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Individual Variability and Predictors of Driving Simulator Impairment in Patients with Obstructive Sleep Apnea

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Study Objectives: Obstructive sleep apnea (OSA) is associated with driving impairment and road crashes. However, daytime function varies widely between patients presenting a clinical challenge when assessing crash risk. This study aimed to determine the proportion of patients showing "normal" versus "abnormal" driving simulator performance and examine whether anthropometric, clinical, and neurobehavioral measures predict abnormal driving.

Methods: Thirty-eight OSA patients performed a 90-min simulated driving task under 3 conditions: normal sleep, restricted sleep (4 h in bed), and normal sleep + alcohol (BAC~0.05 g/dL). Patients were classified as "resilient" drivers if, under all 3 experimental conditions their mean steering deviation fell within 2 standard deviations of the mean steering deviation of 20 controls driving under baseline normal sleep conditions, or a "vulnerable" driver if mean steering deviation was outside this range in at least one experimental condition. Potentially predictive baseline anthropometric, clinical, neurocognitive, and cortical activation measures were examined.

Results: Of the 38 OSA patients examined, 23 (61%) and 15 (39%) were classified as resilient and vulnerable drivers, respectively. There were no differences in baseline measures between the groups, although the proportion of females was greater and self-reported weekly driving exposure was less among vulnerable drivers ($p < 0.05$). On univariate analysis gender, weekly driving hours, and auditory event related potential P2 amplitude were weakly associated with group status. Multivariate analysis showed weekly driving hours (OR 0.69, 95%CI, 0.51-0.94, $p = 0.02$) and P2 amplitude (OR 1.34, 95%CI 1.02-1.76, $p = 0.035$) independently predicted vulnerable drivers.

Conclusions: Most OSA patients demonstrated normal simulated driving performance despite exposure to further sleep loss or alcohol. Most baseline measures did not differentiate between resilient and vulnerable drivers, although prior driving experience and cortical function were predictive. Novel measures to assist identification of OSA patients at risk of driving impairment and possibly accidents are needed.

Trial Registration: Data presented in this manuscript was collected as part of a clinical trial "Experimental Investigations of Driving Impairment in Obstructive Sleep Apnea." Trial ID: ACTRN12610000009011, URL: http://www.anzctr.org.au/trial_view.aspx?ID=334979.

Keywords: obstructive sleep apnea, driving performance, neurobehavioral function

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SCIENTIFIC INVESTIGATIONS

Obstructive sleep apnea (OSA) affects up to 10% of the middle-aged population.[1,2] It is characterized by repeated nocturnal episodes of oxygen desaturation, and sleep fragmentation, and is associated with increased daytime sleepiness, impaired vigilance, and a 2- to 7-fold increased risk of motor vehicle crashes.[3-6] However there is substantial inter-individual variation in daytime sleepiness and neurobehavioral impairment among OSA patients,[7,8] which is not readily explained by clinical measures of OSA severity such as apnea/hypopnea index (AHI), hypoxemia, and frequency of sleep arousals.[9-13] Many OSA patients report little to no daytime sleepiness and have driven for many years without incident,[14] while others, sometimes with mild disease, appear to be severely affected. Healthy subjects similarly show a wide range of trait-like neurobehavioral responses to repeated nighttime sleep restriction.[15,16]

BRIEF SUMMARY

Current Knowledge/Study Rationale: Obstructive sleep apnea is linked with neurobehavioral abnormalities, poor driving performance and elevated accident risk. However there is large inter-individual variability in daytime neurobehavioral function and the proportion of patients exhibiting driving abnormalities is unclear. This makes clinical identification of patients at risk of impairment and decisions regarding driving ability and accident risk difficult on an individual patient level.

Study Impact: The majority (60%) of patients with obstructive sleep apnea appear to be "resilient" to the sleep disruption caused by OSA and perform a driving simulation task comparable to controls, even after further provocation by sleep loss or alcohol. Routine clinical measures do not discriminate between the resilient and vulnerable patient groups, although shorter self-reported weekly driving exposure and increased cortical activation, potentially in response to chronic sleep disruption, appear to predict poor driving performance.

This suggests that within OSA populations there are different patient phenotypes or susceptibility groupings with respect to neurobehavioral impairment that may be important to recognize clinically, particularly when providing personalized advice to patients regarding their accident risk and treatment needs.

