al.[19] suggested that impaired PVT performance (slower response time, increased lapses, and longer duration on fastest 10% and slowest 10% reaction times) was associated with higher ESS scores. No association was observed between PVT and MSLT. In this report, however, the study sample was elderly (age range 65 to 74 years), a population with typically fewer complaints of EDS compared to younger patients with sleep apnea.[21] Furthermore, no study has examined the association between PVT performance and IL-6 levels.

The goal of our study was to examine the association of PVT with objective (measured by MSLT) and subjective (measured by ESS) sleepiness and peripheral IL-6 levels in a population of middle-aged men and women with moderate to severe OSA.

METHODS

Subjects

The study included 58 untreated research participants in whom OSA had been diagnosed (37 male, 63.8%). The subjects were recruited from the Sleep Disorders Clinic at Penn State Hershey Medical Center and through advertisements from the community. To qualify for the study, patients with OSA had to have apnea of sufficient severity to warrant recommendation for treatment based on a standard clinical polysomnography at the time of screening or clinical evaluation.[22] These criteria included an AHI cutoff of ≥ 10 events/h of sleep for women and ≥ 15 events/h for men, plus clinical symptoms such as EDS and/or the presence of cardiovascular abnormalities (eg, hypertension or cardiac arrhythmias). A lower threshold of AHI was chosen for women because women have on average lower indices of respiratory disturbance and they tend to manifest symptoms at a lower threshold.[23] All of our subjects were recruited prior to any treatment that they may have received for OSA from their clinician.

A thorough medical assessment, including physical examination, routine laboratory tests (including complete blood cell count, urinalysis, basic metabolic profile, thyroid function tests, electrocardiography, and urine drug screen), and sleep history was completed for each subject. Those who were positive for abnormal findings in the battery of clinical tests were excluded from the study. Exclusion criteria for all subjects included a history of type 2 diabetes mellitus, use of antiglycemic agents and/or fasting glucose blood levels > 126 mg/dL at the time of screening, ongoing infections, autoimmune diseases, insomnia, narcolepsy, and use of medications that could affect the outcome variables (psychotropic agents, steroids, sympathomimetic agents, or sympatholytic agents, anti-inflammatory agents, and hormone replacement therapy for women). Subjects with extreme sleep schedules or with a primary circadian disorder were excluded from the study. Patients with OSA in whom continuous positive airway pressure therapy previously were excluded from the study. The study was approved by the Penn State University College of Medicine Institutional Review Board and all participants provided written informed consent.

Sleep Laboratory

All potential participants were screened in the sleep laboratory for 1 night for 8 hours; subjects who met the inclusion criteria were then monitored in the sleep laboratory for 4 consecutive nights (1 adaptation and 3 baseline nights). During this time, the subject's sleep was continuously monitored for 8 hours (24-analogue-channel and 10-DC-channel Aurora TS amplifier system using Gamma software; Grass-Telefactor, West Warwick, Rhode Island, United States). A 4-channel electroencephalogram, 5-channel electrooculogram, and single-channel electromyogram were recorded. The sleep records were subsequently scored independently according to standardized criteria. Respiration was monitored throughout the night by use of thermocouple at the nose and mouth (Pro-Tech, Murrysville, Pennsylvania, United States), nasal pressure (Validyne Engineering, Northridge, California, United States), and thoracic and abdominal strain gauges (model 1312; Sleepmate Technologies; Midlothian, Virginia, United States). A single-channel electrocardiogram was also recorded. All-night hemoglobin oxygen saturation was obtained from the finger (model 8600; Nonin Medical; Plymouth, Minnesota, United States). Anthropometric parameters were obtained and body mass index (BMI) was calculated based on height and weight measured as part of the physical examination. Fatigue was defined by a single question of "Do your sleep problems make you feel tired or fatigued? NO or YES" at the time of screening.

Daytime Sleepiness and Psychomotor Vigilance Performance

Multiple Sleep Latency Test

MSLT was conducted immediately after night 3 (during day 4) of polysomnography (PSG) recording (9:00 AM, noon, 3:00 PM, and 5:00 PM) (**Table 1**). The severity of objective daytime sleepiness was evaluated using MSLT according to the standard protocol.[24] Lower values of MSLT indicate more

Table 1—Study protocol in patients with obstructive sleep apnea.

Tasks	Day 1		Day 2		Day 3		Day 4	
	Day	Night	Day	Night	Day	Night	Day	Night
PSG		X		X		X		X
MSLT							X	
PVT							X	
ESS	X							
Blood drawing							X	X

ESS = Epworth Sleepiness Scale, MSLT = Multiple Sleep Latency Test, PSG = polysomnography, PVT = Psychomotor Vigilance Task.

objective daytime sleepiness.[24,25] None of the participants demonstrated sleep-onset rapid eye movement periods. We modified the standard protocol of MSLT by increasing the time interval between 2 naps from 2 to 3 hours to cover a longer part of the daytime period.

