About the Cover

Children of the Stars; this is what we call Children with autism. Parents try every way to reach and understand their world. Scientists try every way to study and understand the disorder. In this Special Issue on Autism Spectrum Disorder, we present a collection of articles on the developmental mechanism, recent technological advancement, and clinical evaluation (especially in China) of autism spectrum disorder. We are honored that Jingkang Xiao, a talented young painter, has contributed in his unique way by providing this cover image for the special issue.

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Editor's Note

— Yefei Li

We the editorial team would like to express our gratitude to Mr. Jingkang Xiao and his loving mother Ms. Wen Zou, for their generous offer of Jingkang’s drawing to be the cover of this special issue.

Jingkang Xiao, also known as Kangkang, was born in 1998 and diagnosed as having typical autism with intellectual disability. He could only say the word “mama” when four-and-a-half years old. Like an angel from outer space, he is progressing slowly but steadily every day, every year. He speaks, goes to school, and takes public transportation; he has learned to swim, play basketball, run 5 km, go shopping, play video games on a computer, paint, play piano and cucurbit flute, make toast, and cook. All these little activities that are normal in others’ eyes are, to Kangkang’s parents, magnificent achievements and have brought tremendous joy.

At the age of 15, Kangkang played “You and me” on the cucurbit flute at the opening ceremony of the “Sino-Japanese Autistic Children’s Painting Exhibition” in Tokyo, as a representative of young Chinese autistic painters. Kangkang was called “a healing little painter” when his story was reported by CCTV news. Kangkang enjoys painting and is even more enthusiastic about cuisine. He wants to be a great chef, and enjoy delicious food worldwide.

Through sharing the story of the young man here, we hope to raise more attention to the disease itself and more importantly, the patients and their families’ well-being.
Recent Research Progress in Autism Spectrum Disorder


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).

A Volumetric and Functional Connectivity MRI Study of Brain Arginine-Vasopressin Pathways in Autistic Children


Abstract  Dysfunction of brain-derived arginine-vasopressin (AVP) systems may be involved in the etiology of autism spectrum disorder (ASD). Certain regions such as the hypothalamus, amygdala, and hippocampus are known to contain either AVP neurons or terminals and may play an important role in regulating complex social behaviors. The present study was designed to investigate the concomitant changes in autistic behaviors, circulating AVP levels, and the structure and functional connectivity (FC) of specific brain regions in autistic children compared with typically developing children (TDC) aged from 3 to 5 years. The results showed: (1) children with ASD had a significantly increased volume in the left amygdala and left hippocampus, and a significantly decreased volume in the bilateral hypothalamus compared to TDC, and these were positively correlated with plasma AVP level. (2) Autistic children had a negative FC between the left amygdala
and the bilateral supramarginal gyri compared to TDC. The degree of the negative FC between amygdala and supramarginal gyrus was associated with a higher score on the clinical autism behavior checklist. (3) The degree of negative FC between left amygdala and left supramarginal gyrus was associated with a lowering of the circulating AVP concentration in boys with ASD. (4) Autistic children showed a higher FC between left hippocampus and right subcortical area compared to TDC. (5) The circulating AVP was negatively correlated with the visual and listening response score of the childhood autism rating scale. These results strongly suggest that changes in structure and FC in brain regions containing AVP may be involved in the etiology of autism.

Distinct Defects in Spine Formation or Pruning in Two Gene Duplication Mouse Models of Autism


Abstract Autism spectrum disorder (ASD) encompasses a complex set of developmental neurological disorders, characterized by deficits in social communication and excessive repetitive behaviors. In recent years, ASD is increasingly being considered as a disease of the synapse. One main type of genetic aberration leading to ASD is gene duplication, and several mouse models have been generated mimicking these mutations. Here, we studied the effects of MECP2 duplication and human chromosome 15q11-13 duplication on synaptic development and neural circuit wiring in the mouse sensory cortices. We showed that mice carrying MECP2 duplication had specific defects in spine pruning, while the 15q11-13 duplication mouse model had impaired spine formation. Our results demonstrate that spine pathology varies significantly between autism models and that distinct aspects of neural circuit development may be targeted in different ASD mutations. Our results further underscore the importance of gene dosage in normal development and function of the brain.
Sex Differences in Diagnosis and Clinical Phenotypes of Chinese Children with Autism Spectrum Disorder


Abstract  The aim of this study was to explore the differences between boys and girls in the diagnosis and clinical phenotypes of autism spectrum disorder (ASD) in China's mainland. Children diagnosed with ASD (n = 1064, 228 females) were retrospectively included in the analysis. All children were assessed using the Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Observation Schedule (ADOS). The results showed that girls scored significantly higher in ADI-R socio-emotional reciprocity than boys, and also scored lower in ADI-R and ADOS restricted and repetitive behaviors (RRBs). Meanwhile, the proportions of girls who satisfied the diagnostic cut-off scores in the ADI-R RRBs domain were lower than in boys (P < 0.05). Our results indicated that girls with ASD show greater socio-emotional reciprocity than boys. Girls also tended to show fewer RRBs than boys, and the type of RRBs in girls differ from those in boys. The ADI-R was found to be less sensitive in girls, particularly for assessment in the RRBs domain.

