Original article

Epileptic Disord 2019; 21 (1): 78-86

Neuropsychological correlates of obstructive sleep apnea severity in patients with epilepsy

Véronique Latreille, Kim C. Willment, Rani A. Sarkis, Milena Pavlova

Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, USA

Received July 06, 2018; Accepted December 12, 2018

ABSTRACT – *Aims*. Obstructive sleep apnea affects up to 30% of patients with epilepsy. As obstructive sleep apnea represents a clinical risk factor for cognitive deficits, its occurrence in epilepsy patients may exacerbate cognitive deficits associated with this condition. However, the cognitive burden of obstructive sleep apnea in epilepsy remains poorly understood. We conducted a retrospective record review of adults with epilepsy who underwent a polysomnography and a neuropsychological assessment at Brigham and Women's Hospital.

Methods. We examined the relationship between obstructive sleep apnea severity and cognitive functioning, particularly attention/executive functions, memory, and processing speed in untreated obstructive sleep apnea patients with epilepsy. Twenty patients with epilepsy and mild-to-severe obstructive sleep apnea were included in the analyses.

Results. We found significant positive correlations between the oxygen saturation levels during rapid-eye-movement sleep and attention/executive tests ($p<0.05$), as well as time spent with saturation levels $\leq$90% and executive functioning ($p=0.008$). Similarly, worse verbal memory performances were associated with lower oxygen levels ($p=0.003$). In addition, more severe respiratory events during rapid-eye-movement sleep were associated with worse performances on attention tests ($p=0.03$).

Conclusions. Our findings indicate that more severe obstructive sleep apnea-related hypoxemia during sleep is associated with poorer cognitive performances on tests that assess attention/executive functions and verbal memory in patients with epilepsy. Overall, these results are consistent with the sleep apnea literature, and suggest that patients with epilepsy are also vulnerable to the effects of obstructive sleep apnea. Future prospective studies will help in determining whether treatment of obstructive sleep apnea may help improve cognitive functioning in patients with epilepsy.

Key words: epilepsy, polysomnography, obstructive sleep apnea, neuropsychology, cognition

Correspondence:
Department of Neurology, Brigham and Women's Hospital,
60 Fenwood Road,
Boston, MA 02115, USA
<vlatreille@bwh.harvard.edu>

doi:10.1684/epd.2019.1029

Sleep-related breathing disorders, such as obstructive sleep apnea (OSA), are common in adults with epilepsy, affecting up to one third of patients (Lin *et al*., 2017). OSA is one of the most common reported factors associated with reduced quality of life in individuals with epilepsy (Piperidou *et al*., 2008). These patients also frequently report excessive daytime sleepiness (Manni *et al*., 2003; Gammino *et al*., 2016) and are more likely to have seizures during sleep (Malow *et al*., 2000; Manni *et al*., 2003). OSA may exacerbate seizure occurrence by causing nocturnal episodes of intermittent hypoxemia and electroencephalographic (EEG) arousals (Devinsky *et al*., 1994).

When left untreated, OSA can have major negative health consequences; it increases the risk of hypertension, type 2 diabetes, and cardiovascular diseases (Shahar *et al*., 2001); for a review see Maeder *et al*. (2016). OSA is also a well-known risk factor for cognitive deficits (Yaffe *et al*., 2011; Rosenzweig *et al*., 2015). Indeed, accumulating evidence demonstrates the negative impacts of OSA on nearly all domains of cognition, though larger effect sizes are more commonly found for attention, executive functions, and psychomotor speed (Rosenzweig *et al*., 2015; Stranks and Crowe, 2016). Several facets of executive functioning are impaired in adults with OSA as compared to healthy controls, including set-shifting, working memory, inhibition, and problem-solving (Olaithe and Bucks, 2013; Bucks *et al*., 2017). The mechanisms by which OSA may impair cognition are not yet fully clear, but it is postulated that the combination of sleep fragmentation, cyclical intermittent hypoxemia, and hypercapnia, as well as ensuing metabolic consequences, may all play a role (Rosenzweig *et al*., 2015).

Cognitive problems are also often reported in patients with various epilepsy syndromes. On neuropsychological testing, many studies have demonstrated significant impairments in cognitive flexibility, attention, psychomotor speed, and memory functions in patients with epilepsy (Elger *et al*., 2004; Hermann *et al*., 2007; Loughman *et al*., 2014). As OSA is frequent in epilepsy and represents a clinical risk factor for cognitive deficits, its occurrence in epilepsy patients might worsen initial cognitive impairments. However, the cognitive burden of OSA in epilepsy is poorly understood, and only one study to date investigated subjective cognitive functioning in epilepsy patients at risk of OSA (Piperidou *et al*., 2008).

