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Executive dysfunction in children affected by obstructive sleep apnea syndrome: an observational study

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Introduction: The role of sleep in cognitive processes can be considered clear and well established. Different reports have disclosed the association between sleep and cognition in adults and in children, as well as the impact of disturbed sleep on various aspects of neuropsychological functioning and behavior in children and adolescents. Behavioral and cognitive dysfunctions can also be considered as related to alterations in the executive functions (EF) system. In particular, the EF concept refers to self-regulatory cognitive processes that are associated with monitoring and controlling both thought and goal directed behaviors. The aim of the present study is to assess the impact of the obstructive sleep apnea syndrome (OSAS) on EF in a large sample of school aged children.

Materials and methods: The study population comprised 79 children (51 males and 28 females) aged 7–12 years (mean 9.14 ± 2.36 years) with OSAS and 92 healthy children (63 males and 29 females, mean age 9.08 ± 2.44 years). To identify the severity of OSAS, an overnight respiratory evaluation was performed. All subjects filled out the Italian version of the Modified Card Sorting Test to screen EFs. Moreover, to check the degree of subjective perceived daytime sleepiness, all subjects were administered the Pediatric Daytime Sleepiness Scale (PDSS).

Results: No significant differences between the two study groups were found for age ($P = 0.871$), gender ($P = 0.704$), z-score of body mass index ($P = 0.656$), total intelligence quotient ($P = 0.358$), and PDSS scores ($P = 0.232$). The OSAS children showed a significantly higher rate of total errors ($P < 0.001$), perseverative errors ($P < 0.001$), nonperseverative errors ($P < 0.001$), percentage of total errors ($P < 0.001$), percentage of perseverative errors ($P < 0.001$), and percentage of nonperseverative errors ($P < 0.001$). On the other hand, OSAS children showed a significant reduction in the number of completed categories ($P = 0.036$), total correct sorts ($P = 0.001$), and categorizing efficiency ($P < 0.001$). The Pearson's correlation analysis revealed a significant positive relationship between all error parameters and apnea-hypopnea index, oxygen desaturation index, and percentage of mean desaturation of O_2 with a specular negative relationship between the error parameters and the mean oxygen saturation values, such as a significant negative relationship between apnea-hypopnea index, oxygen desaturation index, percent of mean desaturation of O_2, and the number of completed categories.

Conclusion: Our study identified differences in the executive functioning of children affected by OSAS and is the first to identify a correlation between alteration in respiratory nocturnal parameters and EF that has not yet been reported in developmental age. These findings can be considered as the strength and novelty of the present report in a large pediatric population.

Keywords: OSAS, polysomnography, executive functions, sleep, sleepiness, children

Introduction

The role of sleep in cognitive processes can be considered as clear and well established.[1–5] In general, a good sleep may be considered as a strong predictor of a good health,[6,7] and conversely, a disturbed and/or interrupted sleep would be accompanied by many alterations in all aspects of life, in both genders and at all ages.[8,9] In fact, sleep plays a key role for daytime functioning and neurocognitive performance in childhood and adolescence,[10] probably promoting and/or influencing the neural plasticity process and enhancing memory consolidation during life.[11] Different reports have disclosed the association between sleep and cognition in adults and children,[4,5,12,13] as well as the impact of disturbed sleep on various aspects of neuropsychological functioning and behavior in children and adolescents.[14] Moreover, the impact on cognitive and behavior control linked to sleep disruption is well documented in adults affected by obstructive sleep apnea syndrome (OSAS),[15–17] and by periodic limb movement disorder.[18,19]