Modifying the Autism Spectrum Rating Scale (6–18 years) to a Chinese Context: An Exploratory Factor Analysis


Abstract  The purpose of this study was to explore the psychometric properties of the Chinese version of the autism spectrum rating scale (ASRS). We recruited 1,625 community-based children and 211 autism
spectrum disorder (ASD) cases from 4 sites, and the parents of all participants completed the Chinese version of the ASRS. A robust weighted least squares means and variance adjusted estimator was used for exploratory factor analysis. The 3-factor structure included 59 items suitable for the current sample. The item reliability for the modified Chinese version of the ASRS (MC-ASRS) was excellent. Moreover, with 60 as the cut-off point, receiver operating characteristic analysis showed that the MC-ASRS had excellent discriminate validity, comparable to that of the unmodified Chinese version (UC-ASRS), with area under the curve values of 0.952 (95% CI: 0.936–0.967) and 0.948 (95% CI: 0.930–0.965), respectively. Meanwhile, the confirm factor analysis revealed that MC-ASRS had a better construct validity than UC-ASRS based on the above factor solution in another children sample. In conclusion, the MC-ASRS shows better efficacy in epidemiological screening for ASD in Chinese children.

Chinese Norms for the Autism Spectrum Rating Scale


Abstract  This study aimed to establish norms for the modified Chinese version of the Autism Spectrum Rating Scale (ASRS). Participants were recruited from Shanghai, Harbin, Guangzhou, and Changsha, China, and their parents and teachers were invited to complete the Chinese Parent version and the Teacher version of the ASRS. In both versions, boys had significantly higher sub-scale scores and total score (T-score) by 1–3 and 4–5 points respectively, than girls (both P < 0.001). Age had weak correlations with some sub-scores and the T-score (r ranged from –0.1859 to 0.0738), and some reached significance (P < 0.03). The correlations appeared stronger and were more common in females. The T-score based on Chinese norms ideally correlated with the score based on the United States norms in boys and girls for both versions. Norms for the Chinese version of the ASRS for children aged 6–12 years are proposed and may be helpful for screening individuals with autism spectrum disorders from the general population of children.
Assessing the Accuracy of the Modified Chinese Autism Spectrum Rating Scale and Social Responsiveness Scale for Screening Autism Spectrum Disorder in Chinese Children


Abstract The reported prevalence of autism spectrum disorder (ASD) has been increasing rapidly in many parts of the world. However, data on its prevalence in China are largely missing. Here, we assessed the suitability of the modified Chinese version of a newly-developed ASD screening tool, the Modified Chinese Autism Spectrum Rating Scales (MC-ASRS) in screening for ASD in Chinese children aged 6–12 years, through comparison with the Social Responsiveness Scale (SRS) that has been widely used for ASD screening. We recruited the parents/caregivers of 1588 typically-developing children and 190 children with ASD aged 6–12 years to complete the MC-ASRS and SRS, and evaluated the validity of both scales in discriminating children with ASD from those developing typically. The results showed that MC-ASRS performed as well as SRS in sensitivity, specificity, and area-under-the-curve (both >0.95) in receiver operating characteristic analysis, with a fair false-negative rate. These results suggest that MC-ASRS is a promising tool for screening for children with ASD in the general Chinese population.

Reviews

An Overview of Autism Spectrum Disorder, Heterogeneity and Treatment Options

Abstract  Since the documented observations of Kanner in 1943, there has been great debate about the diagnoses, the sub-types, and the diagnostic threshold that relates to what is now known as autism spectrum disorder (ASD). Reflecting this complicated history, there has been continual refinement from DSM-III with ‘Infantile Autism’ to the current DSM-V diagnosis. The disorder is now widely accepted as a complex, pervasive, heterogeneous condition with multiple etiologies, sub-types, and developmental trajectories. Diagnosis remains based on observation of atypical behaviors, with criteria of persistent deficits in social communication and restricted and repetitive patterns of behavior. This review provides a broad overview of the history, prevalence, etiology, clinical presentation, and heterogeneity of ASD. Factors contributing to heterogeneity, including genetic variability, comorbidity, and gender are reviewed. We then explore current evidence-based pharmacological and behavioral treatments for ASD and highlight the complexities of conducting clinical trials that evaluate therapeutic efficacy in ASD populations. Finally, we discuss the potential of a new wave of research examining objective biomarkers to facilitate the evaluation of sub-typing, diagnosis, and treatment response in ASD.