Epworth Sleepiness Scale

On day 1 of the study, subjective sleepiness was assessed using the ESS (**Table 1**). The ESS is a well-validated questionnaire quantifying the self-reported disclosure of the expectation of "dozing" in a variety of situations.[26] Higher scores of ESS indicate more subjective daytime sleepiness.[26]

Psychomotor Vigilance Task

PVT is a test of behavioral alertness, and it involves a simple (as opposed to choice) reaction time (RT) test designed to evaluate the ability to sustain attention and respond in a timely manner to salient signals.[8,13] The primary variables assessed in our study were (1) total number of lapses (RTs $\geq$ 500 ms) subjected to Tukey transform ($[\sqrt{x} + \sqrt{(x+1)}]$), labeled as PVT LAPSES; (2) response speed defined as mean 1/RT (seconds^{-1}) during the 10-minute testing period, labeled as PVT 1/RT; (3) the mean of the reciprocal of the slowest 10% RTs (seconds^{-1}), labeled PVT SLOWEST 10% and (4) the mean of the reciprocal of the fastest 10% RTs (seconds^{-1}), labeled PVT FASTEST 10%. Reciprocal and Tukey transformation ($[\sqrt{x} + \sqrt{(x+1)}]$) were used to provide normal distribution of the variables. Higher scores on 1/RT, SLOWEST 10% and FASTEST 10% indicate better performance; higher scores on LAPSES indicate poorer performance. Four trials of PVT were administered on the fourth day (**Table 1**) at 8:00 AM, 11:00 AM, 2:00 PM, and 4:00 PM. Each PVT trial lasted for 10 minutes, and each subject had three practice trials within 1 hour the night before the next day's testing.

Depressive Symptoms

Depressive symptomatology was assessed both clinically and using the Beck Depression Inventory-II (BDI-II). None of the subjects met the criteria for a current episode of major depression disorder. Of the participants, 3 subjects with OSA scored above the recommended cutoff point above 19 for moderate depression. For the purposes of the current study, we calculated a total score of modified BDI-II (mBDI-II) after excluding item 20 assessing daytime sleepiness/fatigue. We observed no significant difference between mBDI-II (6.86 ± 7.32) and the original score of BDI-II (6.92 ± 5.95, $P = .962$).

24-Hour Blood Sampling

Twenty-four-hour serial blood samples were collected every 60 minutes on the fourth day and night in the sleep laboratory (**Table 1**). An indwelling catheter was inserted in the antecubital vein about 30 minutes before the first blood draw. During the sleep periods, blood samples were obtained from an adjacent room by connecting external tubing to the indwelling catheter through a perforation in the wall.

Hormone and Cytokine Assays

Blood collected from the indwelling catheter was transferred to a tube containing ethylenediaminetetraacetic acid and refrigerated until centrifugation (within 3 hours). The plasma was frozen at −80°C until assay. Plasma IL-6 was measured by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minnesota, United States) as previously described.[27] The lower limit of detection for IL-6 was 0.094 pg/mL. Given that IL-6 has been shown to be the proinflammatory cytokine with the best correlation to daytime sleepiness in humans,[14,15,27,28] we used peripheral IL-6 as a marker of inflammation in this study.

Statistical Analysis

Sleep variables were calculated based on the mean values from nights 2 and 3 in order to avoid the first-night effect as well as the sleep-disturbing effect of blood drawing (night 4). Bivariate correlations were performed in order to explore the associations between PVT performance, MSLT values, ESS scores, and peripheral IL-6 levels as well as demographic and sleep variables. In order to examine the association of PVT with objective and subjective daytime sleepiness and peripheral IL-6 levels, we conducted multiple linear regression models with PVT LAPSES, 1/RT, SLOWEST 10% and FASTEST 10% as predictors and continuous MSLT, ESS values and IL-6 levels as outcomes. Because significant associations among 4 measures of PVT (PVT LAPSES, 1/RT, SLOWEST 10% and FASTEST 10%) were observed (all values of $P < .003$), we examined the association between each measure of PVT and MSLT, ESS and IL-6 levels (24-hour mean, daytime and nighttime) in separate multiple linear regression models.

Table 2—Demographic and sleep characteristics, and their correlations with Psychomotor Vigilance Task variables in patients with obstructive sleep apnea.

