ERJ Express. **Published on March 15, 2011 as doi: 10.1183/09031936.00040410**

Residual sleepiness in obstructive sleep apnoea: phenotype and related symptoms

Cyrille Vernet,[1] Stefania Redolfi,[1, 2] Valérie Attali,[1, 2] Eric Konofal,[1] Agnès Brion,[1] Elisabeth Frija-Orvoen,[1] Michel Pottier,[1] Thomas Similowski,[2] and Isabelle Arnulf[1, 2]

[1]Sleep Disorders Unit, UMR 975, National Reference Centre for Narcolepsy and Hypersomnia, [2]Department of Respiratory and Intensive Care Medicine and EA 2397 Paris 6 University, Pitié-Salpêtrière Hospital, APHP, France.

Submitted to: The European Respiratory Journal

Version: 3

Corresponding author: Isabelle Arnulf

Unité des Pathologies du Sommeil

Hôpital Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital,

75651 Paris Cedex 13, France

isabelle.arnulf@psl.aphp.fr

Phone: +33 1 42 16 77 02

Fax: +33 1 42 16 77 00

Acknowledgments: The project was financed by grants from ANTADIR AO2006 and CARDIF AO2007 and AO2008.

The authors have no conflict of interest regarding the topic of the manuscript

Abstract

The characteristics of residual excessive sleepiness (RES), defined by an Epworth score >10 in adequately treated apnoeic patients, are unknown.

Forty apnoeic patients, with (n=20) and without (n=20) RES, and 20 healthy controls underwent clinical interviews, cognitive and biological tests, polysomnography, a multiple sleep latency test, and 24-hour sleep monitoring.

The marked subjective sleepiness in the RES group (score 16.4±3) contrasted with moderately abnormal objective measures of sleepiness (90% of patients with RES had daytime sleep latencies >8 min). Compared to patients without RES, the patients with RES had more fatigue, lower stage N3 percentages, more periodic leg movements (without arousals), lower mean sleep latencies and longer daytime sleep periods. Most neuropsychological dimensions (morning headaches, memory complaints, spatial memory, inattention, apathy, depression, anxiety, and lack of self-confidence) were not different between patients with and without RES, but gradually altered from controls to apnoeic patients without and then with RES.

RES in apnoeic patients differs markedly from sleepiness in central hypersomnia. The association between RES, periodic leg movements, apathy and depressive mood parallels the post-hypoxic lesions in noradrenalin, dopamine and serotonin systems in animals exposed to intermittent hypoxia.

Keywords: apnoea, CPAP, hypersomnia, OSA, RES, sleepiness

Introduction

Excessive daytime sleepiness and cognitive problems are the most frequent symptoms experienced by patients with obstructive sleep apnoea (OSA). Continuous airway pressure (CPAP) reduces daytime sleepiness [1, 2], and improves but does not normalise the objective measures of sleepiness [2-4]. A minimum 6% of regular CPAP-users experience residual excessive sleepiness (RES) after having improved sleep hygiene and adjusted CPAP pressure, as well as ruled out concomitant sleep pathologies (narcolepsy, restless legs syndrome or idiopathic hypersomnia) [5]. The mechanisms of RES are unknown. Because intermittent hypoxia in animal models damages the arousal brain systems [6], and because OSA patients have been exposed to intermittent hypoxia for years before being treated, we question whether some vulnerable subjects had developed irreversible brain lesions that cause central hypersomnia. There are clinical and neurophysiological markers specific to central hypersomnias (namely narcolepsy and idiopathic hypersomnia). They include a disabling, severe sleepiness despite normal or prolonged (greater than 10 hr) night-time sleep, sleep drunkenness (a prolonged and severe confusion upon awakening) without depression or apathy, executive dysfunction and short (<8 min) mean daytime sleep latencies (plus sleep onset in REM periods [SOREMPs] in narcolepsy), which can be better studied using multiple sleep latency tests (MSLT) and long-term sleep monitoring [7, 8]. We hypothesised that RES would resemble central hypersomnia. To test this hypothesis, we extensively studied the clinical, psychiatric and cognitive characteristics and performed polysomnography, MSLT and long term sleep monitoring in a population of adequately treated OSA patients with RES compared to OSA patients without RES and healthy controls.

METHODS

Subjects

During one year, we prospectively selected 25 patients from a series of around 500 patients treated with OSA who were regularly followed in a University hospital. They were mostly referred by regional pulmonologists for this problem, after they worked the CPAP aspects. They met the following criteria for inclusion: (i) clinical diagnostic of OSA syndrome (including excessive sleepiness) and apnoea/hypopnoea index (AHI) >15; (ii) CPAP use >90% of nights, >6 $h.night^{-1}$, for >6 months, with a residual AHI <5 on polysomnography; (iii) complaints of daily RES (score on the Epworth sleepiness scale >10/24) for >6 months [9]; (iv) usual sleep duration normal for age [10] and no extension of sleep during holidays and week-ends, with behaviourally induced insufficient sleep syndrome ruled out and a careful check of the CPAP time log; and (v) periodic leg movement-associated arousal index $<10.h^{-1}$. We excluded the patients who had defined causes of RES including the following: (i) narcolepsy with cataplexy [7]; (ii) untreated, severe restless legs syndrome (severity score >20/40) [11, 12]; (iii) chronic use of sedative drugs or alcohol; (iv) neurological diseases, as determined by a neurological examination and brain magnetic resonance imaging; (v) psychiatric diseases as determined by a psychiatric interview; (vi) other medical diseases; and (vii) night shift work. Two patients did not speak fluently French enough to undergo the tests and scales, and three patients refused to take part in the study. Eventually, 20 patients with RES completed the study. Twenty compliant, non-retired, CPAP-treated OSA patients without RES, matched for age and sex, were recruited from the same department. In addition, 20 healthy, non-

retired controls were recruited by advertisement from the general population, matched for sex, with a mean age slightly lower (-5 years) than the RES patients, but in an age range that does not affect sleep, sleepiness, cognition and psychological tests [10, 13], They were selected with Epworth score ≤10, without sleep complaints, chronic sleep deprivation, and chronic use of sedative drugs or alcohol. OSA and healthy controls were paid. The participants signed an informed consent. The study was approved by the Institutional Review Board.

