

REVIEW

Hippocampal contributions to biological, behavioral, and cognitive deficits in autism: An updated review

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Citation: Ozcan, O.O., Cevreli, B., Karahan, M., & Konuk, M. (2025). Hippocampal contributions to biological, behavioral, and cognitive deficits in autism: An updated review. *Euchembioj Rev.*, 1, 81-93.
<https://doi.org/10.62063/rev-9>

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Peer review: Externally peer reviewed.

Received: 30.07.2024

Accepted: 03.10.2024

Online first: 15.10.2024

Published: 25.01.2025

Abstract

The most characteristic symptoms for the diagnosis of autism spectrum disorder (ASD) and the future life of the individual are deterioration in social communication and stereotyped or repetitive behaviors. ASD is associated with diverse atypical difficulties, including memory, learning, language, emotion, and cognitive impairment. Consequently, the hippocampus is important for memory, learning, language ability, emotional regulation, and cognitive mapping. Thus, the hippocampus plays an influential role in the pathophysiological mechanisms of ASD. Here, we provide an updated review of hippocampal structural and functional abnormalities and highlight the hippocampus as an important area for future research.

Keywords: autism spectrum disorder (ASD), behavior, biologic, cognitive, brain-derived neurotrophic factor (BDNF), hippocampus, neuroinflammation, synaptic plasticity



Introduction

Autism spectrum disorder (ASD) is a group of complex neurodevelopmental disorders that include impairments in behavioral skills and stereotypic movements that affect social communication and interaction (Solmi et al, 2022). According to current data, 1 in every 36 children is diagnosed with ASD. The risk is four times higher in boys than in girls and the combined prevalence per 1000 Children is 27.6 (23.1-44.9). Additional information on ASD is available from the CDC at <https://www.cdc.gov/autism/data-research/data-table.html>. The pathogenesis of ASD remains to be elucidated, causing a significant limitation in the development of new therapeutic or preventive techniques. Hippocampal research is important in ASD, which is characterized by learning and cognitive impairment. Hippocampal neurogenesis is at the forefront of this research (Gage, 2019) because atypical hippocampal anatomy and neuroplasticity have been observed mostly in individuals with autism (Li et al. 2019). Individuals with ASD present clinical symptoms with impairments in faces, working, and social memory (Wang et al. 2017). ASD in particular is characterized by learning disabilities due to various cognitive dysfunctions. Previous estimates suggest that 75% of individuals with ASD have impaired learning abilities, including learning skills (Georgiou and Spanoudis, 2021; Girolama et al. 2024). Considering the important role of the hippocampus in memory, learning, verbal ability, emotional behavior, and cognitive attitude, it is a brain region that is regarded in the investigation of the pathophysiological mechanisms and therapeutic approaches of ASD (Long et al. 2024). Previous longitudinal research reported that accelerated hippocampal volume loss in ASD results in declines in verbal and short-term memory (Pagni et al. 2022).

The pathogenesis of ASD remains a matter of great curiosity, and it is the most important factor limiting the development of therapeutic and preventive strategies. Since the hippocampus is one of the important regions where neurogenesis occurs, it plays an active role in many learning and memory processes. Therefore, the biological causes of learning difficulties, memory impairments, and behavioral disorders that occur in neurodevelopmental disorders such as ASD are being investigated (Li et al. 2019). Although many brain regions other than the hippocampus have been studied for ASD, thousands of risk genes, proteins, and molecular pathway deficits have been identified, resulting from the many heterogeneous etiologies, phenotypes, and pathophysiologies of ASD in general (Wan et al. 2024).

In this updated review, we highlight the hippocampus as a brain region of interest for investigating the biological, behavioral, and cognitive status of ASD. Here, we will first review biological abnormalities in the hippocampus of individuals with ASD and discuss discrepancies in the results of existing studies. In the next section, we will discuss the hippocampus's known behavioral and cognitive contribution to ASD, mostly in post-mortem studies, mice and rats, that exhibit hippocampal synaptic plasticity impairments and hippocampus-dependent deficits.

Biologic changes in the hippocampus

More than 10,000 cells per person, an average of more than 1860 genes per cell, and 26 primary cortical cell types—including glial cells—have all been linked to ASD. With the wide-use of genomic sequencing, more genomic data on ASD have been obtained through rapid developments in imaging technologies. Studies of different brain regions and their many specific genetic mechanisms associated with increased risk for ASD diagnosis continue to pave the way for a variety of approaches that can help diagnose ASD at an early stage.

