Dyslexia and Neuroscience

Dyslexia and Neuroscience
The Geschwind-Galaburda Hypothesis 30 Years Later

edited by

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About the Editors

Albert M. Galaburda, M.D., Emily Fisher Landau Professor of Neurology and Neuroscience, Harvard Medical School/Beth Israel Deaconess Hospital Medical Center, Boston, Massachusetts

Dr. Galaburda is a cognitive neurologist at Beth Israel Deaconess Medical Center (BIDMC) and, since 1995, the Emily Fisher Landau Professor of Neurology (Neuroscience) at Harvard Medical School. In addition, he serves as Director, Office for Diversity, Inclusion, and Career Advancement at BIDMC and as Codirector, Mind, Brain, and Behavior Interfaculty Initiative at Harvard University. Dr. Galaburda is a native of Chile and a graduate of Boston University's Six-Year Liberal Arts-Medicine Program (1971). After medical school, he trained in internal medicine and neurology at Boston City Hospital (now Boston Medical Center). He directed a National Institutes of Health-funded bench laboratory on the fundamental causes of learning disorders, especially language-based learning disabilities, from 1979 to 2015, and he directed the Division of Cognitive Neurology at BIDMC from 1992 to 2015. He has written extensively on cerebral lateralization and dyslexia. He has published more than 230 original articles, reviews, book chapters, and books and has lectured extensively locally, nationally, and abroad on the general field of cognitive neurology. He has also been recognized for his work with several prizes, including the Pattison Prize in Neuroscience, the IPSEN Prize in Neural Plasticity, the American Academy of Neurology Decade of the Brain keynote speaker award, the Behavioral Neurology Society of the American Academy of Neurology Lifetime Achievement Award, the International Dyslexia Association's Samuel T. Orton Award, and others. Since January 2015, Dr. Galaburda devotes half of his time to diversity and inclusion as well as the career advancement of students and physicians underrepresented in medicine.

Nadine Gaab, Ph.D., Associate Professor of Pediatrics at Boston Children's Hospital, Harvard Medical School, Division of Developmental Medicine, Department of Medicine, Laboratories of Cognitive Neuroscience, and Faculty, Harvard Graduate School of Education, Boston, Massachusetts

Dr. Gaab received a doctoral degree in psychology from the University of Zurich in Switzerland and did postdoctoral training at Stanford University and the Massachusetts Institute of Technology. She joined the faculty at Boston Children's Hospital and Harvard Medical School in 2007. Her current research within the Laboratories of Cognitive Neuroscience addresses contemporary challenges of clinical practice and education with neuroscientific methods from infancy to adulthood. Her work primarily focuses on auditory, language, and music processing in the human brain

and its applications for the development of typical and atypical language and literacy skills. The Gaab Lab utilizes structural and functional magnetic resonance imaging as well as behavioral measurement tools and is currently working on various research questions such as 1) Which brain learns to read best under which circumstances? 2) How do environmental factors influence the brain's ability to read? 3) Can neuroscience help improve the early identification of children at risk for dyslexia, and 4) What factors are important for shaping a resilient (reading) brain? The Gaab Lab employs cross-sectional and longitudinal study designs and works closely with more than 20 private and public schools within the greater New England area. Please visit http://www.gaablab.com for more information.

Fumiko Hoeft, M.D., Ph.D., Associate Professor in the Department of Child and Adolescent Psychiatry and Weill Institute for Neurosciences, University of California, San Francisco (UCSF), California

Dr. Hoeft is the Director of the Multi-UC-Campus Science-Based Innovation in Learning Center and UCSF Laboratory for Educational Neuroscience (http://www.brainLENS.org) and a research scientist at Haskins Laboratories. She is a member of the UCSF Dyslexia Center Board, the International Dyslexia Association (IDA) Board, the National Center for Learning Disabilities scientific advisory board, and the Center for Childhood Creativity scientific advisory board. She was the 2014 Geschwind Memorial Lecturer for for the IDA. BrainLENS focuses on how cognitive science can inform educational and clinical practices; more specifically, in understanding the neurobiological causes of dyslexia, early identification and prediction, and the emotional resilience necessary to succeed.

Peggy McCardle, Ph.D., M.P.H., Consultant, Peggy McCardle Consulting and Haskins Laboratories, New Haven, Connecticut

Dr. McCardle is a private consultant, science writer and editor, and affiliated research scientist at Haskins Laboratories. She is former chief of the Child Development and Behavior Branch of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), U.S. National Institutes of Health, where she also directed the research program in language, bilingualism, and biliteracy, and developed various literacy initiatives. She is a linguist, former speech-language pathologist, and classroom teacher and is the recipient of various awards for her work in federal government, including an NICHD Mentor Award. She received the Einstein Award from The Dyslexia Foundation in 2013. Her publications address aspects of public health, developmental psycholinguistics (e.g., language development, bilingualism, reading, learning disabilities), and education (especially reading and educational services for English language learners). She has extensive experience developing and co-editing volumes and thematic journal issues.

About the Contributors

Irene Altarelli, Ph.D., University of Geneva, Switzerland

Dr. Altarelli completed her doctorate in Paris under the supervision of Franck Ramus and Ghislaine Dehaene. She used magnetic resonance imaging in her doctoral work to investigate the neuroanatomical correlates of developmental dyslexia, revealing sex-related differences in the dyslexic population. She has been a postdoctoral fellow in the Brain and Learning Laboratory, Faculté de Psychologie et des Sciences de l'Éducation at the University of Geneva since 2014, thanks to a Marie Curie postdoctoral grant, focusing on interindividual variability in learning abilities from both a cognitive and a neural perspective, under the supervision of Daphne Bavelier.

Emily Barrett, Ph.D., Rutgers University, New Brunswick, New Jersey

Dr. Barrett is an Associate Professor in the Environmental and Occupational Health Sciences Institute at Rutgers University. Her work focuses on the early origins of health and disease, or how exposures early in life shape our subsequent health and developmental trajectories. Much of her research focuses on prenatal exposure to endocrine disruptors, agents that interfere with the normal activity of hormones in the body.

Courtney Bodge, Ph.D., Butler Hospital, Providence, Rhode Island

Dr. Bodge is the Research Coordinator at Butler Hospital. In her doctoral work on sex differences in rodent models of neonatal brain injury, under Holly Fitch, University of Connecticut, she demonstrated differences in both degree of injury and long-term behavioral outcome, suggesting that potential therapeutic targets may vary for males and females. Subsequently at the Women & Infants Hospital and the Alpert Medical School at Brown University, her work focused on the permeability of the blood-brain barrier and neuroprotective strategies. She currently leads multiple clinical research trials at Butler Hospital, including studies of early onset Alzheimer's disease targeting specific gene mutations.

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Dr. Cutting is the Patricia and Rodes Hart Endowed Professor, Peabody College of Education and Human Development, and holds faculty appointments in the Departments of Special Education, Psychology, Radiology, and Pediatrics at Vanderbilt. She is also a senior scientist at Haskins Laboratories (New Haven, CT) and holds an adjunct faculty position at Johns Hopkins School of Medicine, Department of Neurology (Baltimore, MD). Her research focuses on educational neuroscience, particularly the

neurobiological and behavioral underpinnings of reading, oral language, and dyslexia.

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Ms. Scotto di Covella is a doctoral student at the CNRS, in the Department d'Études Cognitives—École Normale Supérieure, Laboratoire de Sciences Cognitives et Psycholinguistique, Pierre and Marie Curie University (Paris), where she is working with Franck Ramus on the neuroanatomical correlates of developmental dyslexia. More precisely, she studies the brain foldings and cortical sulci using magnetic resonance imaging data from different countries.

