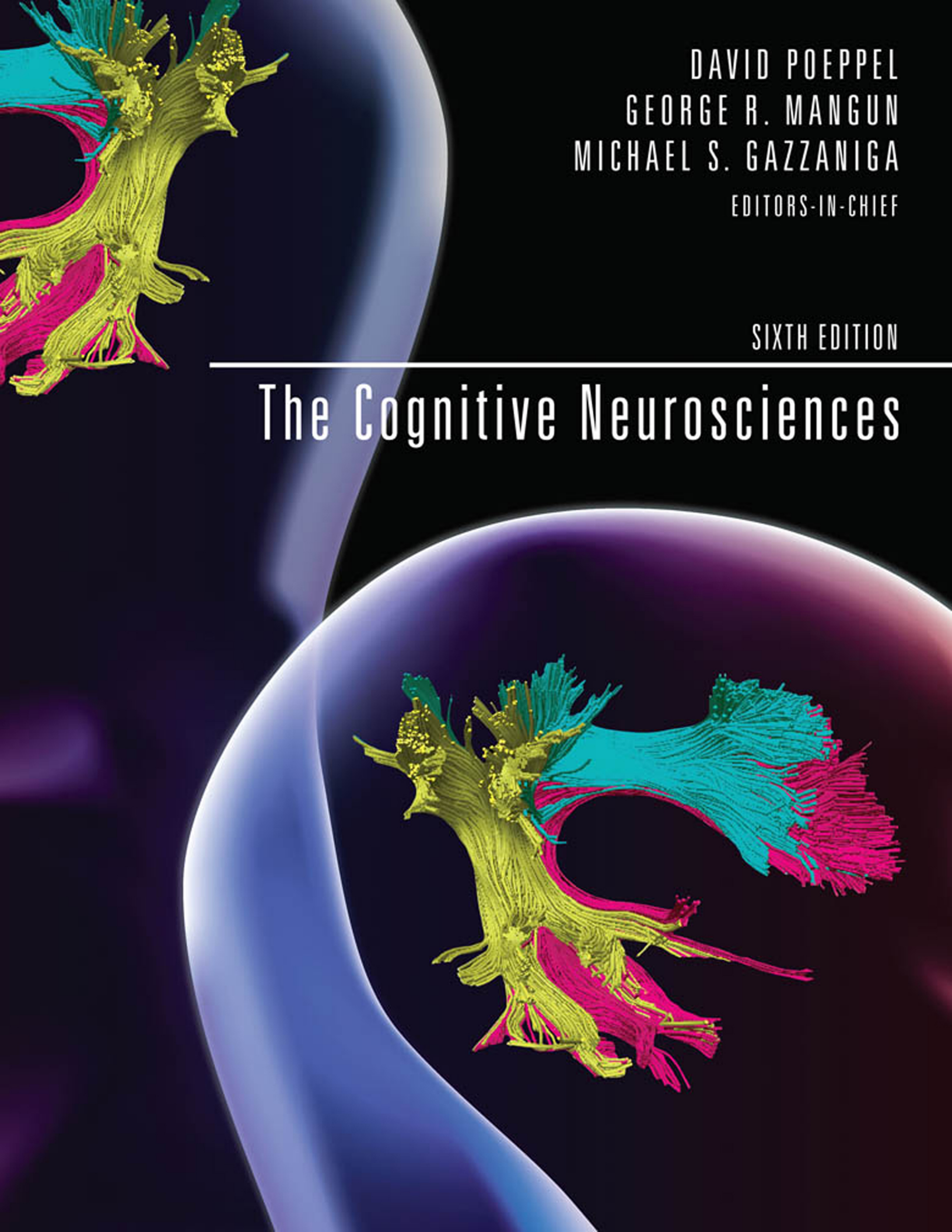




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EDITORS-IN-CHIEF

SIXTH EDITION

The Cognitive Neurosciences

THE COGNITIVE NEUROSCIENCES

THE COGNITIVE NEUROSCIENCES

Sixth Edition

David Poeppel, George R. Mangun,
and Michael S. Gazzaniga, *Editors-in-Chief*

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CONTENTS

Preface xiii

I BRAIN CIRCUITS OVER A LIFETIME

Introduction SARAH-JAYNE BLAKEMORE
AND ULMAN LINDENBERGER 3

- 1 Early Moral Cognition: A Principle-Based Approach
MELODY BUYUKOZER DAWKINS, FRANSISCA TING, MAAYAN STAVANS,
AND RENÉE BAILLARGEON 7
- 2 Imaging Structural Brain Development in Childhood and Adolescence
CHRISTIAN K. TAMNES AND KATHRYN L. MILLS 17
- 3 Cognitive Control and Affective Decision-Making in Childhood
and Adolescence EVELINE A. CRONE AND ANNA C. K.
VAN DUJVENVOORDE 27
- 4 Social Cognition and Social Brain Development in Adolescence
EMMA J. KILFORD AND SARAH-JAYNE BLAKEMORE 37
- 5 A Lifespan Perspective on Human Neurocognitive Plasticity
KRISTINE BEATE WALHOVD AND MARTIN LÖVDÉN 47
- 6 Brains, Hearts, and Minds: Trajectories of Neuroanatomical and Cognitive
Change and Their Modification by Vascular and Metabolic Factors
NAFTALI RAZ 61
- 7 Brain Maintenance and Cognition in Old Age LARS NYBERG
AND ULMAN LINDENBERGER 81
- 8 The Locus Coeruleus-Norepinephrine System's Role in Cognition and
How It Changes with Aging MARA MATHER 91

II AUDITORY AND VISUAL PERCEPTION

	Introduction	KALANIT GRILL-SPECTOR AND MARIA CHAIT	105
9	The Cognitive Neuroanatomy of Human Ventral Occipitotemporal Cortex	KEVIN S. WEINER AND JASON D. YEATMAN	109
10	Population Receptive Field Models in Human Visual Cortex	JONATHAN WINAWER AND NOAH C. BENSON	119
11	Face Perception	BRUNO ROSSION AND TALIA L. RETTER	129
12	Multisensory Perception: Behavior, Computations, and Neural Mechanisms	UTA NOPPENNEY	141
13	Computational Models of Human Object and Scene Recognition	AUDE OLIVA	151
14	Brain Mechanisms of Auditory Scene Analysis	BARBARA G. SHINN-CUNNINGHAM	159
15	Neural Filters for Challenging Listening Situations	JONAS OBLESER AND JULIA ERB	167
16	Three Functions of Prediction Error for Bayesian Inference in Speech Perception	MATTHEW H. DAVIS AND EDIZ SOHOGLU	177

III MEMORY

	Introduction	TOMÁS J. RYAN AND CHARAN RANGANATH	193
17	Ignoring the Innocuous: Neural Mechanisms of Habituation	SAMUEL F. COOKE AND MANI RAMASWAMI	197
18	Memory and Instinct as a Continuum of Information Storage	TOMÁS J. RYAN	207
19	Context in Spatial and Episodic Memory	JOSHUA B. JULIAN AND CHRISTIAN F. DOELLER	217
20	Maps, Memories, and the Hippocampus	CHARAN RANGANATH AND ARNE D. EKSTROM	233
21	Memory across Development with Insights from Emotional Learning: A Nonlinear Process	HEIDI C. MEYER AND SIOBHAN S. PATTWELL	243
22	Episodic Memory Modulation: How Emotion and Motivation Shape the Encoding and Storage of Salient Memories	MATTHIAS J. GRUBER AND MAUREEN RITCHEY	255

- 23 Replay-Based Consolidation Governs Enduring Memory Storage
KEN A. PALLER, JAMES W. ANTONY, ANDREW R. MAYES,
AND KENNETH A. NORMAN 263
- 24 The Dynamic Memory Engram Life Cycle: Reactivation, Destabilization,
and Reconsolidation TEMIDAYO OREDERU
AND DANIELA SCHILLER 275

IV ATTENTION AND WORKING MEMORY

- Introduction SABINE KASTNER AND STEVEN LUCK 287
- 25 Memory and Attention: The Back and Forth A. C. (KIA) NOBRE
AND M. S. STOKES 291
- 26 The Developmental Dynamics of Attention and Memory
GAIA SCERIF 301
- 27 Network Models of Attention and Working Memory MONICA D. ROSENBERG
AND MARVIN M. CHUN 311
- 28 The Role of Alpha Oscillations for Attention and Working Memory
OLE JENSEN AND SIMON HANSLMAYR 323
- 29 A Role for Gaze Control Circuitry in the Selection and Maintenance of Visual
Spatial Information TIRIN MOORE, DONATAS JONIKAITIS,
AND WARREN PETTINE 335
- 30 Online and Off-Line Memory States in the Human Brain EDWARD AWH
AND EDWARD K. VOGEL 347
- 31 How Working Memory Works TIMOTHY J. BUSCHMAN
AND EARL K. MILLER 357
- 32 Functions of the Visual Thalamus in Selective Attention W. MARTIN USREY
AND SABINE KASTNER 367

V NEUROSCIENCE, COGNITION, AND COMPUTATION: LINKING HYPOTHESES

- Introduction STANISLAS DEHAENE AND JOSH McDERMOTT 379
- 33 An Optimization-Based Approach to Understanding Sensory Systems
DANIEL YAMINS 381
- 34 Physical Object Representations for Perception and Cognition
ILKER YILDIRIM, MAX SIEGEL, AND JOSHUA TENENBAUM 399

35	Constructing Perceptual Decision-Making across Cortex ROMÁN ROSSI-POOL, JOSÉ VERGARA, AND RANULFO ROMO	411
36	Rationality and Efficiency in Human Decision-Making CHRISTOPHER SUMMERFIELD AND KONSTANTINOS TSETOS	427
37	Opening Burton's Clock: Psychiatric Insights from Computational Cognitive Models DANIEL BENNETT AND Yael NIV	439
38	Executive Control and Decision-Making: A Neural Theory of Prefrontal Function ETIENNE KOECHLIN	451
39	Semantic Representation in the Human Brain under Rich, Naturalistic Conditions JACK L. GALLANT AND SARA F. POPHAM	469

VI INTENTION, ACTION, CONTROL

	Introduction RICHARD B. IVRY AND JOHN W. KRAKAUER	483
40	The Physiology of the Healthy and Damaged Corticospinal Tract MONICA A. PEREZ	487
41	The Neuroscience of Brain-Machine Interfaces ANDREW JACKSON	499
42	Somatosensory Input for Real-World Hand and Arm Control JEFFREY WEILER AND J. ANDREW PRUSZYNSKI	507
43	Reorganization in Adult Primate Sensorimotor Cortex: Does It Really Happen? TAMAR R. MAKIN, JÖRN DIEDRICHSSEN, AND JOHN W. KRAKAUER	517
44	The Basal Ganglia Invigorate Actions and Decisions DAVID ROBBE AND JOSHUA TATE DUDMAN	527
45	Preparation of Movement ADRIAN M. HAITH AND SVEN BESTMANN	541
46	Visuomotor Adaptation Tasks as a Window into the Interplay between Explicit and Implicit Cognitive Processes JORDAN A. TAYLOR AND SAMUEL D. McDUGLE	549
47	Apraxia: A Disorder at the Cognitive-Motor Interface LAUREL J. BUXBAUM AND SOLÈNE KALÉNINE	559

VII REWARD AND DECISION MAKING

	Introduction DAPHNA SHOHAMY AND WOLFRAM SCHULTZ	571
48	Dopamine Reward Prediction Errors: The Interplay between Experiments and Theory CLARA K. STARKWEATHER AND NAOSHIGE UCHIDA	575

49	Dopamine Prediction Error Responses Reflect Economic Utility WILLIAM R. STAUFFER AND WOLFRAM SCHULTZ	587
50	The Role of the Orbitofrontal Cortex in Economic Decisions KATHERINE E. CONEN AND CAMILLO PADOA-SCHIOPPA	597
51	Neural Mechanisms of Perceptual Decision-Making GABRIEL M. STINE, ARIEL ZYLBERBERG, JOCHEN DITTERICH, AND MICHAEL N. SHADLEN	607
52	Memory, Reward, and Decision-Making KATHERINE DUNCAN AND DAPHNA SHOHAMY	617
53	The Role of the Primate Amygdala in Reward and Decision-Making FABIAN GRABENHORST, C. DANIEL SALZMAN, AND WOLFRAM SCHULTZ	631
54	Cortico-Striatal Circuits and Changes in Reward, Learning, and Decision-Making in Adolescence ADRIANA GALVÁN, KRISTEN DELEVICH, AND LINDA WILBRECHT	641
55	Dopamine and Reward: Implications for Neurological and Psychiatric Disorders ANDREW WESTBROOK, ROSHAN COOLS, AND MICHAEL J. FRANK	651

VIII METHODS ADVANCES

	Introduction DANIELLE BASSETT AND NIKOLAS KRIEGESKORTE	665
56	Representational Models and the Feature Fallacy JÖRN DIEDRICHSSEN	669
57	An Introduction to Time-Resolved Decoding Analysis for M/EEG THOMAS A. CARLSON, TIJL GROOTSWAGERS, AND AMANDA K. ROBINSON	679
58	Encoding and Decoding Framework to Uncover the Algorithms of Cognition JEAN-RÉMI KING, LAURA GWILLIAMS, CHRIS HOLDGRAF, JONA SASSENHAGEN, ALEXANDRE BARACHANT, DENIS ENGEMANN, ERIC LARSON, AND ALEXANDRE GRAMFORT	691
59	Deep Learning for Cognitive Neuroscience KATHERINE R. STORRS AND NIKOLAUS KRIEGESKORTE	703
60	Connectomes, Generative Models, and Their Implications for Cognition PETRA E. VÉRTES	717
61	Network-Based Approaches for Understanding Intrinsic Control Capacities of the Human Brain DANIELLE BASSETT AND FABIO PASQUALETTI	729
62	Functional Connectivity and Neuronal Dynamics: Insights from Computational Methods DEMIAN BATTAGLIA AND ANDREA BROVELLI	739

IX CONCEPTS AND CORE DOMAINS

	Introduction	MARINA BEDNY AND ALFONSO CARAMAZZA	751
63	Concepts of Actions and Their Objects	ANNA LESHINSKAYA, MORITZ F. WURM, AND ALFONSO CARAMAZZA	755
64	The Representation of Tools in the Human Brain	BRADFORD Z. MAHON	765
65	Naïve Physics: Building a Mental Model of How the World Behaves	JASON FISCHER	777
66	Concepts and Object Domains	YANCHAO BI	785
67	Concepts, Models, and Minds	ALEX CLARKE AND LORRAINE K. TYLER	793
68	The Contribution of Sensorimotor Experience to the Mind and Brain	MARINA BEDNY	801
69	Spatial Knowledge and Navigation	RUSSELL A. EPSTEIN	809
70	The Nature of Human Mathematical Cognition	JESSICA F. CANTLON	817
71	Conceptual Combination	MARC N. COUTANCHE, SARAH H. SOLOMON, AND SHARON L. THOMPSON-SCHILL	827

X LANGUAGE

	Introduction	LIINA PYLKKÄNEN AND KAREN EMMOREY	837
72	The Crosslinguistic Neuroscience of Language	INA BORNKESSEL- SCHLESEWSKY AND MATTHIAS SCHLESEWSKY	841
73	The Neurobiology of Sign Language Processing	MAIRÉAD MACSWEENEY AND KAREN EMMOREY	849
74	The Neurobiology of Syntactic and Semantic Structure Building	LIINA PYLKKÄNEN AND JONATHAN R. BRENNAN	859
75	The Brain Network That Supports High-Level Language Processing	EVELINA FEDORENKO	869
76	Neural Processing of Word Meaning	JEFFREY R. BINDER AND LEONARDO FERNANDINO	879
77	Neural Mechanisms Governing the Perception of Speech under Adverse Listening Conditions	PATTI ADANK	889

- 78 The Cerebral Bases of Language Acquisition GHISLAINE
DEHAENE-LAMBERTZ AND CLAIRE KABDEBON 899
- 79 Aphasia and Aphasia Recovery STEPHEN M. WILSON
AND JULIUS FRIDRIKSSON 907

XI SOCIAL NEUROSCIENCE

- Introduction ELIZABETH PHELPS AND MAURICIO DELGADO 919
- 80 Neurobiology of Infant Threat Processing and Developmental Transitions
PATRESE A. ROBINSON-DRUMMER, TANIA ROTH, CHARLIS RAINEKI,
MAYA OPENDAK, AND REGINA M. SULLIVAN 921
- 81 More than Just Friends: An Exploration of the Neurobiological
Mechanisms Underlying the Link between Social Support and Health
ERICA A. HORNSTEIN, TRISTEN K. INAGAKI, AND NAOMI I. EISENBERGER 929
- 82 Mechanisms of Loneliness STEPHANIE CACIOPPPO AND JOHN T.
CACIOPPPO 939
- 83 Neural Mechanisms of Social Learning DOMINIC S. FARERI, LUKE J. CHANG,
AND MAURICIO DELGADO 949
- 84 Social Learning of Threat and Safety ANDREAS OLSSON,
PHILIP PÄRNAMETS, ERIK C. NOOK, AND BJÖRN LINDSTRÖM 959
- 85 Neurodevelopmental Processes That Shape the Emergence of Value-Guided
Goal-Directed Behavior CATHERINE INSEL, JULIET Y. DAVIDOW,
AND LEAH H. SOMERVILLE 969
- 86 The Social Neuroscience of Cooperation JULIAN A. WILLS, LEOR HACKEL,
ORIEL FELDMANHALL, PHILIP PÄRNAMETS, AND JAY J. VAN BAVEL 977
- 87 Interpersonal Neuroscience THALIA WHEATLEY
AND ADAM BONCZ 987

XII NEUROSCIENCE AND SOCIETY

- Introduction ANJAN CHATTERJEE AND ADINA ROSKIES 999
- 88 The Cognitive Neuroscience of Moral Judgment and Decision-Making
JOSHUA D. GREENE AND LIANE YOUNG 1003
- 89 Law and Neuroscience: Progress, Promise, and Pitfalls OWEN D. JONES
AND ANTHONY D. WAGNER 1015
- 90 Neuroscience and Socioeconomic Status MARTHA J. FARAH 1027

- 91 A Computational Psychiatry Approach toward Addiction
XIAOSI GU AND BRYON ADINOFF 1037
- 92 Neurotechnologies for Mind Reading: Prospects for Privacy
ADINA ROSKIES 1049
- 93 Pharmacological Cognitive Enhancement: Implications for Ethics and Society
GEORGE SAVULICH AND BARBARA J. SAHAKIAN 1059
- 94 Brain-Machine Interfaces: From Basic Science to Neurorehabilitation
MIGUEL A. L. NICOLELIS 1069
- 95 Aesthetics: From Mind to Brain and Back OSHIN VARTANIAN
AND ANJAN CHATTERJEE 1083
- 96 Music: Prediction, Production, Perception, Plasticity, and Pleasure
ROBERT J. ZATORRE AND VIRGINIA B. PENHUNE 1093

XIII LOOKING AHEAD: CHALLENGES IN ADVANCING COGNITIVE NEUROSCIENCE

- 97 Toward a Socially Responsible, Transparent, and Reproducible Cognitive
Neuroscience SIKOYA M. ASHBURN, DAVID ABUGABER, JAMES W. ANTONY,
KELLY A. BENNION, DAVID BRIDWELL, CARLOS CARDENAS-INIGUEZ, MANOJ
DOSS, LUCÍA FERNÁNDEZ, INGE HUIJSMANS, LARA KRISST, REGINA LAPATE,
EVAN LAYHER, JOSIAH LEONG, YUANNING LI, FREDDIE MARQUEZ, FELIPE
MUNOZ-RUBKE, ELIZABETH MUSZ, TARA K. PATTERSON, JOHN P. POWERS,
DARIA PROKLOVA, KRISTINA M. RAPUANO, CHARLES S. H. ROBINSON,
JESSICA M. ROSS, JASON SAMAHA, MATTHEW SAZMA, ANDREW X. STEWART,
ARIANA STICKEL, ARJEN STOLK, VERONIKA VILGIS, MEGAN
ZIRNSTEIN 1105
- Contributors 1115
- Index 1121

PREFACE

How compelling is cognitive neuroscience? So compelling that in the summer of 2018, 30 people were willing to spend three weeks in a windowless seminar room when they could have been enjoying one of the most beautiful places on Earth, Lake Tahoe. The seductive allure of the science held sway. A cohort of brilliant fellows showed up to every single session, listening to over 80 talks and peppering the speakers with candid, probing, and even, for the most part, polite questions. To cut to the chase: the state of the field is good.

The first edition of this book—both the inventory of our field and a critical perspective on it—was published in 1995, following the first meeting of the Cognitive Neuroscience Summer Institute, fondly known as “brain camp,” in Tahoe. At that point, electroencephalography (EEG) was a well-established technique; magnetoencephalography (MEG) existed but was not widely appreciated beyond a group of aficionados; and positron emission tomography (PET) was around and available, though rapidly becoming supplanted by functional magnetic resonance imaging (fMRI), which was only a few years old at the time. Twenty-five years later, the technical advances in and the wide availability of fMRI constitute the most dramatic changes in the field. Cognitive neuroscience has also benefited from many additional experimental approaches and novel measurement methodologies. From single-unit, depth-electrode, and grid-based recordings in neurosurgical patients to near-infrared spectroscopy (NIRS) in newborns, no technique has been left unexploited and unexplored. This edition reflects the healthy and exciting methodological pluralism of our field. But mapping with MRI—both structural and functional—is the aspect of the human brain sciences that has most captured the public and professional imaginations.

Maps and Explanations

What is it about making maps that draws us in so powerfully? For starters, scientific success! Identifying a systematic spatial layout at any scale of neural organization suggests we are on the right track to understand function. Nobody questions the utility of knowing the retinotopic layout of visual areas, the sheer coolness of identifying 180 distinct cortical fields per hemisphere, or the payoff of being able to identify a brain region robustly implicated in speaking, or throwing, or remembering. Yet something is missing. To caricature the problem: *localization is not explanation*. Indeed, even spatial organization is not explanation.

The last 25 years have yielded incredible insights into how neural real estate is partitioned. Detailed descriptions have been generated across measurement methods and brain systems (perceptual, motor, cognitive, affective). Yet descriptions they remain, and while “descriptively adequate” is hardly an insult, our yearning should be higher. Our field should strive to achieve “explanatory adequacy.”

David Marr famously argued that the study of a complex phenomenon or system can be profitably pursued by breaking it into three tightly linked levels of analysis: implementational, algorithmic, and computational. Whatever one thinks of Marr’s framework, he identified a serious conceptual challenge. We are, unsurprisingly, enamored of our remarkable new measurement tools, and we use the tools for mapping (a) because we can and (b) because the findings can be so intuitively pleasing. But too often (either for practical reasons or due to our own epistemic insufficiency) we stay in the descriptive safety of the implementational level, without taking the critical additional step of linking to other levels of analysis. The current approaches can and do yield first-rate neuroscience, but do they yield satisfactory *cognitive* neuroscience?

One might point out that we are studying *networks*, not circumscribed areas. But the fundamental issue remains. It may be descriptively more adequate to suggest that a neurocognitive phenomenon is executed by network X-Y-Z rather than, say, area Y. However, invoking a “network” for explanation is no more satisfactory than invoking a single area. One might also argue that we are now using sophisticated computational models in the study of some neural and cognitive phenomena and can even make predictions that illustrate remarkable model-data fits. However, this descriptive use does not meet the standards of computational and algorithmic levels of *understanding*. The goal is to incorporate nuanced and theoretically motivated accounts of behavior that stand a chance of generating persuasive explanations. *Regression is not explanation.*

In short, we should celebrate our considerable successes while remaining fascinated by the even more substantial challenges that lie before us. The notion that we have achieved a deep understanding of any cognitive system “in neural terms” is misleading, counterproductive, and, frankly, no fun at all.

A Postscience Cognitive Neuroscience?

A recurring topic at the Summer Institute—both explicitly and implicitly present in many of the lectures and discussions—was the tension between big data versus deep data. The suite of techniques we now have at our disposal can generate enormous amounts of data. It is, however, reasonable to ask whether colossal amounts of data acquired from a large number of participants are likely to yield the kinds of *answers* we seek. Historically, the very intensive study of individual participants has yielded great success.

Obviously, the approach depends on the nature of the specific question. Some research questions may be best methodologically approached with big data; for others, deep data are likely to generate better insight. Nevertheless, it is appropriate to raise serious questions about our epistemological stance. One thing is certain: there is now an intense (though typically unspoken) compulsion to have truly enormous data sets. The attraction may be due to the computational tools we now have available and, in part, to very real issues with replication that different areas of the psychological sciences are grappling with.

Nobody, or at least nobody rational, is in principle against having a large number of observations for any kind of study. But the orgy of data has not always been accompanied by equally passionate theory building. As it stands, there is a clear and present mandate to obtain and work with data sets of unprecedented size. This

unspoken code of conduct necessitates data-analytic approaches that capitalize on approaches such as machine-learning. However, while we as a field have embraced and enthusiastically pursued big and sometimes deep data, we have not pursued “big theory.” Is this a problem? We are data-rich but theory-poor. Have we thereby maneuvered ourselves into an epistemological local minimum?

Perhaps the cognitive neurosciences have reached a stage at which engineering has supplanted science. In our modern scientific era, do scientists no longer matter? If research questions and approaches are driven not by understanding or mechanism or theory but by prediction or data-driven model fitting, our data *are* our theory. In this case, our science might uncharitably be characterized as the “mother of all regressions.” When a field becomes increasingly theoretically sterile, we are in acute danger of prioritizing approaches that are commensurate with the kind of data and data analyses we currently prefer.

Certainly, science progresses by way of exciting new instruments. However, science also progresses by way of exciting new ideas. As we continue to drown in data sets, we should feel vindicated in emphasizing and prioritizing the value of theory, behavior, observation, and other such old-school scientific habits. A well-motivated hypothesis is a terrible thing to waste.

The Future of the Cognitive Neuroscientist

The Summer Institute was bookended by two terrific lectures on morality: the first on moral cognition in infants (see section I, Brain Circuits over a Lifetime), the last on morality in adults (see section XII, Neuroscience and Society). This was not a happy coincidence but a reflection on the cohort of lecturers. This year’s fellows rightly insisted on discussing the importance of scientific and personal integrity, open science, and transparent and fair processes. Indeed, the fellows wrote a joint chapter for this book. It is noteworthy and heartening that scientific ethics is not an afterthought but a central issue for young researchers.

Science as a social activity and scientific achievement, the fruit of our collective labors, cannot help but reflect our social values. As such, the integrity of all participants is as important as technical competence. Too many examples of problems have existed on both the ethical and the technical sides. It is a welcome, sensible, necessary, and inspiring response of young researchers to refuse to choose one over the other. As a community, we can demand appropriate social interaction *and* appropriate technical validation. We can prioritize careful attention to replication, high ethical standards, and open access, all at once. It is not only scientific output that needs to be considered carefully. The scientific process should be subject to the same level of scrutiny.

Desiderata

In the first edition of this book in 1995, Michael Gazzaniga wrote: “The future of the field ... is in working toward a science that truly relates brain and cognition in a mechanistic way.” As outlined above, that desideratum is still number one on the list. Obtaining it requires the best ideas and theories to be paired with the best techniques and analyses, in large part through open-minded interaction across disciplines. Gazzaniga points out, in the second edition of 2000, that “interdisciplinary cross-pollination seems inevitable in a field whose subject is itself both a coherent whole and a motley conglomerate of components.”

Two decades later, the motley conglomerate is perhaps even more motley. The dangers of interdisciplinary cross-sterilization over cross-fertilization remain. The flavors of the moment include the ubiquity of deep learning, the fascinating data

from electrocorticography (ECoG), the utility of big data, the explanatory power of predictive coding, the insights into neurobiology and perception derived from oscillation-based frameworks, and other promising domains and techniques. Cognitive neuroscience memes such as these penetrate across areas. The spread is in itself exciting, but it is up to this new generation of cognitive neuroscientists—intellectually fearless, technically brilliant, and socially responsible—to take the best ideas and best techniques and address the deepest problems at the heart of the intersection of biology and the mind.

To succeed, the new leaders of the cognitive neurosciences will have to develop and examine hypotheses that plausibly *link* levels of description and yield an *understanding* of the system. For example, in the last few years, neural oscillations and their perceptual and cognitive correlates have been considered by some to be critical ingredients for certain linking hypotheses. However, building bridges and links is really, truly hard. Correlational relations will not suffice, and we, the editors, are relieved that this enormous burden is now also on the shoulders of an energetic new crop of researchers.

As pointed out in the preface to the first edition of this book by one of us (MSG), the field faces “the most fundamental problem of modern science—the problem of the explanatory gap. The gap here is the one between biologic process and the processes of mind.” The gap remains and we look forward to seeing it closed.

Thanks

Huge thanks are due to Jayne Kelly and Marin Gazzaniga. Without Jayne, the Summer Institute would not have happened. Without Marin, this book would not exist. Their professionalism, competence, relentless flexibility, sense of humor, and deep tolerance of our idiosyncrasies allow this kind of scientific exchange to begin with. We are all extremely grateful. The section editors—all international scientific leaders—deserve our deep appreciation. They selected and curated excellent lectures and chapters, for which the entire field thanks them; their section overviews provide enlightenment on the topics in this volume. Enterprises of this scale require considerable support, and we thank the National Institute of Mental Health and the National Institute on Drug Abuse, the Kavli Foundation, and the University of California. As co-principal investigators, Michael Miller’s and Barry Giesbrecht’s contributions to the Summer Institute cannot be overstated, and we are also grateful for the support of staff members at the UC Davis Center for Mind and Brain, the UCSB Sage Center for the Study of the Mind, and the Max Planck Institute for Empirical Aesthetics. Finally, we are indebted to Philip Laughlin and his team and everyone at the MIT Press for the work they dedicated not only to this volume but to the field of cognitive neuroscience. We hope this book provides as much enjoyment and stimulation in the reading as it has to us in the writing. It is a pleasure and a privilege to be part of so heady and fun an intellectual and social enterprise.

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I

BRAIN CIRCUITS
OVER A LIFETIME

<i>Chapter</i>	1	BUYUKOZER DAWKINS, TING, STAVANS, AND BAILLARGEON	7
	2	TAMNES AND MILLS	17
	3	CRONE AND VAN DUIJVENVOORDE	27
	4	KILFORD AND BLAKEMORE	37
	5	WALHOVD AND LÖVDÉN	47
	6	RAZ	61
	7	NYBERG AND LINDENBERGER	81
	8	MATHER	91

Introduction

SARAH-JAYNE BLAKEMORE AND
ULMAN LINDENBERGER

The present section of *The Cognitive Neurosciences* spans human behavioral and neural development from infancy to old age. This change to the section theme is welcome, as it signals that human development does not end with adolescence but continues into advanced old age.

Individuals organize their exchange with the physical and social environment through behavior. On the one hand, the changing brain and the changing physical and cultural environment shape behavioral development. On the other hand, behavior alters both the brain and the environment. Hence, environments and brains act not only as antecedents but also as consequences of moment-to-moment variability and long-term changes in patterns of behavior. The dynamics of this system give rise to the diversity of individuals' trajectories through life (Molenaar, 2012; Nesselrode, 1991).

The general goal of developmental cognitive neuroscience is to identify neural mechanisms that generate invariance and variability in behavioral repertoires from infancy to old age. By identifying the commonalities, differences, and interrelations in the ontogeny of sensation, motor control, cognition, affect, social processing, and motivation, both within and across individuals, the field can move toward providing more comprehensive theories of behavioral development across different periods of the lifespan.

