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Review

Autistic spectrum disorders: A review of clinical features, theories and diagnosis

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ABSTRACT

Autism spectrum disorder (ASD) is a set of neurodevelopmental disorders that is among the most severe in terms of prevalence, morbidity and impact to the society. It is characterized by complex behavioral phenotype and deficits in both social and cognitive functions. Although the exact cause of ASD is still not known, the main findings emphasize the role of genetic and environmental factors in the development of autistic behavior. Environmental factors are also likely to interact with the genetic profile and cause aberrant changes in brain growth, neuronal development, and functional connectivity. The past few years have seen an increase in the prevalence of ASD, as a result of enhanced clinical tests and diagnostic tools. Despite growing evidence for the involvement of endogenous biomarkers in the pathophysiology of ASD, early detection of this disorder remains a big challenge. This paper describes the main behavioral and cognitive features of ASD, as well as the symptoms that differentiate autism from other developmental disorders. An attempt will be made to integrate all the available evidence which point to reduced brain connectivity, mirror neurons deficits, and inhibition–excitation imbalance in individuals with ASD. Finally, this review discusses the main factors involved in the pathophysiology of ASD, and illustrates some of the most important markers used for the diagnosis of this debilitating disorder.

Contents

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1. Introduction

The autism spectrum disorder (ASD) describes a wide range of symptoms, including difficulty with social interaction and communication skills, as well as unusually repetitive behavior (American Psychiatric Association, 2013). According to the diagnostic and statistical manual of mental disorders, 5th edition (DSM-5), individuals with ASD have a tendency to respond inappropriately in conversation and lack the ability to build relationships (American Psychiatric Association, 2013). They often engage in a series of abnormal routines and develop inappropriate obsessions on particular items (American Psychiatric Association, 2013). Individuals with ASD also display a wide variety of cognitive functioning, ranging from severe intellectual disability to superior intelligence (Grzadzinski et al., 2013). However, the DSM-5 does not consider delays in language acquisition to be part of the core symptoms of ASD because this characteristic is not universal to individuals with this disorder (American Psychiatric Association, 2013; Grzadzinski et al., 2013). Among all the diseases from the autism spectrum, autism is undoubtedly the most severe, and can be distinguished from other neurodevelopmental conditions such as Asperger's syndrome (AS) and pervasive developmental disorder not otherwise specified (PDD–NOS) by the delay in language development and the severity of behavioral and intellectual impairments (Levy et al., 2009; Szpir, 2006).

Approximately 20 per 10,000 children are affected by ASD, and the early symptoms of this disorder can be identified from the age of 1 to 3 years old (Levy et al., 2009; Newschaffer et al., 2007). Although the exact cause of ASD is still not known, it is believed that both genetic and environmental factors influence the onset and development of this disorder (Lai et al., 2014; Tordjman et al., 2014). Interaction between multiple genetic variants and epigenetic factors also increase the risk of having ASD (Tordjman et al., 2014). In terms of financial cost, ASD can be a heavy burden to the family of affected children (Newschaffer et al., 2007). Over the life of a child, expenses can go up to US $2.4 million per family, due to special education services by psychologists and speech therapists, and the added expenses of technology-based therapies (Buescher et al., 2014). Moreover, children with ASD often have comorbid medical conditions, including intellectual disability, seizure, anxiety and depression (Gillott et al., 2001; Newschaffer et al., 2007; Tuchman and Rapin, 2002). Therefore, early detection of this disease is crucial since it could help a child with ASD make significant gains in language and social skills. In this review, a closer look will be given at the clinical features and underlying causes of ASD, as well as the tools commonly used to diagnose this neurodevelopmental disorder.