Behavioral and cognitive dysfunctions can be considered to be related to alteration in the executive functions (EF) system. In particular, the EF concept refers to self-regulatory cognitive processes that are associated with monitoring and controlling both thought and goal directed behaviors.[20,21] EF domains include (1) inhibitory control (suppression of actions that are inappropriate in a given context and that interfere with a goal driven behavior), (2) attention (the ability to maintain a consistent behavioral response during continuous and repetitive activity) and the closely related concept of mental flexibility (disengagement of an irrelevant task set and subsequent engagement of a relevant task set despite interference and/or priming), (3) reward sensitivity (the relative dominance of the behavioral activation system driving motivated behavior associated with risk taking behavior), and (4) working memory (active maintenance and flexible updating of goal/task relevant information with limited capacity).[20]

On the other hand, several studies have shown that children aged 3–5 years undergo a significant and rapid development in EF until adolescence.[22,23] Moreover, the prefrontal cortex is closely associated with executive functioning and may be considered as the last region of the brain to mature, with an improvement in each dimension of EF (eg, inhibition, shifting, and working memory).[24] At the same time, the EF system can be considered as quite vulnerable to a specific stressor such as altered/disturbed sleep due to respiratory troubles during childhood. To the best of our knowledge, there are few studies about the correlation between nocturnal respiratory parameters and executive functioning in childhood.[25–29] Therefore, the aim of the present study is to assess the impact of OSAS on EF in a large sample of school aged children.

Materials and methods

Participants

The study population comprised 79 children (51 males and 28 females) aged 7–12 years (mean 9.14 ± 2.36 years) with OSAS recruited to the Sleep Center for Developmental Age of Child and Adolescent Neuropsychiatry Department of Second University of Naples. Exclusion criteria were psychiatric illness (ie, schizophrenia, psychosis, attention deficit hyperactivity disorder, depressive symptoms), mental retardation (IQ < 75), neurological disorder (epilepsy, neuromuscular disorders, cerebral palsy), overweight (body mass index (BMI) ≥ 85th percentile) or obesity (BMI ≥ 95th percentile),[30] and referral for sleep complaints other than OSAS. The control group consisted of 92 healthy children (63 males and 29 females, mean age 9.08 ± 2.44 years) enrolled in schools within the Campania region.

The subjects in both groups were recruited from the same urban area; participants were all Caucasian, and held a middle class socioeconomic status (between class 2 or class 3 corresponding to 28,000–55,000 Euros/year to 55,000–75,000 Euros/year, respectively, according to the current Italian economic legislation parameters) as previously reported.[31] All evaluations were performed after informed parental consent was obtained for all the children enrolled, according to the World Medical Association[32] criteria. The study was approved by the Departmental Ethics Committee at the Second University of Naples.

Cognitive assessment

Intellective functioning was assessed by the Italian version of the Wechsler Intelligence Scale for Children (WISC)-III edition[33,34] which is applicable for children ranging in age from 6 to 16 years. The WISC-III is composed of 13 distinct subtests divided into two scales, a verbal scale and a performance scale. The six verbal scale tests use language based items, whereas the seven performance scales use visual motor items that are less dependent on language. Five of the subtests in each scale produce scale-specific intelligence quotients (IQs) such as verbal IQ and performance IQ, and the ten subtest scores produce a total scale IQ (Total IQ), ranging from 85 to 115 in normal subjects.

Executive functions evaluation

To assess the EF in the entire sample group, the Italian version of the Modified Card Sorting Test (MCST) was administered according to the validation criteria for developmental age.[35] The MCST is a card sorting task that is designed to assess EF such as cognitive flexibility, attention shifting, and set maintenance and has been found to be efficacious for use with young children.[35] After each MCST administration, we calculated all subscores that were identified across MCST literature. We first determined if a participant's errors were perseverative or nonperseverative. As recommended by Nelson,[36] we classified perseverative errors when participants persisted to sort according to previous criteria after receiving feedback that a sort was incorrect. All other errors were classified as non-perseverative.

