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HEAD AND NECK

Correlation between hippocampal sulcus width and severity of obstructive sleep apnea syndrome

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Abstract The aim of the present study was to evaluate the relationship between obstructive sleep apnea syndrome (OSAS) severity and the hippocampal sulcus width in a cohort of subjects with OSAS and controls. A total of 149 OSAS patients and 60 nonapneic controls were included in the study. Overnight polysomnograpy was performed in all patients. Hippocampal sulcus width of the patients was measured by a radiologist blinded to the diagnosis of the patients. Other variables noted for each patient were as follows: gender, age, body mass index, apnea hypopnea index, Epworth sleepiness scale, sleep efficacy, mean saturation, lowest O_2 saturation, longest apnea duration, neck circumference, waist circumference, hip circumference. A total of 149 OSAS patients were divided into three groups: mild OSAS ($n = 54$), moderate OSAS ($n = 40$), severe OSAS ($n = 55$) groups. The control group consisted of patients with AHI <5 ($n = 60$). Hippocampal sulcus width was 1.6 ± 0.83 mm in the control group; while 1.9 ± 0.81 mm in mild OSAS, 2.1 ± 0.60 mm in moderate OSAS, and 2.9 ± 0.58 mm in severe OSAS groups ($p < 0.001$). Correlation analysis of variables revealed that apnea hypopnea index (rs = 0.483, $p < 0.001$) was positively correlated with hippocampal sulcus width. Our findings demonstrated that severity of OSAS might be associated with various pathologic mechanisms including increased hippocampal sulcus width.

Keywords Hippocampal sulcus width · Obstructive sleep apnea

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Introduction

Obstructive sleep apnea syndrome (OSAS) is a common multifactorial disorder characterized by repetitive episodes of upper airway obstruction during sleep leading to intermittent hypoxia or arousal [1–3]. With increased incidence in recent years, OSAS is an important cause of morbidity and mortality, such as increased cardiovascular risk, heart failure, arrhythmias, systemic and pulmonary hypertension [4, 5]. Repeated episodes of apnea/hypopnea in OSAS have been demonstrated to lead to hypoxia and to result in neurostructural changes [6].

Cerebral structural changes have been shown to be associated with OSAS [7]. The limbic system and hippocampus are primary regions of the central nervous system that control sleep-wake patterns, light–dark-cycle adaptation, mood regulation, and neuronal excitation [8]. The hippocampus demonstrates age-related atrophy, and it may be affected by neurotoxic drug abuse, hypoxic injury, diabetes mellitus, hypertension, obesity, sleep disorders, and trauma [9, 10]. Cellular damage to the hippocampus

contributes to neuropsychological impairment, including insomnia and cognitive dysfunction [11, 12].

Magnetic resonance imaging (MRI) modalities have been widely used to evaluate neurological and neuropsychiatric disorders [8, 12]. To our knowledge, no study has examined the relationship between the hippocampus sulcus width and severity of OSAS using MRI. We hypothesized that repeated episodes of apnea/hypopnea might cause neurostructural changes in the hippocampus in OSAS. The aim of the present study was to evaluate the relationship between OSAS severity and the hippocampal sulcus width in a cohort of subjects with OSAS and controls.

Materials and methods

Study design

This study was approved by the local Institutional Review Board (04012013/5). A retrospective study was performed in patients referred to the sleep laboratory of our institution for daytime sleepiness, habitual nocturnal snoring, and witnessed apnea spells from August 2009 to January 2014. Among these patients, 261 patients who had undergone cranial MRI for any reason (head trauma, brain tumors, ischemia, hemorrhage, suspected epilepsy, developmental disorders, diseases of the pituitary gland, parasellar region, brain stem and posterior fossa, evaluation of the cranial nerves, infectious and inflammatory and diseases, post-operative patient evaluation) were included in the study. Fifty-two patients who had undergone MRI for brain tumor, suspected epilepsy, and diseases of the parasellar region were excluded. Finally, a total of 149 OSAS patients and 60 nonapneic controls were included in the study.