2. Clinical features and symptoms of ASD

ASD can be distinguished by a pattern of multiple symptoms, and is typically identified before 2 years of age (Mazurek et al., 2014). The symptoms of ASD are classified into two broad categories: the core and the secondary symptoms (American Psychiatric Association, 2013). The core symptoms consist of reduced language skills and social interaction, as well as the presence of repetitive and stereotypic behaviors (American Psychiatric Association, 2013; Weitlauf et al., 2014). In contrast, secondary symptoms include complications such as self-injury, hyperactivity, aggression, and co-occurring psychiatric disorders such as anxiety and major depression (Dosreis et al., 2006; Kaat et al., 2013; Kim et al., 2011). These symptoms often change depending on the age of the affected individual. Indeed, most individuals with ASD have language deficits and problems with hyperactivity during early childhood, but experience problems with relationships and mood regulation during adolescence (Nazeer and Ghaziuddin, 2012). Moreover, during late adolescence and early adulthood, up to 17% of affected individuals develop catatonia, a potentially life-threatening condition characterized by neurogenic motor and behavioral abnormalities (Stoppelbein et al., 2006; Wing and Shah, 2000).

3. Theories of ASD

3.1. Theory of impeded plasticity

It is widely known that the brain of autistic children presents functional and morphological dysfunctions. Studies using functional magnetic resonance imaging (fMRI) have already demonstrated a significant reduction in long-distance connectivity in the brains of ASD individuals (Dichter, 2012; Just et al., 2012). At the microstructural level, disruption of brain development is caused by abnormal regulation of cell division and apoptosis, as well as increased neuronal inflammation (Polsek et al., 2011). Recently, it has been shown that patterns of both hypo- and hyper-connectivity could be observed in the brain of autistic children (Kana et al., 2014; Muller et al., 2011). This difference in hypo- and hyper-connectivity depends on age-related factors (Kana et al., 2014). A study reported that at 3 months old, children who are at high risk for developing autism show increased connectivity compared to low-risk children, and that this difference starts to gradually disappear between the age of 6 and 9 months (Keehn et al., 2013). There is also evidence suggesting that the autistic brain is characterized by morphological abnormalities such as early overgrowth of several brain structures including the frontal cortex, the amygdala and the cerebellum (Polsek et al., 2011). Indeed, 6 months after birth, the head circumference of infants with ASD grows rapidly compared to normal infants, but starts to decrease during late childhood, resulting in normal adult brain volume and size (Courchesne et al., 2003; Herbert et al., 2003).

3.2. Excitation and inhibition dysregulation

Balanced development of excitatory and inhibitory synapses is essential for the normal function of sensory and cognitive networks in the brain (Takahashi et al., 2012). An imbalance in this development may cause the pathogenesis of several neuropsychiatric disorders, including ASD, schizophrenia and bipolar disorder (Takahashi et al., 2012). In the mature central nervous system, amino butyric acid (GABA)-interneurons send inhibitory synaptic inputs, while glutamatergic neurons send excitatory inputs. Mutations and environmental factors that increase glutamate signaling or decrease GABAergic signaling could lead to an imbalance of excitation and inhibition, and could therefore increase the risk to ASD (Rubenstein and Merzenich, 2003). There is a significant amount of studies suggesting that individuals with ASD have higher than normal glutamate blood levels (Aldred et al., 2003; Shimmura et al., 2011). GABA, which plays a key role in regulating neuronal excitability, is also found altered in individuals with ASD (Pizzarelli and Cherubini, 2011; Blatt and Fatemi, 2011). Alterations in the GABAergic level in the brain of autistic individuals may account for several clinical phenotypes including the development of epileptic seizures and intellectual disabilities (Blatt and Fatemi, 2011). Overall, evidence suggests that there is a marked dysregulation of the excitatory glutamate system and inhibitory GABA system in the brain of individuals with ASD. However, it is still not very well known how these synaptic inputs influence neuronal circuitry and social behavior. Clearly more comprehensive behavioral and electrophysiological studies need to be done to help better define

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the role of inhibitory and excitatory transmission in cognitive and social functions.

