ENCYCLOPEDIA
on Early Childhood
Development

ADHD and Neuroscience

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Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a highly prevalent childhood neuropsychiatric condition, estimated to affect 5%-10% of school-age children worldwide.[1] Because of ADHD core symptoms and frequently associated psychiatric comorbidities, individuals with ADHD are at risk for cognitive, academic, behavioural, emotional, and social functioning.1 Therefore, ADHD exacts an enormous psychosocial and psychiatric burden on the individual, their family and the community.[2]

Problems

- Currently, ADHD is diagnosed according to a set of behavioural criteria,[1] fostering controversy because of the subjective nature of the diagnosis.
- Individuals with ADHD are heterogeneous from a phenomenological standpoint, leading to confusion in clinical as well as in research settings.

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- The expression of symptoms varies with the child's developmental stage and social and academic contexts.[3]
- Current classification does not consider developmental variations in symptoms sufficiently.
- No long-term curative treatments are currently available.[4]
- Medication choice remains based on personal experience and empirical trials.[4]

Subject

Insights from the emerging field of pediatric neuroscience are beginning to provide foundations for delineating the physiological principles of brain function and dysfunction.[5] These advances are expected to lead to objective characterization of patients with more precisely defined "presentations" of ADHD and to the eventual development of effective physiopathology-based treatments *en route* to precision psychiatry.[6]

Research Context

The most fruitful contributions to understanding ADHD are likely to derive from a multidisciplinary translational research framework including physiology, psychology, neurology, psychiatry, bioinformatics, neurogenetics, cellular and molecular biology, and systems neuroscience.

Key Research Questions

Among the issues amenable to investigation by neuroscience methods, the following are pivotal:

1. Is the brain of individuals with ADHD morphologically different from non-ADHD controls?
2. Does the brain of individuals with ADHD function differently?
3. Does brain neurochemistry differ in ADHD?
4. What are the causes of the underlying dysfunctions?
5. What are the developmental pathways of abnormal brain structure and function?

Recent Research Results

1) Is the brain of individuals with ADHD morphologically different?

Large-scale neuroimaging studies have begun to address brain structure in ADHD with appropriate statistical power. The Enhancing Neuro-Imaging Genetics Through Meta-Analyses (ENIGMA) consortium compared 1713 patients with ADHD to 1429 healthy participants and found a significantly smaller intracranial volume (Cohen's d=-0.10) in ADHD after adjusting for sex, age, and site.[7] Additionally, smaller volumes, at the group level, were found in the ADHD group in amygdala (d=−0.19), accumbens (d=−0.15), caudate (d=−0.11), hippocampus (d=−0.11), and putamen (d=−0.11) even after adjusting for covariates including intracranial volume.

In a subsequent ENIGMA-ADHD study comprising 36 centers, lower cortical surface area values were found, especially in the frontal, cingulate and temporal regions; total surface area yielded the largest effect (Cohen's d=-0.21). Fusiform gyrus and temporal pole cortical thickness were also lower than in controls.[8]

Traditional voxel-based morphometry meta-analyses have revealed reduced gray matter volume in ventromedial orbitofrontal cortex and right basal ganglia including globus pallidus, putamen and caudate.[9,10]

A meta-analysis of diffusion tensor imaging studies found both higher and lower fractional anisotropy in multiple white matter (WM) tracts (right inferior fronto-occipital fasciculus, left inferior longitudinal fasciculus) with atypical interhemispheric connection in the corpus callosum being the most common finding.[11]

Does the brain of individuals with ADHD function differently?

The functional imaging literature on ADHD is too voluminous to be systematically explored here. We report results of the main available systematic review/meta-analyses.

A meta-analysis of 55 task-based fMRI studies using inhibitory control, working memory, and attention tasks reported underactivation of the frontostriatal, frontoparietal, and ventral attention networks, and hyperactivation of the somatomotor and visual systems.[12] Interestingly, these findings mirror, in general, the anatomy implicated by structural imaging studies.

Also, impaired functional abnormalities in the default mode network[13] and the cingulo-opercular network[14] have also been reported in individuals with ADHD. A recent longitudinal study showed that worse response to stimuli was significantly associated with an atypical increase in cingulo-

opercular resting-state functional connectivity with increasing age.[15] Stimulants are thought to have a role in stabilizing these networks.