Outcome parameters

Clinical examination included standardized scales for the assessment of respiratory symptoms and subjective daytime sleepiness, that is, the Epworth Sleepiness Scale (ESS) [13]. Body mass index (BMI) was calculated from body weight in kilograms divided by the square of height in meters. Full-night polysomnography (PSG) (Alice-5 Polysomnography System, Respironics Inc., Pittsburgh, PA) was performed. The following physiologic variables were monitored simultaneously and continuously: four channels for the electroencephalogram; two channels for the electrooculogram; two channels for the surface electromyogram (submentonian region and anterior tibialis muscle); one channel for an electrocardiogram; airflow detection via two channels through a thermocouple (one channel) and nasal pressure (one channel); respiratory effort of the thorax (one channel) and of the abdomen (one channel) using plethysmography; snoring (one channel) and body position (one channel); oxyhemoglobin saturation; and pulse rate. Two trained technicians visually scored all PSGs according to standardized criteria for investigating sleep [14]. Apnea was defined as complete cessation of airflow for at least 10 s; hypopnea was defined as a reduction in airflow that was associated with at least a 4 % drop in O_2 saturation. OSA was defined by AHI $\geq$5/h. According to the AHI values, OSA patients were classified into three groups as mild (AHI = 5–15), moderate (AHI = 15–30) and severe OSA (AHI > 30).

Hippocampal sulcus width of the patients (study and control groups) was measured by a radiologist blinded to the diagnosis of the patients. Magnetic resonance imaging was performed on a General Electric (GE) Signa 1.5-T MR imaging system (GE Healthcare, Milwaukee, WI, USA) with an eight-channel head coil. Routine brain MR imaging and fat-saturated 3D T1-weighted gradient-echo sequence in the coronal planes (TR, 12.3 ms; TE, 5.4 ms; flip angle, 8; NEX, 2; section thickness, 0.8 mm; intersection spacing, 0.4 mm; matrix size, 512 × 512, field of view, 200 × 200 mm) was performed (Figs. 1, 2).

Statistical analyses

Data were analyzed using the Statistical Package for Social Sciences 19.0 for Windows (SPSS Inc., Chicago, IL). A normal distribution of the quantitative data was checked using Kolmogorov–Smirnov and Shapiro–Wilk tests. Parametric tests were applied to data of normal distribution and non-parametric tests were applied to data of

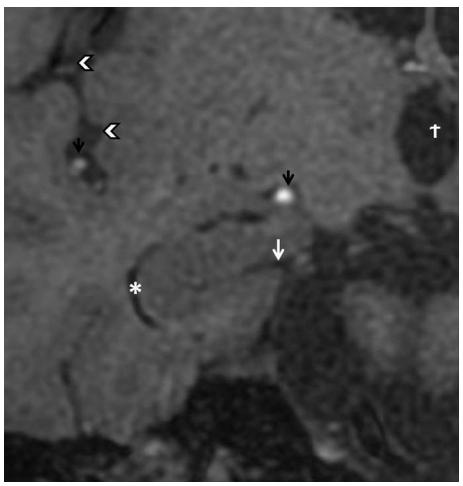

Fig. 1 Magnified coronal T1-weighted image of a 48-year old non-demented control object revealed right hippocampal sulcus (*vertical white arrows*) and choroidal fissure (*asterisk*) within normal limits. The right Sylvian fissure (*white arrowheads*), third ventricle (*dagger*) and branches of anterior and middle cerebral arteries (*vertical black arrows*) were also seen

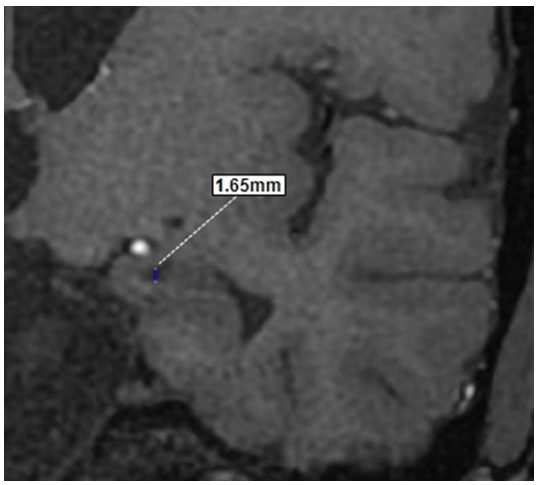

Fig. 2 Magnified coronal T1-weighted image of a 54-year old patient with mild OSAS showed vertical measurement of the hippocampal sulcus on left side

questionably normal distribution. Independent-samples *t* test and Mann–Whiney *U* test were used to compare independent groups. One-way ANOVA test was used to compare groups of independent continuous variables and Bonferroni post hoc analysis was used for multiple comparison tests. To calculate correlation coefficients Partial Correlation test was used. The distribution of categorical variables in both groups was compared using Pearson's Chi-square test. Data are expressed as mean ± SD or median (interquartile range), as appropriate. All differences associated with a chance probability of 0.05 or less were considered statistically significant.