		PVT Performance							
		LAPSES		1/RT (s^{-1})		SLOWEST 10% (s^{-1})		FASTEST 10% (s^{-1})	
Sample Characteristics (n = 58)		***r***	***P***	***r***	***P***	***r***	***P***	***r***	***P***
Age (years)	53.73 ± 7.02	−.187	.171	.015	.914	.062	.648	.005	.971
Male, n (%)	37 (63.8)	.169	.218	.135	.325	−.134	.326	**.272**	**.045**
BMI (kg/m^2)	31.10 ± 5.29	**.369**	**.006**	**−.273**	**.044**	**−.309**	**.020**	−.151	.272
Obesity (≥ 30 kg/m^2), n (%)	37 (63.8)	.213	.119	**−.288**	**.033**	−.180	.186	**−.312**	**.020**
mBDI-II score	6.86 ± 7.32	.137	.320	.043	.758	−.083	.542	.145	.291
Sleep onset latency (min)	16.52 ± 9.67	−.170	.215	.097	.480	.072	.596	.115	.402
Total sleep time (min)	372.44 ± 48.88	.058	.674	−.069	.614	−.036	.794	−.145	.290
Sleep efficiency (%)	77.44 ± 10.25	.056	.687	−.069	.618	−.033	.811	−.147	.284
Stage 1 (%)	19.87 ± 9.61	**.296**	**.028**	−.072	.602	**−.255**	**.057**	.195	.153
Stage 2 (%)	56.55 ± 11.86	**−.076**	**.058**	−.091	.511	.102	.455	−.162	.237
Slow wave sleep (%)	10.06 ± 9.90	**−.274**	**.043**	.175	.201	**.255**	**.025**	−.042	.759
REM (%)	13.52 ± 6.59	.121	.377	−.004	.975	−.196	.147	.064	.644
Wake after sleep onset (min)	79.16 ± 57.48	−.152	.269	.123	.372	.114	.401	.121	.379
REM onset latency (min)	124.10 ± 71.02	−.210	.125	.122	.375	.173	.203	.031	.820
AHI (events/h)	40.93 ± 23.56	.208	.127	−.104	.450	**−.222**	**.100**	.091	.509
Min SaO_2 (%)	79.52 ± 8.07	**−.491**	**< .001**	**.356**	**.008**	**.386**	**.003**	**.265**	**.051**
Self-reported sleep onset latency (min)	23.56 ± 20.21	.070	.625	−.139	.332	−.133	.346	−.090	.529
Self-reported sleep duration (h)	6.64 ± 1.44	−.072	.601	−.067	.628	.010	.942	−.220	.107

Characteristics values are presented as mean ± standard deviation or n (%) as indicated. Values that are associated with a *P* value < .1 are given in bold. 1/RT response speed defined as mean 1/RT ($seconds^{-1}$) during the 10-minute testing period. AHI = apnea-hypopnea index, BMI = body mass index, FASTEST 10% = the mean of the reciprocal of the 10% fastest RTs ($seconds^{-1}$), LAPSES = total number of lapses (RTs ≥ 500 ms) subjected to Tukey transform ($[\sqrt{x} + \sqrt{(x+1)}]$), mBDI-II = modified Beck Depression Inventory score, REM = rapid eye movement sleep stage, RT = reaction time, SaO_2 = arterial oxygen saturation; SLOWEST 10% = the mean of the reciprocal of the 10% slowest RTs ($seconds^{-1}$).

Multiple logistic regression models were used to examine the association between PVT performance and fatigue. Age, sex, and BMI were always entered in the models as covariables using a force entry method, whereas other relevant demographic ($P \leq .1$) and sleep ($P \leq .1$) covariables were entered in the models using a backward method. In models with PVT LAPSES as a predictor, we adjusted for age, sex, BMI, percentage of sleep stage 1, slow wave sleep, and minimum arterial oxygen saturation (SaO_2); in models with PVT 1/RT as a predictor, we adjusted for age, sex, BMI, and minimum SaO_2; in models with PVT SLOWEST 10% as a predictor, we adjusted for age, sex, BMI, percentage of sleep stage 1 and slow wave sleep and minimum SaO_2; in models with PVT FASTEST 10% as a predictor, we adjusted for age, sex, BMI, and minimum SaO_2. Because IL-6 levels exhibit a periodic cosine pattern within 24 hours, 3 parameters (24-hour mean [M], fluctuation amplitude [A], and acrophase [θ, the lag from the reference time point, 8:00 AM, to the time of the zenith of the cosine curve]) were used to characterize the circadian pattern of IL-6 level for each subject. We then used random-effects meta-analysis to evaluate the association between PVT performances and the 3 components (M, A, and θ) at the population level. Regression coefficients generated from the model present the corresponding change in 24-hour mean (in pg/dL), fluctuation (in pg/dL), and delay in the acrophase (in hours), for M, A, and θ, respectively. A general linear model was used to examine dose-response association between ESS and PVT performance.

The circadian analyses were conducted using SAS software (version 9.4, SAS Institute, Cary, North Carolina, United States). All other analyses were conducted using SPSS 22.0 (IBM Corp., Armonk, New York, United States).

RESULTS

Characteristics of the Study Population

Our study included 58 patients with moderate to severe OSA (mean AHI 40.93 ± 23.56) of mean age 53.73 ± 7.02 years, and 37 (63.8%) were men. The mean values of MSLT and ESS scores of our sample were 10.83 ± 4.51 minutes and 11.29 ± 4.82 minutes, respectively; 84.4% subjects reported fatigue. The correlations between PVT performance, demographic and sleep characteristics are presented in **Table 2**.

