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Investigating the Expression of NMDA Receptors and Cognitive Function in Children with ADHD: A Comparative Study

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Abstract

Emerging evidence from clinical, genetic, and animal model studies suggests that N-methyl-D-aspartate (NMDA) glutamate receptors (NMDAR) may contribute to the pathophysiology and etiology of neurological and psychiatric disorders. Patients with impaired NMDA receptors often experience psychological symptoms. Therefore, we hypothesized that NMDAR receptors play a key role in the development of attention deficit hyperactivity disorder (ADHD). In this comparative analytical study, we utilized the Western blotting method to assay the expression levels of NMDA subunits NR1 and NR2 in the blood plasma of 50 male individuals diagnosed with ADHD, comparing them to 20 healthy controls. The findings from the Western blotting analysis provide support for the hypothesis that individuals with ADHD exhibit significantly lower levels of NR1/2 receptors compared to those without the disorder. Further research is needed to explore the potential causal relationship between reduced NR1/NR2 receptor levels and the development of ADHD.

Keywords: NMDA receptors; NR1; NR2; ADHD; Expression

Introduction

Structures

NMDA receptor is a heterotetramer consisting of two NR1 subunits, which bind to glycine, and two NR2 subunits, which bind to glutamate. The binding of both glycine and glutamate is required for the activation of the receptor and the subsequent opening of its ion channel. These receptors are further divided into four subtypes (GluN2A-D) [1]. Each subunit contains an amino-terminal domain, an agonist-binding domain, a transmembrane domain, and a carboxy-terminal domain [2,3]. The NR1 subunit contains the channel pore-forming domain, while the NR2 subunit contains the binding site for regulatory molecules such as Mg2+, Zn2+, and polyamines [1]. In addition, the carboxy-terminal domain of the NR2 subunit contains several protein-protein interaction domains that allow the receptor to interact with other intracellular proteins and signalling pathways [3]. The complex structure of the NMDA receptor allows for its regulation by a variety of factors, including post-translational modifications, and protein-protein interactions [4,5].

Function

NMDA receptors play an essential role in synaptic plasticity, learning and memory, as well as in the pathophysiology of various neurological and psychiatric disorders. Hansen et al. [6], discussed the role of these receptors in the induction of LTP and proposed a model of synaptic plasticity where the activation of NMDA receptors results in calcium ion influx and the subsequent activation of intracellular signalling pathways that strengthen synaptic connections. The diversity of NMDA receptor subunits allows for fine-tuning of synaptic transmission and dysfunction of NMDA receptors is implicated in various neurological and psychiatric disorders [1]. The association between NMDA receptor's disfunction and cognitive state is well stablished. Liu and colleagues' study [7] showed that the dysfunction of NMDA receptors may contribute to the cognitive decline in Alzheimer's disease. Also, in another study Coyle et al. [8], confirmed the association between the NMDA receptor hypofunction, particularly a reduction in the activity of the NR2A subunit and

the development of cognitive deficits observed in schizophrenia.

Furthermore, the impairment of these receptors may play a role in the development of depression [2]. Sanacora et al. [9] reported that the administration of ketamine, a non-competitive NMDA receptor antagonist, produced rapid and significant antidepressant effects in patients with treatment resistant depression. As a result, several therapeutic drugs that interact with NMDA receptor have been developed to treat major depressive disorders. In 2014 Dang and colleagues provided a comprehensive review of these novel therapeutic drugs and their potential in targeting the glutamatergic system for treating MDD [10].

NMDA receptors have been linked to the underlying causes of ADD and ADHD. Although the precise mechanisms are still not completely understood, studies indicate that dysfunction of NMDA receptors may play a role in the observed symptoms of these disorders [11]. This could be due to the impaired synaptic plasticity, which relies on proper functioning of NMDA receptors, or the modulation of dopamine neurotransmission. The involvement of NMDA receptors in ADD/ADHD is an active area of research, and further investigations are necessary to fully comprehend their specific role and develop more targeted treatments.

