Published in final edited form as:
Neurosci Biobehav Rev. 2011 August ; 35(8): 1687–1703. doi:10.1016/j.neubiorev.2011.04.013.

Developmental trajectories during adolescence in males and females: a cross-species understanding of underlying brain changes

Heather C. Brenhouse and **Susan L. Andersen***
Laboratory of Developmental Neuropharmacology McLean Hospital and Department of Psychiatry, Harvard Medical School

Abstract

Adolescence is a transitional period between childhood and adulthood that encompasses vast changes within brain systems that parallel some, but not all, behavioral changes. Elevations in emotional reactivity and reward processing follow an inverted U shape in terms of onset and remission, with the peak occurring during adolescence. However, cognitive processing follows a more linear course of development. This review will focus on changes within key structures and will highlight the relationships between brain changes and behavior, with evidence spanning from functional magnetic resonance imaging (fMRI) in humans to molecular studies of receptor and signaling factors in animals. Adolescent changes in neuronal substrates will be used to understand how typical and atypical behaviors arise during adolescence. We draw upon clinical and preclinical studies to provide a neural framework for defining adolescence and its role in the transition to adulthood.

Keywords

Adolescence; gray matter; pruning; sex differences; white matter

Introduction

Adolescence is a special period in mammalian brain development. Understanding adolescence has been described in a number of reviews at the behavioral level (McCutcheon and Marinelli, 2009; Spear, 2000; Steinberg, 2010; Laviola et al., 1999; Laviola et al., 2003) and the systems level (Ernst and Fudge, 2009), but only discussed to a limited degree at the level of neuronal changes (Andersen, 2003; McCutcheon and Marinelli, 2009; O'Donnell, 2010; Spear, 2000). We will review the neuroanatomy, functional connectivity, genetics, and signaling changes that occur during adolescence. Subsequently, a framework within a neural systems approach will synthesize how adolescent changes in these markers influence behavior.

*To whom correspondence should be addressed 115 Mill Street McLean Hospital Belmont, MA 02478 sandersen@mclean.harvard.edu Tel: 617-855-3211 FAX: 617-855-3479.

1. Overview

1.1 Defining adolescence

Adolescence can be defined as the period between 10–19 years of age in humans (WHO, 2010s), between two-four years in primates (Schwandt et al., 2007), and between 35–60 days of age in rodents (Andersen et al., 2000; McCutcheon and Marinelli, 2009). Spear (2000) begins her discussion of this period with typical adolescence defined as a behavioral transitional period. Such behavioral transitions are consistently observed across diverse mammalian species by an increased sensitivity to peers and social cues (Blakemore, this journal; Forbes and Dahl, 2005; Steinberg, 2010; Panksepp, 1981), risk taking (Laviola et al., 2003), and maturing cognitive control (Casey et al., 2008). Definitions of adolescence can also be reasonably based on gonadal changes as they are relevant to sexual maturation (Sisk and Foster, 2004). The arguments laid out here are by no means exhaustive and should not be used decisively, rather as a point of reference.

A new developmental stage, emerging adulthood, occurs between 18–29 years of age in humans (Arnett, 2000). Defined culturally, emerging adulthood in humans describes observations that while a majority of neurobiological changes associated with adolescence are over, the organism is not yet `mature' as evidenced by delays in attaining a job or marriage. Historically, G. Stanley Hall (1904) described a `new' maturational period that described adolescence from a socioeconomic view points that ultimately led to increased recognition of a distinct stage. As a result, we have identified unique and important neurobiological changes that characterize adolescence. While this review focuses primarily on these neurobiological indices of adolescence, it is important to recognize that in rodent species that a period exists that may capture emerging adulthood (less information is available on non-human primates). As discussed below, rats show marked changes between 40–60 days, but the period between 60–100 days is associated with a slower, steady change that gradually stabilizes. Might this be a new “emerging adult” period that deserves research attention, rather than a media phenomenon to explain a new cultural shift in developed nations? The importance of defining stages is to arrive at a consensus of the maturational state of the organism that is described to facilitate cross-species and sex comparisons.

1.2 Why have such a transitional period?

From an evolutionary perspective, behavior has been shaped by natural selection to prepare an individual to succeed in the social and physical world as an adult, including successfully finding a mate and reproducing. This process culminates during adolescence. Behaviorally, mammals spanning from rodents to humans all experience a tumultuous transitional period where navigation through puberty and decreased parental influence is coupled with increased peer influence, sexual competition, and new decision-making challenges (reviewed by Spear, 2000). Neuroplasticity allows for appropriate responding to emerging environments and this is evident in the development of reward and affect-related systems (Galvan, 2010). However, other developmental processes exhibit steady increases in cognitive control during adolescence that facilitate decision making (Geier and Luna, 2009; Somerville and Casey, 2010). Together, this yin and yang underlie typical development, where the majority of adolescents struggle with the transition to individuate from peers and parents and emerge as independent, self-regulating adults as these processes achieve balance. When these transitions develop normally, individual adaptations are made to unique environmental and social forces. However, errors in this process result in maladaptive behavior. The emergence of psychopathology can be partially attributed to deviance from the normal trajectory of maturation, resulting in life-long issues with reward- and emotion-related processing. Aside from genetically-driven abnormality, errors in overproduction and pruning of neurons or receptors, poor refinement of fiber conductivity or the unmasking of

early life insults are all likely contributors. This review will focus on these developmental processes in the mammalian brain, with an overall emphasis on typical rather than atypical (e.g., Andersen and Teicher, 2008; 2009; Marco et al., 2011).

1.3 Nature of the change

A neural systems approach provides insight to the complexity of the nature of adolescent development. As discussed by Paus (Paus et al., 2008), trajectories of different aspects of brain function clearly illustrate how regional and functional diversity contribute to the multifaceted nature of the adolescent brain. In this review, we examine what is known about changes in developmental trajectories with a focus on adolescent processes as described across mammalian species and between the sexes. Our framework is partially based on the triadic model, described by Ernst and colleagues (Ernst and Fudge, 2009; Ernst and Korelitz, 2009). The triadic model roots behavioral changes in three primary systems, or nodes, namely the affective system, the reward system, and cognition/response inhibition. These three different nodes work together to produce behaviors that typify adolescent maturation. Each node has its own developmental trajectory, which creates an adolescent system in a state of flux. Final behavioral outcomes are likely to depend on the dominant node of a given stage or could result from a weakened node that fails to perform regulatory functions. The triadic model in its simplified form offers to explain adolescent exaggerated reactivity to a number of emotional stimuli, changes in reward sensitivity, and the marked transition in cortical control and cognitive development. Here, we will use this framework to describe detailed changes in adolescent development across species and sex with a focus on cortical and limbic brain regions.

2. The making of a trajectory: Neuroanatomical changes

At the neuronal level, the process of adolescent brain development is one of synaptic refinement. Neurons are initially laid down in an inside-out pattern of innervation in the cortex (Rakic et al., 1986). Neurons that were first born innervate the deeper layers of the cortex, while innervation of the more superficial layers of the cortex occurs later in development. Neuronal targeting is guided by both glia cells (Rakic et al., 1986; Vernadakis, 1975) and chemical gradients that are determined by neurotransmitter expression (Landis and Keefe, 1983; Purves and Lichtman, 1980). Neurotransmitter expression can be either permanent, resulting in innervation into a given region, or ectopic, and transmitters are transiently expressed for the developmental purpose of guidance. Synapses are formed as neurons arrive in their target regions. The complexity of the prenatal and early postnatal parts of this process is reviewed in greater depth elsewhere (Levitt, 2003; Tau and Peterson, 2010), and will not be discussed in such detail here. As adolescence approaches, synapses are overproduced and subsequently lost, referred to as pruning. Pruning is a process that is not the same as apoptosis and cell loss, since pruning is the refinement of dendritic branching and synaptic connections and apoptosis is programmed cell death. Pruning of synapses is quite prominent in the adolescent brain across species and can be quantified in post-mortem analyses (Andersen and Teicher, 2004; Huttenlocher, 1979; Lewis, 1997) or inferred from MRI, where regional changes in gray and white matter are characterized across adolescence and slow as humans approach their third decade of life (Giedd et al., 1999a; Huttenlocher, 1979; Sowell et al., 2004). While synaptic pruning per se is not believed to largely affect volume analyses (Rakic et al., 1986; discussed by Giedd et al., 2008), changes in gray and white matter volumes likely reflect the modification of synaptic components over development.

2.1. Characteristics of Overproduction and Pruning

2.1.1. Synaptogenesis and Pruning—The process of synaptogenesis and pruning is highly conserved across mammalian species. Early post-mortem human studies by Huttenlocher (Huttenlocher, 1979; Huttenlocher and de Courten, 1987) and Benes (Benes et al., 1987) were the first to demonstrate dramatic changes within gray and white matter during the adolescent period. Specifically, pruning within layer 3 of the human frontal cortex is quite significant and approximately 40% of synapses are lost between 7 and 15 years of age. For example, the synaptic marker of synaptophysin in humans rises slowly between birth and 5 year of age, reaches a plateau at 10 years of age, and falls to adult levels by 16 years of age in the dorsolateral prefrontal cortex (PFC) (Glantz et al., 2007). Detailed analysis of synaptogenesis in rhesus monkey motor cortex reveals a similar pattern in that synaptic production continues postnatally and achieves synapse levels that are two times higher than in the adults. The rate of synaptogenesis slows as monkeys reach sexual maturity (3 years of age), and then rapidly declines to the adult level (Zecevic et al., 1989). Comparatively, rat synaptic density values rise between 25 and 40 days of age, and remain relatively stable thereafter (Andersen and Teicher, 2004). However, not all age- age-related changes in volume are due to synaptic pruning (e.g., dendritic retraction). More precise cell counting methods in rats reveal an age-related loss of neurons in the primary visual cortex in all layers (except IV) in rats after adolescence (Yates and Juraska, 2008). Regional differences in cell loss, like synaptic density, are also observed. While the visual cortex demonstrates an 18–20% loss in cells, a smaller 5% cell loss is observed in the ventromedial, but not dorsal lateral, PFC in rats (Markham et al., 2007). While the overproduction and pruning varies between regions and within regions (between different layers), the process is observed across different species with regularity.

Pruning occurs predominantly at asymmetric synapses situated on dendritic spines, as has been shown in the motor cortex (Zecevic et al., 1989), the molecular layer of the hippocampal dentate gyrus and the dorsolateral PFC (Eckenhoff and Rakic, 1991; Shepherd, 1990). Asymmetric synapses are primarily excitatory in nature, whereas symmetric synapses are more inhibitory. The density of GABA neurons (the primary inhibitory transmitter) remains stable across age (Brenhouse et al., 2008; Vincent et al., 1995), which parallels the relatively stable population of symmetric synapses on dendritic shafts (Zecevic et al., 1989). The underlying mechanism of pruning is not fully understood. However, recent analyses have partially identified the genetic regulation of the pruning of excitatory synapses. Adolescent reductions in *NRG1*, a gene involved in neuregulin signaling, may play a role in excitatory/inhibitory balance and synaptic selection (Harris et al., 2009). Complexins, which are presynaptic proteins that regulate neurotransmitter release and are associated with the SNARE complex, also change with age. Complexin 2 (CX2), a marker of excitatory synapses, demonstrates a curvilinear pattern of development and plateaus by 10 years of age in humans. In contrast, complexin 1 (CX1) density, which is associated with inhibitory synapses, gradually rises through young adulthood in human dorsolateral PFC (Salimi et al., 2008).

While glutamatergic synapses change during adolescence, GABA also demonstrates profound age-related changes that bear mention. These GABA changes are functional in nature, whereas glutamatergic changes are structural. Initially, GABA has excitatory actions early in postnatal development. GABA gains its inhibitory influence through chloride channel development that transitions during the second week of life in the rat; GABA maintains this inhibitory action through adulthood (Ben-Ari, 2002). This excitatory-inhibitory transition is produced by large oscillations in calcium levels during development, which facilitates synaptic development (Ben-Ari, 2002). Neonatal blockade of the mechanism responsible for early elevated chloride activity (e.g., the Na(+)-K(+)-2Cl(−)

cotransporter [NKCC1]) produces permanent alterations in cortical circuitry in adulthood (Wang and Kriegstein, 2010). Thus, significant changes in neuronal activity during this transitional period could re-sculpt the immature circuitry permanently.