We conducted a retrospective study to examine the effects of sleep apnea severity on cognitive functioning in untreated OSA patients with epilepsy. We hypothesized that more severe OSA would be associated with poorer cognitive performances, particularly on tests assessing attention/executive functions and processing speed.

Material and methods

Participants

We retrospectively reviewed clinical data of all adult individuals with epilepsy seen in the neurology clinic at Brigham and Women's Hospital who underwent a polysomnography (PSG) for evaluation of OSA and complete neuropsychological testing (with an interval of less than 18 months), from May 2012 to November 2017. The study was approved by the institutional review board.

Diagnosis of epilepsy was confirmed by expert epileptologists using history, seizure semiology, EEG, and neuroimaging data. Patients with non-epileptic seizures were not included in the study. Subjects were also excluded from the analysis if they received treatment for OSA at the time of the neuropsychological assessment, and if they were diagnosed with dementia. For each subject, we examined demographic and clinical data, including education level, body mass index (BMI), neck circumference, cardiovascular risk factors (such as hypertension, diabetes, and hypercholesterolemia), smoking status, epilepsy refractoriness (defined as the persistence of seizures despite adequate trials of two antiepileptic drugs [AEDs]), epilepsy duration, seizure characteristics, and the number of AEDs. We also collected data on subjective daytime sleepiness, as measured by the Epworth Sleepiness Scale (ESS), when available.

Polysomnographic recordings

All subjects underwent in-laboratory overnight sleep recordings. The PSG montage included EEG, electrooculography, electromyography, and electrocardiography recordings. Respiration was monitored continuously using nasal thermistor flow, nasal pressure, pharyngeal snoring, and thoracic and abdominal belts. Oxygen saturation was monitored using finger pulse oximetry sensors. Leg movements were recorded using surface electrodes on anterior tibialis muscles. Sleep stages were visually scored per standard criteria (Iber *et al*., 2007). Apneas were documented if they occurred for 10 seconds or longer and hypopneas were scored when there was at least 30% decrement in nasal pressure signal for at least 10 seconds in combination with either a 3% oxygen desaturation or EEG arousal (Berry *et al*., 2012). The apnea-hypopnea index (AHI) was defined as the sum of all apnea and hypopnea events divided by total sleep time.

Baseline PSG variables included total sleep time, sleep latency and efficiency, rapid-eye-movement (REM) sleep latency, wakefulness after sleep onset, apnea-hypopnea arousal index (number of apnea and

hypopnea events associated with an EEG arousal per hour), periodic limb movement during sleep index, and duration of sleep stages. In addition to the well-studied AHI in OSA research, we also included for analysis variables that reflected the severity of OSA associated hypoxemia, such as the nadir oxygen saturation (SaO_2) levels and percent of time spent with SaO_2 levels lower or equal to 90%. Such variables have been suggested to be more sensitive measures of the effects of OSA on cognition, as compared to solely the number of apnea events (Quan *et al*., 2011). Thus, in the present analysis, OSA-related variables of interest included total and REM AHI, apnea-hypopnea arousal index, total and REM nadir SaO_2, and percent of total sleep time with $SaO_2 \leq 90\%$.

Neuropsychological assessment

Complete neuropsychological testing was performed at Brigham and Women's Hospital either as part of the pre-surgical assessment or upon referral from the treating physician (as part of the epilepsy evaluation). The neuropsychological battery assessed several cognitive domains, including attention, executive functions, episodic memory, language, visuospatial skills, and speed processing. To focus the number of comparisons, and given that previous studies have shown more consistently that OSA has a negative impact on attention, executive, and speed functions (Rosenzweig *et al*., 2015; Stranks and Crowe, 2016), we included tests that assess attention/executive functions, episodic memory, and processing speed.

Moreover, because the testing was performed as part of a clinical investigation, and therefore individualized for each patient, we selected for analysis only the tests for which sufficient data (>50% of patients) were available (with the exception of episodic memory tests; see details below). Converted z-scores of the following neuropsychological variables were included in the analyses: (1) *Attention/Executive functions*: Trail Making Test Part A and B (time), Digit Span subtest from the Wechsler Adult Intelligence Scale (WAIS-III or IV editions), and Phonemic (F, A, and S) Verbal Fluency; and (2) *Speed processing*: the Coding subtest from the WAIS-III or IV editions. For episodic memory tests, composite scores were computed for the verbal and non-verbal domains using averaged z-scores to account for the large heterogeneity of tests used to assess memory processes. The following tests were included in the composite scores for (3) *Verbal episodic memory*: the Rey Auditory Verbal Learning Test (learning trials, immediate and delayed recalls), Logical Memory (immediate and delayed recalls) subtest from the Wechsler Memory Scale-Third Edition, and California Verbal Learning Test-Second edition (learning trials, short and long delay free recalls); and (4) *Non-verbal episodic memory*: the Brief Visuospatial Memory Test-Revised (learning trials and delayed recall), 7/24 Spatial Recall Test (immediate and delayed recalls), Visual Reproduction (immediate and delayed recalls) from the Wechsler Memory Scale-IV Edition, and Rey-Osterrieth Complex Figure (immediate and delayed recalls).

