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Review Article

A Short Review on the Current Understanding of Autism Spectrum Disorders

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Autism spectrum disorder (ASD) is a set of neurodevelopmental disorders characterized by a deficit in social behaviors and nonverbal interactions such as reduced eye contact, facial expression, and body gestures in the first 3 years of life. It is not a single disorder, and it is broadly considered to be a multi-factorial disorder resulting from genetic and non-genetic risk factors and their interaction. Genetic studies of ASD have identified mutations that interfere with typical neurodevelopment in utero through childhood. These complexes of genes have been involved in synaptogenesis and axon motility. Recent developments in neuroimaging studies have provided many important insights into the pathological changes that occur in the brain of patients with ASD in vivo. Especially, the role of amygdala, a major component of the limbic system and the affective loop of the cortico-striato-thalamo-cortical circuit, in cognition and ASD has been proved in numerous neuropathological and neuroimaging studies. Besides the amygdala, the nucleus accumbens is also considered as the key structure which is related with the social reward response in ASD. Although educational and behavioral treatments have been the mainstay of the management of ASD, pharmacological and interventional treatments have also shown some benefit in subjects with ASD. Also, there have been reports about few patients who experienced improvement after deep brain stimulation, one of the interventional treatments. The key architecture of ASD development which could be a target for treatment is still an uncharted territory. Further work is needed to broaden the horizons on the understanding of ASD.

Key words: Autistic Disorders, Review, Neurobiology, Amygdala

INTRODUCTION

Autism spectrum disorder (ASD) is a set of neurodevelopmental

disorders characterized by a lack of social interaction, verbal and nonverbal communication in the first 3 years of life. The distinctive social behaviors include an avoidance of eye contact, problems with emotional control or understanding the emotions of others, and a markedly restricted range of activities and interests [1]. The current prevalence of ASD in the latest large-scale surveys is about 1%~2% [2, 3]. The prevalence of ASD has increased in the past two decades [4]. Although the increase in prevalence is partially the result of changes in DSM diagnostic criteria and

younger age of diagnosis, an increase in risk factors cannot be ruled out [5, 6]. Studies have shown a male predominance; ASD affects 2~3 times more males than females [2, 3, 7]. This diagnostic bias towards males might result from under-recognition of females with ASD [8]. Also, some researchers have suggested the possibility that the female-specific protective effects against ASD might exist [9].

A Swiss psychiatrist, Paul Eugen Bleuler used the term "autism" to define the symptoms of schizophrenia for the first time in 1912 [10]. He derived it from the Greek word αὐτός (autos), which means self. Hans Asperger adopted Bleuler's terminology "autistic" in its modern sense to describe child psychology in 1938. Afterwards, he reported about four boys who did not mix with their peer group and did not understand the meaning of the terms 'respect' and 'polite', and regard for the authority of an adult. The boys also showed specific unnatural stereotypic movement and habits. Asperger describe this pattern of behaviors as "autistic psychopathy", which is now called as Asperger's Syndrome [11]. The person who first used autism in its modern sense is Leo Kanner. In 1943, he reported about 8 boys and 3 girls who had "an innate inability to form the usual, biologically provided affective contact with people", and introduced the label early infantile autism [12]. Hans Asperger and Leo Kanner have been considered as those who designed the basis of the modern study of autism.

Most recently, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) adopted the term ASD with a dyadic definition of core symptoms: early-onset of difficulties in social interaction and communication, and repetitive, restricted behaviors, interests, or activities [13]. Atypical language development, which had been included into the triad of ASD, is now regarded as a co-occurring condition.

As stated earlier, the development of the brain in individuals with ASD is complex and is mediated by many genetic and environmental factors, and their interactions. Genetic studies of ASD have identified mutations that interfere with typical neurodevelopment in utero through childhood. These complexes of genes have been involved in synaptogenesis and axon motility. Also, the resultant microstructural, macrostructural, and functional abnormalities that emerge during brain development create a pattern of dysfunctional neural networks involved in socioemotional processing. Microstructurally, an altered ratio of short- to long-diameter axons and disorganization of cortical layers are observed. Macrostructurally, MRI studies assessing brain volume in individuals with ASD have consistently shown cortical and subcortical gray matter overgrowth in early brain development. Functionally, resting-state fMRI studies show a narrative of widespread global underconnectivity in

socioemotional networks, and task-based fMRI studies show decreased activation of networks involved in socioemotional processing. Moreover, electrophysiological studies demonstrate alterations in both resting-state and stimulus-induced oscillatory activities in patients with ASD [14].