Geert J. de Vries, Ph.D., Georgia State University, Atlanta

Dr. de Vries is Professor and Director of the Neuroscience Institute at Georgia State University. He is a past president of the Organization for the Study of Sex Differences as well as the Society for Behavioral Neuroendocrinology. Ever since discovering the sexually dimorphic nature of vasopressin innervation of the brain as a graduate student, De Vries has studied the development and function of sex differences in the brain. This culminated in proposing the overarching idea that such differences cause as well as prevent sex differences in physiology and behavior. He currently studies the effects of inflammation and microbiota on the brain.

Heidi M. Feldman, M.D., Ph.D., Stanford University School of Medicine, California

Dr. Feldman is the Ballinger-Swindells Endowed Professor of Developmental-Behavioral Pediatrics at Stanford University School of Medicine and the Director of Developmental-Behavioral Pediatrics Clinical Programs at Stanford Children's Health. As a researcher, she has focused on language and reading outcomes of children born preterm since the late 2000s. Her studies integrate traditional and novel behavioral assessments with advanced neuroimaging techniques. As a clinician, she summarized her approach in a book titled, *Redesigning Health Care for Children with Disabilities.* She argues that strengthening inclusion and functional outcomes should be the priority for health care for all children with disabilities.

R. Holly Fitch, Ph.D., University of Connecticut, Storrs

Dr. Fitch is Professor of Behavioral Neuroscience in the Department of Psychological Sciences, the Institutes for Systems Genomics and Brain and Cognitive Sciences, and Director of the Murine Behavioral Phenotyping Facility. Her research focuses on rodent models of neurodevelopmental disruptions and cognitive disabilities, including genetic risk factors for

cognitive disability, animal models of brain damage typical of premature/term birth insult, and behavior studies of effects of prenatal teratogens. A variety of behavioral and anatomic assessments are employed, with an emphasis on tasks that tap skills foundational to communicative processes in rodents.

Elena L. Grigorenko, Ph.D., University of Houston and Baylor College of Medicine, Texas

Dr. Grigorenko is the Hugh Roy and Lillie Cranz Cullen Distinguished Professor, Department of Psychology, at the University of Houston and Professor, Departments of Pediatrics and Molecular and Human Genetics, at Baylor College of Medicine. Dr. Grigorenko and her laboratory have contributed to numerous studies of neurodevelopmental disorders, including language and reading disorders, conduct disorder, and autism spectrum disorder. Dr. Grigorenko and her colleagues are particularly interested in the etiology and developmental trajectories of these disorders.

Roeland Hancock, Ph.D., University of California, San Francisco

Dr. Hancock is a postdoctoral researcher in the Department of Psychiatry at the University of California, San Francisco, with broad interests in the neurobiology of language. His current research focuses on human auditory processing, the role of neurochemistry in regulating neural oscillations during speech processing, and how these processes may be disrupted in atypical language and literacy development. His other interests include imaging genetics and the use of mobile technology for the early identification of children at risk for dyslexia.

David S. Hong, M.D., Stanford University School of Medicine, California

Dr. Hong is Assistant Professor of Psychiatry at the Stanford University School of Medicine and Associate Director of Clinical Neuroscience in the Division of Interdisciplinary Brain Sciences. His current research examines the role of sex-specific factors on cognitive development, utilizing multimodal neuroimaging and genomic methods. His recent work has focused on neurodevelopmental trajectories in youth with sex chromosome aneuploidies and disorders of sexual development. Hong also directs clinical activities within the Division of Interdisciplinary Brain Sciences to advance the treatment and diagnosis of children with a broad range of neurodevelopmental disorders.

Katarzyna Jednoróg, Ph.D., Polish Academy of Sciences, Warsaw, Poland

Dr. Jednoróg is Adjunct Professor, Laboratory of Psychophysiology, Nencki Institute of Experimental Biology, at the Polish Academy of Sciences, where she teaches and conducts research. Her current research

focuses on structural and functional neural correlates of developmental dyslexia and its early predictors across different orthographies. She is also involved in a longitudinal project on modality general and modality specific neuronal effects of second language learning.

Sergey A. Kornilov, **Ph.D.,** University of Houston, Texas

Dr. Kornilov is the Duncan Scholar in Molecular and Human Genetics, Baylor College of Medicine, and Postdoctoral Fellow at the University of Houston. His work focuses on the neurobiological underpinnings of cognitive development, working with various populations (typically developing children and undergraduates, special and clinical populations) using a variety of approaches (from psychometric to molecular genetic). He received the Society for Research on Child Development Outstanding Doctoral Dissertation in Developmental Science Award in 2014 and the Isabelle Liberman Award in 2013 for his work on molecular and neurophysiological bases of developmental language disorders.

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Dr. Landi is an Assistant Professor of Psychological Sciences at the University of Connecticut and the Director of EEG Research at Haskins Laboratories. Dr. Landi's research seeks to better understand typical and atypical reading and language development through the use of multiple cognitive neuroscience methodologies (MRI, EEG) and neurogenetic analyses. Through this work her lab hopes to identify neurobiological and environmental mechanisms that contribute to individual differences in reading and language skill and to the complex etiology of disorders such as dyslexia, specific comprehension deficit and specific language impairment.

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Dr. Luders is an Associate Professor of Psychiatry at the University of California, Los Angeles (UCLA). Trained in neuroscience and neuropsychology, she received her Ph.D. from the University of Zurich, Switzerland. Her research is focused on understanding the human brain, in health and disease, using high-resolution magnetic resonance imaging and state-of-the-art brain mapping techniques. Central themes of her studies are the brain's sexual dimorphism, brain development and aging, as well as structure-function relationships with emphasis on handedness, intelligence, and mindfulness.

Margaret M. McCarthy, Ph.D., University of Maryland School of Medicine, Baltimore

Dr. McCarthy is Professor and Chair, Department of Pharmacology, Program in Neuroscience, at the University of Maryland School of Medicine. She received her doctorate from the Institute of Animal Behavior at Rutgers University and received postdoctoral training at Rockefeller University and the National Institutes of Health as a National Research Council Fellow. McCarthy has been with the faculty of the University of Maryland School of Medicine since 1993 and became the Chair of the Department of Pharmacology in 2011. She has also served as Director of Graduate Education for the Program in Neuroscience and as Associate Dean for graduate education.

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Dr. Nguyen completed a master's degree and residency in psychiatry at McGill University as well as a postdoctoral fellowship at the National Institutes of Health in the Section on Behavioral Endocrinology and the Section on Integrative Neuroimaging. She currently holds faculty positions at McGill University, jointly appointed in the departments of psychiatry and obstetrics-gynecology, and is the Director of the Reproductive Psychiatry Program at the McGill University Health Center. Her research focuses on investigating the central nervous system effects of steroid hormones, particularly androgens, during development as well as during reproductive stages.

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Dr. Ocklenburg is a lecturer in the Institute for Cognitive Neuroscience, Department of Biopsychology, with the Faculty of Psychology at Ruhr-University, Bochum, Germany. His research is in biopsychology, with a focus on the ontogenesis of hemispheric asymmetries. He uses molecular genetics and neuroimaging techniques to uncover how handedness and language lateralization originate.

Tom O'Connor, Ph.D., University of Rochester Medical Center, New York

Dr. O'Connor is Professor in the Department of Psychiatry and Director of the Wynne Center for Family Research at the University of Rochester Medical Center. His clinical research focuses on the role that early (including prenatal) exposures and experiences play in shaping psychological, physiological, and immunological processes underlying behavioral and somatic health.

Ola Ozernov-Palchik, M.S., Tufts University, Medford, Massachusetts

Ms. Ozernov-Palchik is a doctoral candidate at the Center for Reading and Language Research in the Tufts University's interdisciplinary cognitive science program under the mentorship of Maryanne Wolf. In her research, she is interested in understanding the cognitive and neural mechanisms of deficit and compensation in developmental dyslexia. She also conducts research with Nadine Gaab at Boston Children's Hospital and John Gabrieli at the Massachusetts Institute of Technology using neuroimaging, psychoeducational, and cognitive methods as part of several longitudinal studies of children at risk for dyslexia. Ozernov-Palchik is investigating the association between musical rhythm processing and early literacy development with Aniruddh Patel at Tufts University.