Findings from experimental studies indicate that the association with ASD-related impairment of social recognition memory is specifically supported by the CA2 region of the hippocampus (Hitti and Siegelbaum, 2014). ASD-related social memory deficits emerged due to decreased neurotransmitter release because of decreased axon diameter in the Hippocampo-fusiform pathways associated with face recognition (Trontel et al. 2013). Genome-wide association studies (GWAS), as well as gene expression profiling techniques such as RNAseq identified 2851 differentially expressed genes in the hippocampus of children with ASD, including genes implicated in genetic analysis studies (Coley and Gao, 2018).

Different studies have reported variability in brain metabolite concentrations in ASD compared to neurotypical participants (Ajram et al. 2024, Kurochkin et al. 2019). It has been reported that N-acetyl aspartate concentrations and N-acetyl aspartate/creatine ratios are reduced in the hippocampus of children with ASD (Libero et al. 2016, Thomson et al. 2024). In the ASD group, N-acetyl-aspartate levels in the hippocampal region were positively correlated with IQ in a multivoxel proton magnetic resonance spectroscopy (1H-MRS) study (Dionísio et al. 2024). These metabolites were not associated with the hippocampus. For instance, Graham et al. (2016) used LC-MS to find changes in the concentrations of 37 metabolites in the cerebellum between 11 people with ASD and 11 controls. However, more research is required to understand the biological pathways' activity. Additional research is needed to understand the genetic basis of the metabolic alterations in various hippocampal areas associated with ASD.

ASD is associated with genetic and environmental factors that develop in the brain. Regarding the preclinical aspect of ASD, many animal models and clinical studies show that methods such as neuroimaging focus on areas such as the hippocampus, amygdala, frontal region, and cerebellum (Leisman et al. 2023). The neurogenesis of the perinatal and adult hippocampus involves fundamental activities linked to spatial processing, pattern discrimination, functional integration, cognitive flexibility, and learning. Brain-derived neurotrophic factor (BDNF) is a crucial regulatory marker for long-term potentiation (LTP), learning, and memory. It also has a major function in synaptic transmission and plasticity in the hippocampus (Ilchibaeva et al. 2023).

Common neuroplastic disorders are seen in ASD. These changes in neuroplasticity may result from disturbances in synaptic function (Zhao et al. 2021). In the studies conducted, peripheral BDNF levels in serum or plasma were evaluated differently. However, some research has argued the reverse findings (Meng et al. 2016, Segura et al. 2015). Meta-analysis studies have revealed a positive connection between high blood BDNF levels and autism (Barbosa et al. 2020, Elhamid et al. 2024, Liu et al. 2021). However, hippocampal BDNF levels have generally been studied in animal models of ASD, and this number was quite small. Valproate-induced autism-like rats exhibited an autism-like behavioral profile characterized by deficits in social interaction, anxiety-like behavior, and repetitive behaviors. Valproate induction decreases BDNF levels in the dentate gyrus (DG) and CA3 regions of the rats examined (Camuso et al. 2022, Fuentealba et al. 2019). However, clinical and preclinical studies on hippocampal BDNF levels were still insufficient.

Some postmortem studies are interesting in clinical research. Rexrode et al. recently reported decreased expression of the synaptic proteins PSD95 and SYN1, increased expression of the extracellular matrix (ECM) protease MMP9, and reduced expression of MEF2C on postmortem hippocampus samples from male children with ASD (n=7) (Rexrode et al. 2024). Additionally, postmortem studies have reported that although the concentration of neural cells in the hippocampus in ASD is dense, the cells are abnormally small (Fetit et al. 2021).

Bove et al. 2022 reported that ketamine administration helped mimic the typical symptoms in adult mice at postnatal days 7, 9, and 11 with behavioral aspects. They found decreased BDNF and enhanced glial fibrillary acidic protein (GFAP) expression levels with increased glutamate and reduced GABA levels in the amygdala and hippocampus. In another study, the BDNF protein amount is decreased both in the hippocampus and frontal cortex in the BTBR Mouse Model of Autism (Jasien et al. 2014). As a small dimeric protein, BDNF is structurally homologous to Nerve Growth Factor (NGF), with 50% amino acid identity with NGF, neurotrophin-3 (NT-3), and NT-4/5 (Bathina and Undurti, 2015).

