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Review

Investigating the Efficacy of Transcranial Direct Current Stimulation in Managing ADHD and Co-occurring Conditions

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Abstract: ADHD, a neurodevelopmental condition, is distinguished by a triad of symptoms including inattention, hyperactivity, and impulsivity. It is frequently accompanied by comorbidities such as anxiety, depression, and learning disabilities. As a result, clinicians often face challenges in accurately diagnosing ADHD and differentiating it from other conditions. As a prospective remedy for ADHD, scientists have investigated Transcranial Direct Current Stimulation (tDCS), a non-invasive technique of stimulating the brain. It involves applying low-intensity electrical currents to specific regions of the brain to modulate neural activity. This review paper aims to provide an overview of the comorbidities associated with ADHD and the differential diagnosis of the condition. It also explores the potential of tDCS as a treatment option for ADHD, including its mechanisms of action and efficacy in improving ADHD symptoms. The comorbidities discussed in this review include anxiety disorders, mood disorders, and substance use disorders. These comorbidities are frequently seen in individuals with ADHD and can complicate the diagnosis and treatment of the condition. The paper also highlights the importance of considering comorbidities when assessing ADHD, as well as the potential impact of these conditions on treatment outcomes. The differential diagnosis section of the paper explores conditions that can present with symptoms similar to ADHD, such as anxiety disorders, mood disorders, and learning disabilities. It emphasizes the need for a thorough assessment and differential diagnosis to identify ADHD and differentiate it from other conditions accurately. The final section of the paper discusses the potential of tDCS as a treatment option for ADHD. It examines the mechanisms of action of tDCS and its efficacy in improving ADHD symptoms, including attention, hyperactivity, and impulsivity. It also explores the potential for tDCS to improve comorbid conditions associated with ADHD. Overall, this review provides a comprehensive overview of comorbidities and differential diagnoses in ADHD and the potential of tDCS as a treatment option. The paper highlights the importance of a thorough assessment and personalized treatment plan for individuals with ADHD, particularly those with comorbidities.

Keywords: neuromodulation; brain stimulation; Transcranial Direct Current Stimulation; neurodevelopment Diso%%rder; ADHD; ADD

1. Introduction

The Diagnostic and Statistical Manual of Mental Disorders defines ADHD as a condition that involves persistent and problematic symptoms of inattention, hyperactivity, and impulsivity that can significantly affect an individual's daily functioning[1]. Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that affects approximately 5-6% of children and adults worldwide [104]. ADHD is a highly varied clinical condition, partly due to its frequent co-occurrence with other disorders that emerge during childhood. Research suggests that a significant majority (ranging from 60% to 100%) of children with ADHD experience one or more comorbid conditions, many of which persist into adulthood[2,3]. While medications such as stimulants and behavioral therapies are effective treatments for ADHD, they do not work for all individuals and can have side effects [26]. In recent years, there has been a growing interest in alternative treatments for ADHD,

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specifically non-invasive brain stimulation techniques such as transcranial direct current stimulation (tDCS).

The process of tDCS entails administering a mild electrical current to the scalp in order to regulate cortical activity and excitability. Multiple studies have explored the effectiveness of tDCS for treating ADHD, yielding promising findings. For example, a randomized controlled trial conducted by Cosmo et al. (2015)[4] found that tDCS combined with cognitive training improved working memory performance in children with ADHD compared to cognitive training alone. Another study by Boggio et al. (2010)[5] has shown that a solitary session of tDCS applied to the prefrontal cortex can enhance attentional regulation in adults diagnosed with ADHD.

However, the underlying mechanisms of how tDCS affects the brain and its potential long-term effects are still not fully understood. One proposed mechanism is that tDCS modulates the activity of the default mode network (DMN), a set of brain regions that are active during rest and self-referential processing. Individuals diagnosed with ADHD have been observed to exhibit abnormal activity in their DMN (default mode network), which could be regulated through the use of tDCS to restore normalcy. For example, a study by Schröder et al. (2017)[7] found that tDCS over the left dorsolateral prefrontal cortex decreased DMN connectivity in adults with ADHD.

In addition to potential therapeutic benefits, there are also ethical considerations to be taken into account when using tDCS for ADHD. For example, obtaining informed consent from individuals with ADHD may be challenging, particularly if they have difficulty understanding the complex science behind tDCS. Additionally, researchers and healthcare providers must ensure that the risks and benefits of tDCS are carefully weighed and that patient safety is prioritized.

Despite the potential of tDCS as a non-invasive therapy for ADHD, further research is necessary to gain a complete understanding of its mechanisms of action and any possible long-term impacts. This paper aims to provide an outline of existing research on tDCS and ADHD, including potential mechanisms of action and ethical concerns, while also drawing attention to future research avenues in this field.

2. ADHD-related issues

2.1. Behaviour and conduct problems

Research has demonstrated that children diagnosed with ADHD may exhibit dissimilarities in both the structure and functioning of the prefrontal cortex, an area of the brain that governs executive functions such as attention, working memory, and impulse control[8,9]. In particular, children diagnosed with ADHD may have a diminished volume of the prefrontal cortex, lesser prefrontal cortex activity during tasks that necessitate attention and working memory, and diminished connectivity between the prefrontal cortex and other brain regions[10].

The symptoms of inattention and impulsivity, common in children with ADHD, may be linked to these variations in prefrontal cortex function and connectivity. For instance, reduced activity in the prefrontal cortex during tasks that require continuous attention and working memory may result in challenges maintaining concentration and accomplishing tasks without committing careless errors[11,12]. Likewise, decreased connectivity between the prefrontal cortex and other regions of the brain may result in challenges inhibiting inappropriate behaviors and regulating impulses[13]. Some of the behavioral and conduct problems that can be associated with ADHD include the following.

2.1.1. Inattention

Inattention is a common symptom of ADHD (Attention-Deficit/Hyperactivity Disorder) that refers to difficulties in sustaining attention, staying focused on tasks, and avoiding distractions. Individuals with ADHD may have trouble organizing tasks and activities, forget important details or instructions, and struggle with completing tasks that require sustained effort **[14,15]**. They may also have difficulty following through on instructions and appear not to listen when spoken to directly. Inattention can lead to problems in academic, occupational, and social settings, as well as impact daily functioning and quality of life. While inattention is a core symptom of ADHD, it is

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essential to note that it is a complex and multifaceted issue that can vary in severity and presentation among individuals with ADHD [16].

One study published in the Journal of Neural Transmission in 2017 found that tDCS improved attention and working memory in adults with ADHD. The research revealed that ten tDCS sessions held over two weeks resulted in noteworthy enhancements in attention and working memory when compared to a group that received sham stimulation. The magnitude of the improvement was sizeable, with Cohen's d effect size of 1.11 for attention and 0.93 for working memory[17]. Another study in 2021 meta-analyzed 13 studies and concluded the tdcs promise long-lasting effects on children and adolescents.[18]

Studies indicate that ADHD is associated with weaker structure and function of prefrontal cortex circuits, particularly in the right hemisphere. The prefrontal association cortex is a critical area of the brain that governs attention, behavior, and emotion regulation, with the right hemisphere specifically responsible for inhibiting behavior[19]. Noradrenergic and dopaminergic neurotransmitter systems play a critical role in modulating prefrontal cortex (PFC) function, essential for a range of cognitive processes, including attention, working memory, and executive function. For optimal prefrontal cortex (PFC) functioning, postsynaptic activation of alpha-2A adrenoceptors and D1 receptors is essential[20]. The alpha-2A adrenoceptor is a subtype of adrenergic receptor that is found in high concentrations in the PFC. Stimulation of these receptors by noradrenaline (norepinephrine) is known to enhance prefrontal cognitive function, including attention and working memory. Research has shown that reduced alpha-2A adrenoceptor signaling in the PFC is associated with deficits in working memory and attention in individuals with ADHD [21].

The D1 receptor, which is a particular subtype of dopamine receptor, is abundantly present in the PFC. Activation of these receptors through dopamine stimulation is recognized to augment prefrontal cognitive functions such as working memory and executive function[22]. Research has shown that reduced dopamine signaling in the PFC is associated with deficits in working memory and executive function in individuals with ADHD [23]. Studies have shown that individuals with ADHD exhibit reduced dopamine release in the prefrontal cortex when performing tasks related to working memory, and this is associated with impairments in working memory performance[19]. Studies have shown that there may be reduced connectivity between the prefrontal cortex (PFC) and the striatum in individuals with ADHD. The striatum is a region of the brain involved in reward processing and motivation, among other functions. Reduced connectivity between these regions may contribute to the difficulties that individuals with ADHD have with regulating motivation and maintaining attention [24,25].