In a recent study, we compared afternoon driving simulator performance in newly diagnosed, untreated OSA patients and in healthy age-matched controls under three separate conditions: after a usual night's sleep, after a night in which the sleep period was restricted to 4 hours, and after low dose alcohol.[17] We found that, as a group, OSA patients had worse baseline driving simulator performance than the control group, and that their driving deteriorated more after sleep restriction and alcohol than it did in the control group. However, there was considerable inter-individual variability in responses, particularly in the OSA patient group. The primary purpose of this study was to examine systematically the phenotypic variability in driving performance in individual patients rather than simply in group data, and to examine baseline measures that might be clinically useful predictors of driving simulator outcomes in individual patients. We aimed to determine whether OSA patients could be identified who had normal driving simulator performance under all three experimental conditions ("resilient drivers") and whether such patients could be distinguished from patients who showed impaired driving under one or more experimental conditions ("vulnerable drivers") using baseline anthropometric characteristics, standard clinical measures of OSA severity, self-reported sleepiness or more detailed measures of neurocognitive function; including tests of attention, executive function, psychomotor vigilance, and cortical activation by auditory evoked potentials.

METHODS

A detailed description of the experimental protocol and procedures have been described previously.[17] The study was approved by the Human Research Ethics Committees of the Repatriation General Hospital, University of South Australia and University of Adelaide. All subjects gave written informed consent and were remunerated for their participation.

Subject Selection

Thirty-eight untreated OSA patients of varying disease severity (10 mild, 9 moderate, and 19 severe) were invited to participate in the study following diagnostic polysomnography at the Adelaide Institute for Sleep Health, Repatriation General Hospital and were studied prior to treatment. The OSA severity cutoffs adopted by our laboratory using the 1999 AASM "Chicago" criteria[18] were: normal (AHI < 15 events/h), mild OSA (AHI ≥ 15 events/h), moderate OSA (AHI ≥ 30 events/h), and severe OSA (AHI ≥ 45 events/h), bearing in mind that AHI cutoff values of 15 and 30 events/h using Chicago scoring criteria correspond to approximately 5 and 10 events/h, respectively, using the recent AASM "Recommended" scoring criteria.[19] Twenty healthy control subjects matched for age and gender were recruited from the general population through newspaper advertisements, which provided only a general description of the study and made no mention of driving performance measures.

Exclusion criteria were as follows: professional driver or shift worker; history of driving < 2 years or < 2 h per week; significant medical comorbidities (e.g., cardiac or respiratory failure), periodic limb movement disorder (periodic limb movement arousal index > 5/h), past head injury or depression; use of alertness altering prescription medications that may alter neurocognitive function (e.g. antihistamines, opiates, antidepressants); history of alcohol abuse or current use of recreational drugs. Control subjects were also excluded if they showed abnormal scores on sleep quality and daytime drowsiness questionnaires.

Baseline Measures

Approximately one week prior to driving assessments, all participants underwent overnight standard diagnostic polysomnography with the following recordings: electroencephalography (C3/A2, C4/A1 lead placements), left and right electro-oculograms, submental electromyogram, nasal cannula to measure nasal pressure, limb movement sensors, inductive plethysmography for thoraco-abdominal motion, lead II electrocardiography, and arterial oxygen saturation (finger pulse oximetry). All signals were digitized and stored using a Compumedics-E Series sleep system (Melbourne, Australia). Sleep and sleep arousals were scored using standardized methods.[18,20] Apneas and hypopneas were scored according to internationally agreed criteria.[18] All studies were scored by one technician certified by the Board of Registered Polysomnographic Technicians

All participants also completed a variety of sleep/health questionnaires including a general health questionnaire (assessing medical conditions, medication use, alcohol, caffeine and drug use), the Pittsburgh Sleep Quality Index (PSQI) assessing sleep quality/habits,[21] and the Epworth Sleepiness Scale (ESS) assessing daytime drowsiness in 8 common situations.[22] PSQI ≥ 5 and ESS ≥ 10 were used as exclusion criteria cutoffs when selecting healthy controls.

Neurocognitive Tests

Stroop Color and Word Test (STROOP)

This task measured focused and selective attention and inhibition of interfering habitual responses providing a measure of response speed/slowness.[23] This version of the classic task consisted of 3 sub-tasks: (1) reading names of colors (red, blue, green), (2) naming the color (red, blue or green) of 4 Xs (xxxx), and (3) naming the colors of incongruent color words (e.g., the word blue written in red ink). Each sub-task consisted of 1 page containing 100 stimuli (words, colors, etc.) arranged in 5 columns (20 stimuli in each) with the participants having to read as many of the stimuli as possible with a time limit of 45 seconds for each test page. Overall performance on this task was expressed as a t-score based on their age, education, and the predicted normative data scores on the basic word reading and color naming subtests.

