1

Exploring Emergent Brain Dynamics

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Abstract

Across development, the coupling and synchronization of oscillations among brain areas are thought to mediate network assembly, coordination, and plasticity, and to play supporting roles in sensorimotor functions and cognition, including perception, language, learning, and memory. Ongoing neural plasticity and sensitivity to environmental cues contribute crucially to this process. To explore the complex mechanisms by which the brain evolves and matures, the Ernst Strüngmann Forum gathered experts to examine collectively how dynamic brain coordination emerges during development. This chapter introduces the extended discourse that transpired and summarizes the perspectives that emerged from multiple disciplines. Background information is provided on the key areas of enquiry (prebirth, childhood, early adolescence, and emerging adulthood), remaining gaps in knowledge are highlighted, and innovative ways forward are proposed to further this evolving area of cross-disciplinary study.

Introduction

Throughout the ages, the developing brain has constituted one of the most fascinating areas for study and reflection. Many efforts have been devoted to the delineation and conceptualization of the remarkably dynamic processes by which the brain evolves and matures over time. Yet despite this long history of inquiry, we still do not completely understand how the developing brain is able to cope with myriad challenges over the life span and emerge as a fully functional adult brain.

The developing brain is an exemplar of an emergent, complex (nonlinear) dynamic system (Freeman 1994). Continual, ongoing changes in brain activity throughout organized neural tissue (i.e., brain dynamics) enable cognition, perception, and language to emerge over the course of development. These processes depend crucially on neural plasticity and are exquisitely sensitive to myriad environmental cues present during early brain development. However,

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the mechanisms which enable such transformation—from the establishment of early networks during the initial periods of brain growth and organization, to the reorganization and remodeling in early to late adolescence—have long been a matter of debate.

To explore these processes and underlying mechanisms, both event-related and spontaneous dynamics must be investigated. This, in turn, requires input from diverse research domains: nonlinear dynamics, artificial intelligence, and neural networks as well as all of the basic research and clinical fields that monitor and analyze the brain's activity, including genetic and biochemical parameters, using established and emerging techniques.

This Ernst Strüngmann Forum provided an opportunity to increase our understanding of the key components of brain dynamics at local and large-scale networks across development. To this end, experts from wide-ranging fields were invited to participate in a collective examination of how dynamic brain coordination and synchrony emerge during development. This included the possibility that abnormalities in neuronal synchronization and dynamic integration might be causal in developmental disorders (e.g., attention deficit hyperactivity disorder, language learning impairments, schizophrenia, autism spectrum disorder).

If you are unfamiliar with this institute, we offer a brief overview to lend understanding to this resultant volume. Dedicated to the continual expansion of knowledge in basic science, the Ernst Strüngmann Forum is an independent, science-driven entity that convenes "intellectual retreats" that are carefully crafted to permit in-depth scrutiny of problem areas in research. These are not meetings where one fluxes in and out of lectures or presentations: they are integral parts of an interactive process that creates synergy between experts from multiple areas—a process reliant on active engagement, geared toward the (re) conceptualization of pressing problems and the delineation of approaches to address and ultimately resolve these.

From March 5–10, 2017, forty experts participated in the 25th Ernst Strüngmann Forum. Each invitee brought to the discussion table the expertise needed to extend the exploration of dynamic brain coordination and synchrony, and their underlying mechanisms, from a developmental perspective. Each participant contributed to a specific working group, formed around the developmental stages of (a) fetal to birth, (b) childhood, (c) early adolescence, and (d) emerging adulthood. Interactions within and between groups ensured a cross-fertilization of perspectives and ideas. A set of overarching questions, formulated by the organizing committee, provided the starting point for discussion:

- What is the role of dynamic coordination in the establishment and maintenance of brain networks and of structural and functional connectivity?
- How are local and global functional networks assembled and transformed over normative development?

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- To what degree do oscillatory patterns vary across development? Are there age-linked "oscillatory signatures" that can serve as maturational biomarkers?
- Do early developmental circuit vulnerability deficits in oscillatory domains have relevance for later developmental disorders?
- Is there a way to quantify the multiple intrinsic and extrinsic factors over development and how they may differentially impact early brain mechanisms including plasticity?
- How might emerging technology enhance early identification, diagnosis, prognosis, and remediation of developmental and neuropsychiatric disorders that may reflect early disruption in dynamic coordination and/or a failure to establish structural and functional connectivity and synchronization between cortical areas?