An instance of this is a study that was printed in the Biological Psychiatry journal in 2016, which utilized functional magnetic resonance imaging (fMRI) to scrutinize dissimilarities in brain connectivity between the PFC and striatum in individuals with ADHD in comparison to healthy individuals. According to the study, people with ADHD demonstrated less connectivity between the PFC and the striatum when compared to healthy participants. The study noted that this reduction in connectivity was related to poorer performance on a task that necessitated attention and impulsivity regulation[25]. Another study published in the journal Biological Psychiatry in 2014 used a similar fMRI approach to investigate differences in brain connectivity between the PFC and striatum in children with ADHD who had also experienced early-life stress. The study found that children with ADHD who had experienced early-life stress had reduced connectivity between the PFC and striatum compared to children with ADHD who had not experienced early-life stress. This reduced connectivity was associated with worse performance on a task requiring attention and working memory [27].

In a study published in the Journal of Child Psychology and Psychiatry in 2011, researchers used magnetic resonance imaging (MRI) to examine the gray matter volume in the PFC of individuals with ADHD and healthy controls. The study found that individuals with ADHD had less gray matter volume in the PFC than healthy controls. This reduction in gray matter volume was linked to poorer performance on tasks that required attention and executive function[28]. Moreover, studies have also shown that there may be differences in the levels of neurotransmitters, such as dopamine and

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norepinephrine, in the PFC of individuals with ADHD. A study published in the Journal of Neuroscience in 2007 used positron emission tomography (PET) to investigate dopamine receptor availability in the PFC of individuals with ADHD and healthy controls. The study found that individuals with ADHD had lower dopamine receptor availability in the PFC compared to healthy controls. This reduced dopamine receptor availability was associated with worse performance on tasks requiring working memory and attention [29].

Some studies have suggested that tDCS may enhance D1 dopamine receptor binding and activity in the brain. For example, a study found that anodal tDCS applied over the dorsolateral prefrontal cortex (DLPFC) increased D1 dopamine receptor binding [30]. Another study published in Brain Stimulation in 2016 found that anodal tDCS applied over the left DLPFC improved working memory performance in healthy volunteers and that this effect was associated with increased D1 dopamine receptor binding in the striatum, as measured by PET imaging [31,32].

2.1.2. Hyperactivity

Individuals with ADHD often experience symptoms such as restlessness, fidgeting, and difficulty staying seated or quiet for extended periods of time. The neurobiological research on ADHD indicates that hyperactivity in individuals with ADHD may be associated with problems in inhibitory control and dysregulation of the dopamine system[33].

Studies using neuroimaging techniques have found that individuals with ADHD show differences in brain activity in regions related to movement and inhibitory control. For example, a study published in Frontiers in Human Science in 2018 used fMRI to investigate brain activity in children with ADHD and healthy controls. The study found that children with ADHD had reduced activation in the pre-SMA compared to healthy controls. This reduced activation was associated with more severe hyperactivity symptoms in children with ADHD [34]. Other studies have investigated the role of the dopamine system in hyperactivity in ADHD. A study published in the Journal of Neuropsychiatric Diseases and Treatment in 2008 used PET to measure dopamine transporter binding in the brain of children with ADHD and healthy controls. The study found that children with ADHD had significantly lower dopamine transporter binding in the striatum than healthy controls, suggesting dysregulation of the dopamine system in ADHD [35].

In 2010, the Journal of Abnormal Psychology published a study that employed fMRI to examine inhibitory control in adults with ADHD and healthy individuals. According to the study, compared to healthy individuals, adults with ADHD had less activation in the right inferior frontal gyrus (IFG), a brain region that plays a role in inhibitory control [36]. The impaired performance of individuals with ADHD on tasks that require inhibitory control is linked to reduced activation in the right inferior frontal gyrus (IFG), a brain region that plays a critical role in this function. Catecholamines, such as dopamine and norepinephrine, are important neurotransmitters that regulate attention, arousal, and movement [37]. Dysregulation of catecholamine signaling has been implicated in the development of hyperactivity in ADHD.

Research has found that individuals with ADHD have reduced levels of dopamine transporters in the brain, which are responsible for the reuptake of dopamine from the synapse. This results in increased dopamine signaling, which can contribute to hyperactivity and impulsivity in ADHD [38]. Additionally, studies have found that individuals with ADHD have lower levels of dopamine D2 receptors in the brain, which are essential for regulating the release of dopamine. Lower levels of D2 receptors can lead to reduced dopamine release, which may contribute to hyperactivity in ADHD [39].

Similarly, dysregulation of norepinephrine signaling has also been implicated in hyperactivity in ADHD. Studies have found that individuals with ADHD have altered levels of norepinephrine in the brain, which can contribute to hyperactivity and impulsivity. Norepinephrine is involved in regulating attention and arousal, and dysregulation of this neurotransmitter can lead to increased activity and hyperactivity [40].

Furthermore, animal studies have shown that manipulating catecholamine signaling can lead to changes in motor activity and hyperactivity. For example, the administration of dopamine agonists,

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which enhance dopamine signaling, can lead to increased motor activity and hyperactivity in animal models [41]. Conversely, the administration of dopamine antagonists, which reduce dopamine signaling, can lead to reduced motor activity and hypoactivity. On the contrary, dopamine agonists are medications that mimic the effects of dopamine in the brain. They can be used to treat various conditions, including Parkinson's disease, restless leg syndrome, and ADHD [42].

Dopamine agonists are commonly used to treat ADHD by increasing the levels of dopamine in the brain, which may help improve attention and reduce hyperactivity. The most commonly used dopamine agonists for ADHD are stimulant medications, including methylphenidate and amphetamines[43]. These medications work by blocking the reuptake of dopamine from the synapse, leading to increased dopamine signaling. Studies have shown that these medications can effectively reduce hyperactivity and impulsivity in individuals with ADHD. In fact, stimulant medications are considered the first-line treatment for ADHD due to their effectiveness and safety profile [44]. However, it's important to note that dopamine agonists can have side effects, including insomnia, loss of appetite, and irritability. In rare cases, they can also lead to more severe side effects, such as psychosis or addiction [45].

2.1.3. Impulsivity

Impulsivity is a fundamental characteristic of ADHD that can substantially affect an individual's daily life. Research has demonstrated that people with ADHD are more prone to exhibiting impulsive behaviors, such as substance abuse, reckless driving, and other hazardous activities that can result in accidents or injuries[46]. Studies have indicated that impulsivity is linked to negative academic and occupational consequences, such as lower levels of academic attainment and higher job turnover rates[47].

Impulsivity can also negatively impact relationships, as individuals with ADHD may struggle with social skills and have difficulty understanding social cues. This can lead to difficulties in forming and maintaining relationships, as well as conflicts with family, friends, and colleagues. In addition, impulsivity can contribute to emotional dysregulation, which is common in individuals with ADHD [48]. This can manifest as impulsive outbursts or tantrums, making it challenging for individuals to regulate their emotions and interact appropriately with others.

Research has suggested several theories to explain the link between ADHD and impulsive, risky behavior. One of the prominent theories is related to the neurotransmitter systems that regulate reward and motivation, particularly the dopamine and norepinephrine systems. Studies have found that individuals with ADHD may have an underactive dopamine system, which can lead to difficulties in experiencing pleasure or reward from everyday activities. This, in turn, may result in seeking out high-risk, novel, or exciting activities to stimulate the dopamine system, leading to impulsive, risky behaviors [49].

Another theory suggests that individuals with ADHD may have difficulties with self-regulation, particularly in inhibiting or delaying responses. Research has found that individuals with ADHD have reduced activity in the prefrontal cortex, which is responsible for regulating attention, behavior, and emotion. This can lead to deficits in self-control and inhibition, contributing to impulsive behaviors [50]. Moreover, studies have suggested that individuals with ADHD may have difficulties with processing feedback and rewards, leading to a reduced ability to learn from their mistakes and make better decisions in the future. This can result in continued impulsive and risky behaviors, even when they lead to negative consequences [51].

Finally, environmental factors, such as stress, trauma, or parental neglect, may also contribute to impulsive, risky behaviors in individuals with ADHD. Such experiences can affect brain development and function, leading to difficulties with emotion regulation, decision-making, and impulse control [52].