Results

A total of 149 OSAS patients were divided into three groups: mild OSAS ($n = 54$; 28/26 male/female; mean

Table 1 Demographic characteristics in control subjects and patients with mild, moderate and severe obstructive sleep apnea

	Control group ($n = 60$)	Mild OSAS ($n = 54$)	Moderate OSAS ($n = 40$)	Severe OSAS ($n = 55$)	*p* value	
BMI (kg/m^2)	27.4 ± 4.86	29.9 ± 5.11	30.7 ± 5.23	32.1 ± 4.61	<0.001	p(S–Mi) = 0.021
						p(S–C) < 0.001
						p(Mi–C) = 0.007
						p(C–Mo) = 0.001
AHI	1.8 ± 1.36	8.8 ± 3.04	21.8 ± 4.27	60.8 ± 21.17	<0.001	p(S–Mi) < 0.001
						p(S–C) < 0.001
						p(S–Mo) < 0.001
						p(Mi–C) < 0.001
						p(Mi–Mo) < 0.001
						p(C–Mo) < 0.001
ESS	5 ± 5	5.5 ± 5	6 ± 7	8 ± 8	0.152	
Neck circumference	37.5 ± 3.39	38.6 ± 2.90	40.8 ± 2.93	41.2 ± 3.78	<0.001	p(S–Mi) < 0.001
						p(S–C) < 0.001
						p(Mi–Mo) = 0.002
						p(C–Mo) < 0.001
Waist circumference	97.5	104.7	110.1	111.0	<0.001	p(S–Mi) = 0.010
						p(S–C) < 0.001
						p(Mi–C) = 0.003
						p(Mi–Mo) = 0.042
						p(C–Mo) < 0.001
Hip circumference	104 ± 10	109 ± 11	110 ± 14	114 ± 17	0.001	p(S–C) = 0.001
						p(C–Mo) = 0.040
Hippocampal sulcus width	1.6 ± 0.83	1.9 ± 0.81	2.1 ± 0.60	2.9 ± 0.58	<0.001	p(S–Mi) < 0.001
						p(S–C) < 0.001
						p(S–Mo) < 0.001
						p(Mi–C) = 0.022

BMI body mass index, *AHI* apnea hypopnea index, *ESS* Epworth sleepiness scale, *C* control, *Mi* mild, *Mo* moderate, *S* severe

Table 2 PSG characteristics according to the severity of the OSA

	Control group ($n = 60$)	Mild OSAS ($n = 54$)	Moderate OSAS ($n = 40$)	Severe OSAS ($n = 55$)	p value	
Sleep efficacy (%)	85.75 ± 16.95	84.2 ± 16.7	80.7 ± 11.7	79.4 ± 15.6	0.013	p(S–C) = 0.020
Mean saturation (%)	96 ± 2	95 ± 2	95 ± 2	93 ± 2	<0.001	p(S–Mi) < 0.001
						p(S–C) < 0.001
						p(S–Mo) = 0.001
						p(Mi–C) = 0.006
						p(C–Mo) = 0.004
Lowest O_2 saturation (%)	90 ± 4.5	84 ± 8	86 ± 8	77 ± 17	<0.001	p(S–Mi) = 0.004
						p(S–C) < 0.001
						p(S–Mo) = 0.001
						p(Mi–C) < 0.001
						p(C–Mo) < 0.001
Longest apnea (sn)	21.5 ± 5.5	29.5 ± 11	30.25 ± 9.2	41.5 ± 23.5	<0.001	p(S–Mi) < 0.001
						p(S–C) < 0.001
						p(S–Mo) = 0.001
						p(Mi–C) < 0.001
						p(C–Mo) < 0.001