Specific topics were introduced by background papers. Written, read, and commented on in advance, these papers exposed open issues and posed questions for debate in the working groups. At the Forum, in-depth discussion was cultivated through formal and informal interactions. Throughout, consensus was never forced nor was it necessarily a goal. Instead, long-standing viewpoints were questioned, knowledge gaps were exposed, and novel insights began to emerge. As in any interesting discussion, there is always the danger that emergent, novel ideas might get lost. Thus, the essence of this discourse was captured by the groups in "reports" (see Chapters 4, 7, 11, and 15). These reports are not protocols of the discussions but rather summary statements of the ideas and issues brought forth by each group, from the perspectives of all involved. Their goal is to transfer the ideas, opinions, and remaining contentious issues, along with proposed directions for future research, to a broader audience.

This volume contains the finalized background papers and group reports from this Forum. Our purpose in this introductory chapter is to summarize the main themes covered in this collective examination and to highlight remaining gaps in knowledge and ideas proposed to further this evolving area of cross-disciplinary study.

Emergent Brain Dynamics: A Developmental Perspective

In any living system, effective developmental processes are needed to establish precise relations between the organism's components. In the developing nervous system, functionality depends on highly specific relations among individual neurons, established through biochemical and molecular signaling systems and the electrical activity of neurons.

In his review of the role of oscillations and synchrony in the development of the nervous system (Chapter 2), Wolf Singer discusses the importance of oscillations and their propensity to synchronize in the encoding of relations as

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well as the singular effects that synchronization has on synaptic cooperativity and plasticity. He offers insight into the particular challenges associated with obtaining causal evidence of synchronous oscillatory activity and discusses the use of emerging tools to manipulate selectively oscillating network components so as to interfere with synchrony without affecting discharge rates. His review of the developmental mechanisms that translate temporal relations among neuronal discharges into functional architectures provides an excellent starting point for query into emergent brain dynamics across development.

Fetal to Birth

Prior to birth, the brain undergoes a substantive degree of development and many of these early steps lay the foundation for later maturation. Studying the developing brain in human embryos and fetuses is laden with challenges. In his review, Alain Chédotal (Chapter 3) examines the role of axon guidance molecules in the regulation of cell–cell interactions during normative and atypical development. He points out that although various methods exist to study axon guidance in animals, technical and ethical issues pose significant challenges in the developing human. To visualize and track neuronal connectivity successfully in pre-birth humans, Chédotal stresses the need for improved noninvasive imaging methods (e.g., 3D and 4D obstetrical ultrasonography, 3D power Doppler ultrasound, *in utero* MRI, and diffusion tensor imaging tractography) and recommends development of novel methods. Our current ability to correct axon guidance defects or treat neuronal network dysfunction is severely lacking, and existing surgical methods to improve the effects of monogenic diseases (e.g., some forms of strabismus caused by congenital cranial dysgenesis) cannot generally be applied to more complex disorders. Chédotal suggests that we need to consider whether aberrant projections should be silenced or the growth of new connections promoted. He also recommends that existing observations be expanded to derive general rules of network construction and developmental sequences.

In their discussions, Nicholas Spitzer et al. (Chapter 4) asked: What is the range of normal brain structure and function and how can dynamic changes be studied over time? How constrained is the specification of cortical cell type during development? Where does deterministic organization stop and environmental regulation take over? What happens to spatiotemporal patterns of waves of activity during early cortical development? What are the patterns of activity and their roles in developmental plasticity? What roles does activity fulfill, and do changes in activity prefigure development of pathology?

Spitzer et al. review the difficulties associated with quantifying the range of normal brain structure and function and stress the value of using multiple dimensions. To determine the range of normality, they find it necessary to know the range of variation in genes, cells, networks, and oscillations *combined* with the impact on normal function and/or pathology. They stress

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that brain development requires the maintenance of stability in some states while others are changing and converging, and propose homeostasis as a mechanism by which this is achieved. Further, early patterns of coordinated activity are necessary to assemble the necessary brain networks, whereas subcortical modulatory systems (e.g., cholinergic) seem to shape the activity in all cortical areas. Neurons in the upper layers coordinate the emergence of frequency-specific oscillatory rhythms whereas deeper layers seem to contribute to unspecific activation.