3.3. Theory of mind

Studies on theory of mind (ToM) have dominated research on individuals with ASD since several decades, and have revealed significant impairments in integrating mental state information (Baron-Cohen et al., 1985, 1994). ToM is the capacity to mentally understand subjective mental states, including thoughts and desires, regardless of whether or not the circumstances involved are real (Peterson, 2014). ToM develops early in children without disabilities, but it is significantly delayed in children with ASD (Moran et al., 2011; Peterson, 2014). Indeed, children with ASD generally fail first-order ToM tests, which require them to understand that others can have beliefs about the world that is diverging and factually incorrect (Moran et al., 2011; Scheeren et al., 2013). Failure to succeed standard ToM tests could explain the impairments in social behavior and communication skills observed in individuals with ASD. In contrast, adults with ASD usually succeed on standard tests for ToM, but still fail to understand other people's beliefs and intentions (Frith et al., 1991; Moran et al., 2011). Several researchers have also proposed a social-affective justification, suggesting that a deficit in ToM in individuals with ASD results from a distortion in recognizing and responding to emotions (Mazza et al., 2014; Pileggi et al., 2015). Studying social skills in children with ASD is therefore crucial for the identification of effective rehabilitation programs that could enhance empathic and emotional capacities (Mazza et al., 2014).

3.4. Mirror neurons and ASD

There is accumulating evidence illustrating the importance of mirror neurons in the neuropathophysiology of ASD (Enticott et al., 2012; Oberman et al., 2005). Mirror neurons are brain cells that become active when an individual performs a given action, but also when that same action is observed (Enticott et al., 2012). They are involved in a myriad of functions including the recognition of motor acts by others and the regulation of social, emotional, and cognitive tasks (Dumas et al., 2014; Gallese et al., 2013). Recent studies suggest that a dysfunction of the mirror neuron system might generate social and cognitive impairments related to ASD (Rizzolatti and Fabbri-Destro, 2010). The mirror neuron system enables individuals to understand the action of others, and facilitates social cognitive functions, such as empathy and emotional states (Gallese, 2007). It is also known that mirror neurons promote the coordination between the motor cortex and higher visual processing areas, and are implicated in speech, memory, and the planning of movements (Williams et al., 2001; Rizzolatti et al., 2009).

Evidence for deficits in the mirror neuron system in children with ASD comes from a range of imaging techniques such as fMRI, electroencephalography (EEG) and electromyography (EMG) (Cattaneo et al., 2007; Dapretto et al., 2006; Oberman et al., 2005). It was shown that the mirror neurons activity is altered in children with ASD, and that this dysfunction prevents them from understanding the action of others (Cattaneo et al., 2007). In this study, the activity of the mylohyoid muscle, which is involved in opening of the mouth, was recorded in children while they were observing an experimenter grasp a piece of food for eating. Results showed increased EMG activity in typically developing children but not in children with ASD supporting the hypothesis that individuals with ASD have a dysfunction in mirror neurons that could lead to cognitive and attention deficits (Cattaneo et al., 2007). Conversely, others studies have shown that the function of the mirror neuron system might be preserved in individuals with ASD (Bernier et al., 2013; Fan et al., 2010). In one study, EEG mu rhythm was recorded in children with ASD and age-matched typically developing peers while they were observing an action being performed by an experimenter (Bernier et al., 2013). Results showed that reduced mirror neurons activity during the observation task was not associated with ASD but rather with differences in imitative ability, suggesting a clear dissociation between ASD and mirror neurons system (Bernier et al., 2013). Such discrepancy between studies might be explained by the fact that different methodological approaches were used, such as the type of actions being observed by the individuals, as well as the diagnostic criteria employed when selecting children with ASD.