Association of PVT Performance With Objective Daytime Sleepiness

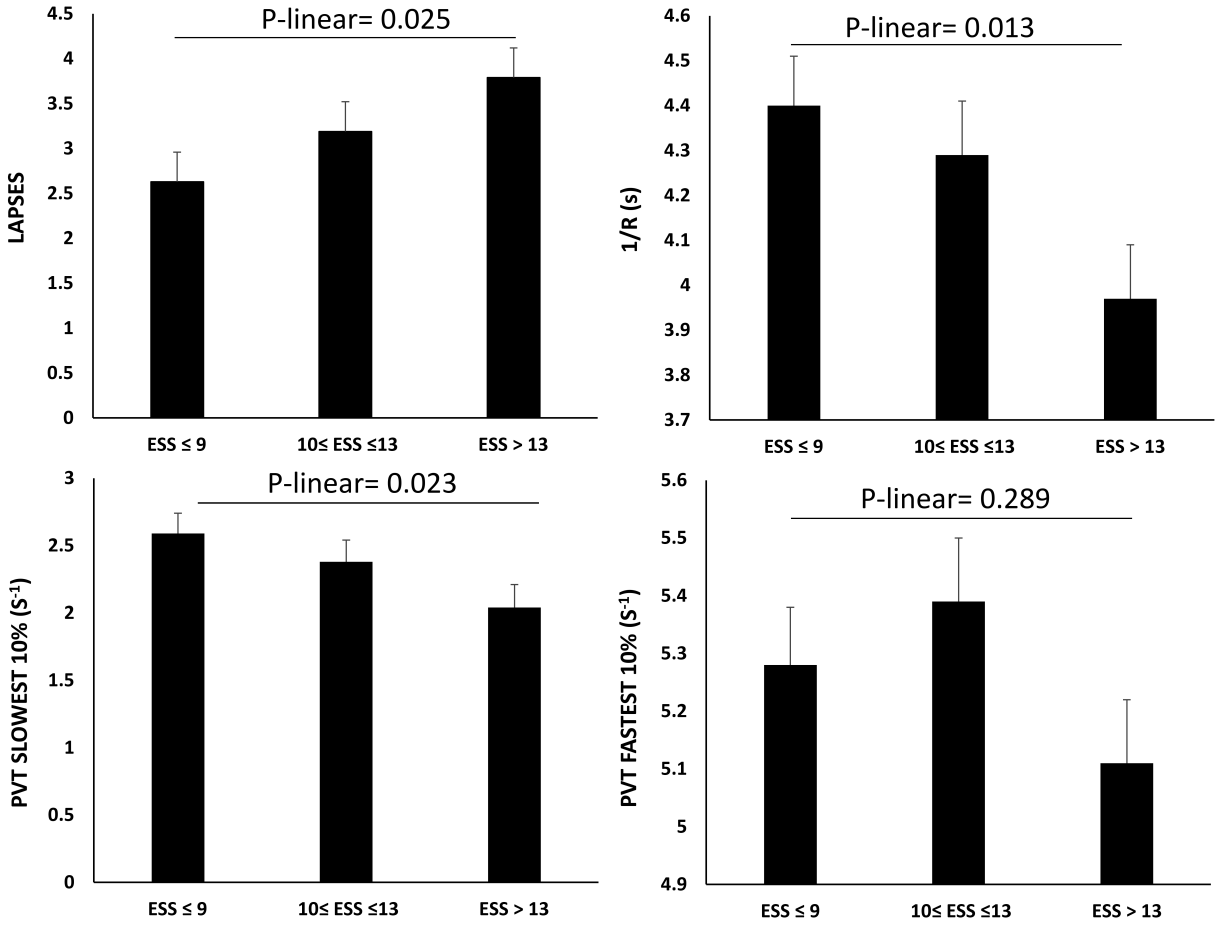
In multiple linear regression models, after adjusting for age, sex, and BMI, as well as other relevant demographic ($P \leq .1$) and sleep ($P \leq .1$) covariables, impaired PVT performance was not significantly associated with lower MSLT values in OSA patients (**Table 3**).

Table 3—The association between Psychomotor Vigilance Task variables, Multiple Sleep Latency Test values, Epworth Sleepiness Scale scores, and interleukin-6 levels in patients with obstructive sleep apnea.