Impulsivity in ADHD has been associated with dysfunction in several neural circuits, including the prefrontal-striatal circuit and the cortico-basal ganglia-thalamo-cortical circuit. These circuits involve interconnected brain regions responsible for executive functions, such as inhibitory control, working memory, and attention [53]. In particular, the prefrontal-striatal circuit has been implicated

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in ADHD-related impulsivity. This circuit includes the prefrontal cortex, striatum, and thalamus and plays a critical role in regulating attention, behavior, and emotion [54]. Dysfunction in this circuit may lead to reduced inhibitory control, resulting in impulsive behaviors. Furthermore, the cortico-basal ganglia-thalamo-cortical circuit has also been linked to impulsivity in ADHD. This circuit includes the prefrontal cortex, basal ganglia, and thalamus and involves motor planning and control. Dysregulation in this circuit may contribute to motor impulsivity and hyperactivity observed in individuals with ADHD [55].

One of the neurotransmitter systems implicated in ADHD-related impulsivity is the dopaminergic system. Studies have suggested that altered dopamine receptor signaling in the prefrontal cortex and striatum may contribute to impulsive behavior in ADHD. Specifically, reduced dopamine D2 receptor availability in the striatum has been associated with increased impulsivity in individuals with ADHD. The dopamine D2 receptor gene (DRD2) is involved in dopamine neurotransmission, a process that regulates mood, reward, and motivation in the brain. Individuals with ADHD have been found to have lower levels of dopamine D2 receptors in the striatum, a region of the brain involved in reward processing and motor function. Research suggests that this reduction in dopamine D2 receptor availability contributes to the impulsive behavior observed in individuals with ADHD [55,56].

Studies have also identified specific DRD2 gene variants associated with ADHD and impulsivity. For example, the Taq1A polymorphism is a DRD2 gene variant that has been linked to reduced dopamine D2 receptor density and increased impulsivity in individuals with ADHD [57]. Another neurotransmitter system that may be involved in ADHD-related impulsivity is the noradrenergic system. Studies have found that medications that increase noradrenaline levels, such as atomoxetine, can reduce impulsivity in individuals with ADHD. This suggests that dysregulation of noradrenergic receptor signaling may contribute to impulsivity in ADHD [58].

2.1.4. Mood Disorders

DMDD stands for Disruptive Mood Dysregulation Disorder, a relatively new diagnosis added to the DSM-5. It is characterized by severe and recurrent temper outbursts that are disproportionate to the situation and inconsistent with developmental level, persistently irritable or angry mood, and is typically diagnosed in children between 6 to 18 years of age[59,60].

Recent studies have shown a high rate of comorbidity between ADHD and DMDD, with estimates ranging from 20% to 50%. This suggests that a significant proportion of children with ADHD also experience symptoms of DMDD, which can complicate their clinical presentation and require additional treatment [61]. Additionally, research has shown that children with both ADHD and DMDD tend to have more severe symptoms of both conditions, lower quality of life, and poorer outcomes compared to those with ADHD alone. Therefore, clinicians need to screen for both ADHD and DMDD in children presenting with disruptive behavior, irritability, and mood dysregulation, in order to provide effective treatment and improve their overall functioning [61].

Intermittent Explosive Disorder (IED) is a psychiatric disorder characterized by recurrent outbursts of impulsive and aggressive behavior, including verbal or physical aggression toward people, animals, or objects. The outbursts are often disproportionate to the provoking events and result in significant distress or impairment in social, occupational, or other important areas of functioning [62].

There is evidence to suggest that ADHD is associated with an increased risk of developing IED. Studies have found that the prevalence of IED is significantly higher among individuals with ADHD compared to those without ADHD. For example, one study found that the prevalence of IED was approximately six times higher among individuals with ADHD compared to those without ADHD [63].

Clinicians need to be aware of the potential co-occurrence of ADHD and IED, as well as other disruptive behavior disorders such as DMDD, ODD (Oppositional Defiant Disorder), and Conduct Disorder, as they can have a significant impact on a person's quality of life, relationships, and overall

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functioning. Proper diagnosis and treatment of ADHD and IED can help individuals manage their symptoms and improve their overall functioning [64].

2.1.5. Oppositional Defiant Disorder (ODD)

Oppositional defiant disorder (ODD) is a psychiatric disorder characterized by a persistent pattern of disobedient, defiant, and hostile behavior towards authority figures, such as parents, teachers, and other authority figures. Children with ODD may argue with adults, refuse to comply with rules, deliberately annoy others, blame others for their mistakes, and be easily annoyed or angered. This behavior typically causes significant distress and impairment in social, academic, or occupational functioning. ODD typically develops in early childhood and can persist into adolescence and adulthood. It is more common in boys than girls and is often co-morbid with other psychiatric disorders, such as attention-deficit/hyperactivity disorder (ADHD), anxiety, and depression [65].

There is some evidence to suggest that individuals with ODD may have smaller brain structures in some areas of the brain. A meta-analysis constituting 29 studies reported that individuals with ODD/CD had abnormalities in the bilateral amygdala as well as in the bilateral stratum and bilateral insula [66].

It is estimated that approximately 60% of children with ADHD also have ODD, and 30% to 50% of children with ODD also have ADHD. Effective treatment for these disorders often involves a combination of medication and behavioral interventions, such as cognitive-behavioral therapy or parent training [67].

Furthermore, a systematic review and meta-analysis published in the journal Neuroscience and Biobehavioral Reviews reviewed 11 studies on brain structure in individuals with conduct disorder (CD) (which often co-occurs with ODD). The researchers found consistent evidence of reduced volumes in the prefrontal cortex, amygdala, and insula, which are brain regions involved in emotional regulation, decision-making, and social behavior [68].

One study published in the Journal of Child Psychology and Psychiatry investigated the association between genetic variations in the serotonin transporter gene (SLC6A4) and ODD symptoms in children. The study included a sample of 225 children aged 5 to 10 years old who were assessed for ODD symptoms using parent-reported questionnaires. DNA samples were also collected from the children to analyze the SLC6A4 gene [69]. The results showed that children with a specific variant of the SLC6A4 gene were more likely to exhibit ODD symptoms compared to those without the variant. Furthermore, the association between the gene variant and ODD symptoms was more substantial in children with a history of physical abuse or neglect. This suggests that genetic factors may interact with environmental factors to increase the risk of ODD.

Another study published in the journal Pediatrics examined the association between genetic variations in several neurotransmitter genes, including SLC6A4, and oppositional behavior in children with ADHD. The study included a sample of 176 children with ADHD, of which 39 also met the criteria for ODD. The results showed that variations in the SLC6A4 gene were significantly associated with oppositional behavior in children with ADHD, even after controlling for other genetic and environmental factors [70].

2.1.6. Aggression

Aggression can be a common feature of ADHD, particularly in children and adolescents. Children with ADHD may show a range of aggressive behaviors, such as physical aggression, verbal aggression, and social aggression. They may struggle to control their anger, have difficulty managing frustration, and lash out impulsively in response to stress or provocation. The aggression associated with ADHD can lead to significant problems in social and academic settings, including difficulties forming and maintaining friendships, problems with authority figures, and poor academic performance [71].

Research suggests that various factors, including genetics, brain function and structure, and environmental factors, such as parenting and exposure to violence, may influence the relationship

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between ADHD and aggression. For example, studies have identified differences in brain function and structure in individuals with ADHD who exhibit aggressive behavior, including reduced activity in the prefrontal cortex and abnormalities in the amygdala and striatum [72]. There is also evidence to suggest that certain neurotransmitters, including dopamine, serotonin, and norepinephrine, may play a role in regulating aggression in individuals with ADHD [73].

2.2. Learning Disorders

ADHD (Attention Deficit Hyperactivity Disorder) is often comorbid with other learning disorders, which can further impact an individual's ability to learn and succeed academically. Some common learning disorders that are often associated with ADHD include the following.

2.2.1. Dyslexia

ADHD and dyslexia often co-occur, with research suggesting that up to 25-40% of individuals with ADHD may also have dyslexia and vice versa [74]. Some studies have found that individuals with ADHD and dyslexia may have similar cognitive profiles, including deficits in working memory, processing speed, and attentional control. However, there is also evidence to suggest that dyslexia may be a particular condition that is not simply a manifestation of ADHD [75].

According to a meta-analysis of 26 studies, the prevalence of dyslexia among individuals with ADHD was estimated to be 21.8%, compared to a prevalence of 5.3% in the general population (Willcutt et al., 2010) [76].

A longitudinal study of children with ADHD and dyslexia found that those with both conditions had worse academic outcomes than those with ADHD alone or dyslexia alone (Mayes et al., 2000) [77].

A study of 44 children with ADHD and dyslexia found that a combination of behavioral therapy and stimulant medication was more effective in improving reading skills than either treatment alone (Tannock et al., 2006) [78].

