Neurodevelopment is a multifaceted, dynamic process that involves gene-environment interactions resulting in both short- and long-term changes in gene expression, cellular interactions, circuit formation, neural structures and behavior over time. The developmental path is malleable and constantly influenced by numerous interacting external and internal influences (genetic, hormonal, behavioral, or environmental) (National Advisory Mental Health Council, 2008).

A scientific consensus is emerging that the origins of adult disease are often found among developmental and biological disruptions occurring during the early years of life. These early experiences can affect adult health in two ways – either by cumulative damage over time or by the biological embedding of adversities during sensitive developmental periods. In both cases, there can be a lag of many years, even decades, before early adverse experiences are expressed in the form of disease. From both basic research and policy perspectives, confronting the origins of disparities in physical and mental health early in life may produce greater effects than attempting to modify health-related behaviors or improve access to health care in adulthood (Shonkoff, Boyce, & McEwen, 2009).

In the 2011 issue of our Journal’s Annual Research Review we celebrate the phenomenal progress of the past three decades in the developmental neurosciences. In last year’s issue we took a close look at our knowledge concerning probromes associated with neurodevelopmental disorders with an eye to early interventions. A logical next step is to examine what is known about neurodevelopment more generally and its relevance to our field. A complex, dynamic story is unfolding of evolutionaryarily conserved genetic programs that guide mammalian brain development and how our in utero and early postnatal interpersonal worlds shape and mold the individuals (infants, children, adolescents, adults and caregivers) we are to become.

Questions abound in this area of research. How much do genes matter? How do our molecular, cellular, hormonal, microbial, interpersonal and social environments influence brain development? What are ‘sensitive periods’ and why do they exist? How useful is ‘evolution’ as an explanatory tool? Can ‘epigenetics’ be best understood as an evolutionary tool to ‘program’ our brain’s development in anticipation of the environments we are to encounter? Can evolutionary theories be tested? How useful are animal models? Indeed, is it even possible to establish a valid animal model for the disorders that we regularly encounter as clinicians and researchers?

What can the developmental brain sciences teach us about the origins and nature of consciousness – those individually unique subjective experiences in which we encounter the world and our embodied selves and that we hear echoed in our voices and in the voices of our patients (Edelman, 2007)? From another perspective, some of our colleagues may wonder what all the ‘fuss’ is about with regard to brain development (Belsky & de Hann, 2011). Ultimately, what is ‘normal development’ and how can we best understand, intervene to treat and, ideally, to prevent, developmental psychopathology and its long-term consequences (NAMHC, 2008, 2010)?

John Rubenstein’s review (2011) provides an up-to-date summary of our knowledge of the development of that brain structure, the neocortex, that distinguishes us most clearly from other primates. He focuses on the genetic, molecular, and cellular mechanisms that regulate cortical size and that are responsible for the generation of cortical excitatory projection and cortical inhibitory neurons and their potential role in neurodevelopmental disorders such as autism spectrum disorders (ASDs). Time will tell whether his predictions are confirmed. It is clear, however, that the relative balance of excitatory projection vs. inhibitory interneurons within cortical-basal ganglia circuits is important. Clarifying the role of sex-specific factors in the pathogenesis of neurodevelopmental disorders such as ASD, attention deficit hyperactivity disorder (ADHD), and Tourette syndrome will doubtless be important (Baron-Cohen, Knickmeyer, & Belmonte, 2005; Rubenstein, 2010). In addition, understanding the vicissitudes of transcription factors, the complexities surrounding the birth of neurons and glia and their migratory journeys within the developing nervous system before their differentiation and the formation of dendrites and axons will also be of crucial importance. The classic story of the cortical projection neurons arising from progenitor cells in the ventricular and subventricular zones that then migrate along the radial glia (Rakic, 1988) is balanced by the reality that a majority of our cortical inhibitory neurons arise from the primordium of the basal ganglia and then tangentially migrate to the cortex (Lavdas, Grigoriou, Pachnis, & Parnavelas, 1999). Add to this spatial-temporal complexity that a significant portion of our microglia, immune cells that are now recognized as important regulators of neuronal cell death and the dynamics of synapse formation, arise from the bone narrow and migrate to the brain through the vascular system shortly after birth.
Over the past decade it has also become abundantly clear that in addition to the remarkable cascade of genetic, molecular and cellular events that ultimately lead to the formation of the billions of neurons that inhabit the human neocortex, the in utero and immediate postnatal environments and the dyadic relations between child and caregivers within the first years of life can have direct and enduring effects on the child’s brain development and behavior. Several of the reviews in this issue directly address aspects of this reality. Vivette Glover (2011) in her provocative review focuses on the importance of prenatal stress. Jennifer Barrett and Alison Fleming (2011) then ask us to consider how ‘mothers mother’ before extensively reviewing what is currently known about the biology of mothering. Next, Tania Roth and David Sweatt (2011) review the experience-dependent epigenetic changes that lead initially to enduring changes in gene transcription, but ultimately determine, in part, aspects of the offspring’s stress response as well as how caring they will become as parents of their offspring.