In attempts to explain the age-related evolution of this system, *maturation* and *senescence* (i.e., aging-related decline) denote the operation of developmental brain mechanisms and their effects on changes in behavior, which are especially pronounced during early childhood and late adulthood, respectively. In addition, *learning*, at any point during ontogeny, denotes changes

in brain states induced by behavior-environment interactions. Note, however, that maturation cannot take place without learning and that some forms of learning cannot take place without maturation. Similarly, the ways in which senescence takes its toll on the aging brain depend on an individual's past and present learning and maturational histories. To complicate matters even more, processes commonly associated with maturation are not confined to early ontogeny, and processes related to senescence are not restricted to old and very old age. For instance, neurogenesis and synaptogenesis, which qualify as maturational mechanisms promoting plasticity, continue to exist in the adult brain; conversely, declines in dopaminergic neuromodulation, which indicate senescence-related changes in brain chemistry, commence in early adulthood. Thus, maturation, senescence, and learning mutually enrich and constrain each other throughout the entire lifespan and should preferably be understood and studied as interacting forces constituting and driving the brain-behavior-environment system (Benasich & Ribary, 2018; Lindenberger, Li, & Backman, 2006).

Thus, developmental cognitive neuroscientists are faced with three challenging tasks. First, there is the need to integrate theoretical and empirical research across functional domains to attain a comprehensive picture of individual development. For instance, sensorimotor and cognitive functioning are more interdependent in early childhood (e.g., Diamond, 2000) and old age (e.g., Lindenberger, Marsiske, & Baltes, 2000) than during middle portions of the lifespan, and developmental changes in either domain are better understood if studied in conjunction.

Second, there is a need to understand the mechanisms that link short-term variations to long-term change. Short-term variations are often reversible and transient, whereas long-term changes are often cumulative, progressive, and permanent. Establishing links between short-term variations and long-term changes is of eminent heuristic value, as it helps to identify mechanisms that drive development in different directions.

Third, to arrive at mechanistic explanations of behavioral change requires the integration of behavioral and neural levels of analysis. At any given point in the lifespan, one-to-one mappings between brain states and behavioral states are the exception rather than the rule, as the brain generally offers more than one implementation of an adaptive behavioral outcome. Therefore, ontogenetic changes in behavioral repertoires are accompanied by continuous changes in multiple brain-behavior mappings. Some of these remapping gradients may be relatively universal and age-graded, whereas others may be more variable, reflecting genetic differences,

person-specific learning histories, the path-dependent nature of developmental dynamics, or a combination of all three. The resulting picture underscores the diversity and malleability of the organization of the brain and behavior as well as the constraints on diversity and malleability brought about by (1) universal age-related mechanisms associated with maturation and senescence, (2) general laws of neural and behavioral organization, and (3) cultural-social as well as physical regularities of the environment.

Research on brain development in the second half of the 20th century focused almost entirely on nonhuman animals and revealed a great deal about early neuronal and synaptic development (Wiesel & Hubel, 1965). These advances in animal research followed pioneering research in developmental psychology, particularly by Vygotsky and Piaget (Chapman, 1988). Their studies, which involved observing and analyzing children's behavior in meticulous detail, changed contemporary thinking about children's minds. Today, theory-guided series of behavioral experiments strongly support the claim that the foundational capacities of very young children are organized by guiding principles in physical, psychological, and sociomoral core domains. In this vein, Buyukozur Dawkins, Ting, Stavans, and Baillargeon propose in the opening chapter to this section that early sociomoral reasoning is guided by the principles of fairness, harm avoidance, in-group support, and authority.

While developmental psychology made great progress in the last century, it remained relatively removed from developmental neuroscience. Research on human neural development was heavily constrained by the technical challenges of studying the living human brain and, until fairly recently, was limited to the study of postmortem brains. In the past decades, however, the field of developmental cognitive neuroscience has undergone unprecedented expansion, at least in part due to technological advances. In particular, the increased and concerted use of various MRI techniques in children has created new opportunities to track structural and functional changes in the developing human brain. The use of these imaging methods has propelled our knowledge of how the human brain develops, and the data from developmental imaging studies have in turn spurred new interest in the changing structure and functions of the brain over the entire lifespan. Fifty years ago, who would have imagined that scientists would eventually be able to look inside the brains of living humans of all ages and track changes in brain structure and function from intrauterine development into old age?

Age-graded changes in the structure of the human brain from childhood to early adulthood are addressed in the chapter by Tamnes and Mills. They focus on

measurements of brain morphometry and measurements derived from diffusion tensor imaging (DTI) while also discussing novel measures and approaches to examine structural brain development. Whereas structural MRI has enriched our knowledge of age-related changes in regional volume and structural connectivity, functional magnetic resonance imaging (fMRI), in concert with electroencephalography (EEG) and near-infrared spectroscopy (NIRS), has revealed developmental changes in regional brain activity and functional connectivity. Today many labs around the world use fMRI to investigate how neural systems associated with particular cognitive processes change with age. Crone and van Duijvenvoorde report the neural correlates of cognitive and affective decision-making in school-aged children, adolescents, and adults. They show that the development of basic to complex levels of cognitive control follows a pattern of specialization with age in the prefrontal cortex and the posterior parietal cortex, such that these areas are more strongly and more selectively recruited for specific tasks. Kilford and Blakemore trace the development of the social brain in adolescence and provide rich evidence for the substantial and protracted development of multiple aspects of social cognition, as well as the structural and functional development of the social brain network, during this period of life.

Inquiries into the plasticity of the brain and behavior are a rich source of developmental information; by assessing “changes in change,” they offer the promise to observe the operation and proximal consequences of developmental mechanisms. Taking a lifespan and phylogenetic perspective, Walhovd and Lövdén review the evidence for age-graded differences in human plasticity from infancy to old age. This sets the stage for the chapter by Raz, who takes a systemic look at senescent changes in the brain and behavior, with particular emphasis on the role of vascular and metabolic factors. The aging brain is notorious for detrimental changes,

but some older adults appear to display brain maintenance, defined as a widespread lack of senescent brain changes and age-related brain pathology. Nyberg and Lindenberger focus on the structural and functional maintenance of the hippocampus and argue that it is the primary determinant of preserved episodic-memory functioning in old age. Finally, Mather directs our attention to the role of the locus coeruleus norepinephrine system and provides evidence that the integrity of this system is crucial for maintaining cognitive functions in old age.

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1 Early Moral Cognition: A Principle-Based Approach

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AND RENÉE BAILLARGEON

ABSTRACT There is considerable evidence that beginning early in life, abstract principles guide infants' reasoning about the displacements and interactions of objects (physical reasoning) and about the intentional actions of agents (psychological reasoning). Recently, developmental researchers have begun to explore whether early emerging principles also guide infants' reasoning about individuals' actions toward others (sociomoral reasoning). Investigations over the past few years suggest that at least four principles may guide early sociomoral reasoning: fairness, harm avoidance, in-group support, and authority. In this chapter, we review some of the evidence for these principles. In particular, we report findings that infants expect individuals to distribute windfall resources and rewards fairly; they expect individuals in a social group to help in-group members in need, to limit unprovoked and retaliatory harm toward in-group members, to prefer and align with in-group members, and to favor in-group members when distributing limited resources; and they expect an authority figure in a group to rectify transgressions among subordinate members of the group. Together, these findings support prior claims by a broad cross-section of social scientists that a small set of universal principles shapes the basic foundation of human moral cognition, a foundation that is then extensively revised by experience and culture.

Beginning in the first year of life, infants attempt to make sense of the world around them. How do they do so? A major hypothesis in developmental research has long been that in each core domain of causal reasoning, a skeletal framework of abstract principles and concepts guides how infants reason about events (Gelman, 1990; Leslie, 1995; Spelke, 1994). Initial investigations focused on infants' *physical reasoning* and found that principles of gravity, inertia, and persistence (with its corollaries of solidity, continuity, cohesion, boundedness, and unchangeableness) constrain early reasoning about objects' displacements and interactions (Baillargeon, 2008; Luo, Kaufman, & Baillargeon, 2009; Spelke, Phillips, & Woodward, 1995). Thus, even young infants realize that an inert object cannot remain suspended when released in midair (gravity); cannot spontaneously reverse course (inertia); cannot occupy the same space as another object (solidity); and cannot

spontaneously disappear (continuity), break apart (cohesion), fuse with another object (boundedness), or change into a different object (unchangeableness).

Next, researchers turned to infants' *psychological reasoning* (also referred to as mental-state reasoning or theory of mind). Investigations revealed that when infants observe an agent act in a scene, they attempt to infer the agent's mental states; these can include motivational states (e.g., intentions), epistemic states (e.g., ignorance), and counterfactual states (e.g., false beliefs) (Gergely, Nádasdy, Csibra, & Bíró, 1995; Luo & Baillargeon, 2007; Onishi & Baillargeon, 2005). Infants then use these mental states, together with a principle of rationality (and its corollaries of consistency and efficiency), to predict and interpret the agent's subsequent actions (Baillargeon, Scott, & Bian, 2016; Gergely et al., 1995; Woodward, 1998). Thus, if an agent wants a toy and sees someone place it in one of two containers, infants expect the agent to reach for the correct container (consistency) and to retrieve the toy without expending unnecessary effort (efficiency).

More recently, researchers have begun to study infants' *sociomoral reasoning*. Initially, it appeared as though the skeletal framework in this domain, unlike those in the previous two domains, might involve no principles. In particular, infants seemed to hold no expectations about whether individuals would refrain from harming others or would help others in need of assistance. In a series of experiments, infants ages 3–19 months were presented with various scenarios depicting interactions among nonhuman individuals (e.g., different blocks with eyes; Hamlin, 2013, 2014; Hamlin & Wynn, 2011; Hamlin, Wynn, & Bloom, 2007, 2010; Hamlin, Wynn, Bloom, & Mahajan, 2011). Each scenario involved two events: a *positive* event, in which a nice character acted positively toward a protagonist (e.g., rolled a dropped ball back to the protagonist or helped the protagonist reach the top of a steep hill), and a *negative* event, in which a mean character acted negatively toward the same protagonist (e.g., stole the ball or knocked the

protagonist down to the bottom of the hill). Across ages and scenarios, infants looked equally at the two events, suggesting that they detected no violations in the negative events and hence did not expect the mean character to either refrain from harming the protagonist or help it achieve its goal. These results did not stem from infants' inability to understand the scenarios presented: when encouraged to choose one of the two characters, infants 3–10 months old consistently preferred the nice one over the mean one (Hamlin et al., 2007, 2010; Hamlin & Wynn, 2011). Together, these results suggested that infants possess abstract concepts of welfare and harm, distinguish between positive and negative actions, and hold affiliative attitudes consistent with these valences. Nevertheless, infants seemed to lack principle-based expectations about individuals' actions toward others, suggesting that the skeletal framework for sociomoral reasoning included moral concepts but not moral principles (e.g., infants held no expectations as to whether the characters would harm or help the protagonist, but they did recognize harm or help when they saw it).

This characterization of early morality began to change, however, as researchers went on to explore other scenarios. It is now becoming clear that the skeletal framework that guides early sociomoral reasoning does include a small set of principles. However, because most of these principles apply only when specific preconditions are met, expectations related to the principles can be observed only with scenarios that satisfy these preconditions. For example, if infants view helping as expected only among in-group members, then they will expect an individual to aid another only when the two are clearly identified as members of the same social group.

Over the past few years, evidence has slowly been accumulating for at least four sociomoral principles (Baillargeon et al., 2015). The most general is *fairness*, which applies broadly to all individuals: all other things being equal, individuals are expected to treat others fairly, according to their just deserts. At the next level of generality is *harm avoidance*: when individuals belong to the same moral circle (e.g., humans), they are expected not to cause significant harm to each other. At the next level of generality is *in-group support*: when individuals in a moral circle belong to the same social group (e.g., teammates), additional expectations of in-group care and in-group loyalty are brought to bear. Finally, at the fourth and most specific level is *authority*: when individuals in a social group are identified as authority figures or subordinates, further expectations related to these group roles come into play (e.g., rectifying transgressions for the authority figures or obeying directives for the subordinates). Thus, each new structure in the

social landscape—moral circle, social group, group roles—brings forth new expectations about how individuals will act toward others.

This emerging characterization of early morality supports long-standing claims, by a broad cross-section of social scientists, that the basic structure of human moral cognition includes a small set of universal foundations or principles (Baumard, André, & Sperber, 2013; Brewer, 1999; Cosmides & Tooby, 2013; Dawes et al., 2007; Dupoux & Jacob, 2007; Graham et al., 2013; Jackendoff, 2007; Pinker, 2002; Rai & Fiske, 2011; Shweder, Much, Mahapatra, & Park, 1997; Tyler & Lind, 1992; Van Vugt, 2006). Although details about the nature and contents of these principles vary across accounts, it is commonly assumed that the principles evolved during the millions of years our ancestors lived in small groups of hunter-gatherers, where survival depended on cooperation within groups and, to a lesser extent, between groups; that the principles interact in various ways and must be rank ordered when they suggest distinct courses of action; and that different cultures implement, stress, and rank order the principles differently, resulting in the diverse moral landscape that exists in the world today. Graham et al. (2013) aptly described this view as “a theory about the universal first draft of the moral mind and about how that draft gets revised in variable ways across cultures” (p. 65).

In the remainder of this chapter, we review some of the recent evidence that principles of fairness, harm avoidance, in-group support, and authority are included in the “first draft” of moral cognition.

Fairness

According to the principle of fairness, all other things being equal, individuals are expected to treat others fairly when allocating windfall resources, dispensing rewards, or meting out punishments (Baillargeon et al., 2015; Dawes et al., 2007; Graham et al., 2013; Rai & Fiske, 2011). Traditionally, investigations of fairness in preschoolers have used *first-party* tasks, in which the children tested are potential recipients, and *third-party* tasks, in which they are not. Perhaps not surprisingly, given young children's pervasive difficulty in curbing their self-interest, a concern for fairness has typically been observed only in third-party tasks (Baumard, Mascaro, & Chevallier, 2012; Olson & Spelke, 2008). Building on these results, investigations with infants have also used third-party tasks to examine early expectations about fairness.

Equality Do infants expect a distributor to divide windfall resources equally between similar recipients?

In a series of experiments (Buyukozer Dawkins, Sloane, & Baillargeon, 2019; Sloane, Baillargeon, & Premack, 2012), 4-, 9-, and 19-month-olds were tested using the violation-of-expectation method (this method takes advantage of infants' natural tendency to look longer at events that violate, as opposed to confirm, their expectations). Infants faced a puppet-stage apparatus and saw live events in which an experimenter brought in two identical items (e.g., two cookies) and divided them between two identical animated puppets (e.g., two penguins). In one event, the experimenter gave one item to each puppet (*equal* event); in the other, she gave both items to the same puppet (*unequal* event; figure 1.1A). At all ages, infants looked significantly longer if shown the unequal as opposed to the equal event, and this effect was eliminated if the puppets were inanimate (i.e., neither moved nor spoke).

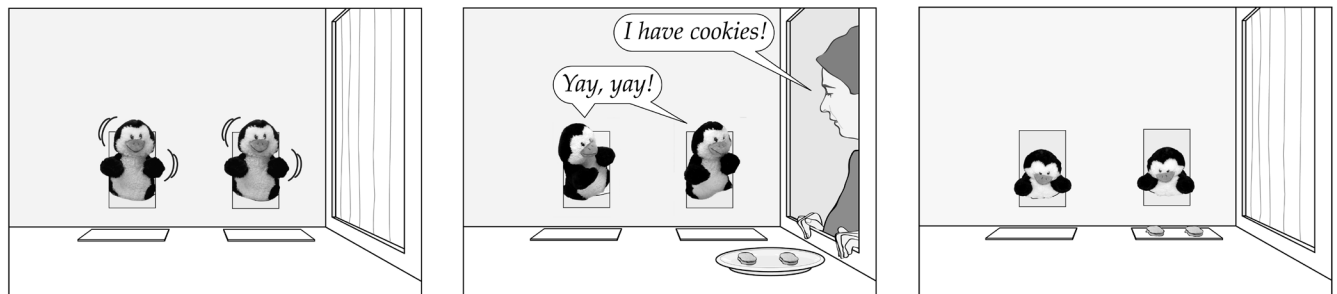
Consistent with the claim that fairness applies broadly, positive results were also obtained when a monkey puppet divided items between two giraffe puppets (Bian, Sloane, & Baillargeon, 2018) and when an orange circle with eyes divided items between two yellow triangles with eyes (Meristo, Strid, & Surian, 2016). At the same time, however, other findings revealed that when the number

of items allocated was increased to four, infants under 12 months of age failed to detect a violation when one recipient was given three items and the other recipient was given one item (Schmidt & Sommerville, 2011; Ziv & Sommerville, 2017). Thus, while a concern for fairness emerges early in life, there are initially sharp limits to the fairness violations young infants can detect, for reasons that are currently being explored.

Equity The preceding findings demonstrate that even young infants possess an expectation of fairness. But how should this expectation be construed? Do infants possess a simple concept of *equality* and expect all individuals to be treated similarly, or do they possess a richer notion of *equity* and expect individuals to receive their just deserts? One way to examine this issue is to present infants with scenarios in which treating individuals the same way would violate fairness. For example, would infants expect a worker, but not a slacker, to receive a reward? To find out, 21-month-olds were shown events in which an experimenter asked two assistants to put away a pile of toys and then left; next to each assistant was a clear lidded box (Sloane et al., 2012). In the *both-help* event, each assistant placed about

Fairness Violations

A. Failing to distribute resources equally



B. Failing to dispense rewards equitably



FIGURE 1.1 Infants detect a fairness violation when (A) an experimenter fails to divide windfall resources equally between two similar recipients or (B) fails to dispense rewards equitably

between a worker, who put away toys as instructed, and a slacker, who did no work.

half of the toys in her box and then closed it. The experimenter then returned, inspected both boxes, and rewarded each assistant with a sticker. The *one-helps* event was similar except that one assistant put away all the toys in her box while the other assistant continued to play. Nevertheless, as before, the experimenter gave each assistant a reward (figure 1.1B). Infants looked significantly longer if shown the one-helps as opposed to the both-help event. This effect was eliminated if the boxes were opaque so the experimenter could no longer determine who had worked in her absence.

Additional experiments indicated that 10-month-olds detected a violation when an experimenter praised two assistants equally even though she could see that only one had performed the assigned task (Buyukozer Dawkins, Sloane, & Baillargeon, 2017); 21-month-olds detected a violation when an experimenter punished two assistants equally even though she could see that only one had not performed the assigned task (Buyukozer Dawkins et al., 2017); and 17-month-olds detected a violation when two workers shared a resource in a manner inconsistent with their respective efforts in obtaining this resource (Wang & Henderson, 2018).

Together, the preceding results suggest that infants' concern for fairness is equity-based: infants expect individuals to get their just deserts, be it an equal share of a windfall resource, a reward commensurate with their efforts, or a punishment that befits their actions.

In-Group Support

According to the principle of in-group support, members of a social group are expected to act in ways that sustain the group (Baillargeon et al., 2015; Brewer, 1999; Graham et al., 2013; Rai & Fiske, 2011; Shweder et al., 1997). The principle has two corollaries, *in-group care* and *in-group loyalty*, each of which carries a rich set of expectations. With respect to in-group care, for example, one is expected (a) to provide help and comfort to in-group members in need and (b) to limit harm to in-group members by refraining from unprovoked harm and by curbing retaliation. Similarly, with respect to in-group loyalty, one is expected (c) to prefer in-group members over out-group members and (d) to reserve limited resources for the in-group. Below, we report evidence that infants already hold these expectations.

Helping the in-group Do infants view helping as expected with an in-group individual but as optional otherwise? In one experiment, 17-month-olds watched events involving three female experimenters, E1–E3, who sat around three sides of an apparatus and announced their group memberships via novel labels (Jin & Baillargeon, 2017).

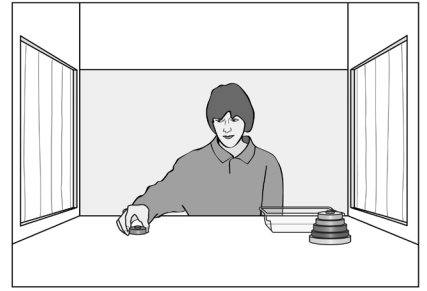
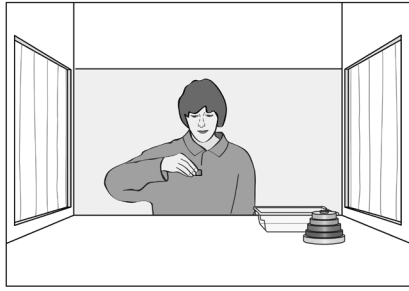
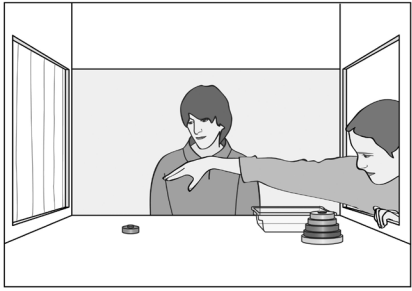
In the *in-group* condition, E1 (on the right) and E2 (in back) belonged to the same group (e.g., “I’m a bem!”; “I’m a bem too!”), while E3 (on the left) belonged to a different group (“I’m a tig!”). In the *out-group* condition, E2 belonged to the same group as E3 instead of E1 (E1: “I’m a bem!”; E2: “I’m a tig!”; E3: “I’m a tig too!”). Finally, in the *no-group* condition, the Es used phrases that provided incidental information about objects they had seen, rather than inherent information about their social groups (E1: “I saw a bem!”; E2: “I saw a bem too!”; E3: “I saw a tig!”). In the test trial, E3 was absent (her main role was to help establish group affiliations), and while E2 watched, E1 selected discs of decreasing sizes from a clear box and stacked them on a base. The final, smallest disc rested across the apparatus from E1, out of her reach (but within E2’s reach). E1 tried in vain to reach the disc until a bell rang; at that point, E1 said, “Oh, I have to go. I’ll be back!” and left. E2 then picked up the smallest disc, inspected it, and either placed it in E1’s box so that she could complete her stack when she returned (*help* event) or returned it to its same position on the apparatus floor, out of E1’s reach (*ignore* event; figure 1.2A).

Infants in the in-group condition looked significantly longer if shown the ignore as opposed to the help event, whereas infants in the out-group and no-group conditions looked equally at the events. Thus, in accordance with the principle of in-group care, infants detected a violation when E2 chose not to help in-group E1. In additional experiments (Jin, Houston, Baillargeon, Groh, & Roisman, 2018), 4-, 8-, and 12-month-olds were shown videotaped events in which a woman was performing a household chore when a baby (who presumably belonged to the same group as the woman) began to cry. The woman either attempted to comfort the baby (*comfort* event) or ignored the baby and continued her work (*ignore* event). At all ages, infants detected a violation in the ignore event, and this effect was eliminated if the baby laughed instead.

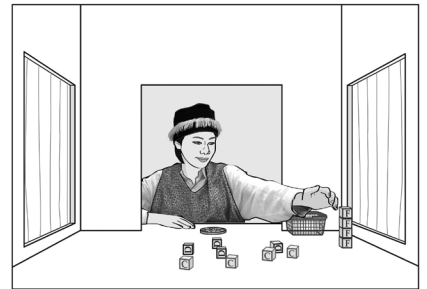
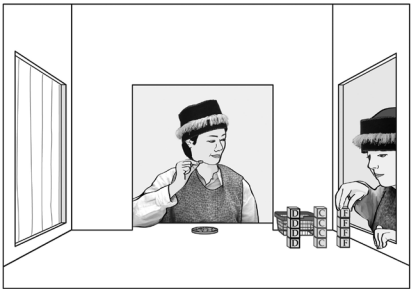
Limiting harm toward the in-group If infants’ sense of in-group care modulates their expectations about harm avoidance, they might expect individuals to direct *less* unprovoked and retaliatory harm at in-group members than at out-group members. To examine these predictions, 18-month-olds were first tested in a baseline *out-group* experiment (Ting, He, & Baillargeon, 2019a). Three female experimenters, E1–E3, sat around three sides of an apparatus, and their group memberships were marked by salient outfits: E1 (on the right) wore one outfit, while E2 (in back) and E3 (on the left) wore a different outfit. While E2 and E3 watched, E1 used small blocks to build two towers of four blocks. In the next trial, E3 was absent and E2 ate crackers from a

In-group—Support Violations

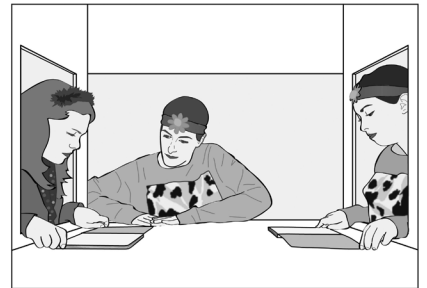
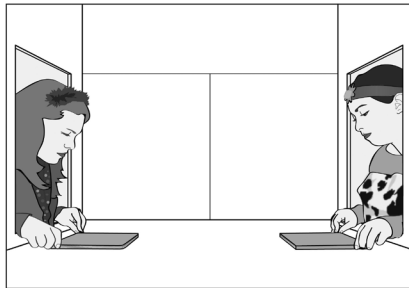
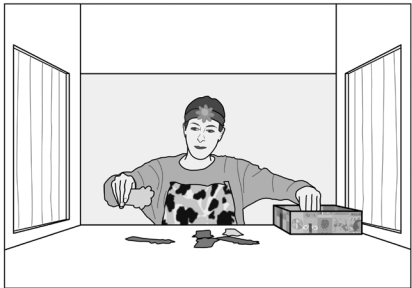
A. Failing to help the in-group



B. Failing to curb retaliation against the in-group



C. Failing to prefer the in-group



D. Failing to favor the in-group when dividing limited resources

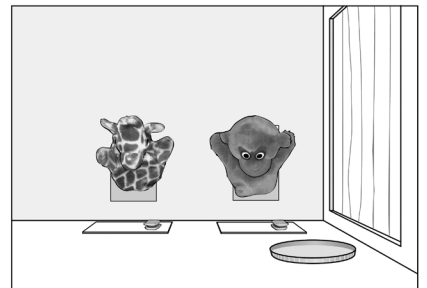
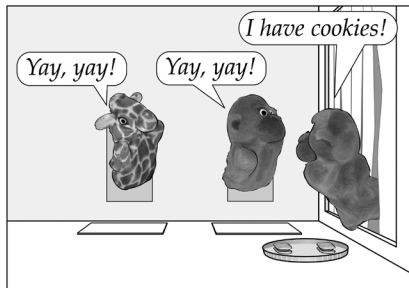
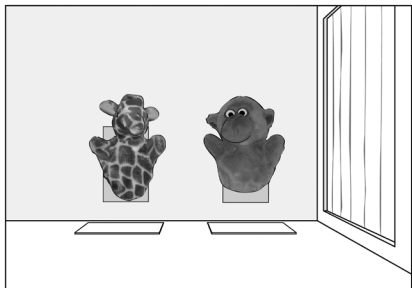


FIGURE 1.2 Infants detect an in-group—support violation when (A) an individual fails to help an in-group member in need of assistance, (B) fails to curb retaliation against an

in-group member who stole and ate a cracker, (C) fails to prefer an in-group member over an out-group member, and (D) fails to favor the in-group when distributing limited resources.

small plate in front of her while watching E1 build a third tower. After completing this tower, E1 either simply left the scene (*no-provocation* condition) or first stole a cracker from E2 and then left the scene (*provocation* condition). In both conditions, E2 then knocked down one block from one tower (*one-block* event), one tower (*one-tower* event), or two towers (*two-tower* event). In the no-provocation condition, infants looked significantly longer if shown the one- or two-tower event as opposed to the one-block event; in the provocation event, in contrast, infants looked significantly longer if shown the one-block or one-tower event as opposed to the two-tower event. Thus, when no provocation had occurred, infants detected a violation in all but the one-block event: mild unprovoked harm to out-group E1 was acceptable, but more significant harm was not. Following provocation, however, infants detected a violation in all but the two-tower event, suggesting that they viewed knocking down at least two of out-group E1's towers as an appropriate retaliatory response for her theft of one cracker (perhaps in a sort of "two-for-one" accounting).

Would infants show similar expectations if E1 and E2 belonged to the same group, or would considerations of in-group care modulate these expectations, leading infants to expect both less unprovoked harm and less retaliatory harm? To find out, infants were tested in an *in-group* experiment identical to that above except that E2 wore the same outfit as E1 and hence belonged to the same group. Across conditions, infants now detected a violation in all but the one-block event of the provocation condition. Thus, when no provocation had occurred, infants expected E2 to refrain from knocking down *any* of in-group E1's blocks; following provocation, knocking down one block became permissible in retaliation for in-group E1's theft—but no more than one block and certainly not two towers, as in the out-group experiment (figure 1.2B).

Together, the preceding results make clear that from an early age, considerations of in-group care modulate expectations about harm avoidance: infants expect stricter limits on unprovoked and retaliatory harm when directed at in-group members. In line with these results, recent experiments have found that infants also expect individuals to *punish* harm to in-group members, at least indirectly, through the withholding of help (Ting, He, & Baillargeon, 2019b). When a bystander saw a wrongdoer harm a victim, and the wrongdoer subsequently needed help to complete a task, 13-month-olds expected the bystander to refrain from providing help if the victim was an in-group member, but not if she was an out-group member. Infants' concern for in-group

care thus leads them to expect individuals both to limit harm to in-group members and to punish such harm, at least indirectly, when perpetrated by others.

Preferring the in-group Do infants expect individuals in a group to prefer in-group members over out-group members, in accordance with the principle of in-group loyalty? In one experiment (Bian & Baillargeon, 2016), 12-month-olds again saw events involving three female experimenters, E1–E3, whose group memberships were marked by salient outfits. In one familiarization trial, E2 (in back) sat alone; she picked up two-dimensional toys on the apparatus floor and placed them in a box near her, thus giving infants the opportunity to observe her outfit. In the next familiarization trial, E2 was absent and E1 (on the right) and E3 (on the left) read identical books; one E wore the same outfit as E2, and the other E wore a different outfit. In the test trial, E1 and E3 were joined by E2, who approached either the E from the same group (*approach-same* event) or the E from the other group (*approach-different* event; figure 1.2C) to read along. Infants looked significantly longer at the approach-different than at the approach-same event, suggesting that they expected E1 to approach her in-group member, in accordance with in-group loyalty, and detected a violation when she did not. This effect was eliminated when the first familiarization trial was modified to reveal that E2's outfit served an instrumental role: she now placed the toys she picked up in the large kangaroo pocket on her shirt, instead of in the box near her. Infants looked equally at the approach-different and approach-same events, suggesting that they no longer viewed the Es' outfits as providing information about their group memberships (in the same way, adults would not view pedestrians holding black umbrellas in the rain on a busy street, or travelers pulling black suitcases in a busy airport, as belonging to the same groups).

Similar results have been obtained in tasks using other cues to group memberships. After watching nonhuman adult characters soothe baby characters, 16-month-olds detected a violation if one baby preferred a baby who had been soothed by a different adult (and hence presumably belonged to a different group) over a baby who had been soothed by the same adult (and hence presumably belonged to the same group) (Spokes & Spelke, 2017). After watching two groups of nonhuman characters (identified by both physical and behavioral cues) perform distinct novel conventional actions, infants 7–12 months old detected a violation if a member of one group chose to imitate the other group's conventional action (Powell & Spelke, 2013). Finally, when faced with a native speaker of their language and a foreign speaker,

infants 10–14 months old were more likely to prefer the native speaker (Kinzler, Dupoux, & Spelke, 2007), to select snacks endorsed by the native speaker (Shutts, Kinzler, McKee, & Spelke, 2009), and to imitate novel conventional actions modeled by the native speaker (Buttelmann, Zmyj, Daum, & Carpenter, 2013). One interpretation of these last results is that in this minimal setting contrasting two unfamiliar individuals, language served as a natural group marker, leading infants to prefer and align with the native speaker, in accordance with in-group loyalty.

