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Early Childhood

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Abstract

During the first years after birth, infants face the enormous task of building a comprehensive and predictive internal model of the external world, allowing them to navigate and interact successfully with their environment. This chapter explores the frontiers involved in understanding the neural bases of this process and how such knowledge could be leveraged to treat and prevent neurodevelopmental disorders. It begins by describing how developing brains form dynamical networks that integrate genetic, epigenetic, and sensory information, emphasizing the interplay between molecules and neural activity. Strategies are highlighted 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. While suitable animal models have greatly contributed to our basic understanding of neural development, revealing the neural basis of cognitive development in humans remains a challenge. To overcome this barrier, new directions are discussed that combine animal and human studies. Finally, this chapter discusses implications of the complexity of the human brain and highlights the potential of data-driven formal models of neurodevelopmental trajectories to enable early detection and individualized treatment of developmental disorders.

Introduction

Early childhood (0–3 years) is a period in life associated with enormous potential as well as significant functional narrowing. A fascinating example can

Group photos (top left to bottom right) Matthias Kaschube, Chuck Nelson, April Benasich, Michael Kobor, Takao Hensch, Matthias Kaschube and Mark Hübener, Mriganka Sur, Wolf Singer, Chuck Nelson, Gyorgy Buzsáki, April Benasich, Pierre Gressens, Mark Hübener, Michael Kobor, Matthias Kaschube, Wolf Singer, Mriganka Sur, Pierre Gressens, Gyorgy Buzsáki, Takao Hensch, Yehezkel Ben-Ari and Wolf Singer

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be found in the acquisition of language, arguably one of the major tasks of infancy. While at birth, a human infant can learn any of ~5000 languages known to humankind, by the age of three or four years, a child is able to speak with native fluency only those few languages to which s/he has been exposed.

This remarkable *flexibility* of the human brain to be susceptible—at least for a limited amount of time—to the particular statistics of the environment may come at a cost; namely, the risk of reducing *stability*, which could be a potential precursor of psychiatric diseases. One of the overarching goals of this chapter is to address the fundamental dichotomy between building a flexible yet stable brain, focusing on the period of postnatal development. At birth, the brain is exposed— for the first time—to the full spectrum of sensory input with which it has to cope for the rest of its life. Thus, the *external* world becomes more effective in driving neural activity, allowing the brain to learn relevant statistics of the sensory environment. The brain, at this point, is already equipped with an elaborate *internal* structure, both in terms of anatomical connections and endogenous neural activity patterns. In the first years of life, a shift from more internally to more externally generated neural activity occurs, during which an internal model of the external world is established. Strategies of the brain appear pivotal to control its susceptibility to sensory input, allowing it to navigate through this complicated process between the poles of flexibility and stability.

Our discussion here is guided by five main questions:

1. How does neural activity evolve during early childhood? How does the continuum from internally to externally driven activity shape the brain?
2. 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?
3. What is the interrelation between activity and epigenetics?
4. What measurements and interventions do we have at our disposal?
5. What are the signatures of typical and atypical development?

We begin by reviewing the neural underpinnings of postnatal brain development in infants, emphasizing the shift from internally to externally generated neural activity and the interrelation with different molecular processes. We identify different strategies that may help to increase the overall level of robustness at this stage in development. We then focus our discussion on the neural basis of critical period plasticity and its relation to adult plasticity. In addition, we highlight novel directions in identifying the role of epigenetics in neural development. Using the important example of language acquisition in humans, we review current methods for measuring cognitive abilities in typically developing infants as well as those displaying atypical development. Here, we address both behavioral assays and noninvasive methods for measuring brain activity, and discuss current and future opportunities for combining animal and human studies to understand and develop novel treatments for developmental disorders. Moreover, we discuss recent conceptual frameworks

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for thinking about typical and atypical cortical development to leverage these concepts toward devising novel strategies for individualized treatments of developmental disorders.

Neural Activity in Early Childhood

Building a Cortical Scaffold and Using It to Establish a Model of the World

As discussed by Singer (this volume), the basic layout of the brain develops according to the same principles of cellular recognition and is based on the same molecular signaling cascades as any other organ. However, once nerve cells become electrically excitable, neuronal activity assumes a self-organizing role, which gains in importance with increasing differentiation of neuronal networks. Initially, activity serves a trophic function as it promotes secretion and uptake of molecules that promote growth and differentiation. As soon as primitive networks are formed, this spontaneous activity undergoes specific spatiotemporal patterning (e.g., traveling waves, periodic bursting, synchronous oscillations), and the emergent correlation structure is exploited for the definition of neighborhood relations. These data are used to refine projection patterns, to establish precise correspondence of maps, and to set up and fine-tune circuits acting as central pattern generators required for the later coordination of movement. The circuit changes follow the Hebbian principle: "neurons that fire together wire together." Once sensory signals become available (beginning in the late prenatal period), the self-generated activity is structured by further taking into account the influence of signals from the environment; thus, signals resulting from active exploration of the environment come to impact development (Held and Hein 1963).

During this postnatal developmental stage, activity is used to translate the statistical contingencies of events and features of the surrounding world into neuronal architectures, to complement the genetically prespecified model with information from the actually experienced environment (see Hensch, this volume). This additional information is used to refine connections to a degree not attainable with genetic instructions alone. Well-examined examples include the establishment of precise binocular correspondence (Wang et al. 2010), the matching of visual and auditory maps in the barn owl tectum (Knudsen and Knudsen 1989; Knudsen 2002), and generation of visual response features in rewired auditory cortex (Sharma et al. 2000; Sur and Rubenstein 2005). Others are the imprinting of species-specific song patterns or the templates of kinship (Brainard and Doupe 2002; Bolhuis and Gar 2006). The rules and molecular mechanisms supporting these experience-dependent circuit modifications are essentially the same as those mediating the effects of self-generated activity and closely resemble those supporting learning in adulthood. As in the latter case, many of these experience-dependent modifications are

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supervised by gating systems to minimize the danger that inappropriate or spurious correlations induce dysfunctional connectivity changes. This is why passive stimulation alone is rather inefficient in causing circuit changes, as first documented by the seminal experiment of Held and Hein (1963). A host of subsequent studies indicate that the developing brain seeks, via active exploration, the signals required for optimization of its functional architecture and is capable of evaluating the consistency of activity patterns before allowing them to modify circuitry. For instance, normal language development depends on normal sociolinguistic interactions; children whose primary exposure to language comes from TV or who are socially isolated, for example, have abnormal language (Kuhl et al. 2003).

