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Edited by Miriam H. Beauchamp, Robin L. Peterson, M. Douglas Ris, H. Gerry Taylor, and Keith Owen Yeates.
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Preface

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Pediatric neuropsychology now boasts a rich history of empirical discovery and clinical innovations. The field has made great strides in recognizing that children and adolescents merit theoretical, methodological, and clinical approaches that take into account the complexity of their unique developmental stages.

This edition of *Pediatric Neuropsychology* builds on the foundations, concepts, and disorders covered in the first and second editions, while also introducing conditions not previously addressed. In determining the content and structure of this third edition, the priorities originally established were maintained, in that the aim is to provide a comprehensive yet manageable overview of the most relevant pediatric conditions that have implications for brain–behavior relations. This edition also continues to prioritize coverage of sound empirical evidence while ensuring that the information presented also has clinical relevance.

The first edition, published in 2000, provided extensive coverage of medical and neurological conditions frequently seen in hospital-based neuropsychological practice, such as metabolic diseases, epilepsy, and acquired brain injuries. The content and focus at the time reflected the established presence of neuropsychologists in tertiary care institutions and their expertise in the diagnosis and follow-up of severe conditions such as renal disease, phenylketonuria, or meningitis.

The second edition, published in 2010, again covered disorders such as traumatic brain injury and epilepsy, but also reflected a significant shift by including neurodevelopmental disorders. Some medical conditions, such as phenylketonuria, that were no longer as prevalent in everyday practice because of advances in early detection and treatment, were omitted in favor of extensive coverage of learning disabilities such as dyslexia and dyscalculia, and other prevalent neurodevelopmental disorders such as autism spectrum disorder and attention-deficit/hyperactivity disorder (ADHD).

In this third edition, just over a decade later, we have made further changes to the content of the book after careful consideration of both the current scientific and clinical state of the field. The challenge was to continue to reserve space for conditions that

warrant inclusion due to their prevalence and relevance, while also ensuring coverage of new conditions and disorders for which evidence has amassed sufficiently to be discussed from historical, etiological, neuropsychological, and therapeutic perspectives. As a result, the sections on medical/neurological and neurodevelopmental disorders include new topics such as congenital heart disease and movement disorders. A major addition is the introduction of a distinct section on genetic disorders, including fragile X, Williams, 22q deletion, and Down syndromes. Those chapters reflect substantial advances in our understanding of the neuropsychological consequences of these conditions, as well as their underlying etiology through advanced genetic techniques.

Readers familiar with the two previous editions will also notice a new section, "Emergent and Controversial Conditions." Our goal in including these chapters is to showcase conditions that account for a significant number of publications and referrals to clinicians, but have not reached consensus status among neuropsychologists or other medical and diagnostic entities. These chapters are included to stimulate discussion and inspire further work that might resolve their ambiguous status among neuropsychologists.

The result of these changes is a slightly lengthier volume than previous editions. As in the previous editions, each disorder or condition is presented in terms of its history, epidemiology, etiology and neural substrates, neuropsychology, developmental considerations, predictors and moderators, and associated treatment or intervention approaches. Emergent conditions are discussed in terms of their history, debate or controversy, current status in the field, and future directions. Each chapter is written by an expert or group of experts, all of whom consider theory, research, and practice, and provide a balanced and unbiased perspective.

The overall greater number of chapters in this edition seems fitting given that pediatric neuropsychologists today are present both in greater numbers and in more varied settings than ever before, reflecting an expansion of their role and breadth of their expertise, as well as the multifactorial needs of children, adolescents, and their families. No longer limited solely to "brain services" such as neurology or neurosurgery, they now practice alongside colleagues in pediatrics, rehabilitation, oncology, genetics, psychiatry, and neonatology, as well as in highly specialized units, such as concussion or craniofacial clinics. They are also more active outside hospital settings, in private practice, schools, and community care clinics, where they are more likely to encounter less acute but more prevalent conditions, such as ADHD and learning disabilities.

We believe that the content of this book will be of interest to a broad base of neuropsychologists, whether they conduct fundamental or clinical research into the neural, cognitive, and affective underpinnings of these disorders or apply their knowledge to practice, regardless of their place of work or particular population of interest. While written by and for neuropsychologists, we also hope that colleagues from medical fields and allied health disciplines such as speech–language pathology, occupational therapy, physiotherapy, and social work will find information applicable to their own research or practice. Many of the conditions discussed are common in the general and special education settings. Thus, the book can provide valuable information to colleagues working in schools (teachers, special educators, school psychologists, counselors). The book should also be useful to undergraduate and graduate students, as well as to psychology interns, residents, and postdoctoral fellows. It is intended to be suitable as a primary text for graduate courses in neuropsychology, neuroscience, or psychology more broadly.