4. Causes of ASD

4.1. Environmental factors

There is accumulating evidence supporting a significant contribution of environmental factors to the pathophysiology of ASD (Larsson et al., 2009; Lyall et al., 2014). Environmental exposure may cause profound changes in brain development and influence neurological processes such as cell differentiation, synaptogenesis and axon myelination (Lyall et al., 2014). For instance, it was shown that maternal lifestyle and diet can have beneficial effects on fetal brain development (Lyall et al., 2014). More particularly, a maternal deficiency in essential nutrients and fatty acids is associated with neurodevelopmental consequences that might influence the risk to ASD (Al-Farsi et al., 2013; Black, 2008; Lyall et al., 2014). Moreover, several studies found that tobacco smoking and exposure to alcohol or recreational drugs during pregnancy could cause structural brain anomalies as observed in children with ASD (Eliasen et al., 2010; Jutras-Aswad et al., 2009; Tran et al., 2013). Chronic use of medications such as antidepressant drugs during pregnancy could also perturb fetal brain development, increasing the risk to ASD in exposed children (Croen et al., 2011). Other potential factors that influence the predisposition to ASD include nutritional disorder, exposure to air pollutants, maternal infection during pregnancy, poor socioeconomic status, and low maternal educational level (Grant and Cannell, 2013; Chaste and Leboyer, 2012; Lyall et al., 2014; Randolph-Gips and Srinivasan, 2012). For instance, a recent study showed that low concentration of vitamin D in typically developing children could cause morphological and functional changes to the brain that are often observed in ASD, stressing the role of maintaining an appropriate nutrition for the prevention of developmental disorders (Jia et al., 2015).

Overall, the role of environmental factors in the development of ASD is a crucial area of research and has been extensively studied over the fast few years. Although several studies have demonstrated the association between the environment and ASD, it is important to point out that no single environmental factor is sufficient to significantly influence the predisposition to ASD. It is rather the combination of several environmental factors that are likely to have a significant impact (Gardener et al., 2009). Clearly more work is needed to better understand how environmental factors are involved in the predisposition to such neurodevelopmental disorders. This should provide accurate information about the potential risks of ASD, and could guide parents and physicians in their decisions.

4.2. Genetics

ASD is a highly heritable disorder associated with complex cognitive changes that lead to impairments in social interaction and language development (Klauck, 2006). The genetic architecture of this neurodevelopmental disease has shown to be complex, as demonstrated by whole-exome sequencing (WES), cytogenetics,

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and association studies (Geschwind, 2011; Lai et al., 2004; Murdoch and State, 2013). Moreover, twin and family studies show a clear contribution of genetic factors to ASD, and a heritability of more than 80% (Egger et al., 2014; Ronald and Hoekstra, 2011). The main syndromes associated with ASD are fragile X syndrome (FXS) and tuberous sclerosis (TS) (Persico and Napolioni, 2013). They both share pathophysiological mechanisms that are very similar to those observed in ASD patients, which include abnormal mRNA translation and increased protein synthesis (Curatolo et al., 2010; Persico and Napolioni, 2013). FXS is an X-linked genetic disorder caused by the unstable expansion of a multiple CGG repeat in the FMR1 gene (Muhle et al., 2004; Persico and Napolioni, 2013). It is denoted by unusual facial features, and cognitive impairments of variable severity (Muhle et al., 2004). TS, on the other hand, is an autosomal dominant disease caused by a mutation in either TSC1 or TSC2 gene (Napolioni and Curatolo, 2008; Persico and Napolioni, 2013). Its clinical manifestations include epilepsy, learning difficulties, and behavioral problems (Napolioni and Curatolo, 2008). Given the high rate of epileptic seizures in both TS and ASD patients, it is not surprising that more than 40% of individuals with TS also have ASD (Bolton et al., 2002; Muhle et al., 2004).

