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Volume 1: Neurobehavioral Disorders and Conditions: Accepted Science and Open Questions

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About the Editors

Gregory G. Brown, PhD, ABPP-CN, is an emeritus professor in the Department of Psychiatry, University of California, San Diego School of Medicine. He grew up in Kokomo, Indiana, where he attended public schools. In the seventh grade, Dr. Brown had the good fortune to be trained in the New Math curriculum developed after the USSR's launch of Sputnik. The curriculum introduced him to exciting concepts in mathematics and provided a core intellectual interest that has persisted throughout his lifetime. Dr. Brown attended Indiana University, where he received a bachelor's degree in psychology and sociology and a master's degree in psychology in 1973 (supervised by Dr. Margaret Petersen). He was accepted into the clinical psychology program in the Department of Psychology at Wayne State University, directed by Dr. Gerald Rosenbaum. There he was supervised by Drs. Melvin Schwartz, Phillip M. Rennick, and Ronald Lewis. Dr. Brown was awarded a PhD in psychology from Wayne State University in 1977 for his use of a computational model of memory to study patients with memory disorder. His dissertation was one of the earliest examples in the clinical neuropsychology literature of the use of methods of mathematical psychology to study individual and group differences. After receiving his degree, he worked as a clinical neuropsychologist at Henry Ford Hospital in Detroit, Michigan, for 17 years and at The New York Hospital/Cornell University Medical College for a year. In 1995 he joined the Department of Psychiatry at the University of California, San Diego, and the Psychology Department at the VA San Diego Healthcare System. Throughout his career, Dr. Brown has taught courses on clinical neuropsychology and mentored trainees whose academic experience ranged from undergraduate training to faculty.

Dr. Brown has 170 papers listed in ResearchGate. His neuropsychological research has been wide ranging—involving studies of the neuropsychological functioning of patients with neurological or neuromedical disorders and studies of these patients using functional and structural brain imaging. He has published on the application of psychometric methods to functional brain imaging and neurobehavioral data and has collaborated on imaging and computational papers of sleep deprivation. Throughout his career, he has used computational models to investigate neuropsychiatric and neurological disorders. Dr. Brown has a board certification from the American Board of Professional Psychology with a specialty in clinical neuropsychology and is a fellow of Division 40 (Society for Clinical Neuropsychology) of the American Psychological Association (APA). He was the editor-in-chief of the APA journal *Neuropsychology* from 2014 to 2019.

Tricia Z. King, PhD, is a tenured professor in the Department of Psychology at Georgia State University (GSU). She is a fellow of Division 40 (Society for Clinical Neuropsychology [SCN]) of the American Psychological Association. Dr. King earned her PhD in clinical psychology with a neuropsychology specialization at the University of Florida. She completed her clinical internship and postdoctoral training at Brown University Medical School Training Consortium with a neuropsychology specialization. She was successful in securing a National Institutes of Health National Research Service Awards F32 postdoctoral grant during this time. She has had continuous funding since receiving the Research Scholar Award from the American Cancer Society for research that focused on long-term survivors of pediatric brain tumors. In 2022, she was awarded a multisite RO1 from the National Cancer Institute that examines the multifactorial socioeconomic context within a culturally sensitive framework, as well as the contribution of genetics (single-nucleotide polymorphisms) to recovery and outcomes. Dr. King continues to investigate the interacting biopsychosocial factors that contribute to optimal outcomes following neurodevelopmental disruption. Her team focuses on what happens to the developing brain many years after an acquired brain injury or onset of medical condition and how those events affect cognitive abilities across the lifespan. She uses neuroimaging to understand the neural mechanisms underlying both cognitive and socioemotional abilities of individuals. The overarching goal of her work is to contribute to advancements in precision medicine, resulting in greater prognostic abilities and enhanced interventions to mitigate neurotoxicity and enable individuals to thrive. Dr. King has collaborated with valued colleagues on an individualized cognitive remediation program (cognitive remediation of executive and adaptive deficits in youth: a family-focused program; C-READY) to prepare youth for transition to adult health care. She has published over 100 peer-reviewed papers and chapters. She is committed to diversifying the trainee pipeline and has enjoyed mentoring and training at the undergraduate and graduate levels. She sponsors an active chapter of the Association of Neuropsychology Students and Trainees at GSU (SCN ANST). She was awarded the GSU Outstanding Undergraduate Mentoring Award (2020). She has served as the chair of the SCN Scientific Advisory Committee and as a member of the SCN Fellows Committee, and in 2021 she was elected treasurer of SCN. Dr. King serves on the editorial board for *Child Neuropsychology* and is an associate editor of *The Clinical Neuropsychologist*.