Investigations

Participants were instructed to follow a regular sleep-wake rhythm one week before the tests, as checked by sleep and CPAP diaries. They underwent a face-to-face interview and a clinical examination. They completed a standardised questionnaire including the following scales: Epworth sleepiness scale [9]; morningness-eveningness Horne-Ostberg scale [14]; Fatigue Severity Score [15, 16]; Beck Depression Inventory (BDI-II) [17]; Hospital Anxiety and Depression (HAD) Rating Scale [18]; Conners' Adult Attention Deficit-Hyperactivity Disorder Rating Scale (CAARS) [19]; and Apathy Scale [20]. The serum ferritin levels (as low levels promote restless legs and periodic leg movements [21]) and class-II human leukocyte antigen genotype (HLA, as DQB1*0602 genotype is associated to sleepiness and narcolepsy) were determined.

The 48-hr long sleep monitoring procedure included a first night followed the next day by five standard MSLT naps (08:00, 10:00, 12:00, 14:00, 16:00) that were terminated after 20 minutes if no sleep occurred and after 15 min asleep if sleep occurred [22]. The next evening included a long-term (24-hour) sleep monitoring, in hospital, with a second, uninterrupted night followed by an attempt to sleep as long

as possible during the next morning and afternoon, lying in the dark [8]. The CPAP was applied during all sleep tests, including the MSLT. Sleep stages, arousals, periodic leg movements, and respiratory events (measured with pneumotachography in patients, and nasal pressure plus tracheal microphone in controls) were scored visually according to standard criteria [23-26].

Cognitive tests, performed at 10:40 the MSLT day, included testing of the executive functions (inhibition and selective attention with the Stroop Color Word Interference Test [27]), and visuo-spatial functions, including visuo-constructional abilities and long-term spatial memory (copy and delayed recall of the Rey–Osterreith Complex Figure [28]). The verbal memory was evaluated with the Free and Cued Selective Reminding Test, a memory task that controls attention and strategy used to maximise learning and provides a measurement of short-term memory that is not confounded by deficits in other cognitive abilities [29].

Statistical analysis

The normal distribution of the measures was first checked. Continuous measures were compared in the three groups with an analysis of variance, with two-groups post-hoc comparisons when the probability of type I error was <5%. We did not perform any adjustment for multiple comparisons. Between-group dichotomous variables were compared using the chi-square test (Statistica 8.0, Stat Soft Inc, Tulsa, OK).

RESULTS

Characteristics of sleep apnoea syndrome

OSA patients had higher body mass indices than controls, but body mass indices were not different between OSA patients with and without RES (Table 1). At time of OSA diagnosis, patients with and without RES had similar sleep patterns and degree of sleepiness as well as OSA characteristics. Although patients found it difficult to assess the exact onset of sleepiness, none of them suffered from excessive daytime sleepiness for more than 10 years before OSA diagnosis. The CPAP was used at the same frequency, with the same pressure and residual apnoea/hypopnoea index, in both groups. The cardiovascular risk factors were similar in the OSA patients with and without RES, and higher than in controls. Upon clinical examination, there were no neurological signs, including parkinsonism (even mild), cerebellar syndrome and upper motor neuron syndrome. The number of patients with treated restless legs syndrome (with a low evening dose of ropinirole, pramipexole, or piribedil) was similar between OSA groups. The patients with RES had brain magnetic resonance imaging within the normal ranges, including a few, asymptomatic lacunae in 2/20 patients. The biological measures (HLA DQB1*0602 genotype and ferritin) were similar in the three groups.

Sleep symptoms

Though the nocturnal symptoms were similar in the three groups, half of patients with RES did not feel refreshed after the night, were tired upon awakening, and had morning headaches (Table 2). They had no cataplexy, hypnagogic hallucinations or sleep drunkenness (a symptom specific for idiopathic hypersomnia, characterised by prolonged difficulty waking with automatic behaviour, confusion, and repeated returns to sleep).

Sleep measures

The three groups had similar nighttime sleep durations, sleep efficiency and latencies to sleep onset and REM sleep (Table 3). Only one patient in the RES group, and none in other groups, had a nighttime sleep duration >600 min (and a total sleep time per 24 hr of 683 min), a definition of hypersomnia with long sleep time. Patients with RES had lower percentages of N3 sleep than patients without RES and controls. Daytime naps were twice as long in patients with RES than in the other groups, but the total sleep time during 24 hr was not different among groups. Patients with RES had higher periodic leg movement indexes than those without RES, with 40 % RES patients having an index >15, but the related arousal indices were low and non-different among groups. The apnoea/hypopnoea indexes were low, similar between patients groups, and lower than in controls (p=0.004).

The MSLT latencies were lower in patients with than without RES and controls (Table 4, Figure 1). There were as many subjects with an MSLT latency <8 min in each group, but more RES patients with an MSLT latency <10 min. Patients with RES had more frequent sleep onset in REM periods (0 SOREMP, n=12; 1 SOREMP, n=4; 2 SOREMPs, n=3; 3 SOREMPs, n=1) than those without RES and than the controls. No patients, however, met the criteria for narcolepsy without cataplexy (combining an MSLT latency <8 min and ≥2 SOREMPs). Two (10%) patients with RES met the criteria used for idiopathic hypersomnia without long sleep time (total sleep time between 360 and 600 min, and MSLT latency <8 min).

Psychological assessment

Almost all patients with RES complained of daytime tiredness, with higher fatigue scores (including severe fatigue in 90% of them) than OSA patients without

RES and controls (Figure 2).Though they had no clinical depression, the OSA patients had higher depression scores than controls, with no difference between patients with and without RES (Table 5). The level of anxiety and the symptoms of attention deficit and hyperactivity were similar in patients with and without RES, but patient with RES scored higher than controls for inattention and self-concept score (indicating a lack of self confidence). The apathy scores were similar among the three groups, but more OSA patients (with and without RES) had abnormal scores than controls.