All the neuropsychological test scores were converted to age-corrected z-scores using standard normative data. The Trail Making Test, Verbal Fluency, and episodic memory scores were also corrected for education.

Statistical analyses

All neuropsychological z-scores, except the Trail Making Test Part B, followed a normal distribution (Shapiro-Wilk test; $p>0.05$). However, none of the OSA-related variables were normally distributed, and therefore non-parametric tests were used for these variables.

First, to identify potential clinical confounding variables, we performed correlations between clinical data (age, BMI, number of AEDs, and duration of epilepsy) and our variables of interest, including both OSA (total AHI, REM sleep AHI, apnea-hypopnea arousal index, nadir SaO_2, REM sleep nadir SaO_2, and time spent in $SaO_2 \leq 90\%$) and neuropsychological variables in all patients. Partial correlation was then used to control for potential confounding factors when a significant relationship was found, and this was done separately for each analysis. If no confounding factors were identified, Pearson or Spearman correlation was used to assess the relationship between OSA-related variables and neuropsychological scores. Statistical analyses were performed using SPSS, version 24. Significance was set at $p<0.05$.

Results

A total of 34 adults diagnosed with epilepsy underwent a PSG and a neuropsychological assessment within an 18-month interval at Brigham and Women's Hospital between May 2012 and November 2017. All patients reported complaints of sleep apnea, including hypersomnolence and snoring, and one patient also reported insomnia symptoms. Twenty-eight patients met OSA criteria (AHI ≥ 5). Of that sample, eight patients were excluded because of dementia (n=1), initiation of OSA therapy at the time of testing (n=6), and invalid test results (n=1). Thus, 20 patients with epilepsy and comorbid OSA were included in the analysis. Demographic, clinical, and sleep data of our study sample of epilepsy patients are presented in *table 1*.

Table 1. Demographic, clinical, and sleep data of all epilepsy patients.

Clinical characteristics	Patients, *n* = 20	Polysomnographic data	Patients, *n* = 20
Age (years)	50.3 ± 15.1	Total AHI	22.4 ± 20.3
Gender (M/F)	13/7	REM sleep AHI	26.5 ± 28.5
Education (years)	15.1 ± 2.9	Total nadir SaO_2	85.8 ± 5.4
Body mass index	30.8 ± 8.9	REM sleep nadir SaO_2	88.6 ± 5.4
Neck circumference (inches)	15.4 ± 1.7	% total sleep time with SaO_2 ≤90%	4.1 ± 5.2
ESS score	10.4 ± 6.9	PLMS index	8.7 ± 23.3
Cardiovascular risk factors (n [%])		Total sleep time (minutes)	293.5 ± 95.4
0	13 (65%)	Sleep latency (minutes)	41.9 ± 69.4
1-2	6 (30%)	Sleep efficiency (%)	73.6 ± 19.2
>3	1 (5%)		
Active smoking status (n [%])	2 (10%)	Wakefulness after sleep onset (minutes)	76.0 ± 55.5
Duration of epilepsy (years)	22.9 ± 20.0	Apnea-hypopnea arousal index	14.6 ± 14.7
Drug-resistant epilepsy (n [%])	6 (30%)	Stage N1 (%)	15.6 ± 12.0
Seizure frequency per month (range)	3.8 ± 9.1 (0-30)	Stage N2 (%)	54.9 ± 13.9
Nocturnal seizures (n [%])	7 (35%)	Stage N3 (%)	9.0 ± 8.8
Number of antiepileptic drugs	1.7 ± 0.8	Stage REM (%)	18.6 ± 8.5
Epilepsy type (n [%])			
Focal	16 (80%)		
Generalized	4 (20%)		

ESS: Epworth Sleepiness Score; ED: epileptiform discharges (ictal and interictal); AHI: apnea/hypopnea index; SaO_2: oxygen saturation; REM: rapid eye movement; OSA: obstructive sleep apnea; PLMS: periodic limb movement during sleep.

