**REVIEW**

# Learning and Memory Impairments With Attention-Deficit/Hyperactivity Disorder

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Received August 3, 2023
Accepted November 2, 2023

**Summary**

ADHD is a common chronic neurodevelopmental disorder and is characterized by persistent inattention, hyperactivity, impulsivity and are often accompanied by learning and memory impairment. Great evidence has shown that learning and memory impairment of ADHD plays an important role in its executive function deficits, which seriously affects the development of academic, cognitive and daily social skills and will cause a serious burden on families and society. With the increasing attention paid to learning and memory impairment in ADHD, relevant research is gradually increasing. In this article, we will present the current research results of learning and memory impairment in ADHD from the following aspects. Firstly, the animal models of ADHD, which display the core symptoms of ADHD as well as with learning and memory impairment. Secondly, the molecular mechanism of has explored, including some neurotransmitters, receptors, RNAs, etc. Thirdly, the susceptibility gene of ADHD related to the learning and impairment in order to have a more comprehensive understanding of the pathogenesis.

**Key words**

Learning and memory • ADHD • Review

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## Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common chronic neurodevelopmental disorder that affects from 3 % to 7 % of children and adolescents worldwide [1]. ADHD is characterized by persistent inattention, hyperactivity, and impulsivity, which are often accompanied by learning and memory impairments [2]. Working memory is an important part of executive function, which serves as both the storage workstation of long-term memory and the basis for advanced cognitive functions including learning, language, and understanding [3,4]. Therefore, working memory deficits are likely to contribute to learning and cognitive processing problems [5].

With research advances, increasing evidence shows that ADHD-related learning and memory impairments play an important role in the disorder's characteristic executive function deficits, which seriously impact academic and cognitive development, and daily social skills, also causing serious burden for families and society [6-8]. There is also ample evidence suggesting that adolescents and adults with ADHD continue to experience obstacles from processing speed, distraction, and learning and memory abilities [9]. Use of methylphenidate (MPH), an effective medicine for treating attention, impulsivity, and cognitive function, has also increased among adult patients [10,11].

With gradual recognition of the importance of learning and memory impairments, researchers have more

deeply, and across many fields, explored the mechanism of this in ADHD. For example, dopamine (DA), serotonin (5-HT), N-methyl-D-aspartate (NMDA), and up- or down-regulation of upstream molecules involved in related pathways, all impact expression of a series of proteins and affect physiological activities [8,12-14]. ADHD is a multifactorial disorder, related to both genetic and environmental factors [15]. International twin studies on children with ADHD have described a hereditary range of 71–90 %; though they have not identified exact genetic profiles, scientists are attempting to find the best gene–trait correlation through research investigating candidate genes, genome-wide association, and copy number variants [16,17].

To develop a more comprehensive understanding of the pathogenesis of learning and memory defects in ADHD, we present the current research on this topic from several perspectives. First, we describe the current animal models of ADHD, which display both the core disorder symptoms and learning and memory impairments. Second, we explore the molecular mechanisms, including involvement of neurotransmitters, receptors, and RNAs. Third, we discuss genetic susceptibility in ADHD, specifically related to learning and memory impairments.

## Animal models of ADHD with learning and memory impairments

Most studies to date on the mechanism of learning and memory impairments in ADHD have been conducted at the non-human animal level; therefore, selecting an appropriate animal model is important [18]. Three factors in establishing a good animal model are important: face, construct, and predictive validities [19]. Regan *et al.* [19] asserted that although there is presently no rodent model that captures all ADHD characteristics, several show promise. Herein, we describe several commonly used ADHD animal models, with learning and memory impairments, in addition to inattention, hyperactivity, and impulsivity (Table 1).

**Table 1.** Animal models of ADHD displaying inattention hyperactivity, impulsivity as well as learning and WM impairment