GABA neurons play a significant role in synchronizing cortical activity through a complex interplay of feedforward and feedback mechanisms that regulate the spatiotemporal flow of information between populations of pyramidal neurons (Constantinidis et al., 2002; Di Cristo et al., 2007). These inhibitory actions of GABA mature in parallel with the development of complex cognitive processing (Luna et al., 2010) and increase substantially during adolescence in humans (Lewis et al., 2004), non-human primates (Cruz et al., 2003; Erickson et al., 1998) or in rats (Tseng and O'Donnell, 2007). GABA is primarily found in three different populations that express the calcium binding proteins parvalbumin, calbindin, and calretinin. Immunohistochemistry of these different proteins can be used to track GABA development. For example, parvalbumin-immunoreactive neurons and the GABA membrane transporter (GAT1) in the non-human primate rise gradually, peak early in life and remain elevated until 15 months of age, and then prune during adolescence to adult levels (Anderson et al., 1995; Conde et al., 1996; Cruz et al., 2003). In addition, the proteins that define the GABA inputs onto cortical pyramidal neurons (e.g., gephryin-labeled portions of the axon initial segment) prune during adolescence (Cruz et al., 2009). GABA synchronizes pyramidal cell information by modulating the speed of different inputs into the cortical areas (many glutamatergic). This process is best evidenced by the emergence of higher-level cognition that includes abstract reasoning during the transition between adolescence and adulthood. Taken together, the immature brain is shaped predominately by excitatory processing with GABA contributing to this process early on in life before becoming inhibitory during adolescence.

2.1.2 Heterosynchrony and pruning—Heterosynchrony in brain development refers to the regional differences in the timing of pruning across the course of development. Overproduction and pruning has been more recently visualized with structural imaging studies (Giedd et al., 1999a; Giedd et al., 1996b; Giedd et al., 1996c; Sowell et al., 2002; Sowell et al., 2001; Sowell et al., 2004; Tau and Peterson, 2010). Gray matter volume changes as detected with MRI suggest a pattern of over-production and subsequent pruning with maturation. These changes reflect predominantly synaptic changes, as these are roughly the unmyelinated point of the neuron. The MRI approach allows for the longitudinal analysis of multiple brain regions within a single subject, which is not possible with other approaches. Such longitudinal studies have provided very clear maps of what heterosynchrony looks like with a time-lapsed movie (http://www.loni.ucla.edu/~thompson/DEVEL/dynamic.html). Within the cortex, this thinning pattern of pruning occurs in a back to front direction, with the earlier developing structures of the sensorimotor cortex pruning first, then association cortices preceding the late-developing frontal poles (Paus et al., 2008). Post-mortem studies show that pruning *within* different layers of the visual, somatosensory, motor, and prefrontal areas, however, occurs simultaneously (Rakic et al., 1986).

Typically, subcortical regions develop earlier than cortical regions (Tau and Peterson, 2010). The amygdala may be one of the earlier regions to develop and develops in a sexually dimorphic fashion. In girls, the amygdala shows relatively little change in gray matter volume during adolescence, as it reaches its maximal volume by 4 years of age; in boys, amygdala volume progressively increases to age 18 years by 53%. Other regions, including the caudate, putamen, and cerebellum show an inverted-U shape in gray matter volume that peaks during adolescence with volumes decreasing by approximately 15% (reviewed (Durston et al., 2001)). Subdivisions of a given structure have also revealed age-related changes that are quite prominent (Gogtay et al., 2006). Early studies of the hippocampus

with MRI demonstrated a modest increase in volume (12%) across age. Reanalysis of this data a decade later reveal striking changes within subdivisions. For example, posterior aspects of the hippocampus appear to overproduce and prune gray matter to a greater extent than the anterior aspects (Gogtay et al., 2006; Insausti et al., 2010).

Regional variations such as these suggest different periods of vulnerability to insult may exist that have not been fully appreciated due to oversampling of a given brain area (Andersen, 2003; 2005; Andersen and Teicher, 2008). Studies on the effects of exposure to adversity during childhood show a general 12–15% reduction in hippocampal gray matter volume in humans (e.g., Bremner et al 1997), and notably, these analyses have focused primarily on these posterior aspects which undergoes the greatest developmental alterations. Heterosynchrony in development within multiple levels of analysis (e.g., region, subregion, and layers) needs to be taken into account when studying normal development or altered development following insult.

While MRI has been invaluable for examining changes in gray matter across the whole brain, this approach provides a limited understanding of the dynamic changes that are happening within the different neurotransmitter systems. Gray matter measurements reflect crude estimates of synaptic density that do not show the functional alterations that are evident during the course of development, such as those discussed above. However, analysis of gene expression during adolescence in human post-mortem tissue (i.e., an invasive approach not possible with MRI) may provide additional clues as to the nature of changes that occur during this period. Genes related to neuronal developmental process, including axon guidance, morphogenesis and synaptogenesis, are reduced in adolescence in rats (Harris et al., 2009). Specific examples include netrins, semaphorins, neuropilin, neurexin and neurolignin. Age-related changes in neurexin are consistent with the axon retraction that characterizes pruning and parallel significant decreases in gene expression observed between 45 and 90 days in the rat (Cressman et al., 2010). Cluster analysis of gene expression with microarray can shed light on new genes that are involved in adolescent overproduction and pruning. In such an analysis, genes grouped into three main functional clusters: a cytoskeletal cluster (25 identified), a Ras/GTP-related cluster (12 identified), and lipid metabolism and steroid-related processes cluster (13 identified). The cytoskeletal cluster reifies the level of anatomical rearranging that occurs during adolescence, the Ras/GTP cluster further suggests functional changes, whereas the third cluster most likely reflects myelination and pubertal-related changes. Finally, adolescent peaks in human neural cell adhesion molecule (NCAMs) proteins demonstrate that these genes are functionally expressed in parallel with rodent findings (Cox et al., 2009).

Not all changes in gene expression are related to structural proteins. For example, genes that are related to glucocorticoid receptors change during adolescence (Perlman et al., 2007; Pryce, 2008). In humans and non-human primates, glucocorticoid receptors increase and peak during adolescence. However, isoforms in glucocorticoid receptors (GR) show different trajectories, with GR isoforms GRalpha-A and 67-kDa GRalpha peaking in toddlers and again in late adolescence; in contrast, the GRalpha-D variant peaks early in development and decreases thereafter (Sinclair et al., 2010). These GR proteins are expressed predominantly in pyramidal neurons, but show transient expression to white matter astrocytes neonatally.

In a unique analysis of 2,979 genes that may explain heterochrony (that is, these genes are differentially expressed between regions, in this case, the dorsolateral PFC and the caudate nucleus in humans), 58% of the genes account for the slower maturation between the cortical and subcortical regions (Somel et al., 2009). Genes were also analyzed for species differences between humans and chimpanzees with regard to heterochrony and postnatal

development. Chimpanzees share great homology with humans, but have a shortened lifespan, which provides another approach to understand heterochrony. In this comparison, similar gene expression diverges between the species at the onset of sexual maturity (Somel et al., 2009), with changes associated with gray matter development.

2.1.3. Sex dependency—MRI morphology studies in humans show that males have a 9% larger cerebral volume than females, with additional sex differences observable in the subcortical structures (Giedd et al., 1996a). The caudate nucleus is larger in females, but additional differences are observed in the rates of increase in size. The size of the amygdala increases faster in males than females, with the opposite observed for hippocampal size. The male caudate shrinks in size, whereas female caudate size does not change significantly across age (Giedd et al., 1996a). Caviness et al (Caviness et al., 1996) conducted a volumetric MRI analysis that showed that subcortical forebrain nuceli (neostriatum) in females are at adult volume between age 7–11. In contrast, the same structures in males of the same age are greater than their adult volume, and by implication must regress before adulthood. By adulthood in the rat, adult males have 18% larger ventral medial PFC (mPFC) than females, that is attributable to both fewer neurons (13% relative to males) and glia cells (18%) (Markham et al., 2007). Similar changes have been described in the rat primary visual cortex, where males have ~20% more gray matter volume due in part to 19% more neurons than females (Nunez et al., 2002; Reid and Juraska, 1992).

How these structural differences influence function is mainly speculation. Pruning itself is believed to streamline processing (Changeaux et al., 1976; Purves and Lichtman, 1980). Once neuronal networks are established in the maturing brain, redundancy within the network is inefficient and synapses are pruned. As discussed above, reductions in synaptic density and cell number are believed to increase the efficiency of processing. These structural changes are further paralleled by reductions in glucose utilization (an indicator of brain activity; discussed below in Section 4.1), which is higher in childhood and adolescence before pruning. Implications of this process is particularly evident when it goes awry. The male caudate undergoes pruning that is associated with greater risk for habit and motor-related disorders, including Tourette's Syndrome and attention deficit hyperactivity disorder (Teicher and Andersen 1995). Regions associated with habit are likely to become streamlined with maturation; other regions involved with new associations and memory that are constantly being updated may not undergo pruning to the same extent (Teicher et al. 1995). Fewer neurons in any region, including the mPFC, is likely to increase efficiency in processing speed.

Sex differences may be organized early in life by gonadal hormones that shape the immature brain (recently reviewed in Viveros et al, 2010). During the neonatal period, conversion of androgens to estrogen by neural aromatase contribute to the effects of gonadal steroids on brain function, including sexual differentiation by “masculinizing” the female brain (MacLusky et al., 1994). Early expression of high affinity androgen-binding sites and metabolic enzymes are found during early development in the hypothalamus, amygdala, dorsolateral and orbital PFC and somatosensory cortex (in the non-human primate: Clark et al 1989; rat: Reid and Juraska, 1992)). The aromatization of testosterone in the brain makes it more complicated to determine which sex hormone is responsible for sex differences. Experiments that use the non-aromatizable androgen, 5α-dihydrotestosterone (DHT), help to parse these steroidal effects, but such uses are limited to the study of lower species or chromosomal abnormalities.

In natural experiments that involve the chromosomal abnormality XXY (e.g., Klinefelters), these individuals have reduced gray matter in the insula, temporal gyri, amygdala, hippocampus, and cingulate-areas (Giedd et al., 1996a). More recent characterization in

humans report that overall gray matter volume was negatively associated with estradiol levels in girls (r= −0.32) and positively with testosterone levels in boys (r=0.32) (Peper et al., 2009). Regional differences for hormonal effects, however, do exist, such as strong relationships between the inferior frontal gyrus and estrogen levels in girls (r=-0.72). Additionally, manipulations of androgens early in life have functional consequences on cortical function. For example, object discrimination, a task associated with the PFC, is better in normal adolescent males and androgen-exposed females relative to normal females (Clark and Goldman-Rakic, 1989). In contrast, pubertal increases in sex hormone levels attenuate pre-pulse inhibition, which may be mediated by organizational effects on subcortical dopamine function (Morris et al., 2010).

Rodent studies suggest that neonatal estrogen suppresses neuronal overproduction in female ventromedial PFC (including the prelimbic and infralimbic regions) (Juraska and Markham, 2004; Markham et al., 2007), which is in contrast to previous reports of estrogen's ability to stimulate extensive arborization in other brain regions such as the hippocampus in adults (Hajszan et al., 2009; Toran-Allerand, 1996). Prepubertal ovariectomy reduces neuronal density in females, which may explain lower gray matter volumes in females (Nunez et al., 2002). Rising levels of testosterone during puberty aid in pruning of dendrites within the adolescent male amygdala (Zehr et al., 2006). Together, these studies suggest gonadal hormones play a complex role in sculpting the adolescent brain.

2.2. Overproduction and pruning of receptor systems

2.2.1 Overproduction of monoamine receptors—The overproduction and pruning of receptor systems is more complex in comparison to synaptic changes, and two waves of age-related changes in density occur. A number of neurotransmitter systems, including dopamine (Gelbard et al., 1990; Kalsbeek et al., 1988; Lankford et al., 1988; Todd, 1992), norepinephrine (Feeney and Westerberg, 1990; Kline et al., 1994) and serotonin (Kuppermann and Kasamatsu, 1984; Lauder and Krebs, 1978; Whitaker-Azmitia and Azmitia, 1986) have age-limited trophic roles in the brain. Ectopic expression of various receptor subtypes during the course of early postnatal development are associated with increased synaptic sprouting, axonal growth, and synapse formation. For example, ectopic expression of serotonin 5-HT7 receptors within the hippocampus occurs briefly during the first two weeks of life in rats (Louiset et al., 2006; Vizuete et al., 1997). Similarly, the serotonin transporter (5-HTT) is found on non-serotonergic neurons embryonically in cortical and striatal neuroepithelia and sensory thalamic pathways postnatally at P0–P10 (Zhou et al., 2000). Transient expression of the 5-HTT and the vesicular monoamine transporter (VMAT) was also observed in sensory cranial nerves, in the hippocampus, cerebral cortex, septum, and amygdala (Lebrand et al., 1998). These transporters and/or receptors are believed to guide neuronal innervation. The effects of trophic neurotransmitters are concentration-dependent (Mazer et al., 1997), suggesting that baseline levels are integrally important for the nature of effect. Similar ectopic receptor expression is also observed in white matter. For example, noradrenergic receptor α2 is observed in immature white matter in the rat (Happe et al., 2004). However, not all receptor expression plays a trophic role.

