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Title page

Severe desaturations increase PVT-based median reaction time and number of lapses in OSA patients

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Take home message: Parameters considering characteristic properties of desaturations have a significant association with impaired vigilance, highlighting the importance of developing methods beyond the AHI for a more detailed assessment of OSA severity.

Abstract

Current diagnostic parameters estimating obstructive sleep apnea (OSA) severity have a poor connection to the psychomotor vigilance of OSA patients. Thus, we aimed to investigate how the severity of apneas, hypopneas, and intermittent hypoxemia is associated with impaired vigilance.

We retrospectively examined Type I polysomnography data and corresponding PVTs of 743 consecutive OSA patients (apnea-hypopnea index (AHI)≥5). Conventional diagnostic parameters (*e.g.* AHI and oxygen desaturation index, ODI) and novel parameters (*e.g.* Desaturation Severity and Obstruction Severity) incorporating duration of apneas and hypopneas as well as depth and duration of desaturations were assessed. Patients were grouped into quartiles based on PVT outcome variables. The odds of belonging to the worst-performing quartile were assessed. Analyses were performed for all PVT outcome variables utilizing binomial logistic regression.

A relative 10% increase in median depth of desaturations elevated the odds (OR_{range}=1.20-1.37, p<0.05) of prolonged mean and median reaction times as well as increased lapse count. Similarly, an increase in Desaturation Severity (OR_{range}=1.26-1.52, p<0.05) associated with prolonged median reaction time. Female sex (OR_{range}=2.21-6.02, p<0.01), ESS score (OR_{range}=1.05-1.07, p<0.01) and older age (OR_{range}=1.01-1.05, p<0.05) were significant risk factors in all analyses. In contrast, increases in conventional AHI, ODI and arousal index were not associated with deteriorated PVT performance.

These results show that our novel parameters describing the severity of intermittent hypoxemia are significantly associated with increased risk of impaired PVT performance, whereas conventional OSA severity and sleep fragmentation metrics are not. These results underline the importance of developing the assessment of OSA severity beyond the AHI.

Introduction

Inadequate sleep, due to sleep disorders and shortened sleep times, is widely recognized as a significant public health burden in Western countries [1]. Good quality sleep is crucial for maintaining neurocognitive performance [1]. Conversely, an increasing number of occupational accidents and absences, as well as traffic accidents, are caused by factors decreasing sleep quality [1]. In Australia alone, the estimated cost of inadequate sleep was $45 billion in health care and society during 2016-2017 [1]. Obstructive sleep apnea (OSA) is one of the most prevalent sleep disorders, affecting at least 20% of the adult population in Western countries [2-4]. OSA is attributed to daytime symptoms of shortened daytime sleep latencies as well as chronic fatigue and sleepiness [5-7]. Furthermore, OSA is related to poor neurocognitive performance and inability to sustain attention [8-10].

Neurocognitive disorders, defined in The Diagnostic and Statistical Manual of Mental Disorders (DSM-5), cover for example the domains of learning and memory, language, executive functioning, and complex attention [11]. PVT evaluates the domain of complex attention, by measuring repeated responses to visual stimuli to assess one's ability to sustain attention [8,12]. PVT is a fast, objective and easily interpretable test that has very little learning effect [13]. PVT is considered highly reliable and sensitive to the effect of sleep deprivation on cognitive performance and demonstrates clearly the cumulative worsening of performance during the task when an individual is unable to sustain attention [14]. As clinical resources for objective evaluation of sleepiness are limited and subjective questionnaires unreliable, PVT could be used, for example, as an initial assessment for the fitness to drive [15], with the constraint that driving also involves other complex skills in addition to sustained attention.

Studies have found impairments in PVT performance with acute sleep deprivation [16], chronic sleep restriction [9], but also high interindividual differences in responses [17]. Furthermore, the association between worsening PVT outcomes and the usual clinical parameters that describe the severity of OSA (*i.e.* the apnea-hypopnea index, AHI) or degree of sleep fragmentation (*i.e.* arousal index, AI) is equivocal [9,18-22]. Previous studies have shown that an increase in the AHI is not directly linked to impaired vigilance [9,22]. Even though patients suffering from severe OSA have on average inferior PVT performance compared to healthy individuals, no significant differences in PVT performance between OSA severity groups have been reported [9,22,23]. This lack of differences in OSA patients could, however, be related to arbitrary, outdated and sub-optimal severity classification thresholds for the AHI [24,25].