The well-conserved sets of genes and genetic pathways were implicated in ASD, many of which contribute toward the formation, stabilization, and maintenance of functional synapses. Therefore, these genetic aspects coupled with an in-depth phenotypic analysis of the cellular and behavioral characteristics are essential to unraveling the pathogenesis of ASD. The number of genes already discovered in ASD holds the promise to translate the knowledge into designing new therapeutic interventions. Also, the fundamental research using animal models is providing key insights into the various facets of human ASD. However, a better understanding of the genetic, molecular, and circuit level aberrations in ASD is still needed [15].

Neuroimaging studies have provided many important insights into the pathological changes that occur in the brain of patients with ASD in vivo. Importantly, ASD is accompanied by an atypical path of brain maturation, which gives rise to differences in neuroanatomy, functioning, and connectivity. Although considerable progress has been made in the development of animal models and cellular assays, neuroimaging approaches allow us to directly examine the brain in vivo, and to probably facilitate the development of a more personalized approach to the treatment of ASD [16].

ETIOLOGY

ASD is not a single disorder. It is now broadly considered to be a multi-factorial disorder resulting from genetic and non-genetic risk factors and their interaction.

Genetic causes including gene defects and chromosomal anomalies have been found in 10%~20% of individuals with ASD [17, 18]. Siblings born in families with an ASD subject have a 50 times greater risk of ASD, with a recurrence rate of 5%~8% [19]. The concordance rate reaches up to 82%~92% in monozygotic twins, compared with 1%~10% in dizygotic twins. Genetic studies suggested that single gene mutations alter developmental pathways of neuronal and axonal structures involved in synaptogenesis [20-22]. In the cases of related with fragile X syndrome and tuberous sclerosis, hyperexcitability of neocortical circuits caused by alterations in the neocortical excitatory/inhibitory balance and abnormal neural synchronization is thought to be the most probable mechanisms [23, 24]. Genome-wide linkage studies suggested linkages on chromosomes 2q, 7q, 15q, and 16p as the

location of susceptibility genes, although it has not been fully elucidated [25, 26]. These chromosomal abnormalities have been implicated in the disruption of neural connections, brain growth, and synaptic/dendritic morphology [27-29]. Metabolic errors including phenylketonuria, creatine deficiency syndromes, adenylosuccinate lyase deficiency, and metabolic purine disorders are also account for less than 5% of individuals with ASD [30]. Recently, the correlation between cerebellar developmental patterning gene ENGRAILED 2 and autism was reported [31]. It is the first genetic allele that contributes to ASD susceptibility in as many as 40% of ASD cases. Other genes such as UBE3A locus, GABA system genes, and serotonin transporter genes have also been considered as the genetic factors for ASD [18].

Diverse environmental causative elements including pre-natal, peri-natal, and post-natal factors also contribute to ASD [32]. Prenatal factors related with ASD include exposure to teratogens such as thalidomide, certain viral infections (congenital rubella syndrome), and maternal anticonvulsants such as valproic acid

[33, 34]. Low birth weight, abnormally short gestation length, and birth asphyxia are the peri-natal factors [34]. Reported post-natal factors associated with ASD include autoimmune disease, viral infection, hypoxia, mercury toxicity, and others [33, 35, 36]. Table 1 summarizes the known and putative ASD-related genes and environmental factors contributing to the ASD.

In recent years, some researchers suggest that ASD is the result of complex interactions between genetic and environmental risk factors [37]. Understanding the interaction between genetic and environmental factors in the pathogenesis of ASD will lead to optimal treatment strategy.

CLINICAL FEATURES AND DIAGNOSIS

ASD is typically noticed in the first 3 years of life, with deficits in social behaviors and nonverbal interactions such as reduced eye contact, facial expression, and body gestures [1]. Children also manifest with non-specific symptoms such as unusual

Table 1. The known and putative ASD-related genes and environmental factors contributing to the ASD

