Biological Aspects and prognosis of ADHD in Children

Essay

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By

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Content

List of Abbreviations

Abb.	Meaning
ACC	Anterior cingulate cortex
ASDs	Autistic spectrum disorders
BPD	Borderline personality disorder
BPT	Borderline personality traits
CAARS	Conners' Adult ADHD Rating Scales
CC	Community controls
CCC	Children's Communication Checklist
CD	Conduct disorder
CNVs	Copy number variants
COMT	Catechol-o-methyltransferase
CPT	Continuous Performance Test
CPT	Continuous performance task
DA	Dopamine
DLPFC	Dorsolateral prefrontal cortex
DOPAC	Dihydroxyphenylacetic acid:
DOPAC	Homovanillic acid (HVA) dihydroxyphenylacetic acid
FA	Fractional anisotropy
GI	Gyrification index
GRIN2A	Glutamate receptor, inotropic, N-methyl D-aspartate 2A
GWAS	Genome-wide association studies
ID	Intellectual disability
IFC	Inferior frontal cortex
LC	Locus coeruleus
MAO	Monoamine oxidase,
MD	Mean diffusivity
MPFC	Medial prefrontal cortex
MPQ	Multidimensional Personality Questionnaire
NA	Nucleus accumbens
NE	Norepinephrine
NMDA2A	Gene that encodes the N-methyl D-aspartate receptor subunit 2A

Abb.	Meaning
ODD	Oppositional defiant disorder
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OFC	Orbitofrontal cortex
OFC	Orbitofrontal cortex
PAI-BOR	The Personality Assessment Inventory-Borderline Features Scale
PCC	Posterior cingulate
PD	Parkinson's disease
PDD	Pervasive developmental disorder
PET	Positron emission tomography
PFC	Prefrontal cortex
SES	Socioeconomic status
SMA	Supplementary motor area
SNPs	Single nucleotide polymorphisms.
SNRI	Serotonin and noradrenaline re-uptake inhibitor
SPET	Single photon emission tomography
SRS	Social Responsiveness Scale
SSRI	Serotonin-specific reuptake inhibitors
TCV	Total cerebral volume
TPH2	Tryptophan hydroxylase,
VCFS	Velocardiofacial syndrome
VCFS	Velo-cardio-facial syndrome
VNTR	variable number of tandem repeats
VS	Ventral striatum
VTA	Ventral tegmental area
WISC-R	Working Memory Index and Freedom from Distractibility Factor of the

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Introduction

Attention deficit hyperactivity disorder (ADHD) is themost common psychiatric disability in childhood with an estimated incidence of 8-10% for children aged 6-12 years approximately 60% of these will persist into adolescence and approximately 4-5% of adults will have ADHD **(Hershoin, 2006).**

Gene-environment interaction increasingly recognized as an important mechanism in the etiology and development of ADHD; with some genes (e.g. DAT1) affecting the individual sensitivity to environmental etiological factors **Thapar et al., 2007.** The dopamine transporter gene (dat1) is associated with ADHD in several studies with an average 1.2 odds ratio and evidence of heterogeneity across data sets **Asherson, 2004.** Moreover, genes and environmental factors that influence the origins of disorder are not necessarily the same as those that contribute to its course and outcome **Faraone et al., 2005.** On the other hand, there is functional imaging evidence that theheteromodal association areas the dorsolateral prefrontal(including brod_mann,s' areas(BA) 44,45,46),lateraltemporal (including 38,21,20) and posteriorparietal regions(including BA 40),forma functionalsystem of neuralnetworks that subservice disengaged, reoriented, and maintainedattentionfocusandinhibitionofcontextuallyirrelevantstimuliand thattheseneural networksaredysfunctional in adolescents withattention deficithyperactivitydisorder, combined type **(Sowellet al., 2003).**

There was increasing interest in the role of the cerebellum in the pathogenesis of ADHD structural anomalies of the cerebellum are among the mostconsistently reported features of ADHD notably reduction in overall volume particularly in the cerebella vermin. Diffusion tensor imaging of cerebella white matter has revealed that attention impairment

is associated with decreased fractional anisotropy in this region **(Kessler, 2006).**

However Limbic structures are implicated in the genesis of attention-deficit/hyperactivity disorder (ADHD) by the presence of mood and cognitive disturbances in affected individuals and by elevated rates of mood disorders in family members of propend with ADHD **(Bedard, 2004).**

According to **Fossati et al. 2002,** 60% of adults with borderline personality disorder meet criteria for childhood ADHD; the two disorders share some similar clinical features e.g. emotional dysregulation and impulsivity. This suggests that child hood ADHD may be a risk factor for borderline personality in adulthood.

By their mid-twenties, when compared to non-ADHD peers, those with ADHD have completed less schooling, tend to hold lower-ranking occupations, and continue to suffer from poor self-esteem and social skills deficits. In addition, they are more likely to exhibit an antisocial personality and (perhaps) a substance use disorder in adulthood. For example, **Fischer et al. 2002** compared young adults who had been diagnosed with ADHD as children to community controls (CC). They found that the ADHD group had significantly higher rates of non-drug psychiatric disorders, were more likely to have ADHD as young adults than the CC group, and had significantly higher rates of major depressive disorder and personality disorders (histrionic, antisocial, passive-aggressive, and borderline personality disorders). Consistent with findings of other researchers, their data indicated that conduct problems in adolescence contributed significantly to the risk of personality disorders, two of which significantly increased the risk for major depression **(Barklyet al., 2002).**

Approximately 70-80% of ADHD patients treated with stimulant medication experience significant relief from symptoms, at least in the short-term. Approximately half of ADHD children seem to "outgrow" the disorder in adolescence or early adulthood; the other half will retain some or all symptoms of ADHD as adults. With early identification and intervention, careful compliance with a treatment program, and a supportive and nurturing home and school environment, ADHD children can flourish socially and academically **(Barkley and Russell, 2007).**

Rationale: ADHD is among the common psychiatric disorder in children, affecting about 3 to 5% of children globally and diagnosed in about 2 to 16% of school aged childrenwith 30 to 50% of those individuals diagnosed in childhood continue to have symptoms into adulthood.