Kathleen Y. Haaland, PhD, ABPP-CN, is a tenured professor in the Department of Psychiatry and Behavioral Sciences at the University of New Mexico Health Sciences Center. She is board certified by the American Board of Professional Psychology and the American Board of Clinical Neuropsychology (ABPP-CN), where she continues to participate in board certification exams. Dr. Haaland has published over 100 papers and chapters largely focused on the cognitive and neuroanatomical correlates of action in stroke, Parkinson's disease, and Huntington's disease. Her research was continuously funded from 1981 to 2014. In addition to serving as the director of neuropsychology at the New Mexico VA Healthcare System for many years, she was a VA Research Career Scientist from 2004 to 2014, when she left the Department of Veterans Affairs. She has been recognized locally with the A. Earl Walker Neuroscience Research Award for outstanding neuroscience research (2004) and the Excellence in Clinical Science Research Award (2013). She is a fellow of the American Psychological Association (APA, 1991), and she received lifetime career contribution awards from the International Neuropsychological Society (2020) and the National Academy of Neuropsychology (2012). She has also served in leadership roles in the International

Neuropsychological Society, the APA, and the American Board of Clinical Neuropsychology. She was the president of the International Neuropsychological Society (2016), the Society of Clinical Neuropsychology (Division 40; 2004), and the American Board of Clinical Neuropsychology (1999–2001). Dr. Haaland was also the symposium editor (1999–2004) and then editor-in-chief (2004–2014) of the *Journal of the International Neuropsychological Society*. She has also served APA as a member of the Board of Scientific Affairs (2011–2014). Since 2017, she has been an associate editor for the Neuroscience and Psychology Section of *Frontiers for Young Minds*.

Bruce Crosson, PhD, ABPP-CN, has published more than 160 refereed journal articles, based on projects funded by the U.S. Department of Veterans Affairs (VA), the National Institutes of Health, and other funding sources, during a career of over 40 years. He mentored 26 faculty, fellows, and graduate students on 39 competitively funded mentored awards. In addition to neuropsychologists, these mentored awardees have included speech-language pathologists, physicians, engineers, and other professionals, indicating his dedication to interdisciplinary research and education. His former mentored awardees have held positions at leading universities around the world. Most recently, Dr. Crosson's faculty affiliations have included the Department of Clinical and Health Psychology at the University of Florida (1989–2012), the Department of Neurology and Department of Radiology and Imaging Sciences at Emory University (2012–2021), and the Department of Psychology at Georgia State University (2012–2021). He held an honorary professorship in the School of Health and Rehabilitation Sciences at the University of Queensland in Brisbane, Australia, for 18 years (2004–2021). He was the recipient of a Senior Research Career Scientist Award from the VA Rehabilitation Research and Development Service (2009–2021, inclusive). Dr. Crosson is considered one of the world's leading experts on subcortical functions in language. This expertise has served as the cornerstone to his systems approach to the neural foundations of cognition. He developed a course on subcortical functions in cognition, taught for more than 20 years at the University of Florida and later at Georgia State University. He is also recognized for his expertise in functional neuroimaging, including assisting colleagues in his laboratory to develop techniques to mitigate artifacts produced while speaking in an MRI scanner. These innovations have allowed for more accurate imaging of the neural basis of spoken language, including recovery from aphasia. Dr. Crosson has been a diplomate in clinical neuropsychology of the American Board of Professional Psychology since 1986, and he is a fellow of the American Psychological Association. He was one of the organizers of the 1997 Houston Conference on Specialty Education and Training in Clinical Neuropsychology, which has guided the training of clinical neuropsychologists for more than 20 years. Nonetheless, Dr. Crosson's skill set extends beyond clinical neuropsychology and the neurosciences. While at the University of Florida, for example, he was twice the recipient of the Hugh C. Davis Award for Dedication to and Excellence in Psychotherapy Supervision, awarded by a vote of the graduate students from his department.

Introduction

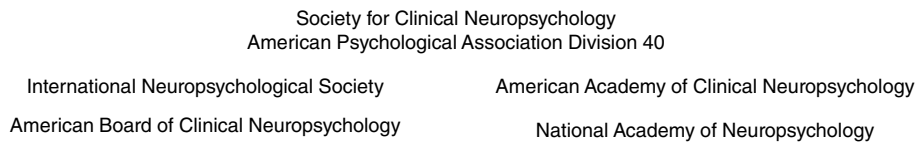
BACKGROUND TO THE FIELD

Neuropsychology is a subdiscipline of psychology composed of scientists and clinicians studying the relationship between behavior and human brain structure and function. The discipline aims to improve our understanding of the neural substrate of psychological phenomena and to guide diagnosis and rehabilitation of disorders of the central nervous system (CNS). Historically, the accumulation of knowledge about brain–behavior relationships has been based on both clinical assessments and laboratory studies. Unlike disciplines where the translation of research findings into clinical practice faces major barriers, neuropsychologists embrace a free-flowing exchange of information between research results and clinical findings. That scientific research and clinical practice are tightly coupled in neuropsychological work is a hallmark of the discipline. Reflecting this tradition, this handbook includes chapters on basic neuroscience, neuroimaging, and statistical methods in addition to chapters on clinical syndromes and disorders, emerging clinical assessment techniques, and rehabilitation.

Over the second half of the 20th century, the field of neuropsychology grew from a highly specialized branch of psychology into a psychological discipline with broad clinical application that has also made key contributions to the neuroscience revolution. The historical development of the profession and the broad range of its clinical and research work are reflected in the rise of journals providing outlets for clinical and research papers, societies supporting the study of brain–behavior relationships, clinical boards to certify the competence of clinical neuropsychological practitioners, and review bodies to accredit neuropsychological training programs (Figure 1). In addition to its traditional focus on the psychological effects of human brain lesions, the body of knowledge acquired by the field provides students, scientists, and practitioners with a pathway to understand the brain basis of psychological disorders among people without conventional neurological disease, such as anxiety disorders. Its body of knowledge has also been fertile ground for the development of cognitive and behavioral theories of healthy brain function. As a marker of neuropsychology's influence on the broader field of psychology, since 2017 the Society for Clinical Neuropsychology (Division 40; <https://scn40.org>) has had more members than any other division of the American Psychological Association (APA, 2020).