Genes related with ASD	Location	Gene name
ADNP [124]	20q13.13	Activity-dependent neuroprotector homeobox
ANK2 [125]	4q25-q26	Ankyrin 2, neuronal
ARID1B [126]	6q25.3	AT rich interactive domain 1B (SWI1-like)
ASH1L [127]	1q22	Ash1 (absent, small, or homeotic)-like (Drosophila)
ASXL3 [128]	18q11	Additional sex combs like 3 (Drosophila)
CHD8 [129]	14q11.2	Chromodomain helicase DNA binding protein 8
DYRK1A [130]	21q22.13	Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A
GRIN2B [131]	12p13.1	Glutamate receptor, inotropic, N-methyl D-aspartate 2B
POGZ [132]	1q21.1	Pogo transposable element with ZNF domain
PTEN [133]	10q23	Phosphatase and tensin homolog (mutated in multiple advanced cancers 1)
SCN2A [134]	2q24.3	Sodium channel, voltage-gated, type II, alpha subunit
SETD5 [135]	3p25.3	SET domain containing 5
SHANK3 [136]	22q13.3	SH3 and multiple ankyrin repeat domains 3
SUV420H1 [137]	11q13.2	Suppressor of variegation 4-20 homolog 1 (Drosophila)
SYNGAP1 [138]	6p21.3	Synaptic Ras GTPase activating protein 1
TBR1 [139]	2q24.2	T-box, brain 1
Environmental factors		**Risk factors**
Prenatal viral infection [140-143]		Influenza, rubella, and cytomegalovirus, etc.
Zinc deficiency [144, 145]		
Abnormal melatonin synthesis [146, 147]		
Maternal diabetes [148]		
Prenatal and perinatal stress [149]		Stress hormones, psychological stress, etc.
Toxins [150, 151]		Valproic acid, thlidomide, organophosphate, etc.
Advenced parental age [152]		

sensory perception skills and experiences, motor clumsiness, and insomnia. Associated phenomena include mental retardation, emotional indifference, hyperactivity, aggression, self-injury, and repetitive behaviors such as body rocking or hand flapping. Repetitive, stereotyped behaviors are often accompanied by cognitive impairment, seizures or epilepsy, gastrointestinal complaints, disturbedd sleep, and other problems. Differential diagnosis includes childhood schizophrenia, learning disability, and deafness [38, 39].

ASD is diagnosed clinically based on the presence of core symptoms. However, caution is required when diagnosing ASD because of non-specific manifestations in different age groups and individual abilities in intelligence and verbal domains. The earliest nonspecific signs recognized in infancy or toddlers include irritability, passivity, and difficulties with sleeping and eating, followed by delays in language and social engagement. In the first year of age, infants later diagnosed with ASD cannot be easily distinguished from control infants. However, some authors report that about 50% of infants show behavioral abnormalities including extremes of temperament, poor eye contact, and lack of response to parental voices or interaction. At 12 months of age, individuals with ASD show atypical behaviors, across the domains of visual attention, imitation, social responses, motor control, and reactivity [40]. There is also report about atypical language trajectories, with mild delays at 12 months progressing to more severe delays by 24 months [40]. By 3 years of age, the typical core symptoms such as lack of social communication and restricted/repetitive behaviors and interests are manifested. ASD can be easily differentiated from other psychosocial disorders in late preschool and early school years.

AMYGDALA AND ASD

The frontal and temporal lobes are the markedly affected brain areas in the individuals with ASD. In particular, the role of amygdala in cognition and ASD has been proved in numerous neuropathological and neuroimaging studies. The amygdala located the medial temporal lobe anterior to the hippocampal formation has been thought to have a strong association with social and aggressive behaviors in patients with ASD [41, 42]. The amygdala is a major component of the limbic system and affective loop of the cortico-striato-thalamo-cortical circuit [43].

The amygdala has 2 specific functions including eye gaze and face processing [44]. The lesion of the amygdala results in fear-processing, modulation of memory with emotional content, and eye gaze when looking at human face [45-47]. The findings in individuals with amygdala lesion are similar to the phenomena

in ASD. The amygdala receives highly processed somatosensory, visual, auditory, and all types of visceral inputs. It sends efferents through two major pathways, the stria terminalis and the ventral amygdalofugal pathway.

The amygdala comprises a collection of 13 nuclei. Based on histochemical analyses, these 13 nuclei are divided into three primary subgroups: the basolateral (BL), centromedial (CM), and superficial groups [42]. The BL group attributes amygdala to have a role as a node connecting sensory stimuli to higher social cognition level. It links the CM and superficial groups, and it has reciprocal connection with the orbitofrontal cortex, anterior cingulate cortex (ACC), and the medial prefrontal cortex (mPFC) [48]. The BL group contains neurons responsive to faces and actions of others, which is not found in the other two groups of amygdala [49, 50]. The CM group consists of the central, medial, cortical nuclei, and the periamygdaloid complex. It innervates many of the visceral and autonomic effector regions of the brain stem, and provides a major output to the hypothalamus, thalamus, ventral tegmental area, and reticular formation [51]. The superficial group includes the nucleus of the lateral olfactory tract [42].