Comprehensive Trail Making Task (CTMT)

The CTMT measures visual search, visuomotor tracking, and set shifting abilities and is a modified version of the original Trail Making Test A and B.[24] The test requires participants to identify 9 different symbols corresponding to numbers 1 to 9. The aim is to match the numbers with corresponding symbols as quickly as possible in 90 seconds. The test is made up of 5 sub-tasks, with the first 3 requiring the subjects to connect

in sequential order encircled numbers (i.e., from 1-25) with greater degree of encircled destructor stimuli with each subtask. In addition, to sequentially connecting numbers, the last 2 subtasks involve shifting from one cognitive set to another, whereby in one subtask the subjects had to connect numbers that alternate between digit and written form (i.e., 2-three-four-5) and in the last subtask the subjects alternate between numbers and letters (i.e., 1-A, 2-B, 3-C). Performance is measured by time (seconds) to completion of each subtask.

Symbol Digit Substitution Task (SDST)

The SDST measures attention, visual scanning, motor speed, and working memory.[25] The test requires participants to identify 9 different symbols corresponding to numbers 1 to 9. The aim is to match the numbers with corresponding symbols as quickly as possible in 90 seconds.

Cortical Auditory Event-Related Potential Recordings

An auditory oddball paradigm was used to record cortical auditory event related potentials (AERP) in OSA patients and controls focusing on the N1, P2, N2, and P3 components of the AERP waveform. Subject responses to target auditory stimuli were captured via a hand held button press to calculate reaction time. Reaction times > 500 ms were defined as attention lapses. Single AERP trials were manually rejected if eye movements (electro-oculogram deflections exceeding ± 50 μV) or artifact (clipping, amplifier drift) intruded into the 1200 ms AERP analysis window. Following rejection of individual artifact contaminated AERP trials, the remaining AERP trials were averaged for each oddball trial block and then combined into single averaged waveforms to reduce non-stimulus related background electroencephalographic activity (noise). Subsequent AERP analysis was performed using custom software that automatically determined peak latencies and amplitudes between predefined time windows for each peak.[26,27] The N1 component was identified as the greatest negative peak between 70-140 msec from stimulus onset (target tone), the P2 as the greatest positive peak between 120-300 ms, the N2 as the greatest negative peak between 150-350 msec, and P3 was the greatest positive waveform occurring 260-500 ms from stimulus onset. The AERP latencies were calculated as the time from stimulus onset (in ms) taken to reach the peak of the component and the amplitude was measured (in microvolts) as the distance from the 200 msec pre-stimulus baseline to the peak.

Driving Simulator Performance

Commencing at 14:00, all OSA patients and control participants underwent a 90-min test on a driving simulator (AusEd, Woolcock Institute of Medical Research, Sydney Australia)[28] under each of the following 3 different conditions on separate days in random order and approximately 1 week apart: following normal sleep; after sleep restriction (4 h sleep opportunity previous night); and after alcohol given 30 min before testing to achieve a blood alcohol concentration (assessed using a breathalyzer, Dräger Alcotest7410^{Plus}) of approximately 0.05 g/dL. The simulator was set up to replicate a nighttime drive on a country road. The main outcome measures were steering deviation and crashes. Steering deviation was measured from the average deviation in cm from the driver's median lane position (each lane was 360 cm wide) sampled at 30 Hz. Subjects were instructed to maintain speed within 60-80 km/h, but to apply the brakes as quickly as possible whenever a slow moving truck was presented ahead in the driving lane. The latter occurred a total of 7 times during the drive. Crashes occurring throughout the driving task were defined as: car left the road (all 4 wheels completely off the road), collision with a truck, or if the car was stationary for > 3 seconds. The main outcome measure for crashes was the number of controls and OSA patients who experienced at least one crash incident. In the current study, only control subject data for the baseline (normal sleep) condition are reported. These data were used to define the boundaries for normal driving simulator performance.

Detailed Experimental Procedures

On a separate day prior to experimental driving simulator assessments all participants underwent an introduction session during which the study procedures were explained in detail, and they were familiarized with the driving simulator by completing a 30-min practice drive to prevent learning effects during the subsequent experimental session. For all 3 experimental conditions, subjects' sleep patterns and duration were monitored throughout the study using actigraphy monitors (Actiwatch, Mini-Mitter Co, Inc, Model-AW64, Oregon, USA), worn from at least 5 days prior to beginning the experiments until study completion to estimate sleep/wake timing, to ensure compliance with the sleep restriction protocol and to ensure patients did not nap in the 24 h prior to the experiments.[29] In addition, during the night of sleep restriction, participants left a message on a time/date stamped answering machine at bedtime (02:00) and wake time (06:00), again to ensure compliance with the protocol. Subjects were instructed to abstain from alcohol, caffeinated beverages, not to nap for 24 h prior to each experimental session and to consume breakfast before 09:00 on the day of each experiment. They were transported by taxi to and from the laboratory.

