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Opinion

Neurobiological and Genetic Correlates of Attention Deficit Disorder (ADD): Are Powerful Psychostimulants the Answer?

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Attention Deficit Hyperactivity Disorder (ADHD) is primarily genetic, prevalent, and complicated. It can be incapacitating in its severity, disrupting normal functioning in every aspect of life [1]. Its underlying neurogenetic etiology, compromises brain function. 60 years of scientific evidence from diverse research investigation supports the statements above. Evidence from neurogenetic, neutra-ceutical amino acid therapy and epigenomic studies have enlarged perspective and provided novel resources for an informed precision response. However many professionals are uniformed of the most recent advancements. Misconceptions persist. They involve individual variances and different forms of ADHD which have led some to believe that ADHD does not really exist, or that all children show symptoms of ADHD in their development. Others feel it is grossly over-diagnosed and that pharmaceutical treatment is expanding at a dangerous pace. Many fear for the children with ADHD who are treated with stimulants at an early age; believing the treatment is dangerous and could lead to drug addiction [2]. Since truth has many elements, and there is often some truth in misconception, we must ask where do we draw the line? How do we as scientists and practitioners progress from misconception to become fully informed for proper diagnosis and personalize precision treatment for the individual? [3].

A literature review reveals mental health disorders, including Attention Deficit Hyperactivity Disorder has numerous investigators. In 2021, there were ten epidemiological studies, investigating the distribution, patterns of ADHD and etiological influences

of ADHD. Over 18 thousand children and their parents participated in these studies. Meta-analysis of ADHD studies in 8 different countries, for young children between the ages of 12 months to 83 months, which is 1 year to 5 ½ years old, found an average prevalence of approximately 20 percent of the sample had some form of general mental disorder. Over eight percent had some form of anxiety disorder. Just under 5% had oppositional defiant disorder. ADHD was 4.3%, and approximately 1 percent had a depressive disorder. Comorbidity of mental health disorders was over 6 percent [4]. One meta-analysis found that Autism Spectrum Disorder and Attention Deficit Hyperactivity Disorder have an interactive relationship which greatly increases the risk of death [5].

Phenomenological experience of ADHD in children includes poor self-esteem, social dysfunction, learning impairments and higher risk for abuse of substances, including tobacco [3]. Since 2008, diagnosis of ADHD with pharmaceutical medication treatment has been steadily increasing. The number of children prescribed stimulants is in the millions [6]. The increase in availability of prescription stimulant medication for adolescents is naturally associated with an increase in ADHD prescription abuse. 20-30% of substance use disorder (SUD) patients have a dual diagnosis of ADHD and 20-40% of adults with a ADHD diagnosis have a history of SUD [7,8].

ADHD is classified as a neurodevelopmental disorder which causes functional impairment [9]. Its descriptive characteristic involves inattention, hyperactivity, and impulsivity. The etiology is complex and multifaceted, with high genetic causal influence [10]. Both inter-individual and intra-individual symptom variability is high. Executive dysfunction includes deficits across several cognitive domains. Ineffective or insufficient treatment for ADHD and interactive comorbid mental health disorders contribute to treatment failures and the decline of the patient over the long-term [11].

Psychoeducation, with personalized pharmaceutical and non-pharmaceutical interventions are included within the current clinical multi-modal treatment guidelines. Available prescription stimulant medications include methylphenidate and amphetamines. Available prescription non-stimulants include atomoxetine, guanfacine, and clonidine [12]. Although short-term randomized clinical trials show large effect sizes with good tolerability, current pharmacotherapeutic strategies can be improved upon to provide expanded options, with development of novel medications.

Studies in molecular genetic studies have pinpointed several genes believed to mediate ADHD susceptibility [13,14]. A literature review suggests agreement that many experience dopaminergic dysfunction in the brain reward cascade (BRC). Those with the hypo-dopaminergic trait, experience low dopamine availability, resulting in their brains needing more dopamine just to avoid feelings of unpleasantness. These individuals are genetically predisposed and at high-risk for multiple drug-seeking behaviors. Drugs of abuse activate a splurge of dopamine release, which diminishes abnormal excessive cravings.

The DRD(2) A1 allele gene variant is involved. It inhibits development of normal expression of dopamine receptors [15,16]. Polymorphic variances in several genes involved in neuro-physiological processing of specific neurotransmitters, have been associated with deficient neurotransmission functionality. These mutations predispose individuals from birth, to have a high risk for addictive, impulsive, and compulsive behavioral propensities [17,18].