The most commonly employed techniques to detect ASD susceptibility genes are the whole-exome sequencing (WES), the chromosomal microarray, and the selective candidate gene analysis (Klauck, 2006; Persico and Napolioni, 2013). WES has been successfully used to identify rare or novel genetic defects in several heterogeneous conditions, including ASD (Rabbani et al., 2014). Using WES on 928 individuals, a recent study showed that that highly disruptive de novo mutations in brain-expressed genes are associated with ASD (Sanders et al., 2012). In another study, it was observed that many of the ASD-associated genes detected using WES were linked with the fragile X protein and involved in synaptic plasticity (Iossifov et al., 2012). On the other hand, chromosomal microarray analysis is a cytogenetic assay used for the detection of chromosomal abnormalities in patients diagnosed with ASD (Zilina et al., 2014). Among these abnormalities, it was found that GABA receptor subunit genes GABRB3, GABRA5 and GABRG3 were closely associated with the pathophysiology of ASD (Kim et al., 2006; Klauck, 2006; Vorstman et al., 2006). A malfunction in any of these genes may have implications for the inhibition of excitatory neural pathways and could lead to abnormal brain development (Klauck, 2006). Finally, the selective candidate gene analysis is a screening tool that is useful in identifying genes involved in ASD (Holt et al., 2010; Klauck, 2006). It is mostly employed to screen for genes that are clinically relevant for human behavior and that belong to a neurodevelopmental pathway in the brain (Klauck, 2006). Studies found that mutations in serotonergic genes and neuroligins, which have implications in depression and synaptogenesis, respectively, increase the risk to ASD (McCauley et al., 2004; Sudhof, 2008). More particularly, the serotonin transporter gene, SLC6A4, has received a lot of attention because of its association with anxiety, attention, and behavioral symptoms related to ASD (Brune et al., 2006; McCauley et al., 2004). Association studies indicate that a genetic variation in the promoter region of SLC6A4 could impact somatosensory functions and lead to more severe social deficits in individuals with ASD (Gadow et al., 2013; Schauder et al., 2015; Wiggins et al., 2014). These findings strongly support the fact that several gene mutations are associated with the development and pathophysiology of cognitive disorders, and provide robust evidence for a role of genetics in ASD.

4.3. Gene-environment interaction

It has been increasingly accepted that most of the diseases result from a complex interaction between an individual's genetic profile and the environment that he is exposed to (Hunter, 2005). Environmental factors can directly act with some susceptibility genes, leading to epigenetic changes in gene expression that could increase the risk to ASD (Lyall et al., 2014; Volk et al., 2014). Epigenetic modifications include DNA methylation and various changes that directly act on histone proteins, such as phosphorylation and acetylation (Tordjman et al., 2014). It is well known that early modifications in DNA methylation could prevent the normal development of functional neuron networks and the differentiation of cells into their normal lineage (Schaevitz and Berger-Sweeney, 2012; Zeisel, 2011). Individuals with ASD often have altered level of DNA methylation in genes that play important roles during processes of brain development such as synaptogenesis (Nardone et al., 2014). Indeed, a study found that ASD is associated with an increase in overall DNA methylation of SHANK3, a gene involved in synapse formation (Zhu et al., 2014). Other evidences for the contribution of epigenetics and gene-environment interaction in the pathogenesis of ASD predisposition comes from animal models. For example, a diet low in choline fed to pregnant mice reduces DNA global methylation and alters the development of the mouse fetal brain (Niculescu et al., 2006). The effect of the interaction of environmental factors with certain gene variants on ASD was also examined in humans (Volk et al., 2014). After analyzing more than 250 cases of ASD patients, it was shown that following exposure to high air pollutants from traffic-related sources, subjects with the genetic variants were at higher risk of ASD compared to subjects with normal genotype (Volk et al., 2014). A variety of other environmental factors have also shown to influence the development of ASD after interaction with the genome, and these include maternal infection during pregnancy, malnutrition, stress, poor maternal care, and exposure to toxins (Mazina et al., 2015; Schaevitz and Berger-Sweeney, 2012; Faulk and Dolinoy, 2011). After analyzing the genome from a pool of 1971 children with ASD, a recent study found interactive effects between prenatal maternal infection and certain genetic variants on ASD symptomatology (Mazina et al., 2015). It was shown that children exposed to maternal infection during pregnancy displayed increased rates of social communicative deficits and repetitive/restricted behaviors compared to other children with ASD (Mazina et al., 2015).

