1

INTRODUCTION

CECIL R. REYNOLDS
SAM GOLDSTEIN

Over the past 25 years, the study of brain–behavior relationships, or neuropsychology, has made increasing inroads into the fields of both clinical psychology and school psychology. Memberships in professional organizations devoted to neuropsychology have increased exponentially, and new organizations have appeared (e.g., the Coalition of Clinical Practitioners in Neuropsychology, or CCPN). Mental health and educational models have increasingly turned to neuropsychology to explain function and dysfunction in human learning, emotion, and behavior. Clinical neuropsychologists—those who apply knowledge in this field to diagnosis and treatment—also have increased in numbers significantly over the last 20 years. Moreover, clinical neuropsychology has taken an increasing role in forensic settings: It is not uncommon to find clinical neuropsychologists involved in competency hearings, criminal trials, and civil litigation. Though it is a new clinical discipline, neuropsychology is approaching maturity quickly. Neuropsychologists have striven to place science squarely at the center of our field.

In our introduction to the child companion to the present volume, we (Goldstein & Reynolds, 1999) reported a MEDLINE search of articles published over the period from January 1993 through November 1998, containing 6,500 peer-reviewed research studies involving chromosomal and genetic disorders in children. An additional 4,000 studies published during that same period of time were identified as specifically dealing with the neuropsychological evaluation and the treatment of children. Yet only 42 studies were found in this data base dealing with both issues. A review of these 42 studies reflected the increasing importance of a simultaneous view and understanding of these two issues for neuropsychologists, physicians, and other medical and mental health professionals. These 42 studies focused upon genetic conditions such as fragile X, Down, and Marfan syndromes, as well as conditions of unknown etiology that were suspected to have a genetic foundation.

In preparing this volume, we completed a series of new searches with a focus upon studies involving the interface of neuropsychology and, in this case, genetic disorders in both children and adults. We began with a current MEDLINE search examining the entire data base through 2004. This time we found 110 studies containing citations for neuropsychological testing and genetic disorders in children and adults. When we searched for genetic disorders and neuropsychological impairments, we found 91 studies, many of which

overlapped with those found in the initial search. When we further searched for chromosomal disorders and neuropsychological impairments, our search yielded 26 studies. However, many of these had already been located in the previous searches. Though our searches may have been limited by keywords and the data base, the lack of new research was surprising. Thus, despite the mapping of the human genome and the dramatic growth in neuropsychology from the perspective of the peer-reviewed, published literature, scientific research has not kept pace with clinical practice and interest in this arena. In fact, as far as we are aware, our 1999 *Handbook of Neurodevelopmental and Genetic Disorders in Children* was the first of its kind. We believe the current volume is the first of its kind as well.

NATURE AND NURTURE

There continue to be few topics as inflammatory, polemic, or controversial in science as the "nature–nurture controversy." Are we human beings simply automatons following predetermined blueprints of development, road maps of behavior? Or are we thinking, feeling organisms capable of shaping and changing our destinies? Or, in fact, has our evolution over millions of years occurred in concert with our environment, so that a discussion of one without the other is likely to bear little fruit? Few contemporary scientists approach this question in a simplistic way. Scientific debate now centers around the relative contributions of nature and nurture—and not in a simplistic additive algorithm (e.g., "Behavior *X* is 80% genetic and 20% environmental in its etiology"), but as existing either in a transactional relationship or, perhaps more likely, in a model of reciprocal determinism of human development and behavior.

A genotype may be considered the raw material and blueprints (genes and chromosomes) provided through the melding of the parental genotypes. Except in the cases of monozygotic twins and cloning, no two human genotypes are alike. The human organism then grows and develops in a unique environment—one that may be shared with other siblings, but is never identical to theirs—to produce the visible, accessible, acting phenotype. No single phenotype is predestined by any single genotype. Attributes that we suggest commonly were genetically determined can often be altered in the course of development or even in later life. Height, known to have a strong heritability in the human population, can be altered dramatically by the manipulation of diet. A walk through the 400-year-old parts of St. Augustine, Florida, quickly reveals that the average height at that time was much less than it is today, and so doorways were lower and furniture was smaller. Many outcomes of genetic disorders may be entirely dependent on or at least strongly determined by changes in the environment. Phenylketonuria (PKU) is an example we have written about before. When phenylalanines are eliminated from the diet of children with PKU, the outcomes for intellect, school adjustment, and other behavioral variables are all much improved. Even behaviors as complex as adult sexual activity and preference, which are strongly genetically influenced, can be altered by significant changes in the stress levels of mothers at particular times during pregnancy. Furthermore, there are critical periods during gestation when hormonal releases affect cell migration and organ development in a preprogrammed fashion. A mother under high levels of stress may alter those hormonal release patterns in ways that affect the developing fetus; in turn, these changes influence the later dyadic interaction of mother and child, which may affect the development of neurochemical systems and even certain aspects of brain development.