The new Reward Deficiency Syndrome (RDS) paradigm proposes polymorphic variances of reward genes, especially dopaminergic genes, are determinant neurogenetic causal influences for RDS. Primary RDS investigators, hypothesize RDS is the phenotype and mental health disorders such as ADHD and SUD are behavioral subtypes, or endotypes [19]. It is also hypothesized by scientists who have been investigating dopamine dysfunction in the Brain Reward Cascade (BRC),that early diagnosis through genetic polymorphic identification, combined with proactive DNA-based customized nutraceutical therapeutic intervention for children, may decrease the severity of ADHD behavioral symptoms [20,21].

The evidence reveals that males are more likely to experience and be diagnosed with ADHD than females. European, Scandinavian, Australian, Asian, Middle Eastern, South and North American studies concur that 5.9% of children and 2.5% of the adults will experience ADHD [22]. Of concern for these individuals and future generations around the planet is the current inadequate diagnostic criteria, which primarily uses subjective testing. Of grave concern is the widespread prescribing of psychostimulants to children, and the potential future development of substance use disorder (SUD), in adolescence and/or adulthood. More gentle dopamine and serotonin releasers might be better options and useful therapeutic adjuncts for the treatment of other RDS behavioral subtypes, including addictions [23].

The US Food and Drug Administration (FDA) has approved Methylphenidate (MP) for treating ADHD in children, six years of age and older, and adults. MP is also approved for second-line treatment of adult narcolepsy. Limited to moderate efficacy has been found in the off-label use of MP for cancer fatigue, treatment resistant depression in elderly patients, Alzheimer's apathy and enhanced memory-cognitive performance. The scientific community should continue to investigate the mechanism of action, which is not fully understood, pharmacology for relevant drug interactions, toxicity levels to avoid adverse events, and monitoring criteria to avoid abuse of such a powerful drug [24].

While MP is extensively prescribed for ADHD, it is only somewhat effective in ameliorating symptoms of ADHD. It is often used illicitly by individuals without ADHD for cognitive-enhancing purposes. The devasting consequences on cessation of brain activity with long term usage are not fully understood. Thanos., *et al*. used positron emission tomography (PET) and fluorodeoxyglucose [18F] (FDG), to scan rats at three points in time: 1) after 13 weeks of treatment; 2) after 1 week of abstinence; and 3) after 4 weeks of abstinence. They found increase in brain glucose metabolism (BGluM) after thirteen weeks of LD and HD MP treatment, concluding that MP treatment during adolescence can significantly alter BGluM. Findings also showed brain activity did not subside in many brain areas, after either 1 or 4 week drug abstinence. There is potential for damage caused by chronic use and illicit abuse, and this is just one example of potential damage [25]. In addition, Thanos' group also found that oral combinations of MP + SSRI can enhance addiction-related gene regulation [26].

Neurotransmitters systems target by MP pharmacokinetics, effect functional connectivity. These effects appear to be modulated by age. Children experience significant developmental alterations of MP targeted neurotransmitters system. Kaiser., *et al*. [27] found decreased measures of connectivity and centrality, in the striatum and thalamus in children with ADHD who were treated with MP, but increases in adults. Evidence shows significant MP induced increases in functional connectivity (FC) in children, in sensorimotor areas, of the circuits associated with the dopamine transporter system (DAT). Thanos., *et al*. found MP induced regional variations in DAT and NET-enriched FC maps were significantly correlated with inter-individual differences in reinforcement-learning task behaviors, concluding that MP induced FC changes, at rest, are best understood through DAT distribution in the brain [28]. What other potential negative effects are induced by MP administration?

Genetic and other less understood factors are involved in ADHD etiology. Research points to disruption in dopamine signaling in brain regions where D2 receptors are reduced as the primary cause of ADHD. This same pattern of reduced dopamine-mediated signaling is observed in various RDS associated food and drug addictions, and obesity. The chronic effects of overconsumption of sugar potentially lead to alterations in mesolimbic dopamine signaling, contributing to the symptoms associated with ADHD [29].

ADHD is associated with early onset and more severe development of SUD, with reduced treatment effectiveness. Adults with SUD diagnosis should be concurrently screened for ADHD [30]. Simultaneous and integrated treatment of ADHD and SUD is recommended, using a combination of pharmaco- and psychotherapy [31].

