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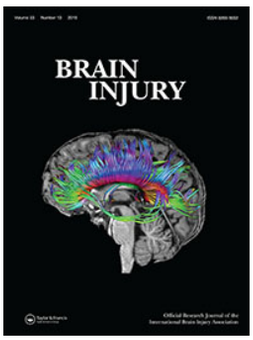

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Case report: neuroimaging analysis of pediatric ADHD-related symptoms secondary to hypoxic brain injury

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ABSTRACT

A 2-year-old male pediatric patient experienced a partial occlusion of the internal carotid and subsequent asphyxiation resulting in hypoxic brain injury that was later misdiagnosed as primary attention deficient hyperactivity disorder (ADHD). Imaging analyses using diffusion tensor imaging (DTI), positron emission tomography (PET), and magnetic resonance imaging (MRI) quantitative volumetrics (QV) were used nine years following the incident to identify whether his development of ADHD is of a primary heritability or secondary hypoxic brain injury sequelae. The patient's DTI analysis generated decreases in fractional anisotropy (FA) values in the anterior corpus callosum, bilateral internal capsule, and hippocampus. Decreases in FA are seen in ADHD patients, but the degree of FA decrease in the patient under study is several orders of magnitude greater than in ADHD patients. Also, not normally observed in ADHD patients were decreases in the metabolism of the orbitofrontal cortex, anterior cingulate, left anterior insular cortex, and left striatum. Additionally, QV showed enlargements of various regions of the brain including the amygdala which is often cited in the literature to be reduced in ADHD patients. The diagnosis of this patient despite having non-characteristic neuroimaging data suggests a unique specificity of the hypoxic injury to the development of a secondary hypoxic brain injury caused ADHD.

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Attention deficit hyperactivity disorder; diffusion tensor imaging; positron emission tomography; quantitative volumetrics; hypoxic brain injury

Introduction

Attention deficient hyperactivity disorder (ADHD) is characterized by abnormal expression of inattention, hyperactivity, and impulsivity by which three subtypes are defined by predominant inattention, hyperactivity/impulsivity, or a combined subtype of inattention and hyperactivity/impulsivity (1). It is a psychiatric disorder of heterogeneous etiology of which the exact cause has been extensively researched and debated(2). Detection of ADHD is possible through neuroimaging techniques that structural and functional characteristics of the brain. Positron emission tomography (PET) utilizes the injection of a radioactive isotope often bound to glucose that acts as a tracer. The radioactive glucose diffuses across the blood–brain barrier and can be used to trace and measure the activity of the brain as a function of glucose metabolic activity and cerebral perfusion (3). Diffusion Tensor Imaging (DTI) is another noninvasive technique of detecting the translational motion of water molecules to generate a functional mapping of the connectivity of the brain (4). The mapping is suggestive of white matter structure and provides insight on axonal characteristics primarily axonal branching and myelination DTI techniques measure indexes of fractional anisotropy (FA) which greater values indicate decreased axonal arborization or bundle density. A quantitative approach or quantitative volumetrics (QV) for magnetic resonance imaging (MRI) data uses statistical analysis to interpret brain region volumes. These neuroimaging techniques have applications for detecting significant findings in ADHD patients. The current literature suggests a large multitude of regions that are affected in children with ADHD. In PET and DTI techniques, most are seen within the areas involved with the frontostriatal circuit, and volumetric data are typical of decreases in hippocampus, accumbens, putamen, amygdala, and caudate volumes (5–7).

The development of ADHD is influenced by biological (heritable) and environmental (non-heritable) risk factors. A challenge is presented in a patient that was diagnosed with ADHD, but its cause is not clearly indicated by the diagnosis of the patient's father's ADHD or the hypoxic incident from which the patient's partial occlusion of left internal carotid at two years old. Hypoxic brain injury is a possible environmental risk factor for ADHD but is not as strongly supported by the scientific literature as traumatic brain injury (TBI) is (8). There is a small selection of research completed relating decreased cerebral perfusion induced by hypoxic obstructive sleep apnea seen in children to correlate with developmental issues related to ADHD symptoms (9,10). However, there is a lack of data associating ADHD as sequelae from an acute hypoxic event. This case report provides a new perspective on how pediatric ADHD and potential causes from brain injury manifests in neuroimaging data and how they relate to or differ from the current ADHD findings.