As Plomin, DeFries, Craig, and McGuffin (2002) note, it is important to understand the different perspectives used to investigate behavior relative to genetic issues, because of the conceptual and methodological implications of these assumptions. Research in behavioral genetics has traditionally focused on within-species interindividual differences, such as why some children have reading disabilities or attention-deficit/hyperactivity disorder (ADHD) and others do not. Yet many areas of psychology and neuroscience seldom mention individual differences and concentrate instead on normative phenomena. That is, the focus is on understanding universal qualities rather than individual differences. Single-gene mutations in human research have been the center of attention. This approach treats all members of a species as if they were genetically the same, except for a few rogue mutations that disrupt normal processes.

In contrast, the individual-difference perspective considers variations as normal. Thus the interest is in the standard deviation (i.e., how far on average each person falls on specified dimensions from the population means). Common developmental and mental health problems reflect quantitative extremes of a normal distribution. Species-universal and individual-differences perspectives form the basis of current behavioral genetic research. Species universals might include language and learning. Genes are studied as nonvarying entities. Rare, severe disorders such as Rett syndrome, which has come to be understood as a condition reflecting an abnormality in the gene coding for MECP2 protein, leads to a single-gene condition. Common, less severe conditions such as learning disabilities or ADHD may reflect multiple-gene etiologies, while specific cognitive abilities may reflect differences in quantitative trait loci. Although 99.9% of the human DNA sequence is identical for all human beings, the 0.1% that differs—3 million base pairs—is ultimately responsible for the varied genetic influence found for complex traits, including behavioral dimensions and mental health disorders (Plomin, DeFries, McClearn, & McGuffin, 2001). Genes involved in multi- or polygenetic phenomena are called "quantitative trait loci" because they are likely to result in dimensions rather than disorders. The current volume reflects conditions falling in all four of these areas.

Consider the complexity of circadian rhythms. We are well aware that the body acts with a certain rhythm and timing for activities such as sleep. When circadian rhythms are poorly modulated, some individuals develop circadian rhythm sleep disorders. An introduction of a small lipid- and water-soluble indoleamine molecule (*N*-acetyl-5-methoxytryptamine, or melatonin) has been found to modify sleep rhythm significantly, leading to improved sleep and improved daily functioning (Jan & Freeman, 2004). At the other extreme, it has been demonstrated that normal developmental processes can be affected adversely, and sometimes subtly, by exposure to certain neurotoxins. Children exposed chronically to what in the 1950s were considered normal levels of lead demonstrate less self-regulated attention, which is likely to have an adverse impact not only on their education and behavior, but on the life course they take (Davis, Chang, Burns, Robinson, & Dossett, 2004). The complexity of the interaction in potential transmission is incomprehensible. No two combinations of genotype and environment have ever been or will ever be identical. Few components of behavior are too simple to be influenced by environment or too complex to be related to genotype. Yet, as our insight into and understanding of gene–environment interactions increase, we come to appreciate the significant impact human biology has on behavior—sometimes more than we would prefer to believe.

A brief discussion of human intelligence is worth revisiting. The extremes of the various scientific arguments place the nature–nurture contributions to intelligence at 80% and 20% or at 20% and 80%, respectively (see Herrnstein & Murray, 1994; Jensen,

1980; Reynolds & Brown, 1984). One could argue cogently for a relative contribution and interaction of these two extremes, but even in the most extreme genetic view, few propositions remain escapable. First, heritability statistics only apply to groups, and the genetic influence on intelligence for an individual may be more or less than the group heritability. Second, even if 80% of an individual's intelligence is genetically determined, changes in intellectual level as a function of environmental influence can be significant; these changes in turn alter the ability of the organism to create further favorable change in the environment, which may further influence intellectual development or other aspects of brain development and function, and so on it continues (even cross-generationally).

Psychological variables such as intelligence and personality are measured with interval scales, which have no true zero point in noting the absence of a trait. With a true zero point, the actual amount of a characteristic such as height can be determined, and such statements as "A height of 6 feet is twice a height of 3 feet" are accurate. However, interval scales have no true zero point. The only point we can locate definitively is the midpoint of a characteristic. We then measure outward toward the two ends of a distribution, each of which is asymptotic to its axis. That is, we do not know where intelligence (for example) begins or ends. An IQ of 100 cannot be said accurately to reflect twice the intelligence of an IQ of 50 (indeed, it may be a third again as much, or twice, or 10 times as much; we just do not know). We believe that here lies the clinician's opportunity to intervene and create potentially meaningful results, even under the adversity of strong genetic determination. To increase an individual's intellectual level by a full 20% may mean an increase of 10, 20, 30, or even more points on a psychometric scale. The same may hold true for other human characteristics that present as complex behavioral phenomena.