	Predictors							
	PVT LAPSES		PVT 1/RT (s^{-1})		PVT SLOWEST 10% (s^{-1})		PVT FASTEST 10% (s^{-1})	
Outcome Variables	**β**	***P***	**β**	***P***	**β**	***P***	**β**	***P***
MSLT (min)	−.182	.206	.127	.362	.196	.157	.023	.872
ESS (score)	.344	.021*	−.356	.013*	−.295	.041*	−.211	.150

β and *P* values of multiple regression models were calculated after adjusting for potential confounders. * = $P < .05$. ESS = Epworth Sleepiness Scale, MSLT = Multiple Sleep Latency Test, PVT = Psychomotor Vigilance Task, PVT LAPSES = total number of lapses (RTs ≥ 500 ms) subjected to Tukey transform ($[\sqrt{x} + \sqrt{(x+1)}]$), PVT 1/RT = response speed defined as mean 1/RT ($seconds^{-1}$) during the 10 minute testing period, PVT SLOWEST 10% = the mean of the reciprocal of the 10% slowest RTs ($seconds^{-1}$), PVT FASTEST 10% = the mean of the reciprocal of the 10% fastest RTs ($seconds^{-1}$), RT = reaction time.

Figure 1—Psychomotor Vigilance Task performance across different levels of subjective daytime sleepiness in patients with obstructive sleep apnea.



Error bars indicate standard error. ESS = Epworth Sleepiness Scale, PVT = Psychomotor Vigilance Task.

Association of PVT Performance With Subjective Daytime Sleepiness and Fatigue

As shown in **Table 3**, impaired PVT performance (ie, higher scores on PVT LAPSES [β = .34, $P = .02$], lower scores on PVT 1/RT [β = −.36, $P = .01$], and PVT SLOWEST 10% [β = −.30, $P = .04$]) were significantly associated with higher ESS scores while adjusting for age, sex, BMI, and other relevant demographic ($P \leq .1$) and sleep ($P \leq .1$) covariables based on findings in **Table 2**. ESS scores were not associated with PVT FASTEST 10% RTs (β = −.21, $P = .15$). Furthermore, among patients with OSA, higher values of PVT LAPSE and lower values of PVT 1/RT and PVT SLOWEST 10% RTs were significantly associated with higher ESS values (when divided by tertile) in a dose-response manner while adjusting for confounding factors (**Figure 1**). Furthermore, fatigue was not significantly associated either with PVT variables (all values of $P > .4$) or with IL-6 levels (all values of $P > .2$).

Table 4—The association between Psychomotor Vigilance Task variables and interleukin-6 levels in patients with obstructive sleep apnea.

		Predictors							
		PVT LAPSES		PVT 1/RT (s^{-1})		PVT SLOWEST 10% (s^{-1})		PVT FASTEST 10% (s^{-1})	
Outcome Variables	**n**	**β**	***P***	**β**	***P***	**β**	***P***	**β**	***P***
Linear regression models									
24-h IL-6 (pg/mL)	58	.014	.928	.157	.289	.027	.857	.056	.705
Daytime IL-6 (pg/mL)	58	−.029	.856	.177	.236	.067	.655	.089	.553
Nighttime IL-6 (pg/mL)	58	.073	.622	.112	.430	−.034	.813	.004	.980
Circadian analyses									
IL-6 mean (pg/mL)	58	.038	.877	.255	.683	.004	.993	.855	.202
IL-6 amplitude (pg/mL)	58	.044	.258	−.082	.435	−.132	.088	.028	.795
IL-6 (pg/mL) theta (h)	58	−.081	.904	−.869	.615	−.009	.995	−1.739	.353

β and *P* values of multiple regression models were calculated after adjusting for potential confounders. IL-6 = interleukin-6, PVT = Psychomotor Vigilance Task, Daytime = 8:00 AM–22:00 PM, Nighttime = 11:00 PM–7:00 AM, PVT LAPSES = total number of lapses (RTs ≥ 500 ms) subjected to Tukey transform ([√x +√(x+1)]), PVT 1/RT = response speed defined as mean 1/RT ($seconds^{-1}$) during the 10 minute testing period, PVT SLOWEST 10% = the mean of the reciprocal of the 10% slowest RTs ($seconds^{-1}$), PVT FASTEST 10% = the mean of the reciprocal of the 10% fastest RTs ($seconds^{-1}$), RT = reaction time.

Association of PVT Performance With IL-6 Peripheral Levels

We used similar models to examine the association between PVT performance and IL-6 peripheral levels. No significant association was observed between PVT performance and 24-hour, daytime (8:00 AM–10:00 PM) and nighttime (11:00 PM–7:00 AM) IL-6 peripheral levels while adjusting for potential confounders. Furthermore, PVT performance was not significantly associated with any of the 3 components (ie, mean IL-6, amplitude of IL-6, and IL-6 theta) of the IL-6 circadian pattern (**Table 4**).

DISCUSSION

The primary findings of the current study are (1) impaired PVT performance is associated with subjective EDS (as measured by ESS) but not objective EDS (as measured by MSLT) and (2) impaired PVT performance is not associated with IL-6 peripheral levels in patients with OSA. We propose that the MSLT assays physiologic sleep propensity, and may be a good predictor of cardiometabolic risk and morbidity in patients with OSA, whereas ESS and PVT are stronger predictors of impaired performance in this population.

