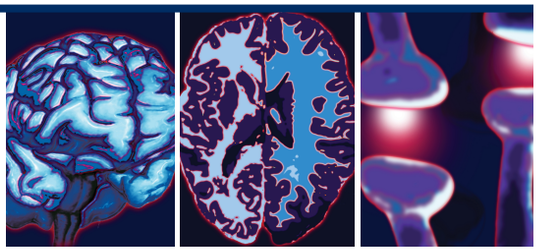
FOREWORD



Recent progress in autism spectrum disorder

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"One day soon, we will be able to characterize the subtypes of autism spectrum disorder based upon the identifiable pathophysiologies that have begun to emerge."

It has been a tremendous opportunity and experience to act as Guest Editor for this special issue of *Neuropsychiatry* with its focus on current topics in autism spectrum disorder (ASD). In collaboration with the editorial staff of Future Medicine, I had the privilege of inviting the world's experts in ASD to write articles on their area of interest. I hope you agree that they have provided us with an outstanding update on many of the important topics in the field of ASD.

Georgiades and colleagues begin with an editorial addressing heterogeneity in ASD [1]. 'Heterogeneity' has become an often-used word for all of those involved with ASD, from special educators to policy makers. This editorial proposes we approach heterogeneity in ASD in a different manner than we have. Rather than compare autism cases to typically developing individuals in research studies, the authors suggest using phenotypic and genotypic variability to 'capture' individual and subgroup differences 'within' ASD. In other words, they view heterogeneity as an opportunity, rather than a barrier, to expand the knowledge base in ASD. Heterogeneity also finds itself at the center of the editorial by Mandy [2]. His comments address the pros and cons of the diagnostic criteria for ASD that appear in the recently published DSM-5. Sensitivity and specificity of the new criteria are addressed, as they have been in a number of previously published studies and commentaries. The fact that Mandy addressed the 'utility' of one of the DSM-IV diagnostic subtypes, Asperger's disorder, from the individual patient's perspective, is enlightening. Until our field discovers the fundamental biological causes of a number of ASD subgroups, we will likely continue to construct diagnostic criteria for ASD based on clinical phenomenology, alternating our approach somewhere between that of 'lumpers' and 'splitters'. One day soon, we will be able to characterize the subtypes of ASD based upon the identifiable pathophysiologies that have begun to emerge.

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Also included in the issue is an interview with Geraldine Dawson [3]. Dawson has been a leader in the field of ASD for nearly 30 years. She has made seminal scientific discoveries and contributions, particularly in regard to early diagnosis and early behavioral treatment interventions. She is currently the Chief Science Office for Autism Speaks. I am certain you will enjoy reading her answers to a number of questions about her career development, accomplishments and future plans.

In their primary research paper, Ung and colleagues describe the clinical characteristics of 108 youth (aged 7–15 years) with high-functioning ASD (full-scale IQ of at least 70) who presented for one of four clinical trials of cognitive behavioral therapy for anxiety at the University of South Florida (FL, USA) or University of California, Los Angeles (CA, USA) [4]. As would be expected, the majority of subjects (91.6%) met criteria for two or more anxiety disorder diagnoses. While many of us would agree that 'anxiety' is common and often interfering in ASD, we do not yet know how to define or treat it. The investigators have attempted to differentiate social phobia from the core social impairment, and obsessive–compulsive disorder from the repetitive stereotypical behavior of ASD. This remains a challenge. As the authors point out, many standard treatments for anxiety disorders, particularly drug treatment with selective serotonin reuptake inhibitors, have not been as efficacious or well tolerated in youth with ASD as they have been for those with primary anxiety disorders. By nature, we like to categorize and simplify things. It is important to remember, however, that not all hyperactivity is ADHD and not all things repetitive represent obsessive–compulsive disorder. As the field moves forward to better understand 'anxiety' in ASD, it will be important to keep its complexity in mind. Ung and colleagues have taken us a step toward that goal [4].

In the next article in this issue, Bauman and Schumann put forth a special report that integrates the 'basic' and 'clinical' science of ASD [5]. This 'translational' approach to research is designed to bring important scientific discoveries from the laboratory 'bench' to application at the patient's 'bedside'. They suggest that a traditional linear translation of basic science to clinical application is unrealistic, considering the complexity and heterogeneity of ASD. Instead, they describe the need for 'team science' and 'cross-disciplinary collaboration'. Multiple basic science approaches, including neuroimaging, post-mortem studies, tissue genetics, neuroimmunology and animal models, geared toward novel pharmaceutical compound development, will be necessary. In other words, 'all hands on deck'. To unravel the heterogeneity of ASD, subjects will need to be assessed from multiple perspectives, utilizing a number of research modalities. The authors and their colleagues at the Medical Investigation of Neurodevelopmental Disorders (MIND) Institute at the University of California-Davis (CA, USA) have been demonstrating the success of this approach for a number of years.

Bearss *et al.* summarize recent work on parent training by the Research Units on Pediatric Psychopharmacology Autism Network [6]. The group has expanded their focus beyond drug treatment to investigate behavior therapy alone and in combination with drugs. The present article pools results from three Research Units on Pediatric Psychopharmacology Autism Network studies that have a parent training component. It describes the process used to develop the parent training manual, along with cross-site training of therapists, establishing and maintaining the treatment integrity throughout the trial, an assessment of how the families accepted the treatment, and the outcome of the three trials. The group concludes with a description of the trial they are engaged in currently, which is a comparison of parent training versus parent education in 180 children with ASD (aged 3–6 years) with at least moderate disruptive behavior.