A systematic review of 22 studies on the relationship between ADHD and dyslexia found that while there is evidence of overlap in cognitive deficits, the two conditions may be distinct and require different interventions (Peterson et al., 2017) [79].

A study of college students with ADHD and dyslexia found that they had lower GPAs and were more likely to drop out of college than those with ADHD or dyslexia alone (Rabiner et al., 2010) [80]

2.2.2. Dyscalculia

Dyscalculia is a specific learning disorder that affects an individual's ability to understand and perform mathematical tasks. It is estimated that up to 60% of individuals with ADHD also have dyscalculia, making it a common comorbidity of the disorder [81].

Despite possessing adequate intelligence and having received appropriate educational opportunities, individuals with dyscalculia experience difficulties with mathematical tasks. Dyscalculia primarily affects an individual's ability to comprehend and perform mathematical operations, with particular challenges in areas such as number sense, arithmetic, and mathematical reasoning.

ADHD is characterized by symptoms such as inattention, hyperactivity, and impulsivity, which can affect a person's ability to focus and organize information. This can lead to difficulties with math skills, which are further complicated by the presence of dyscalculia [82].

Dyscalculia is a learning disability that specifically affects a person's ability to understand and perform mathematical concepts. Individuals with dyscalculia may have difficulty understanding number concepts, performing the basic arithmetic, and solving math problems. The presence of dyscalculia in individuals with ADHD can complicate diagnosis and treatment. Clinicians need to assess both conditions and provide appropriate interventions. Early intervention and support can improve outcomes for individuals with ADHD and dyscalculia. Educational interventions such as

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specialized instruction and assistive technology can help individuals with dyscalculia develop math skills. Medication and behavioral therapy can be effective treatments for ADHD [83].

Despite the challenges associated with ADHD and dyscalculia, many individuals with these conditions go on to lead successful and fulfilling lives. With appropriate support and accommodations, individuals with ADHD and dyscalculia can achieve their goals and reach their full potential.

2.2.3. Dysgraphia

Dysgraphia is a learning disability that affects a person's ability to write. While there is limited research explicitly examining dysgraphia in individuals with ADHD, there is some evidence to suggest that there is a higher prevalence of dysgraphia among individuals with ADHD than in the general population.

Individuals with ADHD and dysgraphia may experience challenges with written communication, including messy handwriting, difficulty with spelling and grammar, and trouble organizing their thoughts on paper. They may also struggle with fine motor skills, such as holding a pencil or pen, which can affect their ability to write or draw accurately [84]. A study published in the Journal of School Psychology found that children with dyslexia, another learning disorder that affects reading and writing, often have writing problems that are under-recognized and under-treated. These writing problems include messy handwriting, spelling difficulties, and difficulty organizing thoughts on paper [85]. It's important to note that having ADHD and dysgraphia can also impact academic performance and self-esteem. Children and adults with these conditions may struggle with written assignments, note-taking, and other tasks that require writing, which can lead to frustration and avoidance of these activities.

A study published in the Journal of Attention Disorders found that children with ADHD had a higher prevalence of dysgraphia than children without ADHD. Another study published in the Journal of Learning Disabilities found that children with ADHD and dysgraphia had more severe writing difficulties than children with ADHD alone [86].

2.2.4. Auditory Processing Disorder

Auditory Processing Disorder (APD) and Attention Deficit Hyperactivity Disorder (ADHD) are two different conditions that can impact an individual's ability to process and integrate auditory information. While there is limited research specifically examining the relationship between APD and ADHD, here is a summary of some of the available evidence:

A study published in the Journal of Speech, Language, and Hearing Research found that children with ADHD and APD had more severe impairments in auditory processing compared to children with ADHD alone. The study also found that children with both ADHD and APD had greater difficulty with language and reading comprehension [87].

Another study published in the Journal of Learning Disabilities found that children with ADHD and language-based learning disabilities (which can include APD) had poorer performance on measures of working memory and attention compared to children with ADHD alone [88]. A meta-analysis of studies examining the comorbidity of ADHD and communication disorders, including APD, found that the prevalence of comorbid communication disorders in children with ADHD ranged from 16% to 67% [89]. A study found that children with ADHD and auditory processing difficulties had greater difficulty with attention and were more likely to exhibit hyperactive-impulsive behavior compared to children with ADHD alone [90].

3. Risk of injuries

Research indicates that individuals with ADHD are more likely to experience injuries compared to those without ADHD. For instance, a meta-analysis found that children with ADHD were almost twice as likely to experience injuries compared to children without ADHD. In this study, the most common injuries reported were fractures and head injuries. Similarly, a study by Loe et al. (2011)

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found that adults with ADHD had a higher risk of workplace injuries, car accidents, and other types of injuries [91]. Various factors contribute to the increased risk of injuries in individuals with ADHD. For example, impulsivity, inattention, and hyperactivity may make individuals with ADHD more prone to accidents and injuries [92]. Additionally, individuals with ADHD may engage in risky behaviors, such as reckless driving or extreme sports, that increase the likelihood of injury [93]. However, research also suggests that medication can help reduce the risk of injuries in individuals with ADHD. A study by Mick et al. (2014) found that children with ADHD who were treated with medication had a lower risk of injuries compared to those who were not treated with medication [94].

4. Mechanisms of action

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that involves applying a low electrical current to the scalp to modulate cortical excitability and activity. The exact mechanisms of action of tDCS in ADHD are not fully understood, but several theories have been proposed.

One proposed mechanism is that tDCS modulates the activity of the default mode network (DMN), a set of brain regions that are active during rest and self-referential processing. Abnormal DMN activity has been observed in individuals with ADHD, with increased connectivity between the DMN and task-negative regions, such as the posterior cingulate cortex, and decreased connectivity with task-positive regions, such as the dorsolateral prefrontal cortex (Castellanos et al., 2008) [95]. The default mode network (DMN) is a set of brain regions that are active when an individual is in a resting state or engaged in self-referential processing, such as daydreaming or introspection. The DMN was first identified through functional magnetic resonance imaging (fMRI) studies, which revealed a consistent pattern of activity across several brain regions when participants were not actively engaged in a task [95,96].

The DMN includes several brain regions, including the medial prefrontal cortex, posterior cingulate cortex, precuneus, and angular gyrus. These regions are interconnected by a network of neural pathways allowing communication and information exchange between them. The DMN has been implicated in various cognitive processes, including autobiographical memory retrieval, self-referential thinking, social cognition, and mind-wandering. However, abnormal DMN activity has also been associated with several psychiatric and neurological disorders, including ADHD, depression, and Alzheimer's.[106]

In ADHD, aberrant DMN activity has been observed in several studies. Specifically, individuals with ADHD have been found to have increased DMN connectivity with task-negative regions, such as the posterior cingulate cortex, and decreased connectivity with task-positive regions, such as the dorsolateral prefrontal cortex [97]. This disrupted balance between task-positive and task-negative regions is thought to contribute to the attentional deficits and other symptoms of ADHD.

The DMN has also been a target of brain stimulation techniques such as transcranial direct current stimulation (tDCS) in treating ADHD. Several studies have investigated the effects of tDCS on DMN activity in individuals with ADHD, with some reporting that tDCS can modulate DMN connectivity and improve attentional control [97].

The DMN is a complex and interconnected network of brain regions that plays a vital role in self-referential processing and cognitive functions. Abnormal DMN activity has been implicated in several psychiatric and neurological disorders, including ADHD, and targeting the DMN through brain stimulation techniques such as tDCS may offer new treatment options for these conditions.

Another proposed mechanism by which tDCS may improve symptoms of ADHD is by modulating the activity of neurotransmitters such as dopamine and glutamate. Dopamine and glutamate are two of the most critical neurotransmitters in the brain, playing key roles in attention, motivation, and learning.

Studies have suggested that tDCS can modulate the activity of dopamine and glutamate in several ways. One mechanism by which tDCS may modulate dopamine activity is altering the activity of dopaminergic neurons in the brain. For example, a study by Monte-Silva and colleagues (2013)

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found that tDCS increased dopamine release in the striatum, a critical brain region involved in reward processing and motivation [98,99].

In addition to modulating dopamine activity, tDCS has also been shown to modulate the activity of glutamate, an excitatory neurotransmitter involved in several cognitive processes. A study by Nitsche and colleagues (2007) found that tDCS increased the levels of glutamate in the cortex, a critical brain region involved in attention and working memory [100]. The precise mechanisms by which tDCS modulates dopamine and glutamate activity are still not fully understood. However, it is thought that tDCS may alter the resting membrane potential of neurons, making them more or less likely to fire action potentials. This alteration in neuronal excitability may, in turn, affect the release and uptake of neurotransmitters such as dopamine and glutamate [101].