In their discussion of the role of activity, Spitzer et al. discuss transmitter switching: the loss of one transmitter and the gain of another, with corresponding changes in postsynaptic receptors to maintain synaptic function. Transmitter switching involves changes in the levels of transmitters, which seems to occur during psychiatric disorders, thus motivating studies of the role of transmitter switching in depression and schizophrenia. Putting a cell in a new environment may change its properties in ways that allow it to develop normally. Moreover, as Spitzer et al. point out, a lot of descriptive data from development is currently at our disposal, but data on mechanisms is lacking. Thus, inferences drawn from adult physiology and plasticity, while attractive, may be misleading.

With a view toward the future, Spitzer et al. suggest:

1. Using all findings achieved to date to construct conceptual frameworks and directions of experimental work should promote the most rapid progress.
2. Acquiring more data will be an important and necessary step to arrive at general principles by which dynamic brain coordination and dynamics is achieved during development.
3. The formulation of computer models for data analysis and testing circuit mechanisms at different scales should be a component in all research programs.

Further, they recommend that future research focus on

- clarifying the mechanism that governs the transition between discontinuous oscillatory activity during neonatal (mouse) or fetal (human) development and continuous rhythms at juvenile age,
- determining the functional role of different frequency oscillations observed at different ages,
- understanding the basis of developmental changes in cortical wiring,
- identifying the cellular and molecular mechanisms by which these patterns of activity exert their effects,
- exploring clinical diagnostics and treatment protocols that will likely follow from this knowledge, and
- including nonhuman primates and humans (via registry databases) in research, while retaining the mice model.

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Early Childhood

After birth, the brain no longer develops solely as the result of internally driven mechanisms. External factors combine with internal mechanisms to shape the brain.

In Chapter 5, Takao Hensch discusses how neural circuitry is shaped by external factors at well-defined periods of time. Using amblyopia as a model of postnatal synaptic plasticity, he reviews the "triggers" and "brakes" that determine the onset and offset of such critical periods. He emphasizes that although the brain may retain the capacity to rewire later in life, adult plasticity may utilize distinct underlying mechanisms. Thus, understanding the differences between developmental and adult plasticity, including differences in how they are measured, is imperative and may enable insights into novel therapies for recovery of visual function from amblyopia in both children and adults. Genetic diversity in mice and humans may provide insight into individual variability and the timing of critical periods and should be pursued. Hensch calls for better models of critical period plasticity across animal species and humans and the identification of biochemical and electrophysiological correlates of these windows.

In Chapter 6, Sarah Moore and Michael Kobor review epigenetic mechanisms involved in the regulation of transcriptional potential. They describe how epigenetic mechanisms shape embryogenesis, neurogenesis and migration, neuronal plasticity, and impact critical windows of development, when neurons and circuitries may be sensitive to external stimulation. They explore the potential role of epigenetic marks as a biological consequence of early forms of social environmental adversity through a review of key animal studies and discuss the existing human literature that links early environments to epigenetic markers and neural structure and function. Despite the limitations in human studies, consistent findings that DNA methylation correlates with early social environment and neural phenotypes suggest that epigenetic marks capture meaningful variation in early environments as well as concurrent neurological measures and mental conditions. Moore and Kobor posit that epigenetic marks in human central and peripheral tissues reflect an important biological substrate of experience-dependent plasticity relevant to current mental health status.

The group discussions by Matthias Kaschube et al. (Chapter 7) focused on the following questions: How does neural activity evolve during early childhood? How does the continuum from internally to externally driven activity shape the brain? What is the role of critical periods? What are the factors that initiate and terminate these periods? How does critical period plasticity differ from adult plasticity? What is the interrelation between neural activity and epigenetics? What measurements and interventions do we have at our disposal? What are the signatures of typical and atypical development?

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To navigate in and interact with their environment successfully, infants must construct a comprehensive and predictive internal model of the external world. Kaschube et al. explore the neural bases of this process and how resulting knowledge could be leveraged to treat and prevent neurodevelopmental disorders. They discuss how developing brains form dynamical networks that integrate genetic, epigenetic, and sensory information, and emphasize the interplay between molecules and neural activity. Further, they highlight strategies that the brain uses to tightly control the impact of sensory input onto its developing networks, which are manifest at the molecular, neural activity, and behavioral levels, and which appear pivotal as the brain strives to maintain a fine balance of flexible yet stable configuration. Stressing contributions made by animal models to our understanding of the neural basis of cognitive development, Kaschube et al. point out that in humans, behavioral assays and noninvasive imaging techniques provide only an indirect account of neural activity. Current knowledge of the developing epigenome of the brain is still very limited. They stress the urgent need to link animal and human studies and propose the following:

- Modern data acquisition, analysis, and computing methods should be used to integrate vast amounts of chronic data from a large number of individuals. This data is needed to advance development of high-dimensional formal statistical and dynamical models of typical and atypical neurodevelopmental trajectories.
- Computational efforts are needed to develop better dynamical and statistical neural circuit models, as well as to establish or adapt machine-learning tools to cope with molecular, neural, and behavioral data.
- Size and complexity appear to be key features for typical and atypical development in humans. Representing these features in animal models, beyond rodents, is an important, outstanding task.