Pharmacology

NMDA receptor antagonists such as ketamine and phencyclidine (PCP) have been used as anaesthetics and recreational drugs, and as noted earlier have potential therapeutic effects for the treatment of MDD and other psychiatric disorders. Namely, Tariq et al. [12] studied the effect of NR2B-selective antagonists such as MK-0657 and CP-101,606 and confirmed for their therapeutic potential in the treatment of depression. Additionally, preclinical studies such as the one conducted by Large (2007) have shown that antagonists selective for the NR2B subunit of the NMDA receptor, such as ifenprodil and Ro25-6981, have antipsychotic-like effects in animal models of schizophrenia. However, there is a lack of consistent evidence indicating that there are differences in the overall levels of NR1 and NR2 receptors between individuals with schizophrenia and those without the disorder [13]. Furthermore, NR2A selective antagonists have been proposed as a potential treatment for Alzheimer's disease [14]. For instance, D-cycloserine, an NMDA receptor agonist has been shown to enhance learning and memory and may have potential therapeutic effects for the treatment of cognitive deficits in disorders such as Alzheimer's disease [7,15].

There is growing evidence that both the dopamine and glutamate systems are involved in attention-deficit hyperactivity disorder (ADHD). In ADHD, there may be excessive activity in the glutamate system, which is linked to a less active state in the dopamine system which will result in ADHD symptoms such as mood swing, altered focus and attention problems (Kristiansen et al., 2007). Many authors have reported the presence of serum NMDA antibodies in varying proportions of patients with ADHD; however, many others have not been able to confirm this. Because of the contradictory findings reported in various studies, more definitive research on this issue is required. Hence, this study investigated the NR1/NR2 subunit of NMDA receptors in patients with ADHD (n=50) and healthy controls (n=20) to evaluate if ADHD behaviours is associated with the expression level of NMDA receptor subunits of NR1/NR2.

Table 1: Associated features, prevalence, and factors influencing ADHD diagnosis.

Associated Features	Prevalence	Major Environmental factors	Principal Neurobiological pathways
impulsivity (American Psychiatric Association [APA] 2013; Winstanley et al., 2006)	The rate of hereditability is estimated as high as 77- 88% (Grimm et al., 2020).	Preterm birth and low /extremely low birth weight. the more extreme the low weight, the greater the risk (APA,2013; Driga & Drigas, 2019)	Altered arousal mechanism (Kleberg et al., 2023)
Difficulty maintaining attention (APA, 2013; Winstanley et al., 2006)	It is highly polygenic and is caused by multiple gene variations and genomic regions rather than one single gene (Faraone & Larsson, 2019).	Maternal hypothyroidism or neonatal thyroid function (Drover et al., 2019)	dysfunction autonomic nervous system (Bellato et al., 2020)