Meta-analyses of EEG data also found differences in ADHD such as elevation in the theta/beta ratio[16] and age-related differences in slow wave activity which were significantly higher in early childhood and lower in late childhood/adolescence in ADHD vs. controls, with an inversion point at 10 years of age.[17]

Taken together, the structural and functional findings suggest widespread anomalies encompassing multiple brain structures and atypical functional connectivity affecting multiple large-scale brain networks.

2) Does brain neurochemistry differ in ADHD?

Empirical findings from neurobiological studies suggest that, rather than changes in any neurotransmitter system at the molecular level, the disorder has been linked to dysfunctions in various systems, including dopaminergic, adrenergic, serotonergic, and cholinergic pathways.[18]

In addition, magnetic resonance spectroscopy studies have shown altered glutamatergic signaling (glutamate, glutamine, and GABA) in frontostriatal pathways.[19]

3) What are the causes of the supposed dysfunctions?

ADHD is highly heritable (heritability ~0.74)[20] with many genetic and environmental risk factors likely contributing. The first genome-wide significant loci has identified several genetic variants, each with a small effect on the risk for ADHD.[21] A recent meta-analysis implicated several risk genes (ADGRL3, ANKK1, BAIAP2, DAT1, DRD4, LRP5, LRP6, and SNAP25) although their mechanisms remain unclear.[22]

A meta-analysis classified environmental correlates of ADHD as 1) exposure to toxic substances (lead, maternal smoking, maternal use of acetaminophen or valproate, etc.), 2) nutrient deficiencies (iron, omega-3, vitamin D, etc.), 3) events during pregnancy and birth (preterm or low birth weight) and 4) deprivation, infection, poverty, stress, and trauma,[22] although these factors are contributory, not diagnostic.

4) What are the developmental pathways of brain abnormalities?

A meta-analysis showed that the most prominent and reproducible structural abnormalities in ADHD are located in the basal ganglia.[23] Structural changes are particularly pronounced in untreated populations.[24] A relationship among the effect of advancing age, the use of stimulant drugs and normalization of structural abnormalities has been suggested.[23] However, a follow-up study revealed abnormalities in white matter tracts which connect various regions involved in sensorimotor and higher-level cognitive functions, regardless of remission status in adulthood.[25]

In addition, the absence of childhood-ADHD history in 90% of adult-ADHD cases[26] has led to questioning the syndromic nature of adult-ADHD and its continuity with the neurodevelopmental disorder.[27]

Research Gaps

- How are structural and functional connectivity abnormalities related?
- At which developmental stages do disruptions in neural networks first emerge and manifest clearly?
- How best can the interactions of genes and environmental (biopsychosocial) variables be understood?
- How do various etiological factors lead to neural anomalies?
- How to conceptualize emotion dysregulation in ADHD?
- What are the potential benefits of pathophysiology-based interventions?
- Is there a clear cut-off on the transdiagnostic diagnosis of ADHD-brain relationships? Can machine learning algorithms capture specific dimensions of ADHD-related psychopathology in neuroimaging datasets?

Conclusions

Insights from neuroscience have unequivocally shown that the brains of children with ADHD differ from those of healthy comparisons. Research on the neurobiological bases of ADHD seeks to provide a better understanding of brain circuit changes associated with etiology, pathophysiology, and treatment response, and to develop illness-specific neural therapy targets. Particularly important are multimodal approaches and mega-analyses that integrate genetic, imaging, and phenotypic data. These reflect the increasing adoption of both open science and best reporting practices.

Although technical and methodological obstacles remain, the genetic bases of dysfunctions in ADHD and the interacting environmental factors are increasingly coming into focus. Challenging and expensive longitudinal studies have begun to yield insights into the developmental pathways of brain abnormalities and their relationships with ADHD symptoms. As these elements become clearer, the field will be better able to design etiopathophysiologically-based interventions for ADHD with the potential for long-term effectiveness.