Upon arrival at the laboratory at 12:00, each subject's blood-alcohol concentration was estimated using a calibrated breathalyzer (Dräger Alcotest7410Plus), sleep diaries were collected, activity monitor data downloaded, and the answering machine checked for compliance with the sleeping regime. Subjects consumed a standardized lunch with a glass of water at 12:15 before electrode application for electroencephalographic monitoring (C3/A2, C4/A1, O1/A2, O2/A1 and EOG) of drowsiness throughout the driving test. At 13:30, all subjects consumed either 375 mL of sugar-free, non-caffeinated control soft drink (in the normal and restricted sleep conditions) or a volume of 40% vodka calculated to achieve a target blood-alcohol concentration of 0.05 g/dL mixed with the same soft drink (in the alcohol condition).

Data Analysis and Statistics

All OSA patients and control participants completed driving simulator assessments under the 3 experimental conditions in a randomized order. For the control group, only the baseline (normal sleep) driving simulator data was used in this report to define the normal range for steering deviation. Specifically, 2 standard deviations (SD) of the mean baseline steering deviation of the control group following normal sleep was used to define a normal range for steering deviation, and to divide

Table 1—Actigraphy-estimated sleep time in control and OSA participants, alcohol consumed, and blood alcohol concentration before and after the driving task in OSA patients.

	OSA Patients (n = 38)
Estimated Sleep Time (min)	
Controls - Normal Sleep	461 ± 16
OSA - Normal Sleep	472 ± 13
OSA - Restricted Sleep	228 ± 10
OSA - Alcohol	458 ± 14
OSA - Alcohol consumed during study (grams)	48.6 ± 1.4
OSA - Blood Alcohol Concentration (g/dL)	
2.00 pm (start of driving task)	0.048 ± 0.003
3.30 pm (end of driving task)	0.023 ± 0.002

Values reported are mean ± SEM.

OSA patients into "resilient driver" or "vulnerable driver" groups. Resilient drivers were defined as OSA patients who drove within the 2 standard deviation cutoff determined for the control group under all 3 experimental settings (i.e. after normal sleep, after sleep restriction, and after alcohol). Vulnerable drivers were defined as patients whose steering deviation exceeded 2 SD of the control group during one or more of the 3 experimental conditions. Steering deviation data, excluding the first minute of acceleration and initial lane positioning, were averaged over the remaining 89 minutes of the 90-min simulated drive. Receiver operator characteristic (ROC) curve analysis was used to examine the relationship between steering deviation and occurrence of at least one crash event under one or more experimental condition. Student unpaired t-tests were used to examine differences in polysomnographic sleep study variables, anthropometric characteristics, subjective sleepiness, driving history questionnaires, and neurobehavioral function between the resilient and vulnerable driver groups. Fisher exact tests were used to test for differences in gender distributions between the resilient and vulnerable driver groups. In OSA patients only, logistic regression (IBM, SPSS Statistics, Version 20) was used to examine the relationship between the predictor variables (polysomnographic sleep study variables, anthropometric characteristics, sleepiness, driving history questionnaires, and neurobehavioral function) and driver status (resilient vs vulnerable drivers). Firstly, univariate analysis was used to explore whether any of the predictor variables predicted steering deviation status. Secondly, any variable resulting in an association with steering deviation at a significance level of $p \leq 0.15$ was selected for a backward stepwise multivariate logistic regression model to determine which variables were strongest predictors of driver status. Data are presented as means ± SEM unless otherwise specified, with $p < 0.05$ considered statistically significant.

RESULTS

Nineteen of the 20 controls and 35 of the 38 OSA patients successfully completed all neurocognitive tests. Nineteen of the 20 controls and 34 of the 38 OSA patients had a complete set of auditory psychomotor vigilance and AERP data. All subjects complied with the sleep restriction protocol and had a blood-alcohol concentration of 0.0 g/dL upon arrival to the laboratory on each experimental day. **Table 1** shows actigraphy estimated sleep duration and blood alcohol concentrations for OSA participants in the 3 experimental settings, and actigraphy estimated sleep duration for control subjects on their normal sleep night. There was no significant difference between control and OSA participants in actigraphy estimated prior sleep duration under the normal sleep condition. Baseline anthropometric characteristics, questionnaire, sleep study, neurocognitive function and cortical AERP results from the control participants, all OSA patients, and the 2 OSA driver status groups (resilient and vulnerable drivers) are shown in **Table 2**.

Individual Steering Deviation

The control group steering deviation under normal sleep conditions was 36.5 ± 9.2 cm (mean ± SD) such that the upper limit of normal (mean + 2SD) above which OSA patients were considered to show abnormal steering deviation, and were defined as vulnerable drivers, was 54.6 cm (**Figure 1**). Based on this definition, 15 of 38 (39%) OSA patients showed abnormal steering deviation under one or more of the experimental conditions.