Once errors were classified, we calculated the following scores for each participant: the number of completed categories (CAT), total errors (TE), perseverative errors (PE), nonperseverative errors (NPE), total correct sorts (CS), the percentage of total errors that were perseverative (%PE), the percentage of total errors that were nonperseverative (%NPE), and failures to maintain set (FMS), which were defined as instances when participants make at least three consecutive correct responses (ie, 50%) needed to complete a category but make an error before successful completion. According to the criteria for developmental age, supplementary scores were derived,[35] such as the percentage of TE (%TE) and the categorizing efficiency (CE), by taking into account the number of cards used by the subject to complete a maximum of six categories. This score ranges from 0 to 48. For each item, the age related T scores were considered for the analyses.

In summary, according to the MCST scoring criteria, higher scores demonstrate better performances for the following parameters: CAT, CS, CE; lower scores show better performances for the following parameters: TE, %TE, PE, %PE, NPE, %NPE, and failures to maintain set.

Pediatric daytime sleepiness evaluation

As reported in a study,[37] to check the degree of subjective perceived daytime sleepiness, all subjects were administered the Pediatric Daytime Sleepiness Scale (PDSS).[38] The PDSS is an eight item, self-reported Likert-type questionnaire that measures daytime sleepiness in school age populations, with possible scores ranging from 0 to 32. Higher PDSS scores indicate greater daytime sleepiness. Along with being easy to administer, score, and interpret, the PDSS has a high internal consistency (α) of at least 0.80 in split-half samples and acceptable factor loadings (0.4).[38]

Sleep evaluation

In all children (with or without OSAS) a cardiorespiratory device (Embletta X10; Embletta PDS, MedCare Flaga, Iceland) was used to perform an overnight respiratory evaluation.[9,39,40] The Embletta device is used to specifically detect the presence of OSAS and to assess its severity, is suitable for use both in a sleep laboratory and at home,[41] has been validated against full polysomnography for the evaluation of nocturnal breathing disorders,[42] and is largely used in the pediatric age group.[39,40] All evaluations were performed overnight in the sleep laboratory at the Sleep Center for Developmental Age of Child and Adolescent Neuropsychiatry at the Second University of Naples. All recordings started at the subjects' usual bedtime and continued until spontaneous morning awakening.

The parameters measured were: nasal airflow using two appropriately placed thermistors (one thermistor for oral breath and the other for nasal breath), thoracoabdominal movements via two piezoelectric bands, pulse oximetry using a finger probe, snoring episodes detected via a vibration sensor placed anterior to the sternocleidomastoid muscle, and continuous actigraphy to monitor and record body position. Recordings were analyzed manually using the device-specific software (Somnologica for Embletta 3.3; Embla, Broomfield, CO, USA). Sleep onset was estimated as the beginning of the first 10-minute period not containing any changes in body position and morning awakening was estimated as the end of the last such 10-minute period.[43] Estimated sleep time was calculated as the time between sleep onset and morning awakening. Recordings were analyzed for artefactual or uninterpretable periods of nasal flow, thoracic effort, abdominal effort, or oximetry. Movement periods and artefactual or uninterpretable periods were excluded from the estimated sleep time if they lasted for more than 5 minutes, and the corrected estimated sleep time was calculated.[43] A minimum of 5 hours of corrected estimated sleep time was required.

All the recordings were visually scored by one of the investigators (MC) according to pediatric criteria.[44–47] Specifically, obstructive apnea was defined as cessation of airflow, lasting for at least two breaths, in the presence of paradoxical ribcage and abdominal movements. The hypopnea index was defined as a reduction in the nasal flow curve signal by more than 50% that was accompanied by either oxygen desaturation or arousal. Central apnea was defined as the absence of airflow at both the nose and mouth with absent inspiratory effort throughout the duration of the event, lasting 20 seconds or longer, or two missed breaths accompanied by at least 3% oxygen desaturation, an arousal, or an awakening. The apnea-hypopnea index (AHI) was defined as the number of obstructive apneas and hypopneas per hour of sleep,[44,45,48] and the lowest oxygen saturation value and number of desaturation events by 4% and to 90%

were counted. The oxygen desaturation index (ODI), defined as events per hour, was also calculated. An AHI and ODI ≤ 1 per hour were considered as normal according to American Thoracic Society criteria.[44,45]