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We would be remiss to not mention the context in which much of the final work leading to the publication of this edition was completed given that when the COVID-19 pandemic was declared worldwide in 2020, some authors were still writing their chapters and the editors were in the midst of reviewing previously submitted chapters. Though COVID-19 itself has thus far largely spared the health of children and adolescents relative to that of adults, its impact on the lives of youth is likely to be more substantial for children diagnosed with the conditions discussed in this book. Emerging evidence highlights an increased impact of COVID-related restrictions on vulnerable populations, including those with disabilities and requiring specialized services for academic achievement, remediation, or psychoeducation. For example, extended school closures, challenges managing and paying attention on virtual learning platforms, reduced access to specialized services, and the psychosocial and mental health effects of physical and social distancing are likely to affect those with preexisting conditions exponentially. Concerns also arise regarding the heightened effects of learning loss, as well as the impact of altered exposure to linguistic and socioaffective stimuli (e.g., masks affecting language learning and social-cognitive development). In future years, we likely will need to consider the effects of the pandemic itself on development and on these groups of children. If nothing else, the pandemic will have provided a lens through which the needs and vulnerabilities of young people living with neuropsychological conditions come into greater focus.

We would like to acknowledge the support and assistance of a number of people without whom this book could not have been completed. First, our appreciation goes to the exceptional group of authors who worked diligently to produce high-quality summaries of their fields, often during some of the most critical stages of the pandemic, when they were faced with increased demands for parenting or caretaking. We thank them for their willingness to incorporate our suggestions and feedback, and their care in following the proposed chapter structure. To those who took on the challenge of tackling the emergent and controversial conditions, a special thanks for embarking with us on this new path and believing that these conditions have a place alongside the more "conventional" disorders. Second, we appreciate the assistance of Rochelle Serwator, Editor at The Guilford Press, who through her good humor, guidance, inspiration, and patience, always manages to get us to the finish line. Finally, we thank our families and friends for their support and encouragement throughout the writing, editing, and publication process.

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CHAPTER 1

Back to the Future

Phenotypes, Risk, Development, Time, and Reserve as Key Concepts in Pediatric Neuropsychology

Keith Owen Yeates

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The first edition of this book, published two decades ago at the beginning of a new millennium, began with an introductory chapter by our late friend and colleague Maureen Dennis (2000), entitled "Childhood Medical Disorders and Cognitive Impairment: Biological Risk, Time, Development, and Reserve." In her chapter, Maureen sketched out an approach to developing an outcome algorithm for childhood medical disorders that conceptualized *cognitive phenotypes* of disorders as determined by the *biological risk* associated with a disorder, as moderated by three key factors: (1) the child's *developmental status*; (2) the *time since onset* of the disorder; and (3) the *reserve* available within the child and their broader environment. Figure 1.1 provides a high-level schematic of this heuristic model.

The concepts outlined by Maureen remain of central importance to the field of pediatric neuropsychology, although major scientific advances since her chapter appeared have broadened and deepened our understanding of them. This chapter revisits the concepts of phenotype, biological risk, development, time, and reserve, and attempts to highlight lessons learned since Maureen's visionary chapter by referencing the remaining chapters in this book, which reflect the empirical evidence accumulated over the past 20 years. In so doing, my hope is not only to acknowledge Maureen and her seminal contributions to the field but also to provide a broad context for understanding the disorders described in the chapters to come.

PHENOTYPE

Maureen defined a cognitive phenotype in terms of mental and behavioral skills. She described phenotypes in terms of both a modal profile, or the typical cognitive strengths and weaknesses associated with a disorder, and variability around that profile, acknowledging the heterogeneity in cognitive outcomes associated with most disorders. She highlighted the possibility of core deficits, or impairments in underlying cognitive processes

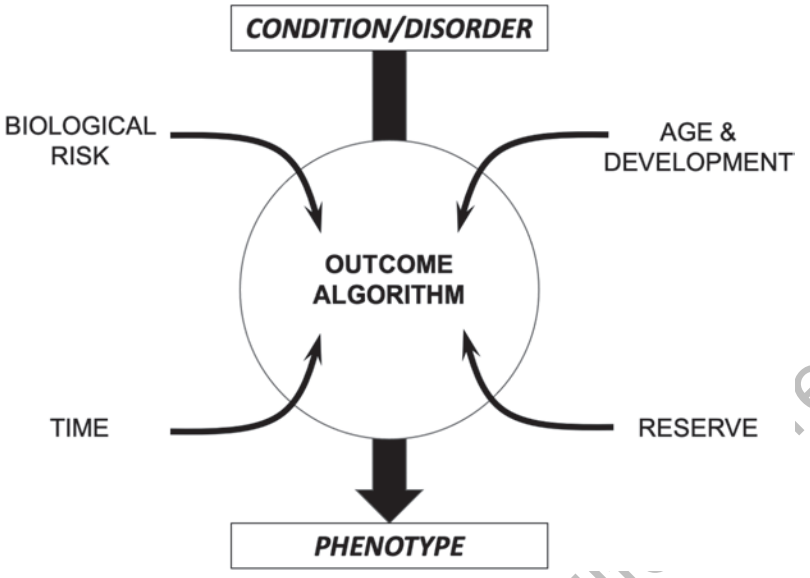

FIGURE 1.1. The relation between condition or disorder and phenotype, as set by biological risk and moderated by development, time, and reserve. Based on Dennis (2000).