Although neuropsychological studies have significantly influenced psychological theory and practice in North America, their reach is international, with vibrant neuropsychological

Societies and Accreditation Bodies



Some English Language Neuropsychological Journals

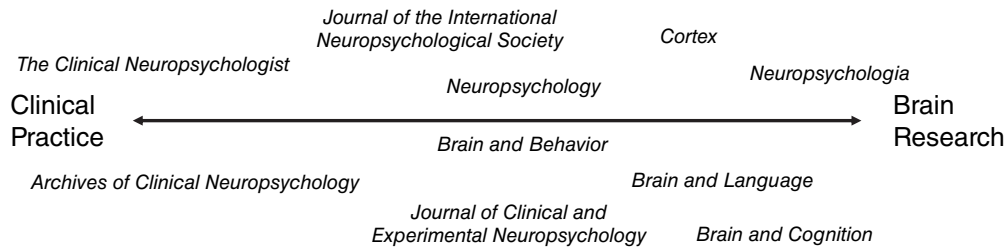


FIGURE 1. Review bodies and professional journals.

societies, researchers, and practitioners in Central America, South America, Europe, Africa, Asia, Australia, and New Zealand (Ponsford, 2017). The field has a lifespan focus, with core assessment principles and brain theories articulated in specialty applications appropriate for different stages of development. From its inception as a psychological subdiscipline, neuropsychology has had a multidisciplinary reach with collaborations with neurologists, psychiatrists, neurosurgeons, pathologists, anatomists, and experimental and physiological psychologists—to name a few historically allied disciplines (for early North American examples of these collaborations, see Geschwind & Kaplan, 1962; Halstead, 1947; Scoville, & Milner, 1957; Tranel, 2009). Neuropsychology continues to be a hub science with fresh collaborations across the disciplines of genetics, imaging, digital technology, and big data. Combined with elegant clinical studies, these collaborations should continue to nurture interventions to prevent and optimize neurobehavioral outcomes for individuals with brain disorders.

EDITORIAL VISION

The aims of this handbook are to describe current knowledge in the field, to guide future research, and to stimulate the development of new neuropsychological methods. The handbook is concerned with the future of neuropsychology as much as it is with the field's current status. The intended audience includes neuropsychologists, behavioral and social scientists, and professionals in allied fields, such as clinical and cognitive neuroscience, neurology, and psychiatry.

One objective of Volume 1 is to aid clinicians and researchers in updating their understanding of disordered brain function. To address this objective, Volume 1 provides chapters on neurobehavioral disorders, such as visual agnosia, and chapters on clinical conditions, such as Alzheimer's disease. Each chapter in Volume 1 provides text boxes that list significant points of accepted science, a summary of questions and controversies, and key references. The text boxes give readers a brief guide to each chapter's content and serve as an interpretive aid to understand the main points of each chapter.

A core aspect of the material covered in Volume 1 is its lifespan focus. Attempts to restrict the discussion of normal and abnormal neurobehavioral functioning to particular age bins ignore the reality that the development and aging of neurobehavioral functions and the risk and progression of neurobehavioral disorders are dynamic and unfold over time. The chapters describe the importance of considering age and developmental status both across time and within the context of individual and environmental risks, resources, and reserves. Some chapters especially focus on the need for neuropsychologists to monitor early or accelerated aging. Other chapters describe the transition of care from youth to young adults—an important topic receiving more attention in health care systems due to improved pediatric long-term survival rates. To facilitate independent functioning as youth with chronic conditions mature into adulthood, the increased demands of managing chronic conditions in adulthood necessitate preparation, starting in youth. The lifespan approach not only consolidates knowledge that might be fractionated when focusing discussion on narrow age bins, it also stimulates questions, such as “How do specific reading disorders detected in childhood influence the vocational and social adaption of adults?” and “What health factors in middle-aged adults increase the risk of Alzheimer’s disease?”

The general goal of Volume 2 is to provide knowledge to guide research on the questions raised in Volume 1 and to stimulate innovative assessment and intervention methods. With its focus on new knowledge and innovation, Volume 2 continues the handbook’s emphasis on the future of neuropsychology.

Chapter authors represent a broad range of expertise ranging from the effects of brain disease on domains of neuropsychological functioning to advanced statistical methods. Chapter authors include members of editorial boards of neuropsychological journals, presidents and members of governing boards of neuropsychological societies, principal investigators on federally funded grants, and career awardees from the U.S. Department of Veterans Affairs (to name a few areas of accomplishment). Authors of all chapters have published widely on the topics they discuss. Although a senior author contributed to each chapter, we also encouraged contributions from more junior neuropsychologists in keeping with the future orientation of the handbook.

