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RECEIVED 03 January 2024

ACCEPTED 10 April 2024

PUBLISHED 23 April 2024

## CITATION

Long J, Li H, Liu Y, Liao X, Tang Z, Han K,  
Chen J and Zhang H (2024) Insights into the  
structure and function of the hippocampus:  
implications for the pathophysiology and  
treatment of autism spectrum disorder.  
*Front. Psychiatry* 15:1364858.  
doi: 10.3389/fpsy.2024.1364858

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# Insights into the structure and function of the hippocampus: implications for the pathophysiology and treatment of autism spectrum disorder

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The hippocampus is one of the brain areas affected by autism spectrum disorder (ASD). Individuals with ASD typically have impairments in hippocampus-dependent learning, memory, language ability, emotional regulation, and cognitive map creation. However, the pathological changes in the hippocampus that result in these cognitive deficits in ASD are not yet fully understood. In the present review, we will first summarize the hippocampal involvement in individuals with ASD. We will then provide an overview of hippocampal structural and functional abnormalities in genetic, environment-induced, and idiopathic animal models of ASD. Finally, we will discuss some pharmacological and non-pharmacological interventions that show positive impacts on the structure and function of the hippocampus in animal models of ASD. A further comprehension of hippocampal aberrations in ASD might elucidate their influence on the manifestation of this developmental disorder and provide clues for forthcoming diagnostic and therapeutic innovation.

## KEYWORDS

autism spectrum disorder (ASD), hippocampus, learning, memory, cognitive map, anxiety, animal models

## 1 Introduction

Autism spectrum disorder (ASD) is a developmental disability resulting from a combination of genetic and environmental factors, with an estimated prevalence of 0.72% globally (1). The most characteristic symptoms of ASD are impaired social communication and stereotyped or repetitive behaviors (2). In addition, ASD is associated with a typical profile of difficulties across various domains of cognition, including memory, learning, language ability, emotion, and cognitive map creation (3, 4). It has long been recognized that impaired memory for faces, working, and social scenes in individuals with ASD contributes to clinical manifestations of the disorder, such as executive dysfunction (5, 6). The co-occurrence of ASD and learning disability is common, with previous estimates suggesting that as many as three-quarters of individuals with ASD have impaired learning abilities, including language learning skills (7). Language delay is an important feature of autistic children – word and speech learning difficulties are noticeable early in development and continue throughout the school-aged years (8, 9). Individuals with ASD often experience emotional dysregulation, including symptoms of anxiety, which are associated with a range of negative mental and physical health outcomes (10). Data from several navigation and search tasks suggest that people with ASD were slower at learning spatial distribution regularities, less efficient in exploring an environment, and more likely to revisit the area they have already explored (11–13).

The hippocampus has consistently been a brain structure of interest in the seek for physiopathological mechanisms and rehabilitation treatment of ASD, given its important role in memory (14), learning (15), language ability (16), emotional regulation (17), and cognitive map creation (14). For example, recently researchers found that increased recruitment of the hippocampus compensated for decreased connectivity between medial temporal lobes and the posterior medial network during relational encoding tasks, which supported preserved episodic memory in individuals with ASD (18). Previous observations in ASD adults have also suggested that altered hippocampal functioning contributes to difficulties with structural learning that are likely to underlie more complex cognitive processes, including episodic memory, learning processes, and cognitive map creation (19). The language impairments observed in some individuals with ASD are linked to abnormalities in the hippocampal regions (20). Moreover, recent evidence indicates that altered neuronal projection and chemical metabolites in the amygdala-hippocampus region modulate emotional regulation in ASD (21, 22).

Herein, we will first review structural and functional abnormalities in the hippocampus of individuals with ASD and discuss discrepancies in the results of existing studies. In the next part, we will discuss the known genetic, environment-induced, and idiopathic animal models of ASD, mostly in mice and rats, that exhibit hippocampal synaptic plasticity impairments and hippocampus-dependent behavioral deficits. Then, we will summarize the main findings from pharmacological and non-pharmacological interventions for ASD that have been shown to positively affect the structure and function of the hippocampus. Directing more attention to the involvement of hippocampal

pathology in the aetiology of ASD and ASD-related behaviors will provide new insights into pathogenic mechanisms, contributing to innovative molecularly or cellularly targeted therapies.

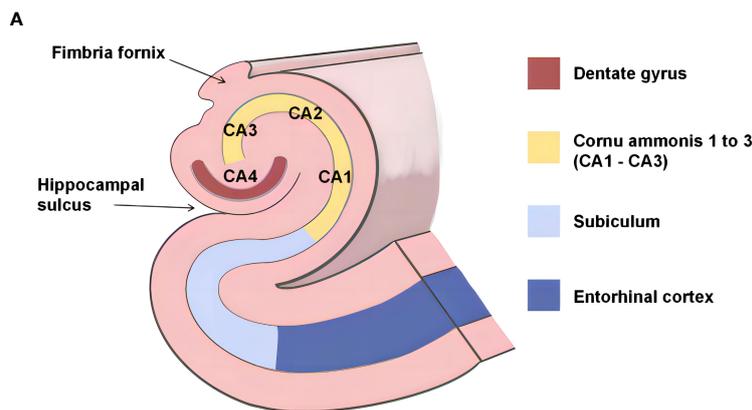
## 2 Hippocampal involvement in individuals with ASD

The adult human hippocampus, a prominent part of the limbic system, has a three-dimensional tortuous structure that resembles a seahorse because of its arched shape in the axial plane. Based on the cellular composition, the hippocampus can be anatomically divided into four subregions, namely cornu ammonis one (CA1) to cornu ammonis four (CA4) (23). In addition to the hippocampus, the hippocampal formation comprises the dentate gyrus, subiculum, presubiculum, parasubiculum, and entorhinal cortex. The dentate gyrus retains the capacity for neurogenesis throughout an individual's lifespan, which is widely believed to play a pivotal role in cognitive processes such as learning and memory (Figure 1A) (24). The fornix is a primary outflow bundle of the hippocampus and wraps around the thalamus. The hippocampus extends its axons into the fornix to establish synaptic connections with neurons in the mammillary body, which then project fibers via the mammillothalamic tract toward the anterior thalamic nucleus. Subsequently, the cingulate gyrus that contains a large number of myelinated fibers receives a connection from the anterior thalamic nucleus. The cingulate gyrus curves over the corpus callosum and stretches into the parahippocampal region and the entorhinal cortex. In this way, it forms a closed loop by returning to the hippocampal formation. This intrinsic neural pathway, known as the Papez circuit, has long been considered to be responsible for regulating emotions, memories, and learning processes (Figure 1B) (25, 26).

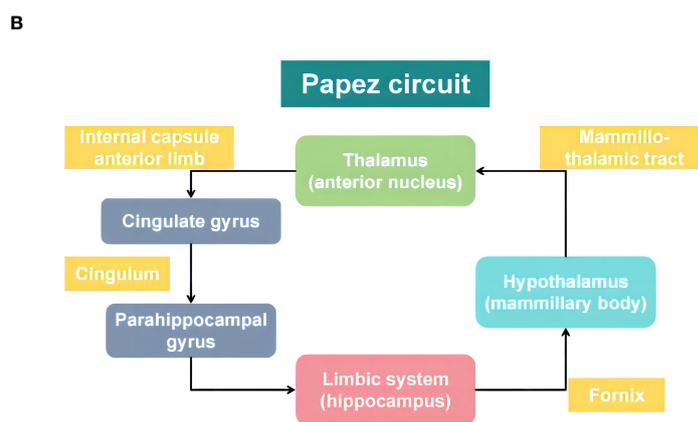
The volume of the human hippocampus increases linearly throughout gestation and the first two years after birth, and continues to increase slowly thereafter, suggesting that the crucial developmental period of the human hippocampus is likely to be before the age of two (27, 28). Extensive research has proven that social and behavioral impairments specific to individuals with ASD also emerge between the ages of one-and-a-half and two years, which lead to diagnostic delays until at least three to four years of age (29, 30). It is therefore argued that the developmental timeline of the hippocampus is probably consistent with the behavioral developmental milestones of ASD (31). To sum up, considering the importance of the hippocampus in learning, memory, language ability, emotional regulation, and cognitive map creation, it could conceivably be hypothesized that gaining an understanding of the structural and functional characteristics of the hippocampus in ASD may offer novel perspectives on the pathogenesis and therapeutic targets for ASD.

### 2.1 Hippocampal volume changes

The advancement of neuroimaging methods has significantly increased the ability to observe alterations in the morphology and



Reference: Parkin AJ. Human memory: novelty, association and the brain. *Curr Biol.* 1997;7(12):R768-9.



Reference: Bubbs EJ, et al. Hippocampal - diencephalic - cingulate networks for memory and emotion: An anatomical guide. *Brain Neurosci Adv.* 2017;1(1):2398212817723443.

FIGURE 1

(A) Anatomy of the adult human hippocampus (Ref: Parkin AJ. Human memory: novelty, association and the brain. *Curr Biol.* 1997;7(12):R768-9); (B) Papez circuit of the human hippocampus (Ref: Bubbs EJ, Kinnavane L, Aggleton JP. Hippocampal - diencephalic - cingulate networks for memory and emotion: An anatomical guide. *Brain Neurosci Adv.* 2017;1(1):2398212817723443). This figure is created by using Adobe Photoshop and PowerPoint.

brain activation patterns of individuals diagnosed with ASD over the past decades. In particular, since the late 1980s, when the first research of ASD using magnetic resonance imaging (MRI) was published, various MRI modalities, including different types of functional MRI, structural MRI, and diffusion tensor imaging, have been reported to effectively facilitate the non-invasive clinical diagnosis of ASD. These publications emphasize that the clinical symptoms of ASD are correlated with volumetric abnormalities in different areas of the brain, including the hippocampus. For instance, extensive MRI research has demonstrated abnormalities in hippocampal volume in individuals with ASD when compared to typically developing people, which is proven to be associated with aberrant autobiographical memory, impaired language skills, social communication deficit, and emotional problems in individuals with ASD (32–34).

Sussman and co-workers (35) have observed a decreased relative volume of the left hippocampus in 72 children and adolescents with ASD. Similarly, a study comparing autistic adults without intellectual disability and healthy community volunteers, found that the reduction in hippocampal volume in the autistic

subjects was apparent when corrected for total brain volume (36). Another research based on the ABIDE database also found decreased gray-matter volume in the posterior hippocampus among a large sample of participants with ASD as compared to typically developing controls (32). As these studies all included high-functioning autistic individuals (Full-Scale IQ > 80), the reduction in hippocampal volume is likely to reflect features of autism itself, rather than features of the intellectual deficits that typically accompany autism (36). In other words, autistic traits have a robust correspondence with reduced brain volume in the hippocampus that is related to social processing, working memory, perceptual reasoning, and spatial learning. One possible hypothesis is that high-functioning autistic populations may experience an adaptive reduction in hippocampal volume as a result of their decreased specific functional demands on the hippocampus and altered interactions with the environment (37). Decreased hippocampal volume in ASD individuals was also related to impaired language skills, including verbal learning and memory (32, 38). It has also been suggested that left hippocampal volume is a positive predictor of early language development in females, but not in males (39). Furthermore, it is worth mentioning that in many

studies that have reported reductions in hippocampal volume among ASD subjects, only reductions in relative hippocampal volume (percentage of total brain volume) have been observed rather than the absolute volume (35, 36, 40). Numerous studies have now firmly established that individuals with ASD have a significantly larger head circumference and a higher prevalence of macrocephaly than age-matched healthy subjects (41), which could explain the reduced relative hippocampal volume in the ASD group.