Most patients had left temporal lobe epilepsy (60%) and seizures were medically well-controlled in 70% of patients. Nine (45%) patients had mild OSA (AHI ≥5 and <15), five (25%) patients had moderate OSA (AHI ≥15 and <30), and six (30%) patients had severe OSA (AHI ≥30). Of note, none of the patients had a seizure during the PSG recordings.

Table 2 shows the averaged neuropsychological z-scores of all epilepsy patients. Overall, worse group performances were observed for the Trail Making Test Part B and the non-verbal memory composite score (mean <1 standard deviation).

Table 2. Neuropsychological z-scores of all epilepsy patients.

Neuropsychological variables	Z-score
Trail Making Test Part A	-0.86 ± 1.66
Trail Making Test Part B	-3.81 ± 4.76
Digit Span	-0.32 ± 1.11
Phonemic Verbal Fluency	-0.72 ± 1.51
Coding	-0.60 ± 1.03
Verbal memory composite score	-0.48 ± 1.16
Non-verbal memory composite score	-1.22 ± 1.37

Association of OSA severity with neuropsychological variables

Significant negative correlations were found between the BMI and REM sleep nadir SaO_2 (r=-0.52, p=0.02), as well as between the number of AEDs and scores on

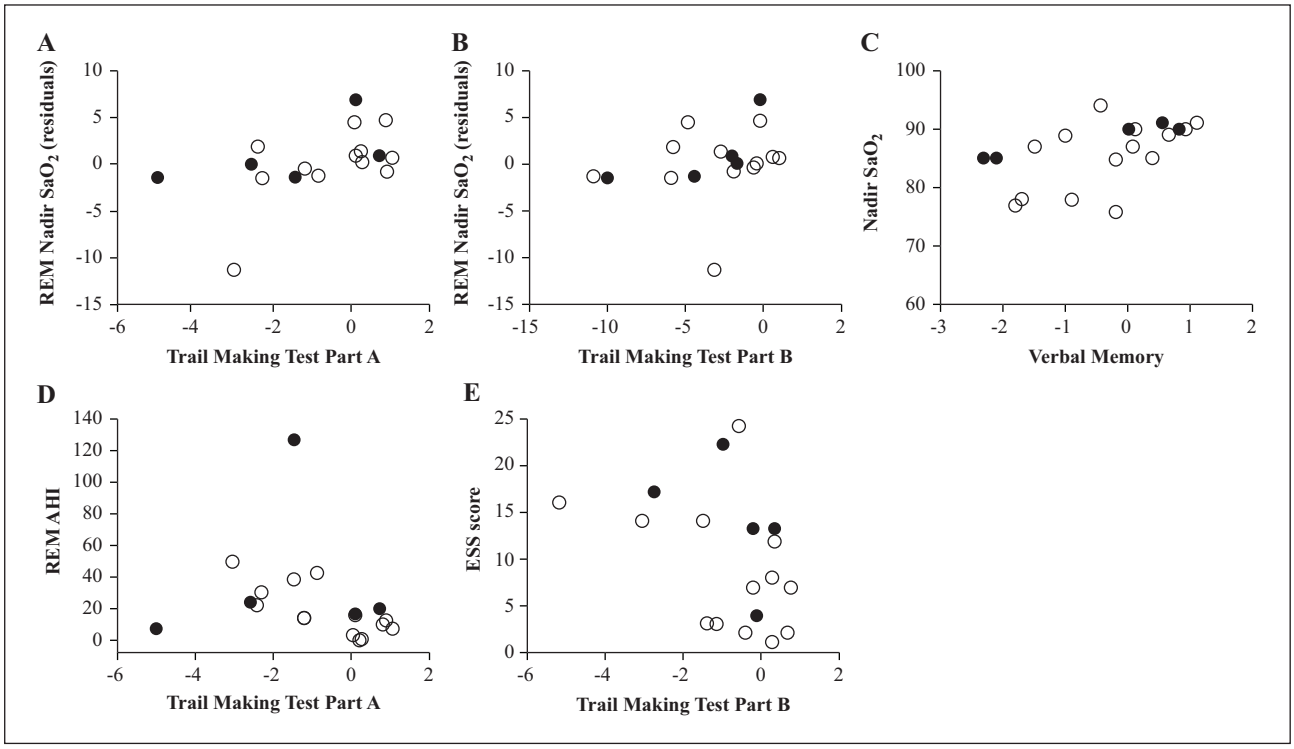

Figure 1. Scatter plots of relationships between OSA-related variables and neuropsychological and sleepiness outcomes in epilepsy patients. BMI-adjusted REM nadir SaO_2 data are represented using unstandardized residuals. Filled dots represent drug-resistant epilepsy patients; empty dots represent medically controlled epilepsy patients.
REM: rapid eye movement; SaO_2: oxygen saturation; AHI: apnea-hypopnea index; ESS: Epworth Sleepiness Scale.

the Digit Span (r=-0.49, p=0.04). No significant correlation was found for any other potential confounding factors (age and duration of epilepsy). The BMI and number of AEDs were therefore used as covariates for these specific analyses.