A second wave of receptor over-expression occurs during adolescence, during which receptors and signaling mechanisms show an inverted U-shape curve of development that results in expression levels that endure into adulthood. In contrast to ectopic, transient expression that is virtually absent by adulthood, these populations of receptors gradually rise, peak, and decline during maturation. A review of adolescent receptor changes is found in Table 1, with an emphasis on receptors within limbic and cortical regions. The timecourse of overproduction and pruning is regionally-dependent (Andersen et al., 2000), and is

observed in a vast array of markers. Different receptor systems include: dopamine, serotonin, norepinephrine, glutamate, GABA, neurotensin, endocannabinoid, and cholinergic (Andersen et al., 2000; Eggan et al., 2010; Lidow et al., 1991). In rhesus monkey, Lidow et al (Lidow et al., 1991) have shown that the density of receptors develops in concert with synaptogenesis.

If we focus further on microcircuits to examine age-related distributions of receptors, recent results suggest even more complex changes during adolescence. Receptor distribution itself changes between different neuronal phenotypes. For example, D1 dopamine receptors do not seem to change their expression level significantly between post-weaning ages to adulthood on GABAergic neurons (Brenhouse et al., 2008; Vincent et al., 1995). In contrast, the overproduction and pruning of D1 receptors occurs significantly on glutamatergic output neurons (Brenhouse et al., 2008). Specifically, only 2% of these glutamatergic projections are D1 immunoreactive in juvenile rats, rising to 44% at P40, and falling down to 6% with maturity at P100. Whether other receptors show differential expression on other neuronal subtypes during adolescence needs to be examined. Table 1 provides information on other receptor classes changes, but identification on specific neuronal types is typically not known. In contrast, D2 receptors inhibit the activity of fast-spiking GABA interneurons after puberty (O'Donnell, 2010; Tseng and O'Donnell, 2007). These neurons are important for efficiently integrating multiple inputs in real-time. Thus, receptor distribution within microcircuits and their functional capacities change dramatically during adolescence.

2.2.2 Sex dependency—The earliest evidence for sex differences in receptor expression comes from a human PET study where DA and 5HT receptor density declines more in males than females from 19–30 years (Wong et al.,1984). We have also demonstrated sex differences in the striatum during younger ages of adolescence, with females demonstrating less receptor overproduction and less pruning (Andersen et al., 1997). For example, the density of D2 receptors increased 144 ± 26% in males versus 31 ± 7% in females between 25 and 40 days of age in the rat. Similarly, receptor pruning was much greater in males than females and occurred between 40 and 120 days (adult). D1 striatal density decreased 34 ± 4% in males, but by only 7 ± 8% in females. For nucleus accumbens, the male and female D1 receptor density curves were parallel after 40 days of age, with each demonstrating a slight dip at 80 days. However, sex differences in D1 receptor density persisted at P120, where D1 receptors were 57.8± 21.2% greater in males than females. Overall, there was no gender difference in D2 density in the nucleus accumbens. The striatal sex difference, however, was not amenable to gonadal hormone manipulations during the adolescent period (Andersen et al., 2002). Gonadectomy immediately before D1 and D2 receptor overproduction did not modulate overall density during adolescence; neither did gonadectomy earlier in life. These results suggest that peripubertal exposure to testosterone does not stimulate dopamine receptor overproduction, nor does estrogen suppress overproduction in general. Limitations of the analysis may have precluded observation of sex-dependent changes. Whereas autoradiography is well-suited for quantifying receptor density changes of a region overall, this technique fails to reveal which population of neurons express these receptors. Thus, the possibility remains that sex-dependent changes, and their hormonal susceptibility, occur on different populations of neurons that have yet to be characterized.

This review will not focus on the functional consequences of these receptor changes, such as those that examine responsivity to receptor-specific agonists or antagonists. However, it is important to note that sex differences in signaling mechanisms are influenced by gonadal hormones, and also undergo developmental changes during adolescence (Andersen et al., 2002; Kuhn et al., 2001).

3. Connections

3.1. Specific innervation of neurotransmitter systems

In this section, we discuss how specific neurotransmitter systems innervate a given brain region. Innervation begins prenatally, but actively continues into the adolescent period and adulthood. However, most studies bypass characterizing adolescence and assume that innervation proceeds in a linear fashion. Human post-mortem studies of connectivity are nearly impossible to conduct, as brain tissue resource centers typically dissect brain tissues into smaller areas that prevent tract tracing. The resolution of MRI does not permit tract tracing of *specific neuronal populations* communicating with each other (other than via tractography, which assess both myelin and axon caliber simultaneously). Transporter density is often used as an indicator of innervation patterns (e.g., (Moll et al., 2000)). However, transporter densities may vary independently of innervation and thus may not be ideally suited for such purposes.

Based on the few animal studies that use standard tracing methods to characterize adolescence, some show a linear progression of innervation across maturation (e.g., (Brenhouse et al., 2008; Brummelte and Teuchert-Noodt, 2006; Cunningham et al., 2002; Erickson et al., 2000), whereas others (Cressman et al., 2010; Rios and Villalobos, 2004) demonstrate an inverted U-shape pattern. We have observed a linear progression of innervation of layer V glutamate neurons of the medial PFC into the nucleus accumbens core between 25, 44, and 100 days in the rat (Brenhouse et al., 2008). In a study by Cunningham and colleagues (Cunningham et al., 2002), a linear innervation pattern was also found in the glutamatergic connections between the amygdala and PFC, which continue from birth into late adolescence/young adulthood (60 days of age) in the rat. Age differences in synaptic connections are qualitative as well. For example, glutamate neurons formed axo-dendendritic (36.5%), axo-spinous (7.7%), and axo-somatic synapses (5.8%) on GABAergic neurons, but 17.3%, 30.8% and 1.9% on non-GABAergic neurons. The formation of these contacts generally followed a curvilinear pattern across age.

In contrast, some patterns of innervation show non-linear courses in their trajectory. For instance, the medial PFC (both prelimbic and infralimbic regions) projections to the basolateral amygdala remain stable between 25 and 45 days of age in the rat, but decrease by about 50% between 45 and 90 (Cressman et al., 2010). Similar findings are observed in mice. Afferents from the dorsalmedial thalamus to the frontal cortex increase until 13 days of age, followed by a 67% decrease in the third week of life, when they progressively increase until adolescence and stabliize (Rios and Villalobos, 2004). The first over-production phase of innervation has been linked to the functional organization of layer III neurons, suggesting that glutamate input drive synaptogenesis. Dopamine neurons follow a comparable pattern of innervation in the primate cortex (areas 4, 9, 46): dopaminergic axons in layer III increased three-fold before 5–7 months of age, with no appreciable change in layers 1 and V (Erickson et al., 1998). Labeled varicosities continued to increase, reaching a peak (six-fold greater than in the youngest monkeys) in animals 2–3 years of age (adolescence) before declining to stable adult levels (Rosenberg and Lewis, 1995; Woo et al., 1997). Gerbils demonstrate a similar pattern. Dopamine innervation into the amygdala increases the first three weeks in life in gerbils, before a slight decline in density during early adolescence that stabilizes into late adulthood (Brummelte and Teuchert-Noodt, 2006). Thus, it is likely (and notably not adequately covered in this review) that other neurotransmitter systems show similar changes in innervation patterns.

At this stage, it is unclear why different patterns of innervation (e.g., linear versus inverted U-shaped) occur in different cortical layers (Figure 2). The first possibility lies in the sampling of ages, where critical discontinuities may exist that were not adequately

characterized. The second possibility lies in the nature/function of the region being innervated. We have raised this issue previously in the context of dopamine receptors (Teicher et al., 1995) and others for innervation (Erickson et al., 1998). Specifically, different regions that are involved in functions that require constant updating may benefit from linear increases that occur relatively early in life (prior to adolescence). In contrast, regions involved in the learning of a life-long function, such as a habit, benefit from streamlining that is associated with pruning. The third possibility is that innervation shows age-specific patterns in the laminar organization, with layer III in the cortex demonstrating an inverted U-shape, and the deep and superficial layers demonstrating a more progressive pattern. Taken together, the unique connectivity in intrinsic and extrinsic afferents critically aids in sculpting neuronal circuitry during adolescence (Benes, 2009).

3.2.1 Myelination—Throughout development, much of the overall gain in brain volume derives from the marked myelination of fiber tracts (Benes et al., 1994). Myelination increases the speed of information exchange, and is at least partially responsible for the emergence of the rich mammalian behavioral repertoire (Fields, 2005). Myelination in the human brain differs by sex and region (Benes et al., 1994; Giedd et al., 1999b). Myelination progressively increases with maturation in both sexes, based on post-mortem studies (Benes et al., 1987) and MRI studies which analyze such changes by segregating white and gray matter (Paus et al., 1999) or through the use of diffusion tensor imaging (DTI) (Paus et al., 1999). The majority of what is known about developmental changes in myelination is been based on studies of the corpus callosum, the largest myelin tract in the brain (e.g., (Keshavan et al., 2002; Teicher et al., 2004)). In contrast to gray matter changes, a rostral - caudal pattern of white matter continues to increase corpus callosal size into young adulthood (Giedd et al., 1996a). Age-related changes occur in the posterior section (Paus et al., 1999). Other white matter tracts, namely the internal capsule and the left arcuate fasciculus, continue to myelinate with maturation. Delayed myelination of frontocortical connections that occurs during the second and third decade in humans may be associated with enhanced behavioral regulation and impulse control that emerges after adolescence (Luna et al., 2010; Paus, 2005).

DTI capitalizes on estimates of water movement, through measurements of mean diffusivity (MD) and fractional anisotropy (FA). Within a given voxel, FA measures vary from 0 (perfectly isotropic diffusion) to 1 (perfectly anisotropic diffusion), and is determined by fiber diameter and density, coherence and the degree of myelination (Basser and Pierpaoli, 1996). FA examines the degree of directionality of water diffusion. Water movement in a single direction, such as what occurs along a tract, has a higher FA value. An extensive characterization of how MD and FA change across age (5–30 years) in a variety of brain regions can be found in reports by Lebel et al (Lebel et al., 2008) and Qiu et al (Qiu et al., 2008). Of the regions characterized in the Liebel et al paper, the most profound loss of MD occurs in the caudate nucleus during adolescence whereas the splenium of the corpus callosum reaches its full loss (~8%) before 15 years of age. However, FA measurements reflect more than myelination, and include estimates of differences in the nature of fiber tracts themselves (e.g., relative alignment of individual axons and their packing “density”; Paus, 2010). Therefore, estimated changes in myelination based on FA measures need to take into account both myelin and axon diameter. The `g' ratio (axon diameter : axon diameter + myelin sheath thickness) has been developed to account for both axon diameter and fiber diameter. Since both axon diameter and myelin thickness affect conduction velocity but do not increase to the same degree after puberty, the `g' ratio may better reflect developmental changes in white matter and conductivity (Paus and Toro, 2009). Estimating the degree of myelination and its relationship to axonal diameter requires electron microscopy. In the rat, non-biased stereological measures show that the number of glial cells changes in a regional-dependent manner. Glia cell number is stable in the ventromedial PFC

between adolescence and adulthood, but increases nearly 40% with maturation in the dorsal PFC (Markham et al., 2007). Thus, changes in DTI reflect both glia and axonal diameter changes.

An alternative way of determining changes in myelination is to examine gene expression. Consistent with more refined anatomical measurements, the genes associated with myelination also increase expression during adolescence in humans (Harris et al., 2009). For example, genes including MBP (myelin basic protein), MOG (myelin oligodendrocyte glycoprotein), and MAG (myelin associated glycoprotein) increase their expression with maturation. While MBP and MOG are related to structural changes in myelin, MAG is involved in coupling axonal caliber (activity) with the degree of myelination (Yin et al., 1998). Taken together, white matter density increases in a progressive, linear fashion that contrasts with the inverted U-shape of gray matter maturation that typically characterizes adolescence.

3.2.2 Sex dependency of myelination—Sex differences occur in myelination and are observed during the onset of puberty. Multiple studies demonstrate significant increases in myelination of multiple brain regions across the course of adolescence into adulthood in males, but not females (Blanton et al., 2004; Leussis and Andersen, 2008; Paus, 2010). Rather, myelination appears to occur earlier in females. For example, sex differences in human hippocampal myelination emerge after 5 years of age, with an average of 37% greater degree of myelination in females than males (Benes et al., 1994). Similar sex differences are observed across species (e.g., humans, rats (Kodama, 2008)). By adulthood, myelination in the corpus callosum is greater in males, although females have fewer glia cells contributing (Nunez and Juraska, 1998; Kim et al 1997). Similarly, the rat PFC has 15% less glia cells in females than males by adulthood, which may contribute to sex differences in volume in that region (Markham et al., 2007).