The provocative element in Glover’s review comes from her invitation for us to reflect on whether or not some forms of psychopathology were, in fact, ‘adaptive’ during our ancestors’ evolutionary history and that there are quasi-Lamarckian mechanisms in play that can program the developing brain so that it will be better able to face the realities of the environment into which it will be born. One of the greatest values of an evolutionary perspective is its ability to provide a framework for the integration of new knowledge from a broad range of scientific disciplines. That said, empirical testing of specific evolutionary theories, at least for our species, is next to impossible (Leckman & Mayes, 1998). While prenatal programming may be adaptive and part of the story, it is also possible that adverse prenatal environments can lead to a failure of conserved neuro-behavioral systems to develop normally. The emerging story that the offspring of mothers who suffer from autoimmune disorders during pregnancy may be at greater risk for ASD and learning disorders is one example (Atladóttir et al., 2009; Lee et al., 2009). Similarly, epidemiologic, clinical, and preclinical investigations have all provided evidence that gestational exposure to infection contributes to the etiology of schizophrenia (Brown & Derkits, 2010).

Working within a translational psychobiological framework, the Fleming laboratory is exemplary for its integration data, from animal model systems to state-of-the-art human investigations. The Barrett and Fleming review summarizes the available data concerning the neuroanatomical origins of mothering, from the circuits associated with sensory perception (touch, olfaction, vision, hearing), executive function (attentional and impulse control, working memory), theory of mind, empathy and affect, as well, as the importance of individual differences in salience, reward, and stress response circuits. They point to the importance of understanding these individual differences based on family or origin, environmental contexts, genotypes and the extent to which mothering and peripartum mood states are affected by early adversity and stress.

Although significant portions of the causal pathways linking environmental conditions, such as the quality of the prenatal environment and the quality of maternal care, to their impact on gene expression and neural function remain in doubt, the review by Roth and Sweatt in this issue provides a comprehensive review of this emerging field of science. Epigenetic changes are functionally relevant modifications to the genome that do not involve a change in the DNA sequence but that alter gene transcription. They typically occur during sensitive periods of pre-and postnatal development and often involve differential patterns of methylation that can have enduring effects on gene expression and ultimately on developmental trajectories. The Sweatt Laboratory, in an effort to model childhood maltreatment and early trauma, exposed infant rats to stressed caretakers that predominately displayed abusive behaviors (Roth, Lubin, Funk, & Sweatt, 2009). They found that early-life adversity left lasting epigenetic marks on the Brain Derived Neurotrophic Factor (BDNF) gene and altered levels of BDNF gene expression in the prefrontal cortex of adult animals. BDNF is one of a network of genes that is implicated in the pathophysiology of major depression and suicidal behavior in humans (Schmidt & Duman, 2007). BDNF is now one of a growing family of genes that have been shown to be epigenetically modified depending on patterns of early maternal care (Champagne et al., 2006; Weaver et al., 2004; Zhang et al., 2010a). Remarkably, these epigenetic changes can be passed on from generation to generation. Some of these findings have also been extended to studies of human brain tissue from individuals abused in childhood (McGowan et al., 2009). Consequently, data from animal and human studies indicate that the interval surrounding the birth is a critical period in the life of mammals – that likely has enduring neurobiological and behavioral consequences. In the future one can safely predict that if epigenetic programming of three genes is true, then the early epigenetic programming of our genomes will be a major factor in many aspects of cardiovascular, metabolic, immunological, and behavioral health. Indeed, the enduring impact of early maternal care and the role of epigenetic modifications of the genome during critical periods in early brain development in health and disease is likely to be one of the most important discoveries in all of science that have major implications for our field.
The next two reviews focus on advances in our knowledge of changes that occur in the brains of children over the course of development. Jay Belsky and Michelle de Hann (2011) first describe the impact of parenting on the child’s brain structure and functional electrophysiology. Then Rhosel Lenroot and Jay Giedd (1999) survey what is known about the longitudinal trajectories of structural brain development in childhood and adolescence.