Significant correlations were observed between OSA-related variables and neuropsychological z-scores in epilepsy patients (a subset of these correlations is illustrated in *figure 1*). More specifically, we found a significant positive correlation between REM sleep nadir SaO_2 and scores on the Trail Making Test Part A (r=0.50, p=0.047) (*figure 1A*) and B (r=0.52, p=0.038) (*figure 1B*), indicating that lower oxygen level during REM sleep is related to lower attentional and executive functioning. Moreover, increased time spent with SaO_2 levels $\leq$90% is associated with worse performances on the Trail Making Test Part B (r=-0.62, p=0.008). We also found significant correlations between the verbal memory composite scores and total nadir SaO_2 levels (r=0.63, p=0.003) (*figure 1C*) and time spent with SaO_2 levels $\leq$90% (r=-0.55, p=0.015), suggesting that higher oxygen levels during sleep were associated with better verbal memory performances in patients.

In addition, we found significant negative correlations between the REM sleep AHI and scores on the Trail Making Test Part A (r=-0.55, p=0.019) (*figure 1D*) and Coding (r=-0.50; p=0.031), indicating that higher OSA severity during REM sleep is associated with poorer cognitive performances on tests assessing attention and processing speed in epilepsy patients. One patient with drug-resistant epilepsy showed a remarkably high REM sleep AHI (126 events/hour; 3 standard deviations above the mean of the sample). The scatter plot shows that this patient strongly affects the correlation analysis (*figure 1D*). Upon exclusion of this subject, the correlation between the REM AHI and Trail Making Test Part A remained (r=-0.53, p=0.03), however REM AHI was no longer associated with scores on the Coding subtest (p>0.05).

Given the limited sample size, supplementary analysis of the relationship between OSA severity and neuropsychological scores according to epilepsy refractoriness was not performed (drug-resistant epilepsy; n=6). However, as illustrated in *figure 1*, these patients were identified using a different symbol, with drug-resistant epilepsy patients represented by filled dots. Overall, there does not seem to be a clear pattern emerging from the data.

We also performed correlations between the ESS and neuropsychological scores and found a significant

negative correlation with the Trail Making Test Part B (r=-0.49, p=0.041), indicating that higher daytime sleepiness is associated with worse executive functioning in epilepsy patients (*figure 1E*).

Finally, although we initially included the number of AEDs as a potential confounding factor in our analyses, our sample size limited specific analysis of AED types and dosages, particularly the AEDs with known cognitive side effects (such as phenobarbital, phenytoin, topiramate, valproic acid, and benzodiazepines) (Eddy *et al*., 2011; Witt and Helmstaedter, 2017). Nevertheless, we examined the number of patients taking these AEDs, and found that only a small number were taking valproic acid (n=6) and benzodiazepines (for anxiety, n=2). None of the subjects were taking phenobarbital, phenytoin, or topiramate at the time of testing, which are the ones associated with the most negative cognitive profile (Eddy *et al*., 2011; Witt and Helmstaedter, 2017). Again, given the limited sample size, supplementary analysis according to polytherapy (n=13) status was not performed, but data are presented visually in *supplementary figure 1*. Patients on polytherapy are represented by the filled stars. Overall, there does not seem to be a clear pattern, with patients on polytherapy being spread at both ends of the data spectrum.

Discussion

Our findings indicate that higher OSA severity and associated intermittent nocturnal hypoxemia is linked to worse cognitive performances in adults with epilepsy. More specifically, we found that lower oxygen levels across all sleep stages are associated with lower scores on tests assessing executive functioning and verbal memory. Impaired breathing during REM sleep appears to have a strong relationship with cognition, affecting predominantly attention and executive functions. Epilepsy patients who reported more daytime sleepiness were also more likely to have lower executive functioning.

To our knowledge, this is the first study that has examined the effects of OSA severity on cognitive functioning as assessed by comprehensive neuropsychological testing in adults with epilepsy. Our results are consistent with the literature findings in the OSA population, showing that OSA is linked with poorer cognitive performances, especially based on tests assessing attention, and executive and psychomotor speed functions (Rosenzweig *et al*., 2015; Stranks and Crowe, 2016). Although larger effect sizes are usually found for the above-mentioned cognitive domains, episodic verbal memory (mainly retrieval processes, which are closely related to executive capacity) has also been reported to be impacted by OSA (Bucks *et al*., 2017).