Surprisingly, in contrast to the aforementioned findings, an MRI study discovered larger volumes of the hippocampus bilaterally in ASD adults with IQ > 100 when compared to healthy controls (42). Likewise, Xu et al. (43) found evidence of larger absolute hippocampal volume in adults with ASD and adequate intelligence than that of healthy adults based on the ABIDE datasets. The *Intense World Theory* posits that ASD traits may be attributed to the activation of a molecular syndrome, which sensitizes gene expression pathways to excessively respond to environmental stimulation. Under normal circumstances, these pathways facilitate brain development through enriched environments; however, when sensitized, they can lead to accelerated brain development in response to environmental stimuli (44). This theory focuses on the neocortex and the amygdala, but it may also apply to other brain regions, such as the hippocampus. For example, the chronic stress process in ASD enhances amygdala activity, which may initially result in hypertrophy of the hippocampus as it moderates the amygdala activity through multiple reciprocal connections (34). The amygdala and hippocampus also play a major role in olfaction. Research has shown that the severity of taste and smell dysfunction is inversely related to the hippocampal volume, and females with ASD have more severe taste and olfactory impairment than males (45). These theories reflect characteristic behavioral variations in ASD and remain to be elucidated in the future. Another possible hypothesis suggests that the increased size of the hippocampus in people with ASD may be due to an enhancement in experience-dependent function (43, 46). Indeed, individuals with ASD have been reported to excel in certain cognitive domains for which the hippocampus is responsible (e.g. visuospatial abilities) compared to typically developing individuals, but these differences may be driven by task demands (31). Current scientific opinion still holds that ASD can lead to a range of hippocampus-related dysfunctions, which are linked to abnormalities in the volume of the hippocampus (32–34). The assertion that individuals with ASD are more proficient than their neurotypical peers in a specific hippocampus-dependent function is a limited occurrence and cannot be generalized to the entire autistic population (4).

In addition to these observations, a number of researches have reported no difference in the hippocampal volume between ASD individuals and healthy volunteers (47–49). The above inconsistent findings on hippocampal size can actually be attributed to the heterogeneity of ASD individuals. For example, the age range is a significant confounding factor because individuals with ASD appear to consistently have larger hippocampus than their healthy peers from childhood to adolescence (46), but in adulthood, their hippocampus begins to decrease (36), or in some cases, remain stable (47). Although several studies have reported no correlation

between age and hippocampal volume in individuals with ASD (35, 42), this may be because of the broad age range of participants, which appears to neutralize the disparities. Second, sex is another important determinant of hippocampal volume in people with ASD. Possibly due to the higher prevalence of ASD in males, existing studies have included a larger sample of male participants. It has been reported that male ASD subjects had faster hippocampal volume growth and greater hippocampal asymmetry than female subjects (50, 51). Relative volumes of both the left and right hippocampus were smaller in females with ASD than in age-matched males (35, 39). Third, many studies have included autism, Asperger's syndrome, and pervasive developmental disorder (32, 46–48), and a mixed population with varying levels of intellectual disabilities (33, 46, 48) and seizure disorders (52). There are also significant variations in medication statuses, brain MRI scanners, measurement approaches, controls for total brain volume, and anatomical definitions of the hippocampus in related studies. Furthermore, hippocampal abnormalities in ASD could potentially be genetically based, as evidenced by the larger hippocampal volume observed in parents of children with ASD compared to control subjects (53). Due to the high variability in hippocampal volume in typical individuals (54), and the current prevalence of cross-sectional studies with limited sample sizes, considerably more MRI studies will need to be done to determine hippocampal volume changes in ASD, particularly for a specific autistic group with large sample sizes and a longitudinal design.

## 2.2 Hippocampal morphological abnormalities

Postmortem examinations were conducted in ten cases of ASD, comprising eight males and two females, with eight individuals presenting intellectual disability and five individuals exhibiting seizure disorder, ranging from 4 to 29 years old. The findings revealed reduced neural size and increased neuronal density within the hippocampal formation (55–57), similar to typical hippocampal developmental trends. It has previously been observed in an immunohistochemical study, that the density of parvalbumin-, calbindin-, and calretinin-immunoreactive interneurons within the subfields of the hippocampus was increased in cases of ASD compared to controls (58). Increased gray matter density was found in the hippocampal formation and peri-hippocampal cortex of children with ASD, correlating with symptoms of impaired social interaction and mnemonic function in ASD (59, 60). These observations of heightened neuron density in the hippocampal formation could be attributed to incorrect neuronal migration (59). The distorted shape of the dentate granule layer, forming irregular circles and loops, was indicative of abnormal neuronal migration and seemed to be another evidence of the phenomenon described above (61). Additionally, Golgi studies of CA4 and CA1 neurons revealed a noticeable decrease in dendritic branching complexity in two ASD children compared to their age-matched controls. Nevertheless, it remains uncertain whether increased hippocampal neuron density, fewer neuron size volumes, and

dendritic branching lead to corresponding reductions in the macroscopic size of the hippocampus. If this is the case, it could account for the decrease in MRI volumes observed in the hippocampus of individuals with ASD. The dentate gyrus development distortion in ASD was manifested by granule cell migration to the molecular layer and the formation of an extra granule cell layer (61). A previous MRI evidence of ASD also suggested that significantly smaller cross-sectional areas of the area dentata than healthy subjects could be attributed to the hypoplasia of the dentate gyrus and CA4 subfield (52). However, caution should be exercised when interpreting these findings as this MRI study and prior neuroanatomical researches have included ASD individuals with seizure disorders that are known to be connected with a decrease in hippocampal volume (62). Moreover, most current autopsy studies have been conducted in males, and it is unclear whether there are sex differences in hippocampal pathological anatomy in ASD. Three-dimensional MRI measurements of hippocampal shape variation in children with ASD indicated an upward curvature in the head and tail of the hippocampus, as well as inward deformation in its medial aspect (48). In terms of morphological structure, the hippocampal regions in children with ASD may be the initial site of alteration and a significant area in brain imaging that can be utilized for diagnosing ASD in children (63). Considering that clinical autistic symptoms were associated with various structural abnormalities in hippocampal regions, additional neuropathological and imaging studies will be needed to obtain the objective criteria for early diagnosis of children with ASD based on the morphological changes of the hippocampus.

### 2.3 Hippocampal blood flow abnormalities

As documented through quantitative MRI and 3D pseudo-continuous arterial spin labeling, cerebral hypoperfusion has been observed in the hippocampus among children with ASD in comparison to healthy controls, which may not be related to sex differences (63–65). Proper brain oxygenation is essential not only for the early development of neurons but also for optimal functioning. Previous research has indicated a positive correlation between hippocampal blood flow and spatial memory performance (66). Therefore, measuring hippocampal blood flow may be an effective method for brain imaging diagnosis in children with ASD. The reduction in cerebral blood flow in the hippocampus also led to a decrease in hemoglobin iron and non-hemoglobin iron in the blood, which ultimately resulted in a decrease in iron content in the hippocampus (63, 65). The hippocampal growth is closely related to blood perfusion, but current findings suggest that reduced blood perfusion and iron ion levels within the hippocampal region do not have a significant impact on the hippocampal volume of ASD children (63–65). One contradictory result was that as compared to healthy controls, high-functioning ASD adults showed a significant cerebral blood flow increase in the right parahippocampal cortex (67). Differences in functional ability and sedative use among the included ASD participants may explain this inconsistency.

### 2.4 Hippocampal metabolite abnormalities

Previous magnetic resonance spectroscopy studies have suggested altered chemical metabolism in hippocampal regions in ASD. Most studies of the hippocampus have reported a trend toward reduced N-acetylaspartate concentrations and N-acetylaspartate/creatine ratios in children with ASD (21, 68, 69). N-acetyl-aspartate synthesis occurs exclusively in the mitochondria of neuronal cells and is widely accepted as a marker for axonal and neuronal integrity and viability (70), so a diminished level of N-acetyl-aspartate may signify an irregularity in hippocampal regional neuronal development and mitochondrial function. This hypothesis was corroborated by a previous study that demonstrated a positive correlation between N-acetyl-aspartate levels in the right hippocampal region and performance IQ in the ASD group (69). However, among adult subjects, Page et al. (71) and O'Brien et al. (72) discovered no variation in NAA levels between the ASD group and the matched comparison group. The impact of age on alterations to metabolites in distinct areas of the brain has been evidenced; for instance, NAA levels are diminished in a neonate and subsequently surge during cerebral development (70). When comparing only boys with and without ASD, there were also no differences in NAA, choline, and creatine concentrations in the hippocampal region (73). People with ASD had a significantly higher concentration of glutamate+glutamine, aka Glx in the amygdala-hippocampal complex than comparison subjects (71), which is consistent with prior data in the auditory cortex of people with ASD (74). As glutamate is the most abundant excitatory neurotransmitter, the pathogenesis of ASD is likely to be associated with increased hippocampal excitability. Previous researches have identified an association between choline/creatine ratio elevation within the hippocampus and the severity of autistic symptoms, including language impairment (69, 75). Similarly, high concentrations of creatine and phosphocreatine in the hippocampal formation of ASD individuals had a significant positive correlation with their aggressive behaviors (70, 76). In sum, it can be hypothesized that disturbances of metabolic substances in the hippocampus are associated with abnormalities in hippocampus-dependent functions.

### 2.5 Hippocampal network connectivity dysfunction

In the study of the autistic human hippocampus, functional MRI has emerged as a powerful tool for mapping disrupted functional connectivity, which denotes the measurement of the temporal synchronization of activity between the hippocampus and other brain regions while a person is at rest or involved in a given cognitive activity. For example, in ASD children and adolescents, the resting-state functional connectivity strength between the left posterior hippocampus and the posterior cingulate cortex has a significant negative correlation with successful memory performance (77). Aberrant circuitry between the hippocampus and posterior cingulate cortex was found to be a common feature in

ASD associated with reduced general and facial memory (78). A preliminary neuropsychological and neuroanatomical investigation has indicated that hippocampal and parahippocampal abnormalities are associated with memory deficits in low-functioning ASD individuals, which in turn undermines their learning and language abilities (20). Earlier data from experimental tasks suggested that adults with ASD had particular difficulties with structural learning due to changes in the function of the hippocampus, which played a critical role in the aetiology of ASD (19). During learning, strong functional connectivity was observed between the hippocampus and caudate in both ASD and typically developing adolescents, but this connectivity was positively associated with task performance in ASD and negatively associated with performance in typically developing adolescents (79). Infants with low familial risk for developing ASD exhibited stronger resting-state functional connectivity between the right posterior superior temporal gyrus and the right hippocampus, as well as parahippocampal gyrus, in comparison to high-risk infants. The atypical and immature functional connectivity in high-risk infants could cascade into their later language deficits (80). During the emotional resonance condition, boys with ASD displayed reduced responses in the bilateral hippocampus, indicating potential difficulties with emotional information integration (81). Neural abnormalities within the hippocampus area may potentially place young individuals with ASD at risk for anxiety or other emotional and behavioral dysfunctions (82). Finally, in spatial memory tasks involving the dorsolateral prefrontal-hippocampal circuit, people with ASD showed worse performance than typical controls (83). When performing the virtual reality shopping task, participants with ASD also displayed lower activation in the parahippocampal gyrus, which is implicated in scene recognition and spatial navigation (84). These studies investigate a range of functional domains linked to the hippocampus, indicating that altered

functional connectivity between the hippocampal region and other brain networks may account for diverse autism symptoms.