The Immune System, Cytokines, and Biomarkers in Autism Spectrum Disorder


Abstract  Autism Spectrum Disorder (ASD) is a pervasive neurodevelopmental condition characterized by variable impairments in communication and social interaction as well as restricted interests and repetitive behaviors. Heterogeneity of presentation is a hallmark. Investigations of immune system problems in ASD, including aberrations in cytokine profiles and signaling, have been increasing in recent times and are the subject of ongoing interest. With the aim of establishing whether cytokines have utility as potential biomarkers that may define a subgroup of ASD, or function as an objective measure of response to treatment, this review summarizes the role of the immune system, discusses the relationship between the immune system, the brain, and behavior, and presents previously-identified immune system abnormalities in ASD, specifically addressing the role of cytokines in these aberrations. The roles and identification of biomarkers are also addressed, particularly with respect to cytokine profiles in ASD.
Cellular and Circuitry Bases of Autism: Lessons Learned from the Temporospatial Manipulation of Autism Genes in the Brain


Abstract  Transgenic mice carrying mutations that cause Autism Spectrum Disorders (ASDs) continue to be valuable for determining the molecular underpinnings of the disorders. Recently, researchers have taken advantage of such models combined with Cre-loxP and similar systems to manipulate gene expression over space and time. Thus, a clearer picture is starting to emerge of the cell types, circuits, brain regions, and developmental time periods underlying ASDs. ASD-causing mutations have been restricted to or rescued specifically in excitatory or inhibitory neurons, different neurotransmitter systems, and cells specific to the forebrain or cerebellum. In addition, mutations have been induced or corrected in adult mice, providing some evidence for the plasticity and reversibility of core ASD symptoms. The limited availability of Cre lines that are highly specific to certain cell types or time periods provides a challenge to determining the cellular and circuitry bases of autism, but other technological advances may eventually overcome this obstacle.

Candidate Biomarkers in Children with Autism Spectrum Disorder: A Review of MRI Studies


Abstract  Searching for effective biomarkers is one of the most challenging tasks in the research field of Autism Spectrum Disorder (ASD). Magnetic resonance imaging (MRI) provides a non-invasive and powerful tool for investigating changes in the structure, function, maturation, connectivity, and metabolism of the brain of children with ASD. Here, we review the more recent MRI studies in young children with ASD, aiming to provide candidate biomarkers for the diagnosis
of childhood ASD. The review covers structural imaging methods, diffusion tensor imaging, resting-state functional MRI, and magnetic resonance spectroscopy. Future advances in neuroimaging techniques, as well as cross-disciplinary studies and large-scale collaborations will be needed for an integrated approach linking neuroimaging, genetics, and phenotypic data to allow the discovery of new, effective biomarkers.

Genes Related to Oxytocin and Arginine-Vasopressin Pathways: Associations with Autism Spectrum Disorders


Abstract  Autism spectrum disorder (ASD) is a highly heritable neurodevelopmental disorders characterized by impaired social interactions, communication deficits, and repetitive behavior. Although the mechanisms underlying its etiology and manifestations are poorly understood, several lines of evidence from rodent and human studies suggest involvement of the evolutionarily highly-conserved oxytocin (OXT) and arginine-vasopressin (AVP), as these neuropeptides modulate various aspects of mammalian social behavior. As far as we know, there is no comprehensive review of the roles of the OXT and AVP systems in the development of ASD from the genetic aspect. In this review, we summarize the current knowledge regarding associations between ASD and single-nucleotide variants of the human OXT-AVP pathway genes OXT, AVP, AVP receptor 1a (AVPR1a), OXT receptor (OXTR), the oxytocinase/vasopressinase (LNPEP), and ADP-ribosyl cyclase (CD38).

Non-human Primate Models for Brain Disorders – Towards Genetic Manipulations via Innovative Technology

Abstract  Modeling brain disorders has always been one of the key tasks in neurobiological studies. A wide range of organisms including worms, fruit flies, zebrafish, and rodents have been used for modeling brain disorders. However, whether complicated neurological and psychiatric symptoms can be faithfully mimicked in animals is still debatable. In this review, we discuss key findings using non-human primates to address the neural mechanisms underlying stress and anxiety behaviors, as well as technical advances for establishing genetically-engineered non-human primate models of autism spectrum disorders and other disorders. Considering the close evolutionary connections and similarity of brain structures between non-human primates and humans, together with the rapid progress in genome-editing technology, non-human primates will be indispensable for pathophysiological studies and exploring potential therapeutic methods for treating brain disorders.

Identification of the Genetic Cause for Childhood Disintegrative Disorder by Whole-Exome Sequencing


All the original articles and reviews in this issue are open access.
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