HANDBOOK CONTENT

Volume 1

After a chapter summarizing the foundational history and future prospects of the field of clinical neuropsychology, Volume 1 begins with Part I, Neurobehavioral Disorders. These chapters include discussions of disordered language (word finding, semantics, and pragmatic discourse), academic disabilities (mathematics and reading), impaired perception (body representation and higher order visual disorders), and disordered skilled movement, executive function, and memory. The chapters variously discuss disorders related to atypical development, focal lesions, and degenerative diseases. Authors typically describe brain systems that form the substrate of healthy functioning of the behavioral domain discussed. Whereas some models of brain systems are based on the syndrome analysis of clinical patients, others are based on cognitive theory. All models discussed in these chapters have some network characteristics. Some models postulate linked brain modules or hubs associated with a specific functional process that can be selectively damaged or preserved. Other chapters postulate functional processes, such as retrieval of lexical information, that arise from connected activation patterns of representational features. All chapters in the

neurobehavioral disorders section of Volume 1 include questions for future research (for examples, see Table 1).

Part II of Volume 1, Clinical Conditions, includes discussions of acquired brain diseases; psychological disorders; leukemia and sickle cell disease; infectious disorders; degenerative diseases; substance use and abuse; eating, sleep, and circadian rhythm disorders; and environmental neurotoxicity. Topics discussed in chapters on clinical conditions include epidemiology of clinical disorders; diagnostic criteria, subtypes, comorbidity, and genetic associations; neuropsychological assessment and implications of assessment findings for intervention; pathological mechanisms causing the condition; and descriptions of disordered brain systems. Each of these chapters also includes questions for future research (see Table 2).

To keep the handbook a manageable length, we had to make some hard decisions about what to exclude. One might have wished for separate chapters on polydrug abuse and chapters on specific mood and anxiety disorders. Because authors who discussed drug use and abuse typically discussed issues related to comorbid drug use, we decided not to include a separate chapter on polydrug abuse. Similarly, the chapters on mood and anxiety disorders included in the handbook presented findings relevant to a broad range of mood and anxiety conditions. We included only one chapter discussing a metabolic disorder, phenylketonuria. Compared with other errors of metabolism, phenylketonuria has been more thoroughly studied with cognitive and neuropsychological tests. Its disorder of metabolism is well understood, and a ready intervention is available. The chapter on phenylketonuria, therefore, can serve as a resource for studies of other disorders caused by metabolic errors. We also did not include a specific chapter on the neuropsychological effects of diabetes.

TABLE 1

Sample Questions Contained in Volume 1: Neurobehavioral Disorders

| Chapter number and title | Question for future research |
|--|--|
| 2. Word Finding and Lexical–Semantic Disorders | What are the relationships between picture-naming performance and discourse word finding in children with word-finding disorders? |
| 3. Discourse and Communicative Pragmatics | How does variability in executive function in health and disease affect the comprehension of figurative language such as metaphor, jokes, and irony? |
| 4. The Neuropsychology of Mathematical Cognition | Has the role of the right hemisphere in mathematical cognition been clarified? |
| 5. Specific Reading Disabilities | How do we translate the science of reading into educational practice? |
| 6. Body Representation Disorders | Is the paucity of cases of selective clinical body representation deficits in childhood due to the lack of a systematic evaluation or, albeit partially, to the development of body representation per se? |
| 7. Higher Order Visual Disorders | To what degree is prosopagnosia a specific form or subtype of associative agnosia? |
| 8. Syndromes of Limb Apraxia | What are the incidence rates and neural correlates of anosognosia in limb apraxia? |
| 9. Disorders of Executive Functioning | Can assessment of discrete elemental processes of executive functioning lead to a better prediction of functioning in daily life? |
| 10. Memory Disorders | To what extent do lesions of distinct nodes within the extended hippocampal network have common or distinct functional consequences? |

TABLE 2

Sample Questions Contained in Volume 1: Clinical Conditions

| Chapter number and title | Question for future research |
|---|--|
| 11. Spina Bifida and Other Neural Tube Defects | How does the prevention and treatment of spina bifida myelomeningocele through medical (fetal surgery, shunting, pharmacological) and behavioral (academic, neurobehavioral) interventions affect long-term neuropsychological outcomes and behavioral adaptation? |
| 12. Very Preterm Birth | Can we identify primary cognitive deficits as targets for intervention? |
| 13. Cerebral Palsy | What are the relative contributions of multivariate predictors (e.g., preterm birth, neuropathology, epilepsy, cerebral palsy subtype) to neuropsychological outcomes? |
| 14. Pediatric Brain Tumors | How can tumor genetics and survivor genetics be leveraged to inform precision medicine to provide individualized adapted treatments that optimize outcomes? |
| 15. Neuropsychological Outcomes in Phenylketonuria | Which cognitive functions will be most affected by abandoning a strict diet? |
| 16. Neuropsychology of Attention-Deficit/Hyperactivity Disorder | Could integration of neuroimaging methods improve the sensitivity of neuropsychological measures? |
| 17. Epilepsy and Neuropsychology | What are the impacts of single and combined somatic (e.g., metabolic, cardiovascular, immunological), social (e.g., economic adversity), and psychiatric comorbidities on cognition and cognitive trajectories in epilepsy? |
| 18. Traumatic Brain Injury | What 21st-century neuropsychological tests and clinical measures are most sensitive and appropriate to the heterogeneous nature of traumatic brain injury? |
| 19. Leukemia and Sickle Cell Disease | What do individual trajectories of cognitive functioning in sickle cell disease look like, and what biological precursors, particularly in the absence of stroke, lead to changes in functioning that require more aggressive therapies? |
| 20. Vascular Disease Including Vascular Dementia | Are there early neuropsychological markers of subtle cognitive decline in patients destined to develop vascular contributions to cognitive impairment and dementia? |
| 21. Infectious Disorders | Does human immunodeficiency virus set into motion accelerated central nervous system aging? |
| 22. Frontotemporal Dementia | Would better characterization of the neuropsychological profiles associated with various protein pathologies and genetic mutations improve differential diagnosis? |
| 23. Alzheimer's Disease | Will continued research identify sensitive objective neuropsychological measures that capture the earliest cognitive changes associated with Alzheimer's disease pathology? |
| 24. Parkinson's Disease and Parkinsonism | What cognitive mechanisms underlie working and episodic memory deficits in Parkinson's disease? |
| 25. Huntington's Disease Across the Lifespan | What clinical trial-ready measures are needed to validate the clinical significance of changes of cognitive and motor function in drug trials of Huntington's disease? |
| 26. Multiple Sclerosis | Under what circumstances is cerebral functional reorganization adaptive or maladaptive? |
| 27. Alcohol Drinking and Alcohol Use Disorder Across the Ages | Does functional improvement represent recovery or compensation? |