Statistical analysis

Comparisons between age, gender, z-score of BMI (z-BMI), intellectual abilities, MCST, PDSS, and respiratory parameters obtained in OSAS children and typical developing individuals were carried out by the *t*-test. To verify the matching sex ratio (M/F), the Chi-squared test was performed. $P < 0.05$ was considered statistically significant. The Pearson's correlation test was computed to analyze the relationship among MCST scores with respiratory indices (AHI and ODI). The commercially available data analysis software STATISTICA version 6 (StatSoft, Inc, Tulsa, OK, USA) was used for all statistical tests.

Results

No significant differences between the two study groups were found for age ($P = 0.871$), gender ($P = 0.704$), z-BMI ($P = 0.656$), Total IQ ($P = 0.358$), and PDSS scores ($P = 0.232$) (Table 1). Table 2 shows the differences in nocturnal respiratory parameters and MCST scores between the two groups. The OSAS children showed a significantly higher quota of TE ($P < 0.001$), PE ($P < 0.001$), NPE ($P < 0.001$), %TE ($P < 0.001$), %PE ($P < 0.001$), and %NPE ($P < 0.001$). On the other hand, OSAS children showed a significant reduction in the number of CAT ($P = 0.036$), total CS ($P = 0.001$), and CE ($P < 0.001$) (Table 2). Moreover, the Pearson's correlation analysis revealed a significant positive relationship between all error parameters and AHI, ODI, and percentage of mean desaturation of O_2 with a specular negative relationship between the error parameters and the mean oxygen saturation values, such as a significant negative relationship between AHI, ODI, percentage of mean desaturation of O_2, and the number of CAT (Table 3).

Table 1 Characteristics of children affected by OSAS and controls

	OSAS (N = 79)	Normal (N = 92)	*P*
Age	9.14 ± 2.36	9.08 ± 2.44	0.871
Sex ratio (M/F)	51/28	63/29	0.704
z-BMI	0.61 ± 0.27	0.59 ± 0.31	0.656
Total-IQ	89.47 ± 4.19	90.16 ± 5.41	0.358
PDSS	12.41 ± 2.68	11.87 ± 2.33	0.232

Notes: The *t*-test and Chi-square test, where appropriated, were applied. *P* values <0.05 were considered statistically significant. Mean differences for age, sex, z-score Body Mass Index (z-BMI), Total Intelligence Quotient (Total IQ) and Pediatric Daytime Sleepiness Scale (PDSS) scores between the group of children affected by Obstructive Sleep Apnea Syndrome (OSAS) and group of typical developing children (Normal).

Table 2 Comparison of nocturnal respiratory indexes and MCST scores between the children affected by Obstructive Sleep Apnea Syndrome (OSAS) and typical developing children (Control)

	OSAS (N = 79)	Control (N = 92)	*P*
AHI	9.914 ± 3.216	0.482 ± 0.302	<0.001
ODI	5.041 ± 1.762	0.481 ± 0.372	<0.001
Mean SpO_2 (%)	94.061 ± 1.243	98.735 ± 0.649	<0.001
Mean SpO_2 desaturation (%)	5.918 ± 1.087	0.948 ± 0.651	<0.001
CAT	53.948 ± 9.349	56.381 ± 5.156	0.036
CS	48.827 ± 8.718	52.972 ± 8.014	0.001
CE	46.148 ± 9.036	50.906 ± 5.783	<0.001
TE	42.062 ± 8.162	36.081 ± 2.053	<0.001
% TE	43.327 ± 8.912	34.918 ± 4.053	<0.001
PE	47.436 ± 13.208	36.024 ± 2.739	<0.001
% PE	47.914 ± 13.895	38.766 ± 5.419	<0.001
NPE	41.093 ± 7.086	37.481 ± 3.244	<0.001
% NPE	31.189 ± 13.053	23.046 ± 4.735	<0.001
FMS	47.073 ± 13.992	45.191 ± 3.718	0.216