that were robust to the severity of the disorder. She discussed the importance of challenge level, noting that evidence of underlying cognitive impairment sometimes becomes apparent only under conditions of high challenge. She also discussed the notion of *cognitive phenocopies,* or phenotypes that are superficially alike but arise from fundamentally different underlying cognitive processes. The model of neurocognitive function in spina bifida that Maureen and her colleagues subsequently set forth epitomizes this approach to cognitive phenotypes (Dennis, Landry, Barnes, & Fletcher, 2006).

Our understanding of phenotypes has been informed by significant scientific developments over the past 20 years. One major advance, as noted in the Preface to the second edition 10 years ago and even further exemplified by the chapters to come, is that the outcomes that characterize childhood disorders are now recognized to extend well beyond cognition to include a broader range of domains, including emotional and social functioning. In that sense, phenotypes can be defined in terms of modal profiles that encompass a broader range of outcomes than the primarily cognitive ones discussed by Maureen. For example, studies of social cognition have found impairments in "theory of mind" to characterize a variety of disorders found in this volume, such as autism spectrum disorder (ASD; Coulter, Skapek, Thomas, & Fein, Chapter 14), traumatic brain injury (TBI; Beauchamp & Yeates, Chapter 5), and Williams syndrome (Mervis & Greiner de Magalhães, Chapter 17). Similarly, complex behavioral phenotypes characterize some disorders, such as the combination of attention-deficit/hyperactivity disorder (ADHD), internalizing symptoms, and social problems seen in association with premature birth (Taylor & Anderson, Chapter 7).

Research has also made it clear that the applicability of the concept of phenotype varies along a continuum, ranging from disorders that are explicitly defined in terms of

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their phenotype to disorders for which a phenotype may not exist. A major change in the second edition of this book, compared to the first, was the inclusion of neurodevelopmental disorders, as opposed to only medical disorders. Neurodevelopmental disorders are often explicitly defined in terms of cognitive and behavioral characteristics; examples in this edition include ASD (Coulter et al., Chapter 14), ADHD (Willcutt, Chapter 11), and learning disabilities (Cirino, Chapter 13; Peterson & Pennington, Chapter 12). For those disorders, diagnosis and phenotype are closely intertwined, such that phenotypic features, including purported core deficits, are incorporated as diagnostic criteria.

The current edition expands even further the list of included disorders to feature several that are considered provisional or even controversial. Controversies about these disorders arise in part because research suggests they are not clearly associated with a specific phenotype. For instance, the existence of a dysexecutive syndrome seems unlikely given the absence of a unitary executive (Gioia, Isquith, & Roth, Chapter 21), and the defining features of nonverbal learning disabilities continue to be debated (Semrud-Clikeman, Chapter 20).

In contrast to neurodevelopmental disorders, most medical disorders are diagnosed based on underlying biological mechanisms, such as the genetic abnormalities linked to fragile X (Schneider, Scott, Shields, & Hessl, Chapter 16) and 22q11.2 deletion syndrome (Lajiness-O'Neill & Swick, Chapter 18) or the disease processes associated with diabetes (Schwartz & Wasserman, Chapter 10) or brain tumors and cancer (Ris, Chapter 4). Medical disorders may or may not be associated with a neurobehavioral phenotype. In some cases, diagnostic criteria for medical disorders include both phenotypic features and underlying mechanisms, as in the case of fetal alcohol spectrum disorders (Bernes, Moore, Vaurio, & Mattson, Chapter 9). But the purported connection between mechanism and phenotype is sometimes controversial, as in acute-onset neuropsychiatric syndrome (Malik, Martino, & Hedderly, Chapter 22).