(continues)

TABLE 2

Sample Questions Contained in Volume 1: Clinical Conditions (*Continued*)

| Chapter number and title | Question for future research |
|--|---|
| 28. Neurocognitive Correlates of Psychostimulant Use | What are the relative contributions of trait and state influences on neuropsychological function in people who frequently use psychostimulants? |
| 29. Cannabis and Neuropsychology | What is the impact of cannabis use on neuropsychological functioning among older adults and among clinical populations? |
| 30. Prenatal Exposure to Opioids | How are type of opioid, sex, and age related to outcomes after prenatal opioid exposure? |
| 31. Environmental Toxicities, Including Lead | How do gene–environment interactions predispose some individuals to neurotoxic effects? |
| 32. Sleep and Circadian Rhythm Disorders | Does treatment of sleep and circadian rhythm sleep–wake disorders slow cognitive decline and/or delay the onset of dementia and other neurodegenerative disorders? |
| 33. Autism Spectrum Disorder | How can we best characterize the core and associated symptoms of autism spectrum disorder in order to advance our understanding of its etiology, neuropsychological profile, and prognosis? |
| 34. Schizophrenia | How can models of neural dysconnectivity shed light on the genetic underpinnings of cognition in schizophrenia? |
| 35. The Neuropsychology of Mood Disorders | How will novel technologies (e.g., smartphone-based ecological momentary assessments) allow us to understand the temporal interplay of cognitive performance in relation to mood states and design better ways to improve real-world functioning? |
| 36. The Neuropsychology of Anxiety | Can computational modeling help to disentangle how the brain processes the complex interplay of different factors (e.g., approach vs. avoidance motivations) contributing to anxiety? |
| 37. Eating Disorders | Can the identification of dimensional constructs underlying eating-disorder symptoms and their neural correlates improve our mechanistic understanding and classification of eating disorders? |

Rather, diabetes is discussed as one of the medical diseases that contribute to the risk of vascular and degenerative disorders. Finally, we did not include a chapter on forensic neuropsychology. Given that forensic neuropsychologists must address issues related to the law, we believe chapters on this specialty would be best included in handbooks on forensic psychology, such as APA's *Handbook of Forensic Neuropsychology* (Bush et al., 2017), which address the many special challenges neuropsychologists face when working within the legal system.

Volume 2

Part I of Volume 2, Neuroscience, begins with chapters on neurobehavioral functioning. The initial neuroscience chapters are general and discuss brain organization, brain development, and genetics of neurocognition. The chapter on brain organization presents research showing that the brain is composed of multiscale, hierarchically organized, and topologically complex networks. Graph theory methods are discussed to define network hubs, links, and internetwork communication, which were only intuitively described in Volume 1.

The chapter on brain development includes topics ranging from the molecular and cellular mechanisms underlying typical brain development to descriptions of distributed brain systems. A special feature of the brain development chapter is the elegant integration of neuroimaging data with the cellular information found in more traditional discussions of brain development. The chapter shows that limiting depictions of brain development to cellular changes is not an adequate description of how the brain develops. The chapter on genetics describes the twin method and genome-wide association studies to determine the heritability of neuropsychological constructs and to estimate polygenic scores that assess the likelihood that a person will manifest more or less of a trait.

The neuroscience of more specific cognitive domains includes discussions of learning and memory, skilled movement, visuoperceptual function, language, executive functions, and social neuroscience. The chapter on memory discusses working, episodic, and semantic memory, not just as dissociable memory systems but as integrated sources of memory that support the interpretation of events. The chapter elegantly combines information from the experimental psychology of learning and memory with the results of lesion studies. The chapter on skilled movement provides a detailed brain-systems description of motor control. The chapter on the neuroscience of visual-object recognition nicely complements the skilled-movement chapter, as it focuses on the neural organization of small graspable and manipulatable objects as an approach to understanding how visual recognition is organized. The author of the chapter on the neuroscience of executive functioning argues that the construct of executive function should encompass abilities engaged in adaptive behavior in daily life. The chapter describes 12 elemental executive functions that form four executive function domains, the brain systems forming the neural substrate of each domain, and their associated clinical syndromes. The social neuroscience chapter describes the use of modern structural and functional neuroimaging methods to investigate brain networks that underlie social cognition. The authors also discuss the wide range of stimuli and task demands researchers have used to investigate the neural substrate of social cognition.