Table 3 Correlation analysis of variables correlated with hippocampal sulcus width

Correlations	rs	p value
Apnea hypopnea index × hippocampal sulcus width	0.483	<0.001
Epworth sleepiness scale × hippocampal sulcus width	0.072	0.307

age: 54.3 ± 13.18 years), moderate OSAS ($n = 40$; 26/14 male/female; mean age: 56.7 ± 8.71 years), severe OSAS ($n = 55$; 32/23 male/female; mean age: 57.8 ± 13.34 years) groups. The control group consisted of patients with AHI <5 ($n = 60$; 23/37 male/female; mean age: 42.9 ± 14.34 years). There were no significant differences between two groups in terms of age and gender. BMI and AHI were significantly different among groups ($p < 0.001$ for each). However, ESS did not differ significantly ($p = 0.152$). Neck, waist, and hip circumferences were significantly different among groups ($p < 0.001$ for each) (Table 1).

Hippocampal sulcus width was 1.6 ± 0.83 mm in the control group; while 1.9 ± 0.81 mm in mild OSAS, 2.1 ± 0.60 mm in moderate OSAS, and 2.9 ± 0.58 mm in severe OSAS groups ($p < 0.001$) (Table 1). Table 2 summarizes PSG characteristics according to the severity of the OSA. Correlation analysis of variables correlated with hippocampal sulcus width was shown in Table 3. Correlation analysis revealed that apnea hypopnea index (rs = 0.483, $p < 0.001$) was positively correlated with hippocampal sulcus width (Fig. 3).

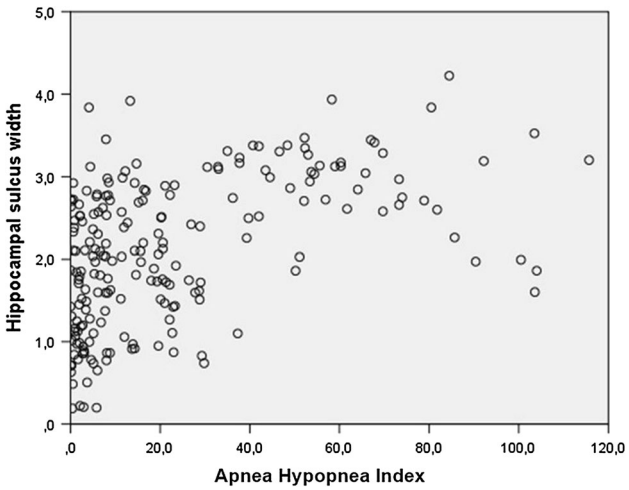

Fig. 3 Correlation between hippocampal sulcus width and apnea hypopnea index

Discussion

In this study, we attempted to demonstrate whether there was a relationship between hippocampal sulcus width and severity of OSAS. Our study showed that apnea hypopnea index was positively correlated with hippocampal sulcus width.

OSAS, characterized by intermittent hypoxemia and arousal from sleep, reduces oxygen content of breathing air with subsequent decreased brain tissue oxygenation during sleep [1]. The cerebral structures showed different vulnerability patterns to hypoxic, hypercarbic, or reduced-

perfusion consequences of repeated attacks of apnea or hypopnea [3].

Several studies have demonstrated the presence of cerebral structural changes in sleep disorders [15]. Cerebral structural changes and chemical compositions might be the underlying cause of functional deficits, defective memory, emotional disorders, learning ability defects, and sleep-wake disturbances [16]. Attention capacity of OSAS patients decreases, which can probably account for memorial difficulties [17]. The damage to the gray matter contributing to cognition, autonomic, and respiratory regulation might be cause those symptoms [18]. Focal gray matter loss in OSAS patients can contribute excessive daytime sleeepiness [19]. White matter, including axonal linking of the limbic system, is also affected in OSAS patient with neuropsychological symptoms [20].