Even though the AHI does not correlate well with reduced PVT performance, Pack et al. [9] reported that impaired performance in PVT seems to result from long-term sleep deprivation and insufficient sleep durations in OSA patients. Furthermore, previous studies suggest that the level of nocturnal intermittent hypoxemia negatively affects PVT performance in OSA patients [10,18]. Sforza et al. [18] showed that the number of lapses correlated moderately with the minimum and mean blood oxygen saturation ($r = -0.454$ and -0.421, respectively), but this was achieved using an atypically long reaction time limit of 1000 ms. In addition, we recently demonstrated that longer and deeper desaturations, regardless of the AHI, significantly increases the risk of objectively measured excessive daytime sleepiness [7].

Based on this apparent connection between intermittent hypoxemia and impaired daytime functioning of OSA patients, we hypothesize that novel, more sophisticated diagnostic parameters considering the duration of respiratory events as well as the depth and duration of desaturations,

have a stronger association to impaired PVT performance than conventional severity indices such as AHI and ODI. In this study, we investigate which OSA severity indices are associated with poor PVT performance in a large patient cohort. In addition, we examine how the severity of desaturations affects PVT performance independently of the number and total duration of the respiratory events.

Patients and Methods

This was a retrospective analysis of 912 consecutive patients undergoing polysomnography (PSG) in the Sleep Disorders Center of Princess Alexandra Hospital (Brisbane, Australia) due to the suspicion of OSA. The Institutional Human Research Ethics Committee of the Princess Alexandra Hospital approved the retrospective data collection (HREC/16/QPAH/021, LNR/2019/QMS/54313). Patients who failed to complete psychomotor vigilance task (PVT) (n = 32), had AHI < 5 (n = 134), or had missing demographic information (n = 3) were excluded. Thus, the studied patient population consisted of 743 individuals, who had successfully undergone Type 1 diagnostic PSG, had AHI ≥ 5 in PSG and successfully completed the PVT. The PVT was conducted between 7-9 p.m. prior to the PSG. The demographic information of the whole patient population is presented in Table 1. PSG recordings were conducted and scored with Compumedics Grael acquisition system and Compumedics ProFusion PSG 4 software (Compumedics, Abbotsford, Australia) during 2015–2017.

All PSG recordings were manually scored by experienced sleep technicians, who regularly participate in scoring concordance activities. All apneas, hypopneas, and desaturations were manually scored in conformity with the AASM 2012 guidelines [26]. A hypopnea was scored if a ≥ 30% reduction in nasal pressure amplitude was observed for ≥ 10 seconds and was associated with

either 3% desaturation and/or an arousal (Recommended hypopnea rule 4A, AASM 2012 [26]). An apnea was scored if a ≥ 90% reduction in amplitude for ≥ 10 seconds in the thermocouple signal was observed. An oxygen desaturation event was manually scored if a ≥ 3% drop in SpO_2 signal was observed. Desaturation events were scored from the last sampling point before the onset of the desaturation to the point when recovery reaches the baseline (Figure 1). If the baseline was not reached, the endpoint was determined at the start of plateau after the desaturation (Figure 1).

For PVT, the PEBL PVT program on an ASUS Transformer Pad with an attached keyboard was used [27]. PVT was performed using the 10-minute protocol, with 120 visual stimuli occurring at 2-10 second intervals. The patients were instructed to monitor the tablet display and press a response button using the index finger or thumb on their dominant hand as soon as the pink stimulus appeared on the screen. Standard PVT outcomes were recorded: median reaction time (RT), mean reciprocal reaction time (RRT), mean of the slowest 10% RT, mean of the fastest 10% RT and the number of lapses (RT>500ms).

Raw oxygen saturation (SpO_2) signals, hypnograms, and the information (*e.g.* duration, start and endpoints) of scored apnea, hypopnea, arousal and desaturation events were exported from ProFusion to MatLab (ver. R2018b, MathWorks Inc, Natick, MA, USA). Total sleep time (TST) and percentages of NREM and REM sleep from TST were based on manual sleep staging results. Apnea-hypopnea index (AHI), oxygen desaturation index (ODI), arousal index (AI), average nocturnal oxygen saturation (Mean SpO_2), minimum nocturnal oxygen saturation (Min. SpO_2), time spent with SpO_2 below 90% ($t_{90\%}$) and the mean and median depth of desaturations were computed. In addition, novel parameters (Obstruction Duration, Desaturation Duration, Desaturation Severity, and Obstruction Severity, Table 3) described in our previous studies [28-

30], were computed based on the arousal, respiratory and desaturation event information and raw SpO_2 signal with custom-made MatLab functions. All types of apneas (obstructive, mixed, central) were considered in the analyses and none of the patients had central sleep apnea (% of central events less than 50% from all events). Physiologically irrelevant SpO_2 values (≤ 50%) within desaturations or in minimum SpO_2 were considered as artifacts and were not used in analyses.

Table 1: Demographic, polysomnographic and psychomotor vigilance task (PVT) data of the studied patient population.