For both neurodevelopmental and medical disorders, research suggests that "signature" or core deficits are not discernible in some disorders, such as congenital heart disease (Cassidy, Chapter 8). However, modal profiles likely exist for many disorders, such as fragile X syndrome (Schneider et al., Chapter 16), TBI (Beauchamp & Yeates, Chapter 5), and ADHD (Willcutt, Chapter 11). As Maureen foreshadowed in her discussion of variability, some disorders may be associated with multiple phenotypic profiles, such as ASD (Coulter et al., Chapter 14). Heterogeneity is often a hallmark of other disorders, such as brain tumors (Ris, Chapter 4) and hydrocephalus (Shishido & Zabel, Chapter 2). Even disorders that present with modal profiles, such as Williams syndrome (Mervis & de Magalhães, Chapter 17) and ADHD (Willcutt, Chapter 11), often display substantial heterogeneity. Indeed, some children with disorders that typically lead to significant neurobehavioral deficits show surprisingly positive outcomes, and this type of resilience is becoming a growing focus of research, as seen in premature birth (Taylor & Anderson, Chapter 7) and TBI (Beauchamp & Yeates, Chapter 5).

As Maureen noted in her discussion of phenocopies, some phenotypic features are shared by different disorders, such as processing speed deficits in learning disabilities (Cirino, Chapter 13, and Peterson & Pennington, Chapter 12), brain tumors (Ris, Chapter 4), and diabetes (Schwartz & Wasserman, Chapter 10); math problems in 22q11.2 deletion syndrome (Lajiness-O'Neill & Swick, Chapter 18); and autistic features in fragile

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X syndrome (Schneider et al., Chapter 16). Careful parsing of phenotypes is sometimes possible to discern distinct cognitive processes underlying shared phenotypic features, as illustrated by research on speech, language, and reading disabilities (Peterson & Pennington, Chapter 12) and premature birth (Taylor & Anderson, Chapter 7). However, research also underscores the inherent associations between specific cognitive processes that may be responsible for shared phenotypic features across disorders, as exemplified by research on dysexecutive disorders (Gioia et al., Chapter 21) and sluggish cognitive tempo (Jacobson, Chapter 23).

Thus, the concepts of equifinality and multifinality are central to understanding phenotypes (Cicchetti & Rogosch, 1996). *Equifinality* refers to the capacity for different underlying biological and cognitive processes to give rise to similar phenotypes, or, as Maureen noted, phenocopies; *multifinality* refers to the capacity for similar underlying biological and cognitive processes to give rise to a range of phenotypes or to the heterogenous expression of any given phenotype. Further complicating matters is that phenotypes associated with a given disorder also can change over the course of development, sometimes appearing quite different at different ages. This phenomenon, sometimes referred to as *heterotypic continuity,* is exemplified by disorders such as Williams syndrome (Mervis & de Magalhães, Chapter 17), learning disabilities (Cirino, Chapter 13, and Peterson & Pennington, Chapter 12), and 22q11.2 deletion syndrome (Lajiness-O'Neill & Swick, Chapter 18).

The search for phenotypes also must consider practical measurement issues. For example, performance tests and rating scales that purport to measure the same function often display limited agreement, as noted in chapters in this volume on dysexecutive disorders (Gioia et al., Chapter 21) and sluggish cognitive tempo (Jacobson, Chapter 23). These discrepancies can raise questions about the construct validity of not only the measures themselves but also the phenotypes they purport to identify. In other cases, traditional neuropsychological tests suffer from floor effects that hamper the delineation of relative strengths and weaknesses, as in the case of fragile X syndrome (Mervis & de Magalhães, Chapter 17). In the end, measurement concerns suggest that pediatric neuropsychology must not rely entirely on scores on tests and rating scales to "paint by numbers." As highlighted in the concluding chapter of this volume, which focuses on the translation of the knowledge base to clinical cases (Bernstein & Cassidy, Chapter 24), the goal is to develop nuanced portrayals of phenotypes informed by a deep knowledge of neurobehavioral systems, using tests and rating scales as tools to achieve this goal rather than as ends in and of themselves.

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BIOLOGICAL RISK

In her introductory chapter, Maureen defined *biological risk* as the cumulative severity of a disorder. She described how severity could encompass a variety of effects, including those related to genotype, metabolism, environmental toxicity, congenital brain dysmorphologies, the primary and secondary effects of acquired brain insult, and treatment morbidity. In the past 20 years, our understanding of biological risk has continued to deepen. We have increasingly come to appreciate that the biological risk associated with

most disorders encompasses multiple dimensions. For example, childhood disorders such as stroke (Greenham, Mackay, Gordon, & Anderson, Chapter 6), TBI (Beauchamp & Yeates, Chapter 5), and brain tumors (Ris, Chapter 4) typically involve both diffuse and focal acquired brain insults that have distinct effects on neurobehavioral outcomes. Similarly, medical disorders such as diabetes (Schwartz & Wasserman, Chapter 10) can affect a variety of biological mechanisms, each potentially having specific effects on neuropsychological functioning.