When DTI analyses are divided into trajectories of FA and MD, different profiles exist between measures, across sex, and across region (Asato et al., 2010). The fiber tracts of the arcuate fasciculus (which connect Wernicke's area and Broca's area) and the inferior fronto-occipital fasciculus (which connects sensorimotor and frontal regions) demonstrate increased FA in girls, but decreased FA in boys between the ages of 6–20 years; no sex differences were observed for MD (Ashtari et al., 2007; Schmithorst et al., 2008). These changes have been related to IQ and elevated verbal processing in adolescent females over males (Ashtari et al., 2007; Schmithorst et al., 2005). In contrast, other tracts fail to show the expected age-related increase in FA, whereas MD decreased (Eluvathingal et al., 2007). Measures that reflect an increase in FA in the absence of changes in radial diffusivity (a possible index of demyelination) may indicate a transition from reduced tortuousity to greater axonal fiber organization (or straighter fibers) during late adolescence (Ashtari et al., 2007). More efficient processing would be the predicted result of such changes.

Testosterone levels are related to `g' changes in human males (Perrin et al., 2008). The `g ratio' increases in human males, but remains unchanged in females (Paus and Toro, 2009). Axonal caliber changes during development and may explain an increase in DTI in males, whereas female changes in DTI may better reflect myelination (Perrin et al., 2009) Basic studies show that the female corpus callosum is sensitive to pubertal hormones, and ovariectomy at 20 days of age in the rat decreases the number of myelinated axons compared to controls (Yates and Juraska, 2008); the total number of axons in this study were not affected, suggesting these changes were due to loss of myelin and not cells. One possible explanation is that sex differences exist in the survival time of oligodendrocytes, where cells die sooner in adolescent females than males (Cerghet et al., 2006). Other possibilities include estrogenic effects that modulate other gonadal hormones (e.g., progesterone), stress-

related hormones, or even growth factors that in turn effect myelination (discussed in Yates and Juraska, 2008). Additional research will fill in the missing mechanistic gaps in how estrogen modulates myelination.

We are only beginning to understand how synaptogenesis and pruning interact with myelinating processes and brain function to shape adolescent behavior (Paus et al., 2008). Myelin plays an important role in development, but more importantly, in coordinating the speed of diverse inputs from various distances to a given region. Synchronous signaling is paramount for normal development to proceed (Fields, 2005), with changes in myelination implicated in a number of mental illnesses.

4.0. Functional changes development

This review has covered the structural changes that occur during the childhood to adult transitions, but functional changes may show their own patterns. The maturing brain uses its evolving structure and resources (e.g., glucose metabolism) to communicate between and within structures to influence behavior. How the brain regions differentially activate in response to a given stimulus can also tell us how they are interconnected functionally. In this section, “functional connectivity” as measured by MRI refers to the correlational relationships that exist between two regions.

4.1. Energy utilization

The morphological changes described above are typically preceded by functional changes within the brain. The original studies on functional changes used PET imaging of glucose to map energy usage in a cross-sectional design (Chugani, 1998; Feinberg, 1988). Glucose utilization in humans reaches adult levels by two years of life (Chugani et al., 1987) but then rises at 4–5 years of age and maintains this plateau until 10 years of age before pruning by ~50% by 16–18 years of age (Chugani, 1998). Genes related to glucose metabolism, e.g., gene acyl coA dehydrogenase (ACADSB), are expressed in high levels during adolescence, although their functional significance is not known at this time (Harris et al., 2009).

Other markers of brain activity that examine brain metabolism, such as n-acetylaspartate (NAA; a marker of neurons and processes), phosphocreatine (PCr; energy dynamics), and membrane phospholipid metabolism (with makers sPME and sPDE) have been examined with magnetic resonance spectroscopic imaging (MRSI) to provide a non-invasive index of development. Changes in these markers were characterized in axial slices of the brain across males and females 6–9.5, 9.5–12, and 12–18 years old in n=106 subjects (Goldstein et al., 2009). Comparisons between 6–9.5 year olds to the 12–18 year olds show no difference in NAA, which suggests no marked neuronal changes. This observation is in direct contrast to well-characterized neuronal loss determined by direct measurement in post-mortem tissue (e.g., Huttenlocher, 1979). However, NAA provides acetate for olidgodendrocytes that are responsible for myelin production. Thus, no net change in NAA across adolescent development could reflect a balance between neuronal loss and increased myelination. PCr was reduced in the younger age group, but elevations in percent gray matter and sPME/sPDE ratios, which reflect membrane phospholipid turnover, were higher. PCr and percent gray matter were highly correlated with age, but NAA, sPME, sPDE, and sPME/sPDE were not. While some potential changes may have been missed by combining males and females, these data suggest that MRSI does not show decisive age-related metabolic changes.

4.2 Functional connectivity as defined with MRI

Functional connectivity is another approach used to show temporal inter-relationships between areas of activation during resting state or during an fMRI task (Fair et al., 2008; Supekar et al., 2009; Thomason et al., 2009; Zuo et al., 2010). Maps of functional

connectivity are also referred to as connectomes (Biswal et al., 2010), with applications to fMRI representing a recent application of this field (Lichtman and Sanes, 2008). This approach provides some insight into adolescent brain development, although it is limited by some observations that `functional connectivity' is observed in areas absent of true anatomical connections (Honey et al., 2009; Koch et al., 2002). Resting state fMRI is based on observations that large-amplitude spontaneous low-frequency (<0.1 Hz) fluctuations occur (Biswal et al., 2010). Approaches to understanding functional connectivity include seed-based (where a starting point is manually identified to identify a starting point), independent component analysis (ICA), and frequency-domain analyses. Functional development of different brain systems includes the combination of decreasing short-range connections (i.e., segregation) and increasing long-range connections (i.e., integration) (Fair et al., 2007; Stevens et al., 2009). In other words, development proceeds from a local to a more distributed network as different regions become more interconnected (Fair et al., 2009). This interconnectivity is not synchronous, but rather individual regions become connected and then interconnected (Supekar et al., 2010).

Functional connectivity studies of resting fMRI show that a “default network” exists in the brain when it is not actively processing information. The default network is comprised of the posterior cingulate cortex, mPFC, medial temporal lobes, and angular gyrus. These structures demonstrate coherent, low frequency oscillations (0.1 Hz) when the individual is in a quiet, resting state. As the brain becomes more integrated inter-regionally between childhood and adolescence (Fair et al., 2008), increased connectivity within the default network occurs during this transition (between 9–12 years of age; Broyd et al., 2009). The default network has been hypothesized to play a role in creativity, whereas a reduction within the default network has been associated with schizophrenia and autism.

Other functional networks, however, certainly exist in the brain. In a study that compares young adolescents (mean age 12.5 ± 0.51 [SD] years) to young adults (22.2 ± 1.67 [SD] years) in mixed sex groups, 13 main functional networks were identified (Jolles et al., 2010). Of these networks, eight showed increased activity between cortical regions during adolescence, two showed no difference in activity, and three were associated with basic visual or sensorimotor functions (i.e., sensorimotor, visual system, and ventral stream networks) and showed less activity during adolescence than young adulthood. Identification of these networks will now facilitate future investigations into why they demonstrate age-related changes.

5. Functional development of circuits

During adolescence, dramatic shifts in behavior are tied to age-related changes within the brain. Extensive reviews of adolescent behaviors are found elsewhere (Spear, 2000), but we present a brief overview of how specific changes in functional processing during adolescence may explain some of these behaviors. Within the orchestration of building a brain, each region has its own developmental timecourse of maturation (Tau and Peterson, 2010). Generally, cortical areas mature later than subcortical areas, as discussed above. Developmental delays or precocial development within individual nodes of neuronal network formation are likely to initiate a domino-like chain of developmental events that alter the trajectory of multiple brain regions (Ernst and Fudge, 2009; Haber and Rauch, 2010). From this perspective, longitudinal studies will be helpful in determining the sequence of regional brain changes as different cascades of events unfold (Gogtay et al., 2006; Sowell et al., 2004). For example, Shaw and colleagues (Shaw et al., 2007) have shown that cortical development lags in children with ADHD relative to their peers, but catches up by adulthood. In contrast, childhood onset of schizophrenia is associated with earlier regressive pruning than observed in typical children (Rapoport et al., 1999). Studies

such as these are important for tracking the course of the disorder, but also simultaneously highlight windows of development that may be more or less susceptible to outside influences.

The emergence of psychopathology during the adolescent period in the overarching domains of reward- and affect-related processing is not a coincidence. Given the number of dramatic changes that occur during this period, processes that either go awry or were misguided earlier in life and unmasked by these changes (Andersen, 2003; Andersen and Teicher, 2008; Weinberger, 1987; Laviola et al., 2003) will manifest during this period. The importance of delineating and manipulating sensitive periods lies in understanding adverse consequences on developmental processes. In addition, many disorders have a basis in neurodevelopmental processes gone awry. Early exposure to adversity is represents a high risk factor for a number of disorders. For example, epidemiology studies have shown that exposure to adversity results in a higher incidence in major depressive disorder (Anda et al., 2006; Anda et al., 2002; Chapman et al., 2004), borderline personality disorder, drug abuse (Andersen and Teicher, 2009), and suicide, with depression as the most common adult sequelae of early abuse (Putnam, 2003; Zisook et al., 2007).

5.1. Functional development of affective circuits

The functional development of circuits and systems in the brain is complex, with many moving pieces to put together. As a way to approach developmental circuits, we provide the following overviews as they relate to both affect and reward during the adolescent period. These approaches do not include the countless and important studies that examine behavioral and pharmacological transitions that occur during adolescence, but are focused on studies that have neuroanatomical relationships at their root.

Much of human behavior and motivation arises from previously-acquired associations between rewarding or aversive stimuli and the contexts in which they occur (Cardinal et al., 2002). These powerful, learned associations drive our present and future behavior (Cardinal et al., 2002) and occur through Pavlovian conditioning mechanisms (Rosenkranz et al., 2003). Information about the environment and emotions is processed within the basolateral amygdala (BLA) (Grace and Rosenkranz, 2002), which forms powerful associations between stimuli that predict the occurrence of an appetitive or aversive outcome, and produces “affect” within the BLA (Cardinal et al., 2002; Laviolette et al., 2005; Schoenbaum, 2004; See et al., 2003). However, responding to a given stimuli needs to be specific and appropriate in terms of mood, emotional significance, or attention as it relates to choice (Paus et al., 1996). This process occurs in the PFC (Cardinal et al., 2003; Rebec and Sun, 2005; Schoenbaum, 2004; Ventura et al., 2007). Noradrenergic and dopaminergic receptors in the PFC mediate the regulation of attention, behavior and emotion by strengthening network connections between neurons with shared inputs (Arnsten, 2009). Within the mPFC, the salience of information is processed to regulate selected attention.

Thus, information from the BLA is relayed to the mPFC by glutamatergic projections (Bechara et al., 1999; Laviolette et al., 2005; McDonald and Pearson, 1989), where it is processed for salience (Schultz, 1998) and errors that are relevant for predicting future outcomes (Falkenstein et al., 2000; Price, 1999). As a result, stimuli that predict an aversive outcome can be responded to in an appropriately adaptive manner (Pezze et al., 2003). This function is performed by dopaminergic signals in the mPFC (Jackson and Moghaddam, 2004), which encode additional information of salience and novelty with emotional information (Cardinal et al., 2002; Milad and Quirk, 2002) to influence goal-directed, motivated behavior. The mPFC sends this information to the nucleus accumbens directly (Goto and Grace, 2005; Voorn et al., 2004), or indirectly via the amygdala. Subsequently,

the resultant activity within the mPFC, directly or indirectly, influences the motivated behavior in the nucleus accumbens.

Immature processing between the amygdala and the PFC has been proposed to underlie the delayed emergence of affective illness until adolescence (Ernst et al., 2006). Within the triadic model proposed by Ernst and colleagues (Ernst et al., 2006), the avoidance system associated with the amygdala drives behavior relatively unchecked by an immature PFC. According to this model, the nucleus accumbens adjusts the strength of the link between appetitive and aversive conditioning (Horvitz, 2002). This theory is one of a rare few that incorporates what is known about the neurobiology of depression within a developmental framework. However, the theory implies that children and adolescents would grow out of their depression with emerging cortical maturity and connectivity, which is not the case (Andersen and Teicher, 2004; 2008).