Favoring the in-group when resources are limited If infants' sense of in-group loyalty modulates their expectations about fairness, they might expect a distributor to favor in-group over out-group recipients, particularly when resources are scarce or otherwise valuable. To examine this prediction, 19-month-olds saw resource-allocation events involving two groups of animated puppets, monkeys and giraffes (Bian et al., 2018). A puppet distributor (e.g., a monkey) brought in either three (*three-item* condition) or two (*two-item* condition) items and faced two potential recipients, an in-group puppet (another monkey) and an out-group puppet (a giraffe). In each condition, the distributor allocated two items: she gave one item each to the in-group and out-group puppets (*equal* event; figure 1.2D), she gave both items to the in-group puppet (*favors-in-group* event), or she gave both items to the out-group puppet (*favors-out-group* event). In the three-item condition, the third item was not distributed and was simply taken away by the distributor when she left. Infants in the three-item condition looked significantly longer if shown the favors-in-group or favors-out-group event than if shown the equal event, suggesting that when there were as many items as puppets, infants expected fairness to prevail: they detected a violation if the distributor chose to give two items to one recipient and none to the other, regardless of which recipient was advantaged. In contrast, infants in the two-item condition looked significantly longer if shown the equal or favors-out-group event rather than the favors-in-group event, suggesting that when the distributor had only enough items for the group to which she belonged (e.g., two items and two monkeys), infants expected in-group loyalty to prevail: they detected a violation if the distributor gave any of the items to the out-group puppet.

Together, these results suggest two conclusions. First, the “first draft” of moral cognition includes not only principles of fairness and in-group support but also a context-sensitive ordering of these principles that befits their contents: one is expected to adhere to fairness except in contexts where doing so would be detrimental

to one's group. Second, a shortage of resources is one such context: when there is not enough to go around, the group must come first.

Authority

According to the principle of authority, when a social group accepts an individual in the group as a legitimate leader, rich expectations come into play that reflect this power asymmetry (Baillargeon et al., 2015; Graham et al., 2013; Rai & Fiske, 2011; Tyler & Lind, 1992; Van Vugt, 2006). On the one hand, the leader is expected to maintain order, provide protection, and facilitate cooperation toward group goals. On the other hand, the subordinates are expected to obey, respect, and defer to the leader. Do infants already possess authority-based expectations about the behaviors of leaders toward their subordinates or about the behaviors of subordinates toward their leaders?

Before addressing this question, developmental researchers first had to determine whether infants could represent power asymmetries. Over the past decade, evidence has steadily accumulated that by the second year of life, infants (a) can detect differences in social power (Pun, Birch, & Baron, 2016; Thomsen, Frankenhuis, Ingold-Smith, & Carey, 2011), (b) expect such differences to both endure over time and extend across situations (Enright, Gweon, & Sommerville, 2017; Mascaro & Csibra, 2012), and (c) distinguish between powerful individuals with respect-based as opposed to fear-based power (Margoni, Baillargeon, & Surian, 2018). Building on these results, recent experiments examined whether infants might also hold expectations about one specific type of respect-based power, the legitimate power of an authority figure (Stavans & Baillargeon, 2019). Specifically, these experiments asked whether infants would expect a powerful individual in a group to rectify a transgression perpetrated by one subordinate against another. The rationale was that positive results would suggest that infants cast the powerful individual in the role of legitimate leader and hence expected this leader to restore order in the group, in accordance with the principle of authority.

In these experiments, 17-month-olds watched live interactions among a group of three bear puppets (Stavans & Baillargeon, 2019). One puppet (at the back of the apparatus) served as the leader, and the other two puppets (on the left and right sides) served as the subordinates; in front of each subordinate was a place mat. In different scenarios, the leader was identified either by its larger size (physical cue) or by the subordinates' compliance with its instructions (behavioral cue); results

Authority Violation

Failing to rectify a transgression

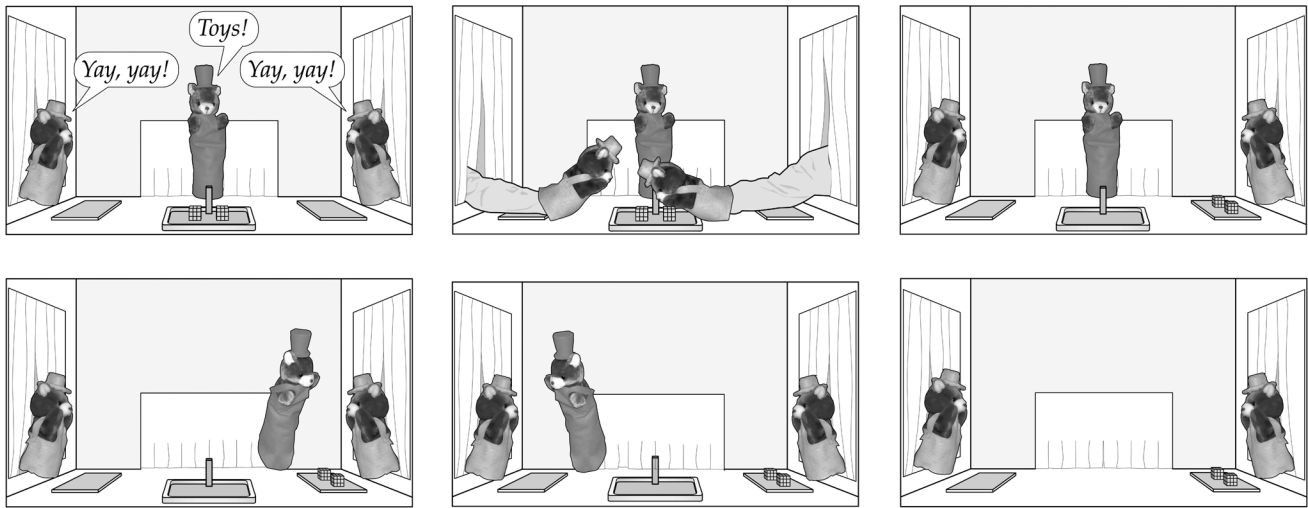


FIGURE 1.3 Infants detect an authority violation when a leader (here marked by its larger size) in a group fails to rectify a transgression between subordinate members of the group.

were identical across scenarios, so the size-based scenario is used here. To start, the leader brought in a tray with two identical toys for the subordinates to share. However, one subordinate (the perpetrator) quickly grabbed both toys and deposited them on its place mat so that the other subordinate (the victim) did not get a toy. In one event, the leader rectified this transgression by taking one of the toys away from the perpetrator and giving it to the victim (*rectify* event). In the other event, the leader again approached each subordinate in turn but did nothing to correct the transgression (*ignore* event; figure 1.3). Infants looked significantly longer if shown the ignore as opposed to the rectify event. This effect was eliminated if the leader was replaced by another member of the group who gave no evidence of being a leader (e.g., another bear of the same size as the two subordinates).

Together, these results suggest that when infants identify an individual as a legitimate leader in a group, they expect this leader to restore order if one subordinate transgresses against another, in accordance with the authority principle.

Conclusions

The evidence reviewed in this chapter suggests that from a very young age a skeletal framework of abstract principles guides infants' sociomoral reasoning. These principles include fairness, harm avoidance, in-group support (with its corollaries of in-group care and in-group loyalty), and authority. Although considerable research is needed to fully understand the "first draft" of human

moral cognition and how experience and culture revises it (Graham et al., 2013), available findings indicate that this "first draft" makes possible surprisingly sophisticated moral expectations, evaluations, and attitudes.

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2 Imaging Structural Brain Development in Childhood and Adolescence

CHRISTIAN K. TAMNES AND KATHRYN L. MILLS

ABSTRACT The human brain undergoes a remarkably protracted development. Magnetic resonance imaging (MRI) has allowed us to capture these changes through longitudinal investigations. In this chapter we describe the typical developmental trajectories of the human brain structure between childhood and early adulthood. We focus on measurements of brain morphometry and measurements derived from diffusion tensor imaging (DTI). By integrating findings from multiple longitudinal investigations with seminal cellular studies, we describe the neurotypical patterns of structural brain development and the possible underlying biological mechanisms. Finally, we highlight several new measures and approaches to examine structural brain development.

Since the 1990s, several longitudinal investigations have examined brain development using MRI. Through these studies we have learned that the human brain undergoes a particularly protracted development, with some aspects of our brain maturing into the third decade of life. This chapter will review the current literature on the development of brain structure as measured through MRI. We will focus on aspects of brain morphometry, as well as tissue microstructure as measured through DTI. We will then discuss the biological mechanisms underlying the developmental changes in brain structure and highlight new imaging and analytic approaches to the study of structural brain development. While there has been a recent concerted effort to understand aspects of brain development during infancy and early childhood using MRI, we will focus primarily on brain development during later childhood and adolescence.

Brain Structural and Microstructural Development

MRI, based on the principles of nuclear magnetic resonance, detects proton signals from water molecules and allows us to produce high-quality images of the internal structure of living organs. MRI protocols designed to

create anatomical images of the brain rely on signal intensities and contrasts to distinguish between gray matter, white matter, and cerebrospinal fluid (CSF), while other protocols can create, for example, images to probe tissue microstructural properties (figure 2.1).

Global volumes It is important to note that the cranial cavity itself continues to grow into the second decade of life. An investigation of four longitudinal developmental data sets presented evidence that intracranial volume increases around 1% annually between late childhood and midadolescence, when it begins to stabilize (Mills et al., 2016). In this regard, the growth of intracranial volume resembles the growth trajectories of other physical measures, such as height and bone density, although changes in body growth do not fully account for these changes in intracranial volume. In contrast to the steady increase in intracranial volume into midadolescence, whole-brain volume (the sum of the gray and white matter) reduces in size during adolescence before stabilizing in the early 20s (Mills et al., 2016). When these findings are considered alongside those from a large meta-analysis of longitudinal studies, it appears that whole-brain volume increases until around age 13 and then decreases until some point in the early 20s, after which it remains relatively stable until around age 40, when it begins to decrease again (Hedman, van Haren, Schnack, Kahn, & Hulshoff Pol, 2012). These findings go beyond early assertions that the brain is close to adult volume by childhood, as it is now clear that the overall size of the human brain continues to change across the first two decades of life.

Critically, volumetric growth of the two main sub-components of the brain, gray matter and white matter, follows distinct developmental trajectories. Gray matter—that is, the cerebral and cerebellar cortex and distinct subcortical structures—is composed of neuronal bodies, glial cells, dendrites, blood vessels,

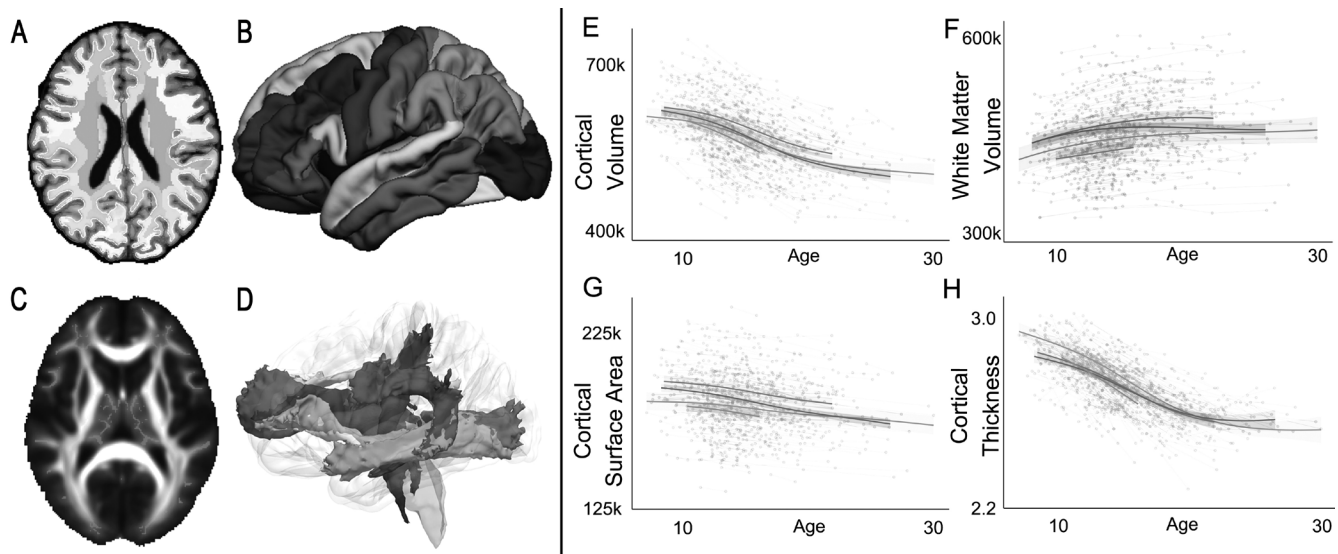


FIGURE 2.1 Illustration of key MRI methods and findings discussed in this review. *A*, Horizontal slice of T1 image showing a whole-brain segmentation used for volumetric analyses. *B*, A left-lateral view of an averaged parcellated cerebral cortex used for surface-based analyses, both from FreeSurfer. *C*, Horizontal slice of Tract-Based Spatial Statistics (TBSS) mean FA white matter skeleton overlaid on a mean FA map. *D*, a left-lateral view of a three-dimensional rendering of probabilistic fiber tracts from the Mori atlas.

extracellular space, and both unmyelinated and myelinated axons. Cortical gray matter increases rapidly after birth, approximately doubling in volume in the first year of life (Gilmore et al., 2012). It then reaches its greatest volume in childhood and begins to decrease in late childhood and throughout adolescence before stabilizing in the third decade of life (Lebel & Beaulieu, 2011; Mills et al., 2016). In a study of four longitudinal data sets, we calculated that cortical volume decreases by (on average) 1.4% annually between late childhood and early adulthood, with the sharpest decline in volume occurring in early to midadolescence (Tamnes, Herting, et al., 2017). In contrast, cerebral white matter, which occupies almost half of the human brain and consists largely of organized myelinated axons, continues to increase in volume into at least the second decade of life but begins to decelerate at some point in midadolescence to late adolescence (Lebel & Beaulieu, 2011; Mills et al., 2016). In addition to these tissue-specific patterns, component-specific and regional differences in brain developmental timing and pace have been linked to adolescent-specific changes in behavior.

The cerebral cortex Because the cerebral cortex is a layer of tissue enveloping the cerebrum, it is often measured in terms of *thickness*, *surface area*, or their product,

volume. Cortical thickness and surface area are influenced by various evolutionary, genetic, and cellular processes and show unique developmental changes (Mills, Lalonde, Clasen, Giedd, & Blakemore, 2014; Tamnes, Herting, et al., 2017; Vijayakumar et al., 2016; Wierenga, Langen, Oranje, & Durston, 2014). While brain size varies substantially in both mature and developing humans, there is less interindividual variability in cortical thickness than in surface area.

Average cortical thickness follows a similar nonlinear, decreasing trajectory as cortical volume (around 1% annually), although the decline in average cortical thickness is more pronounced across the second decade of life, before flattening out around age 20 (Tamnes, Herting, et al., 2017). Cortical thickness begins to decrease much earlier than gray matter volume or cortical surface area, with this process observed as early as 4 years of age (Walhovd, Fjell, Giedd, Dale, & Brown, 2017). In contrast, total cortical surface area increases in early development and begins to decrease in an almost linear fashion (around 0.5% annually) from late childhood to early adulthood (Tamnes, Herting, et al., 2017).

The cerebral cortex does not develop uniformly. Investigations of structural brain development starting in middle childhood have consistently found decelerating change in posterior cortical regions and accelerating

change in anterior regions, in line with the posterior-anterior theory of cortical maturation (Yakovlev & Lecours, 1967). For example, the parietal lobes and lateral occipital cortices (involved in sensory processing) show larger volumetric reductions in late childhood and early adolescence, whereas the medial frontal cortex and the anterior temporal cortex pick up the pace in the teen years (Tamnes et al., 2013). The more pronounced changes in brain structure that occur during the second decade of life are likely related to cognitive processes involved in the developmental tasks of this period of life.

Notably, not all cortical regions undergo significant macrostructural changes between late childhood and early adulthood. Studies of several longitudinal data sets have found evidence for little to no change in the central sulcus, medial temporal, and medial occipital cortices (Mutlu et al., 2013; Tamnes et al., 2013). Given that the central sulcus and the medial occipital cortices are involved in primary sensory processes, they likely undergo more rapid change at earlier ages. Certain cortical regions also show a relatively greater surface area expansion between childhood and young adulthood (Hill et al., 2010). Between ages 4 to 20, this includes the lateral and medial temporal, cingulate, lateral orbitofrontal, superior and inferior frontal, insular, temporoparietal, cuneus, and lingual cortices (Fjell et al., 2015).

Cortical topography The human cortex is highly convoluted, with approximately one-third of the cortical surface exposed on gyri and two-thirds buried within sulci. The gyrification index of the whole brain is defined as the ratio of the total folded cortical surface over the total perimeter of the brain (Zilles, Armstrong, Schleicher, & Kretschmann, 1988), whereas the local gyrification index measures the degree of cortical folding at specific points of the cortical surface (Schaer et al., 2008). The gyrification index of the human brain decreases between childhood and young adulthood, whereas the amount of exposed cortical surface increases from childhood to late adolescence (Alemán-Gómez et al., 2013; Raznahan, Shaw, et al., 2011). One longitudinal study demonstrated that the cortex “flattens” during adolescence, mostly due to decreases in sulcal depth and increases in sulcal width (Alemán-Gómez et al., 2013). The developmental changes in local gyrification vary across the cortex, with regions in the medial prefrontal cortex, occipital cortex, and temporal cortex undergoing little to no change between ages 6 to 30 (Mutlu et al., 2013). However, similar to what has been found in whole-brain (Raznahan, Shaw, et al., 2011) and lobar-level (Alemán-Gómez et al., 2013) analyses, Mutlu et al. (2013) observed linear

decreases in the local gyrification index across the majority of the cortex.

Subcortical structures Several subcortical structures and cortical infolds show substantial structural change between childhood and young adulthood, although generally at a lower rate than observed in the cortex (Tamnes et al., 2013). Longitudinal studies have found that the thalamus, pallidum, amygdala, caudate, putamen, and nucleus accumbens all show significant changes in volume across the second decade of life (Goddings et al., 2014; Herting et al., 2018; Wierenga, Langen, Ambrosino, et al., 2014). The caudate, putamen, and nucleus accumbens undergo linear reductions during this time, whereas the amygdala, thalamus, and pallidum follow nonlinear increases. These findings contradict with hypotheses and developmental models that assume that subcortical structures are mature by adolescence, as it is now clear that subcortical regions undergo structural development throughout the second decade of life.

White matter microstructure Diffusion MRI (dMRI) has over the last two decades grown in popularity as a method to study brain development, particularly that of white matter. dMRI uses the phenomenon of naturally moving water molecules in the brain to indirectly obtain information about the underlying tissue microstructure (Le Bihan & Johansen-Berg, 2012). This is possible since water diffusion in biological tissue is not free and uniform (isotropic) but reflects interactions with obstacles, such as cell membranes and myelin, and is therefore not necessarily the same in all directions (anisotropic). The diffusion patterns can reveal details about tissue architecture at a micrometer scale well beyond the usual millimetric resolution of morphometric MRI.

Typical quantification of dMRI is achieved in a tensor model, and this is referred to as DTI. Several indices can be derived; fractional anisotropy (FA) is used as a measure of the directionality of diffusion, mean diffusivity (MD) reflects the overall magnitude of diffusion, and axial diffusivity (AD) and radial diffusivity (RD) are diffusivity along and across the longest axis of the diffusion tensor, respectively. These indices can be analyzed on a voxelwise basis or in regions of interest. Tractography techniques can be used to reconstruct long-range connections, yielding possibilities for inferring patterns of structural connectivity (Jbabdi & Behrens, 2013). However, current techniques also have known limitations (see, e.g., Maier-Hein et al., 2017).

The major white matter fiber pathways in the brain are present and identifiable at birth, but very rapid

changes in DTI indices are seen across infancy (Qiu, Mori, & Miller, 2015). For example, a large longitudinal study of young children indicated that during the first two years of life, FA in ten major tracts increases by 16%–55%, RD decreases by 24%–46%, and AD decreases by 13%–28%, with faster changes in the first year than in the second for all tracts investigated (Geng et al., 2012). Such massive changes are perhaps not surprising given the enormous behavioral and psychological developments in this period of life.

As for later childhood and adolescence, many cross-sectional, and an increasing number of longitudinal, DTI studies document consistent patterns of continued development in white matter microstructure. With increasing age, FA increases, while MD and RD decrease, in most white matter regions, but the results for AD are less consistent (Tamnes, Roalf, Goddings, & Lebel, 2018). For example, Krogsrud et al. (2016) focused on the preschool and early school years and found that for most white matter regions, FA showed a linear increase over time, while MD and RD showed a linear decrease. Lebel and Beaulieu (2011) studied a much broader age range, 5–32 years, and used tractography for ten major white matter tracts. Almost all showed nonlinear developmental trajectories, with decelerating increases for FA and decelerating decreases for MD, primarily due to decreasing RD (see also Simmonds, Hallquist, Asato, & Luna, 2014).

The timing and rates of the DTI developmental changes vary regionally in the brain. A pattern of maturation in which major tracts with frontotemporal connections develop more slowly than other tracts has emerged (Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008). Lebel and Beaulieu (2011) also found a pattern in which changes in DTI parameters were mostly complete by late adolescence for projection and commissural tracts, while postadolescent development was indicated for both FA and MD in association tracts. Of the major fiber bundles, the cingulum, implicated in, for example, cognitive control, and the uncinate fasciculus, implicated in emotion and episodic memory, are among those shown to have particularly prolonged development (Lebel et al., 2012; Olson, Heide, Alm, & Vyas, 2015).

Relating Structural Brain Development to Biological Development

While most studies assess human brain development in relation to chronological age, other developmental processes, such as body growth and puberty, occur during the first two decades of life that likely have an impact on brain development. For several reasons, age might not be the most appropriate measure against which to judge

brain development. For one, age only explains a certain proportion of the variance in modeled trajectories. Further, age provides little information about the possible cellular and molecular mechanisms underlying observed changes. During late childhood and adolescence, individuals undergo physical changes such as a growth spurt in height and puberty, which happen at different ages across individuals, and, on average, at different times for girls and boys.

Sex differences Although males, on average, show larger global and regional brain volumes than females and sex differences have been reported for many other imaging measures (Ruigrok et al., 2014), the findings are much less clear for sex differences in developmental changes and trajectories across childhood and adolescence (Herting et al., 2018; Mutlu et al., 2013; Vijayakumar et al., 2016). It has also proven difficult to clearly describe how puberty and related hormonal changes affect brain structural and microstructural development, and there are few longitudinal studies (Herting & Sowell, 2017). However, one large longitudinal study found that age and pubertal development had both independent and interactive influences on volume for the amygdala, hippocampus, and putamen in both sexes and the caudate in females (Goddings et al., 2014). The relatively subtle (or inconclusive) evidence for mean sex differences in brain development might suggest that we need to move beyond mean level differences. Robust sex differences in the variability in brain measures have recently been shown in both developmental (Wierenga, Sexton, Laake, Giedd, & Tamnes, 2018) and adult samples (Ritchie et al., 2018), with males showing greater variance at both upper and lower extremities of the distributions, which might have functional and clinical implications.

Cellular and molecular mechanisms underlying structural changes What do developmental changes, as assessed by, for example, T1-weighted MRI or DTI scans, reflect on a cellular and molecular level? To date, studies that have directly tested these relationships in humans are scarce. However, several hypotheses concern the mechanisms underlying these observed developmental changes (Paus, 2013). One hypothesis is that reductions in the gray matter volume during adolescence partly reflect synaptic pruning. However, synaptic boutons are very small and comprise only a fraction of gray matter volume. Even when synapses are particularly dense, they are estimated to represent only 2% of a cubic millimeter of neuropil, or less than 1.5% cortical volume (Bourgeois & Rakic, 1993). Given this small percentage, it is unlikely that the marked decreases in

cortical volume observed across adolescence mainly reflect synaptic pruning. The reduction in the number of synapses might, however, in addition to a reduction in neuropil, also be accompanied by a reduction in the number of cortical glial cells or other processes. These events could together account for more of the cortical structural changes observed during development, although this remains a speculation. The encroachment of subcortical white matter, and/or continued intracortical myelination, likely affects the measurements of cortical gray matter by changing the signal intensity values and contrasts so that the boundary between white and gray matter moves outward with increasing age. Undoubtedly, there is a myriad of both parallel and interacting neurobiological processes underlying the macrostructural changes observed during childhood and adolescence in MRI studies.

Similarly, many factors, including axon caliber, myelin content, fiber density, water content, crossing or diverging fibers, and partial voluming, influence DTI indices (Beaulieu, 2009). Developmental changes in DTI indices are thought to mainly relate to increasing axon caliber and continued myelination, as well as changes in fiber-packing density (Paus, 2010). Animal studies indicate that axonal membranes are the primary determinants of FA, while myelin has a modulating role (Beaulieu, 2009; Concha, Livy, Beaulieu, Wheatley, & Gross, 2010). For example, rodent dysmyelination models show that FA values still indicate anisotropy and only reduce by approximately 15% in the complete absence of myelin (Beaulieu, 2009). Further, a rare study comparing human in vivo DTI with subsequent microscopy in patients with epilepsy found a robust positive correlation between FA and axonal membranes (Concha et al., 2010). Animal studies do, however, consistently indicate that RD is particularly sensitive to demyelination (e.g., Song et al., 2005), and correlations between DTI and myelin content and, to a lesser degree, axon count have also been shown in the postmortem brains of human patients with multiple sclerosis (Schmierer et al., 2007). The myelin content interpretation has, because of these and other findings, often been stressed. Although myelination, a process that begins between weeks 20 and 28 of gestation, has been shown to continue throughout childhood and adolescence (Benes, 1989; Benes, Turtle, Khan, & Farol, 1994; Yakovlev & Lecours, 1967), it does not logically follow from these rodent and postmortem studies that healthy developmental changes in RD in humans reliably indicate myelination (Paus, 2010). DTI parameters are sensitive to the general diffusion properties of brain tissue and are not selective markers of specific biological properties.

The relative roles of specific cellular and molecular processes for developmental changes in brain structure and microstructure are likely also age-dependent, with different contributions, for instance, in infancy, during adolescence, and in old age. Precise interpretations of the underlying mechanisms of morphometric or DTI developmental changes are thus challenging and should be done with great caution. However, investigating multiple imaging indices concurrently might yield additional information to better characterize tissue properties, and new imaging techniques, as well as studies combining imaging and histology, can hopefully increase our understanding of the cellular and molecular developmental processes.

Future Directions

Beyond well-established morphometric approaches and DTI, imaging acquisition and analysis techniques are ever evolving, promising to provide more sensitive or specific measures. In this section, we briefly present a few selected emerging imaging and analytic approaches and discuss their application to structural brain development in childhood and adolescence.

A small but increasing number of studies use surface-based methods and examine age-related differences in specific signal intensity contrasts, such as cortical gray/white matter contrast (Lewis, Evans, & Tohka, 2018; Norbom et al., 2019) or the T1-weighted/T2-weighted ratio, also referred to as cortical *myelin mapping* (Glasser & Van Essen, 2011; Grydeland, Walhovd, Tamnes, Westlye, & Fjell, 2013; see also Geeraert et al., [2017] for a comparison of other neuroimaging markers of myelin content in children). In relation to the more widely used measures, these approaches appear to provide partly independent and possibly more specific biomarkers of brain structural alterations in development, but further studies are needed to test this.

More recent and advanced dMRI methods compared to DTI, including diffusion kurtosis imaging (DKI) and neurite orientation dispersion and density imaging (NODDI), also aim to provide biologically more specific measures. Developmental studies using these methods are becoming more common, yet only cross-sectional studies are so far available (for a review, see Tamnes, Roalf, Goddings, & Lebel, 2018). NODDI studies indicate that the FA increase during childhood and adolescence is dominated by an increasing neurite density index (NDI), which points to increasing myelin and/or axonal packing but negligible changes in axon coherence during development (Chang et al., 2015; Mah, Geeraert, & Lebel, 2017). Moreover, results indicate that NODDI metrics predict chronological age better than DTI

metrics (Chang et al., 2015; Genc, Malpas, Holland, Beare, & Silk, 2017). These initial applications of these methods thus demonstrate utility in studying brain development. However, they currently require relatively long scan times, a hurdle for developmental studies.

An increasingly popular analytic approach is structural covariance, which refers to correlations across individuals in the properties of pairs of brain regions and aims to inform us about structural connectivity (Alexander-Bloch, Giedd, & Bullmore, 2013). A few longitudinal studies have used the approach of *maturational coupling*—that is, covariance in longitudinal changes across subjects. Frontotemporal association cortices show the strongest and most widespread maturational coupling with other cortical areas, while lower-order sensory cortices show the least (Raznahan, Lerch, et al., 2011). Another study looked at cortico-subcortical structural change relationships and found that these partly correspond to known functional networks; for example, a longitudinal change in hippocampal volume was found to be associated with longitudinal changes in the cortical areas involved in episodic memory (Walhovd et al., 2015). Maturational covariance, presumably reflecting coordinated development between brain regions, may also be responsible for cross-sectional structural covariance (Alexander-Bloch, Raznahan, Bullmore, & Giedd, 2013). Finally, a recent study indicates links between verbal intelligence and the strength of structural couplings of cortical regions in children and adolescents (Khundrakpam et al., 2017).

Beyond these measures, graph theoretical analyses are opening up new perspectives on the development of brain networks, potentially across imaging modalities and scales (Betzel & Bassett, 2017). Although many features of complex networks, such as small worldness, highly connected hubs (together forming a rich club), and modularity, are already established at birth, they are thought to mature across childhood and adolescence (Vértes & Bullmore, 2015; Wierenga et al., 2018). Few longitudinal studies have so far been performed, but one such study found that the efficiency of structural networks, as measured from DTI, changes in a nonlinear fashion from late childhood to early adulthood and that such development of network efficiency is related to intelligence (Koenis et al., 2017).

Conclusion

The human brain undergoes considerable changes in structure across the first two decades of life. Cortical gray matter increases into childhood and decreases steadily across adolescence before stabilizing in the

early 20s, whereas white matter increases. The cortex thins around 1% annually throughout the second decade of life, and surface area decreases at approximately half this rate. Crucially, cortical and subcortical changes do not proceed uniformly. Rather, there are regional differences in timing and tempo, with a general trend for posterior regions to develop earlier than anterior regions of the brain. White matter microstructure also continues to change into the third decade of life, with frontotemporal connections developing more slowly than other tracts. Both morphometric properties and diffusion measures derived from MRI cannot currently be mapped to specific cellular processes. Our understanding of the underlying mechanisms driving structural changes in the brain will continue to improve as new measures and approaches become more widely applied to longitudinal investigations.

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3 Cognitive Control and Affective Decision-Making in Childhood and Adolescence

EVELINE A. CRONE AND ANNA C. K. VAN DUJVENVOORDE

ABSTRACT Childhood and adolescence are periods of pronounced cognitive and emotional advancement accompanied by significant changes in brain maturation. This chapter describes the development of cognitive control abilities, including working memory, response inhibition, feedback monitoring, and relational reasoning, vis-à-vis developmental changes in brain maturation. It also discusses the neurocognitive development of affective decision-making, highlighting the role of risk and reward in adolescents' decision-making. These findings are integrated and discussed in relation to neurodevelopmental models of brain development. These models highlight not only the potential vulnerabilities in adolescent development but also the opportunities for adolescents' exploration and learning.

Cognitive and Affective Decision-Making in Adolescence

Fast improvement in cognitive control One of the most consistent observations in the development of cognitive capacities across childhood and adolescence is the rapid increase in cognitive control functions, otherwise referred to as *executive functions*. Cognitive control functions are the capacities that enable us to keep relevant information in mind in order to obtain a future goal (Diamond, 2013; Miyake & Friedman, 2012). Cognitive control functions have been demarcated into correlated yet distinct factors. Such factors include the ability to store and manipulate information in one's mind to inhibit responses, to filter irrelevant information, and to switch between tasks (Friedman et al., 2016). In early development there is a marked improvement in these cognitive control functions that continues during school-aged development, with adult levels of functioning achieved around mid-adolescence (Davidson, Amso, Anderson, & Diamond, 2006). These cognitive control functions are crucial for all kinds of daily activities and central to academic attainment. For example, working memory—a key component of cognitive control—predicts future academic performance in

areas such as reading and arithmetic (Peters, van der Meulen, Zanolie, & Crone, 2017; St. Clair-Thompson & Gathercole, 2006).