Cognitive assessment

OSA patients reported more memory complaints than the controls, with a trend for a higher percentage in patients with RES (p=0.07). Surprisingly, the patients with RES had fewer errors when completing the Stroop test than those without RES (Table 6). Though all groups had similar visuo-spatial abilities, patients (with and without RES) had lower recall scores than controls when copying the figure. All groups had similar performances at the verbal memory test and a similar benefit from the cues.

There was no significant correlation between the Epworth sleepiness score in the patients with RES and any sleep, sleepiness, neuropsychological and cognitive measures (Supplemental Table).

Response to stimulant treatment

Twenty patients with RES used modafinil (400 mg/d) for at least three months. Fourteen patients stopped (side-effects, n=1; no benefit, n=13), hence 6 of 20 (30%) were modafinil-responders. Seven patients tried methylphenidate as a second

choice, with a benefit in two patients (29%). One patient tried mazindol, without benefit. Two patients tried sodium oxybate, without benefit.

DISCUSSION

Patients with RES tended to be more sleepy before CPAP, and had lower stage N3 percentages, more periodic leg movements (without arousals), lower mean sleep latencies and longer daytime sleep durations after CPAP than patients without RES. Only 15% of OSA patients with RES met the international criteria for central hypersomnia. Most neuropsychological dimensions (fatigue, morning headaches, memory complaints, spatial memory, inattention, apathy, depression, anxiety, and lack of self-confidence) were gradually modified from controls to OSA patients without and then with RES.

Clinical profile of sleepiness

With high sleepiness scores in patients with RES, we expected to find symptoms, objective measures of sleepiness and executive functions as abnormal as in narcolepsy and idiopathic hypersomnia. But patients had no sleep drunkenness (despite feeling un-refreshed after having slept), no hallucinations, rare sleep paralysis, mostly subnormal MSLT, rare SOREMPs, no sleep excess on long-term monitoring, and only a weak benefit from the stimulant modafinil. They could not be considered as ‘naturally hypersomnolent’ subjects [30], because the excessive sleepiness was acquired late in life. Compared to other groups, however, the shorter mean sleep onset latency during MSLT (<10 minutes in 40% of them) and the longer

daytime sleep in patients with RES suggest that they feel something not identified by the usual cut-off used to define hypersomnia. Also, their complaint of severe sleepiness may cover a neuropsychological syndrome extending beyond the vigilance problem.

A specific neuropsychological syndrome?

Indeed, most psychological dimensions were gradually modified from controls to OSA patients without and then with RES. Notably, these scales are not used for diagnosis, but to evaluate how patients deviate from norms. The lack of motivation was specific to OSA, not to RES, suggesting that the mesolimbic dopaminergic system [31], which motivated behaviours, is altered. Similarly, no patient with RES had clinical depression, but 70% had mildly abnormal scores. This result could indicate the following: (i) patients with depressed moods score higher on any subjective scale, including the sleepiness and fatigue scales [32]; (ii) RES is disabling enough to impact mood; or (iii) RES and altered mood are two parallel consequences of post-hypoxic damages in mood and alertness brain structures.

Although almost all patients with RES complained of impaired memory, their performances at verbal and spatial memory tests were similar to those of patients without RES (but lower than controls). Similarly, while they complained of attention deficit, they had normal scores (and even lower interference errors) at the Stroop test, which demands sustained attention. The discrepancies between the complaints of impaired vigilance, memory and attention and the subnormal tests suggest that the symptoms are too mild to be identified by tests. Alternatively, the sample may be too small to show significant differences or there are no deficits, but patients pertain to an extreme group of complainers.

Mechanisms of RES

The mechanisms of RES in OSA are numerous [33, 34], including insufficient CPAP adherence and titration, insufficient sleep syndrome and coexisting sleep, psychiatric and medical disorders. All these causes were ruled out before inclusion in our series. Patients with RES had more periodic leg movements than OSA patients and controls, but these movements were not related to restless legs syndrome (it was absent or treated) or to iron deficiency. Because the movements were not associated with repeated arousals, they cannot cause RES, as already discussed by other groups [35-37]. The cause of periodic leg movements is yet unknown; however, because they disappear with low doses of dopaminergic agents [38], they may result from a dysfunction in the dopaminergic system [39].

A post-hypoxic hypersomnia ?

We are confident that the classical causes of RES have been ruled out in our patients. Furthermore, our patients had no morphological abnormalities in the brain imaging as previously shown in OSA patients [40-42]. Hence, we suspect that they suffer from a form of post-hypoxic hypersomnia. In animal models of intermittent hypoxia, sleep time is prolonged (and murine-adapted MSLT are shorter) even weeks after the intermittent hypoxia exposure is stopped [6], paralleling the longer daytime sleep (on average one hour), and 3.6-min shorter MLST of our RES patients. The intermittent hypoxia causes oxidative injury in specific neuronal systems, including the catecholaminergic wake-active neurons [43], the serotonergic dorsal raphe nucleus, the cortex, the cholinergic lateral basal forebrain, and the CA1 region of the hippocampus [44], but does not affect the other arousal systems (hypocretin

and histamine neurons in the lateral hypothalamus). This lack of effect on hypocretin system could explain why no RES patients meet the polysomnographic criteria for narcolepsy. In addition, patients with RES have higher periodic leg movements and apathy scores (possibly indicating a dopamine dysfunction, although they had no parkinsonism), and lower mood (possibly resulting from a serotonin dysfunction). Brain functional imaging of the monoaminergic systems would be necessary to support the concept of selective damage in RES patients.

The patients with RES did not differ from the other patients at the time of OSA diagnosis, indicating that both patient groups were exposed to the same degree of intermittent hypoxia. Hence, the patients with RES could be more vulnerable to the brain consequences of intermittent hypoxia than those without RES. Indeed, a wide spectrum of RES severities is observed in clinical OSA populations [5, 45], but patients with RES were consistently sleepier than others before CPAP. We imagine that the basis of this vulnerability is genetic. Here, HLA DQB1*0602 genotype was not more frequent in the RES phenotype. A large-scale genome-wide study of OSA patients with and without RES would however be more pertinent to identify a potentially genetic vulnerability.

