ADHD and Neuroscience

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Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a highly prevalent childhood neuropsychiatric condition estimated to affect 3 to 7% of school-age children worldwide.[1] Because of ADHD symptoms and frequently associated psychiatric comorbidities, individuals with ADHD are at risk for family conflict, poor peer relationships and academic/work failure. Therefore, ADHD exacts an enormous burden on society.[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 may differ in the clinical presentation, leading to confusion in clinical as well as in research settings.
- Current classification does not account for developmental variations in symptoms.
- No long-term curative treatments are currently available.[3]

Subject

Insights from the emerging field of pediatric neuroscience are required to transition from a classification based on the clinical description of symptoms toward a model based on the causes of the disorder. Such mechanistic models are expected to lead to objective characterization of patients with more precisely defined subtypes of ADHD and to the eventual development of effective physiopathology-based treatments.

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:

- Is the brain of individuals with ADHD morphologically different from non-ADHD controls?
- Does the brain of individuals with ADHD function differently?
- Does brain neurochemistry differ in ADHD?
- What are the causes of the supposed dysfunctions?
- What are the developmental pathways of brain abnormalities?

Recent Research Results

Is the brain of individuals with ADHD morphologically different?

Early structural *MRI* (Magnetic Resonance Imaging) studies have reported several significant morphological differences in ADHD vs. controls, although the findings have not always been consistent.[4] A meta-analysis[5] demonstrated that the brain regions showing the largest area or volumetric reductions in ADHD vs. controls include some specific regions of the brain involved in movement control and organization, as well as the total and right cerebral volume. However, most of these studies were based on a region-of-interest approach with an undue concentration on relatively few and easily measurable cerebral structures. A more recent meta-analysis[6] of *voxel-based morphometric* studies (which are spatially unbiased) found that only right *putamen* volume loss was significant across studies, although this conclusion remains tentative given the limited number (seven) of available studies. Recently, previously overlooked aspects such as thickness, curvature, depth of folds of the brain, and shape of cerebral structures have also been considered. Atypical pattern and decrease in surface area as well as shape anomalies in structures scarcely explored in early studies, such as the *limbic system* and the *thalamus*, have been reported.[7]

Finally, recent studies of *Diffusion Tensor Imaging*, which allow quantitative exploration of white matter, point to altered structural connectivity in tracts connecting the right *prefrontal cortex* to the *basal ganglia* as well as the *cingulate gyrus* to the *entorhinal cortex*.[8]

Does the brain of individuals with ADHD function differently?

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

Pooled evidence[9] from functional MRI studies shows frontal hypoactivity affecting various regions of the cortex (*anterior cingulate*, dorsolateral prefrontal, inferior prefrontal, and orbitofrontal cortex), as well as related regions (such as portions of the basal ganglia, thalamus and *parietal cortex*). Interestingly, these findings mirror, in general, the anatomy implicated by structural imaging studies.

A meta-analysis of quantitative *EEG* studies found *theta power* increase and *beta power* decrease in ADHD vs. controls.[10] The most consistent finding from *event-related potential* studies is *reduced posterior P3* in the auditory

oddball task.[11] Taken together, the structural and functional findings suggest widespread anomalies encompassing multiple brain structures.

Indeed, currently, researchers in the field are focusing on the study of dysfunction in *distributed networks* . A relatively novel approach assessing functional connectivity during rest and task states seems to be particularly promising for gaining insight into the complex network anomalies presumably underlying ADHD.[12] Preliminary evidence supports the so-called default-mode interference hypothesis of ADHD, according to which ineffective modulation of default network fluctuations interferes with optimal functioning of the neuronal circuits underlying active task performance.[13]

Does brain neurochemistry differ in ADHD?

Converging genetic, *neuroimaging*, neuropsychophamacological and animal model data suggest that several neurotransmitter systems (like dopaminergic, noradrenergic, serotonergic and, possibly, nicotinic cholinergic systems) are involved in the pathophysiology of ADHD.[14]

Altered ratios to *creatine* of several compounds (choline compounds, N-acetyl-aspartate and glutamate/glutamine [a regulator of *dopamine*]) have been reported in preliminary spectroscopic studies.[15]

What are the causes of the supposed dysfunctions?

ADHD is highly heritable (heritability ~0.76).[16] However, the findings from genetic studies have been disappointing so far. A genome-wide scan meta-analysis found genome-wide significant linkage only for a region on chromosome 16, suggesting that many genes of moderately large effect are unlikely to exist.[17] A recent meta-analysis of genome-wide association studies failed to find any significant associations.[18] A small but significant contribution of several single candidate genes involving mainly the dopaminergic system (DRD4, DRD5, DAT1, HTR1B and SNAP25) has been supported by meta-analyses but data are inconsistent for many other candidate genes.[19] Recently, the potential role of a novel gene, latrophilin 3 (LPHN3) has been highlighted by genome-wide significant association and linkage identified by positional cloning and multiple replications.[20,21]

Among several candidate environmental risk factors, a recent systematic review[22] has confirmed a plausible role for premature delivery and maternal smoking during pregnancy.