Social affective sensitivities At the onset of adolescence, the influence of social and affective context starts to have an impact on the decisions that adolescents make (see chapters 2 and 4). Adolescence begins with the onset of puberty (approximately 10–11 years of age), although there is individual variability (Goddings et al., 2014). During pubertal development there are substantial changes in terms of hormone release; these changes propagate alterations both in terms of bodily characteristics and social-affective sensitivities. These include an increased tendency toward risk-taking and a greater sensitivity to peer group influence (Crone & Dahl, 2012). Most changes in social sensitivity and increases in risk-taking behavior are adaptive and stimulate explorative learning, thus contributing to mature social functioning. However, in some cases such changes can have serious consequences, including accidents, drug abuse, and in extreme cases suicide attempts (Dahl & Gunnar, 2009).

These developmental patterns have inspired neuroscientists to investigate how different brain regions work together when children, adolescents, and adults make decisions.

The Neurocognitive Development of Cognitive Control

Basic cognitive control: working memory and response inhibition The basic components of cognitive control consist of several processes. Most developmental cognitive control research has focused on the processes of working memory and response inhibition.

Working memory Drawing from the adult literature (D'Esposito, 2007), several developmental neuroimaging

studies have examined the role of the lateral prefrontal cortex (Brodmann [BA] 44 and BA 9/46) and posterior parietal cortex (BA 7) in working memory performance and development. These studies have reported that when 8- to 12-year-old children and adults are performing a visuospatial working memory task, adults' brains showed more activation in the lateral prefrontal cortex and posterior parietal cortex than children's (Klingberg, Forssberg, & Westerberg, 2002; Kwon, Reiss, & Menon, 2002; Scherf, Sweeney, & Luna, 2006; Thomason et al., 2009). Age-related increases in the recruitment of these areas were also found for other domains of working memory, such as verbal working memory (Thomason et al., 2009) and object working memory (Ciesielski, Lesnik, Savoy, Grant, & Ahlfors, 2006; Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006; Jolles, van Buchem, Rombouts, & Crone, 2011). This increase in activation in the lateral prefrontal and posterior parietal cortex correlates with performance in both adults and children (Crone et al., 2006; Finn, Sheridan, Kam, Hinshaw, & D'Esposito, 2010; Olesen, Nagy, Westerberg, & Klingberg, 2003), suggesting that both age and performance have partly independent contributions to activation levels in these areas.

More recently, researchers have highlighted the importance of having large samples, and thus variability in terms of age and task performance, in order to better understand the interplay between these factors and brain development. A large-scale neuroimaging study including 951 participants aged 8–22 years aimed to disentangle the relationship between age and working memory performance (Satterthwaite et al., 2013). Age was associated not only with greater activation in the lateral prefrontal and posterior parietal cortex but also with lower activation in regions of the default network, such as the medial prefrontal and temporal cortex. A similar, but stronger, pattern emerged for task performance and remained even when controlling for age. Finally, activation in the lateral prefrontal cortex mediated the relationship between age and performance improvement. Together, these results suggest that (1) frontal and parietal brain regions are important for successful working memory performance, and (2) greater independence of frontal parietal and default model networks contributes to performance improvements across development.

Demands in working memory tasks also influence age-related changes in prefrontal cortex recruitment. For instance, some studies have reported that adults are more responsive in terms of neural activity to specific task demands (e.g., load dependency or modality dependency) than 7- to 13-year-old children (Brahmbhatt,

White, & Barch, 2010; Libertus, Brannon, & Pelphrey, 2009; O'Hare, Lu, Houston, Bookheimer, & Sowell, 2008), which may benefit performance.

Taken together, a comparison between children, adolescents, and adults shows that as age increases participants recruit the lateral prefrontal cortex and posterior parietal cortex and deactivate other regions of the cortex in a way that is helpful for the successful performance of a given task. In addition, children and adolescents seem less sensitive to different task demands.

Response inhibition A second basic control process contributing to cognitive control is the ability to inhibit inappropriate responses. In order to investigate this, most studies have made use of either stop-signal tasks, in which an already initiated response needs to be inhibited, or a go/no-go task, which involves the inhibition of a response to a rarely presented specific stimulus (e.g., letter X) that is presented in a series of other more prevalent stimuli requiring a response (e.g., other letters of the alphabet).

Neuroimaging studies in adults and patients have consistently reported that the right inferior frontal gyrus (BA 45/47) is important for successful inhibitory control (Aron & Poldrack, 2005) and for the greater attention demands associated with response inhibition (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010). Developmental neuroimaging studies have shown that the right inferior frontal gyrus is recruited more in adults than in children and adolescents (aged 8–17) and that adults perform better on inhibition tasks, suggesting that the right inferior frontal gyrus is important for successful inhibition (Durstun et al., 2006; Rubia et al., 2006; Tamm, Menon, & Reiss, 2002). Indeed, performance on the stop-signal task correlates with activity in the right inferior frontal gyrus in children, adolescents, and adults (Cohen et al., 2010). Besides the age-related increase in activation in the right inferior frontal gyrus, some studies have reported more widespread activation in other parts of the lateral and medial prefrontal cortex in 8- to 12-year-old children than adults when inhibiting responses (Booth et al., 2003; Velanova, Wheeler, & Luna, 2008). Finally, a longitudinal functional Magnetic Resonance Imaging (fMRI) study used an antisaccade task to dissect components of inhibition. This study found that the lateral and medial prefrontal cortex, regions that are important for adjusting performance and signaling errors, showed a protracted developmental change into mid-adolescence and late adolescence (Ordaz, Foran, Velanova, & Luna, 2013).

This evidence suggests that better response inhibition is accompanied by greater activation of the right inferior

frontal gyrus and that both inhibition performance and age drive activation differences in the lateral and medial prefrontal cortex. In addition, children rely on a wider network of areas for successful inhibition.

Adaptive control: feedback monitoring Whereas working memory and response inhibition require the implementation of specific task rules, most of our cognitive control requires us to respond to changing task demands. The ability to demonstrate adaptive behavior in response to changing task demands is referred to as *adaptive control*, a process required when, for example, feedback cues inform us that we need to change our behavior on a subsequent occasion.

Feedback monitoring has been widely studied in neuropsychological literature, using classic tasks such as the Wisconsin Card Sorting Task (WCST). Patient studies have found that several regions of the lateral and medial prefrontal cortex are important for monitoring negative feedback cues that inform participants that a previously applied rule (for example, sorting cards according to color) is no longer correct. This feedback cue (such as a minus sign, or the word *incorrect*) instructs the participant to switch to a new rule (for example, sorting cards according to shape) (Barcelo & Knight, 2002).

It was observed that while learning a certain sorting rule in a rule-learning and application task, both striatal and prefrontal regions were more active during the learning than applying phase. Longitudinal changes between ages 8 and 28 showed that these regions were more engaged when participants were older, with increases in neural activity until late adolescence (Peters, van Duijvenvoorde, Koolschijn, & Crone, 2016). Moreover, the dorsal striatum was most strongly engaged during late adolescence (16–18 years), and stronger activity predicted better learning performance at the testing session, as well as two years later (Peters & Crone, 2017). Together, these findings suggest that enhanced striatal activity is associated with an upregulation of cognitive control regions and, consequently, an increase in cognitive performance.

Other learning tasks focus on differences in valence, comparing positive or negative feedback ensuing from the response to certain task rules. Neuroimaging analyses reveal that in adults, receiving negative feedback results in activation in the same frontal parietal network and medial prefrontal cortex as is activated in working memory and inhibition studies (Zanolie, van Leijenhorst, Rombouts, & Crone, 2008). The negative feedback-related activity was greater for adults and 13- to 17-year-old adolescents than for 8- to 12-year-old children, specifically in the lateral prefrontal and posterior parietal

cortices (Crone, Zanolie, van Leijenhorst, Westenberg, & Rombouts, 2008; van den Bos, Guroglu, van den Bulk, Rombouts, & Crone, 2009; van Duijvenvoorde, Zanolie, Rombouts, Raijmakers, & Crone, 2008). This activation increase correlated with successful performance independent of age, suggesting that these areas are important for updating behavior following negative feedback (Crone, Zanolie, et al., 2008).

In children aged 8–10 years however, the lateral prefrontal cortex and posterior parietal cortex are typically more active in the reverse contrast; that is to say, more activation is reported following positive compared to negative feedback, with a shift occurring in adolescence (Peters, Braams, Raijmakers, Koolschijn, & Crone, 2014; van den Bos et al., 2009; van Duijvenvoorde et al., 2008). This developmental difference is specific to situations in which participants learn new rules and not when applying rules that are already learned (van den Bos et al., 2009).

Together, this suggests that late adolescents may be particularly sensitive to feedback providing the potential for learning a new rule. In addition, there may be valence differences in feedback processing in which adults show more activation in the lateral prefrontal cortex and posterior parietal cortex when updating behavior following negative feedback, while children recruit these same areas more following positive feedback, with a transition occurring in adolescence. These valence differences are, however, specific to more complex rule-learning tasks that require a goal-directed choice.

Complex cognitive control: relational reasoning The ability to interpret problems from multiple perspectives, to integrate knowledge, or to infer new solutions from presently available information probably lies at the highest level of cognitive control. This type of complex reasoning often involves the combination of different control processes for successful performance.

Relational reasoning Previous research in adults and adolescents has demonstrated that this ability to integrate information relies on the most anterior part of the prefrontal cortex, the rostralateral prefrontal cortex (Christoff et al., 2001; Dumontheil, 2014), which is modality independent (Magis-Weinberg, Blakemore, & Dumontheil, 2017). In a series of developmental neuroimaging studies, an adaptation of the Raven's Progressive Matrices task was used to study how neural activation differs when individuals need to integrate one dimension (e.g., follow a horizontal line of reasoning) or two dimensions (e.g., follow and integrate a horizontal and a vertical line of reasoning; see figure 3.1). The rostralateral prefrontal cortex was more

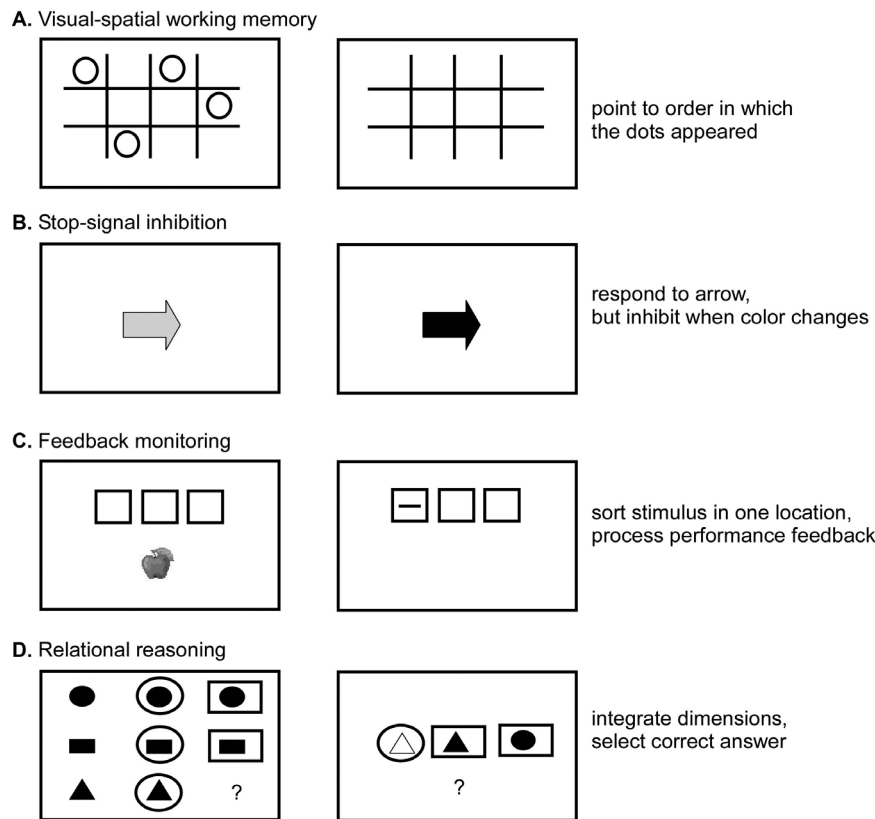


FIGURE 3.1 Examples of cognitive control paradigms. *A*, A visuospatial working memory typically involves the presentation of a grid in which dots are consecutively presented and need to be reproduced on the next trial. More dots will make the task more difficult. *B*, A stop-signal paradigm involves the presentation of a stimulus, which requires a left- or a right-hand response. In some trials, the arrow quickly changes color, which informs the participant that he/she should inhibit responding. *C*, A feedback-learning task typically involves a

stimulus, which needs to be sorted in a specific location. The feedback screen informs the participant whether the response was correct or incorrect. *D*, Relational reasoning requires the participant to integrate dimensions of a presented stimulus. One-dimensional trials are those in which only one direction needs to be followed (e.g., a horizontal line), and two-dimensional trials are those in which more dimensions (e.g., a horizontal line and a vertical line) need to be integrated to come to the correct solution. (See color plate 2.)

active in 8- to 12-year-old children at the onset of stimulus presentation but failed to show sustained activation during problem solving. In contrast, in adults this region showed sustained activation throughout the problem-solving period (Crone et al., 2009). In addition, a study including children, adolescents, and adults showed that children aged 7–10 years recruited the rostrolateral prefrontal cortex for both one- and two-dimensional problems, whereas adolescents aged 11–14 years showed a small differentiation in activation patterns, and adolescents aged 15–18 years recruited the rostrolateral prefrontal cortex for two-dimensional, but not for one-dimensional, problems (Wendelken, O’Hare, Whitaker, Ferrer, & Bunge, 2011). Finally, a study including 95 children and adolescents ages 6–18 years including a pictorial propositional analogy task showed that the left anterior prefrontal cortex (BA 47/45), a brain region important for semantic retrieval,

correlated positively with age and performance (Whitaker, Vendetti, Wendelken, & Bunge, 2018).

Together, these studies suggest that the specialization of the rostrolateral and anterior prefrontal cortex with regard to age is related to relational and semantic integration, respectively.

The Neurocognitive Development of Affective Decision-Making

Risks and rewards In order to understand how affective context influences the way we control our actions and make decisions, research has often focused on how children, adolescents, and adults process rewards. Reward processing has been examined in the context of risk-taking, based on the observation that adolescents are more prone than children and adults to take risks in daily life (Steinberg, 2011). Laboratory studies

have demonstrated an age-related reduction in risk-taking (Crone, Bullens, van der Plas, Kijkuit, & Zelazo, 2008; van Duijvenvoorde, Jansen, Bredman, & Huizenga, 2012), but also nonlinear age effects, suggesting that adolescents take more risks than children and adults when there is a strong affective context (Burnett, Bault, Coricelli, & Blakemore, 2010; Figner, Mackinlay, Wilkening, & Weber, 2009). The specificity of these developmental differences has been studied in more detail using neuroimaging.

One line of research tested risk-taking using experimental laboratory tasks, in which adolescents needed to decide between a certain chance of getting a small reward (safe bet) and an uncertain chance of getting a high reward (risky bet). The value of the choice at hand is reflected in the activation of a number of key brain regions, such as the ventral medial prefrontal cortex, posterior cingulate cortex, and ventral striatum (Barttra, McGuire, & Kable, 2013; Clithero & Rangel, 2014). In addition, it has been suggested that separate brain regions, such as the insula and dorsal medial prefrontal cortex, assess the level of risk during choice (Mohr, Biele, & Heekeren, 2010). In one study, adolescents showed a higher sensitivity to value compared to adults, as reflected in greater ventral striatum activation (Barkley-Levenson & Galvan, 2014). In addition, 16- to 19-year-old adolescents, compared to 9- to 12-year-old children and 25- to 35-year-old adults, also show a greater neural sensitivity to risk, which was reflected in insula and dorsal medial prefrontal cortex activation (van Duijvenvoorde et al., 2015). Similarly, when taking risks a more ventral part of the anterior cingulate cortex (subgenual ACC) was more active in 12- to 17-year-olds compared to 8- to 10-year-olds and 18- to 25-year-olds (van Leijenhorst, Gunther Moor, et al., 2010). Together, these findings suggest that adolescents rely more on striatal and affective prefrontal cortex regions in assessing choices and risks than do adults.

In these laboratory decision-making tasks, each decision to take a risk (or not) will typically lead to a reward or a loss outcome. Several studies have reported that this reward response in the ventral striatum is higher in 13- to 17-year-old adolescents compared to children and adults (Ernst et al., 2005; Galvan et al., 2006; Padmanabhan, Geier, Ordaz, Teslovich, & Luna, 2011; van Leijenhorst, Zanolie, et al., 2010). Adolescents' higher ventral striatum activation response to rewarding outcomes has been confirmed by a formal meta-analysis of neuroimaging studies comparing adolescents and adults (Silverman, Jedd, & Luciana, 2015), as well as by a three-wave longitudinal study testing individuals between ages 8 and 29 (Schreuders et al., 2018). This heightened reward response indicates

greater sensitivity to affective learning signals in adolescence.

An additional line of research used neuroimaging outcomes to predict self-reported risk-taking in daily life. Results showed positive associations between reward activation in the ventral striatum and the self-reported reward drive. That is, participants who indicated they were willing to exert more effort for a reward also showed greater striatum responses to rewards (Schreuders et al., 2018). Other studies showed that reward-related neural activation in the striatum and lateral prefrontal cortex was related to a variety of risky real-life behaviors, including risky sexual behavior, illicit drug use, and binge drinking (Blankenstein, Schreuders, Peper, Crone, & van Duijvenvoorde, 2018; Braams, Peper, van der Heide, Peters, & Crone, 2016; Galvan, Hare, Voss, Glover, & Casey, 2007). Finally, functional coupling between subcortical limbic structures and the orbitofrontal cortex (OFC) has been related to risky real-life behavior. That is, self-reported rule-breaking behavior has been related to a functional coupling of the striatum and OFC (Qu, Galvan, Fuligni, Lieberman, & Telzer, 2015).

Together, this suggests that functional activity and connectivity, within and between the striatal and prefrontal reward network, may be a marker for the propensity to display risk-taking behaviors.

Short-term and long-term consequences How individuals weigh up short- versus long-term consequences is often examined using delay-discounting tasks, where the option of obtaining an immediate (e.g., one dollar now) or a delayed reward (e.g., two dollars later) is presented with variable delays. Individuals tend to opt for the immediate reward more often when the delay for the larger reward is longer. In a delay-discounting task, preference for a delayed reward is associated with activation in the lateral prefrontal cortex, whereas preference for an immediate reward is associated with activation in the ventral striatum in both adolescents and adults (Christakou, Brammer, & Rubia, 2011). In adults, the ventromedial prefrontal cortex is more active than in 11- to 17-year-old adolescents when they choose immediate rewards, compared to 18- to 31-year-old adults. This region also shows age-related increases in functional connectivity within the ventral striatum, suggesting that the ventromedial prefrontal cortex works together with the striatum when selecting or inhibiting impulsive choices. Consistent with this line of reasoning, a diffusion tensor imaging (DTI) study reported that stronger structural connectivity between the (ventromedial) prefrontal cortex and the striatum relates to fewer short-term choices in adults (Peper et al., 2013). A longitudinal

study showed that this brain connectivity increases with age and is predictive for the tendency to balance immediate and delayed rewards two year later (Achterberg, Peper, van Duijvenvoorde, Mandl, & Crone, 2016). These findings suggest that the prefrontal cortex plays a regulatory role when making impulsive choices. Moreover, the development of this connectivity seems to underlie the developmental improvements in the inhibition of impulsive choices between adolescence and adulthood.

Models of Neurocognitive Development

Several models have been introduced to explain how the differential development of various brain regions is important for control and thus influences decision-making in adolescence. These dual-processing models (Casey, 2015; Ernst, 2014; Strang, Chein, & Steinberg, 2013) suggest that affective limbic brain regions, such as the ventral striatum, develop at a faster pace than brain regions important to control and regulation, such as the prefrontal cortex, the dorsal ACC, and the posterior parietal cortex. This imbalance makes

adolescence a sensitive time for risk-taking but also brings opportunities for exploration and adaptive learning.

Crone and Dahl (2012) suggest that puberty could be a driving force for heightened affective sensitivity in adolescence. Extensive animal research has pinpointed the timing of puberty in rodents and has reported specific effects of puberty on brain function and structure (Spear, 2011). Furthermore, pubertal hormones have been found to have a steering influence on the structural development of the human brain (Ladouceur, Peper, Crone, & Dahl, 2011). Finally, puberty influences affective responses to reward in the ventral striatum, independent of age (Forbes et al., 2010; Op de Macks et al., 2011). Puberty strongly influences the way we process affective and social information, preparing adolescents to obtain independence and adapt quickly to changing social contexts. Therefore, pubertal development may be an important contributor to the increased sensitivity to affective information, which, together with flexibility in recruitment of the prefrontal cortex, may facilitate explorative learning (figure 3.2).

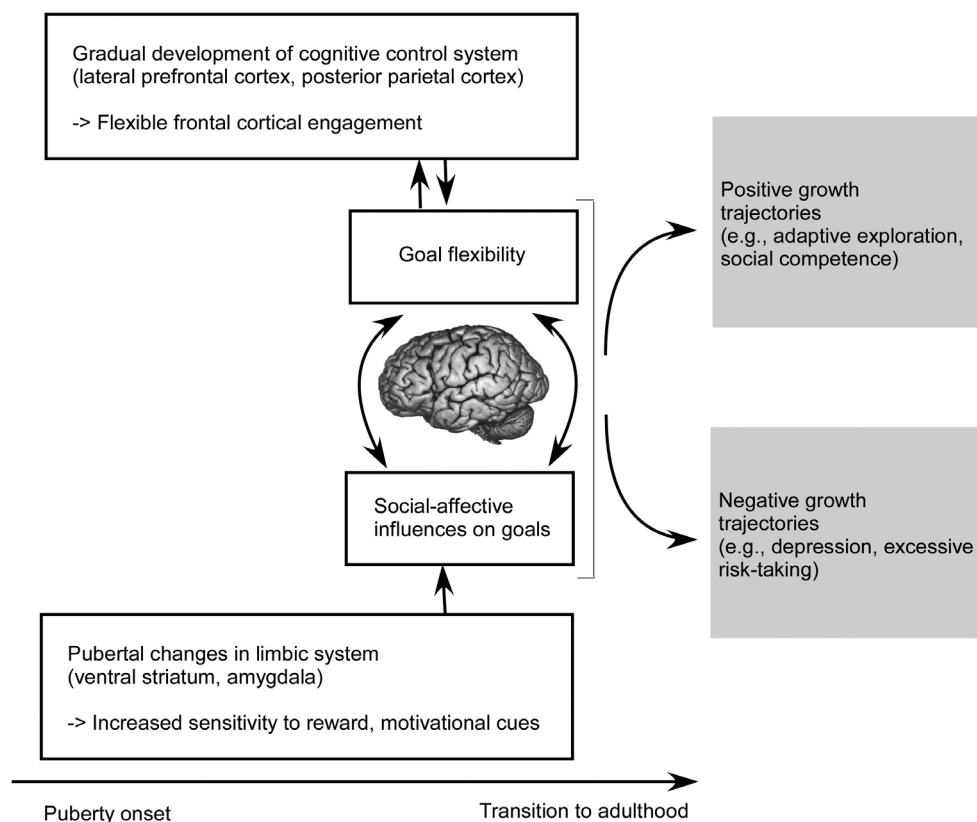


FIGURE 3.2 This model explains the slow developmental trajectory and flexible recruitment of the prefrontal and parietal cortex in adolescence, in combination with puberty-specific changes in the limbic system. This combination leads to positive growth trajectories in adolescence, as this is

a natural time of exploration and social learning. However, in some cases the imbalance between these systems can cause negative growth trajectories, which can result in depression or excessive risk-taking. Adapted from Crone & Dahl (2012).

More formal models have been suggested to help disentangle the process of risk-taking and learning. These types of models rely heavily on a more computational framework. Reinforcement-learning (RL) models are one such example. RL models specify prediction errors as key learning signals. That is, prediction errors signal the difference between expected and observed outcomes and are used to update learning behavior. These prediction errors can be calculated from a behavioral-computational model and combined with neuroimaging methods to find brain regions that track variations in prediction error. The striatum and medial prefrontal cortex are found to signal prediction errors across development—that is, the difference between expected and observed outcomes (van den Bos, Cohen, Kahnt, & Crone, 2012). These models can advance the field by quantifying how learning changes across development. Moreover, they can be applied to learning across contexts, such as learning in social situations. Computational models of social learning may rely on a social Prediction Error (PE) signal that describes how we learn from and about our social world. This could occur through interaction with others or by observing others (vicarious rewards). A growing body of evidence suggests substantial overlap between nonsocial (individual) and social learning (e.g., Ruff & Fehr, 2014).

Conclusion and Future Directions

This chapter has described the neural correlates of cognitive and affective decision-making in school-aged children, in adolescents, and in adults. Literature relating to cognitive control shows that the development of basic to complex levels of control follows a pattern of specialization with age in the prefrontal cortex and the posterior parietal cortex, such that these areas are more strongly and more selectively recruited for specific tasks. The transition from widespread to focused networks takes place during adolescence, which is a period of explorative learning. This development coincides with increased affective sensitivity in mid-adolescence to affective cues, pinpointing nonlinear contributions of control and affective brain regions in development (van Duijvenvoorde & Crone, 2013). This integrative approach, in which the development of cognitive control and decision-making are studied in combination, is expected to allow for a richer description of adolescent brain development.

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4 Social Cognition and Social Brain Development in Adolescence

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ABSTRACT Adolescence is a time of pronounced social, affective, and cognitive development, during which the social world becomes increasingly nuanced and dynamic. Social cognitive processes are critical in navigating complex social interactions and are associated with a network of brain areas termed the *social brain*. Neuroimaging and behavioral studies have demonstrated that the social brain undergoes significant and protracted structural and functional development during human adolescence, as do social cognitive abilities such as face-processing, mentalizing, perspective-taking, and social decision-making. The development of the social brain and social cognition does not occur in isolation but in the context of developments in other neurocognitive systems, such as those implicated in cognitive control and motivational-affective processes. Social contexts are a key source of motivational-affective responses, particularly during adolescence, when social factors increase in salience and value. The successful transition to adulthood requires the rapid refinement and integration of these processes, and many adolescent-typical behaviors, such as peer influence and sensitivity to social exclusion, involve dynamic interactions between these systems.

Adolescence can be defined as the period of life between the biological changes of puberty and the achievement of self-sufficiency and the individual attainment of a stable, independent role in society (Blakemore & Mills, 2014). While the concept of adolescence is recognized across cultures and throughout history, the nature of its biopsychosocial definition can make it challenging to define chronologically, as the timing of both pubertal onset and adult role transition varies both between and within cultures (Sawyer, Azzopardi, Wickremarathne, & Patton, 2018). This transitional period of development has long been associated with physical, social, behavioral, and cognitive changes. More recently, advances in brain imaging technology have enabled an increased understanding of structural and functional changes in the human brain during this developmental period and how they relate to social, affective, and cognitive development.

Many social changes occur during adolescence. These include the fact that, compared with children, adolescents form more complex and hierarchical peer

relationships and are more sensitive to acceptance and rejection by their peers (Brown, 2004; Steinberg & Morris, 2001). Although the factors that underlie these social changes are likely to be multifaceted, one possible contributing factor is the development of the *social brain*, the network of brain areas involved in social perception and cognition (Frith & Frith, 2007). In this chapter we focus on the development of social cognition and the social brain in adolescence.

Social Cognition and the Social Brain

Social cognition refers to the ability to make sense of the world through processing signals generated by other members of the same species and encompasses a wide range of cognitive processes that enable individuals to understand and interact with one another (Frith & Frith, 2007). These include social perceptual processes, such as face processing, biological motion detection, and joint attention, in addition to more complex social cognitive processes involving inference and reasoning, such as mentalizing—the process of mental state attribution. Such social cognitive processes enable us to understand and predict the mental states, intentions, and actions of others and to modify our own accordingly (Frith & Frith, 2007). Social cognition thus plays a critical role in the successful negotiation of complex social interactions and decisions (Crone, 2013).

A wide network of brain areas, referred to as the *social brain network*, is involved in social perception and cognition. Regions within the social brain network include the posterior superior temporal sulcus (pSTS), the temporoparietal junction (TPJ), the dorsomedial prefrontal cortex (dmPFC; medial aspects of Brodmann area 10; mBA10), and the anterior temporal cortex (ATC) (Frith & Frith, 2007).

Structural Development of the Social Brain

Areas within the social brain network are among the regions that undergo the most protracted development

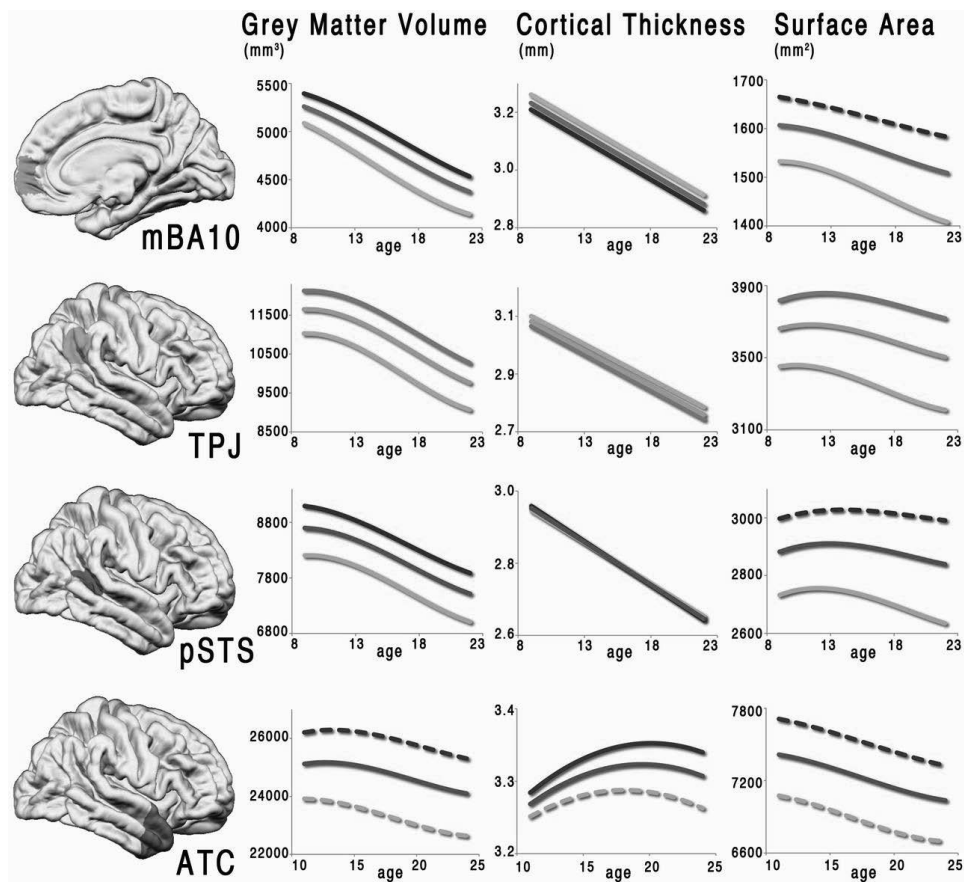


FIGURE 4.1 Structural development of the social brain. Structural developmental trajectories of brain areas associated with mentalizing across adolescence (gray matter volume, cortical thickness, surface area). The best-fitting models for all participants are shown for each region of interest (combined hemispheres). Models are fitted to the middle 80% of the sample (ages 9–22 years for mBA10, TPJ, and

pSTS; ages 11–24 years for ATC). The lighter lines show the fitted models applied to females only, and the darker lines show the fitted models applied to males only. Solid lines indicate the fitted model was significant ($p < 0.05$), whereas dashed lines indicate the fitted model was not significant ($p \geq 0.05$). Reproduced from Mills et al. (2014). (See color plate 3.)

in humans, showing changes throughout adolescence before relatively stabilizing in the early to mid-20s. Mills, Lalonde, Clasen, Giedd, and Blakemore (2014) examined the structural developmental trajectories (gray matter volume, cortical thickness, and surface area) of brain areas associated with mentalizing. In a sample of 288 individuals with at least two brain scans between the ages of 7 and 30, they found that gray matter volume and cortical thickness decreased in the dmPFC, the TPJ, and the pSTS from childhood into the early 20s. In contrast, the ATC increased in gray matter volume until early adolescence (~12 years), decreasing thereafter, whereas cortical thickness increased until early adulthood (~19 years). Surface area in all four regions followed a cubic trajectory, reaching a peak in late childhood or early adolescence before decreasing in the early 20s (figure 4.1).