When deprivation prevents exposure to signals required for circuit adaptation to the typical environment, the genetically prespecified scaffold of connections is not simply frozen in a state prior to sensory signal onset, but rather deteriorates to a level of specificity below that reached at the beginning of the critical period (Crair et al. 1998; White et al. 2001). In other words, the scaffold becomes less precise.

Different Modes of Activity Are Matched to Different Genetic and Molecular Processes during Development

While there is now little doubt about a general central role for electrical activity in successive maturational stages, how this relates to genetic and molecular events is less clear at present; nature and nurture are inseparable. Very early in development, neurogenesis and axon guidance require calcium currents in migrating neurons and axonal growth cones to decode diffusible and membrane-bound molecular recognition signals for path finding and contact formation. These activity-based cues are likely sufficient to establish a coarse scaffold, making activity permissive for growth. Once axons reach their target, they organize topographically into maps, guided by gradients of recognition molecules and broadly structured activity, such as waves of glutamate-driven activity in the early retina or calcium waves in the early hippocampus and cortex. Gene and molecular expression analyses have revealed the crucial role of molecular markers for axon guidance and map formation, and the complementary role of structured electrical activity in regulating gene expression, pathfinding, and contact formation (Sur and Rubenstein 2005; Assali et al. 2014). These processes are fundamentally self-organizing. We still need to resolve how activity intersects with molecules, what mechanisms are engaged, and to what extent the pattern of activity may also have an instructive role. Another open question is how waves of activity across space, which convert space into time, influence the timing and pattern of gene expression that may also underlie map formation.

Later, the fine structure of activity has an instructive role in shaping the specificity of connections. Spike timing-dependent plasticity (e.g., narrow

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windows when individual presynaptic and postsynaptic spikes can bidirectionally adjust synaptic strength) is a physiologically relevant mechanism that translates causal relations into modifications of synaptic connections, and is based on molecular processes involving coincidence-detecting mechanisms such as NMDA receptors. This process can be either unsupervised or controlled by top-down modulation, implementing a mechanism for supervised learning. In this mode, development and learning share many commonalities and the boundary between them becomes fuzzy. Exactly how supervised learning influences development, and its instantiation, remains an important open question.

Plasticity, Stability, and Development

Adaptive processes are deeply embedded in living systems, including the mammalian nervous system, and are present throughout life to a greater or lesser extent. They are observed following manipulations, such as monocular deprivation, which reveal the range of possibilities or potential for plasticity early in life. The development of stereopsis by matching inputs from both eyes is a good example of how activity-dependent circuit selection can build on external information to optimize correspondence between maps (Wang et al. 2010). Another example is the tuning of auditory maps underlying perception (Sanes and Woolley 2011).

Plasticity and stability are fundamentally related processes, and indeed processes of stability are essential elements of plasticity. Hebbian increases in synaptic weight need to be countered by homeostatic processes to constrain (normalize) levels of total drive and to permit neurons to operate within an optimal dynamic range. This process necessarily reduces the weights of unstimulated synapses, thereby providing greater "contrast" for stimulated synapses to influence the target cell.

Developmental plasticity involves strengthening and growth as well as weakening and elimination of synapses (see Figure 7.1). Synapses that undergo activity-dependent weakening may eventually be removed (pruning). Synapse elimination may exist as a process at early stages of development, sometime even prior to birth, as revealed for instance by the elimination of multiple climbing fiber inputs to Purkinje cells (Hashimoto and Kano 2005; Uesaka et al. 2015). In cortex, synapse elimination and synapse formation coexist as dual mechanisms of plasticity (Mataga et al. 2004), though many questions remain about how widespread the phenomenon is and how it might be implemented. In addition, synapse elimination may involve nonneuronal phagocytic cells such as microglia. Some of the molecular bases of this neuron–microglia cross talk have been identified (Paolicelli et al. 2011; Schafer et al. 2012), but several questions remain unanswered, such as the role of neural activity in this interaction.

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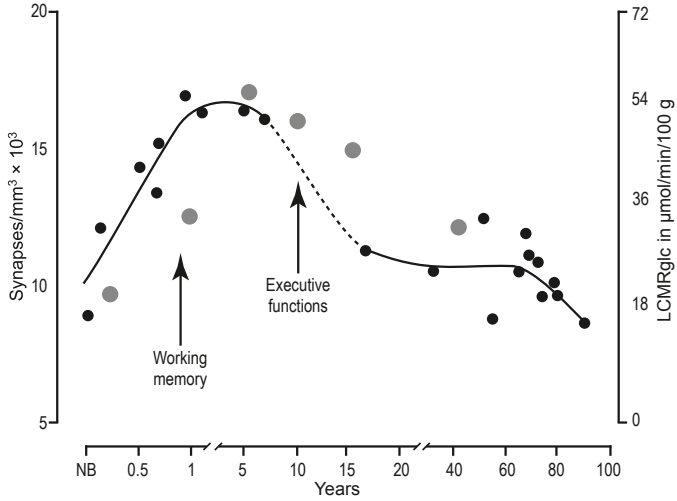

Figure 7.1 Variation in the human prefrontal cortex during development: Density of synapses in layer III of the medial frontal gyrus (black circles) and resting glucose uptake (LCMRglc/PET) in the frontal cortex (gray circles). Arrows point to the approximate periods of emergence of various prefrontal cortex functions. NB: newborn. Adapted with permission from Huttenlocher (1990) and Chugani (1993).

The Log-Normal Scaffold Hypothesis

Interestingly, evidence stemming largely from the hippocampus and neocortex suggests that brain circuits are poised to maintain a robust balance between flexibility and stability, owing to the observed diverse distribution of synaptic weights and firing rates. Diversity is the main "drive" of biology. The brain not only contains numerous neuron types, but a large diversity of neurons within the same type is the norm. The spontaneous firing rates of cortical neurons, and probably all neuron types, in the brain and spinal cord, are distributed over three orders of magnitude in a highly skewed, log-normal distribution. In addition to firing rates, the distribution of the fraction of neurons firing together in a given time window, the strengths of synapses on a given neuron, the volume of spines, and the macroscopic connectivity also show a skewed, typically log-normal form. The multiple levels of such systematic overarching organization may support the competing requirements of sensitivity, robustness, resilience, and plasticity in neuronal circuits (Buzsáki and Mizuseki 2014).