Another theory is the theory of neural plasticity and neurogenesis proposes that tDCS may improve symptoms of ADHD by promoting changes in brain structure and function. Neural plasticity refers to the brain's ability to change and adapt in response to experiences, while neurogenesis refers to the formation of new neurons in the brain. Studies have suggested that tDCS may promote neural plasticity and neurogenesis in several ways. For example, a study by Fritsch and colleagues (2010) found that tDCS increased the excitability of neurons in the motor cortex, leading to changes in the strength of connections between neurons [102]. Other studies have suggested that tDCS can promote the formation of new synapses and the growth of new dendrites, the branching extensions of neurons that receive signals from other neurons [102]. In addition to promoting neural plasticity and neurogenesis, tDCS has also been shown to enhance the effects of behavioral interventions in individuals with ADHD. For example, a study by Brunoni and colleagues (2014) found that tDCS combined with cognitive training improved working memory performance in individuals with ADHD more than cognitive training alone [103].

The precise mechanisms by which tDCS promotes neural plasticity and neurogenesis are still not fully understood. However, it is thought that tDCS may alter the activity of brain-derived neurotrophic factor (BDNF), a protein that plays a crucial role in promoting the growth and survival of neurons. Several studies have found that tDCS can increase the levels of BDNF in the brain, potentially promoting the growth and survival of new neurons and synapses [104].

Overall, while the mechanisms of action of tDCS in ADHD are not fully understood, the available evidence suggests that tDCS may modulate cortical excitability and activity, rebalance disrupted brain networks, enhance neurotransmitter activity, and promote neural plasticity and neurogenesis. Further research is needed to elucidate these mechanisms and to identify optimal stimulation parameters for the treatment of ADHD.

5. Conclusion

In conclusion, the available research on the use of transcranial direct current stimulation (tDCS) in managing ADHD and its comorbidities is still limited and inconclusive. While some studies suggest that tDCS may have a positive effect on certain ADHD-related comorbidities, such as depression and anxiety, more research is needed to establish a clear relationship between tDCS and these conditions. Additionally, there are several other comorbidities associated with ADHD, such as sleep disorders and substance abuse, where the efficacy of tDCS is yet to be explored. Nevertheless, the potential of tDCS as a non-invasive and safe treatment option for ADHD and its related conditions is promising, and further research in this area is warranted to provide more conclusive evidence of its effectiveness.

References

1. American Psychiatric Association and American Psychiatric Association, Eds., Diagnostic and statistical manual of mental disorders: DSM-5, 5th ed. Washington, D.C: American Psychiatric Association, 2013.
2. C. Gillberg et al., "Co–existing disorders in ADHD –implications for diagnosis and intervention," European Child & Adolescent Psychiatry, vol. 13, no. 1, pp. i80–i92, Jul. 2004, doi: 10.1007/s00787-004-1008-4.
3. "Patterns of psychiatric comorbidity, cognition, and psychosocial func tioning in adults with attention deficit hyperactivity disorder," AJP, vol. 150, no. 12, pp. 1792–1798, Dec. 1993, doi: 10.1176/ajp.150.12.1792.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 April 2023 doi:10.20944/preprints202304.0170.v1

4. C. Cosmo et al., "A Randomized, Double-Blind, Sham-Controlled Trial of Transcranial Direct Current Stimulation in Attention-Deficit/Hyperactivity Disorder," PLOS ONE, vol. 10, no. 8, p. e0135371, Aug. 2015, doi: 10.1371/journal.pone.0135371.
5. P. S. Boggio et al., "Noninvasive Brain Stimulation With High-Frequency and Low-Intensity Repetitive Transcranial Magnetic Stimulation Treatment for Posttraumatic Stress Disorder," J Clin Psychiatry, vol. 71, no. 8, p. 12852, Dec. 2010, doi: 10.4088/JCP.08m04638blu.
6. F. X. Castellanos et al., "Cingulate-Precuneus Interactions: A New Locus of Dysfunction in Adult Attention-Deficit/Hyperactivity Disorder," Biological Psychiatry, vol. 63, no. 3, pp. 332–337, Feb. 2008, doi: 10.1016/j.biopsych.2007.06.025.
7. P. A. Schroeder and C. Plewnia, "Beneficial Effects of Cathodal Transcranial Direct Current Stimulation (tDCS) on Cognitive Performance," J Cogn Enhanc, vol. 1, no. 1, pp. 5–9, Mar. 2017, doi: 10.1007/s41465-016-0005-0..
8. E. M. Valera, S. V. Faraone, K. E. Murray, and L. J. Seidman, "Meta-Analysis of Structural Imaging Findings in Attention-Deficit/Hyperactivity Disorder," Biological Psychiatry, vol. 61, no. 12, pp. 1361–1369, Jun. 2007, doi: 10.1016/j.biopsych.2006.06.011..
9. K. Konrad and S. B. Eickhoff, "Is the ADHD brain wired differently? A review on structural and functional connectivity in attention deficit hyperactivity disorder," Human Brain Mapping, vol. 31, no. 6, pp. 904–916, 2010, doi: 10.1002/hbm.21058.
10. P. Shaw et al., "Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation," Proceedings of the National Academy of Sciences, vol. 104, no. 49, pp. 19649–19654, Dec. 2007, doi: 10.1073/pnas.0707741104.
11. C. E. Curtis and M. D'Esposito, "Persistent activity in the prefrontal cortex during working memory," Trends in Cognitive Sciences, vol. 7, no. 9, pp. 415–423, Sep. 2003, doi: 10.1016/S1364-6613(03)00197-9.
12. J. Holmes, S. E. Gathercole, M. Place, D. L. Dunning, K. A. Hilton, and J. G. Elliott, "Working memory deficits can be overcome: Impacts of training and medication on working memory in children with ADHD," Applied Cognitive Psychology, vol. 24, no. 6, pp. 827–836, 2010, doi: 10.1002/acp.1589..
13. G. C. Burgess, B. E. Depue, L. Ruzic, E. G. Willcutt, Y. P. Du, and M. T. Banich, "Attentional Control Activation Relates to Working Memory in Attention-Deficit/Hyperactivity Disorder," Biological Psychiatry, vol. 67, no. 7, pp. 632–640, Apr. 2010, doi: 10.1016/j.biopsych.2009.10.036..
14. S. V. Faraone et al., "Attention-deficit/hyperactivity disorder," Nat Rev Dis Primers, vol. 1, no. 1, Art. no. 1, Aug. 2015, doi: 10.1038/nrdp.2015.20.
15. CDC, "Attention-Deficit / Hyperactivity Disorder (ADHD)," Centers for Disease Control and Prevention, Jan. 25, 2023. https://go.usa.gov/xRAsU (accessed Mar. 25, 2023)..
16. Attention-deficit hyperactivity disorder: A handbook for diagnosis and treatment, 4th ed. New York, NY, US: The Guilford Press, 2015, pp. xiii, 898.
17. I. D. Bandeira et al., "Transcranial Direct Current Stimulation in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder (ADHD): A Pilot Study," J Child Neurol, vol. 31, no. 7, pp. 918–924, Jun. 2016, doi: 10.1177/0883073816630083.
18. H. Brauer, C. Breitling-Ziegler, V. Moliadze, B. Galling, and A. Prehn-Kristensen, "Chapter 4 - Transcranial direct current stimulation in attention-deficit/hyperactivity disorder: A meta-analysis of clinical efficacy outcomes," in Progress in Brain Research, R. C. Kadosh, T. Zaehle, and K. Krauel, Eds., in Non-invasive Brain Stimulation (NIBS) in Neurodevelopmental Disorders, vol. 264. Elsevier, 2021, pp. 91–116. doi: 10.1016/bs.pbr.2021.01.013.
19. A. F. T. Arnsten, "ADHD and the Prefrontal Cortex," The Journal of Pediatrics, vol. 154, no. 5, p. I-S43, May 2009, doi: 10.1016/j.jpeds.2009.01.018.
20. B. P. Ramos, D. Stark, L. Verduzco, C. H. van Dyck, and A. F. T. Arnsten, "α2A-adrenoceptor stimulation improves prefrontal cortical regulation of behavior through inhibition of cAMP signaling in aging animals," Learn. Mem., vol. 13, no. 6, pp. 770–776, Nov. 2006, doi: 10.1101/lm.298006..
21. N. J. Gamo, M. Wang, and A. F. T. Arnsten, "Methylphenidate and Atomoxetine Enhance Prefrontal Function Through α2-Adrenergic and Dopamine D1 Receptors," Journal of the American Academy of Child & Adolescent Psychiatry, vol. 49, no. 10, pp. 1011–1023, Oct. 2010, doi: 10.1016/j.jaac.2010.06.015..
22. J. K. Seamans and C. R. Yang, "The principal features and mechanisms of dopamine modulation in the prefrontal cortex," Progress in Neurobiology, vol. 74, no. 1, pp. 1–58, Sep. 2004, doi: 10.1016/j.pneurobio.2004.05.006.
23. F. X. Castellanos et al., "Developmental Trajectories of Brain Volume Abnormalities in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder," JAMA, vol. 288, no. 14, pp. 1740–1748, Oct. 2002, doi: 10.1001/jama.288.14.1740.
24. A. Cubillo, R. Halari, C. Ecker, V. Giampietro, E. Taylor, and K. Rubia, "Reduced activation and inter-regional functional connectivity of fronto-striatal networks in adults with childhood Attention-Deficit Hyperactivity Disorder (ADHD) and persisting symptoms during tasks of motor inhibition and cognitive