We have recently reviewed developmental changes during the adolescent period that may increase vulnerability to depression (Andersen and Teicher, 2008). Briefly, children have more activity than adults in the amygdala in response to emotional stimuli (Killgore et al., 2001), which is further exacerbated in children and adolescents with social anxiety disorder (Beesdo et al., 2009). However, the nucleus accumbens is more involved in the processing of appetitive and aversive stimuli in adolescence instead to the amygala (Ernst et al., 2005). Recruitment of the PFC in response to emotionally-laden stimuli does not occur until adulthood (Killgore et al., 2001). Preclinically, this is consistent with the tract tracing experiments that show both continued development of BLA to PFC innervation during adolescence (Cunningham et al., 2002), but more importantly, a peak in innervation of PFC to BLA inputs during adolescence (Cressman et al., 2010). Together, increased anatomical connections may provide a basis for the delayed (adolescent) emergence of depressive symptoms and emotional lability that epitomizes this maturational state as regulatory control over affect develops (or fails to develop).

5.2. Functional development of reward circuits

Sophisticated MRI and electrophysiologic studies demonstrate the unique roles of subdivisions within the frontal cortex in reward processing. The mPFC (Broadman areas [BA] 10/12/32 and including the anterior cingulate cortex; BA 24) responds to the outcome of the reward: it is activated if an anticipated reward is received and deactivated when not received (Knutson et al., 2003; Schulz et al., 2004). The orbital frontal cortex (OFC) encodes expected outcomes and estimates motivational value based on potential reward. The OFC plays an important role in reversal learning and delayed reinforcement (Dalley et al., 2004) through its connections to sensory, limbic, frontal, and subcortical regions. The OFC is functionally divided with medial portions responding selectively to reward value, while the lateral portions suppress previous reward-associated processes (Elliott et al., 2000; Elliott et al., 2003; London et al., 2000).

The accumbens (ventral striatal region) responds to the saliency (Ernst et al., 2004), valence (appetitive or aversive) (Jensen et al., 2003) and the predictability of the reward (unpredicted reward activates greater than predicted reward (Berns et al., 2001; Elliott et al., 2000)), but not the motor component (Zink et al., 2004). During adolescence, the accumbens responds greater than the OFC to reward (Galvan et al., 2005). Taken together, these data suggest that the adolescent accumbens drives change in reward processing (Galvan, 2010).

However, evidence of how the cortical and subcortical systems respond to reward stimuli suggests that the cortex plays an even larger role in adolescent transitions in reward processing. Animal studies have shown that reward processing transitions during adolescence through the pruning and potential re-focusing of cortical networks as the

networks mature and become adult-like (Brenhouse et al., 2008; Crews et al., 2007). Clinical fMRI studies suggest that both ventral striatum and the mPFC activate to reward stimuli during adolescence (Bjork et al., 2004). Prior to this transition, reward-related BOLD tasks produce more diffuse and less intense activation of frontal regions in children than in adults (Durston et al., 2003). However, children show greater activation in the ventral striatum (accumbens) (Ernst et al., 2005; Galvan et al., 2006). As we know little mechanistically about reward development in humans, we will draw upon preclinical research for a greater understanding.

The maturation of the mPFC is delayed relative to most other brain regions (Andersen et al., 2000; Huttenlocher, 1979) and reaches peak synaptic density closer to adulthood (Benes et al., 2000). Increased sprouting of dopamine neurons (Benes et al., 1996; Kalsbeek et al., 1988; Verney et al., 1982), receptor density (Andersen et al., 2000; Leslie et al., 1991), and second messenger system activity (Andersen, 2002) culminate in an enhanced dopaminergic drive to the mPFC during adolescence. Recent findings also demonstrate an age-related increase in D1 activation of non-fast spiking cells in the mPFC, which occurs after puberty (Tseng et al., 2006), and a peak in the firing rate of the VTA dopaminergic neurons at this same age (McCutcheon and Marinelli, 2009). The over-expression of D1 receptors on glutamatergic outputs to the accumbens also peaks during adolescence in parallel with drug-seeking behavior (Badanich et al., 2006; Brenhouse et al., 2008). This receptor population has been implicated in drug-relapse, and thus its overexpression during adolescence is noteworthy (Kalivas, 2005). These changes in cortical reward processing are also likely to influence subcortical responses to psychostimulants.

In contrast, basal levels of extracellular dopamine and dopaminergic responses to stimulants do not change appreciably between adolescents and adults in the accumbens (Frantz et al., 2007) or mPFC (Jezierski et al., 2007). However, the ratio between cortical:accumbens expression of the immediate early gene *c-fos* in response to stimulants increases between adolescence and adulthood (Andersen et al., 2001). Additionally, amphetamine produces subcortical > cortical activation patterns of c-fos in juveniles (Andersen et al., 2001), but cortical > subcortical activation in adolescents (Cao et al., 2007). Taken together, these data suggest that juveniles differ markedly from adolescents, who are more adult-like, in their responses to stimulants subcortically. In other words, the likelihood that substance use rises substantially during adolescence follows from either direct or indirect effects of cortical processes on subcortical activity.

5.3. Functional development of cognition

Experimental paradigms such as the Stroop, Simon, Flanker, Go/No-Go, and Stop-Signal tasks require suppression of a more automatic behavior to perform a less automatic one. Attentional regulation, response inhibition, and conflict and error monitoring are cognitive processes that are engaged in the service of cognitive control and successful task performance. Performance on all of these tasks improves steadily throughout development, but does not approach adult levels until at least late childhood or early adolescence (Bunge et al., 2002; Casey et al., 1997; Davidson et al., 2006; Luna and Sweeney, 2004; Rubia et al., 2000). As with working memory, the self-regulatory capacity of children can be overwhelmed easily by increasing task demands. In adults, self-regulation relies on broad cortical areas such as supplementary motor area, frontal eye fields, anterior cingulate cortex, dorsolateral PFC, ventralPFC/lateral orbitofrontal cortex, as well as temporal, and parietal regions all of which have connections with striatum in the subcortex (Leung et al., 2000; Marsh et al., 2007).

Effective responding to environmental stimuli requires selective attention and motivational direction, coupled with suppression of actions that are no longer required or that are

inappropriate. This suppression is measured experimentally via response inhibition, which involves three interrelated processes, as proposed by Barkely (Barkley, 1997): 1) inhibition of an initial pre-potent response, 2) stopping of an ongoing response or delayed responding, and 3) limiting interference or distractibility during delay periods. The basal ganglia and PFC are both implicated in these processes (Casey et al., 2008). In general, while the basal ganglia control the inhibition of inappropriate behaviors (Mink, 1996), the PFC acts to prevent interference with relevant information by competing information (Miller and Cohen, 2001).

In contrast to approach-avoidance, which requires incentive salience attribution and is largely mediated through a triadic cooperation of the PFC, striatum, and amygdala (reviewed (Ernst and Fudge, 2009)), response inhibition recruits circuitries that regulate motor planning and timing (Deiber et al., 1999). The primary role of fronto-striatal networks lends itself to a different developmental profile than that of motivation and selective attention systems.

5.4. Development of Response inhibition

While adolescents can perform sophisticated cognitive tasks, the ability to do so consistently continues to improve during adolescence and into adulthood, This linear improvement throughout development suggests that the neurobiological underpinnings of cognition follow similarly linear progression. Children show significantly higher intensity of activation than adults in frontal lobe regions (Bunge et al., 2002) including bilateral medial frontal gyrus and medial aspects of bilateral superior frontal gyrus (Booth et al., 2003). This is consistent with age-related differences in accuracy and reaction time on go/no-go tasks across childhood. Interestingly, a joint DTI and fMRI study performed by Stevens and colleagues (Stevens et al., 2009) reported a direct relationship between age-related changes in functional connectivity between the bilateral frontopolar, right parietal cortex and right caudate, increased myelination, and improved performance on the Go/No Go task. In another DTI study, response inhibition in 7–13 year olds was significantly associated with higher FA and lower MD in both the right inferior frontal gyrus and the right pre-supplementary motor cortex (Madsen et al., 2010). The linear developmental trajectory of myelination discussed above is therefore consistent with an apparent linear development of cognitive control, relative to the inverted U-shaped trajectory of affect and reward processing. Children also display greater intensity of activation than adults in the left caudate nucleus during go/no-go (Booth et al., 2003) and stop (Rubia et al., 1999) tasks. The basal ganglia has been proposed to be involved in the inhibition of inappropriate behaviors (Casey et al., 2001), and the basal ganglia appears to mature linearly from childhood through adulthood.

The basic neurobiology of these circuits have either been previously discussed above or have yet to be studied within a developmental context. While there is a wealth of neuroimaging data surrounding response inhibition tasks, there has been less investigation of neurochemistry behind these systems (for a comprehensive review, see Eagle et al., 2008). One of the main problems associated with preclinical modeling of these behaviors lies in the weeks that are required to train animals to perform these tasks, which precludes their study during development. Given the importance that cognitive control and impulse regulation during adolescent maturation into adulthood, this field requires more attention than it has received.

6. Experience shapes brain development

While genes provide the blueprint to construct the brain, experience sculpts that brain to match the needs of the environment. The final fate of a given synapse is based on functional

validation. The adolescent brain is not only uniquely susceptible to environmental influences, but adolescence is also a period when early experiences manifest (Andersen, 2003; Andersen and Teicher, 2008). Complex neural networks form during adolescence, and these in turn are sculpted by both spontaneous and experience-driven activity (Ben-Ari, 2002; Francis et al., 2002; Katz and Shatz, 1996; Zhang and Poo, 2001). Our earlier review (Andersen, 2003) discussed the significant impact that environmental influences have on brain development. Other review papers discuss the impact the stress exposure has on adolescent brain development (Andersen and Teicher, 2008; 2009). Exposure to psychotropic drugs during the course of development will also alter the course of a trajectory, with the effects emerging during adolescence (Brenhouse et al., 2009; Ansorge et al., 2008).

Summary

The nature and extent of adolescent changes within brain neuroanatomy is constantly changing as our tools of analysis become more fine-grained. Diversity can only be fully appreciated when regions are studied within functional divisions (e.g. (Gogtay et al., 2006)), with complete timecourse of characterization, and when early experiences (Andersen and Teicher, 2008) and other factors (e.g., sex, Tanner stage) are taken into consideration. Incomplete timecourses in earlier studies have led to incorrect conclusions about the timing of maturation (discussed in McCutcheon and Marinelli, 2009) and whether early experiences do indeed affect development. This review provides an overview of our current understanding of adolescent changes in the brain during its transition from childhood to adulthood. This remarkable process is highly resilient due to plasticity that allows the mammalian system to adapt to the needs of its environment.

References

Adriani W, Laviola G. Windows of vulnerability to psychopathology and therapeutic strategy in the adolescent rodent model. Behav Pharmacol. 2004; 15:341–352. [PubMed: 15343057]

Anda RF, Felitti VJ, Bremner JD, Walker JD, Whitfield C, Perry BD, Dube Sh R, Giles WH. The enduring effects of abuse and related adverse experiences in childhood: A convergence of evidence from neurobiology and epidemiology. Eur Arch Psychiatry Clin Neurosci. 2006; 256:174–86. [PubMed: 16311898]

Anda RF, Whitfield CL, Felitti VJ, Chapman D, Edwards VJ, Dube SR, Williamson DF. Adverse childhood experiences, alcoholic parents, and later risk of alcoholism and depression. Psychiatr Serv. 2002; 53:1001–9. [PubMed: 12161676]

Andersen S. Changes in the second messenger cyclic AMP during development may underlie motoric symptoms in Attention Deficit/Hyperactivity Disorder (ADHD). Behavioral Brain Research. 2002; 130:197–201.