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organisational impairment (APA, 2013; Pievsky & McGrath, 2018)	Some of the identified genes are as follows:	Maternal obesity (Andersen et al., 2018)	volumetric reduction, premature structure, and impaired function in multiple corticolimbic areas of the brain particularly in the left lateral superior temporal gyrus (STG), the left anterior cingulate cortex (ACC) the superior longitudinal fasciculus (SLF) (Hoogman et al., 2017; Si et al., 2021) and the basal ganglia (Nakao et al., 2011) which are involved in executive function and impulse control (Gehricke et al., 2017).
slower pace self-control development (APA, 2013; Mitchell, 2010)	Dopamine D4 receptor gene (DRD4) on chromosome 11p15.5 responsible for dopamine transmission (Thapar & Stergiakouli, 2008)	Gestational diabetics (Rowland & Wilson, 2021)	imbalance in noradrenergic system (Arnsten, 2009).
social participation difficulties (APA, 2013; Mitchell, 2010)	Dopamine D5 receptor gene (*DRD5*) on chromosome 4p15.1-15.3 (Thapar & Stergiakouli, 2008)	Excessive maternal selenium in maternal red blood cell (RBC)	malfunctioned neurotransmitter system (Blum et al., 2008)
difficulty to have effective communication (APA, 2013; Green et al., 2014)	Dopamine transporter gene (*SLC6A3* or *DAT1*) 5p13.3 is responsible for the reuptake of dopamine in the presynaptic cleft (Thapar & Stergiakouli, 2008)	Preeclampsia during pregnancy (Maher et al., 2020)	Sex hormones such as high level of testosterone can impact the level of dopamine, serotonin and epinephrin which are involved in ADHD (Huang et al., 2022).
mild delay in language development (Charney et al., 2013)	Catechol-O-Methyltransferase (*COMT*) on chromosome 22q11.2 is involved in dopaminergic pathway (Mill et al., 2005)	Fetal nutrient status (plasma folate, zinc, magnesium, and vitamins D 3, B12) (Cortés-Albornoz, et al., 2021).	
aggression (Hamshere et al., 2013)	mutation of Synaptosomal-associated protein of 25kD (*SNAP25*) (Thapar & Stergiakouli, 2008; Willcutt et al., 2007)	fetal tobacco exposure increases the risk of ADHD (Gustavson et al., 2017; Knopik et al., 2016).	
Depressive behaviours (Riglin, et al., 2021)	ring Finger Protein 122[RNF122] located on chromosome 4 at the 4q28.1 locus	mother's alcohol consumption during pregnancy (Eilertsen et al., 2017; San Martin Porter et al., 2019; Pagnin et al., 2019)	
minor physical anomalies such as overweight (32%) hypermobility (30 %) visual impairment (24 – 29%) straight eyebrows (22%) (Myers et al., 2017), low-set ears	(Garcia-Martínez et al. 2017)	maternal mental issues such as anxiety and depression (Wannapaschaiyoget. al., 2023)	
hypertelorism (APA, 2013)	protein Tyrosine Phosphatase Receptor Type F [PTPRF] in chromosome 1 (Dark et al., 2018)	socioeconomic status. The rate and severity of ADHH has been reported to be higher in single parent families and those with shortest education. (Torvik et al., 2020)	
highly arched palate (Won et al., 2017)	adhesion G protein-coupled receptor L3 [ADGRL3] located in chromosome 1 (precisely in 1p21.3) (Faraone, & Larsson, 2019)	use of electronic devices has been linked to more severe ADHD in both adults and children. (Anbarasan et al., 2020; Beyens et al., 2018)	
increased risk of suicide attempts when comorbid with mood, conduct or substance disorders (Balazs & Kereszteny, 2017; Charney et al., 2013)	mutation in the CDH2 gene on chromosome 18q12 (Halperin et al., 2021).	dietary pattens such as increased intake of junk, sugary and processed food may increase the risk of ADHD. Additionally, a healthy eating pattern such as the Mediterranean diet has been used as a therapeutic approach for ADHD (Pinto et al., 2022)	

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		Exposure to environmental pollutatnts (e.g., lead Methylmercury (MeHg, or oranic acids) Forns et. al., 2018; Skogheim et al., 2021)	
		Fever and infections during pregnancy and in offspring (Werenberg et al., 2016)	
		parenting style specifically authoritarian and uninvolved parenting (Rakesh, 2023; Shahi-nuzzaman et al., 2022)	

ADHD

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental syndrome that affects both children and adults, characterized by symptoms of hyperactivity, impulsivity, and inattention. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [15], Diagnostic, ADHD can be divided into three subgroups, combined-type ADHD (ADHD-C), predominantly inattentive-type ADHD (ADHD-I), predominantly hyperactive/impulsive ADHD. Clinically, the most common subtypes are ADHD-I and ADHD-C (Willcutt, 2012). The dopamine hypothesis of ADHD proposes that abnormalities in dopamine neurotransmission contribute to the condition, as stimulant drugs that enhance dopamine levels are effective in treating symptoms [13]. Genetic studies have revealed connections between the onset and severity of ADHD symptoms and both the quantity and functionality of glutamate receptors. Likewise, other studies have indicated that impaired glutamate receptors can lead to dysfunction in the dopaminergic systems, resulting in symptoms such as depression, anxiety, difficulty in focusing, and memory disturbances. Table 1 summarizes the associated features of ADHD, explores its prevalence, and discusses the genetic and environmental factors linked to the condition.

