Central Nervous System in Autism Spectrum Disorder

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Autism spectrum disorder (ASD) is a heterogeneous, behaviorally defined, neurodevelopmental disorder that has been modeled as a brain-based disease.

autism autism spectrum disorder central nervous system

1. Introduction

Autism was first described by a psychiatrist named Leo Kanner based on his observations on 11 children with severe communication problems, repetitive behavior, and acute lack of social interaction. Kanner's original description has led to the recognition of autism as a disorder decades later [1]. It is part of a broader range of conditions known as autism spectrum disorder (ASD). The term autism and ASD are used interchangeably. ASD is defined as a complex neurodevelopmental disorder characterized by impairments in social interactions and communication, as well as by the presence of purposeless repetitive behaviors and restrictive interests [2]. Individuals with ASD have difficulty in expressing and understanding certain emotions and moods, abnormal eye contact, restricted ways of using toys, preferences of isolated play and minimal changes to routine. These characteristics have made it difficult for them to establish relationships with others, act in an appropriate way and live independently [3].

Developmental disabilities ranging from mild disabilities such as speech and language impairments, to more serious developmental disabilities such as intellectual disabilities, cerebral palsy and autism, have been identified in approximately 1 in 6 children in the United States. The prevalence of ASD has dramatically increased in the last few decades at the rate of 1 in 2500 children around 1980s to 1 in 150 children in 2007 [4]. According to the data from the Autism and Developmental Disabilities Monitoring (ADDM) Network of the US Centers for Disease Control and Prevention (CDC), approximately, 1 in 68 children have been identified with ASD from 2010 to 2012 [5]. For 2014, the overall prevalence of ASD has increased to 16.8 per 1000 (1 in 59) children aged 8 years [6]. The rate of ASD diagnosis was four times more common in males than females [7]. The increase in ASD prevalence was partly attributed to the increased awareness and reporting practice of the disorder, as well as an improved diagnostic criteria [8].

Approximately, 90 percent of ASD cases have been classified as idiopathic, while about 10 to 20 percent were caused by known genetic etiology [9]. In recent years, intense scientific works have revealed that ASD is genetically driven with heritability indices estimated at 85 to 92 percent and could be triggered by environmental risk factors

especially those influencing fetal and early-life development [10][11]. The symptoms of autism appeared before 36 months of age, while regression or loss of skills usually occurred between 18 and 24 months in 30 percent of the affected children [12]. It may persist throughout life, often in a more muted form [2]. In fact, ASD has affected more children than diabetes, acquired immune deficiency syndrome (AIDS), cancer, cerebral palsy, cystic fibrosis, muscular dystrophy and Down's syndrome combined [13]. The Global Burden of Disease Study 2010 reported that the global prevalence and burden of disease for ASD in 2010 was 1 in 132 individuals, which translated to 52 million cases of ASD and 7.7 million disability-adjusted life-years (DALY) across the globe [14]. Among the mental disorders, ASD was the leading cause of disability in children under 5 years of age in terms of years lived with disability (YLDs). ASD was also ranked among the 20 leading causes of disability for the under 5-year age group. These data indicated that ASD is accounted for indisputable health loss across the lifespan.

The proposed pathogenesis of ASD comprises many distinct mechanisms including chronic neuroinflammation, gamma-aminobutyric acid (GABA) imbalance, monoaminergic dysregulation and mitochondrial dysregulation [15]. However, the precise mechanism underlying the pathophysiology of ASD remained unknown and currently, there is no cure or effective treatment for this disorder. Major challenges toward finding an effective cure for this disorder include heterogeneity of its etiology and the lack of consistent and reliable genetic or biologic diagnostic markers for accurate classification and early diagnosis of ASD [16].

2. CNS and Social Function

Vast parts of brain regions, which are made of the neural circuitry, are involved in various aspects of social cognition and perception. Social cognition is referred to as the fundamental ability to perceive, categorize, remember, analyze, reason with and behave towards others [17]. The ability to perceive is not only dependent on vision and hearing, but also sensation (sense of smell and somato-sensation). It also depends on the connection with memories and emotions in the amygdala-hippocampal complex and other limbic structures [18]. Meanwhile, social response formation involves automatic, stereotyped motor patterns encoded in brain stem nuclei, hypothalamus, central limbic and medial temporal structures, which interplay with the frontal cortex. Some parts of the cerebellum and the corpus callosum are also important for the "social brain". The monoaminergic neurotransmitter systems that are involved in the functioning of the "social" circuits and controlling the activity in vast areas of the brain comprise the serotogenic, mesolimbic dopaminergic and norepinephrinergic systems. In addition, the GABAergic anti-excitatory system, peptidergic systems and neurons under the influence of steroid hormone are all essential for social functioning [18].