It has been suggested that PVT measures the ability to sustain attention on a task and respond in a timely manner to salient signals[8] and has been recommended as a useful assay for sleep deprivation-induced sleepiness or sleepiness occurring in sleep disorders, such as narcolepsy and hypersomnia.[29] In elderly individuals with OSA, Kim et al. observed a significant association between impaired PVT performance and subjective daytime sleepiness (measured by ESS), but not objective daytime sleepiness (measured by MSLT).[19] Similarly, our findings in middle-age OSA patients indicate that impaired PVT performance is significantly associated with subjective but not objective daytime sleepiness. Cumulatively, these studies suggest that these two objective tests, PVT and MSLT, measure different phenomena. MSLT appears to assay physiologic sleep propensity, whereas PVT measures impaired sustained attention. In this study, we used a modified MSLT protocol to cover a longer portion of the daytime period (9:00 AM–5:00 PM) in all participants. However, the effect of MSLT results was the same in all of the participants.

It has been reported that performance in neurobehavioral tests, such as PVT, is influenced by several factors, such as anxiety, depression, motivation, and boredom.[30–33] Interestingly, these factors have also been shown to influence subjective daytime sleepiness.[21,34–37] In our study, impaired PVT performance is associated with the severity of OSA (ie, min SaO_2) and obesity, which is consistent with previous findings.[19,38,39] It is also possible sleepiness as measured by objective and subjective assessments and fatigue reflect different central nervous system processes with possibly different underlying neuroanatomic and neurophysiologic pathways.[40] For example, in late middle-aged and older adults, subjective EDS is associated with reduction of global cortical thickness whereas fatigue is associated with reduction of frontal and temporal cortical thickness and hippocampal volume.[40] In this study, neither mBDI-II scores nor original scores of BDI-II were significantly associated with PVT performance. The lack of association between depression and PVT performance may be explained by the narrow range of depression scores in our samples.

Furthermore, our study indicated that impaired PVT performance, in contrast to MSLT,[7] is not associated with elevated peripheral levels of IL-6. Given that IL-6 is a sleep-inducing cytokine, this finding further supports the hypothesis that these two tests measure two different aspects of physiology and behavior. From a practical standpoint, these data do not suggest that PVT can replace MSLT in patients with OSA.

Our data have some important clinical implications. ESS, which is the most commonly used test in clinical practice to assess sleepiness in patients with OSA, is a useful predictor of impaired sustained attention. Interestingly, it has been shown that subjective sleepiness measured with ESS correlated

significantly with automobile and other accidents.[41–44] Thus, ESS and PVT are inexpensive and easy-to-use protocols that may be useful in routine practice for predicting risks associated with impaired performance and attention, such as traffic accidents., However, MSLT is a useful, albeit expensive and time-consuming, tool to measure physiological sleep propensity, and may be a good predictor of cardiometabolic risk, as assessed by inflammation, in patients with OSA.[7,45]

There are several strengths and limitations of the current study. Strengths include: (1) the design of the study as well as the comprehensiveness of the measures obtained including PVT, MSLT, ESS, and 24-hour serial IL-6 levels in middle-aged patients with OSA, (2) the careful selection of patients, and (3) a rigorous experimental protocol including 4 consecutive nights of 8-hour recordings in the sleep laboratory. Some limitations should be noted. Because our PVT trials lasted 10 minutes, it is possible that longer durations (eg, 20 minutes) may increase the sensitivity of the test in assessing physiologic sleepiness.[20] Furthermore, we did not include a standardized fatigue scale in our study protocol to measure subjects' fatigue levels. The lack of association between fatigue and PVT performance may be related to the categorical (YES/NO) assessment of fatigue and the narrow range of possible answers. Further studies should use standardized fatigue scales (ie, Fatigue Severity Scale) to examine the association between PVT performance and fatigue in patients with OSA. Also, we used a research volunteer sample, which restricts the generalizability of the results. However, the consistency between our data in middle-aged research volunteers with OSA and those of Kim et al.,[19] who examined elderly participants with OSA from a community population, suggests that our findings are applicable to patients with OSA independent of age or method of recruitment.

In summary, our findings suggest that in patients with OSA, PVT performance is influenced primarily by the subjective perception of sleepiness and not its physiological underpinnings. From a clinical standpoint, it appears that MSLT may be useful in predicting cardiometabolic risk in patients with OSA, via inflammation as a surrogate marker, whereas ESS/PVT predict impaired performance but not cardiometabolic risk in patients with OSA.