Early Adolescence

Adolescence is characterized by maturation of reproductive and other social behaviors and social cognition. Although gonadal steroid hormones are well-known mediators of these behaviors in adulthood, their role in shaping the adolescent brain and behavioral development is not fully understood. Reviewing the impact of pubertal hormones on brain dynamics and maturation, Cheryl Sisk (Chapter 8) describes the organizational effects that pubertal hormones have on sex-specific behaviors during adolescence, as well as the neurobiological mechanisms of structural organization in the adolescent brain by pubertal hormones. To guide further study into the relationship between pubertal hormones, the adolescent brain, and experience, Sisk asks:

- What is the role of social experience in survival, differentiation, and functional incorporation of pubertally born cells?

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- Is adolescence a sensitive period distinct from the perinatal period or part of an extended period of postnatal sensitivity for hormone-dependent organization?
- Is adolescent brain development experience expectant or experience dependent?

During adolescence sharp increases in neural plasticity occur as a result of, for example, sensorimotor experiences, stress, diet, drugs, cerebral injury, and the immune system. In Chapter 9, Bryan Kolb reviews different types of neural plasticity: experience-independent, experience-expectant, and experience-dependent. During adolescence he finds that most changes are due to experience-dependent plasticity, although he notes that experience-expectant plasticity (related to gonadal hormones or the increase in socioaffective behaviors) may also occur. Onset of the sensitive period begins around the time of pubertal gonadal hormone production. Offset may be related to the completion of myelination, but likely varies in different cortical regions due to the continuing impact of adolescent socioaffective experiences. Kolb highlights key questions for consideration:

- What is the role of glia in controlling the onset and offset of the sensitive period?
- How do experiences in adolescence vary with exposure age, what are the underlying mechanisms of their effects, and how might they influence brain plasticity later in life?
- What are the sex differences in the timing of the sensitive period and the role of experiences in altering brain plasticity during this period?
- How do changes in gene expression in adolescence influence the duration of the sensitive period?
- What is the role of the immune system in controlling the onset/offset of the sensitive period and synaptic plasticity during this period?

In Chapter 10, Patrick Purdon describes the pivotal role of gamma-aminobutyric acid (GABA) in the maturation of the cerebral cortex. GABAergic inhibition mediates crucial aspects of brain development: the development of structural connections, critical period plasticity, and functional synchronization across large-scale networks. Disturbances in the development of GABAergic circuits are thought to underlie neurodevelopmental disorders (e.g., schizophrenia and autism). Characterizing the developmental trajectory of these circuits in humans is crucial, yet current methods (postmortem studies and noninvasive imaging) provide only indirect links to GABA circuit function. To map the continuous trajectory of GABA circuit function from infancy through adulthood in humans, we ideally need a common set of tools as well as detailed measurements of sensory, cognitive, and language function.

Purdon suggests that studies using anesthesia-induced oscillations provide a way to characterize and track the development of GABAergic oscillatory

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circuits from childhood through adulthood. In both pediatric and adult practice, positive allosteric modulators of GABA receptors are used most commonly as anesthetic drugs. These drugs induce large, stereotyped oscillations in the unconscious state that are likely generated by the same GABAergic circuits responsible for gamma oscillations in the conscious state. Since these drugs are administered to tens of millions of patients each year, under conditions of both neurotypical and atypical development, Purdon argues this anesthetic experiment of nature could be harnessed and used to develop detailed developmental trajectories of GABAergic circuit function in humans.

In their group discussions, Marina Bedny et al. (Chapter 11) explore the time course and mechanisms of experience-based plasticity in early adolescence. They find that the potential for plasticity in the adolescent brain could theoretically follow one of three types of time courses: (a) the adolescent brain may be no more plastic than the adult brain, (b) adolescence could mark the end of critical periods that began in infancy, or (c) adolescence may constitute its own critical period. In view of current evidence, it may be possible that all three coexist in the human brain.