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 April 2023 doi:10.20944/preprints202304.0170.v1

switching," Journal of Psychiatric Research, vol. 44, no. 10, pp. 629–639, Jul. 2010, doi: 10.1016/j.jpsychires.2009.11.016.
25. N. Makris et al., "Attention and Executive Systems Abnormalities in Adults with Childhood ADHD: A DT-MRI Study of Connections," Cerebral Cortex, vol. 18, no. 5, pp. 1210–1220, May 2008, doi: 10.1093/cercor/bhm156.
26. M. E. Raichle, "The Brain's Default Mode Network," Annual Review of Neuroscience, vol. 38, no. 1, pp. 433–447, 2015, doi: 10.1146/annurev-neuro-071013-014030.
27. R. H. Kaiser et al., "Childhood stress, grown-up brain networks: corticolimbic correlates of threat-related early life stress and adult stress response," Psychological Medicine, vol. 48, no. 7, pp. 1157–1166, May 2018, doi: 10.1017/S0033291717002628.
28. E. M. Valera, S. V. Faraone, K. E. Murray, and L. J. Seidman, "Meta-Analysis of Structural Imaging Findings in Attention-Deficit/Hyperactivity Disorder," Biological Psychiatry, vol. 61, no. 12, pp. 1361–1369, Jun. 2007, doi: 10.1016/j.biopsych.2006.06.011.
29. N. D. Volkow et al., "Depressed Dopamine Activity in Caudate and Preliminary Evidence of Limbic Involvement in Adults With Attention-Deficit/Hyperactivity Disorder," Archives of General Psychiatry, vol. 64, no. 8, pp. 932–940, Aug. 2007, doi: 10.1001/archpsyc.64.8.932.
30. M. E. McLaren, N. R. Nissim, and A. J. Woods, "The effects of medication use in transcranial direct current stimulation: A brief review," Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, vol. 11, no. 1, pp. 52–58, Jan. 2018, doi: 10.1016/j.brs.2017.10.006.
31. A. T. Hill, P. B. Fitzgerald, and K. E. Hoy, "Effects of Anodal Transcranial Direct Current Stimulation on Working Memory: A Systematic Review and Meta-Analysis of Findings From Healthy and Neuropsychiatric Populations," Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, vol. 9, no. 2, pp. 197–208, Mar. 2016, doi: 10.1016/j.brs.2015.10.006.
32. A. M. Landau et al., "Elevated dopamine D1 receptor availability in striatum of Göttingen minipigs after electroconvulsive therapy," J Cereb Blood Flow Metab, vol. 38, no. 5, pp. 881–887, May 2018, doi: 10.1177/0271678X17705260.
33. T. J. Spencer et al., "Further Evidence of Dopamine Transporter Dysregulation in ADHD: A Controlled PET Imaging Study Using Altropane," Biological Psychiatry, vol. 62, no. 9, pp. 1059–1061, Nov. 2007, doi: 10.1016/j.biopsych.2006.12.008.
34. K. Rubia, "Cognitive Neuroscience of Attention Deficit Hyperactivity Disorder (ADHD) and Its Clinical Translation," Frontiers in Human Neuroscience, vol. 12, 2018, Accessed: Apr. 05, 2023. [Online]. Available: https://www.frontiersin.org/articles/10.3389/fnhum.2018.00100
35. K. Blum et al., "Attention-deficit-hyperactivity disorder and reward deficiency syndrome," NDT, vol. 4, no. 5, pp. 893–917, Oct. 2008, doi: 10.2147/NDT.S2627.
36. E. D. Burgund, H. M. Lugar, F. M. Miezin, B. L. Schlaggar, and S. E. Petersen, "The development of sustained and transient neural activity," NeuroImage, vol. 29, no. 3, pp. 812–821, Feb. 2006, doi: 10.1016/j.neuroimage.2005.08.056.
37. A. F. T. Arnsten, "Catecholamine Influences on Dorsolateral Prefrontal Cortical Networks," Biological Psychiatry, vol. 69, no. 12, pp. e89–e99, Jun. 2011, doi: 10.1016/j.biopsych.2011.01.027.
38. S. Cortese et al., "Toward Systems Neuroscience of ADHD: A Meta-Analysis of 55 fMRI Studies," AJP, vol. 169, no. 10, pp. 1038–1055, Oct. 2012, doi: 10.1176/appi.ajp.2012.11101521.
39. S. V. Faraone and J. Biederman, "Neurobiology of attention-deficit hyperactivity disorder," Biological Psychiatry, vol. 44, no. 10, pp. 951–958, Nov. 1998, doi: 10.1016/S0006-3223(98)00240-6.
40. A. F. T. Arnsten and S. R. Pliszka, "Catecholamine influences on prefrontal cortical function: Relevance to treatment of attention deficit/hyperactivity disorder and related disorders," Pharmacology Biochemistry and Behavior, vol. 99, no. 2, pp. 211–216, Aug. 2011, doi: 10.1016/j.pbb.2011.01.020.
41. R. R. Gainetdinov, A. R. Mohn, and M. G. Caron, "Genetic animal models: focus on schizophrenia," Trends in Neurosciences, vol. 24, no. 9, pp. 527–533, Sep. 2001, doi: 10.1016/S0166-2236(00)01886-5.
42. J. Biederman et al., "A Randomized, Double-Blind, Placebo-Controlled Study of Guanfacine Extended Release in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder," Pediatrics, vol. 121, no. 1, pp. e73–e84, Jan. 2008, doi: 10.1542/peds.2006-3695.
43. T. Spencer, J. Biederman, T. Wilens, M. Harding, D. O'donnell, and S. Griffin, "Pharmacotherapy of Attention-Deficit Hyperactivity Disorder across the Life Cycle," Journal of the American Academy of Child & Adolescent Psychiatry, vol. 35, no. 4, pp. 409–432, Apr. 1996, doi: 10.1097/00004583-199604000-00008.
44. M. L. Wolraich et al., "Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents," Pediatrics, vol. 144, no. 4, p. e20192528, Oct. 2019, doi: 10.1542/peds.2019-2528.
45. N. D. Volkow, J. S. Fowler, and G.-J. Wang, "The addicted human brain: insights from imaging studies," J Clin Invest, vol. 111, no. 10, pp. 1444–1451, May 2003, doi: 10.1172/JCI18533.
46. R. A. Barkley, "Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD," Psychological Bulletin, vol. 121, pp. 65–94, 1997, doi: 10.1037/0033-2909.121.1.65.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 April 2023 doi:10.20944/preprints202304.0170.v1