The dynamic range of firing rates increases during awake states and decreases during sleep. This implies that faster neurons decrease whereas slow neurons increase their rates during non-REM sleep, resulting in a narrowing and widening of rate distribution during sleep and waking, respectively. Faster firing neurons are more strongly connected to each other, forming a "rich men's club" organization, and have longer axon arbors. Recent findings indicate that

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high firing rate cells are "rigid" and form the backbone of local circuit dynamics. Their largely preserved firing patterns provide "good enough" and fast answers in most situations, since they generalize across situations and carry critical features of the brain's existing knowledge base. In contrast, slow firing neurons act as a large pool of "plastic" cells whose patterns change gradually during behavioral experience (Grosmark and Buzsáki 2016). The developmental origin of log-normal distributions is not known. An intriguing hypothesis is that the fast-firing, rigid end of the distribution represents early-born neurons with high resilience, whereas later-born cells comprise a large reservoir of slow firing, plastic, and perhaps more vulnerable populations.

Critical Periods

Critical periods of brain development are observed at distinct times for different modalities. As such, they constitute windows of malleability during which neural activity can robustly reorganize the circuitry that underlies specific functions. In the most thoroughly studied example, acuity loss (amblyopia) by discordant input to the primary visual cortex (V1), the duration of the critical period scales with the average life span of the species, from weeks (mice) to years (humans). This suggests a biological process that transiently optimizes circuits to best fit the individual's environment early in life followed by enduring stability, a learning rate strategy found to be efficient in artificial neural networks (Takesian and Hensch 2013).

The transition to critical period plasticity arises as inhibition emerges to preferentially suppress responses to spontaneous activity, relative to visually driven input activity, switching learning cues from internal to external sources (Toyoizumi et al. 2013). Thus, the critical period can open without changes in plasticity mechanisms when activity patterns become more sensitive to sensory experience. More broadly, hierarchical organization of sensorimotor pathways may develop through a cascade of critical periods induced as inhibitory circuit maturation progresses from "lower" to "higher" cortical areas (Condé et al. 1996; Werker and Hensch 2015).

Detailed mechanistic exploration of factors which initiate (inhibitory parvalbumin, PV+ cells) or terminate (brakes) a plastic window in V1 offers deeper insight into potential roles for critical periods (see Hensch, this volume). First, as the maturation of inhibition may preferentially suppress responses to spontaneous activity relative to visually driven input (Toyoizumi et al. 2013), critical period onset reflects a switch in learning cues from internal to external sources. Second, rapid plasticity of PV+ cells per se may generate changes in associated (gamma) oscillations relevant for synapse pruning. Third, critical period cascades can be coordinated through a sequential interaction of PV-cell intrinsic clocks with extrinsic, locally released activity-dependent cues. Finally, plasticity is eventually suppressed by molecular brakes. Glycosaminoglycans

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in the perineuronal nets, which gradually enwrap mature PV+ cells, buffer reactive oxygen species generated by these fast-spiking neurons and, in the human brain, are least evident in higher associational areas which have evolved to be plastic throughout life (Brückner et al. 1999). This, in turn, may render those areas most vulnerable to neural degeneration (i.e., Alzheimer disease). Likewise in mice, loss of the Lynx1 "brake" molecule prolongs critical period plasticity and neurodegeneration with age (Morishita et al. 2010; Kobayashi et al. 2014). Thus, closure of a critical period may ultimately be neuroprotective. Notably, all four aspects can be impacted in mental illness, mistiming the typical trajectories of development and contributing to differential rates of emergent psychopathology (Lee et al. 2014).

Normal and Enhanced Ocular Dominance Plasticity in the Adult Visual Cortex

While ocular dominance plasticity in V1 has long been thought to be strictly limited to a critical period, a number of recent studies have shown that monocular deprivation (MD) can also induce changes in adulthood, at least in mice (Sawtell et al. 2003; Tagawa et al. 2005; Hofer et al. 2006). It has also become clear, however, that there are differences between critical period and adult ocular dominance plasticity: the magnitude of MD-induced shifts in adult mice is smaller (Hofer et al. 2006), longer deprivation episodes are needed to induce them (Hofer et al. 2006), it fails to impact visual acuity (Morishita and Hensch 2008), and there is an age-dependent decline in the degree of adult ocular dominance plasticity (Lehmann and Löwel 2008). In addition, the underlying eye-specific changes are different: whereas during the critical period a rapid drop in closed-eye driven responses is followed by a delayed increase in open eye-evoked activity (Frenkel and Bear 2004; Mrsic-Flogel et al. 2007), the latter component alone seems to be the prevalent change in adult mice (Hofer et al. 2006; Sato and Stryker 2008). However, the exact contribution of both components to adult ocular dominance plasticity depends crucially on the conditions during deprivation: when deprived mice are exposed to prolonged stimulation with high contrast moving gratings, clear closed-eye depression is observed (Matthies et al. 2013; Rose et al. 2016), mimicking phenomenologically the situation during the critical period.

A number of behavioral interventions have been shown to promote critical period-type plasticity in the adult visual cortex. Among these are environmental enrichment (Baroncelli et al. 2010) or enhanced social interaction (Balog et al. 2014), as well as high contrast visual stimulation (Matthies et al. 2013; see above) and motor activity coupled to visual feedback (Kaneko and Stryker 2014). Also, an earlier MD episode enhances the effect of a second episode later in life (Hofer et al. 2006). This is likely mediated by the formation of new dendritic spines that outlast the first MD episode and might become reactivated later to promote the second ocular dominance shift (Hofer

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et al. 2009). Finally, dark-rearing prolongs developmental plasticity (Tropea et al. 2010), and a period of dark exposure before MD causes prominent ocular dominance shifts in adult rats (He et al. 2006), a species that seems to show little ocular dominance plasticity in adulthood. This latter observation bears particular relevance, as a clinical study is currently underway[1] to test whether complete light deprivation might mitigate amblyopia in adult humans, on the premise that unlocking plasticity in V1 allows the amblyopic eye's inputs to reestablish connections there. A common theme to several of the above-mentioned interventions is that they induce reduced levels of inhibition and thus rejuvenate cortical excitatory–inhibitory balance, which is known to play a crucial role in the induction of critical period plasticity. More direct molecular manipulations have also provided new insights (see Hensch, this volume).

Interrelation between Neural Activity and Epigenetics

One intriguing pharmacological intervention capable of reopening critical period plasticity in adulthood is epigenetic modification. Both amblyopia in rodents (Silingardi et al. 2010; Lennartsson et al. 2015) and the acquisition of absolute pitch in humans (Gervain et al. 2013) is enabled by histone deacetylase (HDAC) inhibitors. Major epigenetic mechanisms include DNA methylation and demethylation, histone modifications, genomic imprinting, alternate splicing, and noncoding RNAs (micro-RNAs, long noncoding RNAs, small interfering RNAs, and small nuclear RNAs) (see Moore and Kobor, this volume). Significant changes in the epigenome have been associated with all steps of brain development, including neurogenesis, neuronal migration, synaptic transmission, and plasticity, including critical period plasticity in visual cortex (Mellios et al. 2011).