Silvia Paracchini, Ph.D., University of St Andrews, Scotland

Dr. Paracchini holds a Royal Society University Research Fellowship at the University of St. Andrews where she leads the Neurogenetics Group and the Bioinformatics Unit in the School of Medicine. She is a human geneticist whose research is aimed at understanding the biological component of dyslexia and combines genetic mapping (using genome-wide association studies and next generation sequencing) with functional characterization of candidate genes in biological models that include neuronal stem cells and zebrafish. More recently she has become interested in the genetics of handedness and how shared biology might influence both handedness and dyslexia. Dr. Paracchini is a member of the Royal Society of Edinburgh Young Academy of Scotland.

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Dr. Peterburs studied psychology at Ruhr-University in Bochum, Germany, and received her doctorate in psychology in early 2012. She currently is a Postdoctoral Fellow at the Institute of Medical Psychology and Systems Neuroscience at the University of Münster, and she divides her time between Germany and the United States, where she is a Research Associate in the Cognitive Neuroscience Division at the Johns Hopkins School of Medicine. Her research focuses on modulators and neural correlates of performance monitoring in humans and nonmotor functions of the cerebellum.

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Dr. Ramus is Research Director and senior research scientist at CNRS and serves as Adjunct Professor at the École Normale Supérieure. He works at the Laboratoire de Sciences Cognitives et Psycholinguistique, Department of Cognitive Studies, École Normale Supérieure in Paris, where he heads the cognitive development and pathology team. His research bears

on the development of language and social cognition in children, related disorders (developmental dyslexia, specific language impairment, and autism spectrum disorder), their cognitive and neural bases, and their genetic and environmental determinants.

John L.R. Rubenstein, M.D., Ph.D., University of California, San Francisco

Dr. Rubenstein is the Nina Ireland Distinguished Professor of Child Psychiatry at the Nina Ireland Laboratory of Developmental Neurobiology and Professor of Psychiatry at the University of California San Francisco Weill Institute for Neurosciences. He was recently awarded the Ruane Prize for Outstanding Achievement in Child and Adolescent Research from the Brain and Behavior Research Foundation. His research focuses on the regulatory genes that orchestrate development of the cerebral cortex and basal ganglia. These genes serve as entry points to elucidate human neuropsychiatric disorders.

Ana Vallejo Sefair, University of Rochester, New York

Ms. Vallejo Sefair is a graduate student in clinical psychology at the University of Rochester. Her work focuses on the early origins of behavioral and somatic health in children and adolescents.

Amanda Smith, Ph.D., Alkermes, Inc., Watertown, MA

Amanda Smith is a medical writer at Alkermes, Inc., a pharmaceutical company focused on developing treatments for central nervous system diseases. Prior to beginning a career in pharmaceuticals, she conducted her doctoral research at the University of Connecticut within the Department of Psychological Sciences, Behavioral Neuroscience Division. Working under the supervision of Dr. Holly Fitch, she designed a compilation of studies to assess the behavioral consequences following induced hypoxic ischemic brain injury in a rodent model. Her research was specifically focused on sex differences following injury and possible strategies to prevent or ameliorate associated long-term behavioral deficits.

Caitlin Szalkowski, Ph.D., Hilbert College, Hamburg, New York

Dr. Szalkowski is Assistant Professor of Psychology at Hilbert College. She studied neurobehavioral outcomes following genetic disruptions in a rodent model while working under Holly Fitch at the University of Connecticut. Her work demonstrated different patterns in behavioral and anatomical disruption following reduced expression of rodent homologs of candidate dyslexia susceptibility genes *Dyx1c1* and *Kiaa0319,* as well as evidence of sex disparity in reaction to these insults. This suggests possible mechanisms for the observed differences in rates of dyslexia among males and females as well as the varied presentation of specific deficits within the disorder.

David K. Urion, M.D., F.A.A.N., Boston Children's Hospital, Massachusetts

Dr. Urion received his undergraduate degree from Dartmouth College and his medical degree from Stanford University. He trained in internal medicine at the Peter Bent Brigham Hospital, in pediatrics at Boston Children's Hospital, and in child neurology in the Longwood Area Neurology Training Program. He serves as the director of education and residency training programs in child neurology and neurodevelopmental disabilities, as well as the director of behavioral neurology clinics and programs, at Boston Children's Hospital, where he holds the Charles F. Barlow Chair in Neurology. He is the immediate past president of the Professors of Child Neurology.

Xi Yu, Ph.D., Boston Children's Hospital and Harvard Medical School, Massachusetts

Dr. Yu is a postdoctoral fellow in the Laboratories of Cognitive Neuroscience at Boston Children's Hospital. Her research interests lie in the cognitive and neural mechanisms underlying language and reading development in typical and atypical populations. Her work also seeks to identify biomarkers for early diagnosis of dyslexia and compensatory mechanisms in children, which could inform the design of pre-reading treatment for children at risk for dyslexia.

Jingjing Zhao, Ph.D., Shaanxi Normal University and Key Laboratory for Behavior and Cognitive Neuroscience, Xi'an, Shaanxi, China

Dr. Zhao is Professor of Psychology at Shaanxi Normal University in China and a principal investigator affiliated with the Key Laboratory for Behavior and Cognitive Neuroscience of Shaanxi Province. Her current research focuses on children's cognitive and psychiatric disorders. Her laboratory is currently working on various topics but mainly focusing on cognitive, neural, genetic, and environmental determinants of developmental dyslexia, dyscalculia, and psychiatric disabilities in children.

The Dyslexia Foundation and the Extraordinary Brain Series

The Dyslexia Foundation (TDF) was founded by William H. "Will" Baker, in collaboration with notable researchers in dyslexia, in the late 1980s. Funds were provided through the generosity of the Underwood and Baker families to support the establishment of the first Dyslexia Research Laboratory at Beth Israel Hospital, Harvard Medical School, Boston, Massachusetts; the laboratory opened in 1982, with a goal of investigating the neural underpinnings of dyslexia. Baker became the director of research for the Orton Dyslexia Society, and he convened top researchers from cognition, neuroscience, and education in a 1987 meeting at the urging of Dr. Albert Galaburda. That scientific symposium was held in Florence, Italy, under the auspices of the Orton Dyslexia Society, with generous support from Emily Fisher Landau. Ideas were presented and discussed at the symposium, with sufficient time to disagree, identify research challenges, and brainstorm solutions—and the concept of a dyslexia symposium series was born. The National Dyslexia Research Foundation (later renamed TDF) was formed in 1989 to focus more specifically on research while the Orton Dyslexia Society continued its primary focus on treatment and education. The new foundation sponsored the next symposium in Barcelona, Spain, in 1990. The Extraordinary Brain Series was born during this second symposium, which was the first to be held under the foundation's auspices!

This volume celebrates the 15th symposium in the Extraordinary Brain Series. Currently, these symposia result in volumes that reflect the papers presented and the discussion that was spurred by those presentations. The series volumes make the thoughts of scholars across various disciplines accessible to all researchers as they tackle various aspects of the behavior, neurobiology, and genetics of dyslexia and learning to read and write. Following is a listing of TDF symposia and the related volumes to date:

I. June 1987, Florence, Italy. Symposium Director: Albert M. Galaburda.

   Galaburda, A. M. (Ed.). (1989). *From reading to neurons.* Cambridge, MA: Bradford Books/the MIT Press.

II. June 1990, Barcelona, Spain. Symposium Director: Albert M. Galaburda.

   Galaburda, A. M. (Ed.). (1993). *Dyslexia and development: Neurobiological aspects of extra-ordinary brains.* Cambridge, MA: Bradford Books/Harvard University Press.