Patient information

In mid-2006, a 2-year-old boy wandered from the supervision of a daycare facility where a car window left ajar

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caught his attention. The crevice created by the opened car window allowed enough clearance for the patient to insert his head where he was found dangling from the neck. Bystanders found patient HR suffocated, removed him from the car window, and performed CPR. EMS personnel later arrived on scene notating his apneic and unresponsive condition and initiated treatment and transport. The patient resumed spontaneous breathing of 6 respirations per minute after being provided 6–8 ventilations through a bag valve mask. A nasopharyngeal airway was administered for the patient and BVM ventilations continued. Initial assessment of the patient presented with a decreased oxygen saturation, clenched teeth that interfered with the administration of an oropharyngeal airway, and a more dilated right pupil with more delayed reactivity to light than the left pupil. General physical assessment presented with 'rash type' trauma marks on the anterior neck of the patient. Other areas of patient assessment performed by EMS were within normal/functional limits and breathing stabilized to normal ranges by admission at the appropriate facility. Also noted when admitted into the ER was the patient's decorticate posturing.

In 2008, the patient was administered a variety of tests to address concerns of inattentiveness, hyperactivity, and emotional impulsiveness from which he was diagnosed with ADHD and was prescribed psychostimulants. For behavioral measures, the Scales of Independent Behavior (SIB-R) assessment was provided and noted a total score of 90 placing the patient at the 25th percentile. Relevant observational findings noted frequent side to side movement while seated and extraneous concern with minor details.

His father was also diagnosed with ADHD and no other pertinent medical history related to the patient's development of ADHD was noted.

Clinical findings

In 2015, neuroimaging scans of varying methods were obtained from the patient and revealed a collection of significant differences compared to control groups (Figures 1–2). Fifteen controls were used for the PET scans and 42 controls from the Function Biomedical Informatics Research Network (FBIRN) data repository were used for the DTI scans (11). The PET data from the patient presents with decreases in metabolism in various areas of the brain (Table 1). In the more anterior portions of the brain, decreases were found in the orbitofrontal cortex and the anterior cingulate (orbitofrontal cortex, $P = .01$; anterior cingulate, $P = .02$). Other decreases were found on the left side of the brain in the anterior temporal insular cortex and striatum of the internal capsule (anterior temporal insular cortex, $P = .01$; striatum, $P = .0007$). The second set of PET scans that were taken for

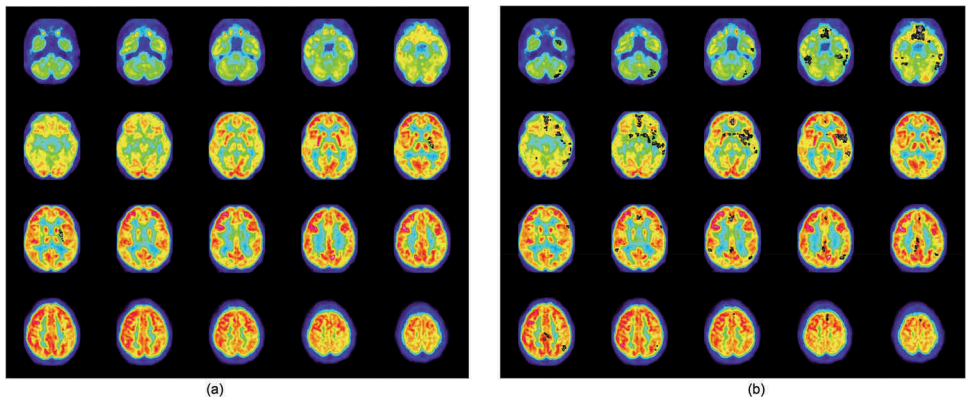

Figure 1. PET Z-map displaying the patient's PET images from the transaxial view with an overlay of results that are significantly higher (a) and significantly lower (b) than controls.