In conclusion, RES in apnoeic patients differs markedly from sleepiness in central hypersomnia and the association between RES, periodic leg movements, apathy and depressive mood parallels the post-hypoxic lesions in noradrenalin, dopamine and serotonin systems in animals exposed to intermittent hypoxia.

REFERENCES

1. Sanchez AI, Martinez P, Miro E, Bardwell WA, Buela-Casal G. CPAP and behavioral therapies in patients with obstructive sleep apnea: effects on daytime sleepiness, mood, and cognitive function. *Sleep Med Rev* 2009: 13(3): 223-233.

2. Giles TL, Lasserson TJ, Smith BJ, White J, Wright J, Cates CJ. Continuous positive airways pressure for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev* 2006(1): CD001106.

3. Morisson F, Decary A, Petit D, Lavigne G, Malo J, Montplaisir J. Daytime sleepiness and EEG spectral analysis in apneic patients before and after treatment with continuous positive airway pressure. *Chest* 2001: 119(1): 45-52.

4. Bedard MA, Montplaisir J, Malo J, Richer F, Rouleau I. Persistent neuropsychological deficits and vigilance impairment in sleep apnea syndrome after treatment with continuous positive airways pressure (CPAP). *J Clin Exp Neuropsychol* 1993: 15(2): 330-341.

5. Pepin JL, Viot-Blanc V, Escourrou P, Racineux JL, Sapene M, Levy P, Dervaux B, Lenne X, Mallart A. Prevalence of residual excessive sleepiness in CPAP-treated sleep apnoea patients: the French multicentre study. *Eur Respir J* 2009: 33(5): 1062-1067.

6. Veasey SC, Davis CW, Fenik P, Zhan G, Hsu YJ, Pratico D, Gow A. Long-term intermittent hypoxia in mice: protracted hypersomnolence with oxidative injury to sleep-wake brain regions. *Sleep* 2004: 27(2): 194-201.

7. American Academy of Sleep Medicine. International classification of sleep disorders, 2nd ed.: Diagnostic and coding manual. American Academy of Sleep Medicine, Westchester, Illinois, 2005.

8. Vernet C, Arnulf I. Idiopathic hypersomnia with and without long sleep time: a controlled series of 75 patients. *Sleep* 2009: 32(6): 753-759.

9. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991: 14(6): 540-545.

10. Ohayon MM, Vecchierini MF. Normative sleep data, cognitive function and daily living activities in older adults in the community. *Sleep* 2005: 28(8): 981-989.

11. Allen RP, Kushida CA, Atkinson MJ. Factor analysis of the International Restless Legs Syndrome Study Group's scale for restless legs severity. *Sleep Med* 2003: 4(2): 133-135.

12. Walters AS. Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group. *Mov Disord* 1995: 10(5): 634-642.

13. Mignot E, Lin L, Finn L, Lopes C, Pluff K, Sundstrom ML, Young T. Correlates of sleep-onset REM periods during the Multiple Sleep Latency Test in community adults. *Brain* 2006: 129(Pt 6): 1609-1623.

14. Horne J, Ostberg O. A self-assesment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int J Chronobiol* 1976: 4: 97-110.

15. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989: 46(10): 1121-1123.

16. Valko PO, Bassetti CL, Bloch KE, Held U, Baumann CR. Validation of the fatigue severity scale in a Swiss cohort. *Sleep* 2008: 31(11): 1601-1607.

17. Beck AT, Steer RA, Brown GK. Manual for the beck depression inventory, 2nd ed. . *San Francisco, TX: The Psychological Corporation* 1996.

18. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983: 67(6): 361-370.

19. Conners CK, Erhart D, Sparrow E. Conners' Adult ADHD Rating Scales, Technical Manual. *New York, NY: Multi-Health Systems* 1999.

20. Starkstein SE, Mayberg HS, Preziosi TJ. Reliabibily, validity and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci* 1992: 4: 134-139.

21. O'Brien LM, Koo J, Fan L, Owusu JT, Chotinaiwattarakul W, Felt BT, Chervin RD. Iron stores, periodic leg movements, and sleepiness in obstructive sleep apnea. *J Clin Sleep Med* 2009: 5(6): 525-531.

22. Carskadon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. *Sleep* 1986: 9(4): 519-524.

23. Rechstchaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. UCLA Brain Information Service/Brain Research Institute., Los Angeles, 1968.

24. American Academy of Sleep Medicine Task Force. Sleep-disordered breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep* 1999: 22(5): 667-688.

25. American Sleep Disorders Association. EEG arousals: Scoring rules and examples. *Sleep* 1992: 15: 174-184.

26. American Sleep Disorders Association Atlas Task Force. Recording and scoring leg movements. *Sleep* 1993: 16: 749-759.

27. Stroop JR. Studies of interference in serial verbal reactions. *Journal of Experimental Psychology* 1935: 18: 643-662.

28. Osterrieth P. [A test of copying a complex figure: a contribution to the study of perception and memory.]. *Archives de Psychologie (Geneva)* 1944: 30: 205-220.

29. Grober E, Lipton RB, Hall C, Crystal H. Memory impairment on free and cued selective reminding predicts dementia. *Neurology* 2000: 54(4): 827-832.

30. Stradling JR, Smith D, Crosby J. Post-CPAP sleepiness--a specific syndrome? *J Sleep Res* 2007: 16(4): 436-438.

31. McAllister TW. Apathy. *Semin Clin Neuropsychiatry* 2000: 5(4): 275-282.

32. Bardwell WA, Moore P, Ancoli-Israel S, Dimsdale JE. Fatigue in obstructive sleep apnea: driven by depressive symptoms instead of apnea severity? *Am J Psychiatry* 2003: 160(2): 350-355.

33. Santamaria J, Iranzo A, Ma Montserrat J, de Pablo J. Persistent sleepiness in CPAP treated obstructive sleep apnea patients: evaluation and treatment. *Sleep Med Rev* 2007: 11(3): 195-207.

34. Black J. Sleepiness and residual sleepiness in adults with obstructive sleep apnea. *Respir Physiol Neurobiol* 2003: 136(2-3): 211-220.