III. June 1992, Santa Fe, NM. Symposium Director: Paula Tallal.

Chase, C., Rosen, G., & Sherman, G. F. (Eds.). (1996). *Developmental dyslexia: Neural, cognitive, and genetic mechanisms.* Baltimore, MD: York Press.

IV. June 1994, Kauai, HI. Symposium Director: Benita Blachman.

Blachman, B. R. (Ed.). (1997). *Foundations of reading acquisition and dyslexia: Implications for early intervention.* Mahwah, NJ: Lawrence Erlbaum Associates.

V. June 1998, Kona, HI. Symposium Director: Drake Duane.

Duane, D. (Ed.). (1999). *Reading and attention disorders: Neurobiological correlates.* Baltimore, MD: York Press.

VI. June 2000, Crete, Greece. Symposium Director: Maryanne Wolf.

Wolf, M. (Ed.). (2001). *Dyslexia, fluency, and the brain.* Baltimore, MD: York Press.

VII. June 2002, Kona, HI. Symposium Director: Barbara Foorman.

Foorman, B. (Ed.). (2003). *Preventing and remediating reading difficulties: Bringing science to scale.* Baltimore, MD: York Press.

VIII. October 2002, Johannesburg, South Africa. Symposium Director: Frank Wood.

Multilingualism and dyslexia. No publication.

IX. June 2004, Como, Italy. Symposium Director: Glenn Rosen.

Rosen, G. (Ed.). (2006). *The dyslexic brain: New pathways in neuroscience discovery.* Mahwah, NJ: Lawrence Erlbaum Associates.

X. June 2007, Campos do Jordão, Brazil. Symposium Directors: Ken Pugh and Peggy McCardle.

Pugh, K., & McCardle, P. (Eds.). (2009). *How children learn to read: Current issues and new directions in the integration of cognition, neurobiology and genetics of reading and dyslexia research and practice.* New York, NY: Psychology Press, Taylor & Francis Group.

XI. January 2010, Taipei, Taiwan. Symposium Directors: Peggy McCardle, Ovid Tseng, Jun Ren Lee, and Brett Miller.

McCardle, P., Miller, B., Lee, J. R., & Tseng, O. J. L. (Eds.). (2011). *Dyslexia across languages: Orthography and the brain-gene-behavior link.* Baltimore, MD: Paul H. Brookes Publishing Co.

XII. June 2010, Cong, Ireland. Symposium Directors: April Benasich and Holly Fitch.

Benasich, A., & Fitch, H. (Eds.). (2012). *Developmental dyslexia: Early precursors, neurobehavioral markers, and biological substrates.* Baltimore, MD: Paul H. Brookes Publishing Co.

XIII. June 2012, Talinn, Estonia. Symposium Directors: Brett Miller and Laurie Cutting.

Miller, B., Cutting, L. E., & McCardle, P. (Eds.). (2013). *Unraveling reading comprehension: Behavioral, neurobiological and genetic components.* Baltimore, MD: Paul H. Brookes Publishing Co.

XIV. June 2014. Horta, Faial Island, The Azores. Symposium Directors: Carol Connor and Peggy McCardle.

Connor, C. M., & McCardle, P. (Eds.). (2015). *Advances in reading intervention: Research to practice to research.* Baltimore, MD: Paul H. Brookes Publishing Co.

XV. June 2016, Saint Croix, U.S. Virgin Islands. Symposium Directors: Albert Galaburda, Fumiko Hoeft, and Nadine Gaab.

Galaburda, A. M., Gaab, N., Hoeft, F., & McCardle, P. (Eds.). (2017). *Dyslexia and neuroscience: The Geschwind-Galaburda Hypothesis 30 years later.* Baltimore, MD: Paul H. Brookes Publishing Co.

Preface

More than three decades ago, Norman Geschwind and Peter Behan reported an increased prevalence of left-handedness and autoimmune disorders in individuals and families with developmental dyslexia. Following that report, Geschwind collaborated with Albert Galaburda and wrote a three-part paper in the *Archives of Neurology* (1985a, b, c) that discussed developmentally relevant associations among brain development, hormones, immune activity, and brain lateralization, which resulted in human diversity in talents and disabilities. The Dyslexia Foundation hosted a symposium in 2016 that was organized by Galaburda, along with Nadine Gaab and Fumiko Hoeft, to review some of the Geschwind-Galaburda Hypothesis (GGH) claims and predictions and assess the current state of the science regarding them. This volume is based on the presentations and discussions at that symposium.

Because much of the information presented and discussed is at times highly technical, the co-editors of this volume asked the contributing authors to include a summary that includes less technical language at the beginning of each chapter. These summaries are intended to make the volume more accessible to a wider audience because they outline the information that will be presented in each chapter and commentary. In addition, an integrative summary for each of the sections integrates thoughts across each chapter of the section.

The design of the volume itself is also intended to make the material more accessible. In Section I, Galaburda (Chapter 1) introduces the GGH and Urion (Chapter 2) reflects on its impact on clinical practice in child neurology and developmental neuroscience since the mid-1980s, with implications for the future. The following five major sections examine specific areas of scientific investigation responding to and influenced by the GGH, with each chapter making suggestions for future research based on what has been learned since Geschwind and Galaburda's publication of those three seminal papers.

In Section II, four chapters and an integrative summary address brain development, hormonal influences, and immunological issues as interconnected issues or processes. Rubenstein (Chapter 3) examines developmental, genetic, hormonal, and random processes that may play a role in the development of language processing circuits and, thus, may influence or underlie some developmental disorders, including dyslexia. He outlines four specific additional mechanisms regulating brain development that scientists should consider as they explore potential underlying mechanisms of dyslexia. De Vries (Chapter 4) discusses the GGH and sex differences from a whole body perspective and offers new thoughts on the influences of sex differences in the brain, circulating sex hormones during postnatal through adult development, environmental context, and vulnerabilities for functional and behavior disorders. O'Connor, Barrett, and Sefair

(Chapter 5) examine what is known about prenatal maternal distress and its association with a range of neurodevelopmental outcomes in children and discuss these in the context of the GGH, noting a striking confluence with implications for future research. Nguyen (Chapter 6) presents the biological processes of brain development and increasing sex hormone production in middle childhood; she addresses the role of androgens in the pattern of brain maturation and the link with developmental cognitive and behavior changes. The final chapter in this section is the integrative summary by McCarthy. She reflects on the central goal of revealing the origins of brain disorders and pulls together thoughts on developmental impacts, from prenatal through adolescent development, and highlights the plastic and dynamic aspects of brain development, citing the GGH as a framework for such revelation.

Section III's four chapters and an integrative summary focus specifically on sex differences. Ramus, Altarelli, Jednoróg, Zhao, and di Covella (Chapter 7) review their own team's studies on the neuroanatomy of dyslexia, which show differences in boys and girls. The authors assert that the key to understanding dyslexia's neuroanatomical basis lies in brain asymmetry, which differs at least, in part, by sex. Luders (Chapter 8) also examines sex differences in brain anatomy, with a focus on brain size differences, and demonstrates how matching males and females for gross brain size may serve to unscramble whether sex are artefactual or exist independently of size effects. Hong (Chapter 9) focuses on sex differences in learning disorders, offering the model of sex chromosome anomalies such as those found in Turner and Klinefelter syndromes. He calls for future work to further explore the mounting evidence that sex plays a role in learning disorders, including dyslexia. Fitch, Bodge, Szalkowski, and Smith (Chapter 10) present findings on sex differences in atypical cognitive outcomes in animal models that are relevant to language and reading and bring these to bear on the issue of greater prevalence of dyslexia among males. Cutting's integrative summary notes the lack of clarity of the relation between sex and dyslexia diagnosis as we look across neuroimaging, genetics, and animal model research linked to the GGH, and it offers suggestions for future directions that research might take to clarify this picture.