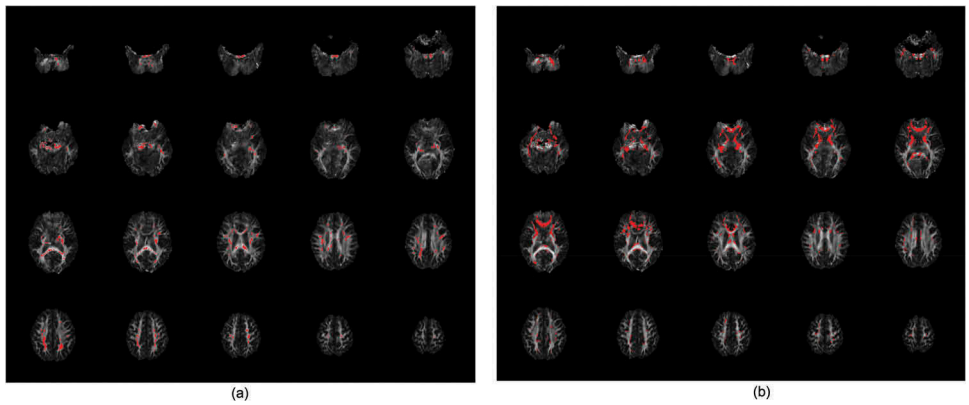

Figure 2. DTI Z-map displaying the patient's DTI images from the transaxial view with an overlay of results that are significantly higher (a) and significantly lower (b) than controls.

Table 1. Table showing the PET values that are significantly lower than controls (note negative Z-scores).

ROI	Patient	Control mean	SD	Z-score	*P*-value
Orbitofrontal cortex	1.05	1.28	0.10	−2.27	2.3×10^{-2}
Anterior cingulate	1.28	1.54	0.11	−2.27	2.3×10^{-2}
Left anterior insular cortex	0.76	0.98	0.09	−2.45	1.4×10^{-2}
Left striatum	1.15	1.50	0.10	−3.40	6.7×10^{-4}

the patient five months following the primary PET scan date corroborates the primary PET scans (Supplemental Figure 1). DTI findings presented with decreased FA in the anterior corpus callosum, bilateral internal capsule, and left optic radiation (Table 2; anterior corpus callosum, $P = 4.4\text{x}10^{-33}$; left internal capsule; $P = 1.5\text{x}10^{-12}$; right internal capsule, $P = 4.4\text{x}10^{-14}$; left optic radiation, $P = 1.1\text{x}10^{-9}$). The volumetric data generated the volumes of various brain regions of the patient against 83 controls from the FBIRN data repository where the results communicate present enlargements from the left side of the brain in the forebrain parenchyma, cortical gray matter, amygdala, and hippocampus (Table 3). The statistical analysis observed for clinical significance within the patient across the controls using absolute volumes in addition to relative volumes as a function of how much a region occupies total intracranial volume.

Table 2. Table showing the DTI values in units of fractional anisotropy (FA) that are significantly lower than controls (note negative Z-scores).

ROI	Patient FA	Control mean	SD	Z-score	*P*-value
Anterior corpus callosum	0.29	0.62	0.028	−11.98	4.4×10^{-33}
Left internal capsule	0.18	0.44	0.037	−7.07	1.5×10^{-12}
Right internal capsule	0.20	0.43	0.031	−7.55	4.4×10^{-14}
Left optic radiation	0.29	0.56	0.046	−6.09	1.1×10^{-9}

To evaluate clinical findings with age-matched controls, the volumetric data was compared against pediatric controls with and without ADHD (Table 4). The findings communicate that the left hippocampus and left amygdala are significantly different from the respective right side in both control groups (12). The patient also presented with a significant difference from these healthy and ADHD pediatric controls. The neuroimaging data was of good technical quality and reliable for clinical analysis.

Diagnostic assessment

From the data sourced from brain imaging, the analysis was done by comparing the patient's neuroimaging data against controls. Regions of interest within the patient are then compared with notable areas of clinical significance found in the literature of pediatric ADHD. Because almost all the regions within the patient presenting with significant differences relative to controls groups did not agree with the neuroimaging data in the literature for ADHD but did agree with the neuroimaging data for hypoxia, the conclusion was drawn that the patient's apparent ADHD is secondary to his hypoxic incident and not due to primary ADHD.