Implications for Parents, Services and Policy

Although neuroscience has helped to advance our knowledge of the etiopathophysiology of ADHD, so far we have not found sensitive and specific neurobiological markers. However, research in this field has mainly begun to take a “group-level approach”; normative modeling can bring the field forward in terms of precision psychiatry.[28]

Future work will primarily focus on the biological and cognitive features of the disorder,[29] improving behavioural diagnosis of ADHD and setting the stage for new treatments supported by biomarker technologies in the long term, as described in the Research Domain Criteria project of the US National Institute of Mental Health.[30] The dimensional approach provides the basis for a broader assessment of the child's potential needs and strengths, and is intended to facilitate linking behaviours and symptoms to underlying brain mechanisms and neuronal circuits. These ambitious goals will not be attained rapidly. In the interim, practitioners and parents must continue to collaborate to understand and support each child’s development, with the goal of minimizing the most pernicious sequelae of ADHD, particularly during adolescence.[31]

References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM–5)*. 5th ed. American Psychiatric Association; 2013.

2. Harpin VA. The effect of ADHD on the life of an individual, their family, and community from preschool to adult life. *Archives of Disease in Childhood*. 2005;90(suppl 1):i2-i7. doi:10.1136/ADC.2004.059006

3. Faraone SV, Asherson P, Banaschewski T, Biederman J, Buitelaar JK, Ramos-Quiroga JA, Rohde LA, Sonuga-Barke EJ, Tannock R, Franke B. Attention-deficit/hyperactivity disorder.

Nature Reviews. Disease Primers 2015;1:15020. doi:10.1038/nrdp.2015.20

4. Cortese S. Pharmacologic treatment of attention deficit–hyperactivity disorder. Ropper AH, ed. *The New England Journal of Medicine*. 2020;383(11):1050-1056. doi:10.1056/NEJMra1917069

5. Castellanos FX. A biased perspective on brain imaging of ADHD. *American Journal of Psychiatry*. 2021;178(8):694-700. doi:10.1176/appi.ajp.2021.21060609

6. Cortese S. Setting the foundations of developmental precision psychiatry for ADHD. *American Journal of Psychiatry*. 2021;178(8):677-679. doi:10.1176/appi.ajp.2021.21050549

7. Hoogman M, Bralten J, Hibar DP, et al. Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis. *The Lancet Psychiatry*. 2017;4(4):310-319. doi:10.1016/S2215-0366(17)30049-4

8. Hoogman M, Muetzel R, Guimaraes JP, et al. Brain imaging of the cortex in ADHD: a coordinated analysis of large-scale clinical and population-based samples. *American Journal of Psychiatry.* 2019;176(7):531-542. doi:10.1176/APPI.AJP.2019.18091033

9. Lukito S, Norman L, Carlisi C, Radua J, Hart H, Simonoff E, Rubia K. Comparative meta-analyses of brain structural and functional abnormalities during cognitive control in attention-deficit/hyperactivity disorder and autism spectrum disorder. *Psychological Medicine.* 2020;50(6):894-919. doi:10.1017/S0033291720000574

10. Nakao T, Radua J, Rubia K, Mataix-Cols D. Gray matter volume abnormalities in ADHD: voxel-based meta-analysis exploring the effects of age and stimulant medication. *American Journal of Psychiatry*. 2011;168(11):1154-1163. doi:10.1176/appi.ajp.2011.11020281

11. Aoki Y, Cortese S, Castellanos FX. Research Review: Diffusion tensor imaging studies of attention-deficit/hyperactivity disorder: meta-analyses and reflections on head motion. *Journal of Child Psychology and Psychiatry, and Allied Disciplines.* 2018;59(3):193-202. doi:10.1111/JCPP.12778

12. Cortese S, Kelly C, Chabernaud C, Proal E, Di Martino A, Milham MP, Castellanos FX. Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. *American Journal of Psychiatry*. 2012;169(10):1038-1055. doi:10.1176/appi.ajp.2012.11101521

13. Sutcubasi B, Metin B, Kurban MK, Metin ZE, Beser B, Sonuga-Barke E. Resting-state network dysconnectivity in ADHD: A system-neuroscience-based meta-analysis. *The World Journal of Biological Psychiatry*. 2020;21(9):662-672. doi:10.1080/15622975.2020.1775889

14. Cortese S, Aoki YY, Itahashi T, Castellanos FX, Eickhoff SB. Systematic review and meta-analysis: resting-state functional magnetic resonance imaging studies of attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2021;60(1):61-75. doi:10.1016/j.jaac.2020.08.014