Patients (male%)	743 (58.7)
Depression (%)	140 (18.8)
Hypertension (%)	329 (44.3)
Smoker (%)	117 (15.7)
COPD (%)	82 (11.0)
Age (years)	56.8 (46.4-66.7)
BMI (kg/m^2)	35.1 (30.3-41.3)
TST (h)	5.0 (4.2-5.9)
NREM (%)	83.3 (78.3-88.4)
REM (%)	16.6 (11.6-21.7)
AHI (events/h)	23.7 (12.5-45.0)
ESS score	10 (6-14)
RRT (1/ms)	2.6 (2.2-2.9)
Median RT (ms)	380.0 (340.0-445.0)
Fastest 10% RT (ms)	297.0 (277.0-335.8)
Slowest 10% RT (ms)	691.0 (544.3-1081.0)
PVT lapses (n)	13 (5-36)

Caption: Data is presented as number (% of population) or median (interquartile range) where appropriate. Abbreviations: COPD = chronic obstructive pulmonary disease, BMI = body mass index, TST = total sleep time, NREM = non-rapid eye movement sleep, REM = rapid eye movement sleep, AHI = apnea-hypopnea index, ESS = Epworth sleepiness scale, RRT = mean reciprocal reaction time, RT = reaction time, Lapses = reaction times exceeding 500 ms.

Obstruction Duration represents the percentage of the total duration of apneas (*ApDur*, Figure 1 and Table 3) and hypopneas (*HypDur*, Figure 1 and Table 3) from TST. Similarly, Desaturation

Duration represents the percentage of the total duration of desaturations (*DesDur*, Figure 1 and Table 3) from TST. Desaturation Severity represents the severity of desaturation events (*i.e.* desaturation area (*DesArea*), Figure 1 and Table 3) normalized by TST. Desaturation areas were computed by using the start and end time of each individual desaturation event and numerically integrating the corresponding desaturation area (Figure 1). In addition, Obstruction Severity is defined as a TST normalized sum of multiplications between apnea or hypopnea duration, and corresponding desaturation area (Table 3).

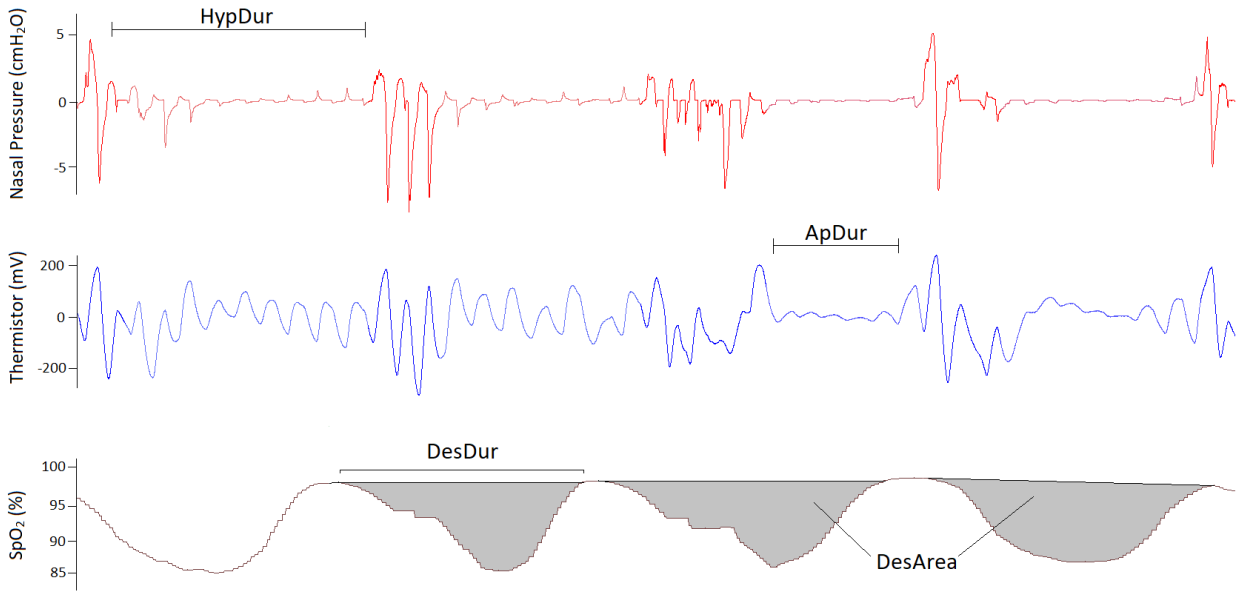

Figure 1: Schematic representation of the variables related to novel parameters. ApDur = the duration of an apnea (s), HypDur = the duration of a hypopnea (s), DesDur = duration of a desaturation (s), DesArea = area of a desaturation (s%).