A conclusion is also made that the case patient's regions of clinical significance and their degrees of FA decrease are consistent with hypoxic encephalopathy. However, this is drawn from case findings of a 76-year-old male with hypoxic encephalopathy against 10 healthy controls. Although the patients in this study and the hypoxic encephalopathy study exhibit extremely robust FA decreases, an issue with this

Table 3. Table showing the data that are significantly different than controls. Positive z-score denote values significantly higher than controls and negative z-scores denote values significantly lower than controls. Volumetric units are in mm3.

ROI	Patient volume	Control mean	Control SD	Z-score	*P*-value
Absolute volumes (mm^3)					
Left forebrain parenchyma	21.57	−8.74	9.02	3.36	7.8×10^{-4}
Right forebrain parenchyma	302.18	301.81	32.52	0.01	n.s.
Left-right forebrain parenchyma	293.06	304.65	31.32	−0.37	n.s.
Left cortical gray matter	302.18	301.81	32.52	0.01	n.s.
Right cortical gray matter	293.06	304.65	31.32	−0.37	n.s.
Left-right cortical gray matter	9.12	−2.84	6.76	1.77	n.s.
Left hippocampus	4.15	4.11	0.48	0.09	n.s.
Right hippocampus	3.02	4.14	0.47	−2.11	.03
Left-right hippocampus	1.13	−0.04	0.55	2.12	.03
Left amygdala	3.47	1.87	0.28	5.64	5.2×10^{-4}
Right amygdala	1.64	1.87	0.25	−0.91	n.s.
Left-right amygdala	1.83	0.01	0.15	12.13	7.3×10^{-34}
Left pallidum	0.86	1.04	0.16	−1.10	n.s.
Right pallidum	0.56	1.15	0.14	−4.31	1.6×10^{-5}
Left-right pallidum	0.3	−0.11	0.17	2.43	.02
Relative volumes (%)					
Left forebrain parenchyma	37.77	33.95	1.21	3.14	1.7×10^{-3}
Right forebrain parenchyma	36.19	34.45	1.34	1.3	n.s.
Left-right forebrain parenchyma	1.58	−0.5	0.49	4.25	2.0×10^{-5}
Left cortical gray matter	22.11	16.9	1.14	4.55	1.0×10^{-5}
Right cortical gray matter	21.44	17.08	1.22	3.56	3.7×10^{-4}
Left-right cortical gray matter	0.67	−0.17	0.37	2.3	2.0×10^{-2}
Left hippocampus	0.3	0.23	0.02	2.96	3.0×10^{-3}
Right hippocampus	0.22	0.23	0.03	−0.39	n.s.
Left-right hippocampus	0.08	0	0.03	2.69	7.0×10^{-3}
Left amygdala	0.25	0.11	0.01	13.42	4.6×10^{-41}
Right amygdala	0.12	0.1	0.01	1.26	n.s.
Left-right amygdala	0.13	0	0.01	12.97	1.8×10^{-38}
Left pallidum	0.06	0.06	0.01	0	n.s.
Right pallidum	0.04	0.07	0.01	−2.94	3.3×10^{-3}
Left-right pallidum	0.02	−0.01	0.01	2.57	1.0×10^{-2}

Table 4. Table showing data that are significantly lower than age-matched controls with and without ADHD. Positive z-score denote values significantly higher than controls and negative z-scores denote values significantly lower than controls.

Plessen controls analysis									
ROI	Patient	Pediatric control mean	Pediatric control SD	Z-score	*P*-score	Pediatric ADHD control mean	Pediatric ADHD control SD	Z-score	*P*-score
Left hippocampus	4.15	3.14	0.43	2.39	1.7×10^{-2}	3.36	0.38	2.08	3.7×10^{-2}
Right hippocampus	3.02	3.18	0.40	−0.39	n.s.	3.38	0.39	−0.92	n.s.
Left-right hippocampus difference*	1.13	−0.04		2.78	5.0×10^{-3}	−0.02		3.01	2.6×10^{-3}
Left amygdala	3.47	2.08	0.41	3.36	7.8×10^{-3}	2.03	0.41	3.55	3.9×10^{-4}
Right amygdala	1.64	2.10	0.42	−1.09	n.s.	2.07	0.38	−1.12	n.s.
Left-right amygdala difference*	1.83	−0.02		4.46	1.0×10^{-5}	−0.04		4.66	3.2×10^{-6}

*Left-right differences conservatively estimated by adding z-score differences of left and right hippocampus or amygdala.

referenced study is presented with a dramatic age gap between the two patients and having a small control group.