Development of Social Cognition and Social Brain Function

While certain social cognitive processes are present from an early age (see chapter 1), behavioral and neuroimaging studies have shown developments in a number of more complex social cognitive abilities and functional changes in associated brain networks across adolescence.

Face-processing A vast array of social information can be extracted from the faces of those around us, including identity, emotional expression, and direction of eye-gaze. In adolescence, new aspects of face-processing become increasingly important as more complex social cognitive abilities develop, such as judgments of attractiveness or social status, which rely on the successful

detection and interpretation of communicative signals from face-processing. A small number of studies have suggested that face-processing abilities continue to improve during adolescence, with some studies observing a dip in face-processing proficiency in early adolescence. While the core face-processing network appears to be present from around 7 years of age, face-processing abilities and the brain systems that support them continue to show age-related changes between adolescence and adulthood (reviewed in Blakemore, 2008).

Evidence indicates that face-processing systems become increasingly specialized, particularly in relation to the more complex aspects of face-processing, such as detecting socially relevant information. Cohen Kadosh, Cohen Kadosh, Dick, and Johnson (2011) and Cohen Kadosh, Johnson, Dick, Cohen Kadosh, and Blakemore (2013) used a series of functional magnetic resonance imaging (fMRI) target detection tasks (detection of facial identity, expression, or eye-gaze direction) to investigate the developmental changes in the functional connectivity of the face-processing network when performing tasks involving face property-specific processes. Children, adolescents, and young adults activated the core face-processing network across all different tasks; however, the extent to which network connectivity was selectively modulated according to face-processing task demands increased between the ages of 7 and 11 (Cohen Kadosh et al., 2011). In adults, detecting a facial identity was associated with selective strengthening of the functional connectivity between the inferior occipital gyrus (IOG) and the fusiform gyrus, whereas detecting an emotional expression modulated connectivity between the IOG and the STS. No such modulation was found in children. A follow-up study indicated that with age there were also increases in task-specific activations that were additionally associated with changes in gray and white matter volume. These changes were distinct from more widespread activations that varied as a function of individual task performance (Cohen Kadosh et al., 2013). Thus, changes in face-processing during the first three decades of life appear to be related both to the continued structural development of underlying brain areas and to individual task performance, which might reflect changing cognitive strategies across development and experience (Cohen Kadosh et al., 2013).

Mentalizing Mentalizing describes the ability to make attributions about the mental states of others, including their beliefs, thoughts, desires, intentions, and feelings. There is a rich literature on the development of mentalizing in childhood, pointing to changes in the ability to understand others' mental states during the first five

years of life (Frith & Frith, 2007). While certain aspects of mentalizing are present in infancy (Baillargeon, Scott, & He, 2010), it is not until around age 4 that children begin to explicitly understand that someone else can hold a belief that differs from their own and that this can be false. Until fairly recently, there was a shortage of studies looking into mentalizing after childhood, as it was generally assumed that these abilities were already mature by mid-childhood in typically developing children. However, adolescence is marked by substantial changes in social competence and social behavior, as well as structural development within the social brain (Mills et al., 2014). These changes may be paralleled by changes in the neural processing of mentalizing.

Neuroimaging studies of mentalizing have consistently found associations with activity within the dmPFC, TPJ, pSTS, and ATC, suggesting these regions are key to the process of mental state attribution. A number of developmental fMRI studies of mentalizing report decreases in dmPFC recruitment between adolescence and adulthood (reviewed in Blakemore, 2008). These studies have used a variety of tasks that require mental state attribution, such as thinking about social emotions such as guilt (Burnett, Bird, Moll, Frith, & Blakemore, 2009), understanding intentions (Blakemore, den Ouden, Choudhury, & Frith, 2007), thinking about the preferences and dispositions of oneself or a fictitious story character (Pfeifer et al., 2009), and making attributions about the emotional states of others (Gunther Moor et al., 2012). An example of such a task is the Reading the Mind in the Eyes Test (RMET; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001), which assesses the ability to perceive, categorize, and make attributions about other people's mental and affective states based only on photographs of their eyes. Gunther Moor et al. (2012) used fMRI to compare brain activation while performing the RMET between early adolescents (10–12 years), mid-adolescents (14–16 years), and young adults (19–23 years) relative to a control condition (age and gender categorizations of the same stimuli). Whereas participants of all ages showed increased activation in the pSTS during the task, participants in the youngest group exhibited additional engagement of the dmPFC (Gunther Moor et al., 2012). A follow-up study that retested the same participants two years later indicated that these cross-sectional differences reflected longitudinal changes within individuals. Specifically, dmPFC activation during the RMET followed a quadratic developmental trajectory, being lowest during mid-adolescence (Overgaauw, van Duijvenvoorde, Moor, & Crone, 2015).

In some studies, higher activity in more posterior regions of the social brain, such as the pSTS/TPJ

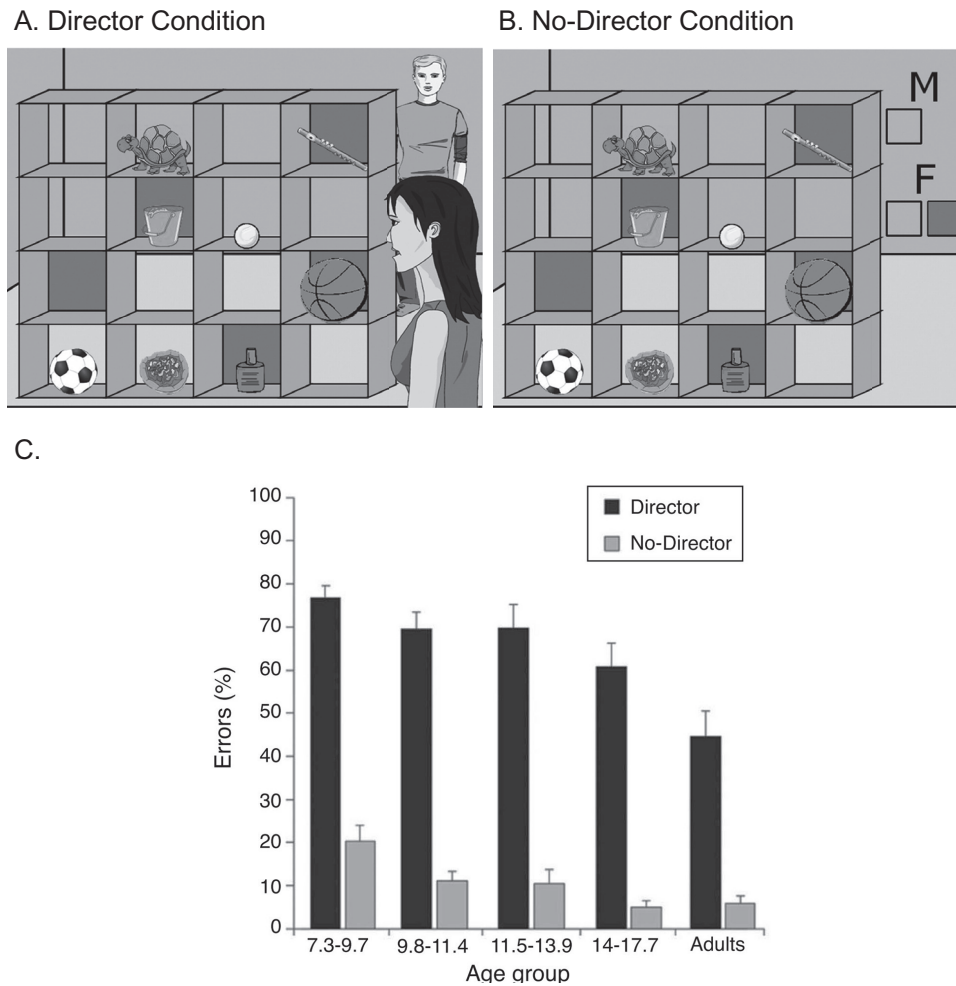


FIGURE 4.2 The Director task. Example stimuli from the Director task, including a social (A: Director) and nonsocial control condition (B: No-Director). In this example, in both conditions participants hear the instruction “Move the large ball up” in either a male or a female voice. In both examples, if the voice is female the correct object to move would be the basketball because in the Director condition (A) the female director is standing in front of the shelves and can see all the objects, and in the No-Director condition (B), the two boxes below the *F* (for “female”) indicate that all objects can be moved by the participant. If the voice is male, the correct object to move would be the football (soccer ball) because in

the Director condition (A) the male director is standing behind the shelves and therefore cannot see the larger basketball in the occluded slot, whereas in the No-Director condition (B) the single clear box below the *M* (for “male”) indicates that only objects in open shelves can be moved/that no objects in front of a gray background can be moved. C, Adolescents (14–17 years) make more errors than adults in the Director condition, whereas in the No-Director condition no difference is found between these age groups. Adapted from Dumontheil, Apperly & Blakemore (2010); Dumontheil, Hillebrandt, Apperly & Blakemore (2012).

(Blakemore et al., 2007), and in the ATC (Burnett et al., 2009), was observed in adults as compared to adolescents.

Perspective-taking The ability to take another person’s point of view into account, known as perspective-taking, is an important determinant of successful social functioning in everyday life. Fundamental aspects of perspective-taking develop during childhood. However, the ability to use these social competencies online continues to develop throughout adolescence.

The Director task can be used to investigate the ability to use perspective-taking to guide decisions in a referential communicative context. Participants are instructed to move objects around a set of shelves by a director, who cannot see some of the objects that the participant can see (figure 4.2; Apperly et al., 2010; Dumontheil, Apperly, & Blakemore, 2010). Correct interpretation of the instructions requires participants to use the director’s perspective and only move objects that the director can see. Adult participants frequently make errors in this task, suggesting that despite

possessing the ability to use mentalizing to understand that the director's perspective differs from their own, they often fail to use this information to guide decisions (Keysar, Lin, & Barr, 2003).

In a sample of participants aged 7–27 years, Dumontheil, Apperly, et al. (2010) used a computerized adaptation of the Director task. To differentiate between the general impact of cognitive control demands on task performance and effects that have a specific impact on the social components of the task, a control condition was included. In this condition the director was absent, and participants had to use a nonsocial rule to guide their decisions while following the (otherwise) identical instructions as in the Director condition. Although accuracy improved until mid-adolescence in both conditions, accuracy in the Director condition continued to improve after mid-adolescence. Similar findings were also observed in a more recent study (Symeonidou, Dumontheil, Chow, & Breheny, 2015). These findings suggest that the ability to use another's perspective to guide decisions continues to develop in late adolescence, over and above developmental improvements in more general cognitive control processes recruited by both conditions.

However, the improved integration of social cognition and cognitive control systems in adolescence may also contribute to developmental advances in perspective-taking (Dumontheil, Apperly, et al., 2010). Using a variant of the Director task adapted for fMRI (Apperly et al., 2010; Dumontheil, Küster, Apperly & Blakemore, 2010), in which the cognitive demands of the task were also manipulated, Dumontheil et al. (2012) demonstrated developmental differences in brain areas associated with both social cognitive and more domain-general cognitive control processes. In both social and nonsocial conditions, adults recruited frontoparietal regions associated with cognitive control more than adolescents. When social cues were needed to accurately perform the task, both adults and adolescents (11–16 years) recruited the dmPFC; however, adolescents also recruited the dmPFC when social cues were not needed. The authors suggest that this engagement of the dmPFC for irrelevant social stimuli may reflect the use of social brain regions even when they are not necessary, consistent with a pattern of increasing specialization within networks supporting social cognition.

Social decision-making Another line of research into the dynamic and interactive aspects of social cognition has employed paradigms from the field of behavioral economics to study the development of the cognitive and neural mechanisms that underlie more complex aspects of social exchanges, such as social preferences

for fairness, trustworthiness, or cooperation (van Duijvenvoorde & Crone, 2013). Even though a basic sense of fairness in bargaining is observed in young children (Güroğlu, van den Bos, & Crone, 2009), the understanding of intentionality in social interactions develops gradually over the course of adolescence and early adulthood (Güroğlu, van den Bos, & Crone, 2009; van den Bos, Westenberg, van Dijk, & Crone, 2010). Age-related changes in social behavior beyond childhood, such as increases in trust and reciprocity during social interactions (Belli, Rogers, & Lau, 2012; van den Bos et al., 2010), may be associated with the increasing tendency to consider others' viewpoints and intentions.

In an fMRI study, young adolescents (12–14 years), older adolescents (15–17 years), and young adults (18–22 years) played the role of the second player in the Trust Game (van den Bos, van Dijk, Westenberg, Rombouts, & Crone, 2011). An anonymous first player would give an amount of money as an investment, which the participant could either divide equally between herself and the investor or keep the majority for herself. Participants' tendency to take the perspective of the first player into account was investigated by examining their sensitivity to the degree of risk (i.e., the amount of money that could be lost) taken by the investor. Whereas older adolescents and young adults were more likely to reciprocate when the investor trusted them and therefore risked losing larger amounts of money, the younger adolescents did not differentiate. These findings suggest that adolescence is not necessarily characterized by general increases in prosocial behavior but by an increase in sensitivity to the perspective of others.

These forms of perspective-taking behavior were associated with increased involvement of the left TPJ and the right dorsolateral PFC (dlPFC), which the authors suggest indicates a role for both social cognitive and cognitive control systems in the development of social behavior in adolescence. When participants observed that the first player trusted them, recruitment of the left TPJ increased with age, and this level of activation correlated with participants' sensitivity to the first player. Participants also showed increased engagement of the right dlPFC with age when receiving trust, which the authors speculate may indicate a regulatory role of the right dlPFC in social exchange—for example, in the inhibition of more egocentric behavior—although the precise psychological mechanisms cannot be ascertained from neural activity patterns (van den Bos et al., 2011).

Fett, Shergill, et al. (2014) investigated the relationship between perspective-taking and social processes—such as trust and reciprocity—in adolescence, using two variants of the Trust Game and the Director task.

Adolescents (13–18 years) with a higher perspective-taking tendency (measured as accuracy on the Director task) demonstrated greater trust toward others (initial investment in the Trust Game) and higher levels of trust during cooperative interactions (higher investments). While all adolescents modified their behavior in response to unfair interactions (decreased investments and more malevolent reciprocity) when they were treated unfairly, high perspective-takers did so more drastically, suggesting a greater decrease in trust. The authors propose that increases in perspective-taking tendencies in adolescence are therefore associated with specific developmental changes in trust and reciprocity, as opposed to simply generalized increases in prosocial behavior. Although this study did not include adult participants, the behavioral patterns of high perspective-takers were similar to those observed in adults in another study using this paradigm (Fett, Gromann, Giampietro, Shergill, & Krabbendam, 2014).

Behavioral findings add support to this conclusion. In a series of allocation games in which the identity of the interaction partner was manipulated (friends, antagonists, neutral classmates, anonymous peers), younger adolescents (9 and 12 years) showed similar levels of prosocial behavior to all interaction partners (Güroğlu, van den Bos, & Crone, 2014). However, older adolescents (15 and 18 years) showed increasing differentiation in prosocial behavior according to their relation with the partner, displaying the most prosocial behavior (both costly and noncostly) toward friends. This suggests that with age, *who* you are interacting with becomes more important. The age-related increase in noncostly prosocial behavior toward friends was mediated by self-reported perspective-taking skills.

Interactions between Social Cognition, Cognitive Control, and Motivational-Affective Processing in Adolescence

While there is a growing body of work investigating the interplay between cognitive control and motivational-affective processing, less is known about the way in which these processes interact with social cognitive processes, social contexts, and stimuli. Social interactions are a key source of elicited motivational-affective responses: social cues can elicit robust affective responses, and those around us can be a salient source of potential rewards and punishments. Socioaffective context, such as the heightened motivational salience of peers or the affective appraisal of the value of an outcome, appears to exert a great influence on the extent to which cognitive control systems are recruited in adolescence. This context can be external—for

example, one's social context—or internal, such as one's affective state.

Social cognition and affective processing The perception, understanding, and interpretation of others' emotions is a fundamental aspect of social interaction and requires the integration of a range of perceptual, social cognition, and affective skills (Garcia & Scherf, 2015). These include basic aspects of affective processing, such as emotion perception and recognition, and more complex social cognitive processes, such as the ability to understand the affective states of others, sometimes referred to as *affective mentalizing*.

Affective mentalizing requires the integration of both social cognitive and affective processing networks. Sebastian et al. (2012) examined the development of affective (understanding emotions) and cognitive mentalizing (understanding thoughts, perspectives, and intentions) and their neural substrates during adolescence using cartoon vignettes. Both types of mentalizing were associated with activation in social brain network regions (including dmPFC, pSTS/TPJ, and ATC); however, affective mentalizing also elicited activation in the ventromedial PFC, which was greater in adolescents compared to adults. These findings extend the pattern of decreased dmPFC activation between childhood and adulthood to aspects of medial PFC more typically associated with affective processing and highlight the importance of considering the integration, overlap, and interplay of multiple developing brain regions and networks when investigating the development of complex social skills and behaviors during adolescence.

Affective consequences of social interactions *Social affect* refers to the interaction between our emotions and our behavior in the context of communication with others. The highly rewarding nature of peer interactions during adolescence is believed to increase the impact of both positive and negative aspects of such interactions. Social situations can evoke strong emotional responses, and there is evidence that this is particularly great in adolescence.

Studies of peer rejection in adolescence, using a range of experimental paradigms, repeatedly find that peer rejection is associated with worsened mood, increased distress, and increased anxiety in adolescents compared to child and adult groups, particularly in younger adolescents (reviewed in Platt, Cohen Kadosh, & Lau, 2013). Similarly, Silvers, McRae, Gabrieli, and Gross (2012) found that when viewing socioaffective stimuli, as opposed to nonsocial affective stimuli, younger adolescents had greater difficulty regulating their emotions than did older adolescents and adults.

Studies of the neural bases of emotional regulation in the context of social rejection have implicated prefrontal regions—notably, the right ventrolateral PFC (vLPFC). Compared to adults, adolescents show reduced activation of this region during experimental manipulations of social rejection, such as the Cyberball game (Bolling et al., 2011; Masten et al., 2009; Sebastian et al., 2011). It has been suggested that developmental increases in vLPFC activation may be associated with an increased regulation of social distress following exclusion. Consistent with this hypothesis, within adolescents, greater right vLPFC activation during exclusion has been associated with higher levels of parent-reported interpersonal competence, lower self-reported distress (Masten et al., 2009), and lower self-reported resistance to peer influence (Sebastian et al., 2011). Furthermore, Bolling et al. (2011) found age-related increases in functional connectivity between the right vLPFC and the ventral anterior cingulate cortex, an effect found only during social exclusion and not during a similar task in which social expectancies were violated but participants were not excluded.

Social context and peer influence Social context can have an impact on decision-making, such as the propensity to engage in prosocial or risky behaviors. Adolescents are often characterized as prone to engage in risky decision-making, which, although probably adaptive in many circumstances (Blakemore & Mills, 2014; Willoughby, Good, Adachi, Hamza, & Tavernier, 2013), can sometimes result in negative real-life outcomes, such as unsafe sexual behavior, substance abuse, and dangerous driving (Viner et al., 2011; Willoughby et al., 2013). As a result of these epidemiological findings, experimental studies of social context in adolescence have largely focused on the impact of peer influence on adolescent risk-taking behavior.

The presence of peers affects how likely adolescents are to take risks in a driving-simulation game. While adolescents (13–16 years), young adults (18–22 years), and adults (24 years and older) have been shown to take around the same number of driving risks when alone, in the presence of their friends adolescents took significantly more risks, whereas peer presence had no impact on risk-taking in adults and an intermediate effect in young adults (Gardner & Steinberg, 2005). Adolescents are also sensitive to the presence of peers when performing other experimental tasks involving risky and reward-related decisions (O'Brien, Albert, Chein, & Steinberg, 2011; Smith, Chein, & Steinberg, 2014).

The increased sensitivity to the presence of peers found in risky and reward-related decision-making appears to extend to other aspects of cognition. One

study found that the presence of peers had a detrimental effect on female adolescents' performance on a high-level cognitive task (relational reasoning; Wolf, Bazargani, Kilford, Dumontheil, & Blakemore, 2015). Pairs of female friends were randomly assigned as either a participant or an observer. The participant then performed the task in three social contexts: alone, observed by a friend, or observed by an experimenter. Social context affected adolescent, but not adult, performance, an effect that was also influenced by the participants' age and the task difficulty. Older adolescents (14.9–17.8 years) exhibited poorer performance when being observed by their friend relative to the experimenter, independent of task difficulty, while younger adolescents (10.6–14.2 years) only showed this effect for easier reasoning trials (Wolf et al., 2015).

Social context can also modulate adolescents' attitudes toward risk (Engelmann, Moore, Capra, & Berns, 2012). A study investigated the development of social influence on risk perception from late childhood to adulthood by asking participants to rate the riskiness of everyday situations (Knoll, Magis-Weinberg, Speekenbrink, & Blakemore, 2015; figure 4.3). After recording their rating, individuals were informed about the ratings of a social-influence group (teenagers or adults) before rating each situation again. All age groups showed a significant social-influence effect, changing their risk ratings in the direction of the provided ratings, and this social-influence effect decreased with age. Most age groups adjusted their ratings more to conform to the ratings of the adult social-influence group than to the ratings of the teenage social-influence group. Only young adolescents (aged 12–14) were more strongly influenced by the teenage social-influence group than by the adult social-influence group, which suggests that to early adolescents, the opinions of other teenagers about risk matter more than the opinions of adults.

In contrast to the presence of peers, parents can have a protective effect on risk-taking in adolescence. Telzer, Ichien, and Qu (2015) showed that adolescents demonstrated reduced risk-taking behavior when their mothers were present compared with when alone. Safe decision-making was associated with greater recruitment of the vLPFC and greater functional coupling between the ventral striatum (VS) and the vLPFC, while risky decision-making was associated with decreased activation in the VS. The authors propose that heightened adolescent sensitivity in neural circuitry that is associated with greater risk-taking can also be redirected toward making thoughtful, more deliberative, and safer decisions.

Peer influence is largely associated with negative outcomes; however, peers can also have a positive influence

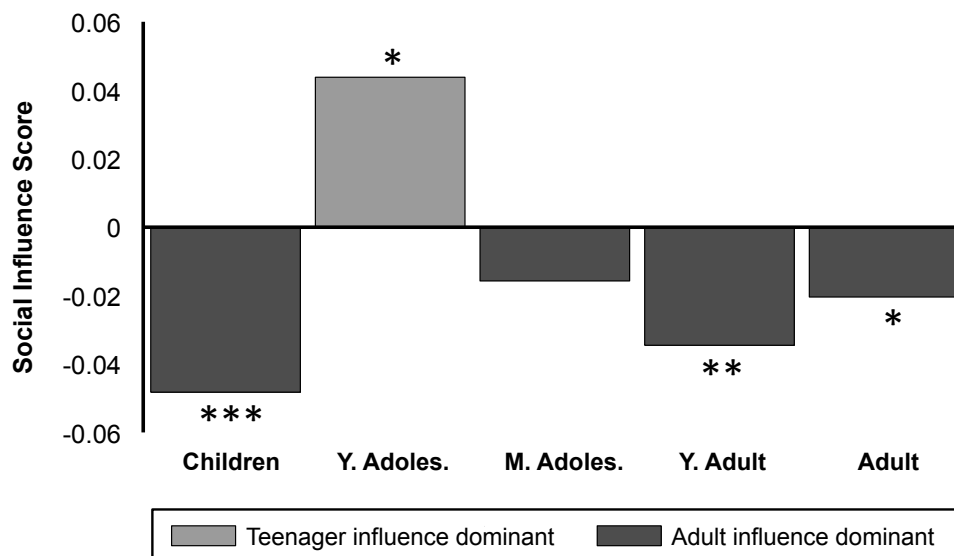


FIGURE 4.3 Effect of social influence on risk ratings. Participants ($N=563$) rated the riskiness of everyday situations before and after they were informed about the ratings of a social influence group (teenagers or adults). Social influence score, an index of conformity to other people's ratings, is shown relative to the source of the social influence for five age groups: children (aged 8–11 years), young adolescents (Y. Adoles., aged

12–14 years), mid-adolescents (M. Adoles., aged 15–18 years), young adults (Y. Adult, aged 19–25 years), and adults (aged 26–59 years). The difference in social influence effect between social influence groups (adults vs. teenagers) is shown for each age group (** $p < 0.001$; * $p < 0.01$; * $p < 0.05$). Adapted from Fuhrmann, Knoll, & Blakemore, 2015; data published in Knoll et al. (2015).

on behavior. A study demonstrated that prosocial feedback from peers was associated with increased prosocial behavior compared to either no feedback or to antisocial feedback, which was associated with decreased prosocial behavior (van Hoorn, van Dijk, Meuwese, Rieffe, & Crone, 2014). The tendency to moderate behavior in line with the values of the people we are with likely involves both regulatory and social cognitive processes. Greater neural activity within cognitive control regions during a response inhibition task predicted safer decisions in the driving-simulation game, specifically when in the presence of a peer who expressed risk-averse attitudes, as compared to a risk-promoting peer (Cascio et al., 2015). The authors suggest that the ability to override risky tendencies in the presence of cautious peers may therefore be associated with individual differences in the systems involved in top-down cognitive control. In a follow-up fMRI study of the influence of peers on prosocial behavior, van Hoorn, van Dijk, Güroğlu, and Crone (2016) demonstrated that the presence of peers during decision-making resulted in increased activity in several social brain regions, including the dmPFC, TPJ, and pSTS, and that TPJ activity was positively associated with the degree to which peer feedback increased prosocial behavior. These findings may suggest that individual differences in social cognitive processes, such as perspective-taking, result in variation in the influence of peers on prosocial behavior.

In everyday life, the attitudes and values of those around us are not always explicitly expressed but must instead be inferred using social cognitive processes. Studies investigating the relationship between risk-taking and social exclusion in adolescence suggest that in addition to cognitive control processes, social cognition processes may also be uniquely implicated in adolescents' vulnerability to peer influence on risk-taking. Falk et al. (2014) used the Cyberball game to examine whether neural activation during simulated social exclusion predicted peer influence on risky decisions in the driving-simulation game one week later in 16- to 17-year-olds. Activity in the social brain network (dmPFC, right TPJ, posterior cingulate cortex) during social exclusion was positively associated with increased risk-taking when playing the game in the presence of a peer, relative to alone. In a further study, adolescent participants (14–17 years) completed the driving-simulation game—while in the implied presence of two online peers—before and after being socially excluded by these peers (Peake, Dishion, Stormshak, Moore, & Pfeifer, 2013). Exclusion was associated with greater behavioral risk-taking among adolescents with low self-reported resistance to peer influence (RPI). When making risky decisions after social exclusion, adolescents who had lower RPI exhibited higher levels of activity in the right TPJ, and this response was a significant mediator of the

relationship between RPI and greater risk-taking after social exclusion. Lower RPI was also associated with lower levels of activity in the lateral PFC during risks following social exclusion, but this did not mediate the relationship between RPI and greater risk-taking after social exclusion.

Conclusion

Research over the past decade has demonstrated the substantial and protracted development of multiple aspects of social cognition, as well as the structural and functional development of the social brain network, across human adolescence.

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5 A Lifespan Perspective on Human Neurocognitive Plasticity

KRISTINE BEATE WALHOVD AND MARTIN LÖVDÉN

ABSTRACT *Plasticity* can be defined as the ability of the brain to change its structure in response to a mismatch between its capacity and environmental demands. Taking a phylogenetic perspective, we review the evidence for qualitative and quantitative differences in human plasticity across the lifespan. In this perspective, humans, relative to other animals, possess low plasticity but develop greater flexibility. Current evidence emphasizes heightened vulnerability, rather than high experience-dependent plasticity, in early human life, with little evidence of qualitative age differences (e.g., critical periods) in plasticity other than those involved in the development of species-mandatory functions. Quantitative differences in plasticity, evident as decreases in higher ages, are likely to be more pronounced, although age-comparative studies of human structural brain plasticity are rare. Emerging evidence on the time course of brain changes in sensorimotor learning suggests that human data follow predictions from an exploration-selection-refinement model that have arisen in work on animal models. However, our phylogenetic considerations underscore that it cannot be automatically assumed that animal models directly inform the principles of human plasticity and that future work must address whether principles of plasticity for basic functions apply to other forms of human cognition.

A Phylogenetically Informed Perspective on Human Plasticity throughout the Lifespan

In this chapter we review the evidence on the lifespan development of human plasticity. This task requires precision in our definition of plasticity and, we argue, a phylogenetically informed perspective that can lend nuance to interpretations of extant findings. We define *plasticity* as the ability of the brain to undergo structural (i.e., anatomical) changes that are driven by a mismatch between environmental requirements (demand) and the organism's current capacity (supply). Altered environmental demands, but also changes in the organism's capacity (e.g., after injury), can induce such mismatches (Lövdén, Backman, Lindenberger, Schaefer, & Schmiedek, 2010). With this definition, human beings may not be particularly plastic compared to many other species (Paredes, Sorrells, Garcia-Verdugo, & Alvarez-Buylla, 2016; Rakic, 1985; Walhovd,

Westerhausen, et al., 2016). The relative number of new neurons formed in life is much larger in fish and crustaceans than in mammals (Simoes & Rhiner, 2017; Zupanc, 2006, 2008). Compared to many "lower" vertebrates, the rate of neurogenesis in adult mammals also decreases more with age (Amrein, Isler, & Lipp, 2011). Many major structural changes in "lower" animals are arguably at least partly driven by mismatches between functional supply and environmental demands. The changes thus, by our definition, qualify as manifestations of plasticity. For instance, crustaceans, such as crabs, self-amputate legs and claws in response to being held in a fight and then grow new ones (Fleming, Muller, & Bateman, 2007), necessitating neural reorganization, too. Zebra fish regenerate functional nervous system tissue after injury (Mokalled et al., 2016). Among mammals there are similarities but also important differences. Neurogenesis might, for instance, be manifested differently in the brains of mice and men (Lazarov & Marr, 2013), and most Alzheimer's disease mouse models do not exhibit neuronal loss (Ameen-Ali et al., 2017), which is a characteristic of this disease that yields decreased plasticity in humans.