35. Chervin RD. Periodic leg movements and sleepiness in patients evaluated for sleep-disordered breathing. *Am J Respir Crit Care Med* 2001: 164(8 Pt 1): 1454-1458.

36. Haba-Rubio J, Staner L, Krieger J, Macher JP. Periodic limb movements and sleepiness in obstructive sleep apnea patients. *Sleep Med* 2005: 6(3): 225-229.

37. Scofield H, Roth T, Drake C. Periodic limb movements during sleep: population prevalence, clinical correlates, and racial differences. *Sleep* 2008: 31(9): 1221-1227.

38. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisir J. Restless legs syndrome: diagnostic criteria, special considerations, and

epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med* 2003: 4(2): 101-119.

39. Connor JR, Wang XS, Allen RP, Beard JL, Wiesinger JA, Felt BT, Earley CJ. Altered dopaminergic profile in the putamen and substantia nigra in restless leg syndrome. *Brain* 2009: 132(Pt 9): 2403-2412.

40. Davies CW, Crosby JH, Mullins RL, Traill ZC, Anslow P, Davies RJ, Stradling JR. Case control study of cerebrovascular damage defined by magnetic resonance imaging in patients with OSA and normal matched control subjects. *Sleep* 2001: 24(6): 715-720.

41. O'Donoghue FJ, Briellmann RS, Rochford PD, Abbott DF, Pell GS, Chan CH, Tarquinio N, Jackson GD, Pierce RJ. Cerebral structural changes in severe obstructive sleep apnea. *Am J Respir Crit Care Med* 2005: 171(10): 1185-1190.

42. Robbins J, Redline S, Ervin A, Walsleben JA, Ding J, Nieto FJ. Associations of sleep-disordered breathing and cerebral changes on MRI. *J Clin Sleep Med* 2005: 1(2): 159-165.

43. Zhu Y, Fenik P, Zhan G, Mazza E, Kelz M, Aston-Jones G, Veasey SC. Selective loss of catecholaminergic wake active neurons in a murine sleep apnea model. *J Neurosci* 2007: 27(37): 10060-10071.

44. Zhan G, Serrano F, Fenik P, Hsu R, Kong L, Pratico D, Klann E, Veasey SC. NADPH oxidase mediates hypersomnolence and brain oxidative injury in a murine model of sleep apnea. *Am J Respir Crit Care Med* 2005: 172(7): 921-929.

45. Koutsourelakis I, Perraki E, Economou NT, Dimitrokalli P, Vagiakis E, Roussos C, Zakynthinos S. Predictors of residual sleepiness in adequately treated obstructive sleep apnoea patients. *Eur Respir J* 2009: 34(3): 687-693.

Legend of the figures

Figure 1. Individual mean sleep onset latencies (0-20 min) during the multiple sleep latency test in OSA patients with and without residual excessive sleepiness, and in healthy controls.

Figure 2. Subjective assessment of various neuropsychological dimensions in healthy controls (light gray bars) and in OSA patients without (medium gray bars) and with (black bars) residual excessive sleepiness: sleepiness using the Epworth sleepiness scale, fatigue using the Fatigue Impact Scale, depression and anxiety using the Hospital Anxiety and Depression Rating Scale, inattention and hyperactivity using the Conners Adult Scale, and apathy using the Starkstein Scale. The scores are expressed as percentage of the maximum disability score in each scale. *$p<0.05$ between OSA patients with and without RES, $^{\dagger}p<0.05$ for OSA patients with RES vs. healthy controls, ‡ $p<0.05$ for OSA patients without RES vs. healthy controls.

Table 1. Clinical, biological and basal characteristics and efficacy of CPAP in OSA patients with residual excessive sleepiness (RES) compared to patients without RES and healthy controls.

Patients	OSA with RES	OSA without RES	Healthy controls	P
Number	20	20	20	
Age, y	61.1 ± 9.9	61.8 ± 9.0 ‡	55.6 ± 10.0	0.09
Women, %	25.0	35.0	20.0	0.48
BMI, kg/m2	31.3 ± 5.4 †	35.4 ± 9.2 ‡	25.2 ± 3.5	<0.001
Measures before using the CPAP				
Epworth sleepiness score (0-24)	15.9 ± 5.5	13.2 ± 3.4[a]	NA	NA
Apnoea/hypopnoea index, n/h	40.7 ± 17.3	48.9 ± 19.0	NA	NA
3% oxygen desaturation index, n/h	44.9 ± 34.2	53.4 ± 14.0	NA	NA
Time with a SaO_2 below 90%, min	50.9 ± 66.7	53.8 ± 46.4	NA	NA
Lowest sleeping SaO_2	80.9 ± 8.4	76.8 ± 10.5	NA	NA
Usual sleep duration, h	6:53 ± 0:55	7:00 ± 1:51	NA	NA
Measures with the CPAP				
Epworth Sleepiness score (0-24)	16.4 ± 3.0 *,†	6.2 ± 2.9	5.7 ± 2.7	<0.001
Delta sleepiness score	+ 0.7 ± 2.2 *	- 7.0 ± 3.4	NA	NA
Time using CPAP, months	65 ± 41	76 ± 41	NA	NA
Use days, %	94.5 ± 6.4	93.8 ± 10.9	NA	NA

CPAP use, h/night	6:56 ± 0:56	6:44 ± 1:33	NA	NA
Mean pressure level, cmH2O	10.3 ± 1.8	9.9 ± 2.2	NA	NA
Residual apnoea/hypopnoea index, n/h	4.3 ± 2.3	3.5 ± 2.3	NA	NA
Co-morbidities and cardiovascular risk factors				
Diabetes mellitus, %	0.0 *	25.0 ‡	0.0	0.006
Blood hypertension %	60.0 †	50.0	30.0	0.13
Coronary heart disease and stroke, %	25.0 †	15.0	0.0	0.08
At least one cardiovascular risk factor, %	60.0 †	65.0 ‡	30.0	0.05
Biological results				
HLA DQB1*0602 genotype, %	15.0	25.0	25.0	0.75
Serum ferritin level, pg/L	152 ± 93	160 ± 68	250 ± 218	0.13

* P<0.05 for OSA patients with vs. without RES, † P<0.05 for OSA patients with RES vs. healthy controls, ‡ P<0.05 for OSA patients without RES vs. healthy controls. Measures with CPAP initiation are based on the time using a mask provided by the CPAP machine counter during the three last months before formal evaluation. Mean ± SD. [a]n=18

Table 2. Sleep and daytime symptoms in 20 OSA patients with RES compared to 20 patients without RES and 20 healthy controls.