Thus far, as pointed out in the Belsky and de Hann review, the study of parenting and its impact on brain development is largely focused on the effects associated with physical or sexual maltreatment and institutionalization. More recently, investigators have found evidence that the sensory systems involved in processing and relaying the averse sensory input may be specifically affected (Pollak, Messner, Kistler, & Cohn 2009; Tomoda et al., 2009). This review closes by pointing to the need for future studies to consider the very real possibility that parenting – and other environmental factors – do not affect the brains of all children equally and that there is likely to be genetically determined differential susceptibilities to early adversity (Belsky & Pluess, 2009).

Lenroot and Giedd (2011) echo the call to examine how genetic and environmental factors interact differently across development. While longitudinal studies of typically developing children as well as children with ADHD and childhood-onset schizophrenia are well under way at the National Institute of Mental Health (Giedd et al., 1999; Rapoport & Gogtay, 2008), stratification of these longitudinal data based on genetic variation is just getting started (Raznahan et al., 2010a,b). This ongoing observational work exemplifies the vision and enduring contributions of this superb team of investigators based at the NIMH Intramural Program. It is clear from their ongoing studies that each brain region has its own developmental time course of maturation. Cortical areas typically mature later than subcortical areas. In this context, it appears that cortical development lags in children with ADHD compared with their peers but catches up by early adulthood in a majority of individuals (Shaw et al., 2007). In contrast, childhood onset of schizophrenia is associated with an accelerated pattern of cortical maturation that likely reflects a profound alteration of a host of neurodevelopmental processes (Rapoport et al., 1999). Neuroimaging findings may eventually lead to the capacity to identify individuals at high risk for various conditions and to understand the processes associated with remission. Their recent finding that allelic variations in the Disrupted-in-Schizophrenia-I (DISC1) gene have differential effects on the timing of cortical maturation suggests that these variations might operate (in concert with other genetic and environmental factors) to shape risk for diverse phenotypes by impacting the maturation of frontal-temporal cortices over the course of development (Raznahan et al., 2010a,b).

In the last three reviews, we hope to capture some of the excitement of this burgeoning area of science and how it may inspire future advances in treatment, with an emphasis on translational strategies. Holly Robertson and Guoping Feng (2011) review progress in the development of transgenic animal models of neurodevelopmental disorders from ASD and schizophrenia to mood disorders, ADHD and disorders on the obsessive-compulsive disorder (OCD) spectrum. Next, Susan Andersen and Carolyn Navalta (2011) examine the evidence that a deeper understanding of neurodevelopment can lead to early pharmacological interventions that could be used to prevent the emergence of full syndromes. Finally, Flora Vaccarino and her colleagues (2011) provide a stimulating and timely update on the development and use of patient-specific neural stem cells to determine how genetic differences and basic cellular processes contribute to individually unique nervous systems.

While we may not have true models for mental illness, animal systems of developmental neuropsychiatric disorders are potentially useful tools to illuminate aspects of the neural circuitry involved and to assess the existing and novel interventions (Insel, 2007; Thompson & Levitt, 2010). Despite the difficulties inherent in modeling human phenotypes in animals, there has been recent success identifying mutations in mice that give rise to some of the characteristic features of neurodevelopmental disorders. Although transgenic animal models of ‘candidate genes’ abound, the modeling of single gene disorders such as Fragile X syndrome, Rett syndrome, or disorders associated with chromosomal deletion/duplication events with major effects on development (Angelman’s syndrome, Prader–Willi syndrome, Williams syndrome) will likely be of greater benefit to the field. In addition, animal models of some of the rare genetic variants of major effect in conditions such as ADHD, schizophrenia, Tourette syndrome and OCD may also be of value in identifying the neural pathways and networks that are key to specific disorders (Abelson et al., 2005; Chen et al., 2010; Ercan-Sencicek et al., 2010; Hauser, McMillin, & Bhatara, 1998; Millar et al., 2000; Welch et al., 2007). At the close of their review, Robertson and Feng outline promising next steps that should permit investigators to target specific brain circuits rather than specific genes. Given that many early-onset neuropsychiatric disorders are etiologically heterogeneous and involve multiple susceptibility genes, having model systems that target specific neurons or brain circuits may be invaluable (Arenkiel et al., 2007; Thompson & Levitt, 2010; Zhang et al., 2010). In this context, the use of advanced genomic technologies and novel computational approaches has begun to yield dividends in defining the genetic mechanisms at work within specific brain regions during particular developmental
periods (Bill & Geschwind, 2009; Johnson et al., 2009).