15. Norman LJ, Sudre G, Bouyssi-Kobar M, Sharp W, Shaw P. A longitudinal study of resting-state connectivity and response to psychostimulant treatment in ADHD. *American Journal of Psychiatry*. 2021;178(8):744-751. doi:10.1176/appi.ajp.2021.20091342

16. Arns M, Conners CK, Kraemer HC. A decade of EEG Theta/Beta Ratio Research in ADHD: A Meta-Analysis. *Journal of Attention Disorders.* 2012;17(5):374-383. doi:10.1177/1087054712460087

17. Biancardi C, Sesso G, Masi G, Faraguna U, Sicca F. Sleep EEG microstructure in children and adolescents with attention deficit hyperactivity disorder: a systematic review and meta-analysis. *Sleep*. 2021;44(7). doi:10.1093/sleep/zsab006

18. Cortese S. The neurobiology and genetics of Attention-Deficit/Hyperactivity Disorder (ADHD): What every clinician should know. *European Journal Of Paediatric Neurology*. 2012;16(5):422-433. doi:10.1016/j.ejpn.2012.01.009

19. Naaijen J, Lythgoe DJ, Amiri H, Buitelaar JK, Glennon JC. Fronto-striatal glutamatergic compounds in compulsive and impulsive syndromes: A review of magnetic resonance spectroscopy studies. *Neuroscience & Biobehavioral Reviews* 2015;52:74-88. doi:10.1016/j.neubiorev.2015.02.009

20. Faraone SV, Larsson H. Genetics of attention deficit hyperactivity disorder. *Molecular Psychiatry*. 2018;24(4):562-575. doi:10.1038/s41380-018-0070-0

21. Demontis D, Walters RK, Martin J, et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nature Genetics*. 2018;51(1):63-75. doi:10.1038/s41588-018-0269-7

22. Faraone S V., Banaschewski T, Coghill D, et al. The World Federation of ADHD International Consensus Statement: 208 Evidence-based conclusions about the disorder. *Neuroscience & Biobehavioral Reviews* 2021;128:789-818. doi: 10.1016/j.neubiorev.2021.01.022

23. Nakao T, Radua J, Rubia K, Mataix-Cols D. Gray matter volume abnormalities in ADHD: voxel-based meta-analysis exploring the effects of age and stimulant medication. *American Journal of Psychiatry*. 2011;168(11):1154-1163. doi:10.1176/appi.ajp.2011.11020281

24. Frodl T, Skokauskas N. Meta-analysis of structural MRI studies in children and adults with attention deficit hyperactivity disorder indicates treatment effects. *Acta Psychiatrica Scandinavica*. 2012;125(2):114-126. doi:10.1111/j.1600-0447.2011.01786.x

25. Cortese S, Imperati D, Zhou J, et al. White matter alterations at 33-year follow-up in adults with childhood attention-deficit/hyperactivity disorder. *Biological Psychiatry*. 2013;74(8):591-598. doi:10.1016/j.biopsych.2013.02.025

26. Moffitt TE, Houts R, Asherson P, et al. Is Adult ADHD a Childhood-Onset Neurodevelopmental Disorder? Evidence From a Four-Decade Longitudinal Cohort Study. *American Journal of Psychiatry.* 2015;172(10):967-977. doi:10.1176/appi.ajp.2015.14101266

27. Castellanos FX. Is adult-onset ADHD a distinct entity? *American Journal of Psychiatry*. 2015;172(10):929-931. doi:10.1176/appi.ajp.2015.15070988

28. Marquand AF, Rezek I, Buitelaar J, Beckmann CF. Understanding heterogeneity in clinical cohorts using normative models: beyond case-control studies. *Biological Psychiatry*.

2016;80(7):552-561. doi:10.1016/j.biopsych.2015.12.023

29. Cortese S, Coghill D. Twenty years of research on attention-deficit/hyperactivity disorder (ADHD): looking back, looking forward. *Evidence-Based Mental Health*. 2018;21(4):173-176. doi:10.1136/ebmental-2018-300050

30. Insel TR. The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. *American Journal of Psychiatry*. 2014;171(4):395-397. doi:10.1176/APPI.AJP.2014.14020138

31. Klein RG, Mannuzza S, Olazagasti MAR, et al. Clinical and functional outcome of childhood attention-deficit/hyperactivity disorder 33 years later. *Archives of General Psychiatry*. 2012;69(12):1295. doi:10.1001/archgenpsychiatry.2012.271