Neurochemistrial studies revealed high density of benzodiazepine/GABAa receptors and a substantial set of opiate receptors in the amygdala. It also includes serotonergic, dopaminergic, cholinergic, and noradrenergic cell bodies and pathways [52]. Since some patients with temporal epilepsy and aggressive behavior experienced improvement in aggressiveness after bilateral stereotactic ablation of basal and corticomedial amygdaloid nuclei, the role of amygdala in emotional processing, especially rage processing has been investigated [53-56]. Some evidences for the amygdala deficit in patients with ASD have been suggested. Post-mortem studies found the pathology in the amygdala of individuals with ASD compared to age- and sex- matched controls [57-59]. Small neuronal size and increased cell density in the cortical, medial, and central nuclei of the amygdala were detected in ASD patients.

Several studies proposed the use of an animal model to confirm the evidence for the association between amygdala and ASD [60, 61]. Despite the limitation which stems from the need to prove higher order cognitive disorder, the studies suggested that disease-associated alterations in the temporal lobes during experimental manipulations of the amygdala in animals have produced some symptoms of ASD [62]. Especially, the Kluver-Bucy syndrome, which is caused by bilateral damage to the anterior temporal lobes in monkeys, has characteristic manifestations similar to ASD [63, 64]. Monkeys with the Kluver-Bucy syndrome shows absence of social chattering, lack of facial expression, absence of emotional reactions, repetitive abnormal movement patterns, and increased

aggression. Sajdyk et al. performed experiments on rats and discovered that physiological activation of the BL nucleus of the amygdala by blocking tonic GABAergic inhibition or enhancing glutamate or the stress-associated peptide corticotropin-releasing factor (CRF)-mediated excitation caused reduction in social behaviors [65]. On the contrary, lesioning of the amygdala or blocking amygdala excitability with glutamate antagonist increased dyadic social interactions [60]. Besides animals, humans who underwent lesioning of the amygdala showed impairments in social judgment. This phenomenon is called acquired ASD [66-68]. The pattern of social deficits was similar in idiopathic and acquired ASD [69]. Felix-Ortiz and Tye sought to understand the role of projections from the BL amygdala to the ventral hippocampus in relation to behavior. Their study using mice showed that the BLS-ventral hippocampus pathway involved in anxiety plays a role in the mediation of social behavior as well [70].

The individuals with temporal lobe tumors involving the amygdala and hippocampus provide another evidence of the correlation between the amygdala and ASD. Some authors reported that patients experienced autistic symptoms after temporal lobe was damaged by a tumor [71, 72]. Also, individuals with tuberous sclerosis experienced similar symptoms including facial expression due to a temporal lobe hamartoma [73].

Although other researchers failed to find structural abnormalities in the mesial temporal lobe of autistic subjects by performing magnetic resonance imaging (MRI) studies [74-76], recent development in neuroimaging has facilitated the investigation of amygdala pathology in ASD. Studies using structural MRI estimated volumes of the amygdala and related structures in individuals with ASD and age-, gender, and verbal IQ- matched healthy controls [77]. Increase in bilateral amygdala volume and reduction in hippocampal and parahippocampal gyrus volumes were noted in individuals with ASD. Also, the lateral ventricles and intracranial volumes were significantly increased in the autistic subjects; however, overall temporal lobe volumes were similar between the ASD and control groups.

There was a significant difference in the whole brain voxel-based scans of individuals with ASD and control groups [78]. Individuals with ASD showed decreased gray matter volume in the right paracingulate sulcus, the left occipito-temporal cortex, and the left inferior frontal sulcus. On the contrary, the gray matter volume in the bilateral cerebellum was increased. Otherwise, they showed increased volume in the left amygdala/periamygdaloid cortex, the right inferior temporal gyrus, and the middle temporal gyrus.

Recently, the development of functional neuroimaging also provided some evidence for the correlation between amygdala deficit and ASD. A study using Technetium-99m (Tc-99m) single-photon emission computed tomography (SPECT) found that regional cerebral blood flow (rCBF) was decreased in the bilateral insula, superior temporal gyri, and left prefrontal cortices in individuals with ASD compared to age- and gender- matched controls with mental retardation [79]. Also, the authors found that rCBF in both the right hippocampus and amygdala was correlated with a behavioral rating subscale.