As later chapters in this book describe, many genetic disorders have a high degree of variable expressivity, and this occurs for reasons that may not be well understood. We believe many of these reasons to be treatment-related, or at least associated with biological and environmental interplay in a reciprocal relationship. Early involvement (i.e., during infancy and childhood) of professionals who understand brain–behavior relationships is necessary if adults with neurodevelopmental disorders are to achieve optimal outcomes. Even in the case of a phenomenon such as elevated blood lead levels, researchers have demonstrated that enriched environments may moderate the behavioral and neurotoxic effects of lead exposure, or even the propensity to accumulate lead in the body. Schneider, Lee, Anderson, Zuch, and Lidsky (2001) demonstrated the effects of environmental stimulation promoting changes in hippocampal neurochemistry protect or stimulate repair of lead-damaged hippocampal neurons and functional circuits involved in learning and memory. Thus the caregiving environment can reset the genotype following trauma. Furthermore, cortical development is genetically preprogrammed in many ways; however, not all genetic disorders have full phenotypic impact at the same time. Environments can alter the timing of development in change—and in brain development, timing can be absolutely crucial and can have dramatic effects on the resulting phenotype.

OBJECTIVES OF THIS VOLUME

As in our previous volume, we have set out to provide readers with a stand-alone compendium covering genetic disorders and neurodevelopmental issues, but this time in adults. We have divided the present volume into three sections. Part I covers basic principles and applications, revisiting our perspective on the role of neuropsychology in the assessment, treatment, and management of adults with neurodevelopmental and genetic disorders.

Chapter 2 provides a discussion of neuropsychological assessment in adulthood. Chapter 3 provides an overview of neurodevelopmental disorders and basic concepts in medical genetics. Finally, Chapter 4 provides an overview of current knowledge about neuroimaging and genetic disorders in adulthood.

Part II provides an overview of disorders primarily affecting learning and behavior. Chapters cover learning disabilities, ADHD, Tourette syndrome, anxiety disorders, depressive disorders, autism spectrum disorders, and substance use and abuse. Many of these disorders have an accepted though not yet well-identified genetic etiology. Year by year, we gain a better understanding of the role genetics plays in these conditions' presentation, course, and response to treatment. Most of these conditions occur more frequently in the general population than those covered in Part III.

Part III, by far the lengthiest section, contains 13 chapters providing an overview of conditions that have a lower incidence in the general population, specific etiologies, and overt physical/medical manifestations. Despite the relative infrequency of these conditions, neuropsychologists can expect to see increasing numbers of adults with these problems, especially within medical settings. These conditions are also likely to be faced increasingly by other professionals, such as school psychologists, educational staff members, and primary care physicians—not just those involved in specialty care.

Quality of life has become a paramount issue in the fields of medicine and mental health. An increasing body of research has demonstrated that even those with significant genetic conditions can and do overcome adversity, and are increasingly able to live satisfying and fulfilled lives. As a field, neuropsychology has begun to ask important questions about how individuals with genetic and neurodevelopmental problems overcome many of the obstacles they face in life. How do some of them manage to succeed? What kinds of experiences do they have that may be absent in the lives of those who are not successful? How much of their survival and success can be predicted by genetics, parenting, education, mentoring, temperament, and/or mental health? In a world in which stress and adversity seem to multiply exponentially from one generation to the next, the answers to these and related questions have become increasingly important. We have come to realize that it is just as important to understand strengths and assets as it is to understand liabilities and impairments, perhaps even more so when it comes to intervention. This volume provides readers with a thorough understanding of genetic and neurodevelopmental disorders in adults; more importantly, however, it conveys an appreciation for the importance of creating a treatment model focused not just on relieving liabilities, symptoms, and deficits, but on identifying and harnessing the strengths of all individuals so that they can learn to live happy, successful, fulfilled lives.

REFERENCES

Davis, D. W., Chang, S., Burns, B., Robinson, J., & Dossett, D. (2004). Lead exposure and attention regulation in children living in poverty. *Developmental Medicine and Child Neurology*, *46*, 825–831.

Goldstein, S., & Reynolds, C. R. (1999). Introduction. In S. Goldstein & C. R. Reynolds (Eds.), *Handbook of neurodevelopmental and genetic disorders in children* (pp. 3–8). New York: Guilford.

Herrnstein, R., & Murray, H. (1994). *The bell curve*. New York: Free Press.

Jan, J. E., & Freeman, R. D. (2004). Melatonin therapy for circadian rhythm sleep disorders in children with multiple disabilities: What have we learned in the last decade? *Developmental Medicine and Child Neurology*, *46*, 776–782.

Jensen, A. R. (1980). *Perspectives on bias in mental testing*. New York: Plenum Press.

Plomin, R., DeFries, J. C., Craig, I. W., & McGuffin, P. (Eds.). (2002). *Behavioral genetics in the post-genomic era*. Washington, DC: American Psychological Association.

Plomin, R., DeFries, J. C., McClearn, G. E., & McGuffin, P. (2001). *Behavioral genetics* (4th ed.). New York: Worth.

Reynolds, C. R., & Brown, R. T. (1984). Bias in mental testing: An introduction to the issues. In R. T. Brown & C. R. Reynolds (Eds.), *Perspectives on bias and mental testing* (pp. 1–26). New York: Plenum Press.

Schneider, J. S., Lee, M. H., Anderson, D. W., Zuch, I., & Lidsky, T. I. (2001). Enriched environment during development is protective against lead induced neurotoxicity. *Brain Research*, *896*, 48–55.

Guilford Publications
72 Spring Street
New York, NY 10012
212-431-9800
800-365-7006
www.guilford.com