Part II, *Assessment: Emerging Methods*, focuses on nontraditional methods of neuropsychological assessment. Because first-rate texts are available that discuss assessment methods neuropsychologists historically have used, our focus is on emerging assessment approaches that might complement current methods. The initial chapter in this section presents a framework to guide neuropsychological assessment of people from diverse cultural, racial/ethnic, linguistic, and educational backgrounds. Topics discussed range from a history of cultural neuropsychology to descriptions of advanced psychometric techniques to identify differential item function and measurement variability across diverse groups. The chapter also provides advice for the assessment of individuals who do not fit into well-studied racial, cultural, or linguistic groups. Just as standard neuropsychological assessment of neurocognitive function is not always appropriate for all people, standard neurocognitive assessment is not appropriate to assess all forms of behavior, such as social cognition, altered by brain disease. The chapter on evaluating social cognition presents an extensive discussion of tests useful to assess social cognition across the age spectrum. Both strengths and weaknesses of these tests are presented, including comments on reliability, validity, and adequacy of norms.

A particular assessment focus of this handbook is the use of digital technologies that may move the field beyond direct face-to-face, paper-and-pencil assessment. These chapters include discussions of automated neuropsychological testing, wearable sensors and digital technology, assessment of daily function, and teleneuropsychology. The teleneuropsychology

chapter is especially relevant for neuropsychological research and practice transformed by the COVID-19 pandemic (transformations that are likely to endure). Although computer-assisted testing makes teleneuropsychology practical, concerns are emerging about the use of computerized testing. Both the chapter on teleneuropsychology and the chapter on automated neuropsychological testing describe these concerns, which include issues related to end-user qualifications, validity threats due to variability of testing environments, and concerns about safety, security, and privacy of data transmitted and stored across dispersed digital networks. Authors of the chapter on wearable sensors and digital technologies discuss not only these technologies but also digital linguistics (i.e., the use of machine learning to analyze voice, speech, and text) that promises to extend the reach of neuropsychological assessment to behavior emitted during daily activities. The chapter on assessment of daily functioning continues the discussion of innovative technologies, including virtual reality, to assess real-world functioning.

We hope readers will find the handbook's assessment chapters thought provoking. These chapters are intended to stimulate ideas about how to create reliable and valid assessment methods that extend neuropsychological assessment beyond the clinic.

Part III, Interventions, describes techniques intended to be useful across a variety of disorders or conditions. Rather than focus narrowly on a single disorder, the chapters emphasize rehabilitative principles that could be applied to many specific interventions. This approach may facilitate the creation of general theories of rehabilitation and may suggest new treatments for neurobehavioral disorders where treatment gaps exist.

Two rehabilitation chapters discuss compensatory rehabilitation methods and the integration of compensatory with restorative approaches. The chapter on compensatory methods describes empirically validated techniques to assess daily performance and methods to aid patients to compensate for their deficits, including digital assistive technologies and telerehabilitation. The chapter on restorative interventions provides detailed examples to support the view that restorative techniques need to be combined with compensatory methods to provide an integrated brain-rehabilitation approach.

Other chapters on rehabilitation discuss narrower topics. A chapter on pediatric rehabilitation describes the need for rehabilitative and habilitative interventions for acquired brain injury in children to recognize the interplay among neurological disease, social and environmental factors, and neural development. Interventions to manage acquired brain injury in children need not only to aid the recovery of lost functions but also to stimulate the acquisition of new skills. The chapter on the rehabilitation of social functioning presents a model that links neurogenic to psychogenic disorders that underlie psychosocial dysfunction associated with acquired brain disease. The model can be used to guide treatments to target core dysfunctional psychosocial processes. The chapter with the narrowest focus discusses the treatment of aphasia. However, aphasia treatment has had such a long and productive history that the many lessons learned can inform interventions of other neurocognitive disorders.

Three additional chapters describe technology-driven approaches to brain rehabilitation, including computer applications (i.e., apps), virtual reality, and neuromodulation. The use of computer apps and virtual reality to augment current rehabilitation methods aims to provide a stronger link between clinic-based intervention and real-world functioning. Neuromodulation, which involves several techniques to directly stimulate neural activity, aims to restore neural functioning. Empirical tests of these interventions continue. Another chapter evaluates the empirical evidence for the view that regular physical activity and an

evidence-based diet may improve some measures of cognitive capacity and reduce the risk of some neurobehavioral syndromes.

The final chapter discusses implementation science, which seeks to maximize the adoption and use of evidence-based interventions. A core finding of implementation science is that empirically based interventions are not always readily adopted by clinical practitioners or the general public. To demonstrate issues that might reduce the adoption of an effective intervention, the chapter describes challenges to the use of masks in order to reduce the transmission of COVID-19. The chapter authors also provide an extensive comparison of aspects of research design used to establish a treatment's efficacy, effectiveness, and implementation. In our experience, few neuropsychologists are familiar with implementation research. We believe that adding the principles of implementation design to neuropsychological treatment studies will increase their novelty and utility.