Section IV on laterality contains only two chapters and an integrative summary. Grigorenko (Chapter 11) presents information on genetic concepts—mosaicism, epigenetic, and the endophenotypes—and how using these can help us understand complex human traits such as laterality and its underlying processes by breaking complexity down into component parts. Ocklenburg and Peterburs (Chapter 12) focus on genetic factors underlying handedness and left-hemisphere language dominance; they argue that the assumptions of the GGH offer an opportunity for development of a multifactorial model that could integrate neurogenetic evidence into those core constructs. Paracchini's integrative summary points out that complex processes must be controlled by more than simple genetic models

and embracing advances in genetic sequencing will likely be important in advancing our understanding of laterality.

Reading and dyslexia are specifically addressed with regard to genes and behavior in Section V. Kornilov and Grigorenko (Chapter 13) begin this section with an overview of genetics and reading disability, including genome-wide association studies, studies using neuroimaging phenotypes, and those examining the role of common genetic variants. They argue strongly for the importance of studies that integrate all three in the study of reading disability. Hoeft and Hancock (Chapter 14) describe their work on intergenerational transmission of reading and the brain networks that underlie it. These authors introduce the intergenerational neuroimaging approach to studying the relation of cognitive and neural phenotypes across generations from parent to child; they hope this process will affect early identification and intervention and result in the identification of modifiable intervention targets. Gaab, Yu, and Ozernov-Palchik (Chapter 15) also examine the heritability of dyslexia and early identification and intervention, combining neuroimaging of infants and young children with behavioral research to identify children at risk. Feldman (Chapter 16) examines a different risk factor (i.e., preterm birth) and compares white matter brain differences and their correlations with reading and language skills in children born pre- and full-term. Her findings suggest a loss of hemispheric specialization in the preterm group, and she calls for additional studies to explore the GGH and determine these children's specific reading intervention needs. Landi's integrative summary notes the value of being able to more accurately identify the relative contributions of genes and environment in the atypical development of reading brain regions, but it also notes that the advanced methods that have been discussed come with an increased need for specialized training and with a requirement to communicate to educators and policy makers both the importance and the nuances of the findings these tools enable us to obtain.

These section chapters and integrative summaries explore key elements of the GGH, looking at how far we have come and how many questions have been answered. They also look, however, at how we might build on both the original GGH and the recent work that addresses many of the issues it raised. They suggest how the field might move forward with modern technologies and advanced methods to continue to tease apart the puzzles of the developing brain, learn what underlies differences in brain development, how genes and environment interact with our neurocircuitry and neurochemistry in ways that result in individuals who read well or who have difficulty learning to read, and how best to prevent or remediate those difficulties. The contributing authors have attempted to communicate highly technical information in ways that are accessible to an audience broader than just scientific colleagues, and the editors have attempted to design a book that also facilitates information sharing for a broader audience. The information gained since the mid-1980s and the directions

recommended for the future are important and clearly worth sharing not only with researchers but also with practitioners, parents, and all those interested in dyslexia, its origins, and its prevention and remediation.

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SECTION I

The Geschwind-Galaburda Hypothesis and Dyslexia

CHAPTER 1

The Geschwind-Galaburda Hypothesis

Albert M. Galaburda

SUMMARY

The Geschwind-Galaburda Hypothesis (GGH), which was first published as three consecutive papers (1985a, b, and c), is, despite its name, a theory comprising several testable hypotheses that address associations among brain development and function, sex hormones, immunological health, and brain lateralization. Clinical manifestations of this theory may lead to individuals with special talents or disabilities. The theory was inspired by the report of Geschwind and Behan (1982), indicating a relationship among left-handedness, developmental dyslexia, and immune disorders.

The GGH suggested that testosterone in utero slowed development of the left hemisphere, increasing the risk for left-handedness and language-based learning disorders, as well as superior development of right hemisphere skills, both of which would occur more often in boys. Testosterone also suppressed immune function, leading to an excess of immune-based disorders. An elaboration of the theory posited that the retardation of left-hemisphere development could lead to neuronal migration anomalies, which represented the mechanism underlying the language-based learning disorders. The neuronal migration anomalies were recreated in rodents by using various approaches, including early, timed brain injury and knock-down of dyslexia risk genes, but not simply by the effects of testosterone, although the latter did alter the functional consequences of the developmental anomalies. Additional work in genetically modified mice (Truong et al., 2014; Wang et al., 2011) showed that structural anomalies could, but were not necessary to produce cortical dysfunction. In addition, recent work on the effects of cilia function (Hamada, Meno, Watanabe, & Saijoh, 2002) on organ laterality were suggested to play a role in the anomalous brain lateralization seen in dyslexia, especially as cilia dysfunction is associated with some dyslexia risk genes. The GGH generated a great deal of research, which continues to this date.

INTRODUCTION: THE ORIGINS OF THE GESCHWIND-GALABURDA HYPOTHESIS

This chapter reflects a presentation and subsequent discussions that took place during a conference in June 2016, which was organized and sponsored by The Dyslexia Foundation. Both the presentation and this chapter

rely heavily on the three-part paper published by Geschwind and Galaburda (1985a, b, c).

The GGH is an attempt to relate observations not only about a specific learning disorder (i.e., dyslexia) but also other male-predominant developmental disorders (e.g., stuttering, autism spectrum disorder, Tourette syndrome) to cerebral lateralization for a variety of cognitive tasks, including handedness and hemispheric dominance for language, certain autoimmune disorders, and hormonal and genetic characteristics. The papers specifically stressed male–female differences in the incidence and occurrence of these phenomena and attributed the male sex steroid testosterone, or its metabolites, as a main causative role, rather than the environment or direct genetic influences. The hypothesis states that intrauterine testosterone increases anomalous functional or physiological lateralization (left-handedness, ambidexterity, and right-hemisphere or bilateral language in the brain), anatomical brain asymmetry (affecting the language-relevant planum temporale [PT]), learning disabilities (dyslexia, stuttering, Tourette syndrome, autism spectrum disorder), learning superiority (architects, visual artists), and immunological and other disorders (asthma, thyroid disorders, ulcerative colitis, premature graying of the hair).

The GGH is not really a hypothesis but a theory that is complex enough to generate several testable hypotheses on sex differences, handedness, and hemispheric dominance, specifically regarding the relations and interactions among brain development, hormones, immune activity, and brain lateralization, which resulted in human diversity in talents and disabilities. The work of Peter O. Behan, a neuroimmunologist from Glasgow, Scotland, initially contributed to the GGH; thus, the theory has also been called the Geschwind-Behan-Galaburda Hypothesis. Most important, however, is that the theory is primarily the brainchild of Norman Geschwind (see Figure 1.1; see the dedication in this volume).

The Planum Temporale and Cerebral Asymmetry

Although Geschwind died in 1984, only months before the publication of the GGH, it is likely that kernels of the theory had their origin as early as the mid-1960s, when he and Levitsky (1968) revisited a set of findings by Von Economo and Horn (1930) and Pfeifer (1936). These findings suggested that the PT, the triangle-shaped cortical region lying immediately posterior to the transverse gyrus of Heschl containing the primary auditory cortex, was larger on the left-side.

Geschwind and Levitsky (1968) were stimulated by these anecdotal reports and dissected 100 human brains. They determined that the left planum was larger in 65% of the brains, it was larger on the right in 11%, and it was of equal size on the two sides in the remaining 24%. Geschwind became curious about the fundamental causes of cerebral asymmetry and its

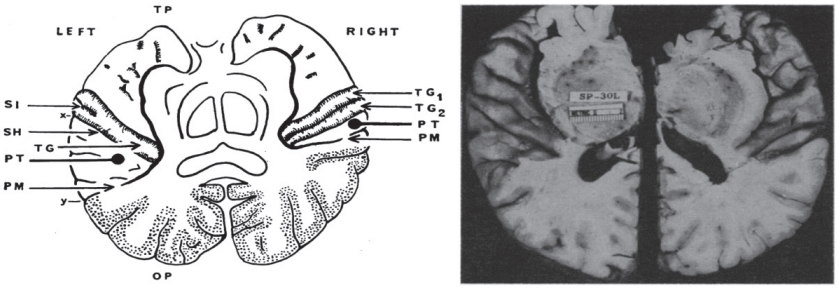

Figure 1.1. Original figure from Geschwind and Levitsky (1968) showing a larger right planum temporale (PT) and a second observation, the more common duplication of Heschl's gyrus or transverse gyrus on the right side. From Geschwind, N., & Levitsky, W. (1968). Human brain: Left-right asymmetries in temporal speech region. *Science, 161*(3837): 186–187; reproduced with permission.

biological associations. In 1976, he encouraged Albert Galaburda, a physician in the last year of neurology residency training, to look deeper for the underlying causes of brain asymmetry. But anatomical brain asymmetry was only part of the investigation of brain functioning. Links between this asymmetry and behaviors, such as handedness and learning, and to other conditions involving the immune system were also of interest.