Cerebral MR imaging is more sensitive to detecting on abnormalities of brain morphology and function. MP-RAGE is a pulse sequence for high resolution 3D T1-weighted volumetric imaging consisting of an inversion recovery pulse followed by rapid gradient echo readout, and introduces by the reproducibility of a particular algorithm of brain volume change from other sources of variability [21]. In recent studies, MR spectroscopy, T2-relaxometry MR, 18F-fluoro-2-deoxy-D-glucose positron emission tomography, Voxel based morphometry shows various hippocampal changes in OSAS [22, 23]. Unilateral, bilateral, and non-reduced hippocampal cortical gray matter concentrations have been reported, inwith some studies additional basal ganglia, thalamus and pontine concentration reductions appeared in OSAS [24]. In the present study, we used 1.5-T MR imaging system with an eight-channel head coil.

Hippocampus has been shown to be highly vulnerable to hypoxic damage both in humans and animals [20]. In a rodent model, intermittent hypoxia was shown to trigger apoptosis, neurodegeneration, neuronal damage, altered the dendritic arborization, and reduced neurotransmission in hippocampus [25]. On the other hand, chronic recurring episodes of apnea-hipopnea have been resulted excessive release of neurotransmitters. Over-stimulation of postsynaptic receptors occurred subsequently in the hippocampal neurons [26, 27]. In a rat study, there was a marked apoptosis in the hippocampus in conjunction with chronic episodes of hypoxia [28]. In the present study, we observed significant difference in the hippocampal sulcus width between the OSAS and the control groups.

The main limitations of our study were retrospective design and relatively small size of our series. Second, some details of history and factors that may influence the outcome may not be completely documented and our study findings may potentially have been influenced by these confounding factors. Third, this was a single-institution study, and some caution should be taken before generalizing the findings to other settings. Due to these restrictions, associations should be interpreted with caution.

Conclusion

Our findings demonstrated that severity of OSAS might be associated with various pathologic mechanisms including increased hippocampal sulcus width. However, further randomized, prospective, controlled trials on larger series are necessary for making more precise interpretations to clarify these complex mechanisms.

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Conflict of interest The authors declare no competing interest.

References

1. Akhan G, Ayik S, Songu M (2012) Cerebral oxygenation during sleep in patients with obstructive sleep apnea: a near-infrared spectroscopy study. J Otolaryngol Head Neck Surg 41:437–442
2. Songu M, Yilmaz H, Yuceturk AV, Gunhan K, Ince A, Bayturan O (2008) Effect of CPAP therapy on catathrenia and OSA: a case report and review of the literature. Sleep Breath 12:401–405
3. Songu M (2010) Surgical management of sleep-disordered breathing. In: Lefebvre E, Moreau R (eds) Snoring: causes, diagnosis and treatment. Nova Science Publishers, New York. ISBN:978-1-60876-215-6
4. Songu M, Adibelli ZH (2010) Diagnostic imaging studies in sleep-disordered breathing. In: Lefebvre E, Moreau R (eds) Snoring: causes, diagnosis and treatment. Nova Science Publishers, New York. ISBN:978-1-60876-215-6
5. Songu M, Adibelli ZH, Tuncyurek O, Adibelli H (2010) Age-specific size of the upper airway structures in children: magnetic resonance imaging analysis. Ann Otol Rhinol Laryngol 119:541–546
6. Hambrecht VS, Vlisides PE, Row BW, Gozal D, Baghdoyan HA, Lydic R (2007) Hypoxia modulates cholinergic but not opioid activation of G proteins in rat hippocampus. Hippocampus 17:934–942
7. Desseilles M, Dang-Vu T, Schabus M, Sterpenich V, Maquet P, Schwartz S (2008) Neuroimaging insights into the pathophysiology of sleep disorders. Sleep 31:777–794
8. Dusak A, Ursavas A, Hakyemez B, Gokalp G, Taskapilioglu O, Parlak M (2013) Correlation between hippocampal volume and excessive daytime sleepiness in obstructive sleep apnea syndrome. Eur Rev Med Pharmacol Sci 17:1198–1204
9. Fotuhi M, Do D, Jack C (2012) Modifiable factors that alter the size of the hippocampus with ageing. Nat Rev Neurol 8:189–202
10. Maguire EA, Gadian DG, Johnsrude IS, Good CD, Ashburner J, Frackowiak RS, Frith CD (2000) Navigation related structural change in the hippocampi of taxi drivers. Proc Natl Acad Sci USA 97:4398–4403
11. Lal C, Strange C, Bachman D (2012) Neurocognitive impairment in obstructive sleep apnea. Chest 141:1601–1610
12. Hauw JJ, Hausser-hauw C, De Girolami U, Hasboun D, Seilhean D (2011) Neuropathology of sleep disorders: a review. J Neuropathol Exp Neurol 70:243–252