ABBREVIATIONS

AHI, apnea-hypopnea index
BMI, body mass index
CPAP, continuous positive airway pressure
EDS, excessive daytime sleepiness
ESS, Epworth Sleepiness Scale
IL-6, interleukin-6
MWT, Maintenance of Wakefulness Test
MSLT, Multiple Sleep Latency Test
OSA, obstructive sleep apnea
PSG, polysomnography
PVT, Psychomotor Vigilance Task
RT, reaction time
SOREMPs, sleep-onset REM periods

REFERENCES

1. Guilleminault C, Brooks SN. Excessive daytime sleepiness: a challenge for the practising neurologist. *Brain*. 2001;124(Pt 8):1482–1491.
2. Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A. Effects of age on sleep apnea in men: I. Prevalence and severity. *Am J Respir Crit Care Med*. 1998;157(1):144–148.
3. Bixler EO, Vgontzas AN, Lin HM, et al. Prevalence of sleep-disordered breathing in women: effects of gender. *Am J Respir Crit Care Med*. 2001;163(3 Pt 1):608–613.
4. Kapur VK, Baldwin CM, Resnick HE, Gottlieb DJ, Nieto FJ. Sleepiness in patients with moderate to severe sleep-disordered breathing. *Sleep*. 2005;28(4):472–477.
5. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med*. 1993;328(17):1230–1235.
6. Cao MT, Guilleminault C, Kushida CA. Clinical features and evaluation of obstructive sleep apnea and upper airway resistance. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 5th ed. Philadelphia, PA: WB Saunders; 2011:1206–1218.
7. Li Y, Vgontzas AN, Fernandez-Mendoza J, et al. Objective, but not subjective, sleepiness is associated with inflammation in sleep apnea. *Sleep*. 2017;40(2).
8. Dinges DF, Powell JW. Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. *Behav Res Methods Instrum Comput*. 1985;17(6):652–655.
9. Dorrian J, Rogers NL, Dinges DF. Psychomotor vigilance performance: a neurocognitive assay sensitive to sleep loss. In: Kushida C, ed. *Sleep Deprivation: Clinical Issues, Pharmacology and Sleep Loss Effects*. New York, NY: Marcel Dekker, Inc.; 2005:39–70.
10. Dinges DF, Pack F, Williams K, et al. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. *Sleep*. 1997;20(4):267–277.
11. Batool-Anwar S, Kales SN, Patel SR, Varvarigou V, DeYoung PN, Malhotra A. Obstructive sleep apnea and psychomotor vigilance task performance. *Nat Sci Sleep*. 2014;6:65–71.
12. Sforza E, Haba-Rubio J, De Bilbao F, Rochat T, Ibanez V. Performance vigilance task and sleepiness in patients with sleep-disordered breathing. *Eur Respir J*. 2004;24(2):279–285.
13. Van Dongen HP, Maislin G, Mullington JM, Dinges DF. The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep*. 2003;26(2):117–126.
14. Vgontzas AN, Zoumakis E, Bixler EO, et al. Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. *J Clin Endocrinol Metab*. 2004;89(5):2119–2126.
15. Pejovic S, Basta M, Vgontzas AN, et al. Effects of recovery sleep after one work week of mild sleep restriction on interleukin-6 and cortisol secretion and daytime sleepiness and performance. *Am J Physiol Endocrinol Metab*. 2013;305(7):E890–E896.
16. Franzen PL, Siegle GJ, Buysse DJ. Relationships between affect, vigilance, and sleepiness following sleep deprivation. *J Sleep Res*. 2008;17(1):34–41.
17. Bédard MA, Montplaisir J, Richer F, Malo J. Nocturnal hypoxemia as a determinant of vigilance impairment in sleep apnea syndrome. *Chest*. 1991;100(2):367–370.
18. Barbé, Pericás J, Muñoz A, Findley L, Antó JM, Agustí AG. Automobile accidents in patients with sleep apnea syndrome. An epidemiological and mechanistic study. *Am J Respir Crit Care Med*. 1998;158(1):18–22.
19. Kim H, Dinges DF, Young T. Sleep-disordered breathing and psychomotor vigilance in a community-based sample. *Sleep*. 2007;30(10):1309–1316.
20. Dinges DF, Weaver TE. Effects of modafinil on sustained attention performance and quality of life in OSA patients with residual sleepiness while being treated with nCPAP. *Sleep Med*. 2003;4(5):393–402.
21. Bixler EO, Vgontzas AN, Lin HM, Calhoun SL, Vela-Bueno A, Kales A. Excessive daytime sleepiness in a general population sample: the role of sleep apnea, age, obesity, diabetes, and depression. *J Clin Endocrinol Metab*. 2005;90(8):4510–4515.