Humans appear to have evolved limitations of plasticity, along with the ability to rely heavily on accumulated experience (Paredes et al., 2016; Rakic, 1985, 2004). Though acquiring knowledge requires plasticity, maintaining it requires stability. Efficient synaptic plasticity and limits to larger-scale plasticity (e.g., neural turnover) may strike a balance that enables humans to expand their functional capacity during their protracted life-course (Hubener & Bonhoeffer, 2014; Meyer, Bonhoeffer, & Scheuss, 2014; Takesian & Hensch, 2013). Hence, humans may possess relatively constrained plasticity but have developed all the more *flexibility*. Flexibility-based reactions to environmental demands are based on existing functional supply (Lövdén et al., 2010). Flexibility is thus synonymous with functional capacity. Flexibility increases in childhood development, while a commonly held view is that plasticity decreases (Kühn & Lindenberger, 2016). It may be tempting to see increased flexibility as a result of the

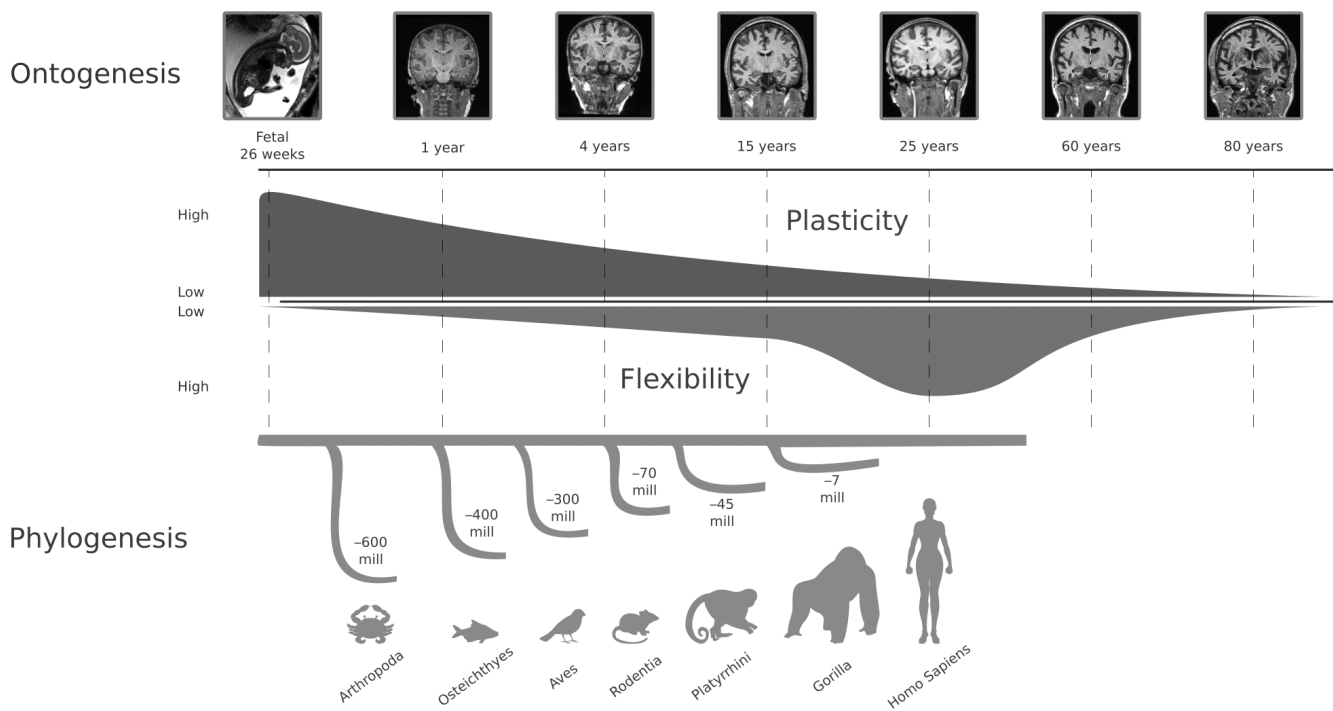


FIGURE 5.1 Schematic figure depicting plasticity (i.e., the capacity for anatomical brain changes induced by environmental demands) and flexibility (i.e., functional capacity) as a function of ontogenesis and phylogenesis. Note that

early plasticity is linked to vulnerability, which for a number of functions and their neural substrates appears highest when flexibility is at its lowest in ontogenesis. (See color plate 4.)

brain being increasingly “completed” and less malleable to change. In this regard, plasticity and flexibility may be seen as opposing forces in phylogenesis and ontogenesis alike (figure 5.1). However, flexibility is not continuously increasing throughout the human lifespan (Baltes, Staudinger, & Lindenberger, 1999), and it cannot a priori be assumed that we have continuously decreasing plasticity. A number of mechanisms for altering functional supply remain also in adult human beings (Zatorre, Fields, & Johansen-Berg, 2012).

In the remainder of the chapter, we first briefly review the ontogenesis of the human brain. This is a necessary background to appreciate what anatomical changes in the brain may be influenced by experience at which times. Next, we turn to reviewing the evidence on lifespan differences in plasticity. The phylogenetic differences in plasticity, combined with differences in the timescales of ontogeny (Austad, 2010; Jones et al., 2014) and the uniquely human nature of some cognitive functions (MacLean, 2016), limit the knowledge to be directly inferred from animal models of human neurocognitive plasticity. Animal models yield invaluable insights that cannot be obtained otherwise (Hensch, 2005; Hubener & Bonhoeffer, 2014), and a better coordination of animal and human research on plasticity is needed (Lindenberger, 2018). However, in

our view, especially given phylogenetic differences in plasticity, a challenge is that it cannot be assumed, without empirical evidence, that findings on lower animals can always be generalized to human beings. We therefore focus on and argue for the consideration of possible unique features of the *human* condition with regard to neurocognitive plasticity across the lifespan. Taking the same phylogenetic perspective, we will also be fully open to the possibility that mechanisms of plasticity may not generalize from sensorimotor functions to other cognitive functions (e.g., language, episodic memory, executive functions). In line with our definition of plasticity, our review is mainly restricted to brain plasticity, with a limited review of cognitive changes. We discuss whether there is evidence for variations in human plasticity across the lifespan, qualitatively (in terms of mechanisms) and quantitatively (in terms of magnitude), and before concluding, we review the emerging evidence on the maintenance and time course of experience-dependent structural brain changes.

Ontogenesis of the Human Brain

While the brain is made mainly in the womb, it does continue to change throughout life, and more so in

early childhood than later. During the first year, the brain more than doubles its size, and it reaches 90% of its maximum before school age (Dekaban, 1977, 1978). The birth of new neurons, *neurogenesis*, takes place in fetal development (Rakic, 1988). While new neurons have been found in the dentate gyrus of adult humans (Eriksson et al., 1998), this has been debated (Boldrini et al., 2018; Sorrells et al., 2018). There is mixed evidence for the functional significance of postnatal neurogenesis, but it may contribute to new learning (Opendak & Gould, 2015). Uncertainties prevail regarding techniques for evaluating cellular age, but new neurons may also be added in the striatum and olfactory bulb, though not in the neocortex (Bhardwaj et al., 2006; Ernst et al., 2014; Lotsch et al., 2014). There is consensus that adult human neurogenesis is severely restricted in location and amount (Paredes et al., 2016).

While the birth of new neurons in fetal life is genetically programmed (Rakic, 1988), there is no evidence they are programmed to die in aging (Kirkwood & Melov, 2011). Contrary to previous estimates of 1% neocortical neuron loss per year (Anderson, Hubbard, Coghill, & Slidders, 1983; Brody, 1955), methodologically advanced studies indicate that humans do not lose a great proportion of neurons with age (Haug, Kuhl, Mecke, Sass, & Wasner, 1984; von Bartheld, 2017). However, there is neuronal shrinkage (Haug et al., 1984) and average neocortical neuron losses of 2%–4% from early to late life (von Bartheld, 2017). When neurons are born, they *migrate* to the places in the brain where they will reside, largely during fetal life. Neuronal *differentiation* is also defined early, by the place and time the neuron is born (Rakic, 1988). Many neurons undergo apoptosis, programmed cell death. This too is genetically determined, largely belongs to early development, and is not a candidate for later plastic changes. One can increase apoptosis, though—for instance, by exposing human fetal brain cells to drugs such as opioids (Hu, Sheng, Lokensgard, & Peterson, 2002).

While *synaptogenesis* starts at fetal stages, the peak amount of synapses in the human brain is reached postnatally (Huttenlocher, 1979), and synaptic changes are also seen in adulthood. Through development, including adolescence, there is considerable *pruning*, or elimination of synapses, as indicated by human cross-sectional data (Huttenlocher, 1984; Petanjek et al., 2011). While in part genetically programmed, synaptic remodeling can be affected by species-mandatory experience, such as visual input (Greenough, Black, & Wallace, 1987). In contrast, the evidence for variation in pruning related to normal variation in experience is weaker and in human beings, nonexistent. While animal models have shown variation in spine remodeling

to covary with learning (Yang, Pan, & Gan, 2009), this cannot be generalized to indicate that normal variation in the experience of children determines whether a massive amount of their synapses survive.

Finally, *myelination*, the insulation of nerve connections by glial cells, while also beginning in fetal life, chiefly takes place after birth, in infancy, and continues well into adulthood (Yeung et al., 2014). While the number of glial cells does not differ much in young versus older adults (Pakkenberg et al., 2003), cross-sectional data indicate a considerable loss of myelinated fibers in normal aging (Marner, Nyengaard, Tang, & Pakkenberg, 2003). Characteristics of myelinated nerves can be influenced by experience (Walhovd, Johansen-Berg, & Karadottir, 2014) at different ages. There is considerable variation across cortical regions with regard to the ontogenetic timing, extent, and intraindividual variability of myelination, and these differences may relate to differences in plastic potential (Flechsig, 1901; Nieuwenhuys, 2013; Walhovd, Westerhausen, et al., 2016; Yakovlev & Lecours, 1967). In addition to the neural processes, changes in vasculature may take place at all ages.

In principle, the above structural changes may be detectable by modern in vivo imaging of human brains. In practice, the achievable resolution limits the possibility. The number of glial cells and axons, for instance, that can reside in one image voxel (e.g., in T1 or diffusion-weighted magnetic resonance imaging (MRI) scans) is enormous. By counting contents as visualized by electron micrograph images in a rodent 100 μm^3 white matter volume (1 mm^3 would be 1,000,000,000 μm^3), we found a median of 3,000 axons and on average 86 oligodendrocytes and 22 astrocytes. If axon density were equal in human beings, we estimate that a 2 mm^3 voxel could contain about 0.5 to 5 million axons (Walhovd et al., 2014). Thus, detecting true volume changes of the size of a few voxels requires growth or retractions of neural tissue of a magnitude not necessarily expected from short-term variations in motor learning or knowledge acquisition. However, alterations in the density and the composition of the tissue within a voxel may be detectable. For example, changes in dendritic spine density can account for experience-induced signal changes observed with MRI of the mouse brain (Keifer et al., 2015). Unfortunately, reverse inferences, from MRI changes to biological changes, are not readily possible. This is a weakness of our operational definition: human plasticity in terms of structural brain changes may not be readily detected with MRI, their interpretation will depend on sequence parameters, and we do not know exactly what the changes may entail. Work that includes the coordination of

human and animal research data on plasticity may provide insight into the mechanisms involved (Sagi et al., 2012), and further such models are needed. However, we need to be aware that animal data do not necessarily provide accurate representations of the human condition. This makes human MRI studies with direct histological confirmation crucial for our understanding of tissue changes (Concha, 2014).

Lifespan Differences in Plasticity

The human brain is thus mostly made during fetal life, which is also when the environment can affect it the most. Toxins, drugs, and a lack of nutrients and oxygen at this stage can cause profound damage or restrictions (Barnes & Ozanne, 2011; Walhovd, Krogsrud, et al., 2016) that cannot be mended with postnatal intervention. The rapid brain growth after fetal life has been used to argue that this is when the brain responds best to training. This is flawed logic (Thompson & Nelson, 2001)—none would argue that we should impose the most weight training in infancy because that is when the muscles grow most rapidly. Early brain development is genetically programmed (Rakic, 1988), and though this program expects environmental stimulation, the maturational processes cannot be initiated or stopped, massively sped up, or slowed down by *normal* variation in environment and experience. That does not mean these processes cannot be influenced. For instance, there is evidence to suggest that relatively more deprived pre- or postnatal environments can act to lower cognitive scores as well as genetic variance (i.e., the heritability suppression hypothesis; see Scarr-Salapatek, 1971; Tucker-Drob & Bates, 2016; Turkheimer, Haley, Waldron, D’Onofrio, & Gottesman, 2003). However, we need sobriety in the conceptualization of plastic potential. By normal variation, we mean variations in the environment that the human species has been selected through evolution to operate in (for a broader account of behavioral genetics and sources of variation, see, e.g., Griffiths, Gelbart, Miller, & Lewontin, 1999). In other words, experience-expectant plasticity, the dependency of brain maturation on ubiquitous and species-mandatory environmental information (e.g., visual stimulation) must be separated from experience-dependent plasticity—that is, the incorporation of idiosyncratic environmental information (e.g., specific memories and skills) that is relatively more unique to the individual (Greenough, Black, & Wallace, 1987). Greenough and colleagues indicated different neural mechanisms for the two, with emphasis on the selection among numerous early synaptic connections for experience-expectant plasticity and the formation of new synaptic

connections for experience-dependent plasticity (Greenough, Black, & Wallace, 1987). Early brain development is, in our opinion, a period of heightened plasticity mainly in the sense that it is primarily vulnerable to variations in the environment that are in conflict with that expected (such as sensory deprivation). In this sense, experience-expectant plasticity and vulnerability are invariably coupled. (For a perspective on individual differences in genetic vulnerability and plasticity, see, e.g., Belsky et al., 2009.) In contrast, variations within the normal environment have comparably less impact on brain development. Below, we review the evidence supporting our position on this issue, which is critically linked to the question of whether plasticity differs qualitatively with age.

Qualitative differences in plasticity with age The question of whether there are qualitative age differences in plasticity is intertwined with the concepts of critical or sensitive periods. A critical period denotes a specific time window within which the central nervous system is especially sensitive to environmental stimuli and must encounter that type of stimulus for an ability to develop or develop optimally. Hence, it is the functions that are species-mandatory and important to survival that likely have evolved to develop early and in critical periods through experience-expectant plasticity. Examples of such fundamental functions would be sight and hearing, while memorizing pi with a tremendous number of decimals would not usually be important to survival. It follows that the issue of whether we can elicit plastic changes with targeted training does not pertain to the brain’s adaptation to species-mandatory and essential information, as in experience-expectant plasticity, but rather to the incorporation of unique information, as in experience-dependent plasticity. Yet critical periods and the importance of early experience are being mentioned in connection with anything from mathematics to music (Nelwan & Kroesbergen, 2016; Steele, Bailey, Zatorre, & Penhune, 2013). Do kids miss out forever on anything else other than fun, if they are not given huge amounts of homework?

There is unequivocal evidence for the existence of a critical period, and hence qualitative age differences, in the effect of sensory deprivation. Torsten Wiesel and David Hubel (1963) were among the first to show this, studying the functional and cortical consequences of different types of visual deprivation in newborn and older animals (Wiesel, 1982). They found that monocular deprivation (suturing one eye) during specific time spans early in life yielded permanent functional blindness in the closed eye, along with marked changes in the primary visual cortex (striate cortex). Here, cells are

organized in ocular dominance columns, with alternating groups of cells responding primarily to stimulation of each eye. In animals monocularly deprived at a young age, connections with signals from the nondeprived eye will permanently occupy the space of connections from the deprived eye. This will not happen in mature animals deprived for long periods. We know that critical periods for perception also hold true for human beings, based on the phylogenetic similarity of these brain areas across mammals and the observed permanent consequences of untreated strabism or cataracts in early childhood. The fine-grained mechanisms of critical periods for sensory experience are still being researched. Importantly, studies of visual impairments in sight-recovery individuals with congenital, relative to late-onset, cataracts have yielded new knowledge suggesting that sight impairments may predominantly arise at higher cortical-processing stages (Sourav, Bottari, Kekunnaya, & Roder, 2018). Intriguingly, there is also evidence to suggest ways to alter or extend ocular dominance plasticity for longer time periods (Greifzu et al., 2014), which will further enhance the understanding of plasticity.

Upon receiving the Nobel Prize in 1981, Wiesel concluded his Nobel speech by saying that “it may well be that other aspects of brain function, such as language, complex perceptual tasks, learning, memory and personality, have different programs of development. Such sensitivity of the nervous system to the effects of experience may represent the fundamental mechanism by which the organism adapts to its environment during the period of growth and development.”

For all his genius, we would say Wiesel has not yet been proven right about programs of development for various functions, other than sensory perceptual, with regard to such specific sensitivity of the nervous system. Nearly four decades later, the kind of exact and permanent neural mechanism for the effect of early experience so eloquently identified for sensory deprivation and cortical columns has yet to be shown for other types of environmental variation or experience.

There is no true experimental controlled study of human developmental deprivation, yet children are sometimes the victims of untreated conditions, cruelty, and neglect, the consequences of which have been studied. Based on this, it has, for example, been concluded that there is a critical period for language exposure, as select cases have not seemed able to acquire a first language fluently after entering the teenage years (Fromkin, Krashen, Curtiss, Rigler, & Rigler, 1974; Grimshaw, Adelstein, Bryden, & MacKinnon, 1998). A lack of language exposure rarely occurs amid otherwise optimized conditions, and there is uncertainty as to the brain

mechanism, insofar as language is uniquely human, and no animal model can be created. Natural lesion studies do, however, support some early plasticity of the neural substrates of language in that left-hemisphere lesions in small children less often yield substantial aphasia or language disorders than equivalent lesions in adults (Chilosi et al., 2008). Note that this cannot be generalized to less serious effects of childhood brain damage in general. Lesions in the language and motor areas may, to some extent, yield lesser function loss at younger ages (Chilosi et al., 2008; Kennard & Fulton, 1942). However, this should not be taken to mean that early lesions cannot also yield serious language consequences (Chilosi et al., 2008), and one study found that for some language tests, stroke suffered prenatally or during the first nine months of life yielded poorer performance than stroke suffered between the ages of 1 and 14 years (Max, Bruce, Keatley, & Delis, 2010). Notably, for general cognitive ability and psychosocial functions, cerebral lesions at younger ages have been associated with worse outcomes than equivalent lesions at older ages (Anderson, Damasio, Tranel, & Damasio, 2000; Duval et al., 2008). So, while evidence suggests a sensitive period for first-language acquisition, an exact definition of a critical period for language exposure and its possible brain substrate remains unclear and cannot readily be likened to that for sight, where the exact qualitatively distinct cerebral mechanism has been established.

Beyond language, early cognitive and emotional deprivation effects in institutionalized children have been studied extensively, and a history of institutionalization has been associated with both cognitive, psychosocial, and cerebral differences relative to never institutionalized or foster-care children (Berens, Jensen, & Nelson, 2017; Rutter, 2012; Rutter, O'Connor, & English and Romanian Adoptees Study, 2004; Sheridan, Fox, Zeanah, McLaughlin, & Nelson, 2012). However, it is difficult to isolate physical and psychological environmental effects here. Furthermore, there is substantial heterogeneity in outcomes after such adversities, so the effects are not deterministic (Rutter, 2012; Rutter et al., 2004). Considerable variation is masked in the average group differences reported, where differences in brain characteristics are more of degree than kind. Again, an exact cerebral mechanism for permanent early change as an effect of experience of the kind reported for deviant early visual stimulation has not been identified for other functions, and this pertains also to cognitive and emotional neglect in childhood.

The concept of critical periods is also sometimes used as a way of giving preponderance to variations in *normal* cognitive experience in early childhood rather

than later (Nelwan & Kroesbergen, 2016; Steele et al., 2013) and rather in childhood than in adulthood. The reasoning rests on the time course of synaptic pruning described for childhood and adolescence (Huttenlocher, 1984), with the idea that whether synapses persist and perish depends on how they are used. This is currently impossible to investigate in humans. Furthermore, experience-dependent pruning has also been shown to be a mechanism in adult mice (Chen et al., 2012; Xu et al., 2009; Yang, Pan, & Gan, 2009).

In summary, we have established that convincing evidence of qualitative age differences is currently restricted to sensory-perceptual functions and mainly to a dependency of brain maturation on normal, species-mandatory, environmental information. In contrast, there is no evidence for clearly defined age periods wherein the brain can and cannot change as a result of normal variations in experience. Thus, the massive campaigns for the importance of “early stimulation” (Thompson & Nelson, 2001) for children’s development are misguided. There is little evidence suggesting that any additional early stimulation is necessary or should be undertaken. However, we need to consider whether there may be quantitative age differences in plasticity that are of degree more than kind.

Quantitative differences in plasticity with age Few studies have systematically compared brain plasticity in younger and older individuals. However, skill acquisition and the behavioral effects of cognitive training at different ages have been extensively studied. Training effects on performing trained tasks are seen throughout the lifespan. However, there is no indication that cognitive training serves to even out interindividual differences. Either proportional differences stay the same or those who have more to begin with gain more from intervention. This also goes for the typical adult age differences in cognition (Kliegl, Smith, & Baltes, 1990). Older adults, on average, do less well at baseline and do not “catch up” to young adults who also receive training. At best, they may improve proportionately as much as younger adults at some tasks (Brehmer, Shing, Heekeren, Lindenberger, & Backman, 2016; Carretti, Borella, & De Beni, 2007; Lövdén et al., 2012), but more often training appears to widen individual differences (Baltes & Kliegl, 1992; de Lange et al., 2017; Kliegl, Smith, & Baltes, 1990), with lesser gains in older age (Baltes & Kliegl, 1992; Burki, Ludwig, Chicherio, & de Ribaupierre, 2014; Dahlin, Nyberg, Backman, & Neely, 2008; de Lange et al., 2017; Nyberg et al., 2003). There is some evidence to suggest that children, although performing similar to older adults at baseline, tend to gain more from mnemonic training than older adults but not as much as

higher-performing younger adults (Brehmer, Li, Muller, von Oertzen, & Lindenberger, 2007).

While training effects are found in most studies, the far transfer of effects to tasks that do not overlap with the trained tasks in terms of perceptual and motor expertise or strategic cognitive processing is relatively seldom seen (Melby-Lervag, Redick, & Hulme, 2016; Nelwan & Kroesbergen, 2016; Sala & Gobet, 2017). Does the potential for such transfer differ across age groups? Given the controversies surrounding the existence of transfer effects to begin with, this is especially hard to answer. For far transfer, meta-analytic studies suggest that any such effects are at best small (max ≈ 0.2 Standard Deviation) and may even be nonexistent when training groups are compared to active control groups. Comparing small effects across age groups requires massive sample sizes to achieve sufficient statistical power, and few such studies exist. However, in one study, roughly 100 younger and 100 older participants practiced working memory, episodic memory, and perceptual speed tasks for about 100 days. Compared to controls, younger adults showed the transfer of training effects on reasoning ability, but no transfer was observed in older adults (Schmiedek, Lövdén, & Lindenberger, 2010). Meta-analysis, however, shows no statistically significant differences between younger and older adults (Karchach & Verhaeghen, 2014). The evidence concerning the transfer of training effects, and potential age differences in such effects, thus remains inconclusive.

With respect to quantitative differences in brain plasticity, we know of no studies directly comparing children with adults, but some studies serve to illuminate adult age differences. Sensorimotor skill acquisition, such as juggling, and cognitive experience, such as spatial navigation training, have been shown to affect gray matter in both younger and older adults (Boyke, Driemeyer, Gaser, Buchel, & May, 2008; Draganski et al., 2004), either by cortical increases (Boyke et al., 2008) or relatively less hippocampal atrophy (Lövdén et al., 2012), compared to controls. With juggling training, the cortical changes were smaller in older adults, but they also showed increases in medial temporal lobe areas not evident in younger adults (Boyke et al., 2008; Draganski et al., 2004). However, for navigation training, regional cortical thickening was observed in younger, but not older, adults (Wenger et al., 2012). With strategy-based mnemonic training, though, both hippocampal and cortical gray matter increases have been observed in older adults (Engvig et al., 2010; Engvig et al., 2014), such as has been seen with juggling training (Boyke et al., 2008), but the extent of these relative to younger adults are unknown.

As for white matter, there is ample evidence for training effects at both younger and older ages. Increases in corpus callosum microstructural markers of integrity (in terms of decreased mean diffusivity [MD] and increased fractional anisotropy [FA]), as well as the anterior collosal area, have been observed in both younger and older adults training for a set of different cognitive tasks (Lövdén, Bodammer, et al., 2010). With mnemonic strategy training, regional changes in white matter microstructure, with decreased MD and increased FA, encompassing in part the anterior corpus callosum, have been observed in older and not younger adults (de Lange, Brathen, Rohani, Fjell, & Walhovd, 2018; de Lange et al., 2017). Of note, although the cognitive task-training study adjusted task difficulty to performance at baseline, it did not apply an adaptive training regimen with task difficulty adjusted to performance increases (Lövdén, Bodammer, et al., 2010). While the mnemonic study did (de Lange et al., 2017, 2018), there may be difficulties in making the training equally subjectively challenging to younger and older adults, and this may affect the neural changes. It is methodologically challenging to make sure that training programs are equally demanding to individuals of different ages. There are systematic differences in performance, brain structure, and function across the lifespan, making objectively identical interventions differentially demanding for different age groups. Because individual adjustments to ensure environmental demands exceed the current capacity are pivotal to maximize training gains (Brehmer, Westerberg, & Backman, 2012) and elicit plastic changes (Lövdén, Backman, et al., 2010), differential demands may thus bias the assessment of plasticity (i.e., capacity for changes).

The reviewed evidence does not imply qualitative differences in neural plastic potential in younger and older adults and remains inconclusive with respect to quantitative age differences in brain plasticity. However, the known age changes in brain and cognition imply that there may be quantitative differences. Age differences in gray and white matter characteristics (Sexton et al., 2014; Storsve et al., 2014) are indicated to affect plasticity: baseline hippocampal volumes are predictive of learning and retention across minutes and days in development (Ostby, Tamnes, Fjell, & Walhovd, 2012; Tamnes et al., 2014), recall over weeks and months in adulthood (Walhovd et al., 2004), and cognitive-training gain across weeks in aging (Engvig et al., 2012). Furthermore, white matter microstructure in areas of established age differences is predictive of cognitive training gains (de Lange et al., 2016). Hence, the conclusion at this time is that cognitive training gains and neural plasticity are seen across the lifespan, but

the differences in neural integrity seen with normal aging are likely to, if anything, impact plasticity in a manner of degree but not kind. This is not proven but implied by what we know of how brains are built and maintained, together with the limited evidence from training studies so far.

The Time Course of Plastic Changes

What is the fate of training-induced changes of brain and cognition over time? Behaviorally, some extent of maintenance of training effects over prolonged periods is indicated (Schmiedek, Lövdén, & Lindenberger, 2014), but there is relatively little evidence at the neural level. On the one hand, cross-sectional studies reveal differences in gray and white matter characteristics between individuals with various degrees of expertise, suggesting that experience-dependent human brain changes may be relatively long lasting (de Manzano & Ullen, 2018; Maguire et al., 2000). These studies are, however, confounded by potential innate difference between groups and can rarely separate between past and present differences in behavior. There is mixed evidence on the maintenance of experience-dependent brain changes, with decreases, increases, or stability of training-related changes in gray matter structure observed after the termination of training (Draganski et al., 2004, 2006; Lövdén et al., 2012). A recent study investigated the temporal dynamics of brain plasticity across periods on and off memory training in older adults during a 40-week program, including two training periods separated by periods with no intervention (de Lange et al., 2018). A general decline in white matter microstructure was observed across the duration of the study but was moderated by the training periods, indicating that cognitive training may mitigate age-related brain deterioration. The training-related improvements were estimated to subside over time, indicating that continuous training may be a premise for the enduring attenuation of neural decline. Memory improvements were, however, largely maintained after the initial training period and thus may not rely on continuous training to the same degree as the neural changes. The results may also suggest that the structural changes observed with MRI are relatively transiently supporting learning or relate to use rather than learning, while representations of acquired skills (i.e., memories) are stored in a small subset of the structural changes.

Theoretical work and evidence from animal models suggest that learning sensorimotor skills involves several neural stages (Changeux & Dehaene, 1989; Edelman, 1987; Kilgard, 2012). Early in learning, the brain

explores numerous candidate circuits that may execute the behavior. Probably based on reinforcement (Dhawale, Smith, & Olveczky, 2017; Makino, Hwang, Hedrick, & Komiyama, 2016), the best candidate circuit is then selected for further local refinement. This exploration-selection-refinement model is consistent with evidence indicating that rodents exhibit expanded cortical maps early in behavioral training but that these expansions later subside despite continued training and stable behavioral performance (Molina-Luna, Hertler, Buitrago, & Luft, 2008; Reed et al., 2011). The model is also consistent with findings that novel dendritic spines rapidly form in the deeper layers of the motor cortex of rodents during motor skill acquisition, but with continued training the phase of growth is followed by stabilization of the new spines and elimination of old spines, almost returning the overall number of spines to pre-training levels (Xu et al., 2009; Yang, Pan, & Gan, 2009). Thus, in the exploration-selection-refinement model, initial activity-related net structural growth may be helpful for learning, but not necessary for continued learning and maintenance of skill.

The dynamics of dendritic spines and their morphology and density are probably key to understanding the acquisition of sensorimotor skills (Hofer & Bonhoeffer, 2010; Kassem et al., 2013; Keifer et al., 2015). Experience-dependent alterations in the morphology of dendritic spines have been reported to account for a substantial amount of variance in changes of gray matter structure observed with MRI of the rodent brain, suggesting that these changes may also be possible to detect with imaging of the human brain (Kassem et al., 2013; Keifer et al., 2015). At the level of macroscale measurements of the brain structure with MRI, the microstructural processes related to the exploration-selection-refinement model may be reflected in expansion followed by partial renormalization of the gray matter during acquisition of a sensorimotor skill. A recent study tested this hypothesis by acquiring 18 structural (T1-weighted) MR images over a seven-week period during which young adults practiced left-hand writing and drawing every day. Results showed that the volume of the human primary motor cortices increased during the first weeks of learning and then partially renormalized during continued practice (Wenger et al., 2017). Thus, human structural gray matter changes during the acquisition of sensorimotor skills may be relatively transiently observable during an initial exploration phase. Adaptive skill acquisition, with repeated novel exploration phases for acquiring new subskills (e.g., learning complex skills such as playing musical instruments), may still result in larger and more permanent structural changes. However, in the study of left-hand

writing and drawing, other brain regions (e.g., the cerebellum) than the primary motor cortices displayed more linear changes. In addition, it is difficult to interpret changes observed on T1-weighted images in terms of their microstructural nature. Notably, the T1-weighted image is also highly sensitive to myelin (Tardif et al., 2015), and the deeper layers of the cortex, in particular in the motor cortex, are densely myelinated (Whitaker et al., 2016). Experience-dependent myelination (Sampaio-Baptista & Johansen-Berg, 2017) of the deeper cortical layers in the later phases of skill acquisition could therefore result in the estimated decreases of gray matter thickness. Myelin content is influencing apparent cortical thickness, as derived from anatomical MRI scans (Glasser & Van Essen, 2011), and myelin proliferation is assumed to be one factor causing apparent cortical thinning during development (Walhovd, Fjell, Giedd, Dale, & Brown, 2017). For instance, this has been indicated by multimodal imaging of the observed “decreases” of the thickness of the visual cortex in human childhood development combined with adult postmortem histology (Natu et al., 2018). It is thus unknown whether the skill-related renormalization of the gray matter structure reflects the true retraction of tissue (e.g., of dendritic spine density) or a late phase of myelination. Much work remains to elucidate the temporal dynamics of human structural changes during skill acquisition.

Conclusions and Outlook

A major challenge for future studies is to identify which factors constrain and augment plasticity in human neurocognitive function and thus when and how they can be influenced. It should be clear from the above that one needs to employ a life-course perspective. Importantly, as the augmentation of human plasticity is often desired for complex neurocognitive functions, there is a need to acknowledge that principles derived from research on sensory and perceptual functions (the early critical periods included) may not be directly translatable to other aspects of human cognition and to the effects of allowable variation in human environment and experience across the life course. More basic and higher-order cognitive functions may be seen along a dimension, rather than as distinct categories, and functions usually thought of as forms of higher-order cognition are typically complex and draw on multiple capacities, including those that are more basic. However, we do not know if plasticity observed in the sensory and the motor cortices in the context of perceptual and motor skill acquisition offers a viable analogy of the role of the association cortices in the

context of higher-order or complex cognitive abilities such as episodic memory, working memory, task set switching, and fluid intelligence (Lindenberger, 2018). We believe that in view of the protracted development of human higher-order functions and their reliance on the incorporation of unique information, as in experience-dependent plasticity (Greenough, Black, & Wallace, 1987), the critical-period plasticity framework and animal and human models of sensory and motor plasticity are likely to be insufficient to understand the breadth of human neurocognitive plasticity across the life span. This poses substantial challenges to experimental designs. While there is little to suggest major qualitative or quantitative differences in plasticity at different ages, there may still be critical age differences in when our capacity for change can be changed. To further test this, we suggest systematically comparing the effects of sensorimotor and higher-order cognitive training with repeated multimodal imaging and testing to delineate their temporal and neural dynamics. To partly mend the inherent confounds associated with age, such as differences in novelty, one may utilize new technologies such as apps and virtual reality paradigms, enabling rich enough settings for the systematic manipulation of sensory, motor, working, and episodic memory training. This may require the creation of alternative virtual worlds, where other rules apply, for the systematic training of different domains, which is an exciting future possibility.