Links between neuronal activation and impact on epigenome are emerging but represent a new avenue of research. As examples, in adult brains, neuronal activation has been shown to induce changes in DNA methylation, especially in genes involved in brain development and plasticity. This suggests a role of DNA methylome in activity-dependent epigenetic regulation of plasticity (Baker-Andresen et al. 2013). Similarly, studies in young adult rodents have shown that natural behavior, exploration of a novel environment, and raising neuronal activity through sensory or optogenetic stimulation increased neuronal DNA double-strand breaks (DSBs) in postmitotic neurons of relevant, but not of irrelevant, networks (Suberbielle et al. 2015). These DSBs were repaired within 24 h through a nuclear phosphoprotein that plays a role in maintaining genomic stability, BRCA1. DSBs have been associated with epigenetic remodeling and, in particular, with removal of DNA methylation marks.

[1] https://clinicaltrials.gov/ct2/show/NCT02685423 (accessed Oct. 21, 2017).

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To achieve a more complete picture of child development, epigenetics provides numerous opportunities that include, but are not limited to,

- creating an "epigenetic growth chart" in the pediatric age range,
- careful intersection of allelic variation and epigenetic marks and their respective contributions to developmental programs,
- mapping concordance and discordance of epigenetics marks between accessible peripheral tissues and the brain during development, and
- determining the utility of epigenetics in measuring the impact of interventions.

At present, minimal information exists about the formation of epigenetic marks in early life in rodents and humans. Longitudinal assessments would be ideal to close this important gap, although for mapping these dynamics in the brain, the constraint of having to use postmortem tissues would necessitate the careful integration of a series of cross-sectional measures. Regardless, such maps of early-life epigenome "evolution," ideally across different salient tissue and involving samples from multiple subjects, offers the opportunity to make progress on several important aspects. It would provide a blueprint for normative variation of the epigenome that could be contrasted with patterns obtained from children with atypical development. As such, the high-dimensional assessment of the epigenome would become an integral part of the multimodal assessment of child development that could lead to personalized assessment of a given atypical child (see below). In addition, the existence of such a map in combination with careful environmental measures would also enable a rigorous assessment to which extent epigenetic patterns during development are shaped by intrinsic (i.e., genetic) factors versus extrinsic ones (i.e., environment), or a combination thereof.

For humans, epigenetic measures will be limited to accessible peripheral tissues (e.g., blood, buccal epithelial cells, saliva). Evaluating the information content of epigenetic patterns derived from these sources for epigenetic patterns in the brain is challenging as it requires parallel analysis of postmortem brain samples. In part, creating cross-tissue blueprints of epigenetic patterns in model organisms could close this knowledge gap. At the same time, a stronger focus on model organisms would allow a much deeper interrogation of the epigenome of individual cell types in the brain, and how the epigenome might change in relationship to their physiology and to pathological conditions. This would then serve as the basis for mechanistic research on the role of epigenetics in brain development and function, in typical and atypical developmental trajectories. Indeed, innovative modeling of early-life environments relevant for human development in model organisms will be crucial to tease apart complex variables (e.g., socioeconomic status, parental neglect, exposure to potentially toxic conditions such as alcohol, heavy metals, pollutants, and inflammatory stimuli associated with the human epigenome) as well as to move from correlations toward causality.

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Measurements and Interventions

For a number of selected animal models, tools are rapidly emerging that allow us to directly measure and manipulate different aspects of the developing nervous system. However, in humans, the tools we currently have at our disposal are much more limited and indirect. A major issue in the future will be to bridge this gap so that the insights gained from animal studies can be leveraged to interpret measurements in the human brain, with the end goal of developing adequate treatments of developmental disorders. To illustrate some of the current challenges, we turn to language acquisition in infants—one of the most important developmental milestones in early childhood.

Acquisition of Language in Infants

Although there is individual variation in the rate of development, mastery of language is a universal phenomenon that occurs across cultures. Research into early infant abilities clearly shows that, as a group, even very young infants preferentially pay attention to and discriminate the sounds of language. As early as in the first few weeks after birth, infants can discriminate phoneme contrasts such as /pa/ and /ba/, not only for their own language, but for those in other languages as well. However, by 6–12 months, infants (like adults) are only able to discriminate these contrasts present in their own language. Over the course of the first two years, children produce their first words and begin to combine these words into short sentences, incorporating many aspects of the syntactic structures present in adult grammar (Bates et al. 1987; Benasich and Tallal 2002; Ortiz-Mantilla et al. 2013).

Thus, during the first year of life, perceptual abilities in an infant develop from a wide-ranging capacity to discriminate general sensory information to a finely tuned capability that favors the processing of selective, more relevant input from their environment. Ontogenic specialization (perceptual narrowing) promotes neural representation as language-specific phonemic maps are established and essential information is processed efficiently, and is particularly important as infants assemble the foundations of their native language. As early as the 30th gestational week, the cortical organization of premature neonates allows discrimination of phonemic variations between syllables (Mahmoudzadeh et al. 2013; Maitre et al. 2013). Subsequently, exposure to native language in the natural environment fosters construction of language-specific phonemic maps and commitment to their native language (Kuhl et al. 2006). As infants become language experts, they preferentially process characteristic features of their native language (Werker et al. 2012; Ortiz-Mantilla et al. 2013). Newborns and young infants begin favoring distinctive suprasegmental elements (rhythm, intonation, stress) of their own language (e.g., Mehler et al. 1988). Shortly after birth, they show enhanced electrophysiological responses (Cheour et al. 1998) and better behavioral categorization of familiar versus

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nonfamiliar vowels (Kuhl et al. 1992; Moon et al. 2013). At 6–8 months of age, infants still discriminate most native and nonnative consonant contrasts, but by 10–12 months, the ability to discriminate foreign contrasts attenuates while discrimination of native language phonemes strengthens (Werker and Tees 1984; Rivera-Gaxiola et al. 2005; Tsao et al. 2006). Despite strong evidence of this transitional time line from universal to native language phoneme specialization, the neural mechanisms underlying this transition remain unclear. Some progress has been made, however, in tracking this maturational process.