Neurotrophic factors are highly effective in cell proliferation and differentiation, neuroto- and synaptogenesis, synaptic function, and synaptic plasticity. There have not been many studies on NT-3, NT4/5, and the insulin-like growth factors IGF-1 and IGF-2. It has been reported that VPA-induced significantly increased levels of pro-inflammatory markers (IL-1 β , TNF- α , IL-6, IFN- γ , IL-17, TGF- β) and decreased anti-inflammatory (IL-10) levels in the hippocampus of experimental animals (Barzegari et al. 2023, Eissa et al. 2019). However, these results are controversial depending on age. Hippocampal neuroinflammation occurs in VPA-induced rats during adolescence and may also occur with microglial and astrocyte activation in the postnatal period, possibly with VPA exposure. Improvements in the expression of neuroglial markers in the hippocampus of adult rats exposed to VPA may be a finding of improvement in the neuroinflammatory phenotype (Gifford et al. 2022). In particular, hippocampal research is limited when the status of neurotrophic factors in ASD is evaluated.

To date, many transgenic animal models that mimic ASD have been studied. The genetic cause has been identified in cases of syndromic ASD, which often co-occurs with ASD-related behavioral phenotypes (Li et al. 2021). Duarte-Campos et al. 2024 discovered elevated levels of interferon-gamma (IFN- γ) and monocyte chemoattractant protein 1 (MCP-1) in the hippocampus, suggesting increased inflammation, alongside a reduction in the anti-inflammatory enzyme arginase 1 (ARG1) in the hippocampus of adult male C58/J mice. Animal models, such as the C58/J-inbred mouse strain, are used to study the biological properties of ASD. This type is considered a model of idiopathic autism because of reduced social preferences and repetitive behaviors. Therefore, neuroinflammatory markers identified in the hippocampal region of an animal model are of great importance to understanding biological effects in the hippocampus for ASD.

According to Fuchs et al. (2018), Cdkl5 +/- mice had respiratory issues, significant difficulties with motor coordination and memory, and showed autistic-like behavior. These defects are associated with neuroanatomical changes, such as decreased dendritic arborization and decreased spine density in hippocampal neurons. Decreased pyramidal neurons in the CA1 region, reduced dendritic maturation, and reduced dentate gyrus were reported in Mecp2 mutant mice (Sun et al. 2019). Interestingly, this was potentially associated with inadequate BDNF expression in hippocampal neurons (Bertoldi et al. 2019).

Current research on behavioral and cognitive changes in the hippocampus

ASD is typified by focused, repetitive actions and difficulties in social communication. Alongside these behavioral symptoms are sensory and cognitive issues, including episodic memory, working memory, spatial reasoning, and executive function deficiencies (Bangerter et al. 2017). Although the relationship between brain activity to social integration in ASD has been investigated in neuroimaging studies, symptoms, and preclinical studies, memory, orientation, and spatial deficits are also

important in the etiology of this disorder. Individuals with ASD have also consistently reported deficits in episodic memory, a major hub of sensory-perceptual-conceptual-affective processing (Cooper and Simons, 2019). In ASD participants, more activity was found in the occipital region (hippocampus, premotor region, and ventral (occipitotemporal) areas in the left hemisphere compared to the right hemisphere. Functional impairment in episodic memory has been highlighted by an fMRI study, which has highlighted neuronal connectivity deficits in the hippocampus (Desaunay et al. 2023). Atypical memory processes in ASD include the dominance of verbal information over spatial information, disruption of working memory, and impaired processing in episodic memory. It is believed that these cognitive and behavioral effects in the hippocampus may be due to biological causes in the hippocampus (Figure 1).

Recently, a meta-analysis on declarative memory in ASD was conducted, highlighting areas of working memory (especially verbal), visual recognition, and episodic long-term memory. As a result, visual-spatial memory appears to be more impaired than verbal memory, making it more difficult to recognize faces than verbal behavior (Griffin et al. 2021). Individuals with ASD experience more problems with working memory than with episodic long-term memory. Recent studies have linked ASD to impaired social memory capacity and neuronal connectivity in hippocampal CA2, suggesting that the role of CA2 in social memory encompasses both short-term and long-term social memories (Cum et al. 2024).

Increased hippocampal activation was detected in individuals with ASD associated with over-reactivity to auditory and visual stimuli (Long et al. 2024). Allsop et al. (2018) reported that the anterior cingulate cortex-basolateral amygdala integration plays an important role in the acquisition of fear conditioning to various stimuli in individuals with ASD and impaired social activity and that hippocampus-related 5-7 Hz oscillations are effective in social behaviors such as lack of empathy. Social recognition impairment was associated with inadequate oxytocin receptor expression in the medial amygdala and hippocampus (Raam et al. 2017).