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6 Brains, Hearts, and Minds: Trajectories of Neuroanatomical and Cognitive Change and Their Modification by Vascular and Metabolic Factors

NAFTALI RAZ

ABSTRACT Aging is accompanied by substantial reductions in brain volume, alterations in structural properties of the white matter, shifts in iron metabolism, and selective cognitive declines. Although it is assumed that brain changes precede and mediate cognitive aging, empirical support for this assumption is sparse. Cross-sectional studies cannot provide an adequate solution to the age-brain-cognition (ABC) triangle, and multiwave longitudinal investigations that can reveal mediation and moderation relationships among these variables are rare. Moreover, the trajectories of neural and cognitive aging and the distribution of variance in the ABC triad can be influenced by multiple factors reflecting vascular and metabolic risk and the propensity for neuroinflammatory response. To complicate matters further, the BC part of the trilateral relationship is not necessarily described by the brain's unidirectional effects on cognition. Rather, empirical evidence suggests that those are frequently connected by bidirectional paths. In addition, vascular, metabolic, and inflammatory risk factors modify and moderate the trajectories of age-related change. Although the extant literature is still scant, certain trends can be discerned, and the paths to elucidating the neural mechanisms of age-related changes through studying neuroanatomical changes in the context of the brain energy crisis can be outlined.

I list not prophecy; but let Time's news
Be known when 'tis brought forth.
—Shakespeare, *Winter's Tale*

Act IV, Scene 1

Whoever came up with the “time takes its toll” cliché knew what they were doing, for it is incontrovertible that in adult mammals, changes in virtually all systems and organs accompany the passage of time. Advanced age is associated with reduced lean mass and bone

density, limited respiratory fitness, increased insulin resistance, low-grade chronic inflammation, lowered energy expenditure, and elevated vascular risk factors (Manini, 2010; Margolick & Ferrucci, 2015). Conceptualization of the multifarious aging process as a slow-rolling energy crisis (de la Torre, 2008) aligns with the dominant views of modern gerontology: the free radical accumulation model (Garaschuk, Semchyshyn, & Lushchak, 2018; Harman, 1956) and the disposable soma theory (Kirkwood, 1977). These theories converge on the conceptualization of postreproductive aging as an unprogrammed stochastic wear-and-tear process, driven by shifting of the dynamic equilibrium between the benefits of reactive oxygen (ROS), nitrogen (RNS), and carbonyl (RCS) species—RONCS (Garaschuk et al., 2018)—and the declines they cause through damaging mitochondria and inducing energetic deficit.

The inability to meet energy demands may underpin the differential age-related changes, and despite its universality, aging preferentially affects organs and systems with the highest energy requirements—the muscles, the liver, and the brain (Manini, 2010). The latter, while constituting only 2% of body weight, draws more than 20% of the organism's total energy (Attwell & Laughlin, 2001), most of which supports the brain's information-processing capability through maintaining neurotransmission (Howarth et al., 2012), while the remainder is allocated to building and maintaining structural components.

At any moment, the size and structural composition of the brain is determined by multiple forces and actors that make a veritable Robinson Crusoe list of things

good and evil. Nature is a mighty seamstress toiling over alterations in the never-quite-perfect fabric of the brain, shortening and extending and widening and narrowing to meet the demands, within genetic constraints, of many biological processes and environmental experiences. On the one hand, neuropil volume grows through the expansion of dendritic arborization, synaptogenesis, myelin synthesis, angiogenesis, astrocyte proliferation, and neurogenesis. On the other hand, attrition and shrinkage of neurons, synapse stripping by microglia, dendritic spine retraction, demyelination, and loss of astrocytes offset the expansion. The complexity of forces at play makes inferring neurobiological mechanisms of cognitive aging from gross structural changes extremely challenging and calls for evaluating their molecular and metabolic underpinnings. Although animal models exploring the fundamental physiology of aging are plentiful, their translation to noninvasive studies of the human brain is lagging.

The Free-Radicals-Induced Energetic and Neural Decline in Senescence (FRIENDS; Raz & Daugherty, 2018; figure 6.1) model inspired by the free-radical (Harman, 1956) and the energy crisis (de la Torre, 2008) theories casts the gradual decline in the availability of energy resources as the core phenomenon of cognitive aging. The age-related waning of mitochondria is exacerbated by endothelial dysfunction that impairs the delivery of energy substrates and the removal of by-products and debris of cellular decay (e.g., Singer et al., 2014). Whereas maintaining ion pumps is critical for neurotransmission and is unlikely to slow down and accommodate the dwindling energy supply, the upkeep of the metabolically expensive myelin sheath (Bartzikis, 2011), cellular membranes, and dendritic spines (Morrison & Baxter, 2012) is affected by energetic scarcity. Moreover, endothelial dysfunction may directly impair the maintenance of the myelin sheath (Rajani et al., 2018). Thus, brain connectivity is disrupted (Damoiseaux, 2017), and it becomes a progressively noisier system. Noise propagates in the information-processing networks (Myerson et al., 1990) and is likely to affect them in proportion to their complexity. Aging, therefore, is bound to induce a differential failure of those cognitive skills that depend on novel connections and the reconfiguration of existing networks rather than those that rely on existing “greased paths.”

Despite significant advances in the understanding of the mechanisms that translate brain cellular activity into cognitive operations undergirding complex reasoning, the specifics of the associations between brain aging and age-related cognitive changes remain unclear, and elucidating the mechanisms of brain aging is a critical priority for understanding and mitigating senescent

cognitive declines. Yet, because it is an integral part of the organism, clarifying the brain’s role in age-related cognitive changes is impossible without describing the contributions of other organismic components that affect its properties and the trajectories of change (Fjell et al., 2014; Kennedy & Raz, 2015; Raz & Rodrigue, 2006). Below, I survey the current literature on age-related changes in brain structure and their relation to cognitive changes, as well as the role of various risk factors in shaping individual trajectories of neurocognitive aging. Functional brain changes are reviewed in chapters 5 and 7 of this volume.

Postmortem Studies

Neuroanatomical postmortem studies have demonstrated that the brains of older adults are smaller and lighter than those of their younger counterparts and exhibit significantly larger cerebrospinal fluid cavities (Kemper, 1994). Older brains evidence shrinkage, dysmorphology and the selective attrition of neurons (Pakkenberg et al., 2003), the impairment of neurogenesis and synaptogenesis, sparser dendritic spines (Morrison & Baxter, 2012), and lower myelin content in the cortex and subcortical white matter (Kaes, 1907). Iron content is elevated in older brains, especially in the basal ganglia, the substantia nigra, and the red nucleus (Hallgren & Sourander, 1958). With iron as a key player in mitochondrial energy production (Zecca et al., 2004), its excessive deposits may signal the disruption of energy metabolism with age as well as set off multiple paths to age-related neurodegeneration (Ashraf, Clark, & So, 2018). Postmortem studies, though indispensable in elucidating the natural history of mammalian aging, represent only a cross-sectional snapshot of the brain state. They reveal nothing about the temporal dynamics and individual differences in change, which became accessible only with noninvasive neuroimaging techniques.

Aging of the Brain Structure: In Vivo Evidence

For the past three decades, noninvasive neuroimaging has produced a substantial body of cross-sectional studies of age differences in the brain’s gross structural properties. The findings from in vivo studies agree with the postmortem record. They document age-related differences in almost all brain regions, including smaller total and regional volumes, a thinner cortex, and larger cerebral ventricles in persons of advanced age compared to their younger counterparts (Raz, 2000). Meta-analyses of the extant studies and mega-analyses of aggregated samples show differential age-related alterations across brain regions: stronger

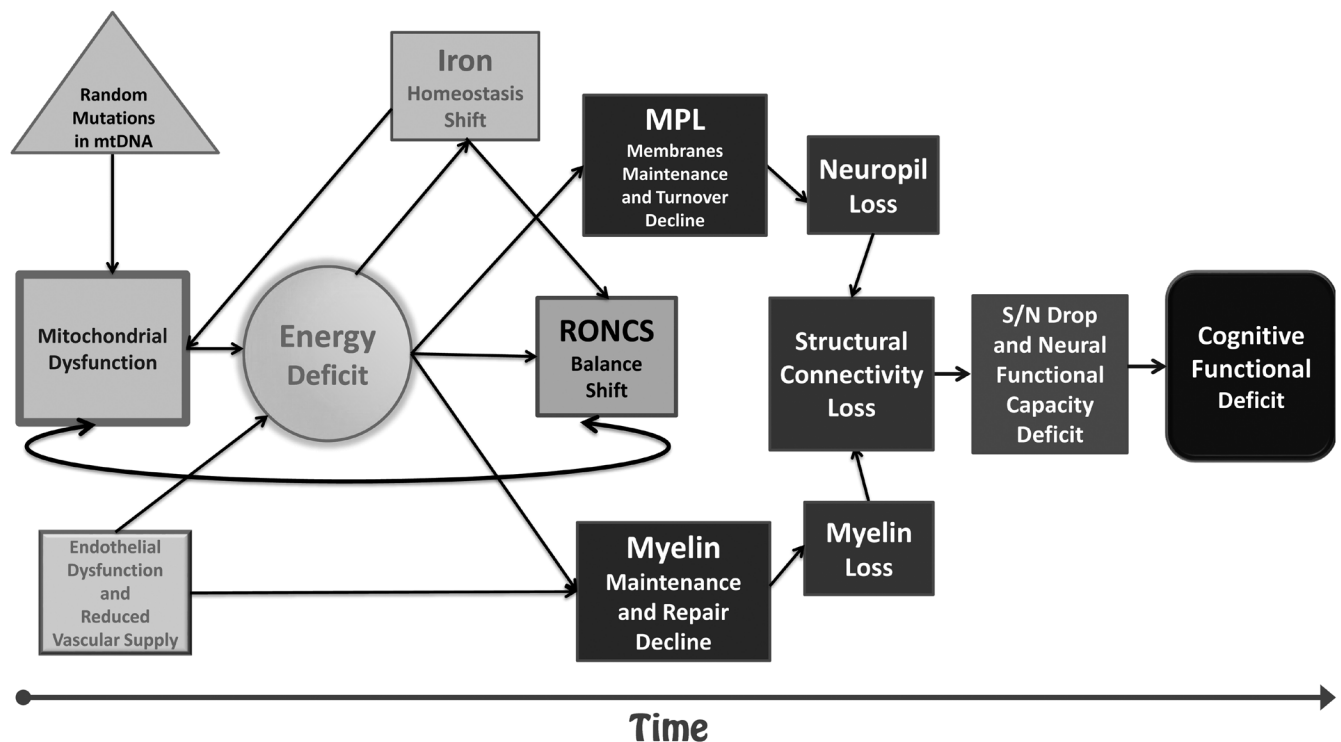


FIGURE 6.1 The FRIENDS model of cognitive aging. Random mutations accumulate in the mitochondrial DNA, and mitochondrial function declines with age. That decline results in the gradual reduction of energy substrates (ATP and NADH). The sequestration and transport of iron are affected, and the accumulation of iron, in turn, exacerbates mitochondrial declines. Endothelial dysfunction impairs the delivery of glucose and oxygen to the end organs in the brain and may directly stunt the regeneration of myelin. An energy crisis and further mitochondrial dysfunction ensue. Impaired mitochondrial respiration and the accumulation of iron lead to a shift in the homeostasis of RONCS and their excess

further damages the mitochondria. This cascade of events further reduces the energy available for the maintenance of cell membranes and myelin and for supporting synaptic plasticity. Myelin and neuropil are gradually diminished, and connectivity among the brain regions is lost. That loss impairs the fidelity of neural communication, and the information-processing capabilities of the brain networks are degraded; the system becomes progressively noisier. Noise in the information-processing system affects all cognitive operations, with the more energy-dependent of them faring the worst of all. (See color plate 5.)

age associations in the prefrontal cortex, cerebellum, and neostriatum compared to the primary sensory cortices (e.g., Driscoll et al., 2009; Fjell et al., 2009; Raz et al., 1993, 1997, 2004; Walhovd et al., 2011; see Raz, 2000 for a review).

Despite their multiple advantages—for example, the feasibility of large-sample data collection and the potential for covering a lifespan age range—cross-sectional studies have an irreparable flaw: they yield no true estimates of change and individual differences in change trajectories (Hofer & Sliwinski, 2001; Lindenberger et al., 2011) due to the violation of ergodicity assumption (McArdle, 2009; Molenaar, 2004). These limitations are particularly severe in studies that evaluate the brain's role in mediating age influence on cognition (Raz & Lindenberger, 2011). Therefore, I limit the discussion to longitudinal studies and call upon cross-sectionally sourced findings only when longitudinal data are unavailable.

Longitudinal studies of the cerebral ventricles and the whole brain reveal expansion of the former (e.g., McArdle et al., 2004) and shrinkage of the latter time (Raz & Rodrigue, 2006). Age-related shrinkage happens even in selected samples of healthy adults (Anblagan et al., 2018; Callisaya et al., 2013; Crivello et al., 2014; Fjell et al., 2013; Hua et al., 2016; Leong et al., 2017; Opfer et al., 2018; Pfefferbaum et al., 2013; Persson et al., 2014; Rast et al., 2018; Raz et al., 2005, 2010, 2013; Squarzone et al., 2018; Yuan, Voelkle, & Raz, 2018) within time windows as narrow as six months (Raz et al., 2013). Brain volume change over at least two occasions has been estimated at 0.15% per annum in middle-age adults (Opfer et al., 2018) and .21% (Takao et al., 2012) and .51% in a broad-age sample (Storvse et al., 2014), steadily increasing to .56% (Leong et al., 2017), .61% (Opfer et al., 2018), .55%–.77% (Sigurdsson et al., 2012), .80% (Aljondi et al., 2018), and up to .83% (Crivello et al., 2014) in samples of older participants. Notably,

however, in some highly selected samples the total brain atrophy rates were modest even at the tenth decade of life (Mueller et al., 1998; Pressman et al., 2016).

Despite a general agreement on trends, specific findings vary across studies. The discrepancies may stem from differences in brain measurement methods, sample age ranges, and an admixture of individuals with vascular and metabolic risk factors, as well as frequency of assessments and the time elapsing between measurements. Most longitudinal studies of regional brain volumes reveal significant shrinkage of the neostriatum, cerebellum, posterior cingulate cortex, and tertiary association cortices. Lesser but still significant volume loss is noted in the fusiform, insular, anterior cingulate, and parahippocampal cortices, with minimal changes or no decline observed in the primary visual and somatosensory cortices (Crivello et al., 2014; Driscoll et al., 2009; Jiang et al., 2014; Kim et al., 2018; Leong et al., 2017; Persson et al., 2014; Pfefferbaum et al., 2013; Shaw et al., 2016; Storsve et al., 2014, see Kennedy & Raz for a review). Shrinkage of the hippocampus and the entorhinal cortex may follow a non-linear course, with faster shrinkage in older participants (Crivello et al., 2014; Doré et al., 2013; Gorbach et al., 2017; Jiang et al., 2014; Leong et al., 2017; Persson et al., 2014; Pfefferbaum et al., 2013; Raz et al., 2005, 2010; Storsve et al., 2014; see Kennedy & Raz, 2015, for a review). Other regions (e.g., the prefrontal white matter) exhibit age-accelerated changes in some samples (Raz et al., 2008), whereas in other studies a mixed pattern of acceleration and deceleration is noted, with age-accelerating changes in the temporal and the occipital and deceleration in the prefrontal and the anterior cingulate cortices (Storsve et al., 2014). Notably, cross-sectional designs underestimate age-related changes in cortical volume and thickness (Fjell et al., 2014; Kim et al., 2018; Pfefferbaum & Sullivan, 2015; Rast et al., 2017; Raz et al., 2005; Sigurdsson et al., 2012).

The magnitude of regional declines varies even across studies on the samples drawn from the same population, and some age trends are less replicable than others. Importantly, however, significant individual variability of change is observed in virtually all regions and in all studies that statistically modeled individual differences. For example, substantial shrinkage of the prefrontal cortex and the white matter (Raz et al., 2005) was not observed in other samples studied in the same lab with the same methods (Persson et al., 2014; Raz et al., 2010), whereas shrinkage of the cerebellum, the hippocampus, and the orbitofrontal cortex, accompanied by a relative stability of the primary visual cortex, was consistently replicated (Persson et al., 2014; Raz

et al., 2005, 2010). Cortical thickness trajectories approximate the course of age-related reduction in regional volumes (Storsve et al., 2014; Thambisetty et al., 2010; Yuan et al., 2018; but see Pacheco et al. 2015 for prominent thinning of the primary motor cortex), with the measures of cortical surface yielding lower estimates of age-related change (Storsve et al., 2014). Cortical thinning and volume shrinkage are tightly correlated, but the cortical surface changes at a slower pace (Storsve et al., 2014). The shape of age-related change—linear, quadratic, or accelerated/decelerated exponential—is still unclear, as very few studies included more than one follow-up assessment, thus precluding the trajectory evaluation.

In summary, structural brain aging is heterochronic and individualized. The fact that some persons show minimal change, whereas others exhibit steep declines, spurs the search for influential factors mitigating age-related change and shaping individual trajectories of aging with minimal decline (Lindenberger, 2014). Determining the factors that induce individual variability in the brain aging of healthy adults is a challenge, as by definition, healthy samples are selected for the absence of detectable pathology and have restricted variance in negative modifiers of the brain structure. Nonetheless, several factors have been implicated in moderating the trajectories of brain aging. Physiological and genetic variations associated with vascular, metabolic, and neuroinflammatory risks and affecting endothelial function and energy expenditure while increasing the RONCS burden—the *vascular health triad* (Wadley, Veldhuijzen van Zanten, & Aldred, 2013)—appear particularly important. Arterial hypertension, even when medically controlled, is linked to the accelerated shrinkage of several brain regions, such as the hippocampus (Raz et al., 2005), raising a possibility that this detrimental effect stems not from elevated blood pressure per se but from the concomitant vascular changes. In many samples, gray matter shrinkage is exacerbated by an age-related elevation in vascular risk (Bobb et al., 2014; Kim et al., 2018; Raz et al., 2005, 2007, 2008), and in inflammation (Metz et al., 2015), as well as by genetic variants associated with an increased risk for Alzheimer's disease (AD; Donix et al., 2010; Harrison et al., 2016; Hua et al., 2016; Li et al., 2016; Moffat et al., 2000; but see Persson et al., 2014; Raz et al., 2010; Squarizoni et al., 2018 for negative findings), inflammation (Persson et al., 2014), and endothelial dysfunction (Zannas et al., 2014).

Carriers of the ApoE $\epsilon 4$ allele, a risk factor for AD, show faster shrinkage of the medial-temporal (Moffat et al., 2000), prefrontal, and cingulate (Rast et al., 2017) regions. Amyloid deposits are associated with faster rates of regional shrinkage, especially in the

medial-temporal regions, occipital cortices, and precuneus (Doré et al., 2013). Alterations in the one-carbon metabolic cycle expressed in reduced levels of vitamins B₁₂ and B₆ and elevated homocysteine (Hooshmand et al., 2016), as well as genetic variants associated with high levels of the latter (Persson et al., 2014), have been linked to accelerated shrinkage of the parahippocampal gyrus and the cerebellum.

In some samples, genetic and physiological vascular risks synergistically accelerate the thinning (Rast et al., 2017) and shrinkage (Bobb et al., 2014; Raz et al., 2007) of brain regions that are usually less vulnerable to aging. In other studies, however, the effects of vascular risk are negligible (Raz et al., 2010; Taki et al., 2013). It may take a combination of negative modifiers, such as older age, lower socioeconomic status, elevated vascular risk, and the presence of the ApoE ε4 allele to predict variability in regional shrinkage (e.g., Persson et al., 2016). Of note, most of the participants in large-scale, population-based studies of brain aging had hypertension, especially in samples limited to older adults: more than 80% in the AGES-Reykjavik Study (Sigurdsson et al., 2012), 75% in the Three-Cities Study (Crivello et al., 2014), 48% in the Seattle Longitudinal Study (Rast et al., 2017), and 46% in the Baltimore Longitudinal Study of Aging (Pacheco et al., 2015) but only 32% in the Singapore Brain Aging Study (S-LAB; Leong et al., 2017) and 20%–33% in the Detroit Longitudinal Study (Persson et al., 2014; Yuan et al., 2018). Thus, separating “pure” aging from the effects of cardiovascular and metabolic risk factors is a challenging undertaking.

Selective attrition of the participants is an important caveat in interpreting longitudinal findings, with attrition rates of 35% and below considered favorable (Ritchie, Bastin, et al., 2015). Some studies achieve better retention, with losses of only 12% in the Massachusetts General Hospital Aging Study (McArdle et al., 2004), 21% in the PATH Study (Shaw et al., 2016), 22% in the Three-Cities Study (Crivello et al., 2014), 24% in the Singapore Longitudinal Study (Leong et al., 2016), and 32% in the Norwegian Cognition and Plasticity through the Lifespan Study (Storsve et al., 2014). In many others, however, the loss of participants over the course of the first two waves was greater: 36% in (Jiang et al., 2014), 39% in the Aberdeen 1936 Birth Cohort Study (Sandu et al., 2014), 41% in Yuan et al. (2018), 43% in the Dallas Lifespan Brain Study (Peng et al., 2018), 46% in Persson et al. (2014), 49% in the Women’s Health Initiative Memory Study (Vaughan et al., 2014), 52% in Moscufo et al. (2018), and 67% in the Aging Study of the Memory and Aging Center of the University of California, San Francisco (Pressman et al., 2016).

Particularly problematic is a nonrandom nature of missingness (Lindenberger, Singer, & Baltes, 2002): returning participants tend to have more years of formal schooling (Gorbach et al., 2017), score higher on cognitive tests (Persson et al., 2014; Ritchie, Bastin, et al., 2015; Yuan et al., 2018), and evidence greater gray matter volumes (Ritchie, Dickie, et al., 2015) in comparison to the dropouts. Although longitudinal models can handle missing data (McArdle, 2009), one must always be careful in identifying the contributors to incompletely random missingness and including these variables in the models.

The neurobiological and cytoarchitectonic foundations of differential gray matter shrinkage remain unclear, but the understanding that emerges from rare studies combining histology with antemortem and *ex-vivo* neuroimaging indicates the relative contributions of various components of the cerebral cortex to the structural properties assessed by MRI. For one, in vivo cortical thickness measures are unlikely to reflect neuronal density (la Fougère et al. 2011). The most probable determinant of the gray matter volume is neuropil—the myelinated and unmyelinated axons, dendrites, and their collateral branches that constitute about 55% of the gray matter bulk, whereas neuronal bodies and glia account for 9%–11% each (Kassem et al., 2013). The role of neuropil volume changes as a core phenomenon in differential brain shrinkage gained support from MRI studies in rodents that revealed coupling between gray matter volume changes observed on MRI and changes in the volume of neuropil components, such as dendritic arborization and spine density (Kassem et al., 2013; Qiu et al., 2013).

Unlike the highly localized and relatively modest addition of neuronal bodies via neurogenesis, local variations in dendritic arborization and axonal density and diameter are common, widespread, and related to stress, hormonal cycle timing, and interactions with the environment (Kassem et al., 2013; Qiu et al., 2013). Another potential contributor to cortical volume loss is intracortical myelin (Courchesne & Plante, 1996; Raz, 2000). In the context of age-related shrinkage, this idea has yet to be tested directly, but it is supported by indirect evidence. Staining cortex for myelin reveals an inverted-U relationship between age and the extent of staining, which is greater in brains from young and middle-aged persons in comparison to infants and older adults (Kaes, 1907). Moreover, the age differences in myelin staining are greater in tertiary association than in primary sensory cortices (Kaes, 1907), and the magnitude of regional age differences and age-related shrinkage correlates significantly with myelination precedence rank (Flechsig, 1901). Brain structures

that myelinate earlier show smaller age-related differences and slower change, with 36%–38% of the variance in the age effects explained by the myelination rank of the region (Raz, 2000; Raz & Kennedy, 2009). Thus, the key to understanding age-related changes in the gray matter volume may lie in elucidating the life-span course of myelination and white matter microstructural development.

Age-Related Differences and Changes in White Matter Structure and Organization

White matter is an agglomeration of axons that constitute the brain's long-distance communication infrastructure. Compared to the gray matter, it contains less interstitial fluid and has a sparser blood supply. Although the cortical and white matter myelin content varies by region and tract, most of the white matter axons have myelin sheaths of varying thickness, with myelin envelopes enhancing the speed and fidelity of neurotransmission and promoting an energetic, a transporting, and a neurotrophic function (see Beaulieu, 2014 and Saab, Tzvetanova, & Nave, 2013 for reviews). Myelin, which comprises multiple proteins and lipids, constitutes approximately 50% of the white matter and 35% of the total brain weight (Bartzokis, 2011; Saab et al., 2013). Myelin is energetically expensive to synthesize and maintain, which in the context of its sparse vascularization under the constraints of a reduced blood supply is problematic (Norton & Cammer, 1984). With age, the deficit may become more acute, as in older mammals the synthesis of myelin de novo is reduced due to a phagocytosis impairment that hampers the clearing of myelin-related debris (Hill, Li, & Grutzendler, 2018; Rawji et al., 2018).

Older adults without cognitive impairment show a slow reduction in the white matter volume starting in late middle age (Raz & Rodrigue, 2006), but measuring the white matter volume is a coarse way of gauging its role in cognitive aging. Nonetheless, several MRI approaches to assessing the structural properties of the white matter in intact humans have been developed. The earliest observations of aging brains revealed multiple hyperintense spots on T₂-weighted MRI scans, white matter hyperintensities (WMHs), dubbed *leukoaraiosis* or “white dilution” (Hachinski, Potter, & Merskey, 1987). The volume of WMHs has been linked primarily to advanced age with contributions from cerebrovascular disease (Pantoni & Garcia, 1997; Wardlaw, Valdés Hernández, & Muñoz-Maniega, 2015), metabolic syndrome (Portet et al., 2012), and neuroinflammation (Raz, Yang, Dahle, & Land, 2012; Wright et al., 2009).

WMHs reflect a broad range of changes in the white matter structure: demyelination, microinfarctions, ischemia, hypoperfusion, as well as cerebrospinal fluid (CSF) and interstitial fluid leakage through weakened blood-brain and CSF-brain barriers (Fernando et al., 2006; Haller et al., 2013; Pantoni & Garcia, 1997; Sam et al., 2016; Wardlaw et al., 2015). In healthy older adults, WMH volume increased moderately over time (e.g., Debette & Marcus, 2010; Gorbach et al., 2017; Moscufo et al., 2018; Raz, Yang, Rodrigue, et al., 2012; Silbert et al., 2008; Sudre et al., 2017). The progression may be greater in those with a relatively high WMH load (Silbert et al., 2008) and is exacerbated by genetic and physiological indicators of vascular disease and inflammation as well as amyloid accumulation (Raz, Yang, Dahle, et al., 2012; Sabayan et al., 2015; Scott et al., 2016; Sudre et al., 2017; Wolfson et al., 2013). Because the WMH burden reflects many diverse pathological influences, it has limited use for understanding nonpathological age-related cognitive changes. It is necessary, however, to consider WMHs' effect on normally appearing white matter (NAWM) (Sam et al., 2016).

Currently, the most popular way of evaluating white matter microstructure is diffusion tensor imaging, or DTI (Basser, Mattiello, & Le Bihan, 1994; Salat, 2014), based on measuring the apparent diffusion characteristics of the brain water, representing them in a three-dimensional diffusivity tensor, and summarizing the tensor properties in four scalars: fractional anisotropy (FA), reflecting diffusion asymmetry along the principal axes; mean diffusivity (Md), the apparent diffusion coefficient averaged across three major axes; axial diffusivity (Ad), which represents diffusion along the main axis; and radial diffusivity (Rd), which is an average of the apparent diffusion coefficients of two minor-axes eigenvalues across the plane perpendicular to the main axis. Because DTI-derived indices reflect many aspects of cellular composition and fiber organization (Jones, Knösche, & Turner, 2013), as well as the brain orientation in the magnet (Basser et al., 1994), they are insufficiently specific.

Cross-sectional DTI studies have revealed age-related differences in all DTI-derived indices across most brain white matter tracts (Salat, 2014). These studies have suggested a pattern of differential aging similar to that revealed by cross-sectional investigation of the cortex: greater age differences in the anterior regions and in the association pathways compared to the posterior areas and the projection tracts (Cox et al., 2016; Salat, 2014). These age-related differences are in line with the first-in-last-out hypothesis (Raz, 2000; Raz et al., 1997), which posits that late to mature regions are more vulnerable to age-related declines than those that reach

their developmental peaks early. Most of the DTI studies have not considered the influence of WMH on regional diffusion properties, and those that did found that WMHs alter diffusion properties, as observed on MRI (Vernooij et al., 2008), underscoring the importance of combining WMH assessment with DTI examination of the cerebral white matter.

Longitudinal investigations of white matter aging are still rare. The most consistently reported finding is widespread FA declines (Barrick et al., 2010; Bender & Raz, 2015; Bender, Prindle, et al., 2016; Gorbach et al., 2017; Hakun et al., 2015; Moscufo et al., 2018; Riekman et al., 2016; Ritchie, Bastin, et al., 2015; Sexton et al., 2014; Sullivan, Rohlfing, & Pfefferbaum, 2010; Vik et al., 2015; Storsve et al., 2016; Teipel et al., 2010). In one sample, age predicted a faster reduction over time, suggesting accelerated change (Storsve et al., 2016). In four studies, an increase in Rd over time was observed (Barrick et al., 2010; Moscufo et al., 2018; Sexton et al., 2014; Storsve et al., 2016). With only NAWM examined, two longitudinal studies of healthy adults revealed a more complicated pattern of age-related change: declines in Ad within association and projection fibers but increases in Ad in anterior regions of the corpus callosum, with FA and Rd changes showing even less consistent patterns (Bender & Raz, 2015; Bender, Prindle, et al., 2016). Latent change score analyses revealed significant individual variability in a sample with a broad adult age range (Bender & Raz, 2015) but not among middle-age and older adults (Bender, Prindle, et al., 2016).

As in regional volumes and cortical thickness, age differences in white matter diffusion properties are influenced by the burden of age-related risk factors (e.g., Burgmans et al., 2010; Kennedy & Raz, 2009). White matter changes are exacerbated by vascular (Aribisala et al., 2014) and metabolic (Bender & Raz, 2015) risk and by genetic variants associated with an increased risk for AD (Riekman et al., 2016) and vascular dysfunction (Taylor et al., 2010). These influences are expected to moderate the relationships between changes in the brain and cognition, just as they do for the cortical volumes. The main limitation of the DTI studies is the lack of neurobiological specificity in interpreting the findings (Beaulieu, 2014; De Santis et al., 2014). For example, the most widely used DTI-derived indicator, FA, may reflect axonal degeneration and demyelination, as well as in reorganization of healthy white matter and alteration of a local configuration of fibers.

Several promising techniques have been developed to discern distinct components of the white matter. Myelin content can be estimated via multiecho T₂-weighted

sequences yielding a T₂ relaxation curve. The contribution of its shortest echo, which presumably represents myelin-trapped water, is myelin water fraction (MWF; Mackay et al., 1994). The method produces reliable MWF estimates within specific white matter tracts (Arshad, Stanley, & Raz, 2017) and, unlike DTI-derived indices, shows the inverted-U age differences similar to postmortem findings (Arshad, Stanley, & Raz, 2016). The same method estimates nonmyelin contributions to the T₂ signal that may reflect axonal size and density in a given brain region (Arshad et al., 2016, 2017; MacKay et al., 1994). Other methods of estimating myelin content are a multicomponent-driven equilibrium single-pulse observation of the T₁ and T₂ (mcDESPOT; Deoni et al., 2008) and R₁ relaxation rate (Yeatman, Wandell, & Mezer, 2014). To date, however, there are no longitudinal studies of MWF in normal aging.