Specifically, there is accumulating evidence that dynamic coordination and oscillatory mechanisms underlie the establishment of language across development. Event-related oscillations in the mature system have been characterized by two phenomena: nested phase-locking and asymmetry of temporal processing. In nested phase-locking, evoked oscillations in the lower-frequency bands of delta and theta synchronize to the slower temporal dynamics of sound, such as the speech envelope (Abrams et al. 2009; Luo and Poeppel 2012), whereas fast oscillations in the gamma-frequency range are associated with the encoding of rapid feature analysis, temporal binding of stimulus events, and attention control (Tallon-Baudry and Bertrand 1999; Fries et al. 2007) as well as resolution of segmental/phonemic information (Poeppel et al. 2008; Giraud and Poeppel 2012). Similar to adults, syllable processing in infants is resolved in a multi-time fashion through synchronized activity in low- and high-frequency ranges, and it has been shown to track the evolving time-frequency dynamics supporting phonemic perceptual narrowing as well as processing of temporally modulated nonspeech (Musacchia et al. 2013; Ortiz-Mantilla et al. 2013, 2016). High gamma power in auditory cortex has been shown to index mapping of segmental/phonemic information (Steinschneider et al. 2011) in adults; similarly, high gamma has been shown to index the evolution of perceptual narrowing in infants (Ortiz-Mantilla et al. 2016). Robust associations have also been shown between gamma power in resting EEG at 16, 24, and 36 months of age and later language, specifically phonological memory (nonword repetition) and syntactical skills (Gou et al. 2011). Adding to this picture is research which demonstrates that early, targeted interactive auditory experience in infancy can enhance and accelerate the maturation of acoustic temporal processing in typically developing infants (Benasich et al. 2014). This enhancement of acoustic processing extends to both nonlinguistic and linguistic input, has been shown to be associated with changes in oscillatory encoding and acoustic cortical mapping, and may index neuronal maturation of auditory cortex (Musacchia et al. 2017).

These insights raise a set of fundamental questions:

- How is brain coordination accomplished at multiple levels across age?
- Can we identify particular "oscillatory signatures" (such as those generated by PV+ networks) that will index evolving dynamic coordination as the brain matures?

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- What central mechanisms are critical to maturation of the developing brain, and what role do critical/sensitive periods play as well as the many extrinsic and intrinsic factors that impact developmental trajectories?

To address such questions, we need to define normative/typical developmental trajectories, identify potential biomarkers, measure evolution (or variations) in brain dynamics across maturation, and critically assess how these might reflect the underlying functional local and large-scale circuitry and dynamics. Unfortunately, it is difficult to examine these mechanisms and brain dynamics directly in humans. Thus, we need to use animal models as well as indirect means of measuring brain activity and link these different approaches to establish a more comprehensive understanding of the neural underpinning of acquisition of language and other skills during childhood.

Perceptual-Cognitive Paradigms: Assessing the Speed and Efficiency of Information Processing

A number of perceptual-cognitive paradigms can be used to assess the speed and efficiency of information processing in global and rapid temporal domains, short- and long-term memory and learning of contingencies: habituation, recognition memory, preferential looking, auditory-visual integration, cross-modal transfer (e.g., tactual-visual; auditory-visual), and operant conditioning in infants (e.g., nonnutritive sucking, conditioned head-turn, eye movements, two-alternative forced-choice, and anticipatory looking) (for reviews see Bornstein and Sigman 1986; McCall and Carriger 1993; Rose et al. 2004a, b).

It has been suggested that the lack of correspondence seen between the commonly used infancy tests and later assessments of later child cognitive competence may be a function of the nature and content of the standardized tests themselves (Rose et al. 2008). The items that comprise global tests of infant intelligence are strongly dependent on sensorimotor capabilities (reaching, grasping, hand-eye coordination), skills which apparently do not relate to differences in cognitive ability later in life. As tests in later childhood add items that utilize discrimination, memory, categorization, and abstraction, the correlations rise substantially with cognitive competence later in life. Therefore, the key to demonstrating continuity and thus predictability of cognitive ability is to utilize conceptual processes similar to those exhibited in psychometric tests of IQ.

Recent literature suggests that promising candidates for an infant analogue for later information processing may be habituation and recognition memory. In addition, operantly conditioned nonnutritive sucking, head-turn or eye movements, two-alternative forced-choice paradigms as well as delayed match (or mismatch) to sample tasks can be useful in assessing various emerging abilities, including language acquisition. Another strength of these types of paradigms is that they echo those used in animal models, thus providing

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continuity between animal and human studies. Relatively few studies, however, have examined the neural substrates of such developmental tasks in human infants, although more sophisticated techniques—including dense array EEG, magnetoencephalography (MEG) and functional near infrared spectroscopy (fNIRS)—are increasingly being employed, thus opening a developmental window on the neural correlates and underlying brain dynamics of human cognition (e.g., Mash et al. 2013; Nordt et al. 2016; Emberson et al. 2017; Lee et al. 2017a).

Understanding the Neural Processes That Underlie Behavioral Observations in Humans

Brain dynamics change over the course of development as well as across different states of consciousness and cognition (including sleep). The question arises as to what we already know about these processes, and how we might capture information about the underlying neural processes. Even more importantly, can we determine whether the observed behavioral/imaging developmental data collected in human studies corresponds to information from animal models regarding the underlying dynamics and brain function?

Given the difficulty in observing brain dynamics in humans, indirect means of measuring brain response must be used. These include data from behavioral paradigms (psychophysics, cognitive and linguistic testing), identifying associations between candidate genes and behavioral phenotypes, and various forms of imaging (e.g., fMRI, DTI, resting-state fMRI, EEG and MEG). All can be employed in pursuit of these goals. However, how do we bridge the gap between invasive animal studies and noninvasive human studies? Do EEG or MEG scalp measurements of frequency and power differences map onto oscillatory processes and local field potentials taken from *in vivo* recordings in rodent or nonhuman primate studies?

Many of the hypotheses, models, and paradigms we use arise from animal models, allowing us to examine critical genetic and neural–behavioral links and associations. At the very least, one can derive localization information. However, it is clear that data from invasive and noninvasive recordings in both animals and humans support the view that brain development and maturation are critically dependent on synchronized neuronal activity and activity-dependent plasticity (see Singer, this volume). Moreover, such data further highlight the specific relationship between brain maturation and changes in the frequency, amplitude, and synchronization of neural oscillations.

More often, a particular study using noninvasive methods in humans is motivated by a series of initial findings derived from animal studies. In translating these findings to the human, studies often begin with adults, use similar paradigms, and follow as closely as possible the animal protocol. For example, when examining gamma in dense EEG, gamma oscillations have been shown to represent synchronized activity of local neuronal populations during

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sensory and cognitive processes (Ward 2003; Herrmann et al. 2004; Ribary 2005; Buzsáki 2006; Fan et al. 2007), but they may also play a role in coupling of remote cortical areas (Buzsáki and Schomburg 2015). Low-frequency gamma oscillations appear to support object representations, temporal binding, arousal, attentional selection, and working memory (for reviews see Engel and Singer 2001; Buzsáki 2006; Fries et al. 2007; Uhlhaas et al. 2011).