22. Vgontzas AN, Tan TL, Bixler EO, Martin LF, Shubert D, Kales A. Sleep apnea and sleep disruption in obese patients. *Arch Intern Med*. 1994;154(15):1705–1711.
23. Phillips BA, Collop NA, Drake C, Consens F, Vgontzas AN, Weaver TE. Sleep disorders and medical conditions in women. *J Womens Health*. 2008;17(7):1191–1199.
24. Littner MR, Kushida C, Wise M, et al. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. *Sleep*. 2005;28(1):113–121.
25. American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
26. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14(6):540–545.
27. Vgontzas AN, Papanicolaou DA, Bixler EO, et al. Circadian interleukin-6 secretion and quantity and depth of sleep. *J Clin Endocrinol Metab*. 1999;84(8):2603–2607.
28. Vgontzas AN, Pejovic S, Zoumakis E, et al. Daytime napping after a night of sleep loss decreases sleepiness, improves performance, and causes beneficial changes in cortisol and interleukin-6 secretion. *Am J Physiol Endocrinol Metab*. 2007;292(1):E253–E261.
29. Thomann J, Baumann CR, Landolt HP, Werth E. Psychomotor vigilance task demonstrates impaired vigilance in disorders with excessive daytime sleepiness. *J Clin Sleep Med*. 2014;10(9):1019–1024.
30. van der Meere J, Börger N, van Os T. Sustained attention in major unipolar depression. *Percept Mot Skills*. 2007;104(3 Pt 2):1350–1354.
31. Porter RJ, Gallagher P, Thompson JM, Young AH. Neurocognitive impairment in drug-free patients with major depressive disorder. *Br J Psychiatry*. 2003;182:214–220.
32. Dinges DF, Kribbs NB. Performing while sleepy: effects of experimentally-induced sleepiness. In: Monk TH, ed. *Sleep, Sleepiness and Performance*. Oxford, England: John Wiley & Sons; 1991:97–128.
33. Doran SM, Van Dongen HP, Dinges DF. Sustained attention performance during sleep deprivation: evidence of state instability. *Arch Ital Biol*. 2001;139(3):253–267.
34. Basta M, Chrousos GP, Vela-Bueno A, Vgontzas AN. Chronic insomnia and stress system. *Sleep Med Clin*. 2007;2(2):279–291.
35. Theorell-Haglöw J, Lindberg E, Janson C. What are the important risk factors for daytime sleepiness and fatigue in women? Sleep. 2006;29(6):751–757.
36. Bardwell WA, Ancoli-Israel S, Dimsdale JE. Comparison of the effects of depressive symptoms and apnea severity on fatigue in patients with obstructive sleep apnea: a replication study. *J Affect Disord*. 2007;97(1-3):181–186.
37. Sforza E, de Saint Hilaire Z, Pelissolo A, Rochat T, Ibanez V. Personality, anxiety and mood traits in patients with sleep-related breathing disorders: effect of reduced daytime alertness. *Sleep Med*. 2002;3(2):139–145.
38. Lal C, Strange C, Bachman D. Neurocognitive impairment in obstructive sleep apnea. *Chest*. 2012;141(6):1601–1610.
39. Tanno S, Tanigawa T, Maruyama K, Eguchi E, Abe T, Saito I. Sleep-related intermittent hypoxia is associated with decreased psychomotor vigilance in Japanese community residents. *Sleep Med*. 2017;29:7–12.
40. Carvalho DZ, St Louis EK, Boeve BF, et al. Excessive daytime sleepiness and fatigue may indicate accelerated brain aging in cognitively normal late middle-aged and older adults. *Sleep Med*. 2017;32:236–243.
41. McKay MP. Fatal consequences: obstructive sleep apnea in a train engineer. *Ann Fam Med*. 2015;13(6):583–586.
42. Arita A, Sasanabe R, Hasegawa R, et al. Risk factors for automobile accidents caused by falling asleep while driving in obstructive sleep apnea syndrome. *Sleep Breath*. 2015;19(4):1229–1234.
43. Ward KL, Hillman DR, James A, et al. Excessive daytime sleepiness increases the risk of motor vehicle crash in obstructive sleep apnea. *J Clin Sleep Med*. 2013;9(10):1013–1021.
44. Catarino R, Spratley J, Catarino I, Lunet N, Pais-Clemente M. Sleepiness and sleep-disordered breathing in truck drivers : risk analysis of road accidents. *Sleep Breath*. 2014;18(1):59–68.
45. Ren R, Li Y, Zhang J, et al. Obstructive sleep apnea with objective daytime sleepiness is associated with hypertension. *Hypertension*. 2016;68(5):1264–1270.

ACKNOWLEDGMENTS

The authors would like to acknowledge Dr. Hung-Mo Lin, Research Professor, Mount Sinai Hospital, for her significant methodological contributions.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication March 16, 2017
Submitted in final revised form May 18, 2017
Accepted for publication June 13, 2017
Address correspondence to: Alexandros N. Vgontzas, MD, Penn State University College of Medicine, Department of Psychiatry H073, 500 University Drive, Hershey, PA 17033; Tel: (717) 531-7278; Fax: (717) 531-6491; Email: avgontzas@psu.edu

DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. All authors report no biomedical financial interests or potential conflicts of interest. This work was supported by National Heart Lung and Blood Institute (NHLBI) R01 HL64415.