Our results also extend previous reports that OSA-related hypoxemia variables may be more sensitive measures of the effects of OSA on cognition, by contrast to the frequency of apnea events per hour (Quan *et al*., 2011). Similarly, in older adults with OSA, nocturnal hypoxemia was found to be a significant risk factor of future cognitive decline, while the number of respiratory events was not (Yaffe *et al*., 2011). Besides, we found no significant relationship between OSA-associated arousals (apnea-hypopnea arousal index) and any cognitive measure in our patients. Although we did not have a group of healthy controls as comparison, sleep architecture variables such as sleep latency, duration of sleep stages, and number of awakenings were overall within the normal range. Therefore, our results suggest that nocturnal hypoxemia may be more debilitating for cognition than the number of apnea events and global sleep architecture in adults with epilepsy.

The mechanisms by which OSA may impair cognition are not fully understood. Yet, it has been proposed that both sleep fragmentation and intermittent hypoxemia may play a role (Rosenzweig *et al*., 2015). Several studies have demonstrated that OSA is associated with structural and functional cerebral abnormalities, which are thought to underlie the cognitive deficits observed in these patients. Indeed, adults with OSA have reduced grey matter volume (Shi *et al*., 2017), white matter fiber integrity (Castronovo *et al*., 2014), and cerebral glucose metabolism (Yaouhi *et al*., 2009; Ju *et al*., 2012) in multiple areas, including the frontal and temporal lobes. These areas are known to be involved in executive functions and memory processes, and thus may explain why these are particularly impaired in OSA individuals. Although no study to date has investigated the effects of OSA on specific areas of the brain in patients with epilepsy, it may be postulated that these patients may be more vulnerable and show more pronounced brain abnormalities relative to individuals with OSA but without epilepsy. Future large case-control prospective studies will be needed to examine whether epilepsy patients are indeed more vulnerable to the effects of OSA from a cognitive and neuronal standpoint. Moreover, whether a specific seizure onset zone has a differential vulnerability to the effects of OSA will require further investigation. Importantly, these brain abnormalities and associated cognitive consequences can be, at least partially, reversed by consistent and accurate treatment. Indeed, meta-analytic studies in patients with OSA have shown that treatment with continuous positive airway pressure (CPAP) therapy may improve vigilance, attention, and executive functions (Olaithe and Bucks, 2013; Pan *et al*., 2015). These improvements in cognitive functioning in OSA patients, compliantly treated with CPAP, were paralleled by positive

changes in grey and white matter integrity and cerebral glucose metabolism (Canessa *et al.*, 2011; Ju *et al.*, 2012; Castronovo *et al.*, 2014). Other treatments such as mandibular advancement has also been found to improve executive functioning, psychomotor skills, daytime sleepiness, and quality of life in OSA patients (Galic *et al.*, 2016). In epilepsy patients, studies have also shown that patients treated with CPAP were more than five times more likely to have a significant reduction in seizure frequency and daytime sleepiness compared to untreated patients (Lin *et al.*, 2017). These results suggest that CPAP may help reduce sleep apnea-related hypoxemia and arousals, further improving sleep stability, and thereby reducing seizure susceptibility. CPAP might also help in reducing OSA consequences in epilepsy patients such as cognitive impairment, but also apnea-related cardiovascular, metabolic, and neuronal dysfunctions.

Limitations

Some limitations of our study should be noted. It is a retrospective chart review and uses a patient population that is seen in the regular epilepsy clinic, and as such, our inclusion criteria were more limited. Thus, we cannot exclude that some potential confounding factors such as other OSA-related comorbidities or the effects of AEDs could have had an impact on our sleep and cognitive measurements. However, we have included the number of AEDs as a potential confounding factor in our analysis so that it was controlled for when significantly associated with our variables of interest. Moreover, a minority of subjects were taking AEDs with known cognitive side effects. While this does not preclude any potential contribution of drug-related cognitive side effects on our main results, it is unlikely to explain all of our findings. Visual analysis of the relationships between our OSA and neuropsychological variables according to drug polytherapy status also revealed no clear pattern, with patients on polytherapy being spread at both ends of the OSA or cognitive spectrum. Additionally, the retrospective nature of the study (medical chart review) limited extensive evaluation of OSA-related clinical outcomes, such as duration of OSA symptoms. One could hypothesize that longer duration of OSA symptoms would lead to more severe cognitive impairment in the long-term. However, based on the clinical notes, patients usually reported unclear onset of symptoms ('for several years'), long-standing daytime sleepiness ('always been sleepy'), and/or no bed partner to confirm snoring or witness apneas. We also had a small number of patients, which precluded a more detailed analysis of the effects of OSA on cognition in relation to epilepsy types (*e.g.* temporal versus extra-temporal) or seizure characteristics, in particular, seizure frequency. Since only six patients had drug-resistant epilepsy (with large heterogeneity in seizure frequency), we lacked statistical power to perform correlations between seizure frequency and cognitive functioning/OSA-related variables. Yet, it was shown previously in a cohort of older adults with epilepsy that OSA was associated with a higher seizure frequency (Chihorek *et al.*, 2007). In this study, it was not just the hypoxemia, but also probably the arousals from apnea/hypopnea that lead to the worsening of seizure frequency (Chihorek *et al.*, 2007). Moreover, nocturnal seizures were reported in some patients (7/20). It is likely that nocturnal seizures contribute to worsen sleep quality (sleep fragmentation, lighter sleep), and vice-versa. Yet it is still undetermined whether cognitive dysfunction in epilepsy patients is driven by the impact of nocturnal seizures on sleep quality. It is not possible with our current sample to examine this question, but future work using a mediation model with a large sample of patients could help better understand these mechanisms.