For statistical analyses, patients were grouped into PVT performance quartiles based on each of the five PVT outcome variables (Tables 1-2). After grouping, multivariate binomial logistic regression was used to investigate which parameters were associated with impaired PVT performance. Multivariate binomial logistic regression was chosen due to the assumption that the connection between OSA severity indices and poor PVT performance is non-linear and

multivariate, and because the method does not require any transformations for the PVT outcome variables. The patients belonging to the worst-performing quartiles were compared to the patients belonging to the best performing quartile. Models were first adjusted for sex, age, body mass index (BMI), ESS score, smoking status and existing comorbidities (depression, hypertension and chronic obstructive pulmonary disease [COPD]). The co-existence of depression and all the other comorbidities were reported based on medical history or interview in the sleep clinics. The partial maximum likelihood (ML) estimates of β-coefficients for belonging to the worst-performing PVT quartile were computed individually for every investigated parameter and adjusting factor. Second, the model was adjusted for TST, AHI, AI, and ObsDur to examine how the severity of desaturations affects PVT performance independently. This additionally adjusted model was used for two reasons. First, to test the hypoxemia-hypothesis in a more detailed manner by controlling the number and duration of respiratory events. Second, we wanted to avoid the use of pre-defined limits for OSA severity classes and rather treat AHI as a continuous variable. After computing the β-coefficients for all models, the coefficients were converted to odds ratios according to the logit-function. As examined parameters differ substantially (in the order of magnitude), their values were normalized by the maximum value of each parameter in question before the analyses. However, the normalized 1% increase e.g. in AHI would have produced an increase of 1.7 events/h and for median desaturation depth an increase of 0.29%. Thus, the parameter values were further scaled to equal a 10% relative change to achieve a comparable and clinically more meaningful increase.

Table 2: Demographic and polysomnographic data in the worst-performing PVT quartile (Q4) and best performing quartile (Q1) based on each examined PVT outcome.

	RRT (1/ms)		Median RT (ms)		Slowest 10% RT (ms)		Fastest 10% RT (ms)		Lapses	
	Q1 (>2.9)	Q4 (<2.2)	Q1 (<340.0)	Q4 (>445.0)	Q1 (<544.3)	Q4 (>1081.0)	Q1 (<277.0)	Q4 (>335.8)	Q1 (<5)	Q4 (>36)
Patients (male%)	154 (21.4)	202 (58.4)	189 (22.2)	184 (59.8)	186 (26.8)	186 (50.0)	192 (27.1)	186 (59.7)	189 (25.9)	180 (56.1)
Depression	21 (13.6)	46 (22.8)	25 (13.2)	41 (22.3)	26 (14.0)	40 (21.5)	33 (17.2)	38 (20.4)	26 (13.8)	43 (23.9)
Hypertension	50 (32.5)	92 (45.5)	69 (36.5)	85 (46.2)	69 (37.1)	90 (48.4)	70 (36.5)	86 (46.2)	65 (34.4)	83 (46.1)
Smoker	26 (16.9)	36 (17.8)	33 (17.5)	34 (18.5)	27 (14.5)	36 (19.4)	33 (17.2)	31 (16.7)	31 (16.4)	34 (18.9)
COPD	12 (7.8)	25 (12.4)	14 (7.4)	22 (11.2)	12 (6.5)	24 (12.9)	17 (8.9)	18 (9.7)	14 (7.4)	23 (12.8)
Age (y)	52.5 (42.8-63.7)	58.4 (48.9-68.1)	54.1 (42.9-65.4)	58.9 (49.9-69.4)	52.5 (42.8-63.7)	58.7 (49.0-69.0)	52.5 (43.0-64.8)	58.4 (50.2-68.1)	51.3 (42.8-62.1)	58.9 (49.4-68.5)
BMI (kg/m^2)	34.3 (30.1-40.4)	35.0 (30.1-41.9)	34.0 (30.1-40.4)	35.0 (30.1-42.0)	34.9 (30.1-41.8)	35.0 (29.8-40.7)	35.4 (30.1-40.5)	35.4 (30.4-41.6)	33.9 (29.2-40.4)	34.9 (30.2-42.1)
TST (h)	5.0 (4.0-5.9)	5.0 (4.0-5.9)	5.0 (4.0-5.9)	5.0 (4.0-6.0)	5.1 (4.2-6.0)	5.0 (3.9-5.9)	5.1 (4.0-5.9)	4.9 (4.0-5.8)	5.2 (4.3-5.9)	4.9 (3.9-5.9)
NREM (%)	82.0 (77.5-87.2)	82.9 (78.3-88.2)	82.0 (77.6-87.6)	82.9 (78.3-88.3)	82.1 (77.4-88.5)	82.6 (78.0-88.2)	82.5 (78.4-88.5)	82.6 (78.3-87.8)	82.1 (77.7-88.2)	82.5 (78.1-88.2)
REM (%)	18.1 (12.8-22.5)	17.2 (11.8-21.7)	18.0 (12.4-22.4)	17.1 (11.7-21.7)	18.0 (11.5-22.6)	17.4 (11.8-22.0)	17.5 (11.6-21.7)	17.4 (12.2-21.7)	17.9 (11.8-22.3)	17.5 (11.8-21.9)
AHI (events/h)	25.8 (13.0-47.2)	22.2 (11.5-42.1)	27.0 (13.5-45.7)	22.5 (11.8-42.1)	27.5 (13.0-49.4)	21 (11.4-42.3)	24.7 (12.0-43.7)	22.8 (11.5-42.1)	27.5 (12.9-48.7)	22.9 (11.8-46.9)
ESS score	9 (5-13)	11 (6-16)	9 (5-13)	11 (6-16)	9 (5-13)	11 (6-17)	10 (6-14)	11 (5-16)	9 (5-12)	11 (6-17)