What are the developmental pathways of brain abnormalities?

A recent longitudinal study reported a delay in brain maturation in ADHD of about three years. Persistent ADHD was characterized by a deviant developmental trajectory, while remission tended to be associated with normalization of anatomic deficits.[7]

Research Gaps

- How are structural and functional connectivity abnormalities related?
- At which developmental stages do disruptions in neural networks first emerge and manifest clearly?
- Can genetic factors with small effects be identified if we assemble appropriately large samples? What would be the relevant phenotypes for such large-scale approaches?

- What are the roles of genetic factors beyond *single nucleotide polymorphisms*? A recent study found increased *copy-number variations* (CNV) in ADHD.[23] These structural variations in DNA, such as insertions, deletions and duplications, occur frequently in the population, but their specific clinical significance is uncertain.
- How best can the interactions of genes and environmental (biological as well as psychosocial) variables be understood?
- How do various etiological factors lead to neuronal anomalies?
- What are the potential benefits of pathophysiology-based interventions? For example, neurofeedback[24] and, to a less extent, transcranial magnetic stimulation[25] are promising approaches, although more evidence is needed.

Conclusions

Insights from neuroscience have unequivocally shown that the brains of children with ADHD differ from those of controls. Recently, research on the neurobiological bases of ADHD has shifted from a model based on brain regional differences to a framework characterized by altered connectivity among several areas. Currently, we are still mostly obtaining information on individual elements of these networks. In the near future, we need to gain insight on how these pieces fit together.

We are also discovering, although technical and methodological obstacles remain, the genetic bases of these dysfunctions and the possible environmental factors that interact, in a complex way, with the genetic underpinnings.

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. Therefore, parents need to be aware that ADHD diagnosis is still based on behavioural criteria.

However, the veritable explosion of ADHD research grounded in neuroscience, combined with the rapid pace of technologic advances, will make the next years exciting and fruitful for understanding ADHD. Possible future neurobiological tests for ADHD will not replace clinical judgment. However, in the near future, services will need to integrate methods from neuroscience into clinical practice. Large networks of researchers in the fields of imaging and genetics will be necessary to confront future research challenges. Inevitably, substantial funding will be necessary to support this work but the potential results and their implications in terms of public health are expected to justify the economic costs.

References

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSMIV-TR).* 4th ed. Arlington, VA: American Psychiatric Publishing inc; 2000.
2. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. *Lancet* 2005;366:237-248.
3. Vitiello B. Long-term effects of stimulant medications on the brain: possible relevance to the treatment of attention deficit hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology* 2001;11:25-34.
4. Castellanos FX. Toward a pathophysiology of attention-deficit/hyperactivity disorder. *Clinical Pediatrics*1997;36:381-393.

5. Valera EM, Faraone SV, Murray KE, Seidman LJ. Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. *Biological Psychiatry* 2007;61:1361-1369.

6. Ellison-Wright I, Ellison-Wright Z, Bullmore E. Structural brain change in attention deficit hyperactivity disorder identified by meta-analysis. *BMC Psychiatry* 2008;8:51.

7. Shaw P, Rabin C. New insights into attention-deficit/hyperactivity disorder using structural neuroimaging.*Current Psychiatry Reports* 2009;11:393-398.

8. Konrad K, Eickhoff SB. Is the ADHD brain wired differently? A review on structural and functional connectivity in attention deficit hyperactivity disorder. *Human Brain Mapping* 2010;31:904-916.

9. Dickstein SG, Bannon K, Castellanos FX, Milham MP. The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis. *Journal of Child Psychology Psychiatry* 2006;47:1051-1062.

10. Snyder SM, Hall JR. A meta-analysis of quantitative EEG power associated with attention-deficit hyperactivity disorder.*Journal of Clinical Neurophysiology*

2006;23:440-455.

11. Barry RJ, Johnstone SJ, Clarke AR. A review of electrophysiology in attention-deficit/hyperactivity disorder: II. Event-related potentials. *Clinical Neurophysiology* 2003;114:184-198.

12. Castellanos FX, Kelly C, Milham MP. The restless brain: attention-deficit hyperactivity disorder, resting-state functional connectivity, and intrasubject variability. *Canadian Journal of Psychiatry* 2009;54:665-672.

13. Sonuga-Barke EJ, Castellanos FX. Spontaneous attentional fluctuations in impaired states and pathological conditions: a neurobiological hypothesis. *Neuroscience & Biobehavioral Reviews* 2007;31:977-986.

14. Russell VA. Reprint of “Neurobiology of animal models of attention-deficit hyperactivity disorder”. *Journal of Neuroscience Methods*

2007;166(2):I-XIV.

15. Perlov E, Philipsen A, Matthies S, Drieling T, Maier S, Bubl E, Hesslinger B, Buechert M, Henning J, Ebert D, Tebartz Van Elst L. Spectroscopic findings in attention-deficit/hyperactivity disorder: review and meta-analysis. *World Journal of Biological Psychiatry*

2009;10:355-365.