| Model | Face validity | Construct Validity | Predictive validity | Limitations | Others | References |
|---|---|---|---|---|---|---|
| *SHR* | inattention hyperactivity, impulsivity, learning, and memory impairment | disturbances in dopamine, norepinephrine and glutamate function is parallel with the evidence of ADHD patients | MPH and APH can attenuate ADHD like behaviors. | No gender differences | The control of WKY | [20-27] |
| *DAT-KO mouse* | inattention hyperactivity, impulsivity, learning, and memory impairment | DAT changes found in ADHD patients | MPH can improve hyperactivity and learning disorders | DAT is not absence but reduced in ADHD | ADHD including growth delay and death before maturity | [28-31] |
| *LPHN3-KO mouse and rat* | inattention hyperactivity, impulsivity, learning, and memory impairment | Variants found in ADHD patients | amphetamine, attenuates hyperactivity and activity | New model needs more data | - | [32-36] |
| *NDRG2-KO mouse* | inattention hyperactivity, impulsivity, learning, and memory impairment | SNP in NDRG2 risked to ADHD | not established treatment of | NDRG2 rescued hyperactivity but routine MPH not effective | new idea for the pathogenesis of ADHD | [37-38] |

*Spontaneously hypertensive and Wistar Kyoto rats*

In ADHD research, spontaneously hypertensive rats (SHR), and the control Wistar Kyoto (WKY) rats, are the most widely used animal model. SHR are hyperactive, impulsive, inattentive, and have learning and memory deficits compared with WKY [20]. Effective first-line ADHD drugs can attenuate ADHD-like behaviors in SHR [21]. Additional evidence has shown that the SHR displays disturbances in DA, norepinephrine (NE), and glutamate functions, consistent with evidence of defects on the neural circuits required for learning and memory formation in patients with ADHD [22-24]. The Campden behavior test has shown that total motor activity, average speed, and maximum speed are higher for SHR than for WKY [25]. And in the eight-arm radial maze, there is a clear tendency for errors, indicating hyperactivity, impulsivity, and learning and working memory deficits in SHR [26]. SHR also exhibits dysfunction of the NE system related to movement, learning, and cognition [24]. In addition, with ADHD drug treatment, SHR open field test average speed, time spent in the central area, and number of center visits can be reduced, while Morris water maze (MWM) number of platform penetrations and target quadrant residence time can be increased, indicating improved learning and memory [27]. This cumulative evidence supports SHR as a relatively ideal ADHD animal model.

*Dopamine transporter knockout mice*

DA transporter (DAT) knockout (KO) mice, which lack the gene encoding DAT, exhibit hyperactivity and spatial memory deficits in new environments. Cliff avoidance shows this animal model to be hyperactive and have impaired attention, response inhibition, learning, and memory [28]. MPH can improve hyperactivity and learning ability in DAT-KO mice by augmenting DA levels in the PFC [29]. In these mice, decreased DA receptor D2 may affect long-term potentiation (LTP), leading to decreased synaptic strength and impaired associative learning [30]. However, DAT-KO mice can also show unpredictable phenomenon related to impaired DAT function, such as growth delay and death before maturity [31].

## Latrophilin-3 knockout mice and rats

In recent years, latrophilin-3 (LPHN3), which plays a role in regulating neuroplasticity, has attracted extensive research activity [32]. Among Turkish population, Researchers have found that LPHN3 rs6551665 and rs1947274 polymorphisms are significantly associated with ADHD and LPHN3 rs6551665 polymorphism may be related to poor response to treatment in ADHD [33]. Animal research has also shown that LPHN3 KO (LPHN3-KO) mice have a reduced response to amphetamine compared with baseline. In the open field test, these mice are hyperactive; in the continuous performance test, they have increased premature responses, indicating impulsivity; and in the MWM, they exhibit spatial deficits and memory impairments [34,35]. Studies exploring the mechanism of this have found that it may be related to the downregulation of DA receptor D1 and upregulation of DAT [35,36]. In addition, Fallgatter *et al.* examined the effects of LPHN3 haplotype on neural activity, using a visual task to find that patients with ADHD and two copies of the LPHN3 risk haplotype have more errors compared with those with at least one LPHN3 non-risk haplotype [35,36]. These results indicate that LPHN3 is closely related to ADHD-based learning and memory impairments. Thus, although the LPHN3-KO mouse and rat models may become valuable ADHD animal models, more in-depth research is needed.

*N-myc downstream-regulated gene 2-knockout mice*

There is evidence that the N-myc downstream-regulated gene 2 (NDRG2) plays a role in the pathogenesis of ADHD [37]. Chinese children heterozygous for rs1998848, a single nucleotide polymorphism (SNP) in NDRG2, had higher risk of ADHD compared with children homozygous for rs1998848 [38]. In the open field test, NDRG2-KO mice have a significantly increased total distance and numbers of lines crossed. In the 5-choice serial reaction time task (5-CSRTT), NDRG2-KO mice exhibit display altered attention and impulsivity. In a novel object recognition test, NDRG2-KO mice display impaired memory [38]. Moreover, NDRG2 treatment can rescued hyperactivity in NDRG2-KO mice, but routine MPH is ineffective [38]. This cumulative evidence indicates that NDRG2 deficiency can result in an ADHD phenotype, which is different from the DA deficit hypothesis. This provides a novel direction for evaluating the pathogenesis of ADHD.

## Molecular biology of learning and memory impairments in ADHD

*DA system*

DA system dysfunction is the most classic pathogenesis of ADHD. Rhodes *et al.* found that MPH,

the first-line drug treatment for ADHD, can increase synaptic DA concentration by inhibiting DAT action, to achieve therapeutic effects and improve working memory task performance among children with ADHD [39]. At present, the two most well-studied candidate functional genes are DAT gene DAT1 and DA receptor D4 (DRD4), which are also associated with ADHD learning and memory disability.

DAT1 has a polymorphic variable number tandem repeat (VNTR), with its 10-repeat (10R) and nine-repeat (9R) alleles occurring frequently [40]. Scientists have shown that ADHD carriers of 9R have higher working memory-related activity compared with controls [41]. Chi-Yung *et al.* found significant diagnosis × genotype interactions associated with working memory level, preliminarily suggesting that DAT1 VNTR polymorphism may modulate working memory-related activity among children with ADHD [42]. In addition, when Brown *et al.* studied the relations among DAT1, working memory, and adult ADHD and the results showed 9R is related to ADHD and marginal DAT1 is associated with task-related suppressions [43].

Li *et al.* examined DA receptor levels in the PFC of SHR and compared learning and memory abilities with WKY [44], finding that DRD4, but not other DA receptors, was significantly downregulated in SHR. Considering that there were no other gene marker differences, they thought this memory performance difference may be closely associated with DRD4. Yin *et al.* used ABT-724, a D4R-selective agonist, to find that SHR displayed spatial learning, hyperactivity, and non-selective attention impairments compared with controls, and that ABT-724 treatment can alleviate both hyperactivity and spatial learning impairment in SHR [45]. In addition, most investigators assert that the 7-repeat allele of the DRD4 receptor gene is a risk factor for ADHD, and that children with ADHD who have this gene have lower verbal intelligence, operational intelligence, and working memory abilities compared with those without this gene [46]. However, other studies have found no significant association between this gene and working memory performance [47]. Therefore, more research may be needed.

*5-HT*

Serotonergic system disruption has also been implicated in ADHD [48]. Research on both animal models and adults with psychiatric diagnoses have shown that the neurotransmitter 5-HT is closely associated with learning and memory processes [49]. Previous studies have shown that moderate doses of MPH, can enhance learning and memory abilities, while higher doses have the opposite result [50]. Salma *et al.* further revealed that animals administered moderate MPH doses, and showing improved performance, had higher 5-HT metabolism, while those administered higher doses had impaired memory and downregulated 5-HT receptor expression [51]. However, in youth with ADHD, Zepf *et al.* found no association between 5-HT expression and verbal declarative memory [52]. Therefore, more research concerning the association between 5-HT and ADHD-related learning and memory impairments is warranted, especially in adults with ADHD.

*Glutamate*

Researchers have also identified glutamatergic dysfunction in ADHD pathogenesis [53]. There is a marked increase in glutamate in some brain areas with ADHD, and glutamate level has been associated with the ADHD symptoms of hyperactivity and impulsivity [54,55]. The glial glutamate transporter GLT1 plays an important role in glutamatergic neurotransmission. Hiraoka *et al.* found GLT1 knocko(GLT1-KO) mice exhibit ADHD symptoms of hyperactivity, impulsivity, and impaired memory [56]. Assessing the excitatory synaptic function and analyzing NMDA receptors in an ADHD animal model and control, Shikana *et al.* found that the former has impaired cortical excitatory synapses, based on NMDA receptor dysfunction [57]. Others have also found that MPH, the medicine for treating ADHD, can enhance NMDA receptor-mediated excitatory postsynaptic currents and improve PFC-mediated memory and attention [58]. To explore the mechanism for this, Kawade *et al.* studied caspase-3 and phosphorylated Akt, which is often used to cause a ADHD-like condition, finding that working memory errors were greatly increased and NMDA receptor expression dramatically changed [59]. Moreover, Jensen *et al.* found that transmission in hippocampal CA3-to-CA1 synapses of SHR were significantly reduced, and that NMDAR-containing NR2B subunits contributed substantially to LTP induction, thus leading to learning and memory dysfunction [13].

*Acetylcholine receptors*

Increasing evidence shows that acetylcholine receptors (nAChRs) also play a role in ADHD. Neuronal nAChR agonists improve cognitive function and increase

expressions of DA, 5-HT, and glutamate [60,61]. In animal models, nicotinic ABT-418, a nAChR agonist, can significantly improve SHR memory, and ABT-418 treatment greatly improves expressions of cortical α4 and β2 nAChR subunits, and hippocampal α4 subunit. Moreover, different doses of Moreover, in an animal model, Jeong *et al.* found that treadmill exercise can alleviate spatial learning deficits by enhancing BDNF and TrkB expressions in the SHR [62,63]

*Neurotrophic factors and synaptic proteins*

Brain-derived neurotrophic factor (BDNF), a neurotrophin nerve growth factor family member, is involved in neuronal survival and differentiation, neurotransmitter modulation, and neuronal plasticity, which can significantly affect learning and memory [64]. Corominas-Roso *et al.* found that serum BDNF is altered in patients with ADHD, and that when treated with medications that increase DA levels, levels of BDNF and its TrkB receptor are increased in some brain areas [14]. Liang-Jen *et al.* showed that BDNF is associated with sex-specific ADHD susceptibility; its expression in boys with ADHD is higher than in controls, while levels in girls with ADHD are lower compared with controls. Boys with higher BDNF expression also performed worse on the Wechsler Intelligence Scale for Children, 4th edition, including the working memory test [65]. Moreover, in an animal model, Jeong *et al.* found that treadmill exercise can alleviate spatial learning deficits by enhancing BDNF and TrkB expressions in the SHR [62].

Neurexins are highly polymorphic presynaptic cell-adhesion molecules that play critical roles in establishing and maintaining synaptic connections. Neurexin 1 (NRXN1) has been described in neuro-developmental disorders, including autism spectrum disorder and ADHD [66]. Zhang *et al.* injected intracerebroventricular HBAD-r-NRXN1 virus, showing that NRXN1 overexpression improved learning and memory performance of the SHR, and that expression of synapse-related hippocampal genes was consistent with changes in water maze learning ability. Furthermore, through RNA-seq sequencing, they preliminarily found that the mechanism may be related to the influence of the 5-hydroxytryptamine receptor [67].

Homer proteins, localized at the postsynaptic density of glutamatergic excitatory synapses, play a crucial role in cognitive function [68]. Hong *et al.* found that hippocampal levels of Homer 1a and 2a/b mRNA/protein are significantly lower in SHR compared with WKY rats. SHRs treated with MPH had higher learning and memory abilities, and levels of hippocampal Homer 1a and Homer 2a/b were up-regulated [69]. This indicates that Homer protein, Homer 1a, and Homer 2a/b may be involved in the mechanism of ADHD learning and memory deficits, though further research should be performed.

## Risk genes

Cadherin 13 (CDH13) has been associated with impulsivity and hyperactivity in ADHD [70] (Table 2). Ziegler *et al.* revealed that a common genetic variation of CDH13 has an important impact on neural processing during working memory tasks [71]. Kiser *et al.* found that CDH13-deficient mice have cognitive impairments, highlighting that CDH13 is related to memory formation and cognitive flexibility. In addition, CDH13 KO mice have enhanced inhibitory driving force of pyramidal neurons in hippocampal CA1, resulting in excitatory/inhibitory changes closely related to learning and memory processes [72]. Furthermore, Kiser *et al.* found that Cdh13-deficient mice have cognitive impairments, emphasizing that CDH13 is related to memory formation and cognitive flexibility [73]. Thus, CDH13 may contribute to symptomatic core dysfunctions of social and cognitive impairments in ADHD.

Gastrointestinal tract (GIT) proteins are widely expressed throughout the brain and largely related to genes influencing intellectual disability [74]. With advanced single molecule RNA sequencing, McCafrey *et al.* identified GIT1 as one of several differentially expressed genes between those with ADHD and control [75]. An intronic single-nucleotide polymorphism in GIT1, the minor allele of which causes reduced GIT1 expression, shows a strong association with ADHD susceptibility in humans. Martyn *et al.* found that GIT1 knockdown mice display learning and memory impairments; their exploration of the mechanism for this showed that GIT1 loss can reduce hippocampal synapse density and structural plasticity, leading to cognitive dysfunction [76]. Meanwhile, Won *et al.* found amphetamine can normalize the impaired memory of GIT1-deficient mice [77]. In summary, GIT1 plays a role in learning and memory impairments in ADHD.

As a common childhood central nervous system disorder, ADHD is often comorbid with other dysfunctions [78]. Studies have implicated doublecortin domain containing protein 2 (DCDC2), the reading

disabilities risk gene, which is associated with hyperactivity, inattention, and impulsivity [79] (Table 2). And DCDC2 mutations can lead to long-term memory deficits [80]. Thus, further research exploring the role of DCDC2 in ADHD learning and memory impairments would be valuable.

Studies has already suggested a possible function of ataxin-1 (ATXN1) in learning and memory processes [81]. Ten years ago, Rizzi *et al.* found that ATXN1 and other SNPs in areas 6p25-21.2 and 14q11.2-12 are related to intelligence in ADHD [82]. In addition, a study of five individuals with *de novo* heterozygous truncating mutations in capicua (CIC) who share similar clinical features, including intellectual disability, ADHD, and autism spectrum disorder, indicated that ATXN1 capicua (ATXN1-CIC) may be closely related to some neurobehavioral phenotypes, including learning and memory deficits [83]. Hsiang-Chih *et al.* discovered that in mice, specific deletion of forebrain ATXN1-CIC leads to hyperactivity, learning and memory deficits, and abnormal maturation and maintenance of upper layer cortical neurons [83,84] (Table 2).

As catechol-O-methyltransferase (COMT) is involved in synaptic DA catabolism, many studies have focused on its role in ADHD [85-87]. Gothelf *et al.* found that low COMTVal158Met allele activity can increase ADHD risk [86]. COMT is not only related to ADHD behavior, it may also be associated with cortical thickness and surface area [88]. Numerous studies have also shown that this COMT SNP is related to executive function in ADHD [89]. However, a recent meta-analysis revealed no significant association between COMTVal158Met and ADHD [90] (Table 2). Therefore, more research should be performed to explore its role.

**Table 2.** Some risk genes associated with ADHD and learning and WM impairment

| Gene | Description | Findings | References |
|---|---|---|---|
| *DAT1* | responsible for rapid uptake of DA from the synaptic cleft | modulate WM-related brain activity among ADHD children | [40-43] |
| *DRD4* | highly expressed in central nervous system and regulates signal transduction of nerve cell | 7-repeat allele of D4 receptor gene associated with worse working memory performance | [44-47] |
| *CDH13* | Crucial for neuro- developmental processes | impacts neural processing during working memory tasks | [70-73] |
| *GIT1* | widely expressed throughout the brain and related to intellectual disability genes | loss of GIT1 leads to cognitive dysfunctions in mice | [75-77] |
| *DCDC2* | a member of the doublecortin family related to abnormal neuronal migration | both heterozygous and homozygous mutations of Dcdc2 result in persistent visuo-spatial memory deficits, as well as visual discrimination and long-term memory deficits | [78-80] |
| *ATXN1* | interacts with large protein complexes, binds RNA, and is thought to be involved in transcriptional repression | ATXN1–CIC in forebrain leads to learning and memory deficits in mice | [81-84] |
| *COMT* | important in dopaminergic neurotransmission. | numerous studies have also pointed that this COMT SNP is related to the executive function of ADHD but some meta-analysis revealed no association | [85-90] |

## Conclusion

Impaired learning and memory in ADHD often seriously affects individual's cognitive, academic, social skills, and other development, and may represent a heavy burden on families and society. However, the mechanism of learning and memory impairments in ADHD is as yet unclear, and effective clinical treatment methods are

lacking. Herein, we described several aspects of the research progress related to learning and memory impairments in ADHD, to contribute a more comprehensive understanding of this disorder.

## Conflict of Interest

There is no conflict of interest.

## Acknowledgements

This work was supported by the Youth Program of the National Natural Science Foundation of China (No.82101618) and the Key Discipline of Maternal and Child Health in Jiangsu Province (FXK201705).

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