Note: *t*-Test was applied and *P* values<0.05 were considered statistically significant. Apnea/hypopnea index-AHI; Oxygen desaturation index-ODI; percentage of SpO_2 mean saturation-Mean SpO_2 [%]; percentage of SpO_2 mean desaturation-Mean SpO_2 desaturation [%]; number of completed categories-CAT; total correct sorts-CS; categorizing efficiency-CE; total errors-.TE; percentage of total errors-%TE; perseverative errors-PE; percentage of total errors that were perseverative-%PE; non-perseverative errors-NPE; percentage of total errors that were non-perseverative-%NPE; failures to maintain set-FMS.

Discussion

The main findings of our study can be summarized in that children affected by OSAS presented a lower executive functioning, as showed by the MCST evaluation, with a significant correlation with the severity of nocturnal respiratory impairment. In general, the most common documented cause of sleep related breathing disorders in children can be considered as upper airway obstruction, with prevalence for OSAS of about 1%–3%, and a peak prevalence between 2 and 8 years of age.[49] The symptoms of OSAS include abnormal position during sleep,[50–52] mood disorders,[9,53–56] reduced quality of life, and cognitive problems[57] at all ages. Moreover, considering the increasing prevalence of OSAS and neurocognitive and cardiovascular consequences, an objective evaluation with nocturnal monitoring for children with suspected OSAS has been recommended.[58,59]

Cognitive impairment in subjects affected by OSAS has been studied since the 1980s,[60] and the most common cognitive deficits reported in most adults were in attention or concentration, vigilance, memory and learning abilities, motor

Table 3 Correlation between nocturnal respiratory indexes and MCST scores in our study sample

	AHI	ODI	Mean SpO_2 (%)	Mean SpO_2 desaturation (%)
CAT	**–0.3528**	**–0.1850**	**0.2122**	**–0.2828**
CS	0.0753	0.0339	–0.0193	**0.2039**
CE	0.0325	0.1230	–0.0620	0.1249
TE	**0.4745**	0.1374	**–0.2602**	**0.5000**
% TE	**0.5167**	**0.2517**	**–0.2485**	**0.5314**
PE	**0.4183**	**0.2100**	**–0.3603**	**0.4114**
% PE	**0.3787**	**0.1880**	**–0.3123**	**0.3660**
NPE	**0.3529**	**0.1910**	–0.0176	**0.4220**
% NPE	**0.4199**	**0.2198**	**–0.1636**	**0.4643**
FMS	**0.2086**	0.0353	**–0.1620**	0.0346

Notes: Pearson's correlation test was computed. *P* values < 0.05 are reported in bold characters. Apnea/hypopnea index-AHI; Oxygen desaturation index-ODI; percentage of SpO_2 mean saturation-Mean SpO_2 [%]; percentage of SpO_2 mean desaturation-Mean SpO_2 desaturation [%]; number of completed categories-CAT; total correct sorts-CS; categorizing efficiency-CE; total errors-.TE; percentage of total errors-%TE; perseverative errors-PE; percentage of total errors that were perseverative-%PE; non-perseverative errors-NPE; percentage of total errors that were non-perseverative-%NPE; failures to maintain set-FMS

performance, constructional abilities, and EF. Both excessive daytime sleepiness and nocturnal hypoxemia seem to equally contribute to cognitive deficits.[60–62] Moreover, excessive daytime sleepiness has been mostly related to impairment in attention, vigilance, and memory function, while hypoxemia tends to correlate with deficits in EF.[57,61] In this light, our findings are suggestive for a causative role of nocturnal hypoxemia in executive impairment, considering that the levels of subjective perceived daytime sleepiness are comparable with the normal control subjects ($P = 0.232$). Only about 7% of children affected by OSAS present with symptoms that are compatible with excessive daytime sleepiness.[63]

Alternatively, several studies have reported a nonlinear worsening in cognitive impairment related to the severity of OSAS,[64,65] different from our report of the positive and significant relationships between executive functioning and nocturnal respiratory parameters (AHI, ODI, and mean oxygen desaturation levels) and a negative correlation with the mean oxygen saturation level (Table 3).