Although there is enough evidence for the contribution of gene-environment interaction to ASD risk, it is worth mentioning that the impact of genetic and environmental factors varies according to cases (Chaste and Leboyer, 2012; Tordjman et al., 2014). Moreover, because ASD is a complex and heterogeneous disease, no single and major environmental factor has been identified so far. Further research should focus on developing appropriate animal models of ASD and examining a combination of several factors through an integrated approach that include genetic and environmental interactions. These studies might help us better understand the discrepancy in results found in standard association analyses, and could provide useful suggestions for better preventive care.

5. Diagnosis of ASD

5.1. Diagnosis tools and criteria

Several rating-scale instruments have been developed for a better evaluation of the behavioral characteristics of children with ASD, the most common ones being the autism diagnostic observation schedule (ADOS) and the autism diagnostic interview-revised (ADI-R) (Akshoomoff et al., 2006; Gotham et al., 2008; Hu and Steinberg, 2009). The ADOS is a standardized diagnostic observation tool that helps evaluate the social and communication deficits associated with ASD-related behaviors (Akshoomoff et al., 2006; Lord et al., 2000). It involves the observation of a subject performing a variety of imaginative activities and socials tasks that normally

Table 1
Markers and techniques used for the diagnosis of ASD.

Markers	Techniques	References
Biochemical		
GABA and glutamate	ELISA, MRS	Blatt and Fatemi (2011)
Serotonin level	HPLC, PET	Nakamura et al. (2010)
Urine tryptophan/nicotinic metabolite	NMR spectroscopy, HPLC	Yap et al. (2010)
Immunological		
Inflammatory cytokines	ELISA	Ross et al. (2013)
Presence of autoantibodies	Immunohistochemistry	Wills et al. (2007)
Functional/morphological	MRI, DTI	Schumann et al. (2010)
Brain size and structure	fMRI, EEG	Oberman et al. (2005)
Brain function		
Head size	Head circumference trajectory	Courchesne et al. (2003)
Brain connectivity	fMRI, EEG	Solomon et al. (2009)
Face asymmetry	Statistical face analysis, DSMs	Hammond (2007)
Behavioral/neuropsychological		
Eye contact	Eye-tracking technology	Mercadante et al. (2006)
Language skills	Age at first word	Ruggeri et al. (2014)
Cognitive functions	IQ, EEG, EMG	Cattaneo et al. (2007)

Abbreviation: High-performance liquid chromatography (HPLC), enzyme-linked immunosorbent assay (ELISA).

elicit spontaneous behavior (Lord et al., 2000). It is commonly used in conjunction with ADI-R, which consists of semi-structured interview conducted with the parents in order to detect abnormalities that are consistent with deficits in language, social, behavioral, and cognitive functions (Akshoomoff et al., 2006; Hu and Steinberg, 2009). Since their implementation, ADOS and ADI-R have gained wide clinical use because of their ability to differentiate children with autism from those with other neurodevelopmental disorders (Reaven et al., 2008). Another tool used by physicians for the screening of ASD-related symptoms is the childhood autism rating scale (CARS) (Chlebowski et al., 2010). CARS is a behavioral rating scale that serves as a useful tool to differentiate ASD from other developmental disorders such as intellectual disability and PDD–NOS (Chlebowski et al., 2010; Geier et al., 2013). It is also used to quantitatively describe the severity of the disorder of the child based on direct behavioral observation and using specific diagnostic criteria (Geier et al., 2013).