Andersen and Navalta continue the focus on animal models as they explore their hope that a greater understanding of neurodevelopment will lead to improved treatment options and the possibility that early pharmacological interventions may be used to prevent the emergence of full syndromes. While we share their optimism, this will be a challenge. Timely interventions will require identifying individuals who are in a prodromal state, i.e., an early, nonspecific set of symptoms that indicate the onset of disease before specific, diagnosable symptoms occur. But as reviewed in the 2010 Annual Research Review, in order to identify a prodrome we will need to have an accurate understanding of developmental pathophysiology underlying specific disorders (Costello & Angold, 2010; Leckman & Yazgan, 2010). Andersen and Navalta then go on to enumerate the advantages of using preclinical studies in animals to inform clinical practice as well as noting their inherent limitations. Given the increasing use of psychotropic medications over the past three decades in pregnant and lactating women and that in animal studies there is evidence of serious, delayed, and untoward behavioural consequences (Andersen, Greene-Collozi, & Sonntag, 2010; Anzorge, Morelli, & Gingrich, 2008), it is unfortunate that so little information is available to guide the use of these agents in everyday clinical practice. In brief, there is evidence that antidepressant treatment during late pregnancy may increase the rates of poor pregnancy outcome and neonatal withdrawal/toxic reactions (Gentile, 2010a). No long-term follow-up studies of children exposed to antidepressants during pregnancy have been done beyond 48–72 months, although the adverse phenotypes in animals were ‘delayed’ and evident in adulthood (Gentile, 2010b). Thus far, the human data concerning longer-term outcomes are mixed (Gentile, 2010b). One recent study found that the exposure to prenatal SSRIs and maternal mood had distinct effects on child behavior at 3 years of age, reflected in an increased level of internalizing behaviors. Although there is reason for concern, there is also reason for optimism that safe and novel interventions that target and ‘drive’ GABA, glutamate, and neuropeptides (oxytocin and dynorphin) and biogenic amine (serotonin, norepinephrine, and dopamine) pathways will be developed in the future.

The final contribution of the 2011 annual research review issue is the futuristic article by Vaccarino and colleagues (2011) which in some sense may allow scientists to study the neural development of patient-specific cell lines using stem cells derived from skin fibroblasts. While it is clear that it is virtually impossible to study the dynamic aspects of human neurodevelopment at the cellular and molecular level, a recent technical advance may allow us to begin to approach this challenge. This advance is the development of induced pluripotent stem cell (iPSC) technology. iPSCs can be used to derive neurons using tissue obtained from a living person, and maintain his or her genetic constitution and diversity. When properly used, the derivation of iPSCs from skin or other differentiated somatic cells should allow the study of human neural development for individual genomes in vitro. The application of this technology to developmental neuropsychiatric disorders such as ASD, ADHD, Tourette syndrome, and language and learning disabilities is particularly promising as it may be possible to detect deviations of development in patient-derived iPSCs that will inform our basic understanding of these disorders. Identifiable links may exist between initial developmental processes that could be monitored in iPSCs and the system dysfunction of these childhood disorders. As pointed out by Vaccarino et al. (2011), research with iPSCs has the potential to cross-fertilize genomic studies and anatomical/functional studies. For example, identifying that a certain misstep in cell differentiation occurs in one patient with ASD will allow the specific genes and regulatory components involved in that step to be examined in that patient and others, both in genomic analysis as well as anatomical analysis of post-mortem tissue. This may be a particularly promising approach given the inherent etiological heterogeneity of these disorders. Finally, iPSCs should allow systems-biology-based approaches to aid in drug discovery as well as efficient, large-scale drug production for both large and small molecules that may eventually be used to treat, and hopefully prevent, mental illnesses across the lifespan (Rowntree & McNeish, 2010; Webb, 2009).

Finally, we are pleased to announce that the 2012 annual research review issue will focus on ‘Nosology in developmental psychopathology: DSMV, ICD-11 and beyond.’ Given the importance of this topic and the tremendous amount of effort that is being devoted to this, some would say, imperfect process around the globe, we are especially delighted that the review that had been envisioned as the concluding contribution to the 2012 annual research review issue by Sir Michael Rutter, entitled ‘Child psychiatric diagnosis and classification: Concepts, findings and potential’, is already available online (Rutter, 2011a), as are the commentaries from six leading authorities from across the globe (Steven Hyman [USA], Daniel Pine [USA], Eric Taylor [UK], Yi Zhang [China], Lius Rohde [Brazil], and Yanki Yazgan [Turkey]) and a response (Rutter, 2011b; and references therein).

James F. Leckman (Associate Editor) and John S. March (Duke University Medical Center)

References