Hypothesis: The study hypothesizes the role of the biological aspectsin the etiology and the chronological prognosis of ADHD.

Aim of Work

The aim of this work is to review:

1. The genetic basis in the etiology ofADHD.
2. The anatomical aspects in the pathogenesis of ADHD and other biological factors.
3. The chronological prognosis ofADHD.
4. The comorbid disorders such as anxiety, bipolar, depression and borderline personality disorders and its effect.

Gentices of ADHD

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a strongly genetically determined (heritability ~70–75%) neuropsychiatric disorder **Nikolas and Burt, 2010.** In most cases ADHD is accompanied by one or more neuropsychological impairments, such as executive dysfunction **Willcutt et al., 2005** and impairments in sensory, motor, and timing processes **(Halperin et al., 2008).**

Given that, in the vast majority of patients, multiple genes of small effect seem related to the disorder **Franke et al., 2009** in addition to environmental influences **Wood et al.,2010a,** interest has grown in using neuropsychological measures as measures of ADHD pathology that may have a simpler genetic architecture than ADHD itself **(Gottesman and Gould et al.,2003, Asherson et al., 2005).**

Recent studies have shown the utility of neuropsychological measures for ADHD genetic research **Kuntsi and Stevenson, 2001; Polderman et al., 2006; Doyle et al., 2008; Rommelse, 2008; Rommelse et al., 2008a.**However, error- and/or task-specific variance underlying neuropsychological data may still seriously hamper genetic studies. It may be expected that combining data across tasks increases the heritability estimate of the underlying construct **Fulker et al., 1999; Sham et al., 2000** through a reduction in the error variance underlying the individual measures **Kuntsi et al., 2006; Wood et al., 2008.**This is only feasible when the tasks to be aggregated share considerable common variance both genetic and phenotypic **Epstein, 1983**, reflecting at least partially shared etiologies; the shared portion of which may provide a suitable target for molecular genetic analysis. Therefore, it is of interest to examine to what extent tasks tap onto the same underlying construct and

if such a construct increases the power for detecting gene effects **(Fulker et al., 1999; Sham et al., 2000).**

Attention deficit hyperactivity disorder, like other psychiatric and developmental disorders runs in families. Genetic risk when passed on from parents is known as inherited risk/liability; not all genetic risks are necessarily inherited. First degree relatives of those with ADHD are two to eight times more likely than relatives of unaffected individuals to also show ADHD **Faraone et al., 2005.** Twin studies in many different countries show high heritability rates for ADHD of around 71–90% **Thapar, et al., 1999; Faraone et al., 2005; Nikolas & Burt, 2010** with evidence of shared familial/inherited risks for combined and inattentive type symptoms **(Willcutt et al., 2012).**

Adoption studies allow separation of inherited and postnatal environmental effects by examining the degree of concordance or similarity between individuals who have ADHD and their biologically related and unrelated relatives. All five published adoption studies of ADHD **Morrison & Stewart, 1973; Cantwell, 1975; Cunningham, et al., 1975; Albertset al., 1986; Sprich, et al., 2000** are consistent in showing a strong inherited contribution. Although when taken with family and twin study findings, adoption studies of ADHD suggest an important inherited contribution to ADHD, they do not remove the influence of prenatal risks or early postnatal adversity. Future adoption studies of ADHD will be invaluable, especially those that involve adoption at birth and look more closely at environmental influences that modify the clinical presentation and outcomes in those at higher genetic risk **Rutter et al., 2006.**Thus, associations of environmental risks with ADHD might arise completely or partly through inherited confounds and genetic risks might operate on manifest phenotypes through environmental mechanisms. Genetic risks can also influence

susceptibility by altering individual sensitivity to environmental risks or protective factors (gene-environment interaction) **(Nigg et al., 2010).**

A great deal of research has been carried out on the genetic factors that may play a role in attention deficit hyperactivity disorder (ADHD). Over 1,800 studies have been published on the subject to date. These studies, including family studies as well as those centered on specific genes or genome-wide screening, have produced strong evidence that genes play a role in susceptibility to ADHD. It was found that genetics account for 70 to 80 % of the risk; with a mean estimate of 76 %. Specific gene studies have produced good evidence linking certain genes to the disorder, particularly the dopamine D4 (DRD4) and dopamine D5 (DRD5) genes. However, it is difficult to implicate any specific gene in ADHD “beyond reasonable doubt,” due to the diversity and complexity of the condition.Gene studies, whether focusing on specific genes or scanning the whole genome, aim to link DNA variations with these observable symptoms. They also endeavor to locate the relevant chromosome regions. A recent analysis of genome-wide studies found only one confirmed location on one chromosome (chromosome 16) that has been repeatedly linked to ADHD**(Banaschewski et al., 2010).**

Consequently research aimed at delineating the genetic component of ADHD has focused on DA, especially the DA transporter gene and the gene for the DA D4 receptor **Thapar et al., 1999.**Dopamine receptors have been recognized as important components in the etiology of ADHD for many years. Drugs used to treat ADHD, including methylphenidate and amphetamine, have significant effects on dopamine signaling in the brain. Studies of gene association have implicated several genes within dopamine signaling pathways; in particular, the D4.7 variant of D4 has been consistently