Each neurocognitive system has its own time course of development: some may be stable over the lifespan, others may begin their sensitive periods early in life and taper off in adolescence, while still others may have a specific critical period of sensitivity that spans adolescence (e.g., sensitivity to social stress). Further research is needed to uncover the time course of plasticity across neurocognitive systems and stages of development.

Bedny et al. also discuss the significant alterations that occur within local and large-scale networks. Changes in neural oscillations that continue throughout childhood and adolescence include

- restructuring neurophysiological synchronization among brain areas,
- reduction in overall power of the oscillation,
- reduction in lower-frequency oscillations (<~10 Hz),
- acceleration of the peak frequency of alpha oscillation, and
- increases in higher-frequency oscillations (>~10 Hz).

In task-dependent neurophysiological synchronization, these developmental changes may contribute to early cognitive and behavioral maturation; age-dependent increases in inter-regional synchronization during performance of a language task have been shown to correlate with individual differences in language abilities (Doesburg et al. 2016). Bedny et al. discuss the need to link markers of human brain development to changes in experience, and consider the associated challenges. They hold that research into visual cortex function in individuals who are congenitally blind demonstrate that the basic functional properties of cortical networks can change dramatically as a result of developmental experience. In addition, studies in individuals who became blind as adults suggest that the capacity of cortex to respond to changes in experience is qualitatively different in childhood and adulthood.

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The Transition to Adulthood

The critical period between adolescence and adulthood marks the final stage of brain development prior to the attainment of the mature state. The neurobiological underpinnings of this transition have been notoriously difficult to characterize, thus creating numerous challenges in the diagnosis and treatment of psychopathologies that commonly emerge during this period (e.g., schizophrenia and affective disorders). Certainly, increased understanding will enable us to address and ultimately prevent these neuropsychiatric diseases. But beyond this, better knowledge of physiological changes, social relationships, and social cognition may lead to a novel conceptualization of this developmental period.

To understand why and how psychopathologies emerge during this period, we need to know the underlying biological vulnerability and mechanisms that confer risk. In Chapter 12, Peter Uhlhaas suggests that important modifications in brain coordination occur during the transition from adolescence to adulthood; these changes involve improved generation of rhythmic activity and its synchronization at low and high frequencies, as well as changes in the functional interactions between brain regions that underlie emotion regulation. Because they coincide with the emergence of brain disorders characterized by profound disruption of reality testing and emotional experience, they provide windows of vulnerability for the expression of dysfunctions that can then lead to behavioral anomalies. Important characteristics of these modifications are (a) the nonlinear trajectory of developmental changes and (b) the close relations to the underlying neurobiological parameters. In the adolescent brain, the transient reduction in large-scale synchronization of cortical networks and the accompanying increase of subcortical input may provide a condition that favors critical fluctuations. If these go beyond the critical threshold during the transition toward the adult state, the brain could remain in a faulty bifurcation and fail to accomplish the final development steps: (a) increase in the precision of synchronized, high-frequency oscillations, (b) integration of frontal and subcortical activity patterns, and (c) shift in the balance between local and global coordinated brain states. Uhlhaas describes the implications for the development of interventions designed to target large networks and brain coordination mechanisms.

Applying insights from research on critical periods in early development, Ulman Lindenberger (Chapter 13) outlines how plasticity can be researched throughout the entire life span. He posits that plasticity is triggered by a mismatch between the current range of functioning and experienced demands, and that it is characterized by inertia. A central nervous system in a permanent state of plasticity-induced renovation would not be able to develop a coordinated set of habits and skills, and would constantly drain a large amount of precious metabolic resources. Thus, mismatches in demand and supply must surpass a threshold of intensity and duration to trade the goal of stability for

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plasticity. This dynamic equilibrium shifts with age. To guide future research, Lindenberger proposes a set of hypotheses and stresses the following:

- We need to be aware of the almost ubiquitous and often unavoidable confound between age and experience whenever we wish to make claims about age differences in plastic potential.
- We need a better understanding of how age-based changes and between-person differences in large-scale network topography affect the context for local plastic change.
- We need a mechanistic account of the plasticity of higher-order cognition.
- We lack neural theories of generalization and transfer to predict consequences of plastic change.
- We need to better understand the relationship between brain size and neural efficiency.