Part IV of Volume 2, *Neuroimaging Methods: Tutorial Presentations*, includes discussions of a broad range of structural and functional imaging methods. The chapter on structural imaging describes pulse sequences used in magnetic resonance imaging (MRI) to measure cortical thickness and area, gyrification, and shape of gray matter structures, whereas the chapter on diffusion imaging describes MRI methods to visualize white matter connections in the brain using diffusion scans, diffusion tensor images, and tractography maps and MRI methods to measure white matter integrity. The authors emphasize that structural MRI not only provides valuable information about brain structure but forms the backbone of multimodal imaging. The chapter on functional MRI describes the use of blood oxygen level-dependent (BOLD) signals to image brain activity and then provides a critique of the BOLD method. As an alternative to typical BOLD MRI, the authors describe physiological MRI, which combines arterial spin labeling to measure cerebral blood flow with BOLD signals in order to obtain quantitative physiological measurements of brain function. Complementary chapters on electroencephalography (EEG) and magnetoencephalography (MEG) describe methods to assess changes in neuronal activity at the millisecond time scale. The EEG chapter primarily focuses on the use of EEG and evoked potentials to evaluate brain function of children. The MEG chapter provides detailed descriptions of the various measurements used in MEG studies.

Positron emission tomography (PET) uses radioligands to visualize physiological activity and molecular processes in body organs. The chapter on PET imaging describes the biophysics of the technique in sufficient detail to allow readers to thoroughly understand the method. The authors then describe research and clinical applications that range from fluorodeoxyglucose PET to images of brain amyloid plaques, tau protein, microglial activation, and the signaling of specific neurotransmitters. The chapter ends with a discussion of future applications of this exciting molecular imaging method.

From its inception, neuropsychology has utilized state-of-the-art statistical methods to compare groups, standardize tests, predict clinical phenomena, and test neuropsychological theories, among other uses. Throughout much of the field's history, neuropsychologists typically used descriptive or inferential statistics to analyze directly observed variables, such as test scores and dependent measures obtained from experiments (see Halstead & Settlage, 1943; Weisenberg & McBride, 1935, for some early examples). This emphasis on the analysis of manifest variables was supported by the philosophy of operational definitions of unobserved constructs and by true score theory. In a dramatic shift of statistical methodology, all techniques described in Part V of Volume 2, *Statistical and Probabilistic Models for Neuropsychologists*, involve latent variables, defined as unobserved random variables (Skrondal & Rabe-Hesketh, 2004). Adding latent variables to the analysis of

observable data facilitates the use of theoretical constructs to aid the interpretation of neuropsychological responses. The shift toward including latent variables in data analysis reconciles neuropsychology with the general trend in psychology to draw on cognitive and information-processing theories to explain behavioral data (Lachman et al., 1979). The chapters in this section discuss the strengths and weaknesses of each statistical method and also describe applications and software that might be used to perform analyses. A goal of each chapter is to provide readers with enough practical guidance to stimulate the use of the method discussed when investigating research questions raised in Volume 1.

The chapter on computational models of cognition and behavior describes the use of probability models with parameters representing psychological states, processes, and traits in order to aid the interpretation of behavioral data. Examples are presented where computational models uncover relationships not apparent in the analysis of total scores. The chapter also discusses the use of multiparametric computational models to address the challenges of establishing the construct validity of test scores when tests assess multiple psychological domains, as they do in neuropsychological work.

The chapter on psychometric theory provides a brief history of classical test theory, then describes modern approaches to psychometric theory, including item response theory, generalizability theory, and cognitive psychometrics. The section on cognitive psychometrics presents a novel integration of item response theory with a computational model of recognition memory, showing the close link between item response theory and computational modeling.

Whereas computational models and item response theory describe approaches to modeling unobserved constructs for single tasks, structural equation modeling (SEM) offers an approach to modeling unobserved constructs based on data from multiple tests or tasks. SEM aims to estimate the direction and size of causal effects of quantitative data in cross-sectional and longitudinal studies. Although software to perform SEM is commonly available, standards to judge the quality of SEM analyses lags behind the development of software. To address the issue of standards, the chapter on SEM provides a list of guidelines for the use of SEM described in the APA's revised Journal Article Reporting Standards for Quantitative Studies (JARS-Quant; Appelbaum et al., 2018). The chapter then includes a detailed discussion of issues that especially affect the quality of SEM analyses in neuropsychological research. Interestingly, two of these issues are the excessive reliance on significance testing and the modest training in psychometric theory graduate students in psychology typically receive, at least in North America.

The chapter on multilevel modeling (MLM) describes approaches to analyzing phenomena defined at two or more levels of analysis, such as groups and individuals, where the observed data represent an entanglement of effects at different levels. In traditional statistical analyses, within-group heterogeneity is accounted for by adjusting response variables for covariates and, if successful, increasing the power of group-level tests. But this approach to minimizing within-group variation is usually only a partial adjustment because the investigator might know only some of the relevant covariates or might not have data on the covariates known. Multilevel analysis models the unobserved impact of heterogeneity by including random intercepts, which account for unobserved heterogeneity in the level of the response, and random coefficients, which represent the unobserved heterogeneity associated with the effects of the explanatory variables on the response (Skrondal & Rabe-Hesketh, 2004). To provide practical guidance, the chapter shows how to build multilevel models and offers examples from the neuropsychological literature about MLM's application to cross-sectional and longitudinal designs.

Machine learning uses algorithms to learn a feature vector from a data set in order to predict the classification of discrete values or to predict continuous values in a regression application. The handbook's chapter on machine learning presents a technical discussion of machine-learning models as applied to both multimodal brain imaging and imaging-genetic association studies. Although the reader will find details of the statistical models underlying each analysis, software to conveniently fit these models is not yet generally available.