Relationship between Steering Deviation and Crash Events

There were 12 OSA patients who experienced at least 1 crash event throughout the driving task during one or more experimental conditions (**Figure 1**). Eleven of these OSA patients were in the vulnerable driver group. ROC analysis revealed that in OSA patients steering deviation following normal sleep conditions was strongly predictive of any crash event in any experimental condition (area under curve, AUC = 0.86, 95%CI 0.71-1.01, $p < 0.001$, **Figure 2**), and within each separate condition (AUC normal sleep 0.92, 95%CI 0.72-1.11, $p < 0.001$; sleep restriction 0.99, 95%CI 0.95-1.03, $p < 0.001$; alcohol 0.89, 95%CI 0.73-1.05, $p < 0.001$). Due to the strength of this relationship, steering deviation was chosen as the single outcome measure of driving impairment and was used as the primary outcome variable for all subsequent analyses.

Baseline Measures Comparison between Resilient vs Vulnerable OSA Drivers

Table 2 shows anthropometric characteristics, driving history, sleepiness questionnaire, sleep study variables and neurocognitive function in OSA patients according to resilient and vulnerable driver groups. There were no statistically significant differences between the resilient vs vulnerable driver groups in age, BMI, neck or waist circumferences, subjective sleep quality, sleep study variables, neurobehavioral outcomes, or cortical activation measures. However, compared to the resilient driver group, the vulnerable driver group reported spending less time driving per week and had a greater proportion of females.

Associations between Baseline Measures and Driving Impairment in OSA Patients

Univariate analysis of all baseline measures revealed 3 factors (gender, hours of driving per week, and AERP P2 amplitude) that were associated with driver status (vulnerable

Table 2—Anthropometric characteristics, driving experience, subjective sleepiness, sleep study results, neurobehavioral and cortical function in controls, all OSA patients and resilient and vulnerable OSA patients.

	Controls	All OSA Patients	OSA "Resilient"	OSA "Vulnerable"
N	20	38	23	15
Anthropometric Characteristics				
Age	50.6 ± 2.2	52.0 ± 1.7	52.6 ± 2.3	51.3 ± 2.5
Male/Female (%Male)	15/5 (75%)	28/10 (64%)	20/3 (87%)	8/7 (53%)†
Body mass index (BMI)	24.5 ± 0.6	33.9 ± 1.3*	32.5 ± 1.0	36.0 ± 3.0
Neck circumference (cm)	37.0 ± 0.8	42.4 ± 0.7*	43.0 ± 0.7	41.5 ± 1.3
Waist circumference (cm)	91.3 ± 2.3	109.0 ± 2.6*	109.2 ± 3.1	106.8 ± 4.8
Driving Exposure				
Driving distance (1,000 km/year)	11.5 ± 1.2	14.0 ± 1.8	17.2 ± 2.0	12.4 ± 2.5
Driving time (hour/week)	7.2 ± 1.0	8.6 ± 0.9	10.1 ± 1.3	6.2 ± 1.4†
Subjective Sleepiness				
Pittsburgh Sleep Quality Index (PSQI)	2.9 ± 0.2	9.4 ± 0.8*	9.9 ± 0.9	8.0 ± 1.1
Epworth Sleepiness Scale (ESS)	5.0 ± 0.7	9.3 ± 0.9*	8.4 ± 1.0	10.7 ± 1.2
Sleep Study Results				
Apnea hypopnea index (AHI)	8.3 ± 0.9	46.4 ± 3.5*	47.4 ± 3.8	44.8 ± 4.7
Sleep Efficiency (%)	71.3 ± 3.5	75.3 ± 2.0	73.3 ± 2.8	78.4 ± 3.5
Total arousal index (/h)	14.9 ± 1.5	28.8 ± 2.4*	29.4 ± 2.6	27.9 ± 3.3
Mean SpO_2 desaturation in NREM	96.0 ± 0.3	92.6 ± 0.4*	92.9 ± 0.5	92.3 ± 0.6
Mean SpO_2 desaturation in REM	96.1 ± 0.4	90.1 ± 1.0*	91.7 ± 1.0	88.9 ± 1.3
% Time SpO_2 < 90%	0.1 ± 0.1	6.7 ± 2.4*	3.7 ± 1.5	11.3 ± 5.5
Neurobehavioral Outcomes				
Executive Function				
Stroop (T-Score)	54.8 ± 1.3	51.6 ± 1.2	51.9 ± 1.4	51.2 ± 1.7
Comprehensive Trail Making (CTMT)	59.6 ± 2.4	55.7 ± 1.5	55.1 ± 2.0	56.6 ± 2.5
Symbol Digit Substitution (time, sec)	61.8 ± 3.1	54.0 ± 1.9	53.3 ± 2.6	55.2 ± 3.3
Psychomotor Vigilance				
Mean Auditory Reaction Time (sec)	0.37 ± 0.01	0.43 ± 0.02*	0.44 ± 0.02	0.43 ± 0.03
Lapse Frequency (%)	0.07 ± 0.03	0.22 ± 0.04*	0.26 ± 0.06	0.14 ± 0.05
Auditory Event Related Potentials				
Peak Latency (msec)				
N1	98.5 ± 3.0	99.6 ± 2.8	101.3 ± 3.3	96.9 ± 4.2
P2	172.1 ± 3.2	179.6 ± 4.5	180.0 ± 3.7	179.1 ± 10.0
N2	213.5 ± 4.7	232.4 ± 4.9*	233.1 ± 5.8	231.3 ± 8.5
P3	328.8 ± 5.8	348.8 ± 6.2*	353.6 ± 7.9	341.2 ± 10.0
Peak Amplitude (μV)				
N1	-8.1 ± 0.7	-8.3 ± 0.6	-8.6 ± 0.7	-7.5 ± 0.9
P2	2.2 ± 0.6	4.3 ± 0.7*	3.6 ± 0.8	6.0 ± 1.0
N2	-2.9 ± 0.9	-2.3 ± 0.7	-3.2 ± 0.9	1.0 ± 1.0
P3	11.8 ± 0.8	9.7 ± 0.6	9.5 ± 0.9	10.0 ± 0.9