47. S. S. Lee, B. B. Lahey, E. B. Owens, and S. P. Hinshaw, "Few Preschool Boys and Girls with ADHD are Well-Adjusted During Adolescence," J Abnorm Child Psychol, vol. 36, no. 3, pp. 373–383, Apr. 2008, doi: 10.1007/s10802-007-9184-6.
48. A. D. Anastopoulos et al., "Self-Regulation of Emotion, Functional Impairment, and Comorbidity Among ChildrenWith AD/HD," J Atten Disord, vol. 15, no. 7, pp. 583–592, Oct. 2011, doi: 10.1177/1087054710370567.
49. N. D. Volkow et al., "Motivation deficit in ADHD is associated with dysfunction of the dopamine reward pathway," Mol Psychiatry, vol. 16, no. 11, Art. no. 11, Nov. 2011, doi: 10.1038/mp.2010.97.
50. J. Biederman et al., "The long-term longitudinal course of oppositional defiant disorder and conduct disorder in ADHD boys: findings from a controlled 10-year prospective longitudinal follow-up study," Psychological Medicine, vol. 38, no. 7, pp. 1027–1036, Jul. 2008, doi: 10.1017/S0033291707002668.
51. R. A. Barkley, "Distinguishing Sluggish Cognitive Tempo From ADHD in Children and Adolescents: Executive Functioning, Impairment, and Comorbidity," Journal of Clinical Child & Adolescent Psychology, vol. 42, no. 2, pp. 161–173, Mar. 2013, doi: 10.1080/15374416.2012.734259.
52. C. B. H. Surman et al., "Deficient Emotional Self-Regulation and Adult Attention Deficit Hyperactivity Disorder: A Family Risk Analysis," AJP, vol. 168, no. 6, pp. 617–623, Jun. 2011, doi: 10.1176/appi.ajp.2010.10081172.
53. F. X. Castellanos, E. J. S. Sonuga-Barke, M. P. Milham, and R. Tannock, "Characterizing cognition in ADHD: beyond executive dysfunction," Trends in Cognitive Sciences, vol. 10, no. 3, pp. 117–123, Mar. 2006, doi: 10.1016/j.tics.2006.01.011.
54. S. G. Dickstein, K. Bannon, F. Xavier Castellanos, and M. P. Milham, "The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis," Journal of Child Psychology and Psychiatry, vol. 47, no. 10, pp. 1051–1062, 2006, doi: 10.1111/j.1469-7610.2006.01671.x.
55. A. Cubillo, R. Halari, V. Giampietro, E. Taylor, and K. Rubia, "Fronto-striatal underactivation during interference inhibition and attention allocation in grown up children with attention deficit/hyperactivity disorder and persistent symptoms," Psychiatry Research: Neuroimaging, vol. 193, no. 1, pp. 17–27, Jul. 2011, doi: 10.1016/j.pscychresns.2010.12.014.
56. S. H. Kim, S.-H. Baik, C. S. Park, S. J. Kim, S. W. Choi, and S. E. Kim, "Reduced striatal dopamine D2 receptors in people with Internet addiction," NeuroReport, vol. 22, no. 8, p. 407, Jun. 2011, doi: 10.1097/WNR.0b013e328346e16e.
57. [56] Blum K, Noble EP, Sheridan PJ, Montgomery A, Ritchie T, Jagadeeswaran P, Nogami H, Briggs AH, Cohn JB. Allelic association of human dopamine D2 receptor gene in alcoholism. JAMA. 1990 Apr 18;263(15):2055-60. PMID: 1969501.
58. S. R. Chamberlain et al., "Atomoxetine Modulates Right Inferior Frontal Activation During Inhibitory Control: A Pharmacological Functional Magnetic Resonance Imaging Study," Biological Psychiatry, vol. 65, no. 7, pp. 550–555, Apr. 2009, doi: 10.1016/j.biopsych.2008.10.014.
59. J. B. W. Williams and M. First, "Diagnostic and Statistical Manual of Mental Disorders," Encyclopedia of Social Work, Jun. 11, 2013. https:// (accessed Apr. 05, 2023).
60. E. Leibenluft, "Severe Mood Dysregulation, Irritability, and the Diagnostic Boundaries of Bipolar Disorder in Youths," AJP, vol. 168, no. 2, pp. 129–142, Feb. 2011, doi: 10.1176/appi.ajp.2010.10050766.
61. W. E. Copeland, A. Angold, E. J. Costello, and H. Egger, "Prevalence, Comorbidity, and Correlates of DSM-5 Proposed Disruptive Mood Dysregulation Disorder," AJP, vol. 170, no. 2, pp. 173–179, Feb. 2013, doi: 10.1176/appi.ajp.2012.12010132.
62. L. J. Siever, "Neurobiology of Aggression and Violence," AJP, vol. 165, no. 4, pp. 429–442, Apr. 2008, doi: 10.1176/appi.ajp.2008.07111774.
63. T. E. Wilens, J. Biederman, and T. J. Spencer, "Attention Deficit/Hyperactivity Disorder Across the Lifespan," Annual Review of Medicine, vol. 53, no. 1, pp. 113–131, 2002, doi: 10.1146/annurev.med.53.082901.103945.
64. R. C. Kessler et al., "The Prevalence and Correlates of Adult ADHD in the United States: Results From the National Comorbidity Survey Replication," AJP, vol. 163, no. 4, pp. 716–723, Apr. 2006, doi: 10.1176/ajp.2006.163.4.716.
65. J. D. Burke, R. Loeber, and B. Birmaher, "Oppositional Defiant Disorder and Conduct Disorder: A Review of the Past 10 Years, Part II," Journal of the American Academy of Child & Adolescent Psychiatry, vol. 41, no. 11, pp. 1275–1293, Nov. 2002, doi: 10.1097/00004583-200211000-00009.
66. S. D. S. Noordermeer, M. Luman, and J. Oosterlaan, "A Systematic Review and Meta-analysis of Neuroimaging in Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) Taking Attention-Deficit Hyperactivity Disorder (ADHD) Into Account," Neuropsychol Rev, vol. 26, no. 1, pp. 44–72, Mar. 2016, doi: 10.1007/s11065-015-9315-8.
67. D. F. Connor, "Preschool Attention Deficit Hyperactivity Disorder: A Review of Prevalence, Diagnosis, Neurobiology, and Stimulant Treatment," Journal of Developmental & Behavioral Pediatrics, vol. 23, no. 0, p. S1, Feb. 2002.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 April 2023 doi:10.20944/preprints202304.0170.v1