13. Johns MW (1991) A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 14:540–545
14. Rechtschaffen A, Kales A (1968) A manual of standardized terminology: techniques and scoring system for sleep stages of human subjects. Brain Information Service/Brain Research Institute, Los Angeles
15. O'Donoghue FJ, Briellmann RS, Rochford PD, Abbott DF, Pell GS, Chan CH, Tarquinio N, Jackson GD, Pierce RJ (2005) Cerebral structural changes in severe obstructive sleep apnea. Am J Respir Crit Care Med 171:1185–1190
16. Chambers RA, Sentir AM, Engleman EA (2010) Ventral and dorsal striatal dopamine efflux and behavior in rats with simple vs. co-morbid histories of cocaine sensitization and neonatal ventral hippocampal lesions. Psychopharmacology 212:73–83
17. Riha RL (2010) Clinical assessment of the obstructive sleep apnoea/hypopnoea syndrome. Ther Adv Respir Dis 4:83–91
18. Bartlett DJ, Rae C, Thompson CH, Byth K, Joffe DA, Enright T, Grunstein RR (2004) Hippocampal area metabolites relate to severity and cognitive function in obstructive sleep apnea. Sleep Med 5:593–596
19. Torelli F, Moscufo N, Garreffa G, Placidi F, Romigi A, Zannino S, Bozzali M, Fasano F, Giulietti G, Djonlagic I, Malhotra A, Marciani MG, Guttmann CR (2011) Cognitive profile and brain morphological changes in obstructive sleep apnea. Neuroimage 54:787–793
20. Yaouhi K, Bertran F, Clochon P, Mézenge F, Denise P, Foret J, Eustache F, Desgranges B (2009) A combined neuropsychological and brain imaging study of obstructive sleep apnea. J Sleep Res 18:36–48
21. Cover KS, van Schijndel RA, van Dijk BW, Redolfi A, Knol DL, Frisoni GB, Barkhof F, Vrenken H, neuGRID; Alzheimer's Disease Neuroimaging Initiative (2011) Assessing the reproducibility of the SienaX and Siena brain atrophy measures using the ADNI back-to-back MP-RAGE MRI scans. Psychiatry Res 193:182–190
22. Sarchielli P, Presciutti O, Alberti A, Tarducci R, Gobbi G, Galletti F, Costa C, Eusebi P, Calabresi P (2008) A 1H magnetic resonance spectroscopy study in patients with obstructive sleep apnea. Eur J Neurol 15:1058–1064
23. Algin O, Gokalp G, Ocakoglu G, Ursavas A, Taskapilioglu O, Hakyemez B (2012) Neurochemical structural changes evaluation of brain in patients with obstructive sleep apnea syndrome. Eur J Radiol 81:491–495
24. Macey PM, Kumar R, Woo MA, Valladares EM, Yan-Go FL, Harper RM (2008) Brain structural changes in obstructive sleep apnea. Sleep 31:967–977
25. Wang Y, Guo SZ, Bonen A, Li RC, Kheirandish-Gozal L, Zhang SX, Brittian KR, Gozal D (2011) Monocarboxylate transporter 2 and stroke severity in a rodent model of sleep apnea. J Neurosci 31:10241–10248
26. Varley ZK, Pizzarelli R, Antonelli R, Stancheva SH, Kneussel M, Cherubini E, Zacchi P (2011) Gephyrin regulates GABAergic and glutamatergic synaptic transmission in hippocampal cell cultures. J Biol Chem 286:20942–20951
27. Fung SJ, Xi MC, Zhang JH, Sampogna S, Yamuy J, Morales FR, Chase MH (2007) Apnea promotes glutamate-induced excitotoxicity in hippocampal neurons. Brain Res 1179:42–50
28. Kheirandish L, Gozal D, Pequignot JM, Pequignot J, Row BW (2005) Intermittent hypoxia during development induces long-term alterations in spatial working memory, monoamines, and dendritic branching in rat frontal cortex. Pediatr Res 58:594–599