Andersen SL. Trajectories of brain development: point of vulnerability or window of opportunity? Neurosci Biobehav Rev. 2003; 27:3–18. [PubMed: 12732219]

Andersen SL. Stimulants and the developing brain. Trends Pharmacol Sci. 2005; 26:237–43. [PubMed: 15860370]

Andersen SL, LeBlanc CJ, Lyss PJ. Maturational increases in c-fos expression in the ascending dopamine systems. Synapse. 2001; 41:345–50. [PubMed: 11494405]

Andersen SL, Rutstein M, Benzo JM, Hostetter JC, Teicher MH. Sex differences in dopamine receptor overproduction and elimination. Neuroreport. 1997; 8:1495–8. [PubMed: 9172161]

Andersen SL, Teicher MH. Delayed effects of early stress on hippocampal development. Neuropsychopharmacology. 2004; 29:1988–93. [PubMed: 15316569]

Andersen SL, Teicher MH. Stress, sensitive periods and maturational events in adolescent depression. Trends Neurosci. 2008

Andersen SL, Teicher MH. Desperately driven and no brakes: developmental stress exposure and subsequent risk for substance abuse. Neurosci Biobehav Rev. 2009; 33:516–24. [PubMed: 18938197]

Andersen SL, Thompson AP, Krenzel E, Teicher MH. Pubertal changes in gonadal hormones do not underlie adolescent dopamine receptor overproduction. Psychoneuroendocrinology. 2002; 27:683–91. [PubMed: 12084661]

Andersen SL, Thompson AT, Rutstein M, Hostetter JC, Teicher MH. Dopamine receptor pruning in prefrontal cortex during the periadolescent period in rats. Synapse. 2000; 37:167–9. In Process Citation. [PubMed: 10881038]

Anderson SA, Classey JD, Conde F, Lund JS, Lewis DA. Synchronous development of pyramidal neuron dendritic spines and parvalbumin-immunoreactive chandelier neuron axon terminals in layer III of monkey prefrontal cortex. Neuroscience. 1995; 67:7–22. [PubMed: 7477911]

Ansorge MS, Morelli E, Gingrich JA. Inhibition of serotonin but not norepinephrine transport during development produces delayed, persistent perturbations of emotional behaviors in mice. J Neurosci. 2008; 28:199–207. [PubMed: 18171937]

Arnett JJ. Emerging adulthood. A theory of development from the late teens through the twenties. Am Psychol. 2000; 55:469–80. [PubMed: 10842426]

Asato MR, Terwilliger R, Woo J, Luna B. White Matter Development in Adolescence: A DTI Study. Cereb Cortex. 2010

Ashtari M, Cervellione KL, Hasan KM, Wu J, McIlree C, Kester H, Ardekani BA, Roofeh D, Szeszko PR, Kumra S. White matter development during late adolescence in healthy males: a cross-sectional diffusion tensor imaging study. Neuroimage. 2007; 35:501–10. [PubMed: 17258911]

Badanich KA, Adler KJ, Kirstein CL. Adolescents differ from adults in cocaine conditioned place preference and cocaine-induced dopamine in the nucleus accumbens septi. Eur J Pharmacol. 2006; 550:95–106. [PubMed: 17011546]

Bari A, Eagle DM, Mar AC, Robinson ES, Robbins TW. Dissociable effects of noradrenaline, dopamine, and serotonin uptake blockade on stop task performance in rats. Psychopharmacology (Berl). 2009; 205:273–83. [PubMed: 19404616]

Barkley RA. Attention-deficit/hyperactivity disorder, self-regulation, and time: toward a more comprehensive theory. J Dev Behav Pediatr. 1997; 18:271–9. [PubMed: 9276836]

Basser PJ, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J Magn Reson B. 1996; 111:209–19. [PubMed: 8661285]

Bechara A, Damasio H, Damasio AR, Lee GP. Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. J Neurosci. 1999; 19:5473–81. [PubMed: 10377356]

Beesdo K, Lau JY, Guyer AE, McClure-Tone EB, Monk CS, Nelson EE, Fromm SJ, Goldwin MA, Wittchen HU, Leibenluft E, Ernst M, Pine DS. Common and distinct amygdala-function perturbations in depressed vs anxious adolescents. Arch Gen Psychiatry. 2009; 66:275–85. [PubMed: 19255377]

Ben-Ari Y. Excitatory actions of gaba during development: the nature of the nurture. Nat Rev Neurosci. 2002; 3:728–39. [PubMed: 12209121]

Benes FM. Amygdalocortical Circuitry in Schizophrenia: From Circuits to Molecules. Neuropsychopharmacology. 2009

Benes FM, Majocha R, Bird ED, Marotta CA. Increased vertical axon numbers in cingulate cortex of schizophrenics. Archives of General Psychiatry. 1987; 44:1017–21. [PubMed: 2445320]

Benes FM, Taylor JB, Cunningham MC. Convergence and plasticity of monoaminergic systems in the medial prefrontal cortex during the postnatal period: implications for the development of psychopathology. Cereb Cortex. 2000; 10:1014–27. [PubMed: 11007552]

Benes FM, Turtle M, Khan Y, Farol P. Myelination of a key relay zone in the hippocampal formation occurs in the human brain during childhood, adolescence, and adulthood. Arch Gen Psychiatry. 1994; 51:477–84. [PubMed: 8192550]

Benes FM, Vincent SL, Molloy R, Khan Y. Increased interaction of dopamine-immunoreactive varicosities with GABA neurons of rat medial prefrontal cortex occurs during the postweanling period. Synapse. 1996; 23:237–45. [PubMed: 8855508]

Berns GS, McClure SM, Pagnoni G, Montague PR. Predictability modulates human brain response to reward. J Neurosci. 2001; 21:2793–8. [PubMed: 11306631]

Biswal BB, Mennes M, Zuo XN, Gohel S, Kelly C, Smith SM, Beckmann CF, Adelstein JS, Buckner RL, Colcombe S, Dogonowski AM, Ernst M, Fair D, Hampson M, Hoptman MJ, Hyde JS, Kiviniemi VJ, Kotter R, Li SJ, Lin CP, Lowe MJ, Mackay C, Madden DJ, Madsen KH, Margulies DS, Mayberg HS, McMahon K, Monk CS, Mostofsky SH, Nagel BJ, Pekar JJ, Peltier SJ, Petersen SE, Riedl V, Rombouts SA, Rypma B, Schlaggar BL, Schmidt S, Seidler RD, Siegle GJ, Sorg C, Teng GJ, Veijola J, Villringer A, Walter M, Wang L, Weng XC, Whitfield-Gabrieli S, Williamson P, Windischberger C, Zang YF, Zhang HY, Castellanos FX, Milham MP. Toward discovery science of human brain function. Proc Natl Acad Sci U S A. 107:4734–9. [PubMed: 20176931]

Bjork JM, Knutson B, Fong GW, Caggiano DM, Bennett SM, Hommer DW. Incentive-elicited brain activation in adolescents: similarities and differences from young adults. J Neurosci. 2004; 24:1793–802. [PubMed: 14985419]

Blanton RE, Levitt JG, Peterson JR, Fadale D, Sporty ML, Lee M, To D, Mormino EC, Thompson PM, McCracken JT, Toga AW. Gender differences in the left inferior frontal gyrus in normal children. Neuroimage. 2004; 22:626–36. [PubMed: 15193591]

Booth JR, Burman DD, Meyer JR, Lei Z, Trommer BL, Davenport ND, Li W, Parrish TB, Gitelman DR, Mesulam MM. Neural development of selective attention and response inhibition. Neuroimage. 2003; 20:737–51. [PubMed: 14568448]

Bremner JD, Narayan M, Staib LH, Southwick SM, McGlashan T, Charney DS. Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. Am J Psychiatry. 1999; 156:1787–95. [PubMed: 10553744]

Brenhouse H, Sonntag KC, Andersen SL. Transient D1 dopamine receptor over-expression on prefrontal cortex projection neurons: A mechanism for enhanced motivational salience of drug cues in adolescence. Journal of Neuroscience. 2008; 28:2375–2382. [PubMed: 18322084]

Brenhouse HC, Napierata L, Kussmaul L, Leussis M, Andersen SL. Juvenile methylphenidate exposure and factors that influence incentive processing. Dev Neurosci. 2009; 31:95–106. [PubMed: 19372691]

Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJS. Default-mode brain dysfunction in mental disorders: a systematic review. Neurosci Biobehav Rev. 2009; 33:279–96. [PubMed: 18824195]

Brummelte S, Teuchert-Noodt G. Postnatal development of dopamine innervation in the amygdala and the entorhinal cortex of the gerbil (Meriones unguiculatus). Brain Res. 2006; 1125:9–16. [PubMed: 17112487]

Bunge SA, Dudukovic NM, Thomason ME, Vaidya CJ, Gabrieli JD. Immature frontal lobe contributions to cognitive control in children: evidence from fMRI. Neuron. 2002; 33:301–11. [PubMed: 11804576]

Cao J, Lotfipour S, Loughlin SE, Leslie FM. Adolescent maturation of cocaine-sensitive neural mechanisms. Neuropsychopharmacology. 2007; 32:2279–89. [PubMed: 17299504]

Cardinal RN, Parkinson JA, Hall J, Everitt BJ. Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. Neurosci Biobehav Rev. 2002; 26:321–52. [PubMed: 12034134]

Cardinal RN, Parkinson JA, Marbini HD, Toner AJ, Bussey TJ, Robbins TW, Everitt BJ. Role of the anterior cingulate cortex in the control over behavior by Pavlovian conditioned stimuli in rats. Behav Neurosci. 2003; 117:566–87. [PubMed: 12802885]

Casey BJ, Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Schubert AB, Vauss YC, Vaituzis AC, Dickstein DP, Sarfatti SE, Rapoport JL. Implication of right frontostriatal circuitry in response inhibition and attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 1997; 36:374–83. [PubMed: 9055518]

Casey BJ, Forman SD, Franzen P, Berkowitz A, Braver TS, Nystrom LE, Thomas KM, Noll DC. Sensitivity of prefrontal cortex to changes in target probability: a functional MRI study. Hum Brain Mapp. 2001; 13:26–33. [PubMed: 11284044]

Casey BJ, Jones RM, Hare TA. The adolescent brain. Ann N Y Acad Sci. 2008; 1124:111–26. [PubMed: 18400927]

Caviness VS Jr. Kennedy DN, Richelme C, Rademacher J, Filipek PA. The human brain age 7–11 years: a volumetric analysis based on magnetic resonance images. Cerebral Cortex. 1996; 6:726–36. [PubMed: 8921207]

Cerghet M, Skoff RP, Bessert D, Zhang Z, Mullins C, Ghandour MS. Proliferation and death of oligodendrocytes and myelin proteins are differentially regulated in male and female rodents. J Neurosci. 2006; 26:1439–47. [PubMed: 16452667]

Changeaux JP, Danchin A. Selective stabilization of developing synapses as a mechanism for the specification of neuronal networks. Nature. 1976; 264:705–12. [PubMed: 189195]

Chapman DP, Whitfield CL, Felitti VJ, Dube SR, Edwards VJ, Anda RF. Adverse childhood experiences and the risk of depressive disorders in adulthood. J Affect Disord. 2004; 82:217–25. [PubMed: 15488250]

Chugani HT. A critical period of brain development: studies of cerebral glucose utilization with PET. Preventive Medicine. 1998; 27:184–8. [PubMed: 9578992]

Chugani HT, Phelps ME, Mazziotta JC. Positron emission tomography study of human brain functional development. Ann Neurol. 1987; 22:487–97. [PubMed: 3501693]

Clark AS, Goldman-Rakic PS. Gonadal hormones influence the emergence of cortical function in nonhuman primates. Behav Neurosci. 1989; 103:1287–95. [PubMed: 2610921]

Conde F, Lund JS, Lewis DA. The hierarchical development of monkey visual cortical regions as revealed by the maturation of parvalbumin-immunoreactive neurons. Brain Res Dev Brain Res. 1996; 96:261–76.