Caption: Data is presented as number (% of population) or median (interquartile range) where appropriate. Abbreviations: COPD = chronic obstructive pulmonary disease, BMI = body mass index, TST = total sleep time, NREM = non-rapid eye movement sleep, REM = rapid eye movement sleep, AHI = apnea-hypopnea index, ESS = Epworth sleepiness scale, RRT = mean reciprocal reaction time RT = reaction time, Lapses = reaction times exceeding 500 ms.

Table 3: Equations for computation of the novel parameters described.

Parameter name (unit)	Equation
AHI (1/h)	$\frac{L+K}{TST_h}$
ODI (1/h)	$\frac{P}{TST_h}$
Obstruction Duration (%)	$\frac{\sum_{n=1}^{L} ApDur_n + \sum_{m=1}^{K} HypDur_m}{TST} \times 100\%$
Desaturation Duration (%)	$\frac{\sum_{n=1}^{P} DesDur_n}{TST} \times 100\%$
Desaturation Severity (%)	$\frac{\sum_{n=1}^{P} DesArea_n}{TST}$
Obstruction Severity (s%)	$\frac{\sum_{m=1}^{K} (HypDur_m \times DesArea_m) + \sum_{n=1}^{L} (ApDur_n \times DesArea_n)}{TST}$

Caption: *ApDur* = duration of an apnea (s), *HypDur* = duration of a hypopnea (s), *DesDur* = duration of a desaturation (s), *DesArea* = area of a desaturation (s%), *L* = number of apneas, *K* = number of hypopneas, *P* = number of desaturations, TST_h = total sleep time computed in hours from PSG, *TST* = total sleep time computed in seconds from PSG.

Results

Comparison between the worst and the best performing PVT quartiles

The comparison between Q1 and Q4 was performed individually for every examined OSA severity metric with two different multivariate logistic regression models. When the model was adjusted for demographics, subjective sleepiness and comorbidities, an increase in either $t_{90\%}$, Desaturation Severity, mean desaturation depth or median desaturation depth significantly elevated the odds of longer median RT (OR = 1.17 – 1.26). Slower RRT (OR = 1.24 – 1.26, Table 4) was significantly associated with an increase in mean and median desaturation depth. Only an increase in $t_{90\%}$ (OR = 1.18; p = 0.04) and median desaturation depth (OR = 1.20; p = 0.02) significantly elevated the odds of having a higher number of lapses. An increase in Desaturation Severity (p = 0.06) and mean desaturation depth (p = 0.09) were at the borderline of significantly elevating the odds of belonging to Q4 based on lapses. In addition, an increase in the median desaturation depth showed significantly (OR = 1.25; p = 0.04) elevated odds of belonging to Q4 based on the fastest 10% RT.

With the model additionally adjusted for TST, AI, AHI and Obstruction Duration, the worsening in all examined hypoxemia parameters significantly elevated the odds of belonging to Q4 based on the number of lapses; however, a decrease in the mean SpO_2 (p = 0.10) and increase in mean desaturation depth (p = 0.12) did not significantly affect the odds of having longer median RT compared to other hypoxemia parameters (Table 4). An increase either in Desaturation Severity (OR = 1.43; p = 0.01) or median desaturation depth (OR = 1.36; p = 0.02) significantly elevated the odds of belonging to Q4 based on RRT. In addition, investigation of Slowest 10% RT quartiles showed that an increase in Obstruction Severity (OR = 1.39; p = 0.04), $t_{90\%}$ (OR = 1.19; p = 0.04), or median depth (OR = 1.27; p = 0.02) elevated the odds of belonging to Q4. None of the parameters

were significantly associated with the odds of belonging to Q4 based on the Fastest 10% RT. Results of similar analyses comparing Q4 to all other quartiles are presented in the supplementary material (Table S1).