Changes in hippocampal structure in ASD have been the subject of further research. In particular, recent clinical studies have reported the atypical hippocampal volume of children with ASD compared to normal children (Li et al. 2023, Rexrode et al. 2024). Task-based fMRI studies on ASD have shown impairment in hippocampal region-related learning and memory and decreased perception of social emotions (Hashimoto et al. 2021). Disturbance of hippocampal and caudate nucleus connections during a task has been associated with social performance in individuals with ASD (Solomon et al. 2015).

ASD-like experimental models have reported a critical role of the hippocampus and reduced neuroplasticity in social memory impairment (Sato et al. 2023). Considering that ASD is a neurodevelopmental disorder, neurodevelopmental and neuroimmunological abnormalities occurring in the prenatal period have shed light on the neurobiological features of ASD and trigger hippocampal dysfunction (Carlezon et al. 2019; Hanamsagar et al. 2022; Tsilioni et al. 2019).

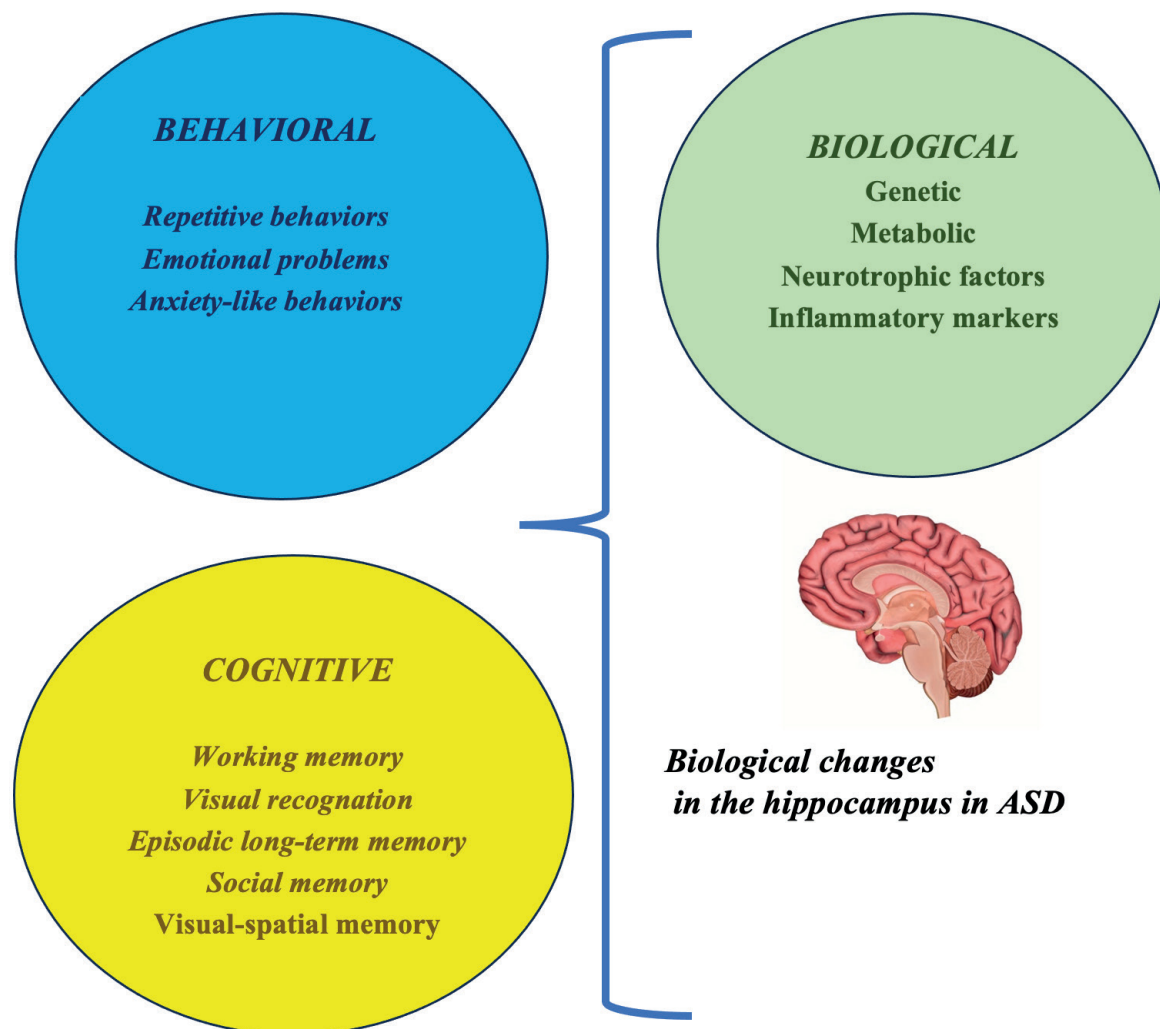
Cognitive and behavioral reflection in ASD

Figure 1. Summary of the cognitive and behavioral implications of hippocampal biological influences on ASD development according to current literature.