The next article addresses the current state of education, vocational training and employment, social supports, housing and healthcare for adults with ASD, particularly those transitioning to adulthood [7]. Adults with ASD have long been, and continue to be, a neglected group of individuals. If the term 'autism' is mentioned to a room of 100 people, 98 of them will probably have a mental image of a child with autism. Adults with ASD live as long as the rest of us. There is no cure and they do not outgrow the disorder. The majority of individuals continue to have prominent symptoms of ASD throughout their lives. To date, adults with ASD have been hidden in society. Soon, we will need to be prepared to care and provide for the large number of teenagers with ASD completing high

school at the age of 22 years. Their lives are only beginning. Society is not prepared to provide them with the essentials of life they will need. Friedman and colleagues begin to identify some of the challenges to be faced and propose next steps toward solutions [7].

A number of review papers focusing on 'translational' neuroscience in ASD are included in this issue. The first, co-authored by Mehta and Nurmi, is one of the clearest and most cogent presentations on the genetics of ASD you will find [8]. The authors provide detailed but easily understood information pertaining to the 10–20% of cases of ASD where a specific genetic etiology can be identified. They discuss the monogenic 'syndromic' forms of ASD and include a table listing syndromes with an ASD-related phenotype. While emphasizing the importance of genetics in the etiology of ASD, they acknowledge the increasing evidence for environmental contributions. A table summarizing six different biochemical pathways, among which specific genes tend to cluster, suggests that the heterogeneity of ASD may begin to clear as the field considers neural systems and circuits, rather than individual neurotransmitters and genes.

We are fortunate to be able to include a review paper on neuroimaging findings in ASD from birth to preschool by Wolff and Piven [9]. Piven has been at the forefront of neuroimaging in the ASD field for nearly 25 years. His work followed from his observations, and those of his colleagues, that children and adults with ASD often have larger heads than neurotypical controls. Wolff and Piven state that the majority of neuroimaging studies in this age group have identified increased cortical gray and white matter volumes along with increased amygdala volumes. They wonder if this increase is due to atypical synaptogenesis, a lack of neuronal pruning or possibly the hyperproliferation of progenitor cells. They also discuss the possibility of reduced functional connectivity in the brains of youngsters with ASD, as measured with diffusion tensor MRI. These findings suggest that excess axonal fibers may result from less responsive developmental elimination. They make the case that interrupted experience-dependent refinement early in life may be the culprit for this brain overgrowth. Infants and toddlers with hearing impairments that have decreased auditory feedback similarly show increased gray matter density as a result of less pruning. The authors propose that a continued focus on neuroimaging in infants and toddlers with ASD may help to identify targets for early or preventive intervention.

The next paper by Mody *et al.* reviews a highly specialized area of neuroimaging, focused on the speech and language network in ASD [10]. The core diagnostic features of ASD have long been characterized by the triad of social and communication impairment along with repetitive, ritualized behavior. Today's training curriculum for most physicians and psychologists includes detailed study of the biology and phenomenology of social and repetitive behavior. Speech and language, however, often receives less attention. This is unfortunate as between 30 and 50% of individuals with ASD remain minimally verbal to nonverbal throughout their life. As emphasized in the review by Wolff and Piven, the lack of sensory input at critical stages of brain development can result in perturbations in neural structure and function, including the critical connections between language areas as this paper describes [9]. A number of the challenges of conducting neuroimaging studies in individuals with ASD that have limited language ability are described by Mody and colleagues [10].

The next article addresses the clinical phenomenology of ASD from the perspective of comorbidity of psychiatric disorders. Considering that mood and anxiety disorders are more common in ASD than the general population, it is striking that there are no published systematic drug treatment studies of mood and anxiety disorders in persons with ASD. Matson and Williams do an excellent job of conveying that comorbid mood and anxiety disorders are more common in persons with ASD than in neurotypical individuals. Many clinicians have the sense that some of their patients may have mood and/or anxiety disorders. As many patients with ASD have limited communicative ability, however, it may be difficult for them to tell us how they feel. Matson and Williams provide a thorough review of available diagnostic instruments for comorbid psychiatric disorders in persons with ASD to assist clinicians in this effort [11].

The final article reviews current knowledge on the use of pharmacological agents to treat behavioral symptoms associated with ASD [12]. These associated symptom clusters include irritability (e.g., aggression, self-injury and severe tantrums), interfering repetitive behavior and

ADHD symptoms. The authors conclude that the atypical antipsychotic agents, such as risperidone and aripiprazole, are the most effective drugs for irritability, but that they can be associated with serious side effects; selective serotonin reuptake inhibitors, the only class of drug that has been shown to be efficacious for obsessive–compulsive disorder, are of some benefit for repetitive behavior in adults with ASD, but less so for children; and that the field is still working to identify a class of medication that is well tolerated with robust effects for ADHD symptoms. Methylphenidate works for approximately 50% of children, but this rate of response is much lower than that seen in children with ADHD; in additon, the drug is more poorly tolerated in those with ASD. The authors conclude with a discussion about agents currently under study, including those with prominent effects on glutamate neurotransmission, the neurohormone oxytocin and immune-modulating approaches. Consistently effective pharmacological treatments for the core symptoms of ASD have yet to be identified.

We hope that you enjoy reading the updates on ASD our expert investigators have provided for this special issue of *Neuropsychiatry*. Their enthusiasm for and commitment to working hard toward identifying causes and improved treatments for individuals with these disorders will undoubtedly necessitate another special issue of the journal focused on ASD in the near future.

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