THEMES

Neuropsychology distinguishes itself from other neuroscience disciplines by being a psychological science. Among the behavioral neuroscience disciplines, neuropsychologists receive the most thorough training in psychological theory and data. Moreover, we are the field most concerned with the psychometric properties of behavioral measures. Modern neuropsychologists, however, operate in an environment of dizzying advances in biological knowledge that near daily alter what we know about the CNS and its disorders. As the chapters in Volume 1 show, today's neuropsychologists must acquire a deep knowledge of the neurobiology of neurologic, neuropsychiatric, and neuromedical disorders and, for some conditions, a working familiarity with genetics to complement the knowledge of neuroanatomy that many neuropsychologists have received in their training. An implicit theme of the handbook is the need for neuropsychologists to continually retrain on the neurobiology of CNS disorders.

Another theme is that technological innovations, including widely used digital devices and wearable sensors, offer opportunities for neuropsychological assessment and rehabilitation to move into real-world settings. The extension of neuropsychological practice and research beyond clinic and laboratory settings is likely to be one of the major growth areas for neuropsychological work in the future. Keeping abreast of technological innovation that could alter how neuropsychological work is done is another challenge for neuropsychologists.

A theme found throughout the handbook is that advances in neuroimaging have added to the body of complex knowledge that neuropsychologists now must master to do clinical or research work. The advent of noninvasive structural imaging has lessened the need for clinical neuropsychologists to aid neurologists and neurosurgeons to localize CNS lesions. However, several factors undermine the claim, which sometimes appears in the literature, that modern imaging has completely abolished the localization mission of neuropsychologists. Neurologists are taught that the interpretation of laboratory tests, such as brain imaging, should be judged in light of the primacy of the clinical findings obtained, in part, from the examination of higher cortical, motor, and sensory function (Victor & Adams, 1981). Diagnosis is most secure when laboratory findings converge with clinical findings. Neuropsychological assessment is well placed to facilitate the convergence of brain imaging findings with clinical findings of CNS dysfunction. Moreover, for some disorders, changes in behavior and cognition antedate imaging changes. Small changes in a critical hub of a brain circuit can produce behavioral impairment prior to observable changes on standard brain imaging. Some imaging findings are false indicators of brain disease reflecting individual differences rather than providing a substrate of a neurobehavioral disorder. Clinical neuropsychological assessment can help determine the clinical significance of these imaging findings. Even after a brain lesion is localized on a brain image, quantitative assessments of its associated symptoms might be needed to monitor disease progression or recovery and to

provide useful information to patients and their families. It remains important for neuropsychological assessment to be predictive of localized brain lesions as well as their respective brain systems.

The development of functional brain imaging has stimulated research into the brain basis of psychological phenomena, although it has had less impact on clinical practice. It is increasingly common that psychology departments have their own MRI devices or share such devices with other departments. As apparent in Volume 1 chapters on neurobehavioral disorders and clinical conditions and in Volume 2 chapters on the neuroscience of various cognitive and social functions, BOLD MRI has become fundamental to the research work of many neuropsychologists. Yet standard BOLD MRI has limitations, which might be overcome with more novel physiological MRI methods.

Neuropsychologists continue to be diagram makers, although adherence to a strict modular organization of brain functions varies among researchers and practitioners. Some of the past challenges to brain diagram-models included their reliance on focal brain lesions to identify network hubs and the absence of *in vivo* methods to identify connections among hubs. Advances in neuroimaging provide exciting tools to identify structural tracts and functional networks *in vivo* among individuals with or without brain disease. The application of graph theory to the study of brain networks provides a mathematical basis for defining hubs, local and remote connections, and interactions among brain networks. Modern network science may offer new perspectives on the old questions of whether brain lesions mostly affect behavior as a function of the location or size of the damage.

Another theme is the emerging use of latent-variable statistical models to analyze neuropsychological data. These methods not only bring neuropsychological data analysis closer to theory construction, they also provide a unified theory of statistics that ranges from psychometric theory to multilevel data analysis and SEM.

A theme that neuropsychology shares with psychology more generally is the need to include more individuals from diverse cultural, racial/ethnic, linguistic, and educational backgrounds in our clinical research. The need is mirrored in the concern that tests and norms often used in clinical practice are not always appropriate for the assessment of individuals whose backgrounds were not adequately represented in normative samples. The field should strengthen its knowledge base and tools to be more representative of varied populations. As a critical first step, the field must identify and address institutional barriers to training neuropsychologists from diverse backgrounds.

The mind-numbing complexity of the information that neuropsychologists must master to practice and conduct research strains the curriculum of current neuropsychological training programs. There is no doubt that different institutions will choose different approaches to training. However, training in psychological science should be central to all neuropsychological training programs. This point would seem to be a truism for a psychology text, but in practice, training and retraining in neuropsychology can be excessively pulled away from psychology and toward neuroscience, neuropathology, and neuroanatomy. With a firm foundation in psychological theory and methods, neuropsychologists will continue to make unique contributions to behavioral neuroscience research and to clinical practice.

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—Gregory G. Brown, Tricia Z. King, Kathleen Y. Haaland, Bruce Crosson

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—Gregory Brown

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—Kathleen Y. Haaland

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—Bruce Crosson

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