Autism at the crossroads: determining the phenotype matters for neuroscience

Understanding Autism: from Basic Neuroscience to Treatment

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An ambitious and comprehensive volume, *Understanding Autism: from Basic Neuroscience to Treatment* summarizes the state of the art in the neuroscience of autism. It strikes a tone of promise and potential but also caution, highlighting the many things we do not yet know about autism.

Autism is more common than was previously recognized. Up to 1% of the population has 'autism spectrum disorders,' a range of neurodevelopmental conditions that are likely to differ in their underlying etiology but share a common phenotype, characterized by impairment in social relatedness and reciprocity. A neuroscientific understanding of autism is important in light of increasing evidence that multiple etiologies may converge to disrupt brain systems critical for social behavior.

The first chapter of the book strikes a cautionary note. Lord and Spence point out that, "because of the lack of a clear neurobiological marker, autism spectrum disorders are necessarily defined by behavior, which is both intriguing and frustrating for researchers." The caveat is necessary because the categorical diagnoses—as set out in psychiatric classification systems—may not represent 'true categories' in nature.

This problem has led researchers to look for more homogenous subtypes of autism. Geneticists have shifted from attempting to identify susceptibility genes for autism *per se* to studying 'endophenotypes'—elementary single aspects of the autism phenotype, such as language development, social cognition or severity of repetitive behaviors. One chapter highlights promising initial findings from such studies, but a major challenge is that we do not know which subtypes are biologically meaningful. Several chapters provide some clues by comparing autism with neurodevelopmental disorders, such as chromosome 15q11-13 disorders, fragile X syndrome and Rett syndrome, with phenotypes that overlap aspects of autism.

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The book does justice to a major advance of the past decade: the recognition that autism is a multi-system disorder. Individual chapters review brain systems and structures that show abnormal development in autism: amygdala and 'the social brain,' cerebellum, prefrontal cortex and thalamus. Each chapter contains detailed, scholarly summaries of the relevant research. The focus on one brain system at a time, however, can lead the reader to lose sight of the clinical phenotype.

Two exemplary chapters summarize evidence for whole-brain abnormalities in the structural and functional connectivity of different brain systems. Although such models are necessarily complex, they may explain both how overdevelopment of local connections leads to enhanced perception of detail in autism and how undergrowth of distant connections leads to underdevelopment of higher cognitive abilities. Other chapters summarize early work on modeling features of autism in animals.

The study of homogeneous subtypes is less common in neuroscience than in genetics. As in other complex neuropsychiatric disorders, the traditional approach in neuroscience is to compare brain structure and function in categorically defined individuals with autism and unaffected controls. However, these studies have not led to a consensus on what defines or causes autism. This is not surprising, as both the etiology and the outcome (in terms of brain and behavior) are likely to be heterogeneous among people who meet clinical diagnostic criteria for autism. Variation among studies seems inevitable in this situation.

If there is one issue that receives less attention than it warrants throughout the volume, it is that autism is far more common in males than females. Several researchers have attempted to explain this sex ratio, most notably Simon Baron-Cohen and David Skuse, although their proposed explanations (respectively, differences in fetal testosterone and an X-linked gene for social cognition) are very different from each other. This topic seems important enough that it should have received more emphasis than it does.

However, the phenotypic challenge presented by autism might go even further. There is increasing evidence that the elements of the autism phenotype might be dimensionally distributed in the population, with no clear boundary between normal population variation and 'disordered' levels of these behaviors. Thus, genetics and neuroscience studies will have to encompass a population as well as a clinical disorder-based approach. Several chapters include such studies, which have found promising associations between the severity of autism features and behavioral, neuropsychological or biological measures.

The volume also includes chapters on epidemiology, pharmacological and psychosocial approaches to intervention and an analysis of the considerable costs to society of autism. However, the main focus of the book is on the biology of autism. A mature neuroscience of autism will need to investigate links back from the brain to heterogeneous genetic and epigenetic etiologies, and also forward from the brain to the impairments in cognition, behavior and development that characterize the complex range of conditions and presentations that we currently can still only describe as 'the autism phenotype.' This book provides a useful summary of where the science of understanding the autistic brain has arrived and provides glimpses of the advances we can anticipate in the next decade.