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EDITORIAL

Recent Research Progress in Autism Spectrum Disorder

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On April 2, 2017, the world will celebrate the ninth annual World Autism Awareness Day. In honor of this occasion, Neuroscience Bulletin has put together a Special Issue of reviews and primary research articles focusing on autism spectrum disorder (ASD). ASD is a heterogeneous developmental neurological disorder characterized by deficits in social communication and social interactions, as well as stereotyped, repetitive behavior and/or restricted interests [1]. In addition, affected individuals often have sensory abnormalities and delayed/absent language. The symptoms are present from early childhood, affecting the individual's daily activity and imposing a huge burden on their families and the community at large. While the global burden of ASD is largely unknown, the annual social cost in the United States and the United Kingdom is estimated to be billions of dollars [2, 3].

The term "autism", deriving from the Greek words "*autos*" (self) and "*ismos*" (action), was first used by Leo Kanner in his landmark paper in 1943 [4] to describe children with an "extreme inability to relate to others". In the introductory review "An overview of autism spectrum disorder, heterogeneity and treatment options" [5], Masi *et al*. revisit the history of the diagnosis and characterization of ASD, from Kanner's time to the currently-used Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders [1]. The review progresses to describe the prevalence, etiology, and clinical presentation of ASD, and discusses factors contributing to its heterogeneity, including genetic variability, co-morbidity, and gender. It concludes with evidence for pharmacological and behavioral treatments, highlighting the complexities of conducting clinical trials in ASD populations.

A key factor behind the emerging interest in ASD is its apparently growing prevalence. A recent survey of 8-year old children in the United States estimates ASD occurrence to be as high as 1 in 68 [6]. A review of the global

As we put the final touches on this special issue, we are very excited that the introductory review has already been downloaded (http://link.springer.com/journal/12264) well over 1600 times. We thank Prof. Shumin Duan, Editor in Chief, for the opportunity to organize this issue at such an exciting time for autism research. The issue could not have come together so quickly without concerted efforts from all authors, reviewers and staff members at Neuroscience Bulletin. In particular, we thank Yefei Li for her enthusiastic and professional assistance.

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prevalence of autism and other pervasive developmental disorders puts the median estimate of ASD prevalence at the slightly lower rate of 62/10,000 [7], with variations between studies, but no obvious evidence for differences in prevalence between geographic regions and/or ethnicities. This global report [7], commissioned by the World Health Organization, notes that changes in diagnostic concepts, service availability, and awareness of ASD may affect prevalence estimates, and highlights the scarcity of epidemiological studies from low- and middle-income countries.

To better estimate the prevalence of ASD in China, the National Health and Family Planning Commission of the People's Republic of China recently initiated a national population-based study to measure ASD prevalence in children aged 6–12 years in 8 cities (over 120,000 individuals). A suitable screening tool in the Chinese language is essential for conducting this large-scale epidemiological study. From the array of available scales, the Autism Spectrum Rating Scales (ASRS, 6-18 years) [8], translated into Chinese, was selected because of its demonstrated high reliability and validity [9]. In an original article in this Special Issue by Yi Wang and colleagues, exploratory factor analysis was used to assess the psychometric properties of the Chinese version of ASRS [10]. The results showed that the modified Chinese version (MC-ASRS) has a 3-subscale structure comparable to the original US version, although some items have been shifted between subscales. In a companion article by Zhou *et al*., the Chinese norms of the MC-ASRS, including its three sub-scales and the total score, were determined for both parent and teacher ratings [11]. A third study, from Xiu Xu and colleagues, compares the MC-ASRS with the Social Responsiveness Scale, another widely-used tool for screening children with ASD [12]. The results showed that both scales have high reliability and validity, further underscoring the suitability of the MC-ASRS for ASD screening in China. Together, these works set the foundation for large-scale epidemiological studies of ASD in China.

ASD has a strong male bias in its prevalence, on average affecting four times as many males as females [13]. However, sex differences in behavior, the presentation of autistic symptoms, or co-morbid intellectual disability are relatively unknown. An original article from Xiaobing Zou and colleagues explores this question by analyzing the Autism Diagnostic Interview-Revised and Autism Diagnostic Observation Schedule scores for a large cohort of boys and girls [14]. Their results show that girls score significantly higher in socio-emotional reciprocity and lower in restricted and repetitive behaviors than boys. Clarifying sex differences in the diagnosis and clinical phenotypes of ASD could help provide better clinical guidance for early screening, diagnosis, and intervention.

ASD is a heterogeneous disorder with a complex genetic basis. Early twin and family studies have shown that ASD is highly heritable [15], suggesting a strong genetic predisposition. In addition to inherited mutations, recent advances in genetics and genomics have identified a large number of *de novo* copy-number variations and single-base-pair mutations in ASD patients, increasing the estimated proportion of patients with identifiable genetic mutations to 20%–40% [15–20]. As many ASD genes are known to regulate brain development and/or synapse function, theories of ASD relating to synaptic dysfunction, including excitatory/inhibitory imbalance and dysfunctional feedback regulation have been proposed [15, 21–24]. Since deficits in social behavior are hallmarks of ASD, molecules and circuits underlying social behavior have received special attention [25, 26]. Of note are the evolutionarily highly-conserved neuropeptides oxytocin and vasopressin, which have been implicated in ASD through genetic studies and have established roles in regulating social behavior [26–28]. Furthermore, intranasal oxytocin administration is currently being tested as a potential therapy for ASD in clinical trials, with mixed results [29]. Zhang *et al*. [30] review current knowledge regarding associations between ASD and single-nucleotide variants in the human oxytocin and vasopressin signaling pathways, and propose that polymorphisms in these signaling pathways may be important for sub-grouping patients in clinical trials of oxytocin.