Regarding volumetric data, the literature states bilateral enlargement of the amygdala in the brain is characteristic of ADHD; thus, the patient's amygdala enlargement overlaps with the current findings of pediatric ADHD. However, because of the patient exhibits robust enlargement in the left amygdala, among the other enlarged left-sided regions, the clinical opinion concluded the patient's ADHD as not consistent with the typical presentations.

An issue with the accuracy of these assessments is that PET is expensive and generally limits the size of a demographically matched control group let alone a control group of preferred size. The DTI analysis experiences the same limitation as the appropriate controls are not selected. In the scope, if determining whether the patient's ADHD diagnosis was consistent with the development of ADHD or suspect of hypoxic brain injury sequelae, the ideal assessment would compare the patient's clinical findings against an age-matched and gender-matched clinical group with ADHD to statistically analyze whether the findings are consistent with controls.

However, the PET and DTI scans are considered to be within an acceptable degree of credibility. Regarding PET analysis, glucose uptake values are found to be greater in children than in adults implying that analysis of significant differences would be populated with less significantly higher values and more significantly lower values if generated with age-matched controls (13). This caveat increases our likeliness of type I error when analyzing for significantly higher values and type II error when analyzing for significantly lower values. Because PET analysis of the patient's brain generated primarily negative values, the confidence level for these contrasts is considered to have a greater than if compared to age-matched controls. With respect to the corpus callosum, FA values in children older than 25 months do not significantly differ from values from adults suggesting credibility to the use of nonage-matched controls for DTI analysis (14).

This model was used in a makeshift assessment comparing QV data from the patient's left and ride sides of the hippocampus and amygdala against those of pediatric patients with and without ADHD. However, because the volumes for these regions were not available for each individual patient, an accurate Z-score for the statistical analysis of the patient against these groups questionably valid as an accurate SD could not be obtained. A *P*-value for these patients was improvised by taking the differences in Z-scores and using the resulting value as the Z-score for the differences between the left and right sides of the hippocampus and amygdala. Because the individual volumes for the Plessen controls were available, *P*-values for region differences were obtained by taking the differences between the Z-scores of the left and right sides of a region. The availability of this data would generate a more accurate analysis of Z-score and *P*-value, however, the current analysis of data is considered valid.

The patient's PET findings overlap with typical ADHD presentations, but because the patient's DTI and QV findings are grossly inconsistent with ADHD literature, the summation of neuroimaging analyses concludes that the patient's neuropsychological profile is secondary to hypoxic brain injury.

Discussion

Brain injury due to hypoxia triggers cell death and, in the case of traumatic brain injury (TBI), increases the risk of developing secondary injury (15,16). Limited data is available regarding the likeliness of non-traumatic brain injury sequelae, but its propensity to develop secondary abnormalities remains as it similarly affects brain function and structure as traumatic brain injury does. From the immediate assessments performed following the hypoxic incident, brain injury is implicated and thus increases the index of suspicion for developing a secondary injury.

The nature of suffocation is dangerous to the brain because a loss of consciousness is indicative of a lack of crucial oxygen to the brain. Additional to the patient's condition of 'unresponsive' upon arrival of EMS personnel, BVM ventilations were administered as indicated by apnea. The apnea increases the suspicion of brain injury because the areas that regulate autonomic respiration located in the brainstem are impaired.

Additionally, the assessment of the pupillary light reflex is used to suggest the brain's condition. By shining a light into an eye at a time, afferent signals of an eye are sent to the ipsilateral pretectal nucleus in the midbrain. From the pretectal nuclei, contralateral and ipsilateral projections reach the Edinger-Westphal nuclei also in the midbrain. These neurons synapse onto the ciliary ganglia via the oculomotor nerve, and the post-ganglionic projections innervate the iris sphincter muscles to contract the iris. Because of the description of the patient's right pupil as 'sluggish' and more dilated than the left pupil, damage to the patient's left pretectal nuclei is suggested and would be consistent with the left-sided nature

of the abnormalities noted on the MRI DTI and the PET. The suspected areas involve the neurons of the Edinger-Westphal nuclei and the projections of the pretectal nuclei.