As discussed above, changes in hippocampal volume, morphology, blood flow, metabolites, and functional connectivity may underlie altered hippocampal functions, including the formation and consolidation of memory, learning, language abilities, emotional regulation, and cognitive map creation (Figure 2).

### 3 Abnormalities in the structure and function of the hippocampus in ASD: evidence from animal models

Over recent decades, numerous animal models have been constructed to examine the mechanisms underlying the pathophysiology of ASD, with growing evidence substantiating abnormalities in the structure and function of the hippocampus in ASD. These animal models can be generally categorized into genetic, environment-induced, and idiopathic models.

#### 3.1 Animal models based on ASD-associated genes

It is widely accepted that ASD is a heritable disorder with origins in copy number variants, unusual mutations of a single gene, and cumulative effects of particular gene variants (85). To date, hundreds of genetically modified models (especially monogenic models) have intentionally replicated identified human autistic syndromes, both syndromic and non-syndromic ASD. The genetic cause has been clearly defined in cases of syndromic ASD, which often presents alongside ASD-related behavioral phenotypes,

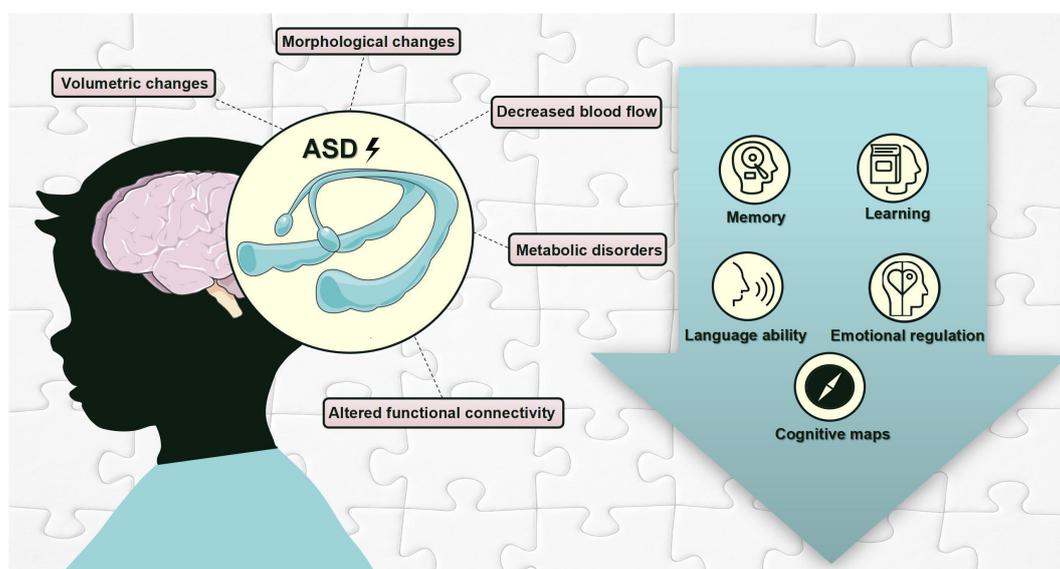


FIGURE 2 Hippocampal pathological changes and hippocampus-dependent behavioral deficits in individuals with ASD. This figure is created by using PowerPoint.

and on the contrary, non-syndromic ASD lacks a distinct phenotype (86).

### 3.1.1 Animal models of syndromic ASD

#### 3.1.1.1 Fragile X syndrome

Transcriptional silencing of the Fragile X messenger ribonucleoprotein 1 (*Fmr1*) gene encoding the Fragile X Messenger Ribonucleoprotein causes fragile X syndrome, the most common monogenic cause of ASD characterized by intellectual and language disabilities (87). Compared to wild-type mice, the dendritic spines of hippocampal neurons in *Fmr1* knockout (KO) mice are longer and thinner, and the density of stubby and mushroom-shaped (mature) spines is lower (88–91). Lazarov and colleagues reported a notable reduction in the number of neural progenitor/stem cells and the subsequent survival of these cells in the subgranular layer of the dentate gyrus in *Fmr1*-KO mice (92). Moreover, hippocampal neurons in *Fmr1*-KO mice had fewer functional synaptic connections, which develop at a slower rate and produce smaller excitatory synaptic currents relative to wild-type controls (93). In agreement, Klemmer et al. (94) discovered that 2-week-old *Fmr1*-KO mice exhibited an early-stage presynaptic phenotype marked by diminutive synaptic structures, decreased number of vesicles per cluster surface, and an overall reduction in the number of synaptic vesicles. *Fmr1*-KO mice also showed a prominent reduction in synaptic density and thickness of postsynaptic density, and an increase in synaptic cleft width (91). On the other hand, while baseline neurotransmitter release and short-term synaptic plasticity are unaffected at CA1 synapse in both younger and older *Fmr1*-KO mice (95), synaptic release probability is excessively elevated in CA1-CA3 areas during repetitive activity, resulting in abnormal short-term plasticity (96). Regarding alterations in long-term plasticity, *Fmr1*-KO mice have specific impairments of glutamatergic signaling in the hippocampus. Abnormally enhanced metabotropic glutamate receptor-dependent long-term depression (mGluR-LTD) in the CA1 region and defective long-term potentiation (LTP) of N-methyl-D-aspartate receptors (NMDA) in the dentate gyrus have been considered as established phenotypes of *Fmr1*-KO mice (95, 97).

These abnormalities observed in the hippocampus may underlie, at least in part, behavioral and cognitive changes of fragile X syndrome animal models. Extensive research has shown that fragile X syndrome murine models have significant deficits in hippocampus-dependent forms of spatial learning and memory as tested using the Morris water maze (91, 98–102). During the novel object recognition test, it was observed that *Fmr1* mutant mice spent significantly more time sniffing the old object and less time exploring the novel object than wild types, suggesting visual recognition memory deficits in these mice (100, 101). Furthermore, *Fmr1*-KO mice had deficiencies in hippocampus-dependent fear memory, characterized by low levels of freezing behavior response to fear conditioning (91, 102). It has previously been noted that *Fmr1*-KO mice had circadian defects involved in hippocampus-dependent memory, which may lead to sleep disturbance (103). The abnormal hippocampal neural activity of *Fmr1*-KO mice during sleep likely leads to adverse consequences for

memory processes (104). As mentioned before, neural abnormalities within the hippocampus also cause emotional problems, including anxiety-like behavior. Current experiment results from the open field test and elevated plus maze indicate that *Fmr1*-KO mice exhibit high anxiety levels (91, 105), and mice of the fragile X premutation (CGG repeat sequences between 55 and 200) demonstrate an indication of “social anxiety” (106).

#### 3.1.1.2 Rett syndrome

Rett syndrome, one of the rare ASDs affecting mainly females, is caused by loss-of-function mutations of the X chromosome-linked gene encoding the Methyl CpG binding protein 2 (MECP2) (107, 108). Rett syndrome animal models reproduce typical neurological features of this disorder, including impairments in hippocampus-dependent memory and learning. For example, *Mecp2* mutant mice present deficits in spatial memory and spatial learning in the Morris water maze task (107, 108), the Barnes maze test (109), and the object location test (110). In addition, compared to wild-type mice, *Mecp2* mutant mice showed declines in contextual fear memory when subjected to the fear conditioning task. This was evidenced by their notable decreases in freezing duration, primarily observed at long but not short time scales (107, 108, 111, 112). It is worth noting that the hyperactive hippocampal network (i.e. an imbalance of synaptic excitation/inhibition in hippocampal neurons) is responsible for learning and memory impairments in Rett syndrome (111, 113, 114). Pervasive spontaneous glutamate release in the hippocampus has been considered a defining characteristic of *Mecp2* KO mice, which contributes to the hyperexcitability of neurons (115). In the hippocampus of symptomatic *Mecp2* mutant mice, Schaffer-collateral synapses exhibited enhanced neurotransmitter release (108), and potentiated glutamatergic synapses (e.g. high surface levels of GluA1) occluded the LTP (116). Moreover, the frequency and amplitude of spontaneous excitatory postsynaptic currents of hippocampal neurons from *Mecp2* KO mice were found to be significantly decreased, revealing a loss of excitatory synaptic response in the inhibitory neurons of the hippocampus (111, 113, 117, 118). The diminished basal inhibitory rhythmic activity in the hippocampus of *Mecp2*-null mice can in turn give rise to a hyperexcitable state of the hippocampal network (119). In morphology, CA1 pyramidal neurons and dentate gyrus granule neurons exhibited delayed dendritic maturation and low dendritic spine density in *Mecp2* mutant mice compared to wild types (114, 120), which could potentially arise from insufficient BDNF expression in hippocampal neurons (109). Taken together, these findings imply that mutation in *Mecp2* causes various forms of hippocampal synaptic plasticity impairment, which in turn affects learning and memory functions.

#### 3.1.1.3 Angelman syndrome

With a high prevalence of comorbid ASD, Angelman syndrome is caused by the deletion of the maternally inherited ubiquitin protein ligase E3A (*Ube3a*) gene in the 15q11-q13 chromosome region, associated with impaired hippocampus-dependent learning, memory, and emotion (121–124). Several animal studies have

collectively reported that learning and memory deficits in Angelman syndrome are due to a marked decrease in hippocampal LTP (121–124). Researchers have demonstrated that hippocampal pyramidal cells of Angelman syndrome mice have elongated axon initial segments (125), reduced activity-dependent calcium dynamics (122), and hyperpolarized resting membrane potentials (125), which can be attributed to increased expression of  $\alpha$ 1-NaKA in the hippocampus. These alternations in intrinsic properties of hippocampal neurons could have driven the hippocampal pathology, namely LTP impairment, and memory and learning deficits revealed by contextual fear conditioning and Morris water maze (121, 122). In addition, increased inhibitory phosphorylation of  $\alpha$ CaMKII (123) and elevated Arc expression (124) in hippocampal slices from Angelman syndrome mice also underlie the hippocampal LTP deficits. As another type of synaptic plasticity involved in learning and memory, mGluR-LTD of excitatory synaptic transmission was enhanced in hippocampal slices of *Ube3a*-deficient mice, possibly due to increased synaptic small conductance calcium-activated potassium channel protein 2 levels in the hippocampus (126). As far as emotional problems are concerned, maternal *Ube3a*-deficient mice are under chronic stress and exhibit anxiety-like behaviors. Within the hippocampus, these mice demonstrate susceptibility to glucocorticoid exposure (127), disrupted glucocorticoid receptor signaling (127–129), and reduced number of parvalbumin-positive inhibitory interneurons (128, 129), resulting in chronic stress, hippocampal hyperactivity and ultimately increased anxiety.