Constantinidis C, Williams GV, Goldman-Rakic PS. A role for inhibition in shaping the temporal flow of information in prefrontal cortex. Nat Neurosci. 2002; 5:175–80. [PubMed: 11802172]

Cox ET, Brennaman LH, Gable KL, Hamer RM, Glantz LA, Lamantia AS, Lieberman JA, Gilmore JH, Maness PF, Jarskog LF. Developmental regulation of neural cell adhesion molecule in human prefrontal cortex. Neuroscience. 2009; 162:96–105. [PubMed: 19393299]

Cressman VL, Balaban J, Steinfeld S, Shemyakin A, Graham P, Parisot N, Moore H. Prefrontal cortical inputs to the basal amygdala undergo pruning during late adolescence in the rat. J Comp Neurol. 2010; 518:2693–709. [PubMed: 20506471]

Crews F, He J, Hodge C. Adolescent cortical development: a critical period of vulnerability for addiction. Pharmacol Biochem Behav. 2007; 86:189–99. [PubMed: 17222895]

Cruz DA, Eggan SM, Lewis DA. Postnatal development of pre- and postsynaptic GABA markers at chandelier cell connections with pyramidal neurons in monkey prefrontal cortex. J Comp Neurol. 2003; 465:385–400. [PubMed: 12966563]

Cruz DA, Lovallo EM, Stockton S, Rasband M, Lewis DA. Postnatal development of synaptic structure proteins in pyramidal neuron axon initial segments in monkey prefrontal cortex. J Comp Neurol. 2009; 514:353–67. [PubMed: 19330819]

Cunningham MG, Bhattacharyya S, Benes FM. Amygdalo-cortical sprouting continues into early adulthood: implications for the development of normal and abnormal function during adolescence. J Comp Neurol. 2002; 453:116–30. [PubMed: 12373778]

Dalley JW, Cardinal RN, Robbins TW. Prefrontal executive and cognitive functions in rodents: neural and neurochemical substrates. Neurosci Biobehav Rev. 2004; 28:771–84. [PubMed: 15555683]

Davidson MC, Amso D, Anderson LC, Diamond A. Development of cognitive control and executive functions from 4 to 13 years: evidence from manipulations of memory, inhibition, and task switching. Neuropsychologia. 2006; 44:2037–78. [PubMed: 16580701]

Davis AM, McCarthy MM. Developmental increase in (3)H-muscimol binding to the gamma-aminobutyric acid(A) receptor in hypothalamic and limbic areas of the rat: why is the ventromedial nucleus of the hypothalamus an exception? Neurosci Lett. 2000; 288:223–7. [PubMed: 10889348]

Deiber MP, Honda M, Ibanez V, Sadato N, Hallett M. Mesial motor areas in self-initiated versus externally triggered movements examined with fMRI: effect of movement type and rate. J Neurophysiol. 1999; 81:3065–77. [PubMed: 10368421]

Di Cristo G, Chattopadhyaya B, Kuhlman SJ, Fu Y, Bélanger MC, Wu CZ, Rutishauser U, Maffei L, Huang ZJ. Activity-dependent PSA expression regulates inhibitory maturation and onset of critical period plasticity. Nat Neurosci. 2007; 10:1569–77. [PubMed: 18026099]

Duncan CE, Webster MJ, Rothmond DA, Bahn S, Elashoff M, Shannon Weickert C. Prefrontal GABA(A) receptor alpha-subunit expression in normal postnatal human development and schizophrenia. J Psychiatr Res. 44:673–81. [PubMed: 20100621]

Durston S, Hulshoff Pol HE, Casey BJ, Giedd JN, Buitelaar JK, van Engeland H. Anatomical MRI of the developing human brain: what have we learned? J Am Acad Child Adolesc Psychiatry. 2001; 40:1012–20. [PubMed: 11556624]

Durston S, Tottenham NT, Thomas KM, Davidson MC, Eigsti IM, Yang Y, Ulug AM, Casey BJ. Differential patterns of striatal activation in young children with and without ADHD. Biol Psychiatry. 2003; 53:871–8. [PubMed: 12742674]

Eagle DM, Baunez C. Is there an inhibitory-response-control system in the rat? Evidence from anatomical and pharmacological studies of behavioral inhibition. Neurosci Biobehav Rev. 2010; 34:50–72. [PubMed: 19615404]

Eagle DM, Tufft MR, Goodchild HL, Robbins TW. Differential effects of modafinil and methylphenidate on stop-signal reaction time task performance in the rat, and interactions with the dopamine receptor antagonist cis-flupenthixol. Psychopharmacology (Berl). 2007; 192:193–206. [PubMed: 17277934]

Eckenhoff MF, Rakic P. A quantitative analysis of synaptogenesis in the molecular layer of the dentate gyrus in the rhesus monkey. Brain Res Dev Brain Res. 1991; 64:129–35.

Eggan SM, Mizoguchi Y, Stoyak SR, Lewis DA. Development of cannabinoid 1 receptor protein and messenger RNA in monkey dorsolateral prefrontal cortex. Cereb Cortex. 2010; 20:1164–74. [PubMed: 19703937]

Elliott R, Dolan RJ, Frith CD. Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies. Cereb Cortex. 2000; 10:308–17. [PubMed: 10731225]

Elliott R, Newman JL, Longe OA, Deakin JF. Differential response patterns in the striatum and orbitofrontal cortex to financial reward in humans: a parametric functional magnetic resonance imaging study. J Neurosci. 2003; 23:303–7. [PubMed: 12514228]

Eluvathingal TJ, Hasan KM, Kramer L, Fletcher JM, Ewing-Cobbs L. Quantitative diffusion tensor tractography of association and projection fibers in normally developing children and adolescents. Cereb Cortex. 2007; 17:2760–8. [PubMed: 17307759]

Erickson SL, Akil M, Levey AI, Lewis DA. Postnatal development of tyrosine hydroxylase- and dopamine transporter- immunoreactive axons in monkey rostral entorhinal cortex. Cereb Cortex. 1998; 8:415–27. [PubMed: 9722085]

Erickson SL, Sesack SR, Lewis DA. Dopamine innervation of monkey entorhinal cortex: postsynaptic targets of tyrosine hydroxylase-immunoreactive terminals. Synapse. 2000; 36:47–56. [PubMed: 10700025]

Ernst M, Fudge JL. A developmental neurobiological model of motivated behavior: anatomy, connectivity and ontogeny of the triadic nodes. Neurosci Biobehav Rev. 2009; 33:367–82. [PubMed: 19028521]

Ernst M, Korelitz KE. Cerebral maturation in adolescence: behavioral vulnerability. Encephale. 2009; 35(Suppl 6):S182–9. [PubMed: 20141770]

Ernst M, Nelson EE, Jazbec S, McClure EB, Monk CS, Leibenluft E, Blair J, Pine DS. Amygdala and nucleus accumbens in responses to receipt and omission of gains in adults and adolescents. Neuroimage. 2005; 25:1279–91. [PubMed: 15850746]

Ernst M, Nelson EE, McClure EB, Monk CS, Munson S, Eshel N, Zarahn E, Leibenluft E, Zametkin A, Towbin K, Blair J, Charney D, Pine DS. Choice selection and reward anticipation: an fMRI study. Neuropsychologia. 2004; 42:1585–97. [PubMed: 15327927]

Ernst M, Pine DS, Hardin M. Triadic model of the neurobiology of motivated behavior in adolescence. Psychol Med. 2006; 36:299–312. [PubMed: 16472412]

Fair DA, Cohen AL, Dosenbach NU, Church JA, Miezin FM, Barch DM, Raichle ME, Petersen SE, Schlaggar BL. The maturing architecture of the brain's default network. Proc Natl Acad Sci U S A. 2008; 105:4028–32. [PubMed: 18322013]

Fair DA, Cohen AL, Power JD, Dosenbach NU, Church JA, Miezin FM, Schlaggar BL, Petersen SE. Functional brain networks develop from a “local to distributed” organization. PLoS Comput Biol. 2009; 5:e1000381. [PubMed: 19412534]

Fair DA, Dosenbach NU, Church JA, Cohen AL, Brahmbhatt S, Miezin FM, Barch DM, Raichle ME, Petersen SE, Schlaggar BL. Development of distinct control networks through segregation and integration. Proc Natl Acad Sci U S A. 2007; 104:13507–12. [PubMed: 17679691]

Falkenstein M, Hoormann J, Christ S, Hohnsbein J. ERP components on reaction errors and their functional significance: a tutorial. Biol Psychol. 2000; 51:87–107. [PubMed: 10686361]

Feeney DM, Westerberg VS. Norepinephrine and brain damage: alpha noradrenergic pharmacology alters functional recovery after cortical trauma. Can J Psychol. 1990; 44:233–52. [PubMed: 2166617]

Feinberg I. Metabolic brain changes in adolescence: one aspect of a global reorganization? Ann Neurol. 1988; 24:464–5. [PubMed: 3228279]

Fields RD. Myelination: an overlooked mechanism of synaptic plasticity? Neuroscientist. 2005; 11:528–31. [PubMed: 16282593]

Forbes EE, Dahl RE. Neural systems of positive affect: relevance to understanding child and adolescent depression? Dev Psychopathol. 2005; 17:827–50. [PubMed: 16262994]

Francis DD, Diorio J, Plotsky PM, Meaney MJ. Environmental enrichment reverses the effects of maternal separation on stress reactivity. J Neurosci. 2002; 22:7840–3. [PubMed: 12223535]

Frantz KJ, O'Dell LE, Parsons LH. Behavioral and neurochemical responses to cocaine in periadolescent and adult rats. Neuropsychopharmacology. 2007; 32:625–37. [PubMed: 16794567]

Galvan A. Adolescent development of the reward system. Front Hum Neurosci. 2010; 4:6. [PubMed: 20179786]

Galvan A, Hare TA, Davidson M, Spicer J, Glover G, Casey BJ. The role of ventral frontostriatal circuitry in reward-based learning in humans. J Neurosci. 2005; 25:8650–6. [PubMed: 16177032]

Galvan A, Hare TA, Parra CE, Penn J, Voss H, Glover G, Casey BJ. Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. J Neurosci. 2006; 26:6885–92. [PubMed: 16793895]

Geier C, Luna B. The maturation of incentive processing and cognitive control. Pharmacol Biochem Behav. 2009; 93:212–221. [PubMed: 19593842]

Gelbard HA, Teicher MH, Baldessarini RJ, Gallitano A, Marsh ER, Zorc J, Faedda G. Dopamine D1 receptor development depends on endogenous dopamine. Brain Res Dev Brain Res. 1990; 56:137–40.

Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, Paus T, Evans AC, Rapoport JL. Brain development during childhood and adolescence: a longitudinal MRI study. Nat Neurosci. 1999a; 2:861–3. [PubMed: 10491603]

Giedd JN, Blumenthal J, Jeffries NO, Rajapakse JC, Vaituzis AC, Liu H, Berry YC, Tobin M, Nelson J, Castellanos FX. Development of the human corpus callosum during childhood and adolescence: a longitudinal MRI study. Prog Neuropsychopharmacol Biol Psychiatry. 1999b; 23:571–88. [PubMed: 10390717]

Giedd JN, Keshavan M, Tomas Paus. Why do many psychiatric disorders emerge during adolescence? Nat Rev Neurosci. 2008; 9(12):947–957. [PubMed: 19002191]

Giedd JN, Rumsey JM, Castellanos FX, Rajapakse JC, Kaysen D, Vaituzis AC, Vauss YC, Hamburger SD, Rapoport JL. A quantitative MRI study of the corpus callosum in children and adolescents. Brain Res Dev Brain Res. 1996a; 91:274–80.

Giedd JN, Snell JW, Lange N, Rajapakse JC, Casey BJ, Kozuch PL, Vaituzis AC, Vauss YC, Hamburger SD, Kaysen D, Rapoport JL. Quantitative magnetic resonance imaging of human brain development: ages 4–18. Cerebral Cortex. 1996b; 6:551–60. [PubMed: 8670681]

Giedd JN, Vaituzis AC, Hamburger SD, Lange N, Rajapakse JC, Kaysen D, Vauss YC, Rapoport JL. Quantitative MRI of the temporal lobe, amygdala, and hippocampus in normal human development: ages 4–18 years. J Comp Neurol. 1996c; 366:223–30. [PubMed: 8698883]

Glantz LA, Gilmore JH, Hamer RM, Lieberman JA, Jarskog LF. Synaptophysin and postsynaptic density protein 95 in the human prefrontal cortex from mid-gestation into early adulthood. Neuroscience. 2007; 149:582–91. [PubMed: 17916412]

Gogtay N, Nugent TF 3rd, Herman DH, Ordonez A, Greenstein D, Hayashi KM, Clasen L, Toga AW, Giedd JN, Rapoport JL, Thompson PM. Dynamic mapping of normal human hippocampal development. Hippocampus. 2006

Goldstein G, Panchalingam K, McClure RJ, Stanley JA, Calhoun VD, Pearlson GD, Pettegrew JW. Molecular neurodevelopment: an in vivo 31P-1H MRSI study. J Int Neuropsychol Soc. 2009; 15:671–83. [PubMed: 19674503]

Goto Y, Grace AA. Dopaminergic modulation of limbic and cortical drive of nucleus accumbens in goal-directed behavior. Nat Neurosci. 2005; 8:805–12. [PubMed: 15908948]

Grace AA, Rosenkranz JA. Regulation of conditioned responses of basolateral amygdala neurons. Physiol Behav. 2002; 77:489–93. [PubMed: 12526988]

Haber SN, Rauch SL. Neurocircuitry: a window into the networks underlying neuropsychiatric disease. Neuropsychopharmacology. 2010; 35:1–3. [PubMed: 20010702]

Hajszan T, Dow A, Warner-Schmidt JL, Szigeti-Buck K, Sallam NL, Parducz A, Leranth C, Duman RS. Remodeling of hippocampal spine synapses in the rat learned helplessness model of depression. Biol Psychiatry. 2009; 65:392–400. [PubMed: 19006787]

Happe HK, Coulter CL, Gerety ME, Sanders JD, O'Rourke M, Bylund DB, Murrin LC. Alpha-2 adrenergic receptor development in rat CNS: an autoradiographic study. Neuroscience. 2004; 123:167–78. [PubMed: 14667451]