Two major advances over the past 20 years have had a particularly profound impact on our understanding of biological risk. One is the so-called "genetic revolution," the influence of which ranges from the development of "generalist genes" models for neurodevelopmental disorders such as math disability (Cirino, Chapter 13) and speech, language, and reading disabilities (Peterson & Pennington, Chapter 12), to complex polygenic models of disorders such as autistic spectrum disorder (Coulter et al., Chapter 14) and ADHD (Willcutt, Chapter 11), to notions of incomplete or variable phenotypic expression in 22q11.2 deletion syndrome (Lajiness-O'Neill & Swick, Chapter 18) and fragile X syndrome (Schneider et al., Chapter 16). The genetic revolution has driven the call for precision medicine, which has been most evident in research on childhood cancers (Ris, Chapter 4) but is now being extended to other disorders, including TBI (Beauchamp & Yeates, Chapter 5).

The second major advance leading to a deeper understanding of biological risk involves neuroimaging. This advance also was noted in the Preface to the second edition of this volume but is even more apparent now. Examples of how neuroimaging is contributing to research on childhood disorders are ubiquitous in the chapters that follow, for both medical and neurodevelopmental disorders. Two exciting examples include the examination of structural and functional brain networks, as in math disability (Cirino, Chapter 13) or epilepsy (Puka & Smith, Chapter 3), and the use of neuroimaging to predict response to treatment, as in congenital heart disease (Cassidy, Chapter 8). Neuroimaging also has helped distinguish the effects of diffuse versus focal injuries, as reflected in research on the correlates of total brain volume versus specific volumes of the corpus callosum, basal ganglia, and cerebellum in fetal alcohol spectrum disorder (Bernes et al., Chapter 9). Furthermore, neuroimaging has also confirmed that "too much" can be just as characteristic of the brain in childhood disorders as "too little," as reflected in the finding of macrocephaly and increased brain volume in ASD (Coulter et al., Chapter 14) versus microcephaly and decreased brain volume in 22q11.2 deletion syndrome (Lajiness-O'Neill & Swick, Chapter 18). Too much connectivity can also be as problematic as too little, as seen in Down syndrome (Lee, Stephan, & LaQuaglia, Chapter 19). Indeed, some disorders are characterized by both excess and insufficiency in the brain, as reflected in smaller gray matter volumes in cortical regions but larger gray matter volume in the caudate in fragile X syndrome (Schneider et al., Chapter 16). Despite the advances that neuroimaging has yielded in our understanding of many childhood disorders, however, the links between neuroimaging and neurobehavioral outcomes are still tenuous for many disorders, such as ASD (Coulter et al., Chapter 14).

An important caveat about biological risk is that it is not static or fixed. Biological risk can change, both increasing and decreasing as a function of development and time. For instance, congenital heart disease is associated with early and continuing maldevelopment

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of the brain, especially in the white matter, with the early abnormalities providing a vulnerable substrate for later injury (Cassidy, Chapter 8). Developmental changes in biological risk also can occur as a function of compensatory neural organization in response to injury, as hypothesized in children with premature birth (Taylor & Anderson, Chapter 7). As Maureen highlighted in her chapter, treatment may also increase biological risk, as seen in the effects of radiation and chemotherapy in children with brain tumors (Ris, Chapter 4) or of antiepileptic medication in children with epilepsy (Puka & Smith, Chapter 3).

Biological risk also can vary as a function of demographic factors. In that regard, biological sex plays an important role in the prevalence and expression of a variety of childhood disorders, such as ASD (Coulter et al., Chapter 14), stroke (Greenham et al., Chapter 6), and fragile X syndrome (Schneider et al., Chapter 16). Sex differences in outcomes are not apparent in all disorders, though, such as 22q11.2 deletion syndrome (Lajiness-O'Neill & Swick, Chapter 18). The role of sex as a moderator of outcomes remains uncertain in other disorders, such as TBI (Beauchamp & Yeates, Chapter 5).

AGE AND DEVELOPMENT

In her chapter, Maureen discussed the need to consider age and development at the time of onset of a disorder to understand neuropsychological outcomes. She described a historical dissonance between views that treated early age of onset as both a risk and a protective factor, concluding that the bulk of the evidence suggested early onset is generally associated with worse outcomes. She considered various factors affecting the expression of disorders characterized by fetal onset, early childhood onset, or older age of onset. She highlighted the possibility that certain time windows were associated with heightened vulnerability. She noted that age at onset of a disorder may be associated with not only the level of functioning at any given time but also the rate of decline across time.