Materials and Methods

Participants

After obtaining approval for the research and acquiring the ethical code from the Ethics Committee of the university, the diagntostic tests were prepared, and a referral letter was obtained for the Roshd rehabilitation clinic. The inclusion criteria for participants were as follows: (a) meeting the diagnostic criteria for mixed ADHD as assessed by the Structured Clinical Interview of DSM-IV [15], (b) being between 6 and 15 years of age, and (c) being male. Limiting the selection to a single gender was done to mitigate potential confounding factors associated with gender differences. The exclusion criteria involved individuals with a history of severe neurological and neuropsychological problems other than ADHD, as well as those with severe physical illness.

Table 2: Participant demographics, clinical characteristics.

	ADHD	Healthy Controls (HC)
N	50	20
Age (Yrs)	11.2 ± 4.6	12.6 ± 2.7
Age of onset (yrs)	9.5 ± 5.2	NA
Illness duration (mos)	14.5 ± 20.6	NA
Mean Standard score FSRCQ IVA 2	86.6 ± 5.3	NA
Mean Standard score FSAQ IVA 2	84.3 ± 6.1	NA
ADHD K-SADS-PL – Screening	2.8 ± 4.4	NA

To recruit healthy subjects, advertisements were utilized, targeting siblings of the patients at Roshd clinic. These potential participants were screened and matched in terms of age and gender to the patient group. Demographic data for both patients and normal controls are summarized in table 2. The selection of study participants was based on convenience sampling [16]. The final sample consisted of 70 male individuals aged 6 to 15 years, including 50 subjects diagnosed with mixed ADHD and 20 age-matched healthy controls. Prior to the assessments and cognitive testing, all participants refrained from taking any medication for a minimum of 24 hours. The demographic characteristics and sample size are presented in table 2.

Ethical considerations

Prior to data collection, written informed consent was obtained from parents and children who participated in this work after providing detailed information about the study to ensure their informed participation. Additionally, the anonymity of the participants and the confidentiality of the collected information was guaranteed. All personal and sensitive information collected from participants was treated with the utmost confidentiality. Identifying information, such as names and contact details, was removed and replaced with unique codes to ensure the anonymity of participants. Only authorized researchers had access to the

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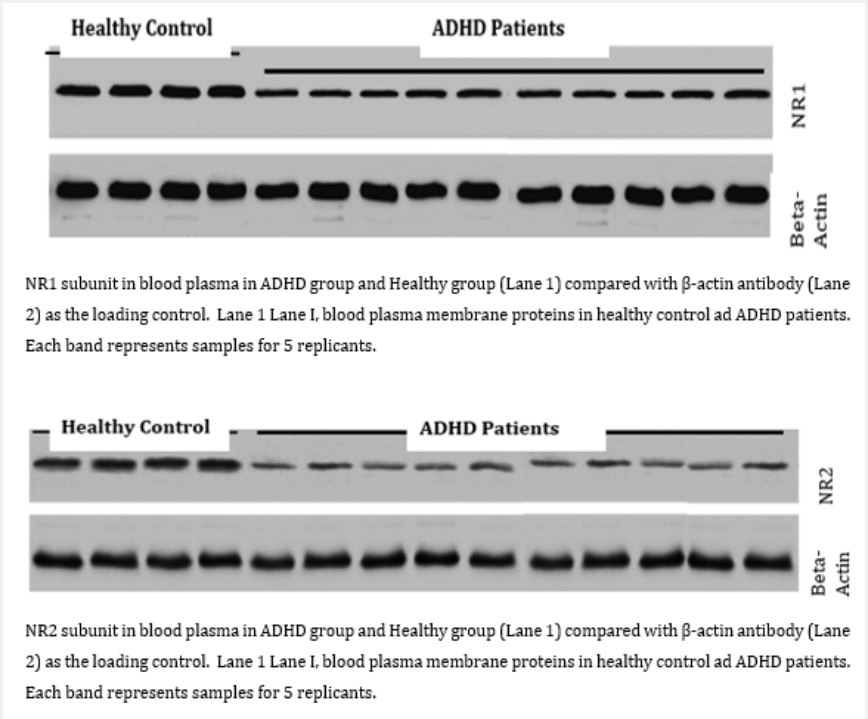
data, and all digital files were password protected. Every effort was made to minimize any potential harm to the participants. The research protocol was designed to avoid any physical, psychological, or emotional harm. Participants were not exposed to any undue stress or discomfort during the study, and they were debriefed after the study to ensure their well-being.