In addition to genetic factors, pre-, neo-, and post-natal environmental risk factors have been implicated in the etiology of ASD. Epidemiological studies have identified various pharmaceutical drugs, toxicants, and metabolic and nutritional factors as increasing the ASD risk, especially during the prenatal period [31, 32]. Immunological risk factors, including maternal infection during pregnancy, immune dysregulation, inflammation, and microbial dysbiosis have been consistently reported across multiple studies [31–33]. The interaction between environmental exposures and an individual's genetic susceptibilities, both complex factors by themselves, add yet another layer of complexity to the heterogeneous phenotype of ASD. To delve into this complex problem at some depth, we focused on one aspect of environmental factors contributing to ASD, that of cytokines and the immune system. The review by Guastella and colleagues focuses on the relationship between the immune system, the brain, and behavior, and summarizes previously-identified immune system abnormalities in ASD, focusing on the role of cytokines. They further discuss the use of cytokines as potential biomarkers to define sub-groups of ASD patients [34].

ASD research has not only progressed at the level of genes and molecules, but also at the level of circuits and neural connectivity. Early findings from several structural magnetic resonance imaging studies have shown that toddlers with ASD, aged on average 2–4 years, have a larger brain volume than typically-developing children, an effect that levels off by 6–8 years [35, 36]. These findings contribute to the notion that the trajectory of brain maturation in ASD is atypical and involves an early period of overgrowth, with each brain region having its distinct trajectory [35, 36]. Further structural neuroimaging studies have revealed ASD to be a disorder with general and regional alterations in brain size, while functional neuroimaging studies have highlighted changes in connectivity between brain regions in ASD patients [35, 37–39]. The review by Li *et al*. summarizes recent progress from neuroimaging studies in young ASD children and discusses the applicability of these results in aiding ASD diagnosis [40]. Since ASD is a developmental neurological disorder, neurological changes detected earlier are more likely to represent the causes rather than the effects of ASD pathogenesis. Furthermore, these results could contribute to future diagnosis and treatment strategies.

One approach to further exploration of the application of neuroimaging to ASD research is to interpret its results in combination with molecular markers. An original article from Ji-Sheng Han and colleagues examines correlations between circulating levels of the neuropeptide vasopressin, changes in structural and functional connectivity, and autistic behavior in young children with ASD. They found a significant reduction in the volume of the hypothalamus, where vasopressin neurons reside, as well as enlargement of the left amygdala and left hippocampus, which receive projections from vasopressin neurons [41]. These and other results presented in this article provide evidence for correlated changes in structural and functional connectivity and vasopressin levels in young children with ASD [41]. Neuroimaging can also be used in combination with genome sequencing to characterize rare disorders. The letter by Wen *et al*. [42] identifies an inherited mutation in *SGSH*, encoding N-sulfoglucosamine sulfohydrolase (MIM: 605270), in two brothers with Childhood Disintegrative Disorder, a rare childhood disorder with autistic phenotypes.

A discussion of advances in ASD research would be incomplete without describing the contribution of animal models. Rodent models of ASD, mostly mimicking the genetic abnormalities identified in patients, including loss-of-function mutations, gene duplications, and mis-sense point mutations, have contributed significantly to our understanding of the synaptic, circuit, and behavioral basis of ASD [15, 16, 22, 43, 44]. A number of mouse models of syndromic ASD display social impairment and repetitive behavior, the core features of ASD, although they vary widely in additional co-morbidities, and in alternations in excitatory and inhibitory synaptic transmission in various neuronal circuits. In investigating synaptic alterations in ASD mouse models, Wang *et al*. [45] examined spine density changes in two relatively well-characterized mouse gene-duplication models of ASD, namely the *MECP2* duplication and human chromosome 15q11-13 duplication models. They found that, in the mouse primary somatosensory cortex, 15q11-13 duplication mostly affects spine formation at 1 month of postnatal development, while *MECP2* duplication interferes with spine pruning at 3 months, without significantly affecting spine formation. To study the function of ASD genes in specific circuits and at specific time points during development, it is important to induce the genetic changes with cell-type and spatial–temporal specificity. The review by Hulbert and Jiang discusses the currently-available tools and assays for investigating ASD in rodent models, comprehensively reviewing the genetic tools available through the Cre/LoxP system for inducing genetic alterations in specific cell types and brain regions with temporal control [46]. The authors also summarize the results of published studies using existing mouse models of ASD in combination with these available genetic tools [46]. An exciting recent development in ASD research is the generation of a non-human primate ASD model through *MECP2* overexpression, mimicking the *MECP2* duplication syndrome in humans [47]. The review by Qiu and Li provides an overview of the existing non-human primate models of brain disorders and describes recent advances in gene-editing technology, advances that will likely accelerate the development of other ASD models in non-human primates [48]. Based on the close evolutionary relationships between non-human primates and humans, as well as similarities in their brain structure, non-human primate models of ASD will likely contribute significantly to understanding the circuit basis of ASD, as well as to testing new treatment strategies.

We live in an exciting time for ASD research, with advances at the genetic, molecular, and circuit levels emerging rapidly, and new diagnostic and treatment tools increasing being tested and becoming available. While by no means comprehensive, this Special Issue on ASD, with its reviews and original articles, is intended to provide a flavor of ongoing research progress. We sincerely hope that our efforts will contribute to generating more excitement in ASD research, and ultimately help children and families affected by ASD in a meaningful and fruitful manner.

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