Finally, we acknowledge that the use of a delay interval of up to 18 months between the PSG and neuropsychological testing constitutes a limitation. Ideally, in a prospective study, the PSG would have been performed at the same time as the neuropsychological testing (and review of epilepsy-related data). For patients with the longest intervals, it is possible that the clinical profile (OSA severity, cognition, and seizure frequency) changed, thereby modifying the relationships we observed. Yet, only a minority of patients (n=3) had more than 12 months delay between the PSG and neuropsychological examination.

As far as we know, this is the first study that has examined the relationship between OSA severity and cognitive dysfunctions in patients with epilepsy using objective measures. These results remain to be tested for replication in larger cohorts of epilepsy patients. Although no comparison group was included, this is a first step towards a better understanding of the potential consequences of OSA in epilepsy. In fact, we were quite surprised that from our chart review, only a small number of patients who were referred for a neuropsychological assessment also underwent PSG. Yet sleep disorders are very common in epilepsy, with OSA affecting up to one third of patients (Lin *et al.*, 2017). This highlights the need for clinicians to screen, on a regular basis, their patients at high risk of OSA so that they can be referred and treated accordingly.

Conclusions

OSA is frequent in adults with epilepsy and is one of the most common reported factors associated with

reduced quality of life. Our study shows that OSA is also associated with worse cognitive functioning in epilepsy, affecting primarily attention, executive functions, and verbal memory processes. These results are consistent with the OSA literature and suggest that patients with epilepsy are also vulnerable to the effects of OSA. Future prospective studies will help in determining whether treatment of OSA may help improve cognitive functioning in patients with epilepsy. □

Supplementary data.
Supplementary figure is available on the www.epilepticdisorders.com website.

Disclosures.
Dr. Latreille is supported by a scholarship from the Canadian Institutes of Health Research. Dr. Sarkis has received compensation for activities with DigiTrace/SleepMed. Dr. Pavlova has received research funding from Lundbeck Inc. and from Biomobie Inc., neither of which is relevant to this study. Dr. Willment has no conflict of interest to declare.

References

Berry RB, Budhiraja R, Gottlieb DJ, *et al*. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. *J Clin Sleep Med* 2012; 8: 597-619.

Bucks RS, Olaithe M, Rosenzweig I, Morrell MJ. Reviewing the relationship between OSA and cognition: where do we go from here? *Respirology* 2017; 22: 1253-61.

Canessa N, Castronovo V, Cappa SF, *et al*. Obstructive sleep apnea: brain structural changes and neurocognitive function before and after treatment. *Am J Respir Crit Care Med* 2011; 183: 1419-26.

Castronovo V, Scifo P, Castellano A, *et al*. White matter integrity in obstructive sleep apnea before and after treatment. *Sleep* 2014; 37: 1465-75.

Chihorek AM, Abou-Khalil B, Malow BA. Obstructive sleep apnea is associated with seizure occurrence in older adults with epilepsy. *Neurology* 2007; 69: 1823-7.

Devinsky O, Ehrenberg B, Barthlen GM, Abramson HS, Luciano D. Epilepsy and sleep apnea syndrome. *Neurology* 1994; 44: 2060-4.

Eddy CM, Rickards HE, Cavanna AE. The cognitive impact of antiepileptic drugs. *Ther Adv Neurol Disord* 2011; 4: 385-407.

Elger CE, Helmstaedter C, Kurthen M. Chronic epilepsy and cognition. *Lancet Neurol* 2004; 3: 663-72.