ASD has been linked to abnormal social brain function and neurological disorder [19]. As a disorder that features profound deficits in several aspects of social perception and cognition, neuroanatomical structure of the brain has become the focus in understanding brain mechanisms in research related to ASD. Additionally, ASD is characterized through behavioral and cognitive features that are predominantly thought to be as a result of atypical development of the brain itself.

3. Central Nervous Changes and ASD

Autism is also referred to as an early-onset disorder of the developing CNS [20]. Although the underlying mechanisms remain largely unknown, autism is commonly described as a brain-based disorder since many documented changes are registered in the brain [21]. In fact, the symptoms of ASD have been associated with pervasive atypicalities in the CNS [22].

3.1. Brain Structure and Function Abnormalities in ASD

Certain brain regions including the limbic system, particularly the hippocampus, amygdala and cerebellum, have been implicated in the pathophysiologic mechanisms and clinical expressions of the disorder [23]. Evidence from neuroimaging and postmortem studies has revealed structural abnormalities in those regions of the brain. Hypothetically, the core abnormalities in the pathogenesis of autism are located in the amygdala, adjacent limbic structures and corpus callosum [18].

The amygdala is a collection of nuclei that lies beneath the uncus of the temporal lobe at the anterior end of the hippocampal formation and the inferior horn of the lateral ventricle of the brain [24]. It influences drive-related behavior and related emotions. Amygdala stimulation is commonly followed by fear emotion, while bilateral destruction of amygdala causes reduced aggression. Amygdala deficit in autism might lead to abnormal fear responses in children; they may either show too little or too much fear compared to non-autistic children [24]. The hippocampus is also the key component of the neural system and one of the most thoroughly studied areas of the mammalian CNS. It mediates the emotion perception and regulation, and hence is also thought to be involved in the pathophysiology of autism [25].

Studies have shown that the damage to the amygdala is associated with impairments in social cognition and interpretation of emotions [26]. Abnormal patterns of the amygdala and hippocampal development were found during childhood and adolescence phases of autistic cases. In a previous study by Pierce, et al. [27], structural and neurofunctional activities in the brain regions related to face processing were evaluated using functional magnetic resonance imaging (MRI). The study revealed a significant decrease in amygdala volume in autistic adults compared to normal control subjects. The study is consistent with an earlier MRI study by Aylward, et al. [28], which demonstrated a significantly smaller amygdala volume in non-mentally retarded autistic male adolescents and young adults compared to healthy community volunteers. A significant reduction in hippocampal volume in relation to total brain volume was also noted in autistic subjects. The authors concluded that these volume reductions were related to reduction in dendritic tree and neuropil development, which likely reflected the underdevelopment of neural connections of limbic structures with other parts of the brain.

Findings of another study, however, documented that amygdala lesions did not lead to autistic symptoms [29]. The subjects were two women with developmental-onset bilateral amygdala lesions. By using comprehensive interviews, behavioral observations and widely used ASD screening questionnaires, it was found that both subjects did not exhibit autistic symptomatology despite having the amygdala lesions. This suggests that it is the abnormal

connectivity between the amygdala and other structures rather than overt amygdala pathology, which contributes to ASD.

On the contrary, several studies have found that amygdala and hippocampal volumes of ASD subjects were increased from childhood to young adulthood. Three-dimensional coronal MRI measurement acquired from autistic children revealed enlargement of amygdala and hippocampi [23]. Schumann, et al. [30] showed that autistic children had larger right and left amygdala volumes than control children; however, similar changes were not seen in the adolescent group. The hippocampal volume was enlarged in all study groups. The authors speculated that amygdala is initially larger in children with autism, but they did not undergo the age-related increase in volume that normally occurs in developing children. In another study, Groen, et al. [25] measured amygdala and hippocampal volumes in a group of adolescent with autism and found significant enlargement of these parts of the brain compared to control group [25].