In Chapter 14, Adriana Galván explores agents of change that impact neurobiological development in the adolescent brain. She begins with a discussion of the concept of "adolescence" and proposes that it be defined using neurobiological criteria, psychosocial responsibilities, and skill-based capabilities. This means that each parameter needs a clear operational definition, but which brain metric should be used, for example, to determine a "mature" versus an "immature" brain? Which skills are necessary for reaching maturation? Resolving these questions requires drawing on input across multiple disciplines. Galván discusses the prevailing neurobiological models of adolescent brain development and considers the impact that physiological changes (e.g., puberty, sleep), social relationships, and risk-taking have on adolescent brain development. She highlights promising areas for future consideration and posits a positive attribute to adolescent brain maturation. Empirical research has shown that the ontogenetic changes in the adolescent brain are adaptive. She encourages a view of the adolescent brain as "a sponge thirsty and receptive for new knowledge"; on the power of the adolescent brain to learn, to engage in prosocial behavior, and to explore the environment in a positive way.

Effective transitioning from adolescence to adulthood is a basic component of a functional society, and increased understanding of this developmental stage has far-ranging benefits—to individuals as well as society. In their group discussions, Jennifer Gelinas et al. (Chapter 15) describe how the numerous nonlinear modifications in the adolescent brain distinguish it from both the child and adult brain. Characterized by a predilection for specific forms of plasticity, these changes predominantly affect neural networks involved in higher cognitive and emotional processes. Gelinas et al. recommend that future research should

- take a multidisciplinary approach focused on the changing patterns of both physiologic and pathologic brain dynamics across adolescence;

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- combine multiple research modalities and encourage dedicated and standardized initiatives to collect the relevant longitudinal studies in humans and animal models as well as computational models (e.g., of artificial neural systems); and
- assay the neurophysiologic processes of typical adolescent development and identify neural network level biomarkers and therapeutics for the neuropsychiatric diseases that characteristically emerge during this phase.

Such approaches may enable us to gain a more positive understanding of the adolescent brain as being one that is more adventurous, social, and cognitively mature than a child's, but not yet under the inevitable influences of senescence.

Final Reflections

Dividing a discourse into succinct periods of development (fetal to birth, childhood, early adolescence, transition to adulthood) to give structure to our debate, enabled focused discussion, but it requires us to step back and integrate perspectives. In this final section, we wish to highlight several areas for consideration.

As we think of plasticity and critical periods across brain development, we must bear in mind that it is not optimal to segregate them into specific time windows. Plasticity and critical periods may be active across the entire life span and should be newly defined, enabled by parallel and/or overlapping mechanisms, on smaller or larger timescales, in a nonlinear way, controlled by intrinsic and extrinsic factors. Critical periods previously closed (e.g., in childhood) may reopen at a later stage. Plasticity can be environmentally reopened through a two-step process involving (a) the reactivation of plasticity machinery (the permissive step) and (b) focused sensory experience to stimulate perceptual learning (the instructive step). As Hensch (Chapter 5) states, we need to identify the optimal sensory stimulation that drives change.

As research continues, it will be important to gather multidimensional information on cognition, genomes, epigenomes, molecular biology, neurochemistry, brain structure, and brain function at different points in human development. This information is needed to gain a rich description of the trajectory of development, and could be further enhanced through machine learning and formal statistical and dynamical models. With respect to functional brain dynamics, a focus on nonlinear and multi-scale changes across the life span is needed to determine network stability, network flexibility, and network plasticity.

Clearly many important questions were raised that are as yet unanswered, perhaps because the research has not or cannot be done in humans given the current state of technology and research techniques. Alternatively, we may not yet know the exact research questions to pose to unravel the many layers

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that still shield us from direct observation of the key neural mechanisms that underlie trajectories of neurophysiological maturation. One intriguing line of inquiry unaddressed here concerns the maintenance of flexibility beyond adolescence: Why do some people remain highly cognitively functional into old age, and what terminates functionality in others at the end of adolescence? Can cognitive flexibility be maintained and, if so, how? Can personality or cultural changes be explained or related to some network shifting or epigenetic factors? These broader questions await well-designed, inclusive longitudinal studies.

By fostering introspection, synergy, and expansion in research foci on dynamic coordination across development, we should be able to move forward to produce a lasting, meaningful impact across disciplines. Such an approach will ultimately facilitate new insights and formulate pragmatic research goals. We hope that both seasoned scientists and the emerging generation of cross-disciplinary minded young scientists will use the issues, collective ideas, and opinions raised here as a guide to further elucidate how the developing brain manifests across development as a mature, healthy, and fully functioning adult human brain.

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