Human hippocampal formation performs grid-like mapping of the visual field, and previously learned structures are projected onto newly lettered information, generating the repetitive behaviors associated with ASD, according to a small number of studies using magnetoencephalography (MEG) and electroencephalography (EEG) (Staudigl et al. 2018). These results suggest that the hippocampus impacts the formation of cognitive maps. Complex functions, such as memory, spatial reasoning, and socialization all require a hippocampal neurogenesis system that allows for flexible planning and decision-making (Barón-Mendoza et al. 2024).

In a study by Fuchs et al. (2018), *Cdk15* $-/-$ female mice showed cognitive impairment, and hippocampus-dependent learning and memory were evaluated using the Morris water maze (MWM). Additionally, *Fmr1*-KO mice exhibited impaired hippocampus-dependent fear memory; these deficits were suggested by low levels of freezing behavior response to fear conditioning. Metabotropic

glutamate receptor-dependent long-term depression (mGluR-LTD), which is excessively increased in the CA1 region, and N-methyl-D-aspartate receptors (NMDA) in the dentate gyrus, have been reported to negatively affect LTP (Chen et al. 2022). In a novel object recognition test study, *Fmr1*-mutant mice were reported to be indifferent to the new object and spent significantly more time sniffing the old object. This finding highlighted visual recognition memory deficits in mice (Jeon et al. 2022).

Neural deficits in the hippocampus also cause emotional problems, including anxiety-like behaviors. Updated reports from open field tests and elevated plus maze showed that *Fmr1*-KO mice had high anxiety behaviors (Chen et al. 2022). Rett syndrome-like animal models have provided important scientific data on hippocampus-related impairments in memory and learning. For example, *Mecp2*-mutant mice exhibit impaired spatial memory and learning in the Morris water maze task (Hao et al. 2015).

The current literature mostly consists of known genetic, environmentally mediated, and idiopathic ASD animal models in mice and rats that exhibit hippocampal synaptic plasticity disorders and hippocampus-related behavioral deficits. This situation causes translational limitations in the obtained data. Additionally, the limited investigation into hippocampal-focused functions, such as memory and spatial reasoning has been devoted to ASD research because impairments in these functions have not been recognized as core aspects of the ASD phenotype.

Conclusions

The current literature is quite conflicting regarding ASD pathophysiology, and studies have shown few brain regions with consistent or descriptive functional changes in ASD. Considering this biological infrastructure, the etiology of ASD remains a matter of research and curiosity, as it includes less than 1% of clinical cases. However, most behavioral symptoms are similar and common across cases. The hippocampus has been the focus of very few clinically relevant post-mortems and GWAS studies in ASD, perhaps because the current literature lacks evidence of hippocampal involvement in social behavior that is also included in clinical diagnostic criteria. In summary, recent research has demonstrated that hippocampus abnormalities in ASD frequently result in cognitive learning and memory issues, which may have a variety of biological causes. These biological effects are mostly understood through genetic, metabolic, neurotrophic, and inflammatory markers. Because this overall assessment was obtained on very few postmortem and many different animal models, it seems that further studies are needed for ASD. Post-mortem studies are limited due to legal permissions, budget issues, and etiology. Very few studies have focused on the hippocampus. In future studies, it is recommended to conduct more behavioral and hippocampus-focused biological studies in ASD-like animal models in the current literature. In particular, it is recommended to increase the numbers of neuroinflammatory responses, neurotrophic factors, ASD-related gene expressions, proteomic analyses, or volumetric studies in the hippocampal region of different types of animal models and compare them. Because ASD has a multifactorial etiology from a clinical perspective, clinical research should focus on GWAS studies related to disease subtypes or studies that conduct correlative and risk association studies of cognitive aspects.

Funding

No funding to declare.

Conflict of interest

The authors declare no conflicts of interest.

Data availability statement

Data sharing was not applied to this review article as no datasets were generated or analyzed during the current study.

Ethics committee approval

Ethics Committee approval was not required for this study.

Authors' contributions

All authors contributed equally to this work.

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