The importance of age and development has already been highlighted in the two previous sections, when describing how clinical phenotypes and biological risk can vary by age or development. Further examples of how age at onset affects the expression of childhood disorders are seen in many of the subsequent chapters in this volume, including those on stroke (Greenham et al., Chapter 6), brain tumors (Ris, Chapter 4), and diabetes (Schwartz & Wasserman, Chapter 10). The importance of developmental status is seen specifically in the increasing study of key age-related transitions, such as the entry into adulthood, as discussed in chapters in this volume on congenital heart disease (Cassidy, Chapter 8) and brain tumors (Ris, Chapter 4), as well as the growing interest in adult outcomes of childhood disorders, as described in chapters on epilepsy (Puka & Smith, Chapter 3) and fragile X syndrome (Schneider et al., Chapter 16). Other examples of the important role of development are seen in the varying effect of comorbidities across ages in Down syndrome (Lee et al., Chapter 19) and changes in the heritability of reading skills with age (Peterson & Pennington, Chapter 12).

The growing appreciation of the role of development in childhood disorders over the past two decades has had two important consequences. One, which was noted in the Preface to the second edition, is an increased recognition of the importance of understanding

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normal development as a context for the study of childhood disorders, as highlighted in the chapter in this volume on math disability (Cirino, Chapter 13). The second is recognition of the need for "lifespan" models of childhood disorders, as discussed in chapters in this volume on diabetes (Schwartz & Wasserman, Chapter 10), brain tumors (Ris, Chapter 4), and ADHD (Willcutt, Chapter 11). Many of these models rest on broader conceptualizations of the developmental origins of health and disease (Silveira, Portella, Goldani, & Barbieri, 2007) or life course health development (Halfon, Larson, Lu, Tullis, & Russ, 2014).

When thinking about age and development as moderators of the outcomes of childhood disorders, an important distinction needs to be drawn between age at onset and age at diagnosis. For some of the disorders discussed in subsequent chapters in this volume, such as epilepsy (Puka & Smith, Chapter 3), neuropsychological morbidity very often precedes diagnosis. In other disorders, diagnosis can be delayed because of uncertainty about diagnostic criteria at younger ages or delays in referral for clinical evaluation, as can occur in ASD (Coulter et al., Chapter 14) or ADHD (Willcutt, Chapter 11). Precise determinations of age of onset are in fact often impossible other than in disorders marked by a specific event, such as TBI (Beauchamp & Yeates, Chapter 5).

TIME

In her chapter, Maureen discussed time since onset as an important moderator of cognitive phenotype. She noted that *time* is not a synonym for *recovery* but may instead involve changes in expression of a disorder or even disease progression and deterioration. She emphasized that time since onset can affect both the level of function and the rate of acquisition, underscoring the need to study developmental trajectories. In this regard, she highlighted the relative paucity of research on the natural course of childhood disorders into adulthood, a topic that, as already noted, is now beginning to receive increased attention. Maureen also stressed the complex interplay between developmental change and recovery from specific disorders.

Maureen's comments on the role of time presaged the increasing attention paid to understanding the outcomes of childhood disorders in terms of trajectories rather than just outcomes at a given time, as highlighted in chapters in this volume on Down syndrome (Lee et al., Chapter 19) and premature birth (Taylor & Anderson, Chapter 7). Her admonishment that *time* is not a synonym for *recovery* foreshadowed discussions of accelerated aging that appear in chapters in this volume on brain tumors and cancer (Ris, Chapter 4) and diabetes (Schwartz & Wasserman, Chapter 10). Similarly, Maureen's appreciation for the complex interplay between development and recovery is reflected in a variety of chapters in this volume, including those on congenital heart disease (Cassidy, Chapter 8), 22q11.2 deletion syndrome (Lajiness-O'Neill & Swick, Chapter 18), and epilepsy (Puka & Smith, Chapter 3). More generally, many of the chapters in this edition highlight changes in the expression of disorders over time, including both neurodevelopmental disorders such as learning disabilities (Cirino, Chapter 13; Peterson & Pennington, Chapter 12) and ASD (Coulter et al., Chapter 14) and medical disorders such as stroke (Greenham et al., Chapter 6) and epilepsy (Puka & Smith, Chapter 3).

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Methodologically, the increasing focus on understanding outcomes in terms of trajectories has been reflected in a call for longitudinal rather than cross-sectional studies. Longitudinal studies are becoming more common in some disorders in this volume, such as prematurity (Taylor & Anderson, Chapter 7), brain tumors (Ris, Chapter 4), and TBI (Beauchamp & Yeates, Chapter 5), but are badly needed in others, such as fetal alcohol spectrum disorders (Bernes et al., Chapter 9) and stroke (Greenham et al., Chapter 6). The increase in longitudinal studies of childhood disorders has been paralleled by the application of statistical techniques that explicitly examine trajectories over time, such as mixed models for longitudinal data and developmental trajectory analysis. These techniques have the potential to provide substantial insights into the factors that predict intraindividual change in outcomes over time, at both an individual and group level. One challenge to researchers in the application of these techniques is the inherent confounding of age at onset, time since onset, and age at assessment. These age- and time-related factors are inextricably linked and can only be disentangled through careful research design (Taylor & Alden, 1997).