In a more recent study, volumetric MRI of amygdala and hippocampal subfields were measured in infant subjects with risk of ASD [31]. The authors showed significant enlargements of amygdala and hippocampi in each hemisphere and whole brain in ASD group compared to normal control. Amygdala enlargement at an early age has been related to severity of social, communication and emotional problems in ASD group [25][30]. The volumetric enlargement of amygdala and hippocampus were postulated to be an adaptive response to increased neuron activity throughout childhood and adolescence in autism. It is also plausible that the hippocampus is enlarged in response to heightened amygdala activity since the hippocampus has a regulatory role on amygdala activity through a dense network of reciprocal connections [25].

Considering this, abnormalities in those brain regions seemed to follow a different time course and the findings in adolescence and adult were quite sparse, which are summarized in **Table 1**. There are certainly limitations that may contribute to this discrepancy. For instance, the small sample size in some studies may result in insufficient statistical power. Several studies have included a broader age range, which may hinder the detection of developmental changes in the brain. These results need to be replicated before a definitive conclusion can be made. Nonetheless, the changes in amygdala and hippocampal structure and function reported in previous studies were in accordance with the theory that autism is caused by abnormalities of certain brain regions.

Table 1. Summary of previous studies on brain structure and function abnormalities in autism spectrum disorder (ASD).

Reference	Subjects	Sex	Age Group	Test Samples/Regions	Method	Major Findings
[27]	7 autistic adults, 8 normal control	Male	21 to 41 years	Brain: Fusiform gyrus, inferior temporal gyrus, middle temporal gyrus, amygdala	fMRI	⇓ bilateral amygdala volumes in autistic subjects; fusiform gyrus volume was ⇓ but not

Reference	Subjects	Sex	Age Group	Test Samples/Regions	Method	Major Findings
						statistically significant.
[28]	14 autistic subjects, 14 normal control	Male	11 to 37 years	Brain: Hippocampus, amygdala	MRI	⇓ amygdala volume (with and without total brain volume correction); ⇓ hippocampal volume (with correction) in autistic subjects.
[29]	2 adults with bilateral damage to amygdala	Female	23-and 48-years	Autism Diagnostic Questionnaire Observation Schedule, Social Responsiveness Scale and other questionnaires		No evidence of autistic changes in all measurements.
[23]	45 children with ASD, 26 typically-developing (TD), 14 developmentally-delayed (DD) children	Male, female	36 to 58 months	Brain: Cerebellum, cerebrum, amygdala, hippocampus	MRI	⇑ cerebral volume in ASD compared to TD and DD children; ⇑ cerebellar volume in ASD compared to TD; ⇑ bilateral amygdala and hippocampi volume in ASD.
[30]	19 low-functioning autism (LFA), 27 high-functioning autism (HFA), 25 Asperger's and 27 typically developing control children	Male	7.5 to 18.5 years	Brain: Amygdala, hippocampus	MRI	⇑ right and left amygdala in children with autism than control (7–12.5 years old); ⇔ amygdala volume in adolescent group (12.75–18.5 years old).
[25]	23 adolescents with autism, 29 control	Male, female	12 to 18 years hippocampus	Brain: Amygdala,	MRI	⇑ right amygdala and left hippocampus in adolescent with autism.

Reference	Subjects	Sex	Age Group	Test Samples/Regions	Method	Major Findings
[31]	60 infants with risk of ASD, 211 normal control Brain: Amygdala,	Male, female	23 to 27 months	Brain: Amygdala, hippocampus	MRI	⇑ amygdala and hippocampus in each hemisphere and the whole brain in ASD group.

All main findings were compared to control. Abbreviations: ASD, autism spectrum disorder; TD, typically developing; DD, developmentally delayed; LFA, low-functioning autism; HFA, high-functioning autism; MRI, magnetic resonance imaging. Symbols: ↓ decreased, ↑ elevated, = no changes.

stasis [32]. astroglia. glial cells anization, neuroaxonal guidance and synaptic plasticity [33]. During normal homeostatic condition, astrocytes facilitate neuronal survival by producing growth factors and mediating uptake or removal of neurotransmitters including glutamate from the synaptic microenvironment [34]. However, during astroglial activation secondary to injury or response to neuronal dysfunction, astrocytes may secrete pro-inflammatory cytokines, chemokines and metallo-proteinases that could magnify immune reactions in the CNS [35]. Likewise, microglial activation might produce similar neuroglial responses to injury or dysfunction.