Diagnostic assessment of ADHD

All ADHD participants underwent a thorough diagnostic process conducted by a consultant psychiatrist with expertise in ADHD. This process involved the utilization of pre-assessment questionnaires and semi-structured interviews aligned with the diagnostic criteria outlined in the DSM-5 [15]. To enhance the validity of the diagnosis, a trained assessor, working as part of the research team, administered the K-SADS-PL (Kiddie Schedule for Affective Disorders and Schizophrenia) [17], and the IVA2 (Integrated Visual and Auditory Continuous Performance) [18], tests. The assessor received specialized training from a consultant child and adolescent psychiatrist to ensure accurate administration and interpretation of these assessment tools. Trained administrators introduced the purpose of the K-SADS-PL [17,19], to the parents and the child, explaining the scoring requirements to transition from the screening interview to the diagnostic supplement. Questions were posed to both the parent and the child, with the assessor integrating their responses. While the ADHD module of the K-SADS-PL involves parent-child participation, we primarily relied on the parent's or caretaker's accounts of the child's behavior. In the screening interview, responses were rated as absent (coded as 1), subthreshold levels (coded as 2), or threshold levels (coded as 3). This interview focused on four items related to ADHD symptoms, namely: (a) "Difficulty sustaining attention," (b) "Easily distracted during task or play activities," (c) "Difficulty remaining seated," and (d) "Impulsivity." The IVA-2 CPT [18] assesses attention and impulsivity by measuring responses to 500 intermixed auditory and visual stimuli presented 1.5 seconds apart. The task involves clicking the mouse when the target stimuli, represented by an auditory or visual "1," appear, while refraining from clicking for the foil stimuli, represented by an auditory or visual "2." Quotient scores for all IVA-2 scales are reported as standard scores, with a mean of 100 and a standard deviation of 15 as reported in table 2.

Evaluation of the blood samples

Sample collection: Blood samples were collected from both the study and control groups by drawing 7ml blood from the antecubital vein. No specific timing or fasting requirements were imposed for the blood collection process. The collected blood was placed in standard biochemistry tubes and then centrifuged at a speed of 1,000× g for a duration of 25 minutes. After centrifugation and washing, the serum samples were separated and promptly transferred to a freezer set at -80°C. These samples were stored under the same conditions for both the patients and the blood doners (control group).



NR1 subunit in blood plasma in ADHD group and Healthy group (Lane 1) compared with β-actin antibody (Lane 2) as the loading control. Lane 1 Lane I, blood plasma membrane proteins in healthy control ad ADHD patients. Each band represents samples for 5 replicants.

NR2 subunit in blood plasma in ADHD group and Healthy group (Lane 1) compared with β-actin antibody (Lane 2) as the loading control. Lane 1 Lane I, blood plasma membrane proteins in healthy control ad ADHD patients. Each band represents samples for 5 replicants.

Figure 1

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Quantifying NR1 and NR 2 receptors: The stored serum samples were utilized for quantifying the expression levels of NR1 and NR2 receptors using Western blotting. Briefly, Plasma proteins were separated on a 7% reducing SDS gel and transferred to PVDF (polyvinylidene difluoride) membrane. The membrane was incubated with Beta-Actin antibodies, followed by washing steps to remove unbound antibodies. The protein bands corresponding to NR1 and NR2 receptors was visualized using fluorescence. The intensity of these bands was then be quantified using computer-assisted imaging analysis software (ImageJ) [20], to determine the relative abundance of NR1 and NR2 receptors in the blood samples from both the study and control groups (Figure 1).