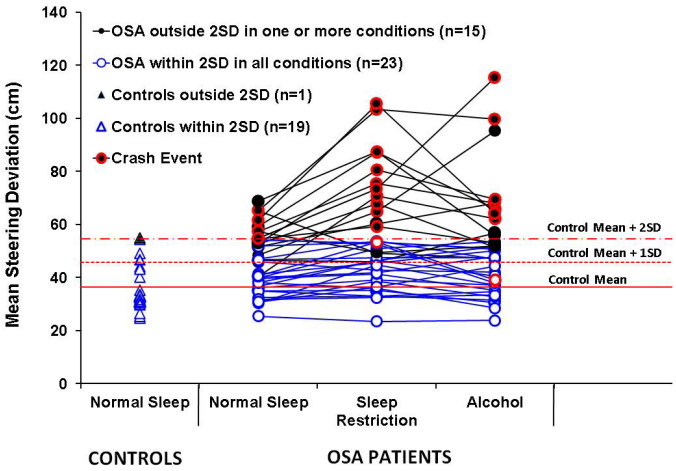
Values reported are mean ± SEM. * Significant difference between Controls and All OSA patients, $p < 0.05$. † Significant difference between Resilient and Vulnerable OSA groups, $p < 0.05$.

vs resilient) at a significance level of $p \leq 0.15$. However, in the multivariate model, only hours of driving per week (OR = 0.69, 95%CI 0.51-0.94, p = 0.019) and P2 amplitude (OR = 1.34, 95%CI 1.02-1.76, p = 0.035) were significant predictors of vulnerable driver status. This implies that each additional hour of driving per week is associated with a 30.7% decrease in the odds of being classified as a vulnerable driver (i.e., exhibit abnormal steering deviation) and that each microvolt increase in P2 amplitude is associated with a 1.3 times greater likelihood of being classified as vulnerable.

DISCUSSION

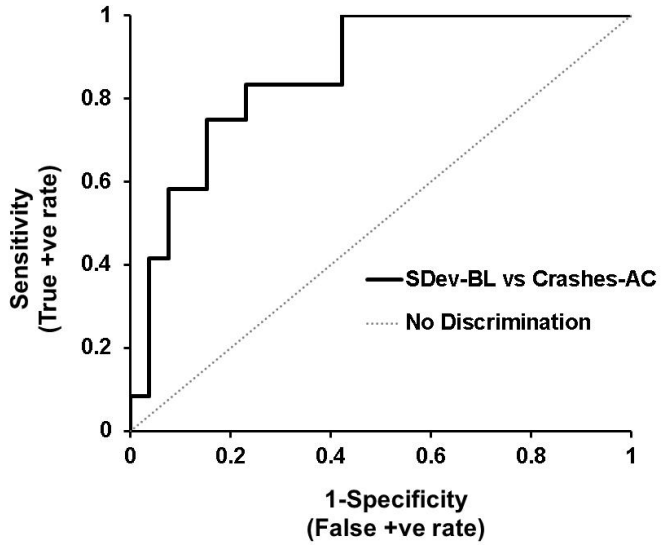
This study confirms that driving simulator performance varies widely between patients with OSA. Although, as a group, OSA patients showed poorer steering performance and exhibited more crashes than healthy age-matched controls, there was wide heterogeneity in driving performance among patients. The new finding from our study is that the majority (approximately 60%) of OSA patients showed trait-like resistance to simulator performance impairment, such that they were able to

Figure 1—Individual steering deviation data for control (n = 20) and OSA participants (n = 38) averaged over the 90-min drive.