68. L. Passamonti et al., "Neural Abnormalities in Early-Onset and Adolescence-Onset Conduct Disorder," Archives of General Psychiatry, vol. 67, no. 7, pp. 729–738, Jul. 2010, doi: 10.1001/archgenpsychiatry.2010.75.
69. Z. Hawi et al., "The molecular genetic architecture of attention deficit hyperactivity disorder," Mol Psychiatry, vol. 20, no. 3, Art. no. 3, Mar. 2015, doi: 10.1038/mp.2014.183.
70. "Family-Based Genome-Wide Association Scan of Attention-Deficit/Hyperactivity Disorder - Journal of the American Academy of Child & Adolescent Psychiatry." https://www.jaacap.org/article/S0890-8567(10)00290-X/fulltext (accessed Apr. 05, 2023).
71. K. E. Saylor and B. H. Amann, "Impulsive Aggression as a Comorbidity of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents," Journal of Child and Adolescent Psychopharmacology, vol. 26, no. 1, pp. 19–25, Feb. 2016, doi: 10.1089/cap.2015.0126.
72. "Neuroimaging of Inhibitory Control Areas in Children With Attention Deficit Hyperactivity Disorder Who Were Treatment Naive or in Long-Term Treatment | American Journal of Psychiatry." https://ajp.psychiatryonline.org/doi/full/10.1176/ajp.2006.163.6.1052 (accessed Apr. 05, 2023).
73. T. Archer and M. Oscar Berman, "Epigenetics in Developmental Disorder: ADHD and Endophenotypes," J Genet Syndr Gene Ther, vol. 2, no. 1, 2011, doi: 10.4172/2157-7412.1000104.
74. E. G. Willcutt, B. F. Pennington, R. K. Olson, N. Chhabildas, and J. Hulslander, "Neuropsychological Analyses of Comorbidity Between Reading Disability and Attention Deficit Hyperactivity Disorder: In Search of the Common Deficit," Developmental Neuropsychology, vol. 27, no. 1, pp. 35–78, Feb. 2005, doi: 10.1207/s15326942dn2701_3.
75. E. G. Willcutt and B. F. Pennington, "Comorbidity of Reading Disability and Attention-Deficit/ Hyperactivity Disorder: Differences by Gender and Subtype," J Learn Disabil, vol. 33, no. 2, pp. 179–191, Mar. 2000, doi: 10.1177/002221940003300206.
76. E. G. Willcutt et al., "Etiology and neuropsychology of comorbidity between RD and ADHD: The case for multiple-deficit models," Cortex, vol. 46, no. 10, pp. 1345–1361, Nov. 2010, doi: 10.1016/j.cortex.2010.06.009.
77. S. D. Mayes, S. L. Calhoun, and E. W. Crowell, "Learning Disabilities and ADHD: Overlapping Spectrum Disorders," J Learn Disabil, vol. 33, no. 5, pp. 417–424, Sep. 2000, doi: 10.1177/002221940003300502.
78. R. Tannock, A. Ickowicz, and R. Schachar, "Differential Effects of Methylphenidate on Working Memory in ADHD Children with and without Comorbid Anxiety," Journal of the American Academy of Child & Adolescent Psychiatry, vol. 34, no. 7, pp. 886–896, Jul. 1995, doi: 10.1097/00004583-199507000-00012.
79. R. L. Peterson and B. F. Pennington, "Developmental Dyslexia," Annual Review of Clinical Psychology, vol. 11, no. 1, pp. 283–307, 2015, doi: 10.1146/annurev-clinpsy-032814-112842.
80. D. L. Rabiner, A. D. Anastopoulos, E. J. Costello, R. H. Hoyle, S. E. McCabe, and H. S. Swartzwelder, "Motives and Perceived Consequences of Nonmedical ADHD Medication Use by College Students: Are Students Treating Themselves for Attention Problems?," J Atten Disord, vol. 13, no. 3, pp. 259–270, Nov. 2009, doi: 10.1177/1087054708320399.
81. V. Gross-Tsur, O. Manor, and R. S. Shalev, "Developmental Dyscalculia: Prevalence and Demographic Features," Developmental Medicine & Child Neurology, vol. 38, no. 1, pp. 25–33, 1996, doi: 10.1111/j.1469-8749.1996.tb15029.x.
82. J. J. Rucklidge and R. Tannock, "Neuropsychological profiles of adolescents with ADHD: effects of reading difficulties and gender," Journal of Child Psychology and Psychiatry, vol. 43, no. 8, pp. 988–1003, 2002, doi: 10.1111/1469-7610.00227.
83. [82] "The cognitive correlates of third-grade skill in arithmetic, algorithmic computation, and arithmetic word problems." https://psycnet.apa.org/doiLanding?doi=10.1037%2F0022-0663.98.1.29 (accessed Apr. 05, 2023).
84. R. Lingam, J. Golding, M. J. Jongmans, L. P. Hunt, M. Ellis, and A. Emond, "The Association Between Developmental Coordination Disorder and Other Developmental Traits," Pediatrics, vol. 126, no. 5, pp. e1109–e1118, Nov. 2010, doi: 10.1542/peds.2009-2789.
85. V. W. Berninger, K. H. Nielsen, R. D. Abbott, E. Wijsman, and W. Raskind, "Writing problems in developmental dyslexia: Under-recognized and under-treated," Journal of School Psychology, vol. 46, no. 1, pp. 1–21, Feb. 2008, doi: 10.1016/j.jsp.2006.11.008.
86. E. Adi-Japha, Y. E. Landau, L. Frenkel, M. Teicher, V. Gross-Tsur, and R. S. Shalev, "ADHD and Dysgraphia: Underlying Mechanisms," Cortex, vol. 43, no. 6, pp. 700–709, Jan. 2007, doi: 10.1016/S0010-9452(08)70499-4.
87. M. Sharma, S. C. Purdy, and A. S. Kelly, "Comorbidity of Auditory Processing, Language, and Reading Disorders," Journal of Speech, Language, and Hearing Research, vol. 52, no. 3, pp. 706–722, Jun. 2009, doi: 10.1044/1092-4388(2008/07-0226).
88. J. B. Hale et al., "Executive Impairment Determines ADHD Medication Response: Implications for Academic Achievement," J Learn Disabil, vol. 44, no. 2, pp. 196–212, Mar. 2011, doi: 10.1177/0022219410391191.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 April 2023 doi:10.20944/preprints202304.0170.v1

89. [88] Cohen NJ, Vallance DD, Barwick M, Im N, Menna R, Horodezky NB, Isaacson L. The interface between ADHD and language impairment: an examination of language, achievement, and cognitive processing. J Child Psychol Psychiatry. 2000 Mar;41(3):353-62. PMID: 10784082.
90. R. Tannock, R. Martinussen, and J. Frijters, "Naming Speed Performance and Stimulant Effects Indicate Effortful, Semantic Processing Deficits in Attention-Deficit/Hyperactivity Disorder," J Abnorm Child Psychol, vol. 28, no. 3, pp. 237–252, Jun. 2000, doi: 10.1023/A:1005192220001.
91. I. M. Loe and H. M. Feldman, "Academic and Educational Outcomes of Children With ADHD," Journal of Pediatric Psychology, vol. 32, no. 6, pp. 643–654, Jul. 2007, doi: 10.1093/jpepsy/jsl054.
92. R. A. Barkley, K. R. Murphy, and M. Fischer, ADHD in adults: What the science says. in ADHD in adults: What the science says. New York, NY, US: The Guilford Press, 2008, pp. xii, 500.
93. M. J. Groom, E. van Loon, D. Daley, P. Chapman, and C. Hollis, "Driving behaviour in adults with attention deficit/hyperactivity disorder," BMC Psychiatry, vol. 15, no. 1, p. 175, Jul. 2015, doi: 10.1186/s12888-015-0566-y.
94. Z. Chang, B. M. D'Onofrio, P. D. Quinn, P. Lichtenstein, and H. Larsson, "Medication for Attention-Deficit/Hyperactivity Disorder and Risk for Depression: A Nationwide Longitudinal Cohort Study," Biological Psychiatry, vol. 80, no. 12, pp. 916–922, Dec. 2016, doi: 10.1016/j.biopsych.2016.02.018.
95. M. E. Raichle, A. M. MacLeod, A. Z. Snyder, W. J. Powers, D. A. Gusnard, and G. L. Shulman, "A default mode of brain function," Proceedings of the National Academy of Sciences, vol. 98, no. 2, pp. 676–682, Jan. 2001, doi: 10.1073/pnas.98.2.676.
96. R. L. Buckner, J. R. Andrews-Hanna, and D. L. Schacter, "The Brain's Default Network," Annals of the New York Academy of Sciences, vol. 1124, no. 1, pp. 1–38, 2008, doi: 10.1196/annals.1440.011.
97. T. Chou, J. M. Hooley, and J. A. Camprodon, "Transcranial Direct Current Stimulation of Default Mode Network Parietal Nodes Decreases Negative Mind-Wandering About the Past," Cogn Ther Res, vol. 44, no. 1, pp. 10–20, Feb. 2020, doi: 10.1007/s10608-019-10044-9.
98. K. Monte-Silva et al., "Induction of Late LTP-Like Plasticity in the Human Motor Cortex by Repeated Non-Invasive Brain Stimulation," Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, vol. 6, no. 3, pp. 424–432, May 2013, doi: 10.1016/j.brs.2012.04.011.
99. M. A. Nitsche, M.-F. Kuo, R. Karrasch, B. Wächter, D. Liebetanz, and W. Paulus, "Serotonin Affects Transcranial Direct Current–Induced Neuroplasticity in Humans," Biological Psychiatry, vol. 66, no. 5, pp. 503–508, Sep. 2009, doi: 10.1016/j.biopsych.2009.03.022.
100. M. A. Nitsche, D. Liebetanz, A. Antal, N. Lang, F. Tergau, and W. Paulus, "Chapter 27 Modulation of cortical excitability by weak direct current stimulation – technical, safety and functional aspects," in Supplements to Clinical Neurophysiology, W. Paulus, F. Tergau, M. A. Nitsche, J. G. Rothwell, U. Ziemann, and M. Hallett, Eds., in Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation, vol. 56. Elsevier, 2003, pp. 255–276. doi: 10.1016/S1567-424X(09)70230-2.
101. C. J. Stagg and M. A. Nitsche, "Physiological Basis of Transcranial Direct Current Stimulation," Neuroscientist, vol. 17, no. 1, pp. 37–53, Feb. 2011, doi: 10.1177/1073858410386614.
102. B. Fritsch et al., "Direct Current Stimulation Promotes BDNF-Dependent Synaptic Plasticity: Potential Implications for Motor Learning," Neuron, vol. 66, no. 2, pp. 198–204, Apr. 2010, doi: 10.1016/j.neuron.2010.03.035.
103. A. R. Brunoni and M.-A. Vanderhasselt, "Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: A systematic review and meta-analysis," Brain and Cognition, vol. 86, pp. 1–9, Apr. 2014, doi: 10.1016/j.bandc.2014.01.008.
104. G. Polanczyk, M. S. de Lima, B. L. Horta, J. Biederman, and L. A. Rohde, "The Worldwide Prevalence of ADHD: A Systematic Review and Metaregression Analysis," AJP, vol. 164, no. 6, pp. 942–948, Jun. 2007, doi: 10.1176/ajp.2007.164.6.942.
105. S. V. Faraone, C. Bonvicini, and C. Scassellati, "Biomarkers in the Diagnosis of ADHD – Promising Directions," Curr Psychiatry Rep, vol. 16, no. 11, p. 497, Oct. 2014, doi: 10.1007/s11920-014-0497-1.

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