Also noted on the patient's vitals from EMS assessment was decorticate posturing which indicates suspected lesions to the cerebral hemisphere white matter, internal capsule, and thalamus (17).

Damage to the neurons, such as from a suffocation incident, has a propensity to change neuronal characteristics. Because of the incident in 2006 leading to developmental abnormalities in 2015 scans. One of which is synaptic pruning, an important process in development that reduces the presence of excess dendritic and axonal arborizations and is the mechanism that is suspected to have been altered from acute hypoxia (18). The purpose of synaptic pruning is to reduce the number of unnecessary synapses and neurons, a process that improves neuronal efficiency and increases networking capacity or the brain (19). Continuous interference with this process within the brain would result in enlarged neurons that has been detected in the patient's clinical findings as well as possible behavioral abnormalities (ROIs). The suspicion that the synaptic pruning process is hampered due to hypoxia also suggests that other maintaining processes of the brain are vulnerable to hypoxic brain injury sequelae. This would suggest an increased risk of neurodegenerative diseases such as dementia, Alzheimer's disease, and Parkinson's disease as is the case with traumatic brain injury (20).

In other hypoxic injuries, a study was conducted on pediatric patients with chronic obstructive sleep apnea. The study showed that chronic hypoxic sleep apnea correlated with a higher risk of developing attention-deficit and ADHD-related symptoms. Neuroimaging data on these patients can extrapolate further interpretation of the role of hypoxia in the developmental phases. However, based on the current data regarding hypoxic injury in the developmental phase, the patient in question who suffered an acute hypoxic event could be reflecting the development of ADHD-related symptoms as the pediatric patients with chronic hypoxic sleep apnea have.

Conclusion

A 2-year-old male patient presents with developmental pathologies that mimic ADHD symptoms due to a partial occlusion of the left internal carotid and subsequent asphyxiation incident that left him apneic and unresponsive. The incident presented with clear brain injury due to hypoxia which led to secondary characteristics that can be seen in PET, DTI, and QV analyses. Clinical findings demonstrated that the patient's neuroimaging data does not reflect ADHD characteristics although conventional ADHD evaluations determined so. Further explanation suggests a possible mechanism to how hypoxia alters neuronal characteristics during development and leads to sequelae. Additional research into brain injury can expand on this case patient by exploring the incidences of non-traumatic brain injury, particularly hypoxia, for secondary developments.