Triangles represent individual steering deviation data for control participants following normal sleep, highlighting the mean, 1 SD and 2 SD (horizontal red lines) of these control data. Circles indicate individual OSA patients showing, *in blue,* OSA patients with values within 2 SD under all 3 experimental conditions of the control steering data and, *in black,* patients outside 2 SD in one or more of the experimental conditions. OSA patients who experienced a crash event during the driving task are circled in red.

Figure 2—Receiver operator characteristics (ROC) curve showing that averaged steering deviation (SDev) in OSA patients following normal sleep (NS) conditions was a significant predictor of experiencing at least one crash incident under one or more of the experimental conditions.



SDev-NS, steering deviation under normal sleep; Crashes-AC, crashes under any condition.

sustain attention and steer normally to avoid a crash during a 90-minute simulated country drive even when further stressed by prior sleep restriction or alcohol. None of the patient parameters that are routinely measured in sleep clinics such as age, BMI, ESS, or PSG parameters (AHI, sleep efficiency, arousal and oxygen desaturation indices) discriminated between resilient and vulnerable OSA drivers. Neither did more detailed measures of sleep history (PSQI), neurocognitive/executive function (STROOP, CTMT, SDST), attention/vigilance (auditory psychomotor vigilance), or most components of the AERP (N1, N2, P3).

The only baseline measures predictive of abnormal driving simulator performance in this study were driving exposure (self-reported hours of driving per week) and P2 amplitude of AERP. Patients who spent more time behind the wheel each week were less likely to show abnormal driving simulator performance, while patients with higher P2 AERP amplitudes were more likely to display abnormal driving. The relationship between gender and driving observed in the univariate analysis was likely explained by differences in driving exposure since it was not retained in the multiple regression model.

There is evidence that both more experience and older age may be important factors mitigating crash risk.[30,31] Our study showed that in OSA patients a greater level of prior driving experience was associated with better driving simulator performance. However, prior driving experience effects are likely to also apply to non-OSA drivers. Consequently, this finding should not be interpreted to indicate that more driving experience is specifically beneficial to OSA patients or that it would necessarily negate the deleterious effects of OSA on driving performance.

The P2 component of ERP is believed to reflect stimulus classification response (i.e., identification of target vs non-target stimuli).[32,33] Some evidence suggests larger P2 amplitude may reflect compensatory sensory "overprocessing" in sleep deprived healthy subjects and in untreated OSA patients.[34,35] Thus, elevated P2 amplitude may suggest slowed stimulus identification processes thereby providing a marker of OSA related attention/vigilance impairment and driving risk. However, in the absence of differences in other AERP components between resilient and vulnerable OSA groups, some caution is needed, and we recommend that confirmatory evidence be sought in future studies before employing AERP P2 amplitude as a marker of impaired alertness and driving risk in clinical practice.

Although as a group, OSA patients are at increased risk of experiencing a motor vehicle crash,[4,6] only a small fraction of the variance in driving impairment or crash risk is explained by clinical markers of OSA severity. Consequently, identifying individual OSA patients at greatest crash risk remains a major challenge in clinical practice. There is a need to explore novel correlates of neurobehavioral function in OSA that could be readily used clinically to identify OSA patients at risk of sleepiness related driving impairment. Recent studies have reported inconsistent and at best weak relationships (R^2 ranging from 0.06 to 0.1) between OSA/sleepiness severity (e.g. AHI, hypoxemia, sleep arousals, self-reported sleepiness) and neurobehavioral outcomes such as motor/processing speed,[10,36] attention and intelligence,[10] and memory and signal discrimination.[37] Furthermore, driving simulator studies in untreated OSA patients report relatively weak relationships between ESS and steering deviation ($R^2 = 0.32$) or crashes ($R^2 = 0.26$) on a

driving simulator.[38-40] Objective clinical measures of daytime sleepiness such as the MWT and MSLT have been shown to be useful at discriminating between sleepy vs alert drivers with OSA and other sleep disorders.[13,41-43] However, the associations between MSLT/MWT and simulated[13,41-43] and real[44] driving performance are often weak to moderate (MSLT R^2 range 0.18-0.25, MWT R^2 range 0.11-0.68), and the cost/duration of these tests restricts the widespread use of these measures in the majority of patients.