On proton magnetic resonance spectroscopy (MRS) in the right hippocampal-amygdala region and the left cerebellar hemisphere, autistic subjects showed decreased level of N-acetyl aspartate (NAA) in both areas [80]. There was no difference in the level of the other metabolites, such as creatine and choline. This study implies that a decreased level of NAA might be associated with neuronal hypofunction or immature neurons.

These findings support the claim that amygdala might be a key structure in the development of ASD and a target for the management of the disease.

PREFRONTAL CORTEX AND ASD

Frontal lobe has been considered as playing an important role in higher-level control and a key structure associated with autism. Individuals with frontal lobe deficit demonstrate higher-order cognitive, language, social, and emotion dysfunction, which is deficient in autism [81]. Recently, neuroimaging and neuropsychological studies have attempted to delineate distinct regions of prefrontal cortex supporting different aspects of executive function. Some authors have reported that the excessive rates of brain growth in infants with ASD, which is mainly contributed by the increase of frontal cortex volume [82, 83]. Especially, the PFC including Brodmann areas 8, 9, 10, 11, 44, 45, 46, and 47 has been noted for the structure related with ASD [84]. The PFC is cytoarchitectonically defined as the presence of a cortical granular layer IV [85], and anatomically refers to the regions of the cerebral cortex that are anterior to premotor cortex and the supplementary motor area [86]. The PFC has extensive connections with other cortical, subcortical and brain stem sites [87]. It receives inputs from the brainstem arousal systems, and its function is particularly dependent on its neurochemical environment [88].

The PFC is broadly divided into the medial PFC (mPFC) and the lateral PFC (lPFC). The mPFC is further divided into four distinct regions: medial precentral cortex, anterior cingulate cortex, prelimbic and infralimbic prefrontal cortex [89]. While the lPFC is thought to support cognitive control process [90], the mPFC has reciprocal connections with brain regions involved in emotional processing (amygdala), memory (hippocampus) and higher-order

sensory regions (within temporal cortex) [91]. This involvement of mPFC in social cognition and interaction implies that mPFC might be a key region in understanding self and others [92].

The mPFC involves in fear learning and extinction by reciprocal synaptic connections with the basolateral amygdala [93, 94]. It is believed that the mPFC regulates and controls amygdala output and the accompanying behavioral phenomena [95, 96]. Previous authors investigated how memory processing is regulated by interactions between BLA and mPFC by means of functional disconnection [97, 98]. Disturbed communication within amygdala-mPFC circuitry caused deficits in memory processing. These informations provide support for a role of the mPFC in the development of ASD.

NUCLEUS ACCUMBENS AND ASD

Besides amygdala, nucleus accumbens (NAc) is also considered as the key structure which is related with the social reward response in ASD. NAc borders ventrally on the anterior limb of the internal capsule, and the lateral subventricular fundus of the NAc is permeated in rostral sections by internal capsule fiber bundles. The rationale for NAc to be considered as the potential target of DBS for ASD is its predominant role in modulating the processing of reward and pleasure [99]. Anticipation of rewarding stimuli recruits the NAc as well as other limbic structures, and the experience of pleasure activates the NAc as well as the caudate, putamen, amygdala, and VMPFC [100-102]. It is well known that dysfunction of NAc regarding rewarding stimuli in subjects with depression. Bewernick et al. demonstrated antidepressant effects of NAc-DBS in 5 of the 10 patients suffering from severe treatment-resistant depression [103].

Two groups reported about the neural basis of social reward processing in ASD. Schmitz et al. examined responses to a task that involved monetary reward. They investigated the neural substrates of reward feedback in the context of a sustained attention task, and found increased activation in the left anterior cingulate gyrus and left mid-frontal gyrus on rewarded trials in ASD [104]. Scott-Van Zeeland et al. investigated the neural correlates of rewarded implicit learning in children with ASD using both social and monetary rewards. They found diminished ventral striatal response during social, but not monetary, rewarded learning [105]. According to them, activity within the ventral striatum predicted social reciprocity within the control group, but not within the ASD group.

Anticipation of pleasurable stimuli recruits the NAc, whereas the experience of pleasure activates VMPFC [106]. NAc is activated by incentive motivation to reach salient goals [106]. Increased activation in the left anterior cingulate gyrus and left mid-frontal gyrus was noted during both the anticipatory and consummatory phase of the reward response [104, 107, 108]. However, the activity within the ventral striatum was decreased in autistic subjects, which caused impairment in social reciprocity [105].