#### 3.1.1.4 Tuberous sclerosis complex

Tuberous sclerosis complex is a rare form of ASD that is often accompanied by epilepsy and cognitive deficits, caused by mutations in either of the Tuberous sclerosis complex 1 or 2 (*Tsc1/2*) gene. These genes act as inhibitors of the mTOR signaling, and their mutations lead to hyperactivity of the pathway (130). Like other syndromic ASDs, tuberous sclerosis complex mice also have impairments in hippocampus-dependent spatial learning (131–133), contextual fear memory (131–133), and spatial working memory (131), associated with hippocampal synaptic excitation/inhibition imbalance induced by up-regulated mTORC1 signaling (131, 134). This hippocampal hyperactivity likely results from a reduced synaptic inhibition of pyramidal cells, while the excitatory transmission is unaffected (131, 134, 135). Previous studies have identified a potential link between hippocampal hyperexcitability and epilepsy phenotypes in mice deleting *Tsc1* or *Tsc2* (134, 136), but Koene et al. found the hippocampal excitation/inhibition imbalance only present in the epileptic state, which suggests that these changes in the hippocampus are unlikely to drive epileptogenesis (135). Additionally, dysfunctional glutamate homeostasis (137), impaired astrocytic gap junction coupling (138), and altered potassium clearance (138), as well as microgliosis (139) and astrogliosis (140) in the hippocampus of tuberous sclerosis complex mice, are correlated with seizure onset. Prior studies have noted that mGluR-LTD was not enhanced but rather

reduced in tuberous sclerosis complex mutant mice (141–143), indicating divergent synaptic plasticity phenotypes from fragile X syndrome and Angelman syndrome. A possible explanation for this is that the deletion of *Tsc1/Tsc2* genes heightened the expression of mGluR5 and exaggerated ERK signaling, which developed a novel mTOR-independent LTP in the CA1 hippocampus (141, 142). Several studies have also reported the enlargement of hippocampal neurons and dendritic spines in mutant mice (143, 144), whilst significantly increased basal cerebral blood flow and oxygen consumption in the hippocampus of rats with tuberous sclerosis complex could partially explain this observation (145, 146).

#### 3.1.1.5 Phelan-McDermid syndrome

As major synaptic scaffolding proteins, SH3 and multiple ankyrin repeat domains protein 1/2/3 (SHANK1/2/3) are highly concentrated in the postsynaptic density of hippocampal excitatory synapses (147–149). Shank family genes (*Shank1/2/3*), especially the Shank 3, are well-known ASD-related genes. Deletions or mutations of the *Shank3* gene can lead to Phelan-McDermid syndrome, characterized by autistic behavior, intellectual disability, and speech delay (150). It has been reported that the disruption of major *Shank3* isoforms in mouse/rat models decreases levels of other post-synaptic density scaffolding components and glutamatergic receptors in the hippocampus, including the HOMER1 (147–149), PSD95 (148), mGluR5 (148), GluA1 (149), and GKAP (149). At the level of hippocampal synaptic morphology, these animals had smaller postsynaptic density structures (151), lower spine density (149, 151, 152), and longer dendritic spines (149, 151) as compared to wild types. Unlike these profound synaptic changes, however, there have been no distinct alterations in the frequency and amplitude of miniature excitatory (149, 153–155) and inhibitory (149, 154, 155) postsynaptic currents, as well as field excitatory postsynaptic potentials (147, 156) in CA1 pyramidal neurons from mice and rats lacking different *Shank3* isoforms. These data indicate that basal synaptic transmission, neurotransmitter release probability, and short-term plasticity at hippocampal synapses may be preserved in Phelan-McDermid syndrome. Indeed, *Shank3* is critical for long-term hippocampal synaptic plasticity. *Shank3*-deficient mice and rats have reduced LTP (147, 149, 155–157) but unaltered LTD (155–157), and a hippocampal excitation/inhibition imbalance (153, 154). These deficits result in impaired social recognition memory (147, 156, 158), object location memory (147, 149, 155), and spatial learning and memory (149, 152, 153, 155, 156), particularly affecting long-term memory processes. In contrast to the above observations, Peça et al. (159) have reported that the frequency and amplitude of miniature excitatory postsynaptic currents and Morris water maze performance in *Shank3B* mutant mice are comparable to those of controls. Similarly, Cope et al. (160) have found impaired social but not object location memory in *Shank3B* KO mice. Contradictory findings across these studies may be attributed to mutations of various *Shank3* isoforms. This hypothesis is backed by recent transcriptomics investigating gene dosage-differential changes in the hippocampus of *Shank3* mutant mice (161).

### 3.1.2 Animal models of non-syndromic ASD

#### 3.1.2.1 Neuroligin (NLGN)

The NLGN family of synaptic cell adhesion molecules is fundamental in regulating excitatory and inhibitory synapses. There are four isoforms (*Nlgn1-4*) expressed in rodents or humans, all of which are linked with ASD symptoms. *Nlgn1* is predominantly localized to glutamatergic synapses, and *Nlgn1* overexpression in mice enhances the number and maturity of excitatory synapses and spines in the CA1 region (162). As for *Nlgn1*-KO mice, it is highly probable that their hippocampal NMDAR-LTP deficits (163, 164) result from diminished glutamate receptor functions, including reductions in NMDAR-mediated excitatory transmission (163, 164), expression levels of synaptic AMPA and NMDA (163), and the NMDAR/AMPA ratio (164, 165) in perforant path-granule cell synapses and CA1 pyramidal neurons. In contrast, the *Nlgn2* is principally localized to inhibitory GABAergic synapses with a key role in enhancing inhibitory but not excitatory synaptic function (165). *Nlgn2*-deficient mice displayed reduced postsynaptic gephyrin and GABAAR cluster numbers in the dentate gyrus, decreased inhibitory GABAergic synaptic transmission, and increased granule cell excitability (166). This observation matches those observed in recent studies that mice overexpressing *Nlgn2* have a reduced hippocampal excitation/inhibition ratio, thereby inhibiting their aggressive behaviors and impairing spatial memory performances (167, 168). *Nlgn3* is the only NLGN isoform that is found in both excitatory and inhibitory synapses. In *Nlgn3* KO mice, the number of excitatory synapses in the CA1 stratum oriens (169) and neuronal excitability in the CA2 area (170) were increased. Deleting *Nlgn3* also reduced hippocampal gamma oscillations and sharp wave ripples, which could lead to abnormal fear memory retention and extinction (170, 171). *Nlgn3*-R451C mutant mice exhibited large increases in both excitatory (172, 173) and inhibitory (174) synaptic transmission in the hippocampal CA1 region, and particularly the increased NMDA/AMPA ratio may have enhanced NMDAR-dependent LTP (172, 173). This also accords with several observations, which showed that these mice have better spatial learning and memory performance than wild-type controls (173, 174). However, it has also been shown that the *Nlgn3*-R451C mutation can cause loss-of-function effects in neonatal mice, characterized by premature hyperpolarizing effect of GABA at immature hippocampal MF-CA3 synapses and fail to express spike time-dependent LTP (175). The specific subcellular localization of *Nlgn4* in synapses is not fully understood, but *Nlgn4* is certainly expressed in the mouse hippocampus (176). A prior study has shown that the loss of *Nlgn4* caused postsynaptic changes at inhibitory synapses and aberrant inhibitory neurotransmission, heavily disrupting  $\gamma$ -oscillations in the CA3 region of the mouse hippocampus (176). Unexpectedly, Muellerleile and colleagues discovered increased network inhibition within the dentate gyrus of adult *Nlgn4* KO mice but unaltered in neonatal *Nlgn4* KO mice (177). Guneykaya et al. (178) found that hippocampal  $\gamma$ -oscillations were disrupted and hippocampal microglia density was reduced only in male *Nlgn4* KO mice. Hence, contradictory results in the hippocampal inhibitory state may partly be explained by sex-dependent and age-related impacts of *Nlgn4* loss.

#### 3.1.2.2 Phosphatase and tensin homolog detected on chromosome ten (*Pten*)

Like *Tsc1/2*, the *Pten* gene functions as a mTOR pathway negative regulator, and alteration of this pathway is involved in ASD pathogenesis. Activation of mTOR via *Pten* deletion from hippocampal dentate granule cells re-initiates additive growth, which leads to hypertrophied neurons (179–182), enlarged mossy fiber axons (179, 180, 183), elongated dendrites (179, 180, 184) and increased dendritic spine density (179–181, 184). These hippocampal morphological changes partly underlie the macrocephaly and epilepsy that are notable features of inherited *Pten* mutations. The observed increase in spontaneous excitatory synaptic current frequency (particularly in females) (181, 184) and field excitatory postsynaptic potential slope (185, 186) suggests increased excitatory synapses on cells and enhanced basal synaptic transmission in the hippocampus of *Pten* KO mice. The increased epileptogenic activity of *Pten* KO mice is largely due to hippocampal hyperexcitability (182, 184). More importantly, these mouse models display impaired hippocampal LTP and LTD (185, 187), as well as spatial memory (187) during postnatal development, which has been shown to precede the appearance of their morphological abnormalities (185).

#### 3.1.2.3 Cyclin-dependent kinase-like 5 (*Cdkl5*)

Mutations in the X-linked *Cdkl5* gene cause severe neurodevelopmental disorders marked by early-life autistic behaviors and intractable epilepsy (188). The *Cdkl5* is highly expressed in the hippocampus, and its deficiency in mice reduces dendritic length, branches, and maturation of hippocampal pyramidal and granule neurons (189–192). Meanwhile, *Cdkl5* KO mice exhibit an elevated incidence of newborn cell apoptosis within the hippocampal dentate gyrus leading to diminished granule neuron counts (189, 190), coupled with accelerated senescence and death of hippocampal neurons during the aging process (191). Strikingly, the increase in apoptosis is paralleled by the rapid proliferation of neuronal precursor cells in the dentate gyrus, which modulates the equilibrium between precursor proliferation and survival (190). Additionally, it is noted that hippocampal neurons of *Cdkl5* KO mice demonstrate heightened susceptibility to neurotoxicity, excitotoxicity, and oxidative stress (192, 193), implying that the absence of *Cdkl5* augments neuronal vulnerability. These neuroanatomical alterations are associated with hippocampus-dependent learning and memory impairment observed in multiple tasks (189–191). The robust seizures in *Cdkl5* KO mice have been demonstrated to be correlated with microglial activation (192), BDNF-TrkB signaling enhancement (194), and postsynaptic overaccumulation of GluN2B-containing NMDAR (195) in the hippocampus.

## 3.2 Animal models of environment-induced ASD

It is clear now ASD etiology involves both genetic and environmental factors or their possible combinations. Exposure of animals to given chemicals, toxins, viruses, and other agents during gestation can induce models of ASD in their offspring.