An earlier study by George et al.[13] is in broad agreement with the results of the current study. George found that while mean tracking error (steering deviation) was worse in OSA patients than controls, approximately half the patients drove within the range of control subjects, and when the OSA patients were divided into "Good" or "Bad" driver groups based on a median split, the groups could not be distinguished by factors such as age, AHI, MSLT scores, or arousal frequency.[13] Our study extends these findings by showing that not only is driving relatively unimpaired in a significant proportion of OSA patients, but these same patients may also exhibit a trait-like resistance to the central nervous system depressant effects of sleep deprivation and alcohol.

Landmark sleep deprivation studies in young healthy subjects have shown that the vulnerability to sleep deprivation is highly variable between individuals, but appears to produce a stable trait-like response within individuals, suggesting that genetic factors are important in determining the response to sleep loss.[15,45] This study showed large inter-individual differences in driving simulator performance amongst OSA patients that were not explained by the severity of OSA, and a seemingly trait-like behavior wherein some patients consistently function normally on a driving simulator in the face of OSA, low-dose alcohol or sleep restriction whereas others exhibit impairments. These findings are consistent with the idea that genotype importantly influences the neurobehavioral response to sleep disruption (and other central nervous system stressors). It is also possible, however, that years of sleep fragmentation and hypoxemia causes permanent brain injury in some OSA sufferers but not others, and that the presence or absence of this injury dictates whether or not they function poorly or normally on a sustained driving task. It is not possible to deduce from the current study which scenario is more likely, nor is it possible to assume stable trait-like responses to specific stimuli (as seen in healthy subjects on repeated exposures to sleep loss) in OSA patients. These questions should be addressed in future studies.

Methodological Considerations

It is difficult to directly extrapolate findings of driving simulation studies to on-road driving performance and MVA risk. However, the AusEd driving simulator is sensitive to fatigue and alerting/sedating substances (e.g., caffeine, alcohol, and benzodiazepines) in a range of experimental settings[28] and direct comparison studies show simulator results correlate well with on-road driving performance.[46] It should be noted that the normative cut point chosen to define resilient and vulnerable OSA drivers in this study was obtained from a relatively small sample of 20 healthy age-matched participants and should be confirmed in a larger normal sample. Furthermore our cut point may not be comparable to other studies, including those using the AusEd driving simulator, since normative data from other driving simulators or even the AusEd simulator with different track settings would likely produce different cutoffs.

The sample size limited the number of predictor variables that could be explored via multivariate logistic regression. Thus we may have missed potentially useful predictors of driving impairment. MSLT or MWT data were not collected and these tests may have shown some discriminatory power in separating resilient versus vulnerable OSA drivers.

We excluded patients who were using opiates, antihistamines, and psychotropic medications that could affect alertness in order to limit confounding effects on driving performance. However, these substances are commonly used in clinical OSA patient populations. Thus, the proportion of OSA patients in a "real world" clinic population who exhibit driving impairment could be greater than we have reported.

In summary, this study demonstrated that just over half of patients from an OSA clinic sample, spanning a wide range of OSA severity and sleepiness levels, had comparable driving simulator performance to that of healthy age-matched controls. This was despite being subjected to a prolonged and monotonous driving test and with additional neurobehavioral stressors of sleep restriction or low-dose alcohol. Our data suggest that only a minority of OSA patients might exhibit impaired driving simulator performance. Baseline clinical measures such as OSA severity, daytime sleepiness and anthropometric characteristics and most additional, non-routine baseline measures of neurobehavioral function (including attention, executive function, psychomotor vigilance) failed to differentiate between vulnerable and resilient OSA drivers. Self-reported weekly driving time and AERP P2 amplitude were the only significant predictors of abnormal steering deviation.

Clinical Implications

The observation that over half of OSA patients were capable of performing a 90-minute driving simulator task normally, even when additionally stressed by prior sleep restriction or alcohol, is an important new finding with potential clinical implications for assessing fitness to drive and MVA risk.[3,14] Currently, patients diagnosed with severe OSA, particularly if there is self-reported excessive daytime sleepiness, are assumed to have elevated MVA risk, while patients with milder OSA and/or no self-reported sleepiness are not.[3] These clinical scenarios, albeit justified on the basis of available group data,[37-41] are not supported by normal simulator driving performance in the majority of patients in this study and the lack of differences in routine clinical measures between "resilient" and "vulnerable" OSA driving groups. There is a major need to investigate further the genetic and neurophysiologic basis for the heterogeneity in neurobehavioral responses seen among OSA patients and to develop reliable and practical bedside tests to help clinicians advise patients on their individual crash risk.

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