Cortical activity in the gamma-frequency range has also been linked in humans and animals to a wide variety of higher cognitive processes and language. In addition, it has been hypothesized that correlations between the occurrence of higher amplitude activity centered in the high gamma range (over 70 Hz) and cognitive performance (as observed in human adult subjects using EEG and MEG recordings) may reflect increased synchronization of neural ensembles important for cognitive processing (Ribary et al. 1991; Rodriguez et al. 1999; Singer 1999). Specifically, synchronization of neuronal firing, often associated with gamma-frequency oscillations (Engel and Singer 2001; Varela et al. 2001), appears to be critically involved in the organization of cortical networks. Moreover, increasing evidence suggests that oscillatory mechanisms may support the coordination of distributed neural responses that underlie cognitive and perceptual function, and may thus be critical to normative development of cortical circuits. The emergence of specific patterns of oscillatory activity in relation to cognitive developmental milestones as well as the correlation between the appearance of certain brain disorders at different developmental periods and electrocortical signs of abnormal temporal coordination support the view that "neural synchrony is not epiphenomenal but plays a role in the functions of cortical networks" (Uhlhaas et al. 2010:79).

Further, gamma oscillations seem to be developmentally regulated. EEG studies that examined frontopolar, central, and occipital scalp locations in 3- to 12-year-old children showed that gamma power increased significantly across age, most strikingly over frontal regions (Takano and Ogawa 1998), which is parallel with the slow maturation of inhibitory PV+ networks in these higher-order areas (Condé et al. 1996). As children mature, there is a gradual shift in peak power as activity in the lower-frequency bands decreases and activity increases in the higher-frequency bands (Clarke et al. 2001; Uhlhaas et al. 2010). Importantly, EEG power indices of children that significantly deviate from this pattern seem to reflect distinct differences in the maturational time course of brain development (John et al. 1980).

In many instances of EEG and MEG measurements, specific features of evoked potentials can, at least partly, be related to ongoing activity within specific cortical and even subcortical structures. Certain spontaneous oscillations, such as awake resting-state alpha oscillations, have well-known origins within sensory cortical and thalamocortical circuits. The evoked potentials can in part be accounted for by stimulus-induced phase reset (synchronization) of ongoing oscillations. Source localization analyses, of either evoked potentials or

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spontaneous oscillations, can provide additional insights by identifying putative cortical regions or networks that may be generating the scalp signals.

Bridging Human and Animal Studies to Understand Developmental Disorders

Despite these advancements and the substantial gains made over the last two decades in our ability to image the developing human brain, the vast majority of imaging studies (whether EEG, NIRS, MRI or MEG) tend not to be grounded in neurobiology. This is particularly problematic when it comes to the study of neurodevelopmental disorders, where one hopes to gain insight into the neurobiological mechanisms that underpin a given disorder (e.g., autism). Accordingly, the ability to conduct translational research—where one moves from, say, mouse to human and back again—is very limited. One approach (LeBlanc et al. 2015) adopted by Takao Hensch, Charles Nelson III, and Michela Fagiolini is to use EEG, the visual-evoked potential (VEP), and the auditory-evoked potential (AEP) in both species, thus testing mice and human children under very similar conditions. Resting EEG is recorded from the scalp surface, followed by visual- and evoked-potential testing: in the case of VEP, phase reversing checkerboards are presented whereas in AEP, tones of different frequencies are presented. In so doing, one can characterize the same "spontaneous" (EEG) versus "evoked" (VEP, AEP) brain state in both species.

To extend their investigations to the study of neurodevelopmental disorders, Fagiolini and Nelson (LeBlanc et al. 2015) recorded the VEP from girls with Rett syndrome and the equivalent mouse mutant. Their studies show remarkable similarity across both species; specifically, the spatial frequency of the visual stimuli and the underlying specific mutation affects the amplitude and latency of the VEP in the same way in both mouse and human.

By using identical bridging tools across species and testing both species under near-identical conditions, it becomes possible to ground the human brain response on more solid neurobiological footing. This, in turn, offers promise for developing new therapeutics for rare genetic disorders that can first be tested in the mouse and then extended to the human, based on shared mechanisms of dysfunction in synapses and circuits (Banerjee et al. 2016).

Signatures of Typical and Atypical Development

Capturing High-Dimensional Neurodevelopmental Trajectories

Typical development is a progressive unfolding of developmental programs: while functional development of the brain and the expression of behavior and cognition grows steadily and even monotonically through the first few years of life (and is very pronounced in years 0–3), the actual dynamics of the

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underlying processes is far from monotonic. Different sets of genes, together with available modes of activity and environmental influences, have different patterns of expression during this period (Sur and Rubenstein 2005; Majdan and Shatz 2006). Genes related to neurogenesis and migration are expressed early and then decline; molecules of axon growth and targeting have developmental programs with specific onsets and offsets; synapses require a large number of molecules to be constructed; some of these may decline after an early construction phase, others may persist into adulthood, and still others may be expressed pleiotropically to affect multiple processes necessary for synapse maintenance or plasticity throughout life (Sur et al. 2013).

The development of behavior and cognition also has different components with different onsets and rates. The measurement of cognition and hence tracking its development is presently challenging in infants. Thus, a major question for the field is if, and how, more refined and even rapid measurements are possible.

Such multidimensional measurements in humans—spanning cognition, genomes, epigenomes, molecules, brain structure, and brain function at different points of time—would, in principle, provide a rich description of the trajectory of development (Figure 7.2). Such data would allow us to "model" development in a principled way, potentially within a hierarchical Bayes framework with priors being updated with new information as development unfolds. If such rich descriptions could be standardized and made available for large numbers of children, it would enable the construction of a population model of developmental trajectories. Of course, such measurements need not be made all at once; they could be done progressively as the project evolves. Indeed many different research and clinical groups are already involved in making subsets of measurements or have subsets of data that could be explored for concatenation within this framework. Such a model, however, will require large numbers of children explored at multiple time points. In addition, behavioral-cognitive data will need, in terms of items, to match, up to some level, the rich data provided by different omics, genetics, and epigenetics of sophisticated MRI. To combine, store, and process such heterogeneous, cross-domain data, advanced technologies appear necessary to solve this important challenge.