Left-Handedness, Language-Based Learning Disorders, and Immunological Conditions

Geschwind was a dedicated and keen clinical observer. He used to say that most of his ideas came from listening to and observing his patients. An informal cataloguing of conversations and observations led him to two conclusions.

1. Unusual manifestations of acquired aphasia (an impairment of language comprehension or production usually caused by injury to the left-hemisphere of the brain) and various forms of language-based LDs occurred more frequently in left handers.
2. His left-handed patients seemed to complain of more ailments than his right-handed patients, especially allergic and autoimmune conditions.

These anecdotal observations led to studies with Behan, first of self-reported immunological conditions and then of a hospital record-confirmed assessment of left-handed people arriving at a shop for left-handed objects in London (Geschwind & Behan, 1982). Both indicated more autoimmune conditions and language-based LDs in left handers and their family members.

Sex Differences, Handedness, and Hemispheric Dominance: The Testosterone Hypothesis

Sex differences is the fourth component of the theory. LDs that affected left-hemisphere brain functions (e.g., dyslexia, stuttering, autism

spectrum disorder) were far more common in boys than in girls. In addition, the affected individuals often exhibited superior performance in right-hemisphere functions (e.g., visuospatial abilities). These gender differences could have been the result of X or Y chromosome factors. If the differences were linked to the X chromosome, however, then the male predominance would be very high—much higher than that observed—or if the differences were linked to the Y chromosome, then these disorders would be nonexistent in females. Thus, Geschwind posited that the excess of left-handedness and LDs in males suggested a failure of proper development of left-hemisphere dominance patterns that were testosterone mediated; this was possible because males and females are exposed to intrauterine testosterone, albeit at different concentrations. This was the origin of the testosterone hypothesis of the GGH, and the testosterone hypothesis was at the core of the theory. Summing up, LDs linked to left-hemisphere function are noticeably more prevalent in males, but they also occur in females, which suggests that testosterone exposure in utero mediates the development of proper patterns of left-hemisphere dominance. The fact that male fetuses are exposed to greater concentrations of testosterone may be linked to the greater prevalence of these LDs among males.

ELEMENTS OF THE GESCHWIND-GALABURDA HYPOTHESIS

The GGH represented an attempt to link observations on left-handedness, brain asymmetry, learning differences, immune disorders, and male–female differences. Testosterone effect (a combination of testosterone level, the distribution of testosterone receptors, and the sensitivity and specific activity at these receptors) is the unifying causal factor that occurs during development. In brief, the theory postulated that testosterone acting in utero slowed the development of the left hemisphere of the human cerebrum, which, in turn, led to

- Possible enhancement of right-hemisphere development and more left-handedness (or underdeveloped right-handedness)
- Possible LDs involving left-hemisphere functions
- Possible superior skills in right-hemisphere functions
- Greater prevalence in males
- A disturbance in the development of the immune system by the direct action of testosterone on the thymus gland and other immunological targets that are poorly understood

Related Research: Gross Cerebral Asymmetries

The theory depended heavily on the finding of structural brain asymmetries. Several early observers (Flechsig, 1876; Pfeifer, 1936; Von Economo & Horn, 1930) reported on PT asymmetries as well as others (e.g., asymmetry

of the crossing of the motor tracts in the brain stem on their way to the spinal cord). LeMay (1976) examined human brain endocasts that were 30,000 years old and reported asymmetries in Neanderthals. She also examined cerebral arteriograms of adult humans and found asymmetries in the sylvian point, the spot where the middle cerebral artery exits to the surface of the brain posteriorly (LeMay & Culebras, 1972). The main observations were that the sylvian fissure was longer on the left and the sylvian point was higher on the right side than on the left side. It was shown later that the length asymmetry reflected the longer PT on that side.

It became important to find the cause(s) of these asymmetries. The right shift theory is a genetic explanation proposed by Annett (1964) that suggests the presence of a laterality gene causes the brain to acquire the standard asymmetry, causing the individual to become right handed. The absence of this laterality, or right shift gene, produced an individual who would be randomly right or left handed 50% of the time. Annett even calculated the prevalence of the gene in the population to explain the numbers of right and left handers. Annett could not distinguish between right handers having the gene and right handers arising from random assignment, but no left handers possessed the gene. The GGH, however, predicted that even in the presence of the right shift gene, testosterone in utero could affect the degree of expression of this gene in an epigenetic fashion and impede the full shift to the right-handed pattern, leading to incomplete left-greater-than-right asymmetry, or even asymmetry in the opposite direction, as well as LDs. The tension between the Annett theory and the GGH is that the former did not require any nongenetic factors, whereas the latter introduced a factor in the form of testosterone, which acted as an epigenetic regulator of the gene effect. As of this writing, the Annett theory, which has in practice been replaced or expanded on by the new discoveries on cilia function—which responds to multiple genetic and epigenetic actions (Hamada, Meno, Watanabe, & Saijoh, 2002)—has not included any additional testosterone effect. This said, without hormonal influences (see Chapter 6), neither the Annett theory nor the cilia biology can explain the male predominance that inspired the GGH.

Related Research: Architectonic Cerebral Asymmetries

Galaburda and colleagues (Galaburda & Sanides, 1980; Galaburda, Sanides, & Geschwind, 1978) published a series of papers attempting to find the fundamental underpinnings of brain asymmetries. First, they found that asymmetries in gross anatomy reflect asymmetries in the volume (surface area x cortical thickness) of architectonic areas (cf. Brodmann areas), and asymmetries in the PT are specifically accounted for by asymmetries in the auditory temporoparietal association area on the posterior upper surface of the temporal lobe. Other architectonic areas comprising the perisylvian language zones (e.g., Brodmann area 44 and 39) also tended to favor

the left side (Eidelberg & Galaburda, 1984; Galaburda, 1980; Galaburda & Geschwind, 1980). The GGH attempted to provide explanations for these language-related asymmetries and for the cases in which the asymmetries develop anomalously, and here are some of the findings of the architectonic work that followed the publication of the GGH but did not support the GGH. This work was carried out on an adult rodent cerebral cortex because technical aspects for the preparation of tissue could be better controlled for precise quantitative assessment (Galaburda, Aboitiz, Rosen, & Sherman, 1986).

Thus, one claim of the GGH in the case of anomalous asymmetry (i.e., less left-sided predominance) was that as the left hemisphere was inhibited during development by the effect of testosterone, the right hemisphere grew larger than normal, shifting brain structures from the left to the right. It was as if there was a given amount of brain that was variably distributed more to the left, more symmetrically, or even more to the right, according to the magnitude of the testosterone effect. In the case of language areas, correcting for variability of general brain size, everyone was supposed to have an equivalent amount, and the only thing that changed was how this equivalent amount was stored in the left and right hemispheres. Thus, correcting for the overall variation in brain size, the GGH predicted that the left planum area plus the right planum area was constant (Galaburda, Rosen, & Sherman, 1990). In fact, this was not the case when asymmetric and symmetric areas were compared. The total amount of tissue in the area did not remain constant in human and animal studies, in which there is variation in degree of asymmetry of a given gross or architectonically defined area. Instead, it varied inversely with the degree of asymmetry—the more asymmetric the areas were between the two sides of the brain, the smaller their sum. Thus, symmetric areas were larger than asymmetric areas, which suggested that asymmetry could represent a pruned-down version of the symmetric case and not simply a different distribution. Furthermore, at the architectonic level, symmetric brain areas in one brain contained a larger complement of neurons (as opposed to larger neurons) than homologous asymmetric brain areas in another brain (see Figure 1.2) (Galaburda et al., 1986; Rosen, Sherman, & Galaburda, 1991, 1992).