RESERVE

Maureen defined reserve as all those factors that are available either to buffer dysfunction or to exacerbate it. This definition was broader than some traditional approaches, which focus exclusively on characteristics of the child, and encompassed characteristics of the family or the broader social context of peers and school. Maureen described how pre-insult reserve may involve demographic, cognitive, physical, or socioeconomic factors. She suggested that changes in physical and mental health may alter reserve after the onset of a disorder, and thereby play a key role in cognitive outcomes, highlighting the dynamic nature of reserve. She also indicated that family resources have a critical, and likely bidirectional, relationship to outcomes, and that school and rehabilitation interventions could play an important role as moderators.

Research discussed in the subsequent chapters in this volume highlights both biological and psychological factors that reflect the role of intrapersonal reserve as an important moderator of the outcomes of childhood disorders. For instance, comorbid genetic conditions can moderate the outcomes of medical disorders such as congenital heart disease (Cassidy, Chapter 8). Similarly, psychological resilience appears to be an important factor in predicting the severity of postconcussive symptoms after mild TBI (Beauchamp & Yeates, Chapter 5).

At the same time, extrapersonal factors, particularly parent and family functioning, also play a powerful role in the outcomes of childhood disorders, as discussed in relationship to many disorders, including congenital heart disease (Cassidy, Chapter 8), 22q11.2 deletion syndrome (Lajiness-O'Neill & Swick, Chapter 18), and prematurity (Taylor & Anderson, Chapter 7). Critically, many extrapersonal factors are potentially modifiable; hence, parent- or family-based interventions to foster better child outcomes are becoming more common, as seen in the chapters in this volume on movement disorders (Mahone, Chapter 15), TBI (Beauchamp & Yeates, Chapter 5), and fragile X syndrome (Schneider et al., Chapter 16).

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Of course, the existence of an association between parent or family factors and outcomes does not automatically ensure that modifying the environment will change outcomes. Some of the variance in children's outcomes related to parent or family variables may reflect shared genetic influences, as noted in the chapter in this volume on speech, language, and reading disabilities (Peterson & Pennington, Chapter 12). Research designs such as twin and adoption studies can help to tease out the roles of genetic and both shared and nonshared environmental factors as elements of reserve. Additionally, a distinction should be drawn between aspects of children or their environments that account for variation in outcomes, in addition to the effects of a given disorder, versus those that moderate the effects of that disorder. The application of the term *reserve* probably should be limited to situations in which a variable is a moderator, and either buffers or exacerbates the effects of a given disorder, rather than simply helping to account for variance in outcomes.

The recognition of the importance of extrapersonal factors, and the corollary that phenotypes may be more malleable than first appreciated, is reflected in increasing focus in this volume on treatment to modify the outcomes of many childhood disorders, including prematurity (Taylor & Anderson, Chapter 7) and congenital heart disease (Cassidy, Chapter 8). The study of treatment or intervention is becoming more refined, as researchers try to determine which interventions are most effective for which children, consistent with the move to precision medicine. Indeed, many of the subsequent chapters in this volume highlight exciting new research on the moderators of treatment outcomes, such as the timing of intervention in ASD (Coulter et al., Chapter 14) or brain tumors (Ris, Chapter 4). In some cases, though, treatments have been promoted without sufficient empirical support, perhaps especially in the case of controversial diagnoses such as acute-onset neuropsychiatric syndrome (Malik et al., Chapter 22).

One important facet of reserve that was paid relatively little attention in previous editions but is highlighted in the current edition is the potential role of cultural and international variation in what factors reflect reserve and how they operate. Important cultural and international differences are noted in multiple chapters on both neurodevelopmental and medical disorders, including ASD, 22q11.2 deletion syndrome (Lajiness-O'Neill & Swick, Chapter 18), fragile X syndrome (Schneider et al., Chapter 16), diabetes (Schwartz & Wasserman, Chapter 10), epilepsy (Puka & Smith, Chapter 3), and hydrocephalus (Shishido & Zabel, Chapter 2)

The burgeoning research on reserve reflected in this edition calls for broader models that identify intrapersonal and extrapersonal elements of reserve as aspects of risk and resilience that can act to exacerbate or buffer against poor outcomes in childhood disorders. One example of such a model is seen in the chapter in this volume on congenital heart disease (Cassidy, Chapter 8, Figure 8.1). However, because we are dealing with children, such models must also acknowledge that variation in age or developmental status and time since onset of a disorder may modify the nature of risk and resilience factors, as well as their association with outcomes. Indeed, as Maureen noted, the various moderators of the outcomes of childhood disorders do not operate in isolation but instead interact in complex ways. Research has begun to identify how biological risk, age and developmental status, time, and reserve interact, but this will remain a major task for pediatric neuropsychology into the future.