With respect to the other few studies in a pediatric population, our results can be considered quite different. In fact, Archbold et al in 2004[25] and Kohler et al in 2009[29] both reported the effect of adenotonsillectomy on executive functioning, with no significant correlation with nocturnal respiratory parameters. On the other hand, Beebe et al failed to indicate any clear relationship between neuropsychological functioning and objective indices of hypoxia or sleep disruption in a small sample of children,[26] similar to a report by O'Brien et al.[27] This report cannot be considered as properly focused on executive functioning evaluation in children affected by sleep related breathing disorders (SRBD) because the authors considered the effect of the sleep pressure score linked and due to the SRBD on behavior and on generic neuropsychological functioning. Finally, according to Calhoun et al in 2009[28] no clear relationship between neuropsychological functioning and objective indices of hypoxia or sleep disruption was identified.

Furthermore, as reported in a study, the MCST evaluation results may be considered to be related to changes in blood flow levels, particularly in the frontal cortex and in the hippocampus regions.[66] In this perspective, our results suggest a putative relationship between the executive efficiency of the frontal lobes and the severity of night breathing alterations as shown by the correlation between high AHI and ODI values and the increase in MCST error rates (PE and NPE). On the other hand, gray matter reduction level in the frontal-parietal and in the hippocampus regions[67,68] may explain the perseveration tendency in our OSAS children that is related to their respiratory nocturnal abnormalities.

Alternatively, our results also support the hypothesis that the deficit in executive functioning may be related primarily to the severity of nocturnal hypoxemia rather than daytime sleepiness[69,70] in children, although further studies are needed. Moreover, the neurocognitive deficits in domains such as manual skills, planning abilities, and in particular, executive functioning, do not seem to improve after continuous positive airway pressure (CPAP) treatment[71,72] in adults, suggesting that OSAS related hypoxemia resulted in permanent brain injury leading to enduring cognitive deficits. In fact, studies[71,72] evaluating cognitive functioning in OSAS patients seem to suggest that CPAP improves only some cognitive functions, with long-term cognitive deficits most pronounced for executive functioning. On the other hand, in adult patients with untreated OSAS, the impact on verbal and intellectual functioning was minimal, irrespective of vigilance and executive functioning impairment.[73] In this light, our finding would suggest the importance of EF assessment in children affected by OSAS, and the need for an early rehabilitation and ventilatory therapy to avoid establishment of permanent executive functioning damage.

In conclusion, the following limitations of this study need to be taken into account: (1) subjects were recruited from a specific region in southern Italy (and cannot be considered as derived by the whole Italian pediatric population), (2) our data was derived from a nocturnal cardiorespiratory evaluation and not from full polysomnography (with a lack of correlation with the sleep stages percentages), (3) assessment of the excessive daytime sleepiness was not performed using objective methods such as the Multiple Latency Sleep Test, (4) this can be considered as an observational resting study on a small sample of children affected by OSAS, (5) follow-up data was not available, and (6) neuroimaging evaluations were not performed.

However, our study does identify differences in executive functioning in children affected by OSAS and is the first to identify a correlation between alteration in respiratory nocturnal parameters and EF not yet reported in the developmental age group, and these findings can be considered as the strength and novelty of the present report in a large pediatric population.

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Disclosure

The authors report no conflicts of interest in this work. None of the authors have any personal, financial support, or involvement with organizations that hold financial interest in the subject matter.

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