Demographic variables as risk factors for impaired PVT performance

When demographical risk factors, subjective sleepiness (ESS), and risk of comorbidities were assessed, only female sex, higher ESS score, and older age were significantly associated with elevated odds of impaired PVT performance. Female sex (OR_{range} = 2.21-6.02, $p < 0.01$) and increase in ESS (OR_{range} = 1.05-1.07, $p < 0.01$) were significant risk factors with all PVT outcome variables, whereas increasing age was significant in all analyses with quartiles based on RRT, median RT, and lapses (OR_{range} = 1.01-1.05, $p < 0.05$). BMI, smoking and co-existence of depression, COPD, or hypertension had no association with impaired PVT performance.

Table 4: The odds of belonging to the worst-performing PVT quartile (Q4) compared to best performing quartile (Q1), when parameter values are increased by 10%. Quartiles and the corresponding odds are defined separately for each PVT outcome variable.

	RRT (1/ms)	Median RT (ms)	Slowest 10% RT (ms)	Fastest 10% RT (ms)	Lapses (RT>500ms)
Model adjusted for sex, age, BMI, ESS and comorbidities					
TST (h)	1.05	1.07	0.99	1.06	1.02
AHI (1/h)	1.05	1.04	0.91	1.05	0.96
ODI (1/h)	1.07	1.09	0.95	1.07	1.00
AI (1/h)	0.99	0.98	0.93	0.96	0.95
ObsDur (%)	1.04	1.01	0.92	1.05	0.97
DesDur (%)	1.07	1.09	0.97	1.07	1.02
DesSev (%)	1.24	**1.26**	1.04	1.20	1.17
ObsSev (s%)	1.18	1.17	1.07	1.13	1.14
Mean SpO_2 (%)	0.51	0.63	0.69	0.82	0.54
Min. SpO_2 (%)	0.88	0.94	0.97	0.97	0.94
$t_{90\%}$ (s)	1.14	**1.17**	1.11	1.08	**1.18**
Mean Depth (%)	**1.21**	**1.21**	1.07	1.19	1.16
Median Depth (%)	**1.26**	**1.25**	1.10	**1.25**	**1.20**
Model adjusted for sex, age, BMI, ESS, comorbidities, TST, AHI, AI, and Obstruction Duration					
DesSev (%)	**1.43**	**1.52**	1.33	1.31	**1.48**
ObsSev (s%)	1.33	**1.38**	**1.39**	1.22	**1.36**
Mean SpO_2 (%)	0.55	0.60	0.54	0.83	**0.47**
$t_{90\%}$ (s)	1.11	**1.16**	**1.19**	1.06	**1.23**
Mean Depth (%)	1.27	1.26	1.19	1.21	**1.27**
Median Depth (%)	**1.36**	**1.34**	**1.27**	1.32	**1.37**

Caption: All odds are adjusted for smoking status and co-existence of hypertension, depression and chronic obstructive pulmonary disease (COPD). Bolded odds are statistically significant (p<0.05). Abbreviations: ESS = Epworth Sleepiness Scale, ms = milliseconds, TST = total sleep time, AHI = apnea-hypopnea index, ODI = oxygen desaturation index, AI = arousal index, ObsDur = obstruction duration, DesDur = desaturation duration, DesSev = desaturation severity, ObsSev = obstruction severity, $t_{90\%}$ = time spent under 90% oxygenation, Mean Depth = mean depth of all desaturations, Median Depth = median depth of all desaturations.

Discussion

In this study, we investigated the role of conventional and novel PSG parameters in predicting PVT performance in a sample of 743 OSA patients. We found that our novel parameters describing the severity of intermittent hypoxemia are significantly associated with increased risk of impaired PVT performance, whereas conventional OSA severity and sleep fragmentation metrics (*i.e.* AHI, ODI and AI) are not. This finding is supported by our previous study [7], showing that OSA-related objective daytime sleepiness is more strongly associated with the severity of individual desaturations than the number of apneas and hypopneas. Furthermore, these results correspond with previous studies [8,9,18-22], by showing that conventional AHI-based assessments of OSA have little connection to poor PVT performance. These findings highlight, together with recent studies [7,24,29,31], the clinical importance of a more detailed analysis of PSG recordings when assessing OSA severity, symptoms and daytime functioning. As the presented novel parameters are based on routine manual scoring of PSG, they can be easily implemented to clinics without any extra work required of technical or medical staff [32].