Such a model is a formal description of a complex multidimensional process with many latent variables, similar to atmospheric (climate, weather) or geophysical (seismic phenomena, earthquakes) models. These types of models rely on large quantities of data, which are drastically reduced in dimension to features that capture large amounts of variance, and which drive increasingly sophisticated statistical and dynamical models of the phenomenon with enormous explanatory and predictive power. In developmental and clinical neuroscience, this predictive power of formal models would be at the heart of their utility and importance for neurodevelopmental disorders and atypical development (Sahin and Sur 2015).

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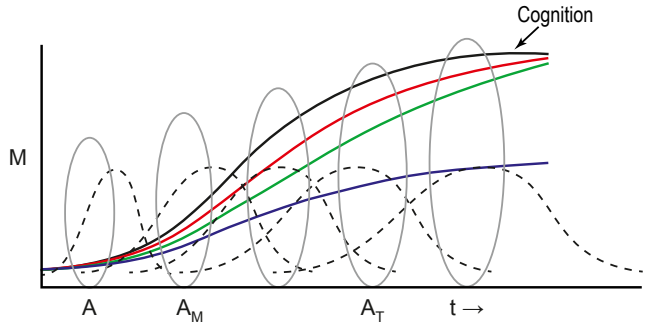

Figure 7.2 Schematic of developmental events underlying brain maturation and cognitive development. Brain development unfolds in time (x-axis) as a series of events involving gene expression, molecular signaling events, and cell–cell interactions (depicted schematically as dashed Gaussian curves). The effect or magnitude (M) of these events is depicted schematically on the y-axis. At each time point, development can be described quantitatively and computationally as the net vector average of these events (elongated gray ovals at multiple time points). Five are shown in the figure, though in principle as many multidimensional vectors as possible could be obtained. The evolution of these vectors in time describes the systems biology of brain development, which is manifest as growth of brain regions, connections between regions, and synaptic architectures (depicted as sigmoidal curves). Together, these events and circuits underlie the development of cognition (black sigmoidal curve). The role of electrical activity is different at different points in time as development proceeds. At the earliest stages of development, the presence of activity, A, may be sufficient for gene and molecular expression. Later, the magnitude of activity, A_M, may be permissive for neuronal and axon growth. Still later, the timing of activity, A_T, may play an instructive role in development of synaptic connections and circuits.

Our current understanding of atypical development is intuitive: it is based on a few measurements within each investigator's field of expertise, building on the understanding ("model") of typical development that the investigator brings or has derived from previous data. Variations that characterize atypical development are weighed against the range of normal variation. A large-scale, multidimensional set of measurements, coupled with machine learning and formal statistical and dynamical models, would help formalize and enrich this understanding.

Such an understanding is critical for weighing or evaluating atypical development. The "observables" of behavior and cognition, particularly in neurodevelopmental disorders, are the expression of latent variables in the developing brain, which span interactions between brain regions, circuits within and across structures, synaptic and neuronal processing, the molecules that underlie function and structure, and the genes that express these molecules. These variables change and evolve as development proceeds. Changes build upon previous deviations and may rectify or exacerbate deviations from typical profiles.

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Detecting Atypical Development: Early Identification of Autism and the Issue of Specificity

There are a variety of childhood disorders and conditions that greatly increase the risk of developing autism, which is currently estimated at 1:68 in the United States, with comparable prevalence figures reported in many other countries. For example, children with a number of different monogenic and polygenic disorders (e.g., Down syndrome, Fragile X syndrome) have a greatly elevated risk of autism, as do children who are born prematurely (especially in the context of chorioaminionitis, intrauterine growth restriction, or ventriculomegaly) or endure their early years of life in deprived settings (e.g., orphanages). Infants who have at least one older sibling with the disorder are, however, at highest risk for developing autism: from 1:68 to 1:5. If more than one older sibling is affected, the risk for males can increase to 1:3.

Using a variety of neuroimaging tools (EEG, VEP, NIRS), Nelson and his collaborators have studied such at-risk infants for more than a decade. They consistently find that by three months of age, EEG measures can detect a difference between high-risk infants who subsequently go on to receive a diagnosis of autism at 3 years of age and those who do not. Thus, it would appear that EEG (in this case beta and gamma power) is able to predict who does and does not develop autism. This approach has important implications for the early identification of autism and other disorders, which is important given that children who receive early intervention have better outcomes than those who receive later intervention.

As promising as this work is, there are several conundrums that must be addressed. First, how specific to autism is this pattern of EEG findings? Is it possible that all the EEG is doing is telling us which brains have gone off track generally, rather than which brains will develop autism specifically? Second, the findings to date apply solely to the group level; at least thus far, such tools could not be applied at the level of the individual. Finally, until comparable studies are performed in the animal, we are unable to determine the neurobiological mechanisms that underpin these EEG patterns. For example, is there an imbalance between excitation and inhibition? Do these patterns reflect differences in long- versus short-range connectivity?

A deep understanding of atypical development requires in-depth description of typical development that integrates as many measurements as possible, spanning both observable and latent variables, to construct as rich models as possible.

Assessing an Individual Child's Trajectory and Individualized Treatments

Developing a population model of developmental trajectories would set the stage for evaluating an individual child's trajectory on the basis of his/her

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profile. Significant deviations from the population in a cognitive variable, for example, can be weighed alongside other measurements. This would allow the assessment of risk at an individual level for a particular neurodevelopmental outcome. It might also enable the application of noninvasive therapies intended to return the child to typical profiles.

The vision of individualized assessments may be the future for neurodevelopmental and neuropsychiatric disorders, where symptoms are highly variable and the outcome of events that span individual genetic variations, genetic backgrounds, and experiences—most of which influence the latent variables of the brain. The effects of these latent variables are expressed as the observables of brain activity, behavior, and cognition, and are evaluated as the "symptoms" of neuropsychiatric disorders.

In the far-off future, this approach may be used to develop combination therapies utilizing multiple pharmacological and behavioral approaches (Sahin and Sur 2015). In effect, our present one disorder–one treatment approach also invokes a model, but a very simple one. We need larger quantities of data, richer ways to capture their essence, sophisticated models to tell us what they mean, and a range of approaches to utilize this information meaningfully for treating the very complex signs that mark deviations in development. Without this, we believe there is no other way to understand, treat, and prevent disorders of neurocognitive development!

These approaches, however, could pave the way for developing and testing novel intervention techniques and provide us with unprecedented opportunities to assess the empirical evidence for their efficiency. Potential candidates currently include gene therapy in some cases, specific cognitive training, targeted psychophysical training, transcranial magnetic stimulation, transcranial direct-current stimulation as well as pharmacological interventions and selective deprivation. For example, Benasich and colleagues have used an infant-driven, interactive auditory training intervention to induce more robust and precise acoustic mapping in 4- to 7-month-old human infants: dense array EEG was used to obtain measurements of altering patterns of theta- and gamma-band expression and compared against passively exposed or nonintervened naïve infants (Benasich et al. 2014; Musacchia et al. 2017). The observed dynamic changes resulted in improved automatic sound processing and more accurate detection of rapid frequency change, and thus may influence the course of developmental language learning disorders.