These findings indicate that reward network function in ASD is contingent on both the temporal phase of the response and the type of reward processed, suggesting that it is critical to assess the temporal chronometry of responses in a study of reward processing in ASD. NAc might be one of the candidates as a target of DBS which is introduced as below.

TREATMENT

Various educational and behavioral treatments have been the mainstay of the management of ASD. Most experts agree that the treatment for ASD should be individualized. Treatment of disabling symptoms such as aggression, agitation, hyperactivity, inattention, irritability, repetitive and self-injurious behavior may allow educational and behavioral interventions to proceed more effectively [109].

Increasing interest is being shown in the role of various pharmacological treatments. Medical management includes typical antipsychotics, atypical antipsychotics, antidepressants, selective serotonin reuptake inhibitors, α2-adrenergic agonists, β-adrenergic antagonist, mood stabilizers, and anticonvulsants [110, 111]. So far, there has been no agent which has been proved effective in social communication [112]. A major factor in the choice of pharmacologic treatment is awareness of specific individual physical, behavioral or psychiatric conditions comorbid with ASD, such as obsessive-compulsive disorder, schizophrenia, mood disorder, and intellectual disability [113]. Antidepressants were the most commonly used agents followed by stimulants and antipsychotics. The high prevalence of comorbidities is reflected in the rates of psychotropic medication use in people with ASD. Antipsychotics were effective in treating the repetitive behaviors in children with ASD; however, there was not sufficient evidence on the efficacy and safety in adolescents and adults [114]. There are also alternative options including opiate antagonist, immunotherapy, hormonal agents, megavitamins and other dietary supplements [109, 113].

However, the autistic symptoms remain refractory to medication therapy in some patients [115]. These individuals have severely progressed disease and multiple comorbidities causing decreased quality of life [44, 110]. Interventional therapy such as deep brain stimulation (DBS) may be an alternative therapeutic option for these patients.

Two kinds of interventions have been used for treating ASD; focused intervention practices and comprehensive treatments [116]. The focused intervention practices include prompting, reinforcement, discrete trial teaching, social stories, or peer-mediated interventions. These are designed to produce specific behavioral or developmental outcomes for individual children with ASD, and used for a limited time period with the intent of demonstrating a change in the targeted behaviors. The comprehensive treatment models are a set of practices performed over an extended period of time and are intense in their application, and usually have multiple components [116].

Since it was approved by the FDA in 1997, DBS has been used to send electrical impulses to specific parts of the brain [117, 118]. In recent years, the spectrum for which therapeutic benefit is provided by DBS has widely been expanded from movement disorders such as Parkinson's disease, essential tremor, and dystonia to psychiatric disorders. Some authors have demonstrated the efficacy of DBS for psychiatric disorders including refractory obsessive-compulsive disorder, depression, Tourette syndrome, and others for the past few years [119-121].

To the best of our knowledge, there have been 2 published articles of 3 patients who underwent DBS for ASD accompanied by life-threatening self-injurious behaviors not alleviated by antipsychotic medication [122, 123]. The targets were anterior limb of the internal capsule and globus pallidus internus, only globus pallidus, and BL nucleus of the amygdala, respectively. All patients obtained some benefit from DBS. Although the first patient showed gradual re-deterioration after temporary improvement, the patient who underwent DBS of the BL nucleus experienced substantial improvement in self-injurious behavior and social communication. These experiences suggested the possibility of DBS for the treatment of ASD. For patients who did not obtain benefit from other treatments, DBS may be a viable therapeutic option. Understanding the structures which contribute to the occurrence of ASD might open a new horizon for management of ASD, particularly DBS. Accompanying development of neuroimaging technique enables more accurate targeting and heightens the efficacy of DBS. However, the optimal DBS target and stimulation parameters are still unknown, and prospective controlled trials of DBS for various possible targets are required to determine optimal target and stimulation parameters for the safety and efficacy of DBS.

CONCLUSION

ASD should be considered as a complex disorder. It has many etiologies involving genetic and environmental factors, and further

evidence for the role of amygdala and NA in the pathophysiology of ASD has been obtained from numerous studies. However, the key architecture of ASD development which could be a target for treatment is still an uncharted territory. Further work is needed to broaden the horizons on the understanding of ASD.

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