Recent evidence documented that localized inflammation in the CNS could contribute to the pathogenesis of ASD. Several studies have shown that inflammatory cytokines including tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin-1β (IL-1β) and interleukin-12 (IL-12) were elevated in the blood mononuclear cells, plasma and serum of autistic children [36][37]. However, these findings were observed peripherally and not directly related to immune-mediated pathology within the CNS.

Vargas, et al. [12] measured 79 proteins including cytokines, chemokines and growth factors in the post-mortem brain of autistic patients to detect the presence of neuroinflammation. The levels of pro-inflammatory cytokines including transforming growth factor (TGF-β1), macrophage chemoattractant protein (MCP)-1, interleukin-6 (IL-6) and interleukin-10 (IL-10) were found elevated in brain tissues of autistic patients compared to control patients. Meanwhile, immunocytochemical analyses showed marked activation of microglia and astroglia, indicating that increased neuroglial response was part of the neuroinflammatory reactions. The authors reported that these responses could be linked to the CNS innate immune system in which microglial activation was the main cellular response to CNS dysfunction [12].

In another study, Li, et al. [38] further investigated both innate and adaptive immune responses in the brain tissue of ASD patients using Multiplex Bead Immunoassays. The results showed that proinflammatory cytokines (TNF-α, IL-6, and GM-CSF), Th1 cytokine (IFN-γ) and chemokine (IL-8) were significantly increased in the brain (cerebral cortex) extracts of ASD patients compared to the control. The high inflammatory cytokine levels were indicative of heightened immune response and may be associated with localized brain inflammation and tissue necrosis.

Taken together, peripheral immune dysregulation observed in early studies could be associated with neurotoxic events in brain. In normal condition, microglia exist in resting state and constitutively express growth factors, not cytokines or excitatory amino acids [39]. In ASD, the upregulation of peripheral chemokines/cytokines such as TNF-α, IL-6 and IL-1β might trigger the activation of microglia. Primary microglial activation can be caused by disturbances in microglial function or neuronal-microglial interactions during brain development. Meanwhile, secondary activation might be contributed by unknown factors that disturb pre- or postnatal brain development [40].

Excessive or prolonged microglial activation involving microglia-induced inflammatory cytokines and excitotoxicity might disrupt neurogenesis and neurodevelopment [41]. **Table 2** describes previous studies examining neuroglial activation and neuroinflammation in ASD.

Table 2. Summary of previous studies on neuroglial activation and neuroinflammation in ASD.

Reference	Subjects	Sex	Age Group	Test Samples/Regions	Method	Major Findings
[36]	12 children with autism (group 1), 35 children with autism (group 2), 12 control	Male, female	2.7 to 10 years	CSF (group 1), serum (group 2) ELISA	ELISA	Changes in indicator of immune response (CSF: ⇑ biopterin, ⇓ quinolinic acid and neopterin, serum: ⇑ TNF receptor II in serum) in autistic children.
[37]	20 children with ASD, 20 matched control	Male	3 to 11 years	Peripheral blood mononuclear ELISA cells	ELISA	⇑ IL-13/IL10 and IFN-γ/IL-10 in children with ASD.
[38]	8 autistic patients, 8 matched control	Male, female	4 to 37 years	Frontal cortex brain tissue	Multiplex Bead Immunoassay	⇑ proinflammatory cytokines (TNF-α, IL-6 and GM-CSF), Th1 cytokines (IFN-γ) and chemokine (IL-8) in autistic patients.
[12]	11 autistic patients, 6 control	Male, female	4 to 45 years	Middle frontal gyrus, anterior cingulate gyrus, cerebellar hemisphere	Immunohisto-chemistry, protein tissue array, ELISA	Marked activation of microglia and astroglia (immunohistochemical studies); MCP-1 and TGF-β1 were the most prevalent cytokines in brain tissue (cytokine profile) of autistic patients.

All main findings were compared to control. Abbreviations: ASD, autism spectrum disorder; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; TNF, tumor necrosis factor; IL, interleukin; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; MCP-1, macrophage chemoattractant protein-1; TGF-β1, transforming growth factor beta 1. Symbols: ⇓, decreased; ⇑, elevated.