Several additional studies showed that the lateral difference in the number of neurons was neither the result of differential neuronal proliferation prior to neuronal migration, nor differential cell death or pruning after neuronal migration (Rosen et al., 1991). Although this was not looked at directly, it was likely that asymmetry in the number of neurons on the two sides reflected early patterning events before neuroblast proliferation, neuronal migration, or neuronal death and maturation (see Chapter 3). If there was pruning at all, then it had to occur very early in the life of the embryo. The GGH considered that a mechanism for shifted dominance to the right hemisphere by testosterone implicated greater cell death on the left, with compensatory lesser cell death on the right, and this was implicitly

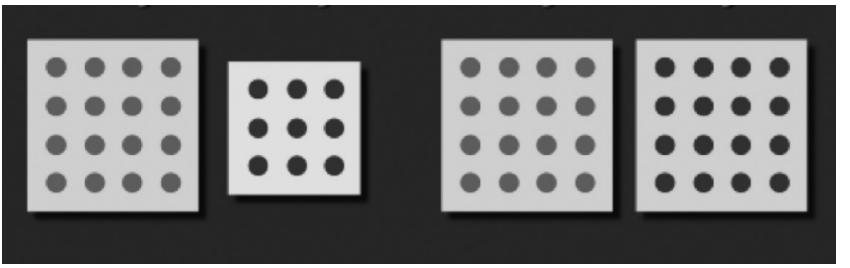

Figure 1.2. The generation of asymmetric brain areas requires developmental reduction from an originally symmetric state. Indirect evidence suggests that this reduction occurs before neuronal proliferation and neuronal migration to the incipient cerebral cortex and may be mediated by cilia function.

considered to be a postmigrational event. Instead, the likely scenario is that initial patterning of the cortex is symmetric, and early events, perhaps under the effect of cilia and possibly still modulated at least in part by testosterone, produce reduction of one side—the right side in the case of language areas—so that fewer neuroblasts remain available on the right side and a smaller architectonic area is subsequently generated.

Related Research on Language-Based (Left-Hemisphere) Learning Disabilities: Cortical Malformations and Left-Handedness

The GGH made a strong claim about the origin of left-hemisphere learning disabilities such as dyslexia, autism spectrum disorder, and stuttering. Thus, implicating testosterone again, another hypothesis of the theory was that retardation of growth of the left hemisphere was so severe in some cases that it caused neuronal migration anomalies on that side, which, in turn, caused the LDs, either alone or in combination with decreased leftward asymmetry of the language areas and left-handedness. No attempt was made to distinguish cases in which dyslexia versus stuttering versus autism would result, but the implicit assumption at that time was that testosterone acted on different genetic backgrounds to produce different disorders. Suffice it to say, testosterone effects occurred in all three conditions, thus explaining the male prevalence in all three. Subsequent experimental research failed again to support the notion that testosterone was responsible for neuronal migration anomalies, although another, previously unsuspected action of the male hormone probably did play a role in the gender difference.

Cortical Malformations Galaburda and Kemper (1979) reported the case of a dyslexic young man whose brain showed neuronal migration anomalies. Multiple instances of molecular layer heterotopia were present

in the perisylvian regions of both hemispheres, but they were substantially more prominent on the left, as well as one focus of micropolygyria affecting the auditory regions of the left temporal lobe. Similar small cortical malformations were present in several other dyslexic brains later studied at autopsy (Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985). The first strike against the GGH suggesting that neuronal migration anomalies were the result of excessive inhibition of left-hemisphere development was the fact that neuronal migration abnormalities were found on both sides, even if more commonly on the left. Although the theory hypothesized an inhibitory effect on the left, it also claimed a stimulatory effect on the right. Although there was the possibility that neuronal migration anomalies could result from over-inhibition or over-stimulation and would be worse with inhibition than with stimulation, no data were ever gathered to support this possibility. In the end, the pathogenesis of the malformations was related to different factors such as injury, infection, toxic exposure, or genetic defects (Kuzniecky & Barkovich, 1996; Pilz, Stoodley, & Golden, 2002), without evidence that testosterone has any role to play in neuronal migration abnormalities.

Neuronal heterotopias in the molecular layer of the cortex and micropolygyria (both found in the dyslexic brain) have been induced in rodent brains by applying a freezing probe on the skull of the newborn animal during a time when neuronal migration to the cerebral cortex is continuing. Neuronal migration anomalies can only occur if the causative agent acts during the time neuronal migration is actively proceeding to the cerebral cortex and not later (see Figure 1.3) (Humphreys, Rosen, Press, Sherman, & Galaburda, 1991). Different, but perhaps associated, forms of neuronal migration anomalies have also been caused in the fetal rat brain exposed to short hairpin micro ribonucleic acid sequences constructed against genes in the rat homologous to human dyslexia risk genes (Rosen et al., 2007; Szalkowski et al., 2012; Wang et al., 2006) and, in some cases, in mice knocked out for these genes (Truong et al., 2014; Wang et al., 2011). These manipulations were identical in males and females, and the cortical effects were also the same, but there was an effect of testosterone. Thus, males with induced cortical malformations showed secondary changes in the thalamus, whereas females did not. But the secondary thalamic changes emerged in female rats when they were exposed perinatally to testosterone (Rosen, Herman, & Galaburda, 1999). Thus, testosterone did not influence cortical malformations per se during the experiment on the rodent, but rather a form of secondary thalamic plasticity. An additional interesting finding was that induction of cortical malformation resulted in auditory processing deficits in male animals but not female animals, suggesting that it was the response to the initial manipulation that produced the deficits, rather than the cortical malformations themselves. The human thalamus is asymmetric (Eidelberg & Galaburda, 1982); thalamic anomalies have also been reported in the human dyslexic brain (Galaburda &

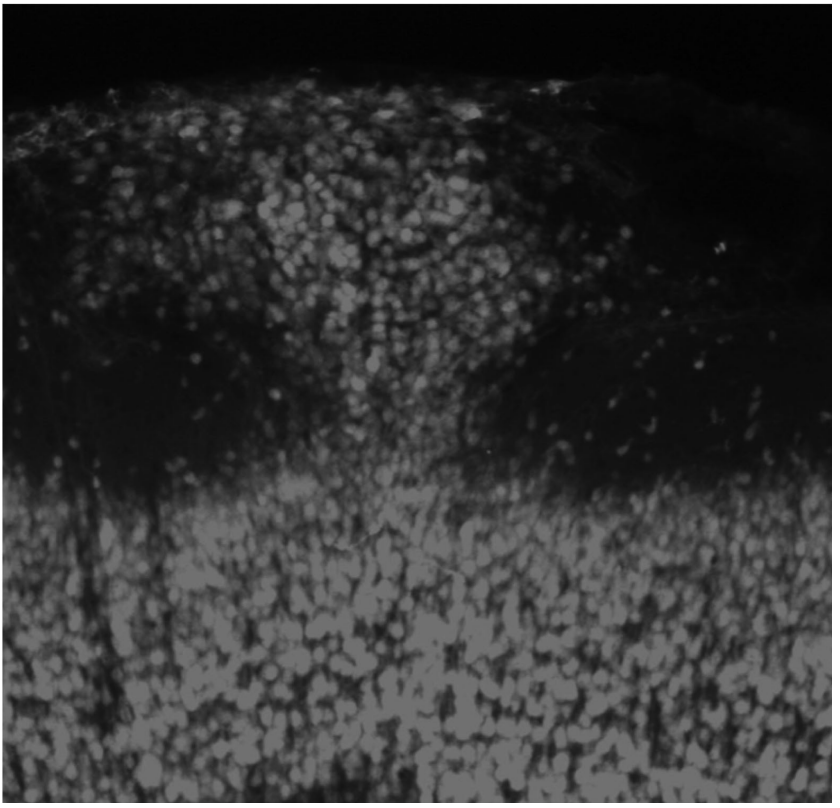

Figure 1.3. Molecular layer ectopia in the rat cortex. Neurons are stained with red-fluorescent protein. The cloud of neurons lying above in the photograph have migrated abnormally beyond their standard locations in the subjacent cortical layers. These malformations occur spontaneously in the dyslexic cerebral cortex and can be induced in rodent brains for further analysis.