16. Mick E. Molecular genetics of attention deficit hyperactivity disorder. *Psychiatry Clinics of North America*2010;33:159-180.

17. Zhou K, Dempfle A, Arcos-Burgos M, Bakker SC, Banaschewski T, Biederman J, Buitelaar J, Castellanos FX, Doyle A, Ebstein RP, Ekholm J, Forabosco P, Franke B, Freitag C, Friedel S, Gill M, Hebebrand J, Hinney A, Jacob C, Lesch KP, Loo SK, Lopera F, McCracken JT, McGough JJ, Meyer J, Mick E, Miranda A, Muenke M, Mulas F, Nelson SF, Nguyen TT, Oades RD, Ogdie MN, Palacio JD, Pineda D, Reif A, Renner TJ, Roeyers H, Romanos M, Rothenberger A, Schäfer H, Sergeant J, Sinke RJ, Smalley SL, Sonuga-Barke E, Steinhausen HC, van der Meulen E, Walitza S, Warnke A, Lewis CM, Faraone SV, Asherson P. Meta-analysis of genome-wide linkage scans of attention deficit hyperactivity disorder. *American Journal of Medicine Genetics part B: Neuropsychiatric Genetics* 2008;147B:1392-1398.

18. Neale BM, Medland SE, Ripke S, Asherson P, Franke B, Lesch KP, Faraone SV, Nguyen TT, Schäfer H, Holmans P, Daly M, Steinhausen HC, Freitag C, Reif A, Renner TJ, Romanos M, Romanos J, Walitza S, Warnke A, Meyer J, Palmason H, Buitelaar J, Vasquez AA, Lambregts-Rommelse N, Gill M, Anney RJ, Langely K, O'Donovan M, Williams N, Owen M, Thapar A, Kent L, Sergeant J, Roeyers H, Mick E, Biederman J, Doyle A, Smalley S, Loo S, Hakonarson H, Elia J, Todorov A, Miranda A, Mulas F, Ebstein RP, Rothenberger A, Banaschewski T, Oades RD, Sonuga-Barke E, McGough J, Nisenbaum L, Middleton F, Hu X, Nelson S; Psychiatric GWAS Consortium: ADHD Subgroup. Meta-analysis of genome-wide association studies of attention-deficit/hyperactivity disorder. *Journal of the American Academy Child and Adolescent Psychiatry*2010;49:884-897.

19. Banaschewski T, Becker K, Scherag S, Franke B, Coghill D. Molecular genetics of attention-deficit/hyperactivity disorder: an overview. *European Child and Adolescent Psychiatry* 2010;19:237-257.

20. Arcos-Burgos M, Jain M, Acosta MT, Shively S, Stanescu H, Wallis D, Domené S, Vélez JI, Karkera JD, Balog J, Berg K, Kleta R, Gahl WA, Roessler E, Long R, Lie J, Pineda D, Londoño AC, Palacio JD, Arbelaez A, Lopera F, Elia J, Hakonarson H, Johansson S, Knappskog PM, Haavik J, Ribases M, Cormand B, Bayes M, Casas M, Ramos-Quiroga JA, Hervas A, Maher BS, Faraone SV, Seitz C, Freitag CM, Palmason H, Meyer J, Romanos M, Walitza S, Hemminger U, Warnke A, Romanos J, Renner T, Jacob C, Lesch KP, Swanson J, Vortmeyer A, Bailey-Wilson JE, Castellanos FX, Muenke M. A common variant of the latrophilin 3 gene, LPHN3, confers susceptibility to ADHD and predicts effectiveness of stimulant medication. *Molecular Psychiatry* 2010.

21. Ribasés M,Ramos-Quiroga JA, Sánchez-Mora C, Bosch R, Richart C, Palomar G, Gastaminza X, Bielsa A, Arcos-Burgos A, Muenke M, Castellanos FX, Cormand B, Bayés M, Casas M.Contribution of Latrophilin 3 (LPHN3) to the genetic susceptibility to ADHD in adulthood: a replication study. *Genes Brain and Behavior*. In press.

22. Faraone SV. The aetiology of ADHD: Current challenges and future prospects. Paper presented at the 1st International EUNETHYDIS meeting. 26-28 May, 2010. Amsterdam, Netherlands.

23. Williams NM. Rare chromosomal deletions and duplications in attention-deficit hyperactivity disorder: a genome-wide analysis. *Lancet*. In press.

24. Arns M, de RS, Strehl U, Breteler M, Coenen A. Efficacy of neurofeedback treaArns M, de RS, Strehl U, Breteler M, Coenen A. Efficacy of neurofeedback treatment in ADHD: the effects on inattention, impulsivity and hyperactivity: a meta-analysis. *Clinical & EEG Neuroscience Journal*

2009;40:180-189.

25. Bloch Y, Harel EV, Aviram S, Govezensky J, Ratzoni G, Levkovitz Y. Positive effects of repetitive transcranial magnetic stimulation on attention in ADHD Subjects: a randomized controlled pilot study. *World Journal of Biological Psychiatry* 2010;11:755-758.