To account for multiple contributors to the white matter microstructure, new approaches model multiple compartments (intra- and extracellular, intra-axonal water, and CSF) and quantify the distribution of axonal calibers (Assaf et al., 2008), as well as neurite density and orientation dispersion (Zhang et al., 2012). These methods require data acquisition with at least two B values. Currently, the test-retest reliability of these methods is unclear, and there are no longitudinal studies of normal aging with these techniques.

In sum, brain structural properties change with age, with the rate and magnitude of change varying across individuals and brain regions. The heteromodal association cortices, cerebellum, neostriatum, and medial-temporal regions show the steepest declines in volume, whereas the primary sensory regions appear more stable over time. Individual trajectories of structural brain aging are modified by multiple vascular, metabolic, and neuroinflammatory risk factors. The picture is less clear with respect to the white matter microstructure and composition, although age-related changes in water diffusivity and fiber organization, as well as multifarious pathological alterations, also occur under the influence of multiple risk factors. Because of the absence of longitudinal studies, the time course of changes in white matter components—for example, myelin—is unknown.

Changes in structural properties of the aging brain have been described above in terms of the brain components that are innate and have been present since the late stages of embryogenesis, as well as brain entities that “do not belong”—additions to the normal white matter known as WMHs. In the same vein, we can describe another component of the aging brain structure that, although necessary in some amount, does not “belong” to the normal brain tissue—iron. Unlike pathological entities (WMHs), iron is critically

important for normal brain function, and its role as a negative modifier of aging and a biomarker of decline reflects its transformation from a friend to a foe.

Brain Iron Homeostasis and Aging

Iron, acquired through the ingestion of nutrients, plays three vital roles in the brain: binding oxygen to the hemoglobin, aiding the synthesis of adenosine triphosphate (ATP) in mitochondria (Mills et al., 2010), and maintaining myelin (Todorich et al., 2009). The first, accomplished by heme iron, is not relevant to the topic of this review, but the other two, performed by non-heme iron, merit discussion. In the normally functioning, younger brain, iron, a powerful oxidant, is safely sequestered in ferritin and transported into the cell and across the mitochondrial membrane, on demand, while bound to transferrin (see Zecca et al. [2004] for a review). With time the sequestration gradually fails, most likely through an increase in autophagy (Ashraf et al., 2018), and free iron accumulates in the neural tissue (Hallgren & Sourander, 1958). A shift in iron homeostasis entails the accumulation of ROC (Harman, 1956), with ensuing oxidative stress impairing basic cellular machinery, including the main energy generator—the mitochondria (for reviews, see Raz & Daugherty, 2018; Zecca et al., 2004). Mitochondrial ferritin is pivotal for the emergence of a labile iron pool that contributes to oxidative stress and the release of proinflammatory cytokines (e.g., interleukin-1 β , IL-1 β and tumor necrosis factor α , TNF α). Autophagic destruction of the ferritin envelope causes the release of iron into the intracellular space and can trigger cell death by ferroptosis, a newly characterized form of cell elimination that is distinct from apoptosis and necrosis (Ashraf et al., 2018). The role of iron as a good-turned-bad force in the aging brain makes estimating iron content in vivo important for elucidating the structural brain changes described above.

Because of its strong paramagnetic properties, iron induces significant local changes in tissue susceptibility, which can be evaluated through MRI techniques sensitive to the relaxation properties of the iron-rich particles. One such technique, susceptibility weighted imaging (SWI), allows for the estimation of iron content in vivo (Haacke et al., 2005; Langkammer et al., 2012). Cross-sectional studies of iron deposits in healthy adults concur with postmortem investigations in establishing age-related differences in the iron content of the striatum and substantia nigra (Daugherty & Raz, 2013). In addition, elevated iron has been estimated in several cortical areas of healthy older adults (Buijs et al., 2017; Rodrigue, Haacke, & Raz, 2011).

At the time of this writing, little is known about the time course of iron accumulation in the brain. Two longitudinal studies demonstrated an increase in iron content of the striatum in healthy adults in a wide age range (Daugherty et al., 2015; Daugherty & Raz, 2016). Moreover, an increase in estimated striatal iron content precedes and predicts regional shrinkage within a two- (Daugherty et al., 2015) and a seven-year (Daugherty & Raz, 2016) time window. These studies originated in the same lab, and if the discrepancies among samples with respect to volumetric findings is a rule, studies from various populations may produce different results.

Structural Brain Changes and Cognition

As interesting as brain findings can be, the primary interest of the cognitive neuroscience of aging is the role of the brain in cognitive changes. In gauging the relationships between structural brain changes and cognition, several questions are worth examining. First, are changes in the brain and cognitive performance coupled, and what is the magnitude and direction of that association? Second, do changes in the brain precede cognitive alterations, follow them, or exhibit a bidirectional influence? Third, if such associations exist, how are they affected by invariant (genetic), stable, or time-dependent risk factors and positive modifiers, such as exercise and cognitive activity? Fourth, are associations between brain and cognitive changes specific to cognitive domains and types of cognitive operations and stimuli, or do they represent a reflection of generalized neural and cognitive change? Finally, if such relationships exist, do reasonably general mechanisms drive them? The extant literature, alas, reveals the dearth of data pertinent to these questions. Nevertheless, we will try to marshal the available evidence while formulating recommendations for future studies.

Are changes in the brain and cognition coupled? The relationship between rates of change in brain characteristics and cognitive performance can be inferred from studies that assess participants on at least two occasions, although the breadth and validity of such inferences could be improved by increasing the number of assessments. The extant longitudinal studies targeting temporal dynamics of the aging brain and cognition have focused mostly on the quintessential age-sensitive ability—memory or global cognitive measures, such as the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975). In a seminal study that established the best-practice analytic approach to elucidating change in the age-brain-cognition relationship, the

expansion of lateral ventricles over seven years was coupled with a decline in an aggregated index of memory (McArdle et al., 2004). Several studies have linked shrinkage of the prefrontal cortex and white matter and medial-temporal structures to declines or a reduced ability to benefit from repeated testing on cognitive tests (Aljondi et al., 2018; Daugherty & Raz, 2017; Gorbach et al., 2017; Kramer et al., 2007; Leong et al., 2017; Persson et al., 2016; Raz et al., 2008; Rodrigue & Raz, 2004). In some samples, hippocampal shrinkage was coupled with a decline in memory (Fjell et al., 2013; Gorbach et al., 2017; Leung et al., 2016), but in others no such coupling was observed (Anlagan et al., 2018; Persson et al., 2016). A decline in verbal memory was also coupled with a loss of total cerebral volume, shrinkage of frontal and parietal white matter, and ventricular expansion (Leung et al., 2016). Hippocampal shrinkage and ventricular dilation were linked to a decline in executive functions, and general brain shrinkage, as well as frontal, parietal, and temporal (but not occipital) gray matter atrophy, were associated with poorer global cognition (Leung et al., 2016).

An increase in subcortical WMH volume has been linked to declines in episodic memory (Silbert et al., 2008), whereas a total WMH increase over approximately four years was coupled with a decline in language performance but not in memory, and even that only in persons with low language skills (Zahodne et al., 2015). An increase in mean diffusivity in the inferior longitudinal fasciculus was coupled with a decline in executive (Stroop) performance (Fjell et al., 2017). Greater axial diffusivity in the cingulum and uncinate fasciculus at baseline predicted episodic memory decline over three years, whereas none of the regional gray or white matter volumes showed significant associations (Lancaster et al., 2016).

Underscoring the need for examining the bidirectionality of brain-cognition associations, some studies found higher baseline cognitive scores predicting reduced brain shrinkage over time (Persson et al., 2016; Ritchie, Bastin, et al., 2015; Yuan et al., 2018). The meaning of these findings remains unclear. They may reflect better brain maintenance (see chapter 7) as proposed by studies of health and intelligence (Gottfredson, 2004; Kraft et al., 2018) or stem from the effects of cognitive activity that can alter local brain volumes (Draganski, Kherif, & Lutti, 2014). The latter is a less plausible explanation, as brain changes induced by cognitive activity are highly localized, and their durability is uncertain (Wenger et al., 2017).

The impact of white matter changes on cognition is even less clear because of ambiguity in the neurobiological interpretations of the DTI-derived indices and

the dearth of longitudinal studies. In one sample, a change in Md but not FA was coupled with working memory decline (Charlton et al., 2010), whereas in very old persons, declines in perceptual speed correlated with FA reduction (Lövdén et al., 2014), and in septuagenarians, FA decline co-occurred with a drop in fluid intelligence (Ritchie, Bastin, et al., 2015). However, in an adult lifespan sample, greater gains in associative memory were coupled with a reduction in FA and an increase in Rd—that is, presumably negative changes (Bender, Völkle, & Raz, 2016). This finding of cognitive gains associated with a *reduction* in FA has been replicated in a different sample for a different cognitive domain (speed of processing) and a shorter time window (Kievit et al., 2018).

Other properties of the brain tissue, such as iron content, are rarely investigated in longitudinal studies of cognitive change. To date, two results from a two-occasion longitudinal study have been reported. An increase in caudate iron was coupled with lesser repeated-testing gains in verbal working memory (Daugherty, Haacke, & Raz, 2015) and less improvement in navigation performance (Daugherty & Raz, 2017) over a two-year follow-up.

In sum, although the general link between cognitive and brain changes is supported by the extant data, evidence of consistent coupling between localized changes in brain characteristics and specific cognitive functions is lacking.

What is the temporal order relationship between brain and cognitive changes? An important question, especially in the context of the prediction and mitigation of cognitive declines, is whether changes in the brain precede cognitive alterations, follow them, or exhibit a bidirectional influence. To date, the dearth of multioccasion longitudinal studies has hampered obtaining the answers to this question. In semilongitudinal studies with repeated brain but not cognitive assessment, the entorhinal (Rodrigue & Raz, 2004) and hippocampal (Cohen et al., 2006) shrinkage rate was associated with memory scores at follow-up. In studies with a single MRI assessment and repeated measurements of cognition, associations between local brain properties and cognition emerged. Persons with thinner parahippocampal, temporal, and parietal association cortices (Pacheco et al., 2015) or lower fornix Ad and volume (Fletcher et al., 2013) exhibited greater decline in cognitive performance and were more likely to have a diagnosis of cognitive impairment at follow-ups. People who benefited more from the repeated administration of associative memory tests had larger volumes of the CA3 hippocampal subfield and the

dentate gyrus, whereas no relationship was noted for the CA1 subfield or subiculum (Bender, Daugherty, & Raz, 2013). Smaller baseline volumes of the prefrontal white matter, hippocampus, parahippocampal gyrus, and cerebellum predicted a failure to gain from repeated testing of fluid intelligence over two years (Persson et al., 2016). Smaller volumes of the cerebellum, parahippocampal gyrus, lateral prefrontal cortex, and caudate nucleus, as well as greater hippocampal iron content, predicted a greater decline in navigation performance or reduced gains from repeated testing over two years (Daugherty & Raz, 2017). In sum, elucidating temporal dynamics and lead-lag relationships between aging of the brain and cognition remains an important goal for the future, with little evidence available thus far.

What are positive and negative modifiers of the relationships between the brain and cognition in adult development? Many risk factors shape the trajectories of brain aging. However, considerably less is known about their moderating and mediating of the relationship between age-related changes in the brain and in cognition. Although most longitudinal studies include many individuals with age-related vascular risk factors, the influence of the latter on the outcome is rarely examined. Assessment of vascular and metabolic risk influence on brain-cognition associations yielded mixed results. Elevated higher pulse pressure moderated the relationship between baseline hippocampal iron and prefrontal volumes and improvement in navigational performance over time (Daugherty & Raz, 2017). Volumes of the hippocampal subfield CA1 which is sensitive to age-related vascular risks, correlated with gains from retesting on a verbal free-recall task in hypertensive individuals but not in their normotensive counterparts (Bender et al., 2013). Thus, answering this question awaits proper longitudinal studies.

Summary, Conclusions, and Future Directions: A “To-Do List” for the Cognitive Neuroscience of Aging

This survey of the extant literature on age-related cognitive changes and their neuroanatomical correlates converges on the following points:

1. Aging, even in its most benign forms, is accompanied by a decline in brain health markers: regional brain volumes, white matter diffusion properties, and iron content.
2. These changes occur within a relatively short time and can be reliably assessed by current MRI methods.
3. Age-related changes in the brain are differential: Heteromodal association cortices and association white matter fibers age faster than primary sensory cortices and projection fiber systems. In some regions, such as the medial temporal lobe, the change accelerates with age.
4. All examined brain properties exhibit individual differences even without average change. Individual variability may be missed if appropriate statistical models are not applied.
5. The rate of age-related cognitive change varies across cognitive domains, but assessment of cognitive performance over time is hampered by repeated exposure to tests that may dampen individual differences. However, when individual differences in cognition are observed, they tend to correlate with brain change.
6. The coupling of age-related changes in the brain and cognition is relatively weak, inconsistent across brain regions and cognitive domains, and requires adequate statistical power to detect. Because a typical longitudinal study of cognitive aging and its brain correlates is underpowered and there is little agreement about cognitive measures, it is difficult to assess the true strength of these associations.
7. A more consistent pattern of results is observed when baseline brain characteristics are assessed. A faster rate of cognitive change is linked to less favorable initial brain characteristics.
8. The relationship between the brain and cognition is probably bidirectional. Better cognitive performance at baseline predicts lesser shrinkage of relevant brain regions. Such reciprocal influence of brain and behavior may stem from specific neural mechanisms, as well as general phenomena, cognitive reserves, and brain maintenance. Disentangling these influences is currently impossible because of a lack of multioccasion studies with adequate statistical power. The “reversed causality” hypothesis, tested only in a handful of longitudinal studies, requires greater attention.
9. Metabolic, vascular, and inflammatory risk factors modify the trajectories of aging. Physiological and genetic risks exacerbate the declines and may alter the relationship between changes in the brain and cognition. Due to significant variability in sample composition, genetic findings are inconsistent, even for well-established, risky genetic variants.

Several obstacles still stand in the way of better understanding the brain-cognition relationship in the context of aging:

1. Although neuroanatomical changes happen fast, studying the vicissitudes of the aging brain structure necessitates long-term multioccasion longitudinal designs. The scarcity of such longitudinal studies impedes our understanding of the temporal dynamics of cognitive aging. This imperative for more longitudinal research, however, is difficult to fulfill because of formidable logistic obstacles, which can be overcome only with a substantial investment of money, time, and human power.
2. Noninvasive neuroimaging provides many exciting opportunities for evaluating brain structural properties. However, no single property, such as regional cortical thickness or regional myelin content, is sufficient for describing and tracking age-related brain changes and their relation to cognition. Multimodal imaging, which is gaining popularity, may advance the field by integrating various aspects of the brain structure and gauging the temporal relations among distinct properties, such as myelin and iron content, neurite density, axonal size, and volume.
3. The study of cognition can benefit from focusing on constructs rather than individual indicators. A single test of recall is just one indicator of memory as a construct. The assessment of cognitive performance at the construct level is, regrettably, quite rare. Even the best of single indicators in any cognitive domain has only modest reliability—a fault that can be addressed, at least to some extent, by employing latent variable analyses driven by an appropriate theory. Moreover, the extant studies vary widely in their selection of indicators, thus impeding comparison and analyses of the findings. Greater uniformity in cognitive measures, with greater attention to their psychometric properties, is needed to harness the collective power of multiple cohorts.
4. Assessing brain properties relevant to aging cannot be isolated from measuring other changes in the organism. Yet few studies assess metabolic and vascular risk systematically, and many do not model its contribution to the variance in brain and cognitive changes. Moreover, like cognitive abilities, risk factors are constructs and are only partially reflected in single indicators, such as systolic blood pressure or blood glucose.
5. To take the need for comprehensive risk-factor assessment further, significant commonality among these negative modifiers of aging should be considered. Lower socio-economic status, poorer educational attainment, lower cognitive performance since the earliest stages of development, and the increased prevalence of behaviors and lifestyles that are detrimental to health, coupled with health-care disparities, high levels of chronic stress, and differential exposure to environmental pollution, can serve as cumulative and conjoint force multipliers that accentuate even seemingly minor genetic and physiological differences. Until modifiable aspects of this risk-factor consortium are addressed, attempts to isolate the effects of its specific components on brain aging and cognition may be futile.
6. The mechanisms of brain aging and its relationship with cognition remain poorly understood. Despite significant progress in elucidating pathways to aging in cellular and animal models, assessing the applicability of these models to humans is hampered by the limitations of noninvasive imaging methods. Evaluation of the cellular mechanisms (Garaschuk et al., 2018, Harman, 1956) and the effects of a cellular energy crisis (de la Torre, 2008) on the human brain can benefit from the development of suitable neuroimaging proxies. For example, the accumulation of iron and changes in the R_1 relaxation rate may serve as indirect but sensitive indicators of free radical damage. Tying changes in brain volume and cortical thickness to changes in neurotransmitter levels and their modulation, as well as energetic and metabolic changes, is vital for understanding the mechanisms of cognitive aging. This can be accomplished by applying methods like ^{31}P (Lin & Rothman, 2014) and functional ^1H magnetic resonance spectroscopy (fMRS; Stanley & Raz, 2018).
7. Further refinement of manual and computer-aided analyses of smaller volumes, such as hippocampal subfields, may advance the understanding of the brain-cognition relationship in normal aging. The hippocampus is not a uniform structure, and its components or subfields differ dramatically in cytoarchitectonic properties, connectivity, vascularization, response to stress, and sensitivity to vascular and inflammatory risk factors (Amaral, Kondo, & Lavenex, 2014; Insauti, 1993; McEwen, 1999; Raz et al., 2015; Shing et al., 2011). Although cross-sectional studies hint at important differences in the strength of associations between age, subfield volumes, vascular risk, and cognition in healthy adults, longitudinal studies are still lacking. A concerted effort aimed at developing reliable and valid

manual and computer-aided protocols (Wisse et al., 2017) will increase the likelihood of obtaining valuable knowledge about the relationship between structure and cognition in normal aging. Improved spatial resolution and shorter acquisition times will be attained with greater use of high-field (7T) scanners and further modifications of the existing sequences.

8. Assessing the RONCS role in the normal aging process may elucidate the neural mechanisms of cognitive aging. Testing their activity and effects in vivo (e.g., the FRIENDS model) posits a challenge because it requires simultaneous assessments of the brain load of RONCS, the state of myelin and neuropil, and cognitive performance. For each of these items, only indirect measures are available. Myelin content can be estimated by MWF, although current methods do not differentiate between myelin and its debris. Neuropil volume is most likely represented by the regional gray matter volumes measured from T₁-weighted MRI scans. Two indirect indices have been proposed to address the challenging problem of assessing the excess free radicals in vivo. First, measures of local brain iron content linked to mitochondrial dysfunction and a shift in RONCS homeostasis can be obtained via MRI in intact humans (Ashraf et al., 2018; Betts et al., 2016; Daugherty & Raz, 2015; Langkammer et al., 2012). Another promising candidate is R₁ relaxation time, which when abnormally prolonged can be shortened by the acute administration of antioxidants (Berkowitz, 2018).
9. Because animal models are crucial to testing hypotheses about the molecular underpinnings of human brain aging and cognitive change, the translational harmonization of animal neuroimaging studies with human investigations is critically important. With notable exceptions (Kassem et al., 2013; Qiu et al., 2013), such studies are still rare. Translationally harmonized studies should reproduce the precision of human neuroimaging tools, human construct-level measures of cognitive performance, and human longitudinal designs, in addition to taking advantage of the invasive procedures available in animal models.

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7 Brain Maintenance and Cognition in Old Age

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ABSTRACT The aging brain is notorious for detrimental changes. However, some older adults display *brain maintenance*, defined as a lack of senescent brain changes and age-related brain pathology. While general brain maintenance seems possible, the selective maintenance of some brain systems in the presence of age-related decline in others appears more likely. Here we focus on the structural and functional maintenance of the hippocampus. We propose that hippocampal maintenance is the primary determinant of preserved episodic-memory functioning in old age. We discuss several potential neural and nonneural mechanisms promoting hippocampal maintenance, including neuronal survival and generation, intact neuronal morphology, and vascular integrity. We provide evidence suggesting that correlated genetic and environmental factors cumulatively influence the operation of these mechanisms, in part through lifestyle choices. Future work should study the contributions of specific connections, transmitter systems, and subregions to hippocampal maintenance; further explore its etiology, prevalence, and behavioral relevance; and examine the generalizability of the maintenance concept for understanding individual differences in human cognitive aging to other regions and circuits.

More than 30 years ago, Rowe and Kahn (1987) introduced the notion of *successful aging* as a complement to the distinction between pathological and normal aging. While defining the criteria for success has stirred some debate, the preservation of broad cognitive abilities, such as episodic memory, is generally considered a hallmark of successful aging. Hence, the sizeable heterogeneity and malleability of human cognitive aging, including the potential for brain maintenance, have attracted increasing attention in recent years (Lindenberger, 2014; Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012).

Cognitive abilities such as episodic memory, perceptual speed, reasoning, and semantic memory are characterized by large individual differences in age-related longitudinal change (e.g., Ghisletta, Rabbitt, Lun, & Lindenberger, 2012; Lindenberger, 2014; Tucker-Drob, Brandmaier, & Lindenberger, 2019). Some individuals show a precipitous decline with advancing adult age, whereas others display high and stable levels of performance well into old age. In the following, we focus on

the preservation of episodic memory as a particularly important aspect of successful cognitive aging (i.e., successful memory aging; see also Nyberg & Pudas, 2019).

Complex interactions among genetic and environmental factors underlie successful memory aging by influencing brain integrity. Major brain changes are linked to pathological memory aging—for example, in Alzheimer’s dementia, as reviewed in detail elsewhere (e.g., Jack, Barrio, & Kepe, 2013). Also, while not of a pathological nature, brain changes at multiple levels (e.g., cellular, regional, and large-scale networks) are normative in aging (Fjell, McEvoy, Holland, Dale, & Walhovd, 2013) and underlie normal memory decline. Even in the presence of normative age-related brain changes, memory aging might be ameliorated through compensatory processes, as, for example, proposed by Reuter-Lorenz and Park (2014). Hence, successful memory aging is likely to proceed along multiple paths (Cabeza et al., 2018; Nyberg & Pudas, 2019; figure 7.1).

We have previously argued that the primary determinant of preserved cognition in older age is *brain maintenance*, or a relative lack of senescent and pathological brain changes in aging (Lindenberger, Burzynska, & Nagel, 2013; Nyberg et al., 2012). Despite its face validity and conceptual appeal, the relative maintenance of structural and functional brain integrity in aging remains an underexplored path toward successful memory aging. In this chapter we summarize relevant findings from studies of brain maintenance and cognition in old age and offer some thoughts on conceptual and theoretical refinements of the maintenance concept.

Brain Maintenance—General or Specific?

Will a group of older individuals who are characterized by, say, minimal cortical and subcortical atrophy, also display other kinds of brain maintenance (e.g., intact neurotransmitter systems, preserved structural connectivity, or low amyloid retention)? Alternatively, in the spirit of a multiple-factor framework (Buckner, 2004; Gabrieli, 1996), will different groups of individuals show

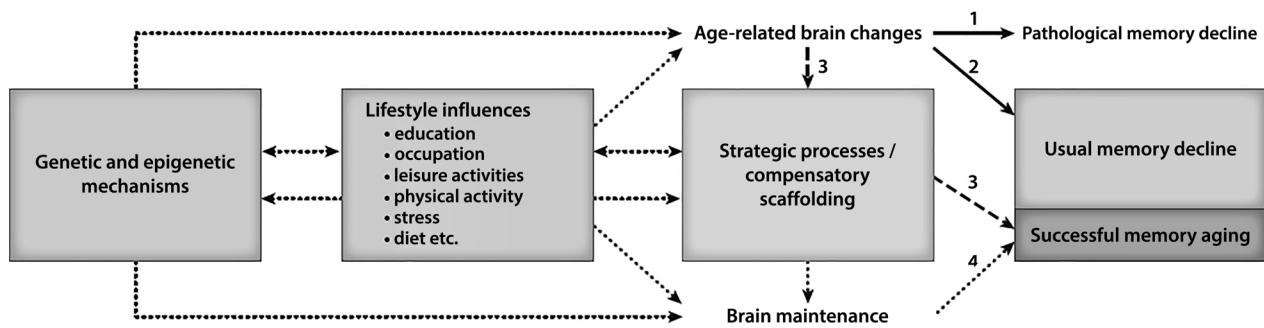


FIGURE 7.1 Model of life course paths to pathological, usual, and successful memory aging. Path 1 (not the focus of this chapter) represents trajectories characterized by pathological memory decline (e.g., dementia). Paths 2, 3, and 4 lead to normal memory aging (usual and successful). Path 2 represents usual memory decline in response to age-related brain changes (e.g., hippocampus atrophy). Path 3 (*dashed line*) is an

indirect path to successful memory aging via compensation for age-related brain changes. Path 4 leads directly to successful memory aging via brain maintenance. The dotted lines reflect the influences of genetics, epigenetics, and lifestyle (“what” factors) as well as strategies (“how” factors) on brain integrity (maintenance versus decline) and memory outcomes. From Nyberg & Pudas (2019). (See color plate 6.)

distinct cascades of age-related degenerative changes that target different brain systems and vary in the rate of progression? In the latter view, it is conceivable that some individuals would display brain maintenance of certain major systems (such as the hippocampal/medial temporal lobe (MTL) system) while showing normal age-related changes in other systems (e.g., the fronto-striatal system). These competing accounts make distinct predictions for patterns of age-related cognitive changes (cf., Rabbitt, 1993).

Some findings from studies comparing the magnitude of age-related changes among different cognitive abilities, which should tax distinct brain circuits, at least in part, are in line with the generality of brain maintenance. For example, Ghisletta and colleagues (2012) found that about two-thirds of the age-based changes in memory are shared with those of other cognitive abilities, including reasoning, vocabulary, and perceptual speed (see also Dekhtyar et al., 2017; Tucker-Drob, Reynolds, Finkel, & Pedersen, 2014). These results were recently confirmed in a meta-analysis comprising 89 effect sizes representing shared variance in cognitive change from 22 unique data sets composed of over 30,000 individuals (Tucker-Drob, Brandmaier, & Lindenberger, 2019).

Broad cognitive abilities require multiple brain circuits and regions for their operation. Hence, individual differences in aging-induced cognitive change may covary across different abilities in the presence of distinct patterns of cerebral deterioration and maintenance. Longitudinal studies of brain aging do not portray a coherent picture as to the generality or specificity of brain maintenance in aging. For instance, analyses of individual five-year changes in the volumes of

specific regions revealed correlations for some of the examined brain volumes, but not others (Raz et al., 2005). The highest change-change correlations were observed for the prefrontal white matter and the hippocampus ($r = .71$) and for the prefrontal white matter and the lateral prefrontal cortex ($r = .70$).

Some cross-sectional studies point to a certain degree of specificity of maintenance (Hedden et al., 2016; Lövdén et al., 2018; Salami, Pudas, & Nyberg, 2014). In a recent report from the COBRA Study, Salami and colleagues used a latent-profile analysis of data from 181 older adults aged 64 to 68 years who performed an n-back working-memory task during functional magnetic resonance imaging (fMRI) scanning. They identified one subgroup with higher performance ($n = 113$; 63%) and a second subgroup ($n = 55$; 31%) with lower performance. Analyses of data from an extensive off-line cognitive test battery confirmed that the lower-performing group had lower working-memory performance but nevertheless relatively intact episodic-memory performance. Moreover, analyses of different markers of brain integrity (cortical and subcortical volumes; functional connectivity; dopamine D2 system integrity) revealed specific alterations in the second group in frontoparietal regions, along with no group differences for other markers, such as hippocampal/default-mode regions.

Taken together, the degree of generality in brain maintenance remains a significant unresolved issue. Future large-scale longitudinal studies with multiple indicators of brain integrity, along with reliable measures of different cognitive functions, are needed to more conclusively address this topic. Awaiting such evidence, we focus on brain maintenance of the

hippocampal system in relation to episodic memory, which is known to be hippocampus-dependent. We will draw on findings from longitudinal studies when available, as they provide more direct evidence on maintenance than cross-sectional comparisons. Select examples of nonhippocampal forms of brain maintenance will be provided in a separate section.

Hippocampus and Successful Episodic Memory

There is evidence that the amount of age-related atrophy, and by inference likely also maintenance, is not uniform across subregions of the hippocampal formation (Leal & Yassa, 2015; Pini et al., 2016; Shing et al., 2011). However, with only a few exceptions that will be noted, the available evidence relevant to brain maintenance refers to the whole hippocampus.

Mounting evidence indicates that hippocampal atrophy in aging underlies normal episodic-memory decline—notably, from change-change analyses (e.g., Gorbach et al., 2016). Hippocampal atrophy has been observed even in normal individuals who, according to genetic, biomarker, and cognitive criteria, are at minimal risk for showing early signs of pathological brain aging (Fjell et al., 2013; Raz et al., 2005). Importantly, there is evidence that some older individuals suffer minimal hippocampal atrophy with advancing adult age (Fjell et al., 2009; Raz et al., 2005), along with intact episodic memory (see Nyberg & Pudas, 2019). For example, Sun and colleagues (2016) reported that a group of “memory super-agers” had hippocampal volumes comparable to those of younger adults, in contrast to typically performing older adults, who had smaller volumes than younger individuals (see also Dekhtyar et al., 2017).

In addition to structure, functional integrity of the hippocampal formation matters as well. An fMRI study from the Betula project (Pudas et al., 2013) compared the brain activity of a group of individuals with maintained memory, as defined by baseline level and change over two to four test waves covering up to 15 years (Josefsson, De Luna, Pudas, Nilsson, & Nyberg, 2012), with individuals with normal memory development (i.e., moderate decline). The successful older adults were found to have a higher activity in the left hippocampus and prefrontal cortex during encoding of face-name pairs compared to the normal participants, and this activity was as high as the average activity observed in a young reference group (see also Düzel, Schütze, Yonelinas, & Heinze, 2011). Hippocampal activity correlated positively with memory performance, and this association continued to be present after statistically controlling for group differences in hippocampal volume. Further evidence for the importance of

hippocampal functional integrity was obtained in a study showing that Betula participants who maintained their memory over up to 20 years had better-preserved hippocampal resting-state connectivity than older individuals with typical memory decline (Salami, Pudas, & Nyberg, 2014).

Additional aspects of hippocampal maintenance include dopaminergic neurotransmission (e.g., Nyberg et al., 2016) and neurovascular functions (Düzel, van Praag, & Sendtner, 2016), as well as minimal tau protein deposition (Schöll et al., 2016). Schöll and colleagues noted that tau is abundant in normal aging, in particular in the medial temporal lobes, and they observed that the amount of tau deposition across individuals was negatively related to episodic memory.

Not all of the above-mentioned studies used a longitudinal design. It has been acknowledged that cross-sectional data cannot serve as proxies for estimating associations between age changes in brain maintenance and age changes and cognitive performance (Lindenberger, von Oertzen, Ghisletta, & Hertzog, 2011; Nyberg et al., 2010; Raz & Lindenberger, 2011). Nevertheless, a cross-sectional data pattern in which older adults with more “youth-like” brain structures and functions show higher levels of cognitive performance is at least consistent with the brain maintenance notion. Hence, the longitudinal and cross-sectional findings taken together give some credence to the maintenance hypothesis as far as the hippocampal formation and episodic memory are concerned.

Brain Maintenance beyond the Hippocampus

Going beyond the focus on the hippocampal formation, other brain characteristics have also been related to well-preserved episodic memory in aging. One prominent example is greater thickness of the cingulate cortex, particularly its anterior segments (Gefen et al., 2015; Sun et al., 2016). Another example is stronger and more youth-like functional connectivity between the hippocampus and anterior brain regions, which have been found to correlate with better memory performance in old age (Fandakova, Lindenberger, & Shing, 2015; Lin, Ren, et al., 2017).

Minimal β -amyloid deposition might also be a salient, more general characteristic of brain maintenance, and it has been found to relate to high episodic-memory functioning in aging (Dekhtyar et al., 2017; Farrell et al., 2017). Also, recent findings suggest that integrity of the locus coeruleus and associated noradrenergic pathways may play an important role in maintaining memory performance in old age (Dahl et al., 2019; Hämmerer et al., 2018; Mather, this volume).