Eidelberg, 1982). It is possible that the action of the human cortical anomalies in dyslexia have been overestimated and the effects of the secondary thalamic changes have been underestimated. Effects of testosterone on injury-related plasticity were not something considered in the GGH, but they appear to account for the sex differences and should be further studied in the biology of left-hemisphere learning disabilities. It seems to account for sex differences not by causing neuronal migration anomalies per se, but rather by modifying plasticity in response to a negative developmental event.

Left-Handedness As previously noted, the biology of cerebrocortical abnormalities in relation to testosterone seems to be more complex than simply slowing the development of the left hemisphere. We do not

understand the relationship of testosterone to handedness. We also do not know why anomalous hand dominance is more common in males, and the answer may have something to do with testosterone; if it does, then it may be by mechanisms other than slowing the development of the left hemisphere. The biology of cilia has come to the forefront in the study of lateralization (Hamada et al., 2002). Cilia seem to play an important role in the lateralization of somatic organs, and the absence of cilia function may lead to situs inversus (Pennekamp, Menchen, Dworniczak, & Hamada, 2015). Interestingly, 50% of animals with abnormal cilia develop a heart pointing to the right, and 50% develop a heart pointing to the left. The same random lateralization is true for the positioning of the liver and spleen.

In other words, the absence of cilia function leads to random lateralization of the body organs, and this is strikingly similar to what Annett's (1964) right shift theory predicts; thus, the absence of the right shift gene leads to random lateralization in the brain. Annett's lateralization gene may not be a single gene but may instead reflect dysfunction of any of the genes that govern normal cilia function. This statement makes a strong assumption that cannot be adequately defended at this time and implicates cilia dysfunction in brain lateralization as well as in body organ lateralization. Furthermore, Annett's theory makes additional predictions. For instance, the cilia and Annett's explanations predict that in any group of right handers there will be some who are anomalous right handers because they randomly became right handed from lack of the normal drive, either cilia or gene based. An equal number of left handers will be anomalous for the same reason. Implications of this biology of handedness would be that there are so-called normal right handers and anomalous right handers based on whether they have the right shift gene or cilia effect, and all left handers are anomalous because all lack the gene or cilia. Is this an obligatory conclusion about left handers? Not necessarily! Thus, for instance, there may be drives equivalent to the right shift drives that make people left handed, and some within this group may also lack this left shift drive. In this newly postulated left shift theory, the presence of left shift factors would produce standard left handers and the absence would lead to random left and right handers who are anomalous because they are missing the left shift effect. The frequency in the population of this postulated left shift factor must be lower than that of the right shift factor; otherwise, there should be an equal number of standard right and left handers, which is not the case. Whether it is from the absence of the right shift factor or the absence of the postulated left shift factor, there should be an equal number of anomalous right- and left-handed individuals, albeit a greater number of standard right handers than left handers. Furthermore, it is not currently possible to distinguish anomalous from standard right handers and left handers; this fact would tend to produce problems for studies attempting to uncover relationships between handedness and other traits, including disorders such as learning

disabilities and immunological disorders, because anomalous right and left handers would be mixed in with the standard groups.

Left Handedness, Immune Disorders, and Language-Based Learning Disabilities Geschwind and Behan (1982) uncovered a relationship among LDs, immune disorders, and left-handedness, which became fodder for the GGH. Yet, following the publication of the three-part paper (Geschwind & Galaburda, 1985a, b, c), several papers failed to find the same relationship, whereas others confirmed the original findings (e.g., Bryden, McManus, & Bulman-Fleming, 1994; Galaburda, 1990; Hugdahl, Ellertsen, Waaler, & Klove, 1989). Leaving aside the null hypothesis (the failure to demonstrate a finding does not mean that there is no finding), there may be other reasons for this inconsistency. Assume that the absence of the right shift factor (or the postulated left shift factor for that matter; I will call them the laterality factors for the present discussion) is accompanied by an altogether different brain organization and represents an important risk factor for language-based learning disabilities (i.e., a sine qua non). If one examines a population of individuals with these disorders, then nearly 50% of them will be right handed and 50% will be left handed because the absence of the laterality factors produces random handedness. Therefore, studies performed in this way will not find a prevalence of left-handedness in a population of individuals with the mentioned disabilities. If, however, a general population of left handers are sampled, then a greater proportion of them will have a language-based learning disability than a similar population of right handers because anomalous left handers represent a greater proportion of the total number of left handers (standard and anomalous) than anomalous vis-à-vis total number of right handers. Unless attention is paid to the way the study is constructed, there will be disagreement as to whether left-handedness is associated with a language-based learning disability. A similar argument can be made regarding immunological conditions. It is also likely that absence of laterality factors occurs in a very small proportion of the population to produce either anomalous left- or right-handedness; studies need large *n*'s to produce robust, replicable findings. This is, in part, a likely explanation for the lack of agreement on the questions of handedness, immune disorders, and language-based LDs among the papers that followed the publication of the GGH.

CONCLUSION

The GGH postulated that in utero testosterone slows the development of the left hemisphere, thus promoting superior development of the right hemisphere, and interferes with the proper setup of the immune system so that males and testosterone-exposed females will exhibit increased left-handedness, language-based LDs, better right-hemisphere skills, and more immunological disorders. The increased incidence of LDs is supposed to be doubly caused by testosterone-based slowing of development of left

hemisphere language areas and malformations caused by inhibited migration of neurons to the cerebral cortex. Several findings from the 1930s through the 1980s provided evidence for building the theory, including excess left-handedness and language-based LDs in boys, the presence of variable handedness in the population, the presence of variable brain asymmetry, the link between left-handedness and language-based LDs, the link between left-handedness and immunologically derived human medical conditions, and the finding of neuronal migration anomalies in the brains of individuals who have dyslexia.

A great deal of research since the publication of the GGH (Geschwind & Galaburda, 1985a, b, c) has shed additional light on the biology of laterality and the mechanisms underlying neuronal migration abnormalities—enough to cast doubt on the role of testosterone, at least the role the GGH attributed to testosterone. Testosterone clearly seems to have a role in developmental plasticity, which may affect handedness, but this remains hypothetical. In fact, the role of testosterone in handedness remains a mystery and will require additional research. Similarly, testosterone does not seem to cause neuronal migration anomalies as proposed in the GGH, but it may modulate the anatomical functional consequences of these neuronal migration anomalies. The role of cilia in the production of organ laterality has come to the forefront of research, but we have yet to learn what cilia have to do with lateralization of the brain, even though they are ubiquitous in the central nervous system. If cilia play a role in handedness formation, then this role will provide a cell-molecular mechanism to explain the observations of Annett (1964) and her right shift theory and will help dovetail some predictions of the GGH. In addition to testosterone's effects on plasticity and recovery of function, it will be useful to investigate whether it plays a role in cilia function and laterality in the brain. Finally, a coherent understanding of the immunological connection to testosterone is beyond the reach of the present discussion.

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