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Declaration of interest

The authors report no declaration of interest.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Fifth. Arlington (VA): American Psychiatric Publishing; 2013. p. 59–65.
2. Thapar A, Cooper M, Eyre O, Langley K. Practitioner review: what have we learnt about the causes of ADHD? J Child Psychol Psychiatry. 2013; 54(1):3–16. doi:10.1111/j.1469-7610.2012.02611.x.
3. Zimmer L. Positron emission tomography neuroimaging for a better understanding of the biology of ADHD. Neuropharmacology. 2009 Dec;57(7–8):601–07. doi:10.1016/j.neuropharm.2009.08.001.
4. Mori S, Zhang J. Principles of diffusion tensor imaging and its applications to basic neuroscience approach. Neuron. 2006;51 (5):527–39. doi:10.1016/j.neuron.2006.08.012.
5. Ashtari M, Kumra S, Bhaskar SL, Clarke T, Thaden E, Cervellione KL, Rhinewine J, Kane JM, Adesman A, Milanaik R, et al. Attention-deficit/hyperactivity disorder: a preliminary diffusion tensor imaging study. Biol Psychiatry. 2005 Mar 1;57 (5):448–55. doi:10.1016/j.biopsych.2004.11.047.
6. Mahone EM. ADHD: volumetry, motor, and oculomotor functions. In: Stanford C, Tannock R, editors. Behavioral neuroscience of attention deficit hyperactivity disorder and its treatment. Current topics in behavioral neurosciences. Vol. 9. Berlin, Heidelberg (Germany): Springer; 2004. p. 17–46.
7. Hoogman M, Bralten J, Hibar DP, Mennes M, Zwiers MP, Schweren L, van Hulzen K, Medland SE, Shumskaya E, Jahanshad N, et al. Subcortical brain volume differences of participants with ADHD across the lifespan: an ENIGMA collaboration. Lancet Psychiatry. 2017;4(4):310–19. doi:10.1016/S2215-0366(17)30049-4.
8. Adeyemo BO, Biederman J, Zafonte R, Kagan E, Spencer TJ, Uchida M, Kenworthy T, Spencer AE, Faraone SV. Mild traumatic brain injury and ADHD: a systematic review of the literature and meta-analysis. J Atten Disord. 2014 Oct;18(7):576–84. doi:10.1177/1087054714543371.
9. Bålfors EM1, KA F. Impairment of cerebral perfusion during obstructive sleep apneas. Am J Respir Crit Care Med. 1994 Dec;150(6 Pt 1):1587–91. doi:10.1164/ajrccm.150.6.7952619.
10. Halbower AC, Degaonkar M, Barker PB, Earley CJ, Marcus CL, Smith PL, Prahme MC, Machone EM. Childhood obstructive sleep apnea associates with neuropsychological deficits and neuronal brain injury. Walsh J, editor. PLoS Med. 2006;3(8):e301. doi:10.1371/journal.pmed.0030301.
11. Keator DB, van Erp TG, Turner JA, Glover GH, Mueller BA, Liu TT, Voyvodic JT, Rasmussen J, Calhoun VD, Lee HJ, et al. The function biomedical informatics research network data repository. NeuroImage. 2016;124(Pt B):1074–79. doi:10.1016/j.neuroimage.2015.09.003.
12. Plessen KJ, Bansal R, Zhu H, Whiteman R, Amat J, Quackenbush GA, Martin L, Durkin K, Blair C, Royal J, et al. Hippocampus and Amygdala morphology in attention-deficit/hyperactivity disorder. Arch Gen Psychiatry. 2006;63(7):795–807. doi:10.1001/archpsyc.63.7.795.
13. Chugani HT, Phelps ME, Mazziotta JC. Positron emission tomography study of human brain functional development. Ann Neurol. 1987; 22(4):487–97. doi:10.1002/ana.410220408.
14. Cancelliere A, Mangano FT, Air EL, Jones BV, Altaye M, Rajagopal A, Holland SK, Hertzler DA, Yuan W. DTI values in

key white matter tracts from infancy through adolescence. AJNR Am J Neuroradiol. 2013; 34(7):1443–49. doi:10.3174/ajnr.A3350.
15. Sendoel A, Hengartner MO. Apoptotic cell death under hypoxia. Physiology (Bethesda). 2014 May;29(3):168–76. doi:10.1152/physiol.00016.2013.
16. Rabinowitz AR, Levin HS. Cognitive sequelae of traumatic brain injury. Psychiatr Clin North Am. 2014; 37(1):1–11. doi:10.1016/j.psc.2013.11.004.
17. Elovic E, Edgardo B, Cuccurullo S. Traumatic brain injury. In: Cuccurullo SJ, editor. Physical medicine and rehabilitation board review. New York (New York): Demos Medical Publishing; 2004. p. 54–55.
18. Tang G, Gudsnuk K, Kuo SH, Cotrina ML, Rosoklija G, Sosunov A, Sonders MS, Kanter E, Castagna C, Yamamoto A, et al. Loss of mTOR-dependent macroautophagy causes autistic-like synaptic pruning deficits. Neuron. 2014;83(5):1131–43. doi:10.1016/j.neuron.2014.07.040.
19. Paolicelli RC, Bolasco G, Pagani F, Maggi L, Scianni M, Panzanelli P, Giustetto M, Ferreira TA, Guiducci E, Dumas L, et al. Synaptic pruning by microglia is necessary for normal brain development. Science. 2011 Sep 9;333(6048):1456–58. doi:10.1126/science.1202529.
20. Mckee AC, Daneshvar DH. The neuropathology of traumatic brain injury. Handb Clin Neurol. 2015;127:45–66. DOI:10.1016/B978-0-444-52892-6.00004-0.