Galic T, Bozic J, Ivkovic N, Gunjaca G, Ticinovic TK, Dogas Z. Effects of mandibular advancement device treatment on arterial stiffness and glucose metabolism in patients with mild to moderate obstructive sleep apnea: a prospective 1-year study. *Sleep Breath* 2016; 20: 69-77.

Gammino M, Zummo L, Bue AL, *et al*. Excessive daytime sleepiness and sleep disorders in a population of patients with epilepsy: a case-control study. *J Epilepsy Res* 2016; 6: 79-86.

Hermann B, Seidenberg M, Lee EJ, Chan F, Rutecki P. Cognitive phenotypes in temporal lobe epilepsy. *J Int Neuropsychol Soc* 2007; 13: 12-20.

Iber C, Ancoli-Israel S, Chesson A, Quan S. The AASM Manual for the Scoring of Sleep and Associates Events: Rules. *Terminology and technical specifications. Sleep (Rochester)* 2007: 59.

Ju G, Yoon IY, Lee SD, Kim YK, Yoon E, Kim JW. Modest changes in cerebral glucose metabolism in patients with sleep apnea syndrome after continuous positive airway pressure treatment. *Respiration* 2012; 84: 212-8.

Lin Z, Si Q, Xiaoyi Z. Obstructive sleep apnoea in patients with epilepsy: a meta-analysis. *Sleep Breath* 2017; 21: 263-70.

Loughman A, Bowden SC, D'Souza W. Cognitive functioning in idiopathic generalised epilepsies: a systematic review and meta-analysis. *Neurosci Biobehav Rev* 2014; 43: 20-34.

Maeder MT, Schoch OD, Rickli H. A clinical approach to obstructive sleep apnea as a risk factor for cardiovascular disease. *Vasc Health Risk Manag* 2016; 12: 85-103.

Malow BA, Levy K, Maturen K, Bowes R. Obstructive sleep apnea is common in medically refractory epilepsy patients. *Neurology* 2000; 55: 1002-7.

Manni R, Terzaghi M, Arbasino C, Sartori I, Galimberti CA, Tartara A. Obstructive sleep apnea in a clinical series of adult epilepsy patients: frequency and features of the comorbidity. *Epilepsia* 2003; 44: 836-40.

Olaithe M, Bucks RS. Executive dysfunction in OSA before and after treatment: a meta-analysis. *Sleep* 2013; 36: 1297-305.

Pan YY, Deng Y, Xu X, Liu YP, Liu HG. Effects of continuous positive airway pressure on cognitive deficits in middle-aged patients with obstructive sleep apnea syndrome: a meta-analysis of randomized controlled trials. *Chin Med J* 2015; 128: 2365-73.

Piperidou C, Karlovasitou A, Triantafyllou N, *et al*. Influence of sleep disturbance on quality of life of patients with epilepsy. *Seizure* 2008; 17: 588-94.

Quan SF, Chan CS, Dement WC, *et al*. The association between obstructive sleep apnea and neurocognitive performance-the Apnea Positive Pressure Long-term Efficacy Study (APPLES). *Sleep* 2011; 34: 303-14.

Rosenzweig I, Glasser M, Polsek D, Leschziner GD, Williams SC, Morrell MJ. Sleep apnoea and the brain: a complex relationship. *Lancet Respir Med* 2015; 3: 404-14.

Shahar E, Whitney CW, Redline S, *et al*. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med* 2001; 163: 19-25.

Shi Y, Chen L, Chen T, *et al*. A meta-analysis of voxel-based brain morphometry studies in obstructive sleep apnea. *Sci Rep* 2017; 7: 10095.

Stranks EK, Crowe SF. The cognitive effects of obstructive sleep apnea: an updated meta-analysis. *Arch Clin Neuropsychol* 2016; 31: 186-93.

Witt JA, Helmstaedter C. How can we overcome neuropsychological adverse effects of antiepileptic drugs? *Expert Opin Pharmacother* 2017; 18: 551-4.

Yaffe K, Laffan AM, Harrison SL, *et al*. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA* 2011; 306: 613-9.

Yaouhi K, Bertran F, Clochon P, *et al*. A combined neuropsychological and brain imaging study of obstructive sleep apnea. *J Sleep Res* 2009; 18: 36-48.

TEST YOURSELF

(1) When left untreated, obstructive sleep apnea can have major impact on cognition. Which cognitive domains are particularly affected by obstructive sleep apnea in the general population?

(2) According to this study, which cognitive domains seem particularly affected by more severe obstructive sleep apnea in epilepsy?

(3) When designing a prospective study to examine the effects of obstructive sleep apnea on cognitive functioning in patients with epilepsy and whether treatment of obstructive sleep apnea may help improve cognition, what would be the most sensitive OSA-related measure?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".