Recently, revisions to the DSM-IV criteria for ASD have been proposed in attempts to increase the specificity of reliability of the diagnosis and reduce the incidence of false positives (American Psychiatric Association, 2013; Barton et al., 2013). In the revised DSM-5, which was released in 2013, the specific diagnostic subcategories for AS and PDD–NOS in the DSM-IV have been eliminated in the DSM-5 (American Psychiatric Association, 1994, 2013). Therefore, people who currently have been diagnosed with these diseases will likely require a different evaluation. Moreover, there have been revisions of the specific criteria for a diagnosis of ASD in order to make it more precise and reliable. Such changes have been made due to the growing number of evidence showing that differentiation between PDD–NOS, AS, and other forms of ASD are not properly made (Huerta et al., 2013; Lord et al., 2012). For example, impaired social interaction and reduced communication have been integrated into one category, and restricted and repetitive behaviors were retained as the second category of symptoms needed for diagnosis of ASD (Barton et al., 2013). The criteria for the social-communication category include deficits in social-emotional reciprocity, impaired nonverbal communicative behaviors, and difficulties in developing relationships. In the category of restricted and repetitive behaviors, the criteria are stereotyped motor movements, adherence to routines, highly fixated interests, and altered sensory input. In order to receive a diagnosis for an ASD, the DSM-5 requires that individuals meet all three of the criteria in the category of social-communication impairments, and two of four criteria in the category of restricted and repetitive behaviors (American Psychiatric Association, 2013; Barton et al., 2013). Moreover, the DSM-5 specifies the severity levels of ASD as follow: 'Level 1' when support is required, 'Level 2' when substantial support is required, and 'Level 3' when very substantial support is required (Weitlauf et al., 2014). These changes will undoubtedly have an impact on the individuals currently diagnosed with ASD, especially for those who present symptoms characteristics of AS or PDD–NOS.

5.2. Diagnostic markers of ASD

A growing number of investigators are pushing their way through the discovering and development of new markers better a diagnosis of ASD. A marker is a variable implicated in the symptomatology of the disease of interest across and within individuals. It can be measured directly from a given patient using sensitive and reliable quantitative approaches (Ruggeri et al., 2014; Gabriele et al., 2014). Table 1 gives an overview of the quantitative approaches used for the measurement of ASD markers. Several of molecules that could act as potential markers for the diagnosis of ASD have been identified, and these include neurotransmitters such as GABA, glutamate and serotonin (5-HT). For instance 5-HT blood level, which is the first biomarker to be identified in individuals with ASD, is found elevated in more than 25% of autistic patients (Gabriele et al., 2014). Given that 5-HT plays a crucial role in the regulation of behavioral, autonomic and cognitive functions, it is not surprising that its level is found altered in patients with ASD (Murphy and Lesch, 2008). Other biochemical markers of interest for the diagnosis of ASD are urinary solutes that mostly consist of tryptophan and nicotinic metabolites (Yap et al., 2010).

Hormonal and immunological biomarkers have also proven efficient in the detection of ASD (Ruggeri et al., 2014). Evidence suggests that ASD is characterized by altered level of hormones including dopamine and oxytocin, which are important neuromodulators in the brain (Ruggeri et al., 2014). Using PET scans, it was found that the dopaminergic system is altered in the brain of children with ASD, and more importantly in the orbitofrontal cortex, a region associated with reward and motivation (Nakamura et al., 2010). Moreover, the plasma level of oxytocin, a hormone that plays an important role in the regulation of repetitive behaviors, is significantly altered in individuals with behavioral and neurodevelopmental problems related to ASD (Alabdali et al., 2014; Hammock et al., 2012). The presence of immunological markers, such as inflammatory cytokines and autoantibodies, also correlate with the underlying features of ADS (Ross et al., 2013; Wills et al., 2007). Increased production of proinflammatory cytokines such as transforming growth factor alpha 1 (TGF-α1), tumor necrosis

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factor alpha (TNFα), interleukin 6 (IL-6), and interleukin 10 (IL-10) is frequently observed in autistic subjects and can be measured from both brain tissues and blood samples (Ross et al., 2013; Vargas et al., 2005).