Based on our results, the severity of nocturnal intermittent hypoxemia is the strongest PSG-related indicator of poor PVT performance. The more severe desaturations leading to longer median reaction times and a higher number of lapses were consistent within each sub-group analysis (Table 4) and consistent with previous studies [10,18]. Our results show that larger desaturation areas and deeper desaturations affect negatively on the vigilance and the ability to sustain attention in OSA patients. Interestingly, the duration of desaturations was not a significant factor in elevating the odds of impaired PVT performance (Table 4). It has been shown, that OSA-related intermittent hypoxemia causes neuronal brain damage and similar changes as in ischemic injury [33]. Furthermore, a recent study shows that systemic intermittent hypoxemia readily

translates to cerebral hypoxemia in healthy individuals, indicating that there are limits to which the autoregulation system can prevent hypoxemia in the cerebral vasculature [34]. The combination of our results with these findings suggests, that the depth of desaturations, in conjunction with the repetitive failure of the cerebral autoregulation system, may drive the cognitive impairment seen in OSA patients.

The highest and most significant odds ratios were induced by DesSev, median desaturation depth and mean desaturation depth across all analyses. Comparisons between the demographically adjusted and additionally adjusted models (Table 4) show that when the number and duration of the apneas and hypopneas are invariant, increasing depth and area of desaturations will elevate the odds of prolonged reaction times. It has been previously shown, that patients with similar AHI values can exhibit highly different responses in peripheral blood oxygenation [29]. These findings suggest that there exist substantial differences between patients in how rapidly peripheral oxygenation decreases and how fast reoxygenation recovers. Therefore, further studies are warranted to consider the morphology of desaturations, as well as the decrease and recovery rates of SpO_2 within desaturation events, and the association of these factors with cardiovascular outcomes and daytime symptoms in OSA patients.

As we hypothesized, the more detailed diagnostic parameters have a significantly stronger connection to impaired PVT performance than AHI or other conventional PSG parameters. Against this hypothesis, our results indicate that the duration of apneas, hypopneas, and desaturations does not seem to affect PVT performance as much as the depth of desaturations. Obstruction Severity metric is defined as the multiplications of desaturation areas and durations of the corresponding respiratory event whereas Desaturation Severity is independent of respiratory

event duration. Therefore, it is reasonable that Obstruction Severity has less significance than Desaturation Severity, as the duration of the events was found insignificant. It is noteworthy, that Obstruction Severity was developed for HSAT and therefore, no arousal-related hypopneas could have been considered. This urges for development of PSG-modified Obstruction Severity, where arousals could be quantified for example using the frequency content and the duration of arousal in a similar manner compared to the desaturation area. Based on the results achieved for the detailed hypoxemia parameters with both adjustment schemes, it can be speculated that deteriorated vigilance is much more dependent on physiological consequences caused by apneas and hypopneas rather than the number or the duration of events per se. In addition, as the emphasis of this study was to assess the role of intermittent hypoxemia in vigilance failure, only a limited number of EEG and sleep fragmentation metrics were investigated in this study. Therefore, further studies are warranted for detailed EEG analyses and their connection to the impaired PVT performance to gain more comprehensive information on the factors causing vigilance deterioration.

This study was based on a relatively large, well-balanced clinical sample of patients whose demographics, symptoms and comorbidities reflect well general OSA populations (Table 1), making the obtained results generalizable to clinical populations. However, clinical and epidemiological populations can include other comorbid sleep disorders, such as insomnia and restless legs syndrome among others, which may have a confusing effect on findings related to PVT outcomes. In addition, the present results show that female sex, subjective sleepiness and older age together with OSA are significant predictors of poor PVT performance. Similar findings have also been reported in other studies investigating cognitive impairment in OSA patients and healthy individuals [9,19,20,22,35]. Moreover, in our recent studies, we reported that a larger

desaturation area is a significant predictor of objective daytime sleepiness and the most detrimental health consequences of OSA [7,29,31]. Together with these findings, this study highlights the urgent need to develop the diagnostics of OSA beyond the AHI. Diagnosis should be made more comprehensive by characterizing OSA severity with demographical information and with more detailed parameters that are better related to the symptoms, daytime functioning and for example, cardiovascular comorbidities of OSA. To support the idea of utilizing these new metrics in normal clinical workflow, we have already published a plug-in for RemLogic (Natus Medical Inc., Middleton, WI, USA) that computes these new metrics automatically based on routine manual scoring of the sleep recording [32]. These metrics could also be implemented in other clinical software in a similar manner.