The Long team's recent meta-analysis found clear and overlapping, structural brain abnormality associated with ADHD and SUD comorbidity in adolescents and young adults. Decreased gray matter volume (GMV) patterns have been found in the left precentral gyrus, bilateral superior frontal gyri, and left inferior frontal gyrus in an ADHD experimental group which were not found in the control group [32]. SUD experimental group participants had increased GMV in the left putamen and insula when compared to the control group. Larger regional GMV in the right parietal lobule, with smaller volumes in both the left putamen and precentral gyrus were found in the ADHD group when compared to the SUD group.

In our opinion, while this appears to be quite a sophisticated study it raises some important caveats. It should not be a surprise that neurobiological differences were found, especially related to brain structural abnormalities in the SUD compared to the ADHD group, by the mere fact that drugs of abuse at least chronically can induce structural changes [33]. We are also concerned as to the actual appropriate screening of the so called "healthy controls" indicated in the studies chosen by Long., *et al*. [32]. It is imperative that only highly screened controls free of "Reward Deficiency Syndrome (RDS)" be utilized in all psychiatric genetic studies, which has been universally ignored [34].

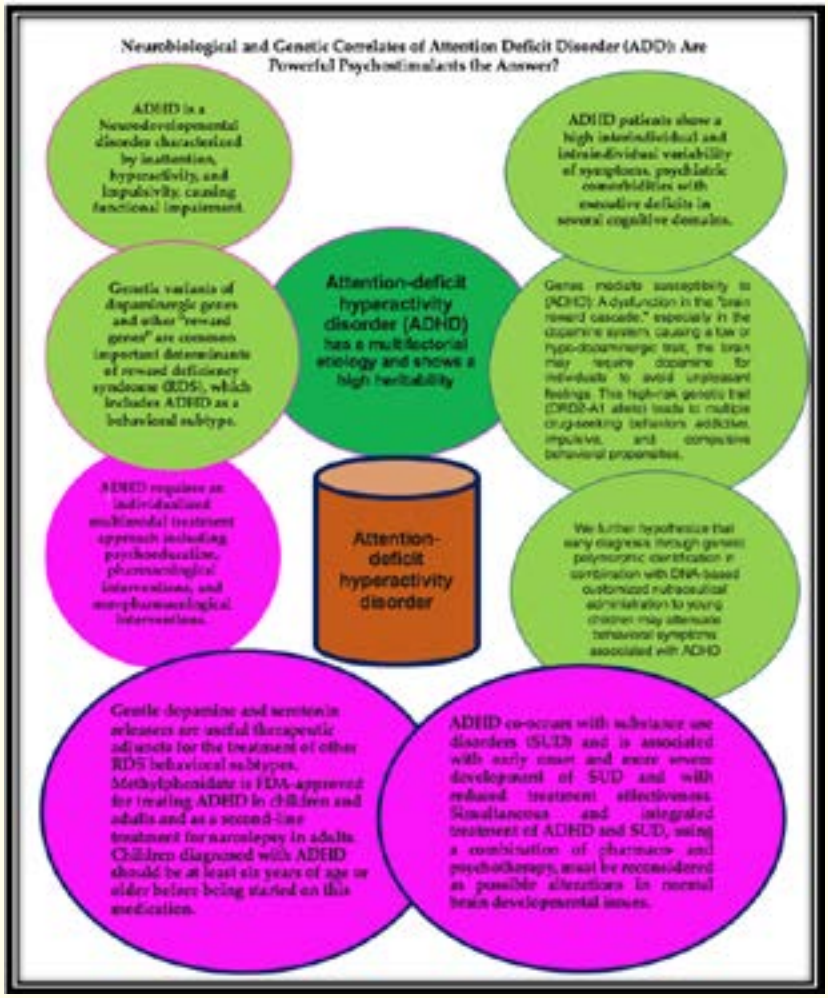

Figure 1: Schematic illustrating Neurobiological and Genetic Correlates of ADD.

We believe that ADD/ADHD especially in our youth requires new thinking and concern for futuristic impact on "normal" brain development in the face of both DNA risk antecedents and epigenetic insults related to best practice involving accurate diagnosis, and novel less problematic harmless treatment.

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Author Contribution

All authors contributed equally.

Conflict of Interest

Dr. Kenneth Blum is the inventor and holds a number of domestic and foreign patents related to GARS and KB220.

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