Harris LW, Lockstone HE, Khaitovich P, Weickert CS, Webster MJ, Bahn S. Gene expression in the prefrontal cortex during adolescence: implications for the onset of schizophrenia. BMC Med Genomics. 2009; 2:28. [PubMed: 19457239]

Hashimoto T, Nguyen QL, Rotaru D, Keenan T, Arion D, Beneyto M, Gonzalez-Burgos G, Lewis DA. Protracted developmental trajectories of GABAA receptor alpha1 and alpha2 subunit expression in primate prefrontal cortex. Biol Psychiatry. 2009; 65:1015–23. [PubMed: 19249749]

Henson MA, Roberts AC, Salimi K, Vadlamudi S, Hamer RM, Gilmore JH, Jarskog LF, Philpot BD. Developmental regulation of the NMDA receptor subunits, NR3A and NR1, in human prefrontal cortex. Cereb Cortex. 2008; 18:2560–73. [PubMed: 18296432]

Honey CJ, Sporns O, Cammoun L, Gigandet X, Thiran JP, Meuli R, Hagmann P. Predicting human resting-state functional connectivity from structural connectivity. Proc Natl Acad Sci U S A. 2009; 106:2035–40. [PubMed: 19188601]

Horvitz JC. Dopamine gating of glutamatergic sensorimotor and incentive motivational input signals to the striatum. Behav Brain Res. 2002; 137:65–74. [PubMed: 12445716]

Huttenlocher PR. Synaptic density in human frontal cortex - developmental changes and effects of aging. Brain Res. 1979; 163:195–205. [PubMed: 427544]

Huttenlocher PR, de Courten C. The development of synapses in striate cortex of man. Hum Neurobiol. 1987; 6:1–9. [PubMed: 3583840]

Insausti R, Cebada-Sanchez S, Marcos P. Postnatal development of the human hippocampal formation. Adv Anat Embryol Cell Biol. 2010; 206:1–86. [PubMed: 20329667]

Jackson ME, Moghaddam B. Stimulus-specific plasticity of prefrontal cortex dopamine neurotransmission. J Neurochem. 2004; 88:1327–34. [PubMed: 15009632]

Jensen J, McIntosh AR, Crawley AP, Mikulis DJ, Remington G, Kapur S. Direct activation of the ventral striatum in anticipation of aversive stimuli. Neuron. 2003; 40:1251–7. [PubMed: 14687557]

Jezierski G, Zehle S, Bock J, Braun K, Gruss M. Early stress and chronic methylphenidate cross-sensitize dopaminergic responses in the adolescent medial prefrontal cortex and nucleus accumbens. J Neurochem. 2007; 103:2234–44. [PubMed: 17924950]

Jolles DD, van Buchem MA, Crone EA, Rombouts SA. A Comprehensive Study of Whole-Brain Functional Connectivity in Children and Young Adults. Cereb Cortex. 2010

Juraska JM, Markham JA. The cellular basis for volume changes in the rat cortex during puberty: white and gray matter. Ann N Y Acad Sci. 2004; 1021:431–5. [PubMed: 15251923]

Kalivas PW, Volkow N, Seamans J. Unmanageable motivation in addiction: a pathology in prefrontal-accumbens glutamate transmission. Neuron. 2005; 45:647–50. [PubMed: 15748840]

Kalsbeek A, Voorn P, Buijs RM, Pool CW, Uylings HB. Development of the dopaminergic innervation in the prefrontal cortex of the rat. J Comp Neurol. 1988; 269:58–72. [PubMed: 3361004]

Katz LC, Shatz CJ. Synaptic activity and the construction of cortical circuits. Science. 1996; 274:1133–8. [PubMed: 8895456]

Keshavan MS, Diwadkar VA, DeBellis M, Dick E, Kotwal R, Rosenberg DR, Sweeney JA, Minshew N, Pettegrew JW. Development of the corpus callosum in childhood, adolescence and early adulthood. Life Sci. 2002; 70:1909–22. [PubMed: 12005176]

Killgore WD, Oki M, Yurgelun-Todd DA. Sex-specific developmental changes in amygdala responses to affective faces. Neuroreport. 2001; 12:427–33. [PubMed: 11209962]

Kim JH, Juraska JM. Sex differences in the development of axon number in the splenium of the rat corpus callosum from postnatal day 15 through 60. Dev Brain Res. 1997; 102:77–85. [PubMed: 9298236]

Kline AE, Chen MJ, Tso-Olivas DY, Feeney DM. Methylphenidate treatment following ablation-induced hemiplegia in rat: experience during drug action alters effects on recovery of function. Pharmacol Biochem Behav. 1994; 48:773–9. [PubMed: 7938134]

Knutson B, Fong GW, Bennett SM, Adams CM, Hommer D. A region of mesial prefrontal cortex tracks monetarily rewarding outcomes: characterization with rapid event-related fMRI. Neuroimage. 2003; 18:263–72. [PubMed: 12595181]

Koch MA, Norris DG, Hund-Georgiadis M. An investigation of functional and anatomical connectivity using magnetic resonance imaging. Neuroimage. 2002; 16:241–50. [PubMed: 11969331]

Kuhn CM, Walker QD, Kaplan KA, Li ST. Sex, steroids, and stimulant sensitivity. Ann N Y Acad Sci. 2001; 937:188–201. [PubMed: 11458537]

Kuppermann BD, Kasamatsu T. Enhanced binocular interaction in the visual cortex of normal kittens subjected to intracortical nnorepinephrine perfusion. Brain Research. 1984; 302:91–9. [PubMed: 6733510]

Landis SC, Keefe D. Evidence for neurotransmitter plasticity in vivo: developmental changes in properties of cholinergic sympathetic neurons. Dev Biol. 1983; 98:349–72. [PubMed: 6873459]

Lankford KL, DeMello FG, Klein WL. D1-type dopamine receptors inhibit growth cone motility in cultured retina neurons: evidence that neurotransmitters act as morphogenic growth regulators in the developing central nervous system. Proc Natl Acad Sci U S A. 1988; 85:4567–71. [PubMed: 3380807]

Lauder JM, Krebs H. Serotonin as a differentiation signal in early neurogenesis. Dev Neurosci. 1978; 1:15–30. [PubMed: 158519]

Laviola G, Adriani W, Terranova ML, Gerra G. Psychobiological risk factors for vulnerability to psychostimulants in human adolescents and animal models. Neurosci Biobehav Rev. 1999; 23:993–1010. [PubMed: 10580313]

Laviola G, Macri S, Morley-Fletcher S, Adriani W. Risk-taking behavior in adolescent mice: psychobiological determinants and early epigenetic influence. Neurosci Biobehav Rev. 2003; 27:19–31. [PubMed: 12732220]

Laviolette SR, Lipski WJ, Grace AA. A subpopulation of neurons in the medial prefrontal cortex encodes emotional learning with burst and frequency codes through a dopamine D4 receptor-dependent basolateral amygdala input. J Neurosci. 2005; 25:6066–75. [PubMed: 15987936]

Law AJ, Weickert CS, Webster MJ, Herman MM, Kleinman JE, Harrison PJ. Expression of NMDA receptor NR1, NR2A and NR2B subunit mRNAs during development of the human hippocampal formation. Eur J Neurosci. 2003; 18:1197–205. [PubMed: 12956718]

Lebel C, Walker L, Leemans A, Phillips L, Beaulieu C. Microstructural maturation of the human brain from childhood to adulthood. Neuroimage. 2008; 40:1044–55. [PubMed: 18295509]

Lebrand C, Cases O, Wehrle R, Blakely RD, Edwards RH, Gaspar P. Transient developmental expression of monoamine transporters in the rodent forebrain. J Comp Neurol. 1998; 401:506–24. [PubMed: 9826275]

Leslie CA, Robertson MW, Cutler AJ, Bennett JP Jr. Postnatal development of D1 dopamine receptors in the medial prefrontal cortex, striatum and nucleus accumbens of normal and neonatal 6-

hydroxydopamine treated rats: a quantitative autoradiographic analysis. Brain Res Dev Brain Res. 1991; 62:109–14.

Leung HC, Skudlarski P, Gatenby JC, Peterson BS, Gore JC. An event-related functional MRI study of the stroop color word interference task. Cereb Cortex. 2000; 10:552–60. [PubMed: 10859133]

Leussis MP, Andersen SL. Is adolescence a sensitive period for depression? Behavioral and neuroanatomical findings from a social stress model. Synapse. 2008; 62:22–30. [PubMed: 17957735]

Levitt P. Structural and functional maturation of the developing primate brain. J Pediatr. 2003; 143:S35–45. [PubMed: 14597912]

Lewis DA, Cruz D, Eggan S, Erickson S. Postnatal development of prefrontal inhibitory circuits and the pathophysiology of cognitive dysfunction in schizophrenia. Ann N Y Acad Sci. 2004; 1021:64–76. [PubMed: 15251876]

Lewis DA. Development of the prefrontal cortex during adolescence: insights into vulnerable neural circuits in schizophrenia. Neuropsychopharmacology. 1997; 16:385–98. [PubMed: 9165494]

Li BM, Kubota K. Alpha-2 adrenergic modulation of prefrontal cortical neuronal activity related to a visual discrimination task with GO and NO-GO performances in monkeys. Neurosci Res. 1998; 31:83–95. [PubMed: 9700714]

Lichtman JW, Sanes JR. Ome sweet ome: what can the genome tell us about the connectome? Curr Opin Neurobiol. 2008; 18:346–53. [PubMed: 18801435]

Lidow MS, Goldman-Rakic PS, Rakic P. Synchronized overproduction of neurotransmitter receptors in diverse regions of the primate cerebral cortex. Proc Natl Acad Sci U S A. 1991; 88:10218–21. [PubMed: 1658799]

Logan GD, Cowan WB, Davis KA. On the ability to inhibit simple and choice reaction time responses: a model and a method. J Exp Psychol Hum Percept Perform. 1984; 10:276–91. [PubMed: 6232345]

London ED, Ernst M, Grant S, Bonson K, Weinstein A. Orbitofrontal cortex and human drug abuse: functional imaging. Cereb Cortex. 2000; 10:334–42. [PubMed: 10731228]

Louiset E, Contesse V, Groussin L, Cartier D, Duparc C, Barrande G, Bertherat J, Vaudry H, Lefebvre H. Expression of serotonin7 receptor and coupling of ectopic receptors to protein kinase A and ionic currents in adrenocorticotropin-independent macronodular adrenal hyperplasia causing Cushing's syndrome. J Clin Endocrinol Metab. 2006; 91:4578–86. [PubMed: 16954157]

Luna B, Padmanabhan A, O'Hearn K. What has fMRI told us about the development of cognitive control through adolescence? Brain Cogn. 2010; 72:101–13. [PubMed: 19765880]

Luna B, Sweeney JA. The emergence of collaborative brain function: FMRI studies of the development of response inhibition. Ann N Y Acad Sci. 2004; 1021:296–309. [PubMed: 15251900]

MacLusky NJ, Walters MJ, Clark AS, Toran-Allerand CD. Aromatase in the cerebral cortex, hippocampus, and mid-brain: ontogeny and developmental implications. Mol Cell Neurosci. 1994; 5:691–698. [PubMed: 7704444]

Madsen KS, Baare WF, Vestergaard M, Skimminge A, Ejersbo LR, Ramsoy TZ, Gerlach C, Akeson P, Paulson OB, Jernigan TL. Response inhibition is associated with white matter microstructure in children. Neuropsychologia. 48:854–62. [PubMed: 19909763]

Marco EM, Macri S, Laviola G. Critical age windows for neurodevelopmental psychiatric disorders: evidence from animal models. Neurotox Res. 2011; 19:286–307. [PubMed: 20607469]

Markham JA, Morris JR, Juraska JM. Neuron number decreases in the rat ventral, but not dorsal, medial prefrontal cortex between adolescence and adulthood. Neuroscience. 2007; 144:961–8. [PubMed: 17137726]

Marsh R, Zhu H, Wang Z, Skudlarski P, Peterson BS. A developmental fMRI study of self-regulatory control in Tourette's syndrome. Am J Psychiatry. 2007; 164:955–66. [PubMed: 17541057]

Mazer C, Muneyyirci J, Taheny K, Raio N, Borella A, Whitaker-Azmitia P. Serotonin depletion during synaptogenesis leads to decreased synaptic density and learning deficits in the adult rat: a possible model of neurodevelopmental disorders with cognitive deficits. Brain Res. 1997; 760:68–73. [PubMed: 9237519]

McCutcheon JE, Marinelli M. Age matters