Patients	OSA with RES	OSA without RES	Healthy controls	P (Anova)
Usual sleep duration, h	7:02 ± 1:53	7:06 ± 1:09	7:14 ± 1:14	0.92
Multiple awakenings, %	25.0	45.0	40.0	0.61
Early awakening, %	45.0	30.0	30.0	0.76
Nocturnal micturitions, %	35.0	50.0	55.0	0.48
Restless legs symptoms (treated), %	30.0	15.0	0.0	0.03
Non refreshing night, %	60.0 *,†	5.0	5.0	<0.001
Sleep drunkenness, %	0.0	0.0	0.0	1.0
Morning headache, %	45.0 †	20.0	5.0	0.03
Sleep paralysis, %	20.0	0.0	5.0	0.22
Hypnagogic hallucinations, %	0.0	0.0	5.0	0.68
Tired on awakening, %	55.0 *,†	15.0	5.0	0.002
Tired during daytime, %	95.0 *,†	20.0	20.0	<0.001
Non refreshing nap, %	50.0 †	35.0	25.0	0.65
Horne-Ostberg score	57.4 ± 7.5	58.3 ± 8.1	57.4 ± 8.9	0.97

* P<0.05 for OSA patients with vs. without RES, † P<0.05 for OSA patients with RES vs. healthy controls, ‡ P<0.05 for OSA patients without RES vs. healthy controls.

Table 3. Sleep measures during night-time and a 24-hour long sleep monitoring in 20 OSA patients with RES compared to 20 patients without RES and 20 healthy controls.

Patients	OSA with RES	OSA without RES	Healthy controls	P
Night-time sleep				
Total sleep time, min	431 ± 70	433 ± 52	452 ± 70	0.51
Sleep efficiency, %	78.4 ± 10.5	81.1 ± 7.6	84.5 ± 9.3	0.17
Latency to, min				
Sleep onset	23.7 ± 17.7	26.0 ± 16.5	28.4 ± 16.6	0.59
REM sleep	91.4 ± 53.1	82.2 ± 33.9	75.6 ± 37.3	0.53
Sleep stages, % total				
Stages N1 and N2	60.7 ± 10.5	55.9 ± 11.8	58.1 ± 6.8	0.14
Stage N3	16.8 ± 7.6 *,†	24.6 ± 12.2	22.2 ± 7.2	0.01
REM sleep	21.2 ± 8.1	19.4 ± 4.3	19.6 ± 4.0	0.66
Sleep fragmentation				
Arousals, n/h	23.9 ± 11.3	18.9 ± 8.5	24.1 ± 10.9	0.17
Periodic leg movements, n/h	22.7 ± 32.2 *	7.3 ± 8.6	11.3 ± 27.2	0.16
Periodic leg movement arousals, n/h	3.8 ± 6.3	1.8 ± 2.4	3.3 ± 5.0	0.46
Apnoea and hypopnoea, n/h	2.4 ± 2.3 †	2.7 ± 3.9 ‡	7.6 ± 5.8	<0.001

Mean SaO_2, awake, %	95.7 ± 2.1	96.0 ± 1.4	95.4 ± 1.4	0.57
Mean SaO_2, asleep, %	95.1 ± 1.4	95.4 ± 1.4	95.1 ± 1.4	0.91
Lowest SaO_2, asleep, %	89.2 ± 4.8	90.1 ± 5.9	88.0 ± 5.8	0.56
Sleep during 24 hour monitoring				
Total sleep time/24h, min	496 ± 95	460 ± 66	471 ± 77	0.39
Total sleep time >11 h, %	5.0	0.0	0.0	0.35
Sleep stages, % total				
Stages N1 and N2	62.9 ± 9.2	57.5 ± 12.6	58.9 ± 6.8	0.06
Stage N3	15.7 ± 7.4 *,†	23.7 ± 12.1	29.9 ± 9.7	<0.001
REM sleep	20.1 ± 6.1	18.7 ± 4.5	19.2 ± 4.0	0.82
Daytime sleep time, min	63 ± 40 *,†	26 ± 33	20 ± 25	<0.001

* P<0.05 for OSA patients with vs. without RES, † P<0.05 for OSA patients with RES vs. healthy controls, ‡ P<0.05 for OSA patients without RES vs. healthy controls. Sleep fragmentation was evaluated during the first night.

Table 4. Sleep measures during the multiple sleep latency tests in OSA patients with residual excessive sleepiness (RES) compared to patients without RES and healthy controls.

Patients	OSA with RES	OSA without RES	Healthy controls	P
Number	20	20	20	
Mean sleep latency ± SE, min	12.2 ± 0.9 *,†	15.8 ± 0.9	15.7 ± 1.0	0.006
Mean sleep latency < 8 min, %	10.0	5.0	10.0	0.84
Mean sleep latency < 10 min, %	40.0 *,†	10.0	10.0	0.04
Number of SOREMPs	0.6 ± 0.9 *,†	0.1 ± 0.2	0.1 ± 0.4	0.01

*P<0.05 for OSA patients with vs. without RES, † P<0.05 for OSA patients with RES vs. healthy controls, ‡ P<0.05 for OSA patients without RES vs. healthy controls. SOREMPs: Sleep onset in REM periods.

Table 5. Psychological assessment in OSA patients with RES compared to patients without RES and healthy controls.