Observation of changes in human brain dynamics as a function of a targeted intervention and assessment of outcomes using cutting-edge advances in imaging techniques provides the means to begin to investigate complex causality patterns previously only explored in animal models. More formal models that better capture the complexity of neural development and are calibrated to explore differences in individual trajectories will allow us to make more accurate predictions about which combination of interventions has the largest likelihood of success.

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Flexibility and Stability Revisited

Given the considerable heterogeneity of genetic and epigenetic risk factors presumed to underlie the development of psychiatric diseases such as autism spectrum disorder, schizophrenia, and bipolar psychosis, one might ask whether there is perhaps a common final pathway and, if so, whether it would not be more efficient to attempt to identify the traits of the final outcome and then work backward. One example is epilepsy, where the causes are numerous and quite heterogeneous but the final outcome is stereotypical. Once the dynamics of seizures were well understood, it was relatively easy to backtrack the various causes with a targeted search.

Could psychiatric disorders be the evolutionary consequence of an increasingly complex brain? If so, it might be worthwhile to examine which specific problems are faced by highly evolved brains. It could be that the processes in these brains are relatively less constrained by sensory input. Compared to intrinsic interactions, input from the sensory periphery plays an increasingly smaller role in controlling cortical activity. Only a small fraction of the synapses in layer four of primary sensory cortical areas, the recipient layer of subcortical sensory projections, actually comes from the thalamus; the rest is of intracortical (intrinsic) origin. The phylogenetically recent cortical areas, in particular in the prefrontal cortex, only communicate with cerebral structures. In a sense, highly evolved brains are "autistic" and concerned mainly with generating internal models and working constructively on stored information. They are coupled only loosely to the environment and are thus relatively little constrained by the embedding environment. This could be one reason for the disturbance of high-level cognitive processes in neuropsychiatric disorders. Others could be related to the high degree of complexity and distributed nature of "big" brains (e.g., problems with cross-modal integration, the inability to distinguish between self-generated and externally induced activity patterns, difficulties with integration of widely distributed processes over large distances). Indeed, epigenetic mechanisms seem to contribute disproportionately to the etiology of neuropsychiatric disorders (Mellios and Sur 2012).

Could it be that complexity is the consequence of a selection process that favors resilience? Complex systems may be more resilient than simple systems because they are capable of self-organization. It could thus be that lesions (genetic, environmental) which would be lethal in simple systems (e.g., the loss of a particular receptor subunit) can be managed by compensatory strategies of complex systems, the outcome of which may be a psychiatric disease. The disease state could thus be the manifestation of an escape strategy. This raises the question as to whether all of the symptoms should actually be treated—if some of them fulfill a protective function. If not, which are the protective and which the deleterious symptoms (e.g., the negative and positive symptoms in schizophrenia)?

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These considerations raise the important question: To what extent can valid animal models be generated to model specific traits of complex psychiatric diseases? Currently, mice serve as the major model system for diseases with a genetic component, even though their brains are orders of magnitude less complex than human brains, because techniques to generate transgenic animals have been developed for this species. Much of our knowledge about the neuronal underpinnings of higher cognitive functions has been obtained through studies on awake, behaviorally trained monkeys. It would be a great step forward if we had valid nonhuman primate models of disease. This approach has been extremely fruitful in the investigation of Parkinson disease, but such models are not yet available for psychiatric diseases. With the advent of recent genetic engineering methods such as the CRISPR-Cas technique (Doudna and Charpentier 2014; Heidenreich and Zhang 2016), this option is now within reach, and large programs investigating the possibility of inducing mutations identified as risk factors for psychiatric conditions in nonhuman primates, in particular the marmoset, have now been initiated.

Conclusion

During the first three years after birth, the human brain faces the enormous task of building a comprehensive internal model of the external world that will allow it to perceive, interpret, and predict the vast amount of parallel streams of input entering the sensory periphery. On the basis of an elaborate scaffold, set up prenatally, this task is achieved through self-organizing dynamical networks which integrate genetic, epigenetic, and sensory information. We are only beginning to understand the mechanisms that orchestrate this process across molecular, neural activity, and behavioral levels. The brain appears to use several strategies for tightly regulating the impact of sensory input on its developing networks, ranging from the molecular control of neural plasticity (as evident in the closing of critical period plasticity), to the diversification into stable "scaffold" and more volatile "plastic" elements, to attentional and behavioral control of sensory input. Such mechanisms appear necessary to safeguard the brain in its difficult journey during the first years of life: on one hand, brain circuits are required to learn how to process specific sets of features imposed by a particular environment (an illustrative example of which is language acquisition), yet on the other, this process must be protected against forgetting and insufficient or detrimental sensory input. This is a nontrivial task, requiring a fine balance between flexible and stable design on various levels. Several neurodevelopmental disorders, including certain forms of autism, appear associated with a malfunction intended to keep just this balance, the details of which remain to be elucidated in the future.

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Tracing the neural basis of cognitive development in humans remains challenging, as behavioral assays and noninvasive imaging techniques provide only an indirect account of neural activity. In addition, our grasp of the developing epigenome of the brain is still very limited. The vast majority of insights gained on the neural basis of brain function stems from studies using suitable animal models. Thus, one of the most important tasks in the years to come will be to link animal and human studies.

Here we have presented examples of promising directions that will result in observables that are comparable between human and nonhuman primates (e.g., properties of oscillatory neural activity). Such methods can then be used to examine developmental disorders caused by mutations in single genes, which can be studied in equivalent mouse mutants. We have identified opportunities that modern data acquisition, analysis, and computing methods provide, which could be leveraged to develop high-dimensional formal statistical and dynamical models of normal and abnormal neurodevelopmental trajectories by integrating vast amounts of chronic data from a large number of individuals. Such approaches could be exploited to achieve early detection of a developing disease and may enable individualized treatment, both of which could greatly improve the rate of successfully treated or even prevention of disease outbreaks. Progress will rely on computational efforts to develop better dynamical and statistical neural circuit models as well as to establish or adapt machine-learning tools to cope with the vast amounts of molecular, neural, and behavioral data. Finally, the size and complexity of the human brain appear to be important factors in understanding typical and atypical development. To represent these crucial features in humans, appropriate animal models, beyond rodents, must be established. This remains an important task to be addressed in the future.

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