3.3. Glutamatergic Neurotransmission Dysfunction in ASD

Neurotransmitters generally play a major role in forming CNS and peripheral nervous system. Glutamate (Glu) is a major excitatory neurotransmitter crucial for brain development. It is important for neural plasticity and maintenance of cognitive function [42]. Various subtypes of glutamatergic receptor can be found on astrocytes, microglia, oligodendrocytes, neuron pre-synapse and axons. Glu receptor system comprises ionotropic and

metabotropic glutamate receptors. Activation of these receptors is required for fast synaptic transmission, synaptic plasticity, learning and memory, motor coordination, pain transmission and neurodegeneration [39].

Major neurotransmitters including Glu, serotonin, dopamine and GABA are implicated in autism [43]. Glu has been shown to be directly involved in general cognitive functions [44]. There are compelling evidence that excess Glu could be a potent neurotoxin that leads to neuronal cell death and plays a role in the pathophysiology of some neurodegenerative diseases [45][46]. Scientific evidence has also revealed that most heterogenous symptoms of ASD are closely connected with the dysregulation of glutamatergic neurotransmission in the brain [39].

Glu levels in the brain can be measured in vivo safely and non-invasively using a neuroimaging technique called proton magnetic resonance spectroscopy (^{1}H-MRS). The combination of Glu and glutamine is referred to as Glx, which represents the overall glutamate/glutamine levels and their functioning in the brain. Glu is associated with the production of oxidative energy and function of excitatory neurotransmitter, while glutamine is involved with Glu recycling and regulation of brain ammonia metabolism [47][48][49].

A study by Page et al. [50] revealed that adults with ASD had a higher concentration of Glx level in the right hippocampus compared to healthy subjects. Brown et al. [51] showed an increased Glx concentration in the auditory cortex in adults with ASD compared to healthy adult control. In other studies, high Glx concentration was also reported in the anterior cingulate gyrus of children and adolescents with ASD [47][52]. Significantly higher brain Glu levels were also detected in the brain regions of autistic children including the anterior cingulate gyrus, left striatum, left cerebellar hemisphere and left frontal lobe [53]. These brain areas were reported to be affected in ASD, causing disturbance in brain processes including cognitive, affective, sensory functions, motor task, join attention and social orienting.

In addition to brain Glu, the levels of peripheral Glu and other excitatory amino acids were also found to be elevated in autistic subjects. Hassan et al. [53] showed that blood Glu level was significantly higher in children with ASD compared to controls. Several other studies have also reported significantly higher Glu levels in plasma/platelet-poor plasma [46][54] and serum [55].

These findings are consistent with those by Aldred et al. [56], which reported significant elevations of plasma Glu in children with autism as well as in their parents and siblings. The levels of other amino acids related to glutamatergic neurotransmission such as phenylalanine, alanine, lysine, tyrosine and asparagine were significantly higher, but plasma glutamine was significantly lower in samples taken from children with autism and their parents compared to age-matched control.

In human, plasma Glu level has been seen correlated with cerebrospinal fluid Glu level, although Glu does not readily cross the blood brain barrier [45][46]. The peripheral Glu level was postulated to reflect the Glu level in the brain *per se*. The increase in Glu concentration was thought to be due to these mechanisms (i) dysfunction in enzymes that are responsible for converting glutamate to GABA [57]; (ii) lack of Purkinje cells in autistic cerebellum

[58]; (iii) production of transporters that translocate Glu from endothelial cells to extracellular fluids [59] and (iv) dysfunction of the glutamate-glutamine cycle.

As for Glx level, several ^{1}H-MRS studies on the brain of autistic subject have shown low Glx levels. As reported by Horder, et al. [60], adults with ASD had a significantly reduced Glx concentration in the basal ganglia, which correlated with the impairment in social communication. There were reports of significantly lower Glx concentration in the anterior cingulate cortex of adults with ASD [61][62]. In addition, two previous studies found reduced cerebral Glx [63] and Glx/creatinine ratio in the frontal lobe of children with ASD compared to healthy control [64]. These findings suggested dysfunction of the brain glutamatergic system and abnormalities of neurotransmission.

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