Patients	OSA with RES	OSA without RES	Healthy controls	P
Beck Depression Inventory score (0-63)	17.4 ± 11.8 †	12.2 ± 6.6 ‡	3.3 ± 3.3	0.002
Depression score >12, %	70 †	40	20	0.02
Cognitive sub-score (0-39)	9.3 ± 8.4 †	6.1 ± 4.3 ‡	1.6 ± 1.8	0.001
Somatic sub-score (0-24)	8.1 ± 3.6 †	6.1 ± 3.2 ‡	1.6 ± 1.8	<0.001
HAD depression score (0-21)	7.8 ± 4.2 †	6.2 ± 3.2	4.0 ± 3.7	0.01
Depression score >7, %	40 †	20	10	0.09
HAD anxiety score (0-21)	10.2 ± 4.2 †	8.2 ± 3.8	6.3 ± 4.2	0.02
Anxiety score >7, %	65 †	55 ‡	20	0.35
Total CAARS score (0-78)	26.4 ± 9.0 †	22.6 ± 12.5	15.3 ± 11.2	0.02
CAARS score >35, %	10	15	5	0.60
Inattention subscore (0-15)	5.4 ± 2.9 †	4.7 ± 3.7 ‡	2.2 ± 1.8	0.006
Hyperactivity subscore (0-15)	3.6 ± 3.2	2.4 ± 2.1	2.6 ± 2.3	0.30
Impulsivity subscore (0-15)	4.3 ± 2.9	4.3 ± 2.9	3.2 ± 3.6	0.44
Self concept subscore (0-15)	6.2 ± 3.4 †	5.7 ± 3.0 ‡	3.5 ± 3.2	0.03
Apathy scale (0-42)	14.3 ± 7.8	12.5 ± 6.3	10.4 ± 5.0	0.22
Apathy scale >16, %	35 †	45 ‡	5	0.03
Fatigue Severity score (1-7)	5.5 ± 1.2 *,†	4.0 ± 1.6 ‡	3.3 ± 1.0	<0.001
Abnormal score>4, %	90 *,†	45	20	<0.001

*P<0.05 for OSA patients with vs. without RES, † P<0.05 for OSA patients with RES vs. healthy controls, ‡ P<0.05 for OSA patients without RES vs. healthy controls. HAD: Hospital Anxiety and Depression Rating Scale. CAARS: Conners' Adult Attention Deficit-Hyperactivity Rating Scale.

Table 6. Cognitive assessment in OSA patients with RES compared to patients without RES and healthy controls.

Patients	OSA with RES	OSA without RES	Healthy controls	P
Subjective memory complaint, %	95.0 †	65.0 ‡	20.0	<0.001
Executive functions (Stroop Colour Word Test)				
Reading time, s	59.3 ± 16.5	60.2 ± 10.2	57.7 ± 18.9	0.89
Colour names time, s	65.4 ± 18.9	68.8 ± 12.0	63.8 ± 18.0	0.76
Interference time, s	106.9 ± 21.3	127.5 ± 41.4	110.1 ± 34.6	0.12
Interference errors	1.8 ± 1.5 *	3.4 ± 2.3	2.8 ± 2.0	0.13
Interference index	24.2 ± 7.4	27.9 ± 11.7	27.2 ± 7.1	0.44
Visuo-spatial abilities and memory (Rey-Osterrieth Complex Figure Test)				
Copy strategy type I or 2, %	60.0	55.0	75.0	0.45
Copy score (0-36)	32.3 ± 2.7	31.6 ± 4.0 ‡	33.4 ± 1.6	0.12
Delayed recall score (0-36)	17.8 ± 7.7 †	18.8 ± 7.6 ‡	23.2 ± 5.8	0.06
Withholding, %	54.1 ± 22.2 †	58.9 ± 22.0	68.6 ± 16.7	0.13
Verbal memory (Free and Cued Selective Reminding Test)				
Immediate free-reminding score (0/48)	28.8 ± 6.8	27.4 ± 5.6	31.0 ± 7.3	0.27
Immediate cued selective-reminding score (0/48)	45.5 ± 3.3	45.4 ± 2.7	44.2 ± 6.2	0.63

Delayed free-reminding score (0/16)	11.5 ± 2.5	11.7 ± 2.7	12.6 ± 2.3	0.41
Delayed cued selective-reminding score (0/16)	15.8 ± 0.5	15.8 ± 0.4	15.4 ± 1.4	0.22
Cue benefit, %	88.9 ± 12.9	87.3 ± 12.8	83.3 ± 18.0	0.52

* P<0.05 for OSA patients with vs. without RES, † P<0.05 for OSA patients with RES vs. healthy controls, ‡ P<0.05 for OSA patients without RES vs. healthy controls.