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CONCLUSION

At the conclusion of her chapter, Maureen outlined a preliminary approach to an outcome algorithm that would consider the biological risk associated with a given disorder and the level of challenge of any given task, which would together determine a floating impairment threshold that would be raised or lowered by development, time, and reserve as moderators. A schematic of that algorithm is presented in Figure 1.2. As suggested in the preceding sections, the development of an outcome algorithm may be even more challenging than Maureen could have realized given that scientific advances of the past 20 years have underscored the complexity of the key concepts. Nevertheless, the search for algorithms or prediction rules that allow us to forecast the outcomes of childhood disorders remains a worthy aspirational goal.

Achieving this goal implies the need to conduct prospective and longitudinal studies with very large samples, across multiple sites, using common data elements that are collected consistently across all studies. The selection and use of common data elements have been promoted by government funding agencies, such as National Institutes of Health and Canadian Institutes of Health Research (e.g., Hicks et al., 2013; McCauley et al., 2012), as well as by large research consortia. The use of common data elements will foster the pooling of data sets from multiple projects and enable the application of big data techniques such as machine learning to develop robust prediction rules that can be used for prognostic purposes.

The utility of machine learning analyses and other big data approaches is generally higher when informed by expert knowledge, which in this case would involve comprehensive, evidence-based models of outcomes of childhood disorders. As already noted,

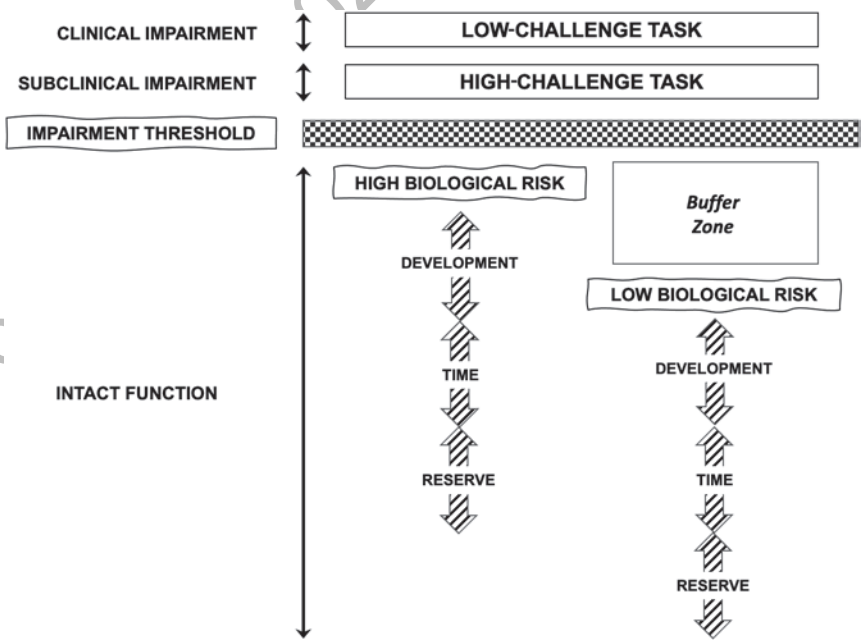

FIGURE 1.2. Outcome algorithm schematic. Based on Dennis (2000).

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research in pediatric neuropsychology increasingly depends on lifespan models of childhood disorders that incorporate insights garnered from broader conceptualizations of the developmental origins of health and disease (Silveira et al., 2007) and life course health development (Halfon et al., 2014). These models help to consider the broad range of factors, including biological risk, age and development, time, and reserve involved in the phenotypic expression of a disorder in the individual child. In the future, these models will need to be even broader and incorporate various aspects of diversity to acknowledge how the expression of disorders is also shaped by cultural, racial, and international factors.

In the end, scientific advances should be made in the service of promoting better outcomes for children. Practically speaking, pediatric neuropsychologists will need new assessment approaches and technologies, such as virtual reality and digital health applications, to tap aspects of children's functioning that cannot be readily assessed using traditional tests but are crucial to defining phenotypes. We will continue to need research to determine whether our measures tell us something meaningful about children's brain status or about their everyday functioning, with neurological and ecological validity often being very difficult to achieve in a single measure. In this regard, further study of the contributions of tests versus rating scales is clearly warranted. More broadly, pediatric neuropsychologists have a responsibility to translate insights garnered from research on childhood disorders into rigorous tests of interventions that will help children and their families achieve more optimal outcomes. Indeed, attempts to translate research into clinical practice is another critical goal for the future. We have Maureen Dennis to thank for delineating key concepts that will need to be considered along the way.

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