Result

All analysis was performed with SPSS software version 26 [20]. The mean expression of NR1 receptors in the experimental group (ADHD) was 97.7 (Table 3 and 4). While the mean expression of NR1 receptors in the healthy control group was 124.25 (Table 5 and 6). The mean expression of NR2 receptors in the ADHD group was 154.6, compared to the mean expression of NR2 receptors in the healthy control group, which was 173.25. This implies a difference in the mean expression levels of NR2 receptors between the ADHD and healthy control groups.

$$t = \frac{(\overline{x_1} - \overline{x_2}) - (\mu_1 - \mu_2)}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}}$$

Using the following formula, the t-value is -19.32149. The p-value is < .00001. The result is significant at $p < .05$ (Table 4)

Table 3: Expression of NR1 proteins in the ADHD group. Each G1-G10 group shows the mean for 5 blood samples.

ADHD	total	G1	G2	G3	G4	G5	G6	G7	G8	G9	G10
N	50	5	5	5	5	5	5	5	5	5	5
MW/ kDa		95	98	93	100	103	98	99	93	93	105

N1: 50, df1 = N - 1 = 50 - 1 = 49, M1: 97.7
SS1: 810.5, s21 = SS1/ (N - 1) = 810.5/(50-1) = 16.54

Table 4: Expression of NR1 proteins in the healthy group. Each G1-G4 group shows the mean for 5 blood samples.

ADHD	total	G1	G2	G3	G4
N	20	5	5	5	5
MW/ kDa		112	128	130	127

N2: 20, df2 = N - 1 = 20 - 1 = 19, M2: 124.25
SS2: 1023.75, s22 = SS2/ (N - 1) = 1023.75/ (20-1) = 53.88

Table 5: Expression of NR2 proteins in the ADHD group. Each G1-G10 group shows the mean for 5 blood samples.

ADHD	total	G1	G2	G3	G4	G5	G6	G7	G8	G9	G10
N	50	5	5	5	5	5	5	5	5	5	5
MW/ kDa		163	168	150	146	140	160	162	158	150	149

N1: 50, df1 = N - 1 = 50 - 1 = 49, M1: 154.6
SS1: 3532, s21 = SS1/ (N - 1) = 3532/(50-1) = 72.08

Table 6: Expression of NR1 proteins in the ADHD group. Each G1-G10 group shows the mean for 5 blood samples.

ADHD	total	G1	G2	G3	G4
N	20	5	5	5	5
MW/ kDa		180	160	170	183

N2: 20, df2 = N - 1 = 20-1 = 19, M2: 173.25, SS2: 1633.75
s22 = SS2/ (N - 1) = 1633.75/ (20-1) = 85.99
The t-value is -8.08756. The p-value is < .00001. The result is significant at $p < .05$ with a $p < 0.05$, we reject the null hypothesis and conclude that there is a significant difference in the mean molecular weight of NR1 receptors between the ADHD and healthy control groups.

Discussion

The present study uncovered a significant association between ADHD and abnormal expression of NMDA glutamate receptors, specifically the NR1 and NR2 subunits, in the blood plasma of individuals with ADHD compared to healthy controls. These findings highlight a potential role for NMDA receptors in the pathophysiology of ADHD, suggesting that impaired NMDA receptor function may contribute to the development

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of this neurodevelopmental disorder [21]. Dysfunction of NMDA receptors can have complex effects on the levels of neurotransmitters like dopamine and epinephrine in the brain, which can contribute to ADHD symptoms [22,23].

NMDA receptors play a crucial role in regulating the release of dopamine in the brain, as demonstrated in numerous studies associated with reward, motivation, and attention [19,23]. When NMDA receptors do not function properly, it can disrupt the balance of dopamine release [22,24]. This dysregulation can lead to both excessive and insufficient dopamine levels in different brain regions [19]. The excessive dopamine release in some areas of the brain can result in hyperactivity, impulsivity, and difficulties in regulating attention, which are hallmarks of ADHD [25,26]. Additionally, low dopamine levels can result in difficulties with motivation, focus, and reward processing, contributing to the inattentive symptoms seen in ADHD [26].