This study has certain limitations. First, the PVT outcome variables used in this study were the standard statistical parameters from the series of 120 reaction times. Individuals have natural differences in their repeated reaction times, and therefore the PVT analysis could also benefit utilizing the complete time series. Nevertheless, the standard parameters used in this study enables us to compare with the existing literature regarding the connection of OSA to PVT outcomes. Second, patients completed their PVT prior to PSG. Individuals suffering from OSA tend to have shorter TST in PSG than normally [36], which can affect the odds obtained for TST. It is acknowledged that TST modulates the values of AHI and ODI to a great extent; however, all novel parameters are also normalized by TST. Furthermore, in a recent study, it was reported that severities of individual apneas, hypopneas, and desaturations increase along increasing TST [37]. Therefore, it is reasonable to assume that mean SpO_2 and minimum SpO_2 would decrease, and $t_{90\%}$, as well as the mean and median depth of desaturations, would increase along increasing TST. Thus, we believe that the timing of the PVT does not diminish the obtained results. Third, although

the models were adjusted with comorbidities, a complete record of patients' medication at the time of PSG and PVT was not available. Psychoactive and sedative medications can especially affect the reaction times and thus PVT performance, which could affect the computed odds ratios to some extent. Fourth, this study did not involve a control group of healthy individuals. However, the objective of this study was to investigate which are the most significant PSG parameters associated with impaired PVT performance in OSA patients. Therefore, patients without OSA were excluded due to the assumption that their impaired vigilance is not caused by the same factors compared to those suffering from OSA. Fifth, no data on patient's habitual sleep (*e.g.* questionnaire, sleep diary or long-term actigraphy) were available. Short sleep duration and chronic sleep deprivation are significantly associated with sleepiness and can, therefore, affect neurocognitive performance [38]; thus, the lack of this information is a limitation of the present study.

In conclusion, we have shown that parameters quantifying desaturations based on their characteristic properties have a significant association with impaired vigilance and ability to sustain attention. Furthermore, an increase in AHI or ODI does not significantly elevate the odds of having impaired PVT performance. These results highlight the importance of developing methods for a more detailed assessment of OSA severity and comprehensive analysis of PSGs. This would enhance the assessment of OSA severity and improve the estimation of risk and severity of related daytime symptoms.

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Supplementary material

Table S1: The odds of belonging to the worst-performing PVT quartile (Q4) when parameter values are increased by 10% compared to the combined group of all other quartiles (Q1-Q3). Quartiles and the corresponding odds are defined separately for each PVT outcome variable.

	RRT (1/ms)	Median RT (ms)	Slowest 10% RT (ms)	Fastest 10% RT (ms)	Lapses (RT>500ms)
Model adjusted for sex, age, BMI, ESS and comorbidities					
TST (h)	1.02	1.06	1.01	1.00	1.02
AHI (1/h)	1.04	1.03	0.96	1.01	1.06
ODI (1/h)	1.07	1.07	0.98	1.06	1.09
AI (1/h)	0.98	0.97	0.96	0.94	1.01
ObsDur (%)	1.02	0.99	0.96	0.99	1.05
DesDur (%)	1.06	1.05	0.99	1.05	1.08
DesSev (%)	1.15	**1.16**	1.03	1.07	**1.18**
ObsSev (s%)	1.08	1.08	1.03	1.02	1.10
Mean SpO_2 (%)	0.85	0.89	0.89	0.93	0.80
Min. SpO_2 (%)	0.97	0.96	0.99	0.99	0.94
$t_{90\%}$ (s)	1.08	1.09	1.02	1.06	**1.10**
Mean Depth (%)	1.15	**1.18**	1.07	1.10	**1.18**
Median Depth (%)	**1.17**	**1.18**	1.08	1.11	**1.20**
Model adjusted for sex, age, BMI, ESS, comorbidities, TST, AHI, AI, and Obstruction Duration					
DesSev (%)	1.24	**1.29**	1.14	1.13	**1.23**
ObsSev (s%)	1.14	1.17	1.13	1.05	1.13
Mean SpO_2 (%)	0.85	0.88	0.83	0.95	0.85
$t_{90\%}$ (s)	1.07	1.07	1.03	1.00	1.08
Mean Depth (%)	**1.20**	**1.26**	1.15	1.16	**1.20**
Median Depth (%)	**1.23**	**1.27**	1.16	1.18	**1.23**

Caption: All odds are adjusted for smoking status and co-existence of hypertension, depression and chronic obstructive pulmonary disease (COPD). Bolded odds are statistically significant (p<0.05). Abbreviations: ms = milliseconds, TST = total sleep time, AHI = apnea-hypopnea index, ODI = oxygen desaturation index, AI = arousal index, ObsDur = obstruction duration, DesDur = desaturation duration, DesSev = desaturation severity, ObsSev = obstruction severity, $t_{90\%}$ = time spent under 90% oxygenation, Mean Depth = mean depth of all desaturations, Median Depth = median depth of all desaturations.