Figure 1

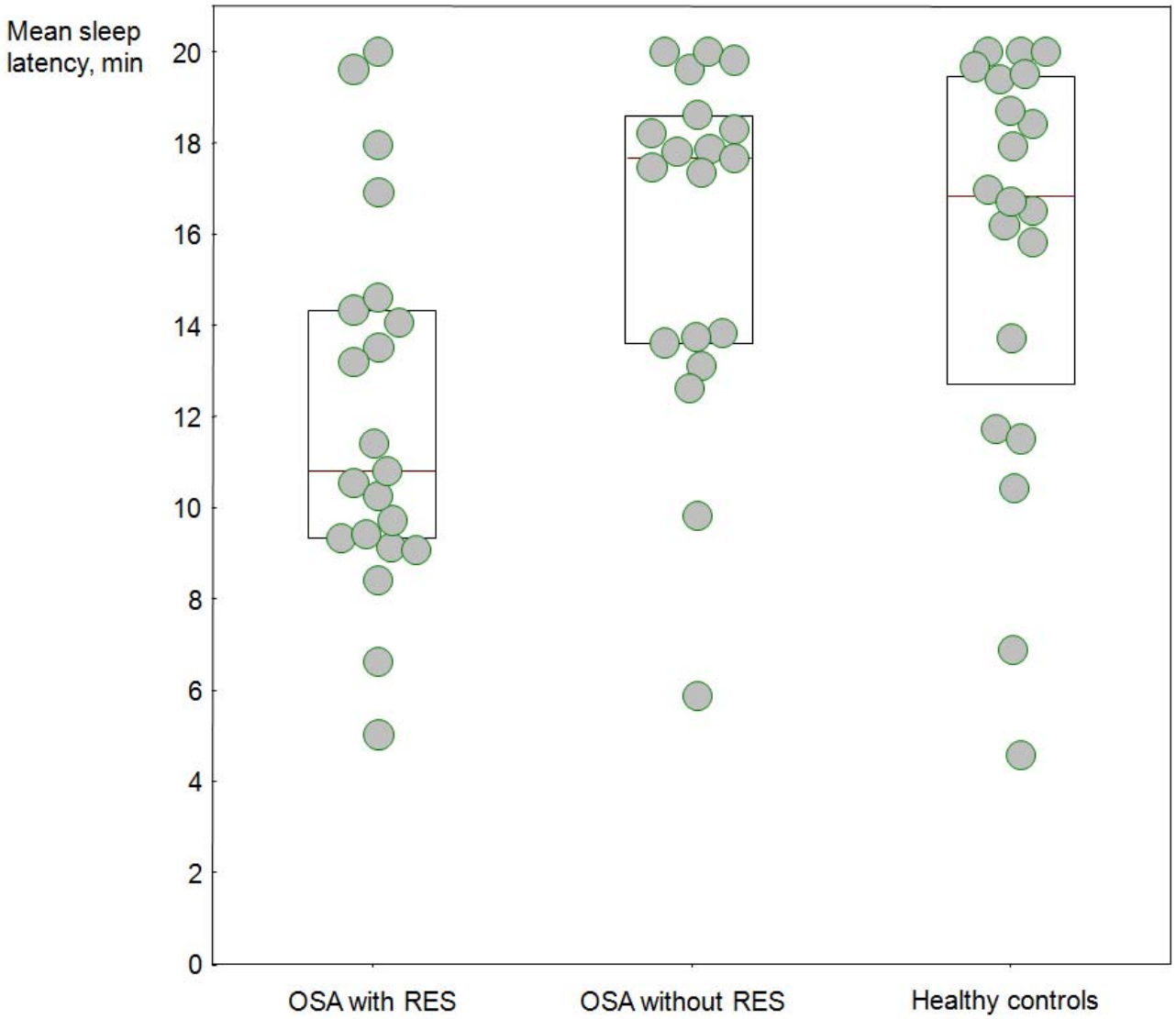
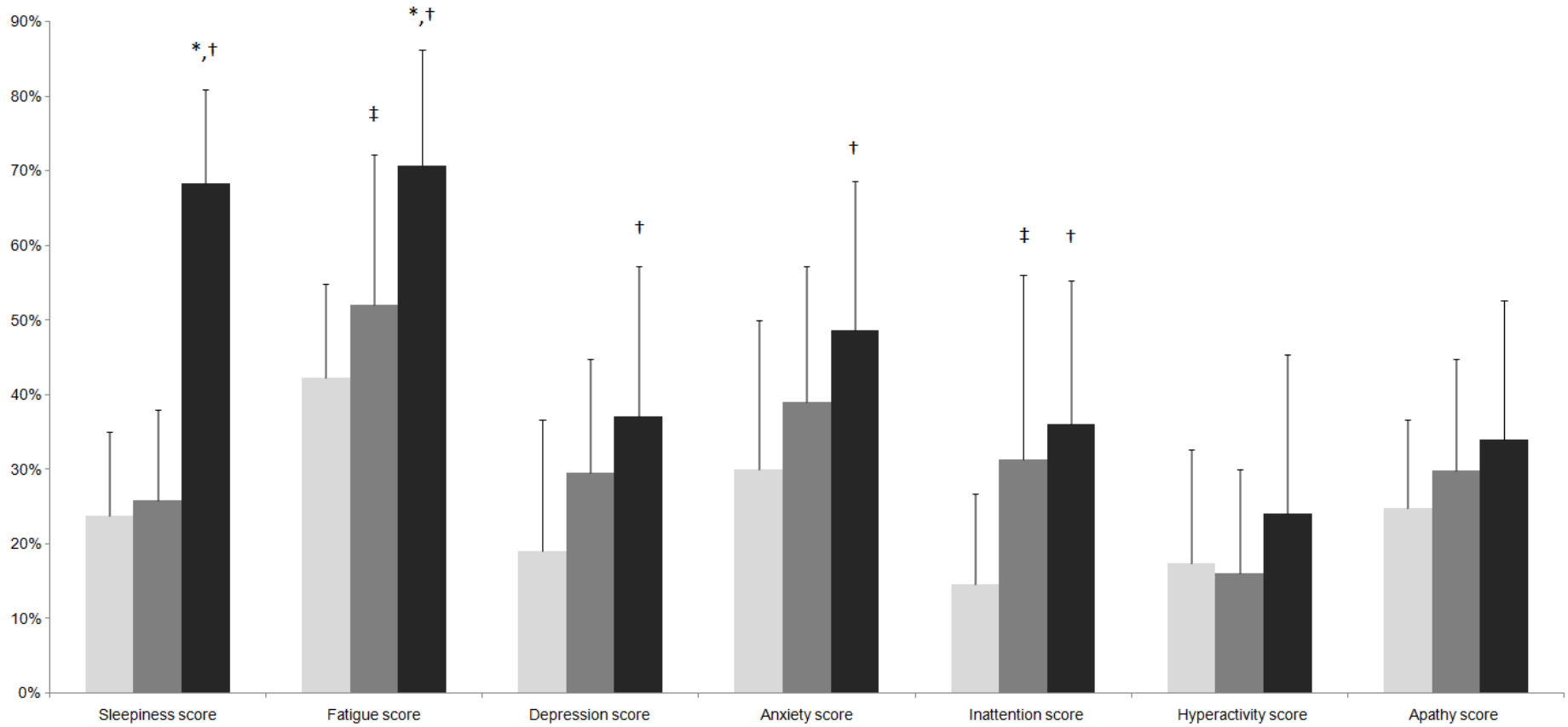

Mean sleep latency, min
20
18
16
14
12
10
8
6
4
2
0
OSA with RES
OSA without RES
Healthy controls

Figure 2


90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
*,†
*,†
‡
†
†
‡
†
Sleepiness score
Fatigue score
Depression score
Anxiety score
Inattention score
Hyperactivity score
Apathy score