With the advances in neuroimaging tool, it is now well established that reduced brain connectivity is an underlying characteristic of ASD symptoms (Ruggeri et al., 2014; Solomon et al., 2009). In individuals with ASD, reduced fronto-parietal connectivity has been visualized in certain brain areas using fMRI, and is correlated to symptoms of attention deficit hyperactivity disorder (Solomon et al., 2009). Imaging studies can also be used to identify deficits in the activation of specific brain areas during cognitive tasks, such as the inferior and middle frontal gyri, the dorsal anterior cingulate cortex, and the basal ganglia (Dichter, 2012). Other tools used to predict future ASD diagnosis in children are structural magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI), which yield information about brain volume and white-matter structure (Dichter, 2012; Schumann et al., 2010).

Other typical features of individual with ASD are facial abnormalities, such as asymmetry in the face, and a prominent forehead. Because the development of the face and the brain are tightly interconnected, abnormalities in facial morphology usually indicate a dysfunction in brain growth (Ercan et al., 2008; Hammond et al., 2008). Atypical facial asymmetry, especially in the right supraorbital and anterior periorbital regions, can help clinicians discriminate between the faces of ASD and healthy children (Hammond et al., 2008). With the development of morphometric analysis techniques such as 3D dense surface models (DSMs) of face shape, scientists are now able to accurately recognize the facial phenotype of individuals with ASD (Claes et al., 2011; Hammond, 2007). Other deficits that can be used to help diagnose ASD include reduced eye contact, which can be measured by eye tracking technologies (Boraston and Blakemore, 2007; Mercadante et al., 2006), and reduced communication and cognitive abilities, which can be evaluated by the intelligence quotient (IQ) and the presence or absence of language. These neuropsychological and behavioral markers have proven efficient in clinical practice for the diagnosis of ASD, but also for the identification of appropriate treatment plans that could help autistic children make significant gain in social and cognitive skills.

6. Conclusion and future directions

Our understanding of ASD has significantly increased over the past few years due to the overwhelming amount of research done in the field. Nonetheless, future work is needed in many areas, not only to understand the origin and development of ASD, but also to explain the differences observed among affected individuals. ASD is a neurodevelopmental disorder that represents a major public health concern, with pronounced risk for failure to adapt at the social, educational, and psychological level (Brentani et al., 2013). This complex neurodevelopmental disorder, which is influenced by both genetic and environmental factors, seems to result from profound changes in brain function and connectivity. Individuals with ASD lack the ability to understand mental states, intentions, thoughts and feelings, irrespective of the emotional state (Peterson, 2014). Moreover, there is an accumulating amount of evidence suggesting that an imbalance in excitation and inhibition synaptic inputs, as well as a dysfunction in mirror neurons, could account for the loss of cognitive and social functions observed in individuals with ASD.

With the rapid advances in sequencing technologies, several target genes involved in ASD have been identified through high-throughput and cost-effective approaches (Rabbani et al., 2012). Studies have reported a number of visible abnormalities spreading over all chromosomes for individual cases of ASD, supporting the notion that genetics plays a strong role in the predisposition to ASD (Klauck, 2006). Also, epigenetic changes due to gene-environment interaction could lead to alterations in the brain anatomy and connectivity that are consistent with abnormal cognitive and social functions observed in individuals with ASD (Schaevitz and Berger-Sweeney, 2012). Hopefully, continued research will focus on developing new tools for the early detection and diagnosis of children at high risk with ASD. This will allow effective and personalized treatments to be implemented early in the life of a child, and will help change the course of early behavior and brain development (Levy et al., 2009). Future research should also be devoted to the identification of new therapeutics targets and the development of effective treatment strategies for ASD through the study of appropriate animal models that harbor the same abnormalities as observed in individuals with ASD.

Conflict of interest

The author states that the present manuscript presents no conflict of interest. Q7

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