Furthermore, when NMDA receptors are disrupted, it can lead to an overactive stress response, causing increased release of epinephrine. This heightened stress response can exacerbate ADHD symptoms, particularly the hyperactivity and impulsivity components [27]. However, it's important to note that while the study establishes a correlation, it does not determine causation. Further research is needed to elucidate the exact mechanisms and causal relationships between reduced NR1/NR2 receptor expression and the development of ADHD, as well as to investigate potential therapeutic interventions targeting NMDA receptors in the management of ADHD symptoms [28-39].

The implications of the study's results are far-reaching and carry significant importance for the field of ADHD research and clinical practice. Firstly, these findings advance the understanding of ADHD by highlighting the involvement of NMDA glutamate receptors, adding a new dimension to the established dopamine-centric model. This complexity underscores the need for a more holistic view of ADHD's neurobiological underpinnings, prompting researchers to explore the intricate interplay between various neurotransmitter systems. Secondly, the results offer potential therapeutic avenues, suggesting that interventions targeting NMDA receptor function may hold promise in managing ADHD symptoms. This could diversify treatment options, potentially minimizing side effects and enhancing treatment efficacy [40-49].

Thirdly, the study contributes to the emerging field of personalized medicine in ADHD, where specific genetic or environmental factors linked to reduced NMDA receptor expression may guide tailored treatment approaches. Lastly, beyond ADHD, these findings have broader implications for understanding brain function, particularly in neuropsychiatric disorders influenced by glutamatergic signaling. In essence, these results matter as they deepen our comprehension of ADHD, offer therapeutic potential, pave the way for personalized care, and contribute to our broader understanding of brain function in neuropsychiatric contexts [50-77].

Limitations

Limitations: This study has several limitations that need to be considered. Firstly, one limitation is the relatively small sample size, which may affect the generalizability of the findings. Secondly, the recruitment of participants was done through convenience sampling, which means that the participants were selected based on their easy accessibility rather than using a random sampling method. It is important to note that random sampling is generally preferred in order to obtain a representative sample and minimize potential biases. Therefore, the findings should be interpreted with caution, considering the limitations of the study design and the sampling method employed.

Suggestion for future research

To build upon these findings, future research avenues should delve into several key areas. Firstly, longitudinal studies could help elucidate whether reduced NR1/NR2 receptor expression precedes the onset of ADHD or is a consequence of the disorder. This would provide critical insights into the causal relationship. Secondly, investigations into the genetic and environmental factors influencing NMDA receptor expression in ADHD could identify at-risk populations and inform targeted interventions. Furthermore, experimental studies exploring the effects of NMDA receptor modulation in animal models of ADHD could help establish causation and assess potential therapeutic approaches. Lastly, a more comprehensive exploration of the interaction between the glutamatergic and dopaminergic systems in ADHD could provide a nuanced understanding of the disorder's neurobiology.

Conclusion

On the basis of findings of this study, we conclude that individuals with ADHD have significantly less NR1/NR2 proteins, and therefore potentially fewer functional NMDA receptors in their blood plasma. Impaired synaptic plasticity can disrupt the normal communication between brain regions involved in attention and impulse control, potentially leading to attention deficits and hyperactivity.

Additionally, reduced expression of NR1/NR2 impairs the dopaminergic system which is closely associated with the regulation of attention and reward processing and further contributing to the symptoms of ADHD.

Additionally, While the findings from our research have indicated a link between NR1/NR2 receptor dysfunction and ADHD symptoms, the precise nature of this relationship and the directionality of the causation have yet to be fully elucidated and it remains uncertain whether ADHD leads to a decrease in NR1/NR2 receptor expression or if the reduced expression of NR1/NR2 receptors contributes to the manifestation of ADHD and associated neurodevelopmental disorders.

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Conflict of Interest Statement

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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