### 3.2.1 Valproic acid induced animal models

Valproic acid (VPA) is a commonly used anti-epileptic or mood-stabilizing drug but is classified as a human teratogen. In animal studies, typical ASD models in newborn mice or rats have been simulated by exposing their mothers to VPA during pregnancy (196). Similar to the ASD traits in humans, male animals might be more susceptible to VPA-induced ASD than females. For instance, male VPA mice exhibited higher locomotor activity and lower social ability index than females, potentially attributed to increased hippocampal cell atrophy and heightened expression of the 5-HT<sub>2A</sub> receptor protein in the hippocampus (197). The VPA exposure in mice or rats can induce several autism-like behaviors related to hippocampal functions, including impairments in spatial learning and memory (198–206), visual recognition memory (198, 203, 207–209), working memory (208, 210), and emotional regulation (199, 200, 204–206, 211–213). It is widely documented that exposure to VPA notably increases levels of the pro-inflammatory markers (IL-1 $\beta$ , TNF- $\alpha$ , IL-6, IFN- $\gamma$ , IL-17, TGF- $\beta$ ) and reduces levels of the anti-inflammatory marker (IL-10) in the hippocampus (199, 208, 211, 213–216). The hippocampal neuroinflammatory state is primarily observed in young ages, perhaps resulting from microglia and astrocyte activation that started in the early postnatal developmental stages. In adult mature VPA rats/mice, however, changes in the expression of neuroglial markers in the hippocampus seem to be mild, with an amelioration of the neuroinflammatory phenotype (212, 217, 218). After exposure to prenatal VPA, biochemical markers associated with neuronal oxidative/nitrosative stress such as MDA, TBARS, and NO were found to be significantly increased contrary to markers such as GSH, SOD, and CAT in the hippocampal regions (198, 202, 212–215, 219). At the same time, increased oxidative stress is accompanied by aberrant mitochondrial electron transport chain enzyme activity, reduced ATP levels, and ultrastructurally destructed mitochondria in the hippocampus (198, 212). Exposure of mice or rats to VPA activates mTOR and Notch signaling, which amplifies autophagic deficiency in the hippocampus, characterized by decreased expression levels of Beclin1 and LC3-II and a small number of autophagosomes (203, 210). Previous studies evaluating hippocampal excitatory/inhibitory imbalance found that VPA exposure enhanced excitatory glutamatergic and impaired inhibitory GABAergic synaptic transmission, with a decrease in the GABA/glutamate ratio (201, 206). Compared to controls, VPA-induced rats showed a significantly larger number of hippocampal apoptotic neurons, accompanied by increased levels of the apoptotic markers “Bax, caspase-3 and p53” and decreased levels of the antiapoptotic marker “BCL2” (201, 204, 219–221). Moreover, reductions in the hippocampal levels of BDNF, synapsin-IIa, DCX, and pCREB are strongly implicated in ASD as these proteins play significant roles in neuronal formation, synaptic transmission, neuroplasticity, and neurogenesis (201, 213–215, 221). Taken together, these pathophysiological processes significantly weaken hippocampal neuron viability in VPA-exposed mice and rats. Furthermore, VPA exposure significantly altered the expression of multiple ASD candidate genes in the hippocampus: *Shank3* (212), *Shank2*

(209), *Nlgn3* (212), and *Pten* (222). This observation further supports that high-risk ASD genes can also be altered by environmental factors – gene-environment interactions have a pivotal role in the pathophysiology of ASD.

### 3.2.2 Maternal immune activation induced animal models

Maternal immune activation (MIA) during pregnancy increases the risk of the unborn fetus developing ASD later in life (223). The most commonly used methods for emulating MIA models of ASD involve the intraperitoneal administration of lipopolysaccharide (LPS) and polyinosinic: polycytidylic acid (poly (I: C)) during gestation. The administration of LPS can induce sex-dependent alterations in hippocampal volume, neuronal morphology, and gliovascular maturation. Compared with female LPS-induced mice, the male LPS group showed a larger size of hippocampus (224), higher hippocampal neuronal spine density (224, 225), and lower vascular coverage of astrocytic end-feet (226) associated with their reduced interest in social novelty (224, 225). Microglial activation and astrogliosis could be functionally important in altering hippocampus-dependent learning and memory performance observed in LPS-induced rat models (227, 228). Surprisingly, at the early postnatal stage, exposure to LPS had no negative effects on hippocampal cellular or tissue morphology but instead stimulated nerve growth by promoting cell proliferation (228), increasing the number of spines (225), and raising the density of mossy fiber synapses (229) in the hippocampal area. It seems possible that these results are due to the M2-biased microglia polarization at the acute inflammatory phase, which releases excessive anti-inflammatory cytokines and growth factors (228). In contrast, MIA induced by poly (I: C) did not alter the density of Iba1+ microglia (or GFAP+ astrocytes), nor did it modify their activation phenotypes in the hippocampal formation of the offspring (230, 231). However, prenatal exposure to poly (I: C) increased hippocampal IL-6 and IL-1 $\beta$  levels, resulting in the promotion of hippocampal kindling epileptogenesis (230, 232). Additionally, the offspring of poly (I: C)-exposed mice displayed a substantial reduction in the relative density of hippocampal pre- and postsynaptic proteins (synaptophysin, bassoon, PSD95, and SynGap) and changed the firing traits of hippocampal place cells in adult offspring (230, 233). The hippocampal synaptic deficits could alter the electrophysiological properties of hippocampal cells, hence affecting the firing activity of hippocampal neurons. These changes may underlie the spatial memory impairments found in MIA mice following poly (I: C) injection (233, 234).

### 3.2.3 Air pollution induced animal models

Gestational exposure to air pollution can increase the incidence of ASD in offspring (223). Hippocampal transcriptome data revealed that gestational nanosized particulate matter (PM) exposure induced multiple differentially expressed genes in young adult offspring. The stratification by sex revealed a twofold increase in the number of differentially expressed genes in males compared to females, and there was male-specific enrichment of differentially expressed genes involved in serotonin receptor signaling,

cAMP-mediated signaling, and endocytosis (235). Other studies have also found that PM2.5-induced mice have aggravated hippocampal neuroinflammation, with elevation in NF-κB, TNF-α, and IL-1β levels (236) and microglial activation (237). Meanwhile, these mice exhibited impaired spatial learning and memory, associated with disrupted hippocampal synaptic ultrastructure, decreased hippocampal neurogenesis, and increased hippocampal neuronal apoptosis (236). These findings can explain the reduction in hippocampal size and structural integrity after exposure to airborne PM (237, 238).

### 3.3 Animal models of idiopathic ASD

As genetic and environment-induced models cannot accurately replicate all the pathological features of ASD, strains of mice and rats have been developed using idiopathic models, which display robust and well-replicated behavioral characteristics of ASD such as social deficits and repetitive behaviors. The BTBR T+Itpr3tf/J (BTBR) strain is one of the most valid models of idiopathic ASD, and inbred strain C57BL/6J is often used as a control for BTBR (239).

#### 3.3.1 BTBR animal models

Recently, the BTBR inbred mouse strain has gained popularity as a rodent model of ASD. In addition to the core symptoms of ASD, BTBR mice also display learning and memory impairments in various settings (240–242). Several histological observations and MRI assessments support separated hippocampal commissure and increased hippocampal volume in BTBR mice relative to controls, and these anatomical changes may underlie their behavioral phenotypes (243–246). Moreover, the hippocampus has lower 5-HT, acetylcholine, dopamine, and histamine content in the BTBR

animals than in the C57BL/6J strain (246–248). In particular, immunofluorescent labeling of 5-HT transporter axons revealed a reduction in the density of innervation to the hippocampus in BTBR mice (246). Premature changes in hippocampal neuronal excitability, involving elevated ERK signaling (248) and increased GABAergic neurotransmission (249) during neonatal development in the BTBR mice, may also contribute to the high susceptibility to epilepsy and aggressive behaviors observed in these mice (248, 250). As for adult and aged BTBR animals, significant reductions in mRNA or protein levels of BDNF, as well as neurogenesis in the hippocampus have previously been reported (241, 245, 250).

To sum up, hippocampal excitatory/inhibitory imbalance is one of the most important pathological mechanisms in ASD. These animal models mainly show impairments in dendrite morphology, neurogenesis, neuronal viability, LTP, and LTD in the hippocampus, leading to dysfunction in learning, memory, emotional regulation, and spatial ability. Figures 3, 4 were used to depict some common hippocampal structural and functional impairments in rodent models of ASD, but it is important to note that each model has its own characteristics of hippocampal dysfunctions and cannot be generalized. In a word, the above animal studies suggest that the hippocampus is strongly implicated in the pathophysiology of ASD and should be considered as an important target for future therapeutic approaches.

## 4 Therapies that positively influence the structure and function of the hippocampus in ASD animal models

To date, amounts of pharmacological and non-pharmacological interventions that positively impact hippocampus-dependent

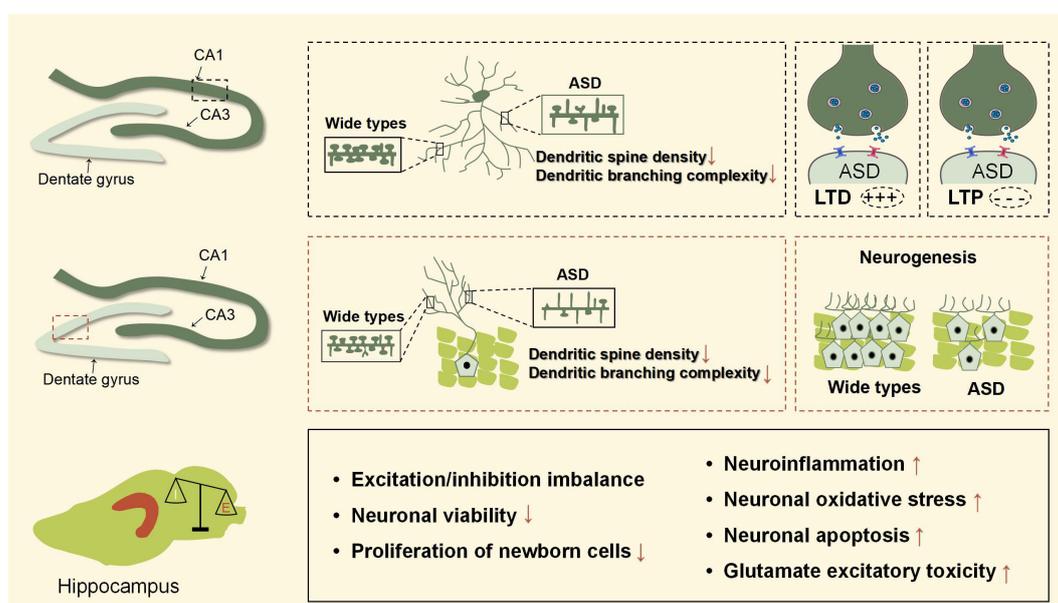


FIGURE 3  
Hippocampal pathophysiological processes of ASD animal models. This figure is created by using PowerPoint.

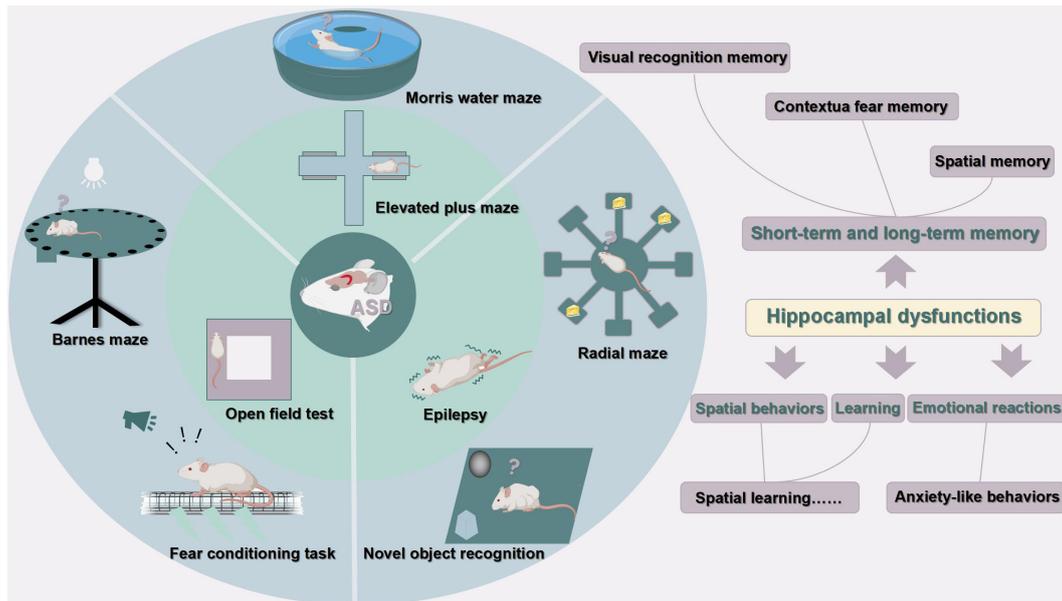


FIGURE 4 Hippocampal dysfunctions in ASD animal models. This figure is created by using PowerPoint.

cognitive functions have been identified through animal experimentation as potential treatments for ASD (Figure 5). Pharmacological interventions mainly include hormones, vitamins and minerals, atypical antipsychotic drugs, phosphodiesterase inhibitors, selective serotonin reuptake inhibitors, mTOR inhibitors, mGluR antagonists, NMDAR antagonists, histamine H3 receptor (H3R) antagonists, and insulin-like growth factor. Non-pharmacological interventions mainly include aerobic exercise and environmental enrichment. Table 1 presents

elaborate cellular and molecular modifications in the hippocampus of animal models of ASD following each intervention.

### 4.1 Hormones

Oxytocin has been proposed as a possible therapeutic agent for ASD due to its potent regulation of mammalian social behavior. The injection of oxytocin into the left lateral ventricle specifically

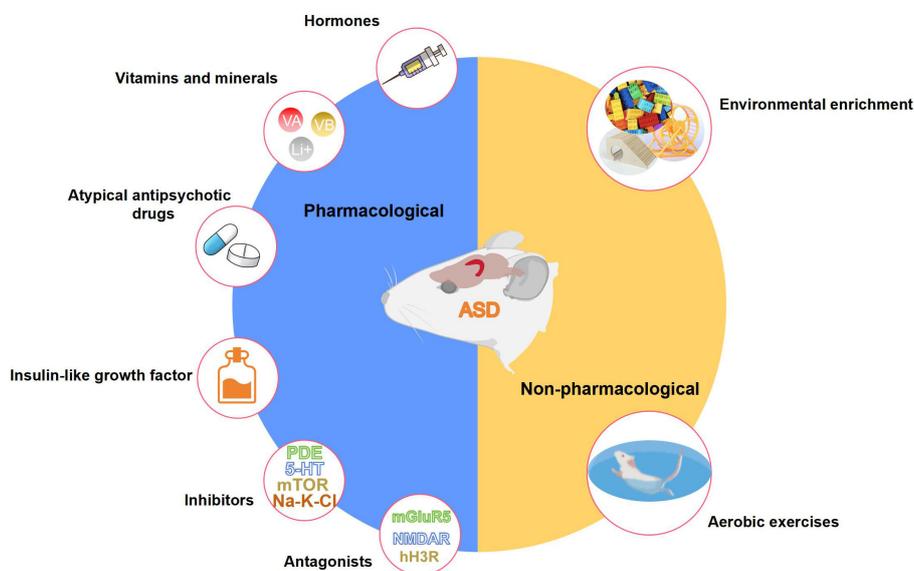


FIGURE 5 Pharmacological and non-pharmacological interventions that positively affect the structure and function of the hippocampus in ASD animal models. This figure is created by using PowerPoint.

TABLE 1 Main effects of each intervention on cellular and molecular changes in the hippocampus of ASD animal models.

Intervention	Animal model	Cellular and molecular changes in the hippocampus	References	
Hormone	Oxytocin	<p>Protein level: Synapsin I↔, PSD95↔</p> <p>Gene expression: Synapsin I↑, Pcd95↑, Nlgn3↑, Nlgn2↑, Nrnx1β↑, Nrnx2α↑, Nrnx2β↑, Rhob↑, Rac1↑, Pak1↑, Pak2↓</p>	(251)	
		VPA-exposed rat	<p>Number of parvalbumin-positive interneurons↑</p> <p>Enzymatic activities of the mitochondrial electron transport chain↔, 4-HNE protein↔</p>	(198)
	<p>Gene expression (transcriptome analysis): Kcnj13↑, KI↑, Prelp↑, Sostdc1↑, Clic6↑, F5↑, Sclc4a5↑, Mdk↑, Folr1↑, Mmp14↑, Tmem72↑, Kcne2↑, Sfrp1↑, Mt-nd3↓, Slc19a3↓</p>		(252)	
	Melatonin	VPA-exposed rat	<p>Protein level: p-CaMKII↑, p-Synapsin I↑, p-NMDAR1↑, p-MARCKS↑, p-PKA↑, p-GluR1↑</p>	(253)
Vitamin and mineral	Vitamin A	VPA-exposed rat	<p>Gene expression (RNA sequencing): lncRNA NONRATT021475.2↓, desert hedgehog gene↓</p>	(254)
	Vitamin B6, folic acid and vitamin B12	PM <sub>2.5</sub> -exposed mouse	<p>Number of damaged mitochondria↓, synaptic cleft↓, PSD thickness↑, synaptic active area length↑, apoptotic ratio↓, neurogenesis↑</p> <p>Protein level: MDA↓, SOD↑, GSH-Px↑, GSH↑, NF-κB↓, TNF-α↓, IL-1β↓, Caspase-3↓</p> <p>Gene expression: NF-κB↓, TNF-α↓, IL-1β↓</p>	(236)
	Folic acid	BTBR mouse	<p>Protein level: GFAP↓, Iba-1↓, IL-1β↓, IL-6↓, IL-18↓, TNF-α↓, MDA↓, SOD↑, GSH-Px↑, GSH↑, p-CaMKII↑, p-CREB↑, GPx4↑, Fpn1↑, SOD1↓, TFR↓</p>	(240)
	Selenium	BTBR mouse	<p>Number of viable neurons↑</p> <p>Protein level: 5-HT↑, Dopamine↓, glutamate↓, IL-6↓, IL-18↓, TNF-α↓</p> <p>MDA↓, SOD↑, GSH-Px↑, GSH↑, CAT↑</p> <p>Gene expression: IL-6↓, IL-18↓, TNF-α↓</p>	(241)
	Lithium	<i>Fmr1</i> mutant mouse	<p>Protein level: GSK-3β↔, pS202-Tau/Tau↓, Tau↓, pS2448-mTOR/mTOR↓, mTOR↔</p>	(255)
		VPA-exposed rat	<p>Number of Iba-1 positive cells↓, IL-6↓</p>	(211)
Atypical antipsychotic drug	Aripiprazole	VPA-exposed mouse	<p>Dendritic spine density↑</p>	(207)
		<p>Number of Nissl-positive cells↑</p>	(210)	
	VPA-exposed rat	<p>Number of intact neurons↑, Number of neurofibrillary tangles↓, Nissl's granules optical density↑</p> <p>Protein level: glutamate↓, GABA↑, BDNF↑, Caspase-3↓, Bax↓, Bcl-2↑, GFAP↓, CREB↔, p-CREB↔</p> <p>Gene expression: Glt-1↑</p>	(201)	
	Risperidone	VPA-exposed mouse	<p>Dendritic spine density↑</p>	(207)
		VPA-exposed rat	<p>Number of viable neurons↑</p> <p>Protein level: cytochrome-c↓, lactate dehydrogenase↓, caspase-3↓, MDA↓, GSH↑, Bcl-2↑,</p> <p>Gene expression: Adar2↑, GluA2 Q:R↓</p>	(219)
	Olanzapine	VPA-exposed rat	<p>Dendritic spine density↑, dendritic length↓, neuron volume↓, number of Nissl-positive neurons↓</p>	(203)
Phosphodiesterase inhibitor	Ibudilast	VPA-exposed rat	<p>Protein level: SOD↑, GSH↑, CAT↑, IL-6↓, IL-1β↓, TNF-α↓, IL-10↑</p>	(199)
	Vinpocetine	VPA-exposed rat	<p>Number of pyknotic and chromatolytic cells↓</p> <p>Protein level: BDNF↑, synapsin-IIa↑, DCX↑, pCREB↑, CREB↑, pCREB/CREB↑, IL-6↓, TNF-α↓, IL-10↑, GSH↑, TBARS↓</p>	(213)
	Cilostazol	VPA-exposed rat		(214)

(Continued)

TABLE 1 Continued

Intervention	Animal model	Cellular and molecular changes in the hippocampus	References	
		Protein level: BDNF↑, pCREB↑, IL-6↓, TNF-α↓, IL-10↑, GSH↑, TBARS↓		
	Papaverine	VPA-exposed rat	Protein level: BDNF↑, synapsin-IIa↑, DCX↑, pCREB↑, IL-6↓, TNF-α↓, IL-10↑, GSH↑, TBARS↓	(215)
	Rolipram	<i>Fmr1</i> mutant mouse	Protein level: GSK-3β↑, pS202-Tau/Tau↓, Tau↑ mTOR↑	(255)
Selective serotonin reuptake inhibitor	Sertraline	<i>Cdk5</i> mutant mouse	Number of doublecortin-positive granule neurons↑, dendritic length and spine density of granule neurons↑, PSD95↑	(256)
	Fluoxetine	<i>Nlgn3</i> mutant mouse	Neurogenesis↑	(257)
		<i>Ube3a</i> mutant mouse	Number of parvalbumin-positive interneurons↑ Protein level: glucocorticoid receptor↑, SGK1↑, BDNF↑, FKBP5↑	(129)
		<i>Fmr1</i> mutant mouse	Cell proliferation↔ Protein level: BDNF↔, TrkB↔	(105)
mTOR inhibitor	Rapamycin	<i>Pten</i> mutant mouse	nuclear diameter↓, dentate gyrus hypertrophy↓ Protein level: p-Ser235/236-S6 (mTORC1 activity)↓, p-AKT-S473↓	(258)
		VPA-exposed rat	Number of autophagosome↑, cell apoptosis↓ Protein level: LC3 II↑, LC3 I↓, p62↓, Bcl-2↑, p53↓, p-PI3K↓, p-AKT↓, p-S6↓	(220)
			Cell apoptosis↓ Protein level: Bcl-2↑, BDNF↑	(221)
Na-K-Cl cotransporter inhibitor	Bumetanide	VPA-exposed rat	Cl <sup>-</sup> level↓	(259)
		<i>Fmr1</i> mutant mouse	Cl <sup>-</sup> level↓	(259)
mGluR5 antagonist	MPEP	BTBR mouse	Protein level: p-ERK1/2↓	(242)
	LY341495	<i>Fmr1</i> mutant mouse	GSK-3β↓, pS202-Tau/Tau↓	(255)
	Mavoglurant	<i>Fmr1</i> mutant mouse	Dendritic spine length↓	(89)
NMDAR antagonist	Agmatine	VPA-exposed rat	Protein level: p-ERK1/2↓	(260)
	Dextromethorphan	VPA-exposed rat	Protein level: NMDA↓, p-ERK1/2↓ Gene expression: NMDA↓, p-ERK1/2↓	(200)
	Ketamine	VPA-exposed rat	Gene expression: Pten↑, Pcd95↔, Glur1↔, Synapsin1↔, Rab3d↔, Vamp3↔	(222)
		<i>MeCP2</i> mutant rat	Gene expression: Pcd95↑, Glur1↑, Pten↔, Synapsin1↔, Rab3d↔, Vamp3↔	(222)
	Memantine	VPA-exposed rat	Number of intact neurons↑, Number of neurofibrillary tangles↓, Nissl's granules optical density↑ Protein level: glutamate↓, GABA↑, BDNF↑, Caspase-3↓, Bax↓, Bcl-2↑, GFAP↓, CREB↔, p-CREB↔ Gene expression: Glt-1↑	(201)
Histamine H3R antagonist	E100	VPA-exposed mice	Protein level: IL-6↓, IL-1β↓, TNF-α↓, TGF-β↓, NF-κB p65↓, iNOS↓, COX-2↓	(216)
	ST-713	BTBR mouse	Protein level: ERK↓, p38↓, JNK↓, IL-6↓, IL-1β↓, TNF-α↓, histamine↑, dopamine↑	(248)
Insulin-like growth factor	Insulin-like growth factor 2	BTBR mouse	Protein level: mTOR↓, p-mTOR↓, p-S6K↓, p-AMPK↓, ULK1↓, p-ULK1↓	(261)
Aerobic exercise	Wheel running	MIA mice	Density of mossy fiber synapses↓, microglial synapse engulfment↑	(229)
		<i>Cdk5</i> mutant mouse		(262)

(Continued)

TABLE 1 Continued

Intervention		Animal model	Cellular and molecular changes in the hippocampus	References
			Neurogenesis↑, BrdU-positive cells↑, size and density of AIF-1-positive microglial cells↓, number of immature spine↓, number of mature spine↑ Protein level: BDNF↑	
		<i>Fmr1</i> mutant mouse	Cell proliferation↑, BrdU positive cells↑	(263)
	Treadmill running	VPA-exposed rat	Neurogenesis↑, Protein level: Reelin↑, PI3K↑, p-Akt↑, p-ERK1/2↑	(204)
	Swimming	<i>Shank3</i> mutant rat	Dendritic spine density↑, number of dendritic branch↑	(152)
		VPA-exposed mouse	Protein level: IL-6↓, TNF-α↓, IFN-γ↓, IL-17↓	(208)
Environmental enrichment	Maternal stimulation	<i>Fmr1</i> mutant mouse	Number of filopodia-like spines↓, number of mature thin and mushroom spines↑	(90)
	Housing condition enrichment	<i>Fmr1</i> mutant mouse	Gene expression (transcriptome analysis): Bdnf↑, Mef2c↑, Gabrg2↑, Drd1↑, Nefm↑, Prkce↑, Ncam2↑, Igsf9b↓ Protein level: BDNF↑, p-TrkB↑, p-PLCγ1↑, p-CaMKII↑	(91)
		VPA-exposed mice	Dendritic spine density↑ Gene expression: Bdnf↑, Psd95↑, Shank2↑	(209)
		<i>Ube3a</i> mutant mouse	Number of PV-positive GABAergic neurons↑ Protein level: GR↑, BDNF↑, pThr286CaMKIIα↓	(264)
		MIA rat	Gene expression: Bdnf↑	(265)

The direction of the arrows indicates increase (↑), decrease (↓), or no change (↔) compared to controls.

improved the long-term social recognition memory and LTP at hippocampal synapses in *Shank3*-deficient rats (147). *In vivo*, subcutaneous oxytocin injections induced upregulation of hippocampal postsynaptic proteins PSD95 and Nlgn3 of *Shank3* deficient mice (251). In rats exposed to VPA prenatally, chronic intranasal oxytocin administration rescued ASD-like behaviors including learning and memory impairments (198), and enhanced the expression of multiple genes in the hippocampus linked to synaptic function, learning, memory, and neurodevelopment (252). Erythropoietin, a glycoprotein hormone, has recently been reported to inhibit the astrogliosis in the hippocampal CA1 subfield in both LPS (227) and VPA (266) induced rat models of ASD, contributing to the enhanced learning and memory task performance (227). A preliminary study in VPA-treated rats has shown that melatonin treatment restored hippocampal CaMKII/PKA/PKC phosphorylation and LTP reduction, which might correlate with amelioration of hippocampus-dependent memory and learning skills (253).

### 4.2 Vitamins and minerals

Recent RNA sequencing research has found that vitamin A supplementation significantly alleviated VPA-induced anxiety behaviors, possibly by regulating lncRNA-mRNA co-expression networks (particularly lncRNA NONRATT021475.2 and Desert hedgehog gene) in the hippocampus of ASD rats (254). Gestational B-vitamin supplementation (vitamin B6, folic acid, and vitamin B12) has the potential to mitigate PM2.5-induced spatial learning and memory defects in mice offspring by

ameliorating hippocampal inflammation, oxidative stress, mitochondrial damage, neuronal apoptosis, and synaptic dysfunction (236). Likewise, using solely folic acid rescued hippocampal neuron death and spatial learning and memory impairments in BTBR mice as it suppressed oxidative stress, inflammation, and ferroptosis in the hippocampus (240). Regarding mineral supplementation, selenium has a protective effect on the hippocampus of BTBR mice, with a comparable mechanism to that of folic acid (241). A six-week zinc water supplementation led to a decrease in anxiety-like behavior and seizure susceptibility in BTBR mice. This effect may be related to the restoration of neural progenitor cell proliferation and excitation/inhibition balance in the hippocampus (250). Lithium treatment can rescue olfactory-based learning and memory defects in drosophila fragile X model, and increase the cAMP signaling by inhibiting GSK-3β activity in the hippocampus of fragile X mice (255). In addition, lithium exerts an anti-inflammatory role probably by reducing microglial activation and inflammatory cytokine release and increasing levels of H3K9 acetylation in the hippocampus of VPA-exposed rats, with beneficial implications for improving social memory and anxiety levels (211).

### 4.3 Atypical antipsychotic drugs

The third-generation, atypical antipsychotic drugs aripiprazole, and risperidone are the only medications approved by the American FDA for ASD treatment. Data from several studies suggest that chronic treatments with aripiprazole attenuated VPA-induced visual recognition memory (207) and spatial learning and

memory (201) impairments in mouse/rat offspring with ASD. More importantly, maternal treatment with aripiprazole prevents working memory deficits and hippocampal cell death in juvenile mice exposed to VPA during the prenatal period (210). Chronic administrations of risperidone improved VPA-induced memory impairment and reductions in hippocampal dendritic spine density, but there was no improvement with acute administrations (207). In addition, risperidone impeded hippocampal glutamate excitotoxicity in the VPA rat model of ASD, ultimately promoting neuronal survival (219). Similarly, the antipsychotic olanzapine can alleviate VPA-induced impairments in recognition and spatial memory by mitigating neuroplastic alterations in the hippocampus, including neuronal hypotrophy, reduced spine density, and elongated dendritic length (203).

#### 4.4 Phosphodiesterase inhibitors

The phosphodiesterase class of enzymes is responsible for the degradation of cAMP, which affects various neurobiological processes from neuroinflammation to learning and memory formation (267). For instance, ibudilast, a phosphodiesterase-4 inhibitor, was found to elevate levels of oxidative stress markers (SOD, GSH, CAT) and lower levels of pro-inflammatory markers (IL-1 $\beta$ , TNF- $\alpha$ , IL-6) in the hippocampus of VPA exposed rats. Meanwhile, these ASD rats administered with two doses of ibudilast showed significantly reduced deficits in learning/memory and anxious behaviors (199). In the same way, Luhach and colleagues have demonstrated that vinpocetine, cilostazol, and papaverine, all of which are phosphodiesterase inhibitors, positively influenced neurogenesis, neuronal survival, synaptic transmission, neuronal transcription, neuronal inflammation, and neuronal oxidative stress in the hippocampus of VPA-exposed rat models (213–215). Both rolipram (phosphodiesterase-4 inhibitor) and BAY-60-7550 (phosphodiesterase-2 inhibitor) treatment abrogated the exaggerated hippocampal mGluR-LTD observed in fragile X mice, which can be attributed to significantly increased cAMP levels (88, 255, 268). In like manner, rolipram treatment rescued the LTP of hippocampal CA1 neurons to a significant level in Rett syndrome mice (269). Lastly, rolipram rescued olfactory-based long-term memory defects of drosophila fragile X models (255, 268).

#### 4.5 Selective serotonin reuptake inhibitors

Sertraline and fluoxetine function as primary selective serotonin reuptake inhibitors, impeding 5-hydroxytryptamine uptake into presynaptic vesicles from the synaptic cleft in the central nervous system. Chronic treatment with sertraline improved autistic-like features in *Cdkl5* KO mice, including hippocampus-dependent spatial learning and memory deficiency. This positive behavioral effect was associated with restored neuronal survival, dendritic development, and synaptic connectivity in the dentate gyrus and CA1 pyramidal neurons (256). Recent evidence suggests that fluoxetine can ameliorate social behavior in *Nlgn3*-KO mice, at least in part, by promoting adult hippocampal neurogenesis (257).

More typically, long-term fluoxetine treatment normalizes hippocampal parvalbumin-positive interneurons number and glucocorticoid signaling of Angelman syndrome model mice, which is important for the restoration of anxiety-like behaviors (129). On the contrary, however, *Fmr1* KO mice after fluoxetine treatment have reduced anxiety but enhanced explorative activity during the open field test, with abnormal changes of BDNF/TrkB signaling in the hippocampus (105). Activation with selective serotonin reuptake inhibitors has been observed in people with fragile X syndrome, which can manifest as mood changes and disinhibited behavior (270). What calls for special attention is the subsequent risk of ASD with exposure to selective serotonin reuptake inhibitors during pregnancy. Recent findings underscored that maternal fluoxetine exposure impaired hippocampal LTP, spatial discrimination, and spatial learning in adult offspring (271), accompanied by decreased hippocampal neurogenesis and hippocampal IL-10, IFN- $\gamma$  and IL-13 levels (272).

#### 4.6 mTOR inhibitors

Dysregulation of mTOR signaling is strongly associated with ASD, and the inhibition of mTOR can prevent the binding of mTOR with other protein components and reduce mTOR phosphorylation (273). For example, rapamycin, as a prominent mTOR inhibitor, has been shown to effectively block the hippocampal mTORC1 signaling of Pten mutant mice (258). Besides, rapamycin plays a crucial role in promoting autophagy (220) and decreasing apoptosis (220, 221) in the hippocampus of VPA-induced neonatal rats of ASD, thereby improving learning and memory ability (221). As discussed earlier, tuberous sclerosis complex models had increased hippocampal neuron volume, blood flow, and oxygen consumption. Correspondingly, the administration of rapamycin has been reported to lower cerebral blood flow and oxygen consumption in hippocampal regions of the *Tsc2* mutant rat, potentially by downregulating Akt signals (146). This also accords with previous observations, which showed that pharmacological inhibition of mTORC suppressed granule cell hypertrophy in Pten mutant mice (258) and inhibited the PI3K/AKT/mTOR signaling pathway in VPA-induced rats (220).

#### 4.7 Na-K-Cl cotransporter inhibitors

Bumetanide, a loop diuretic that inhibits the Na-K-Cl cotransporter, has been reported to improve core symptoms of ASD in children over recent years (274). In VPA-treated rats, even a brief maternal bumetanide treatment can prevent hippocampal overgrowth in their offspring (275). In addition, maternal pretreatment with bumetanide effectively restored elevated hippocampal intracellular chloride levels, increased hippocampal excitatory GABA, and enhanced hippocampal gamma oscillations in offspring of VPA-induced rats and *Fmr1* mutant mice (259). Recently, a new selective Na-K-Cl cotransporter inhibitor called ARN23746 has been reported to improve sociability in VPA-induced mice, similar to bumetanide (276). The oral

administration of torsemide, a diuretic that also acts as a Na-K-Cl cotransporter inhibitor, has the potential to enhance neuronal viability and reduce astrogliosis in the hippocampus of ASD rat models (277).

#### 4.8 mGluR5 antagonists

The dysregulated signaling mediated via mGluR5 contributes to the pathophysiology of ASD since it acts as a crucial regulator of excitatory and inhibitory signaling in the hippocampus (278). After treatment with the mGluR5 antagonist MPEP, epileptiform activity and ERK signaling in the hippocampal slices of *Tsc2* mutant mice can be suppressed. The blocked mGluR-LTD in the CA3 hippocampus via antagonism of mGluR5 also improved reversal learning performance between these mice (142). Similarly, for the BTBR mouse model, MPEP treatment facilitated hippocampus-dependent object location memory and decreased synaptic p-ERK1/2 levels (242). Like lithium and rolipram, fragile X syndrome flies treated with mGluR5 antagonist LY341495 demonstrated an enhanced long-term memory paradigm compared to controls (255). Long-term antagonism of mGluR5 also rescued immature spine phenotype (89) and decreased GSK-3 $\beta$  activity (255) in the hippocampus of *Fmr1*-KO mice.

#### 4.9 NMDAR antagonists

NMDAR-mediated excitation and inhibition imbalance is one of the primary theories explaining the neurotoxicity in ASD. Data from several studies on rats exposed to VPA indicate that the NMDAR antagonist, agmatine (260) and dextromethorphan (200), normalize the overly active ERK1/2 phosphorylation in the hippocampus, which serves as an indicative marker of hippocampal hyperexcitability state. Besides, spatial memory and learning deficits induced by *Fmr1*-KO and VPA were mitigated following agmatine (100) and dextromethorphan (200) administration, respectively. For both rats exposed to VPA and those with a *Mecp2*-KO, the administration of ketamine produces a positive effect on their autistic-like behaviors by improving synaptic molecule levels in the dentate gyrus of the hippocampus (222). Memantine, a non-competitive antagonist of NMDAR, was reported to alleviate anxiety and improve learning and memory deficits in VPA-exposed rats, which could be mediated via the restoration of hippocampal GABA/glutamate balance and inhibition of hippocampal neurofibrillary tangles formation and neuronal apoptosis (201).

#### 4.10 Histamine H3R antagonists

The histamine H3R, as a presynaptic autoreceptor can regulate the production and release of histamine as well as numerous brain neurotransmitters like dopamine and acetylcholine (279). Thus, selective H3R antagonists can improve the cognitive impairment in ASD. It is evident from the observation that the administration of

histamine H3R antagonists ST-2223 (247) and ST-713 (248) significantly elevated the levels of histamine, dopamine, and acetylcholine in the hippocampal tissue of BTBR mice with anxiolytic-like effects. Administration of ciproxifan could improve the VPA-induced LTP decline in the CA1 area and hippocampus-dependent learning and memory capacity (202). Moreover, the histamine H3R antagonist E100 mitigates VPA-induced hippocampal inflammation by reducing the levels of IL-6, IL-1 $\beta$ , TNF- $\alpha$ , and TGF- $\beta$  and by suppressing the expression of NF- $\kappa$ B, iNOS, and COX-2 (216).

#### 4.11 Insulin-like growth factor

The insulin-like growth factor (IGF) system comprising two activating ligands (IGF-1 and IGF-2) greatly impacts the development of the central nervous system. It has been discovered that levels of IGF-1 are reduced in the hippocampus of Rett syndrome mouse model (280). The active peptide derivative of IGF-1 can cross the blood-brain barrier and rescue Rett syndrome symptoms in *MeCP2* mutant mice (281). In addition, daily intraperitoneal injections of IGF-1 for 2 weeks reversed deficits in hippocampal LTP in *Shank3*-deficient mice (282). Previous data revealed that *Nlgn3* KO mice treated with IGF-2 fully recovered the social novelty discrimination. This effect was not accompanied by any alteration in spontaneous glutamatergic synaptic transmission within the CA2 region, but rather by enhanced CA2 neuronal excitability (283). Similarly, the administration of IGF-2 ameliorated social interaction deficits in BTBR mice and enhanced their social novelty memory via hippocampal IGF-2 receptor (261). In the Angelman syndrome mouse model, the impaired contextual and recognition memories as well as working memory deficits were restored following subcutaneous injection of IGF-2 (284).

#### 4.12 Aerobic exercises

The beneficial effects on memory functions of aerobic exercise, as a non-pharmacological intervention, have been well-documented in individuals with ASD (285). Compared to sedentary controls, both *Cdk15* KO mice (262) and VPA-induced rats (204) after one month of wheel/treadmill running showed increased hippocampal neurogenesis, improved memory performance, and reduced anxious and impulsive behaviors. One-month voluntary wheel running not only can decrease hippocampal microglia overactivation in *Cdk15* KO mice (262), but also stimulate microglia-mediated engulfment of surplus synapses in the granule cell axons observed in MIA mice (229). On the other hand, however, high-intensity exercise may produce negative effects on ASD symptoms. For instance, two-month treadmill training with relatively high speed led to impaired social memory in ASD rats with mercury exposure (286). Voluntary running for seven days increased cell proliferation in the hippocampal dentate gyrus of *Fmr1* KO mice, but this effect was not observed when running for 28 days (263). Swimming is another beneficial aerobic exercise that

has been shown to increase hippocampal gray matter volume and dendritic spine density in *Shank3*-KO rats (152) and to prevent hippocampal neuroinflammation in VPA-exposed mice (208). It also contributes to improvements in spatial, working, social, and visual recognition memory (152, 208).

#### 4.13 Environmental enrichment

Environmental enrichment is a novel living condition with increased social exploration opportunities and sensory, cognitive, and motor stimulations, which positively affect the hippocampus-dependent learning, memory, and anxiety behavior of children with ASD (287). Living with the mother and an additional non-lactating female (enhanced maternal stimulation) can rescue the spatial and contextual fear memory deficits displayed in adulthood by *Fmr1*-KO mice (90). In addition to this “social environmental enrichment”, enrichment in housing conditions (running wheel, toys, tunnels, ladders, etc.) also ameliorates impaired anxiety-like behavior (91, 209, 264), visual recognition memory (209, 264), spatial learning and memory (91, 265), and fear memory (91), potentially by acting on the hippocampal BDNF/TrkB-PLC $\gamma$ 1-CaMKII pathway (91, 209, 264, 265), as observed in *Fmr1*-KO mice (91), VPA-exposed mice (209), *Ube3a*-KO mice (264), and MIA rats (265).

## 5 Discussion

In summary, hippocampal involvement in the pathophysiology of ASD is now an acquired knowledge. While the majority of current structural and functional neuroimaging studies concentrate on the social brain networks in ASD, hippocampal formation should not be overlooked as it plays a crucial role in higher non-social cognitive functions that are also significantly impaired in most ASD individuals. Numerous lines of clinical evidence on hippocampal volume, morphology, blood flow, metabolism, and functional connectivity seem to converge toward the hypothesis of a hippocampal neurofunctional deficit in ASD, which concerns learning, memory, language ability, emotional regulation, and cognitive map creation. Furthermore, researches based on different ASD animal models are rapidly enhancing our understanding of the neural mechanisms underlying hippocampus-dependent behavioral deficits. In general, typical hallmarks of hippocampal deviations in ASD involve impairments in neurogenesis, dendritic morphology, neuronal viability, neuronal excitation/inhibition balance, LTP, and LTD. Results from the recent therapeutic approaches for ASD are encouraging, since some behavioral alterations such as learning and memory deficits, could be reversed even when treatment was performed on adult mice/rats, potentially by influencing the structure and function of the hippocampus. By targeting therapy at the site of hippocampal pathology, more effective pharmacological and non-pharmacological approaches may be developed in the future.

Despite these promising results, several questions remain unanswered at present. Firstly, as we noted above it is necessary to further confirm whether hippocampal abnormalities, particularly

changes in volume, are present in all individuals with ASD or only in a specific subgroup. To date, comparable anatomical and morphological alterations have been detected in the hippocampus of individuals with ASD and ASD animal models, but human postmortem analysis is still limited by the relatively small numbers of individual brains. Besides, the developmental profile of hippocampal pathology in ASD remains unknown. It cannot be discounted that alternation in hippocampal structure may be secondary due to the disease process, the emotional stress, or the various treatments of ASD. Integrating the neuropathology of the hippocampus in ASD individuals with the aetiology and pathophysiology of ASD is a major challenge for the coming years. Other issues to be addressed involve ascertaining the precision of diagnosing ASD by detecting hippocampal lesions and determining the significance of hippocampal pathology compared to other affected regions. Finally, it is beyond dispute that individuals with ASD exhibit whole-brain functional connectivity deficits, and it is not possible to simply attribute the symptoms of ASD to specific regions of the brain. More specifically, as discussed above atypical connectivity at the local network level between the hippocampus and other brain regions could potentially account for impaired non-social behaviors in ASD. The utilization of multimodal neuroimaging data, such as CT, MRI, fNIRS, EEG, MEG, etc., is progressively increasing in both scientific research and clinical settings nowadays. In future investigations, it is hoped that this multilevel approach will provide insight into the neural circuits behind the hippocampus-dependent functional deficits in those with ASD, which can in turn elucidate the developmental mechanisms underlying hippocampal pathology in ASD.

### Author contributions

JL: Writing – original draft, Conceptualization. HL: Writing – original draft. YL: Software, Visualization, Writing – review & editing. XL: Software, Visualization, Writing – review & editing. ZT: Software, Visualization, Writing – review & editing. KH: Software, Visualization, Writing – review & editing. JC: Writing – review & editing, Software, Visualization. HZ: Conceptualization, Funding acquisition, Supervision, Writing – original draft.

### Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by National Key Research and Development Program of China (2018YFC2001703) and Changping laboratory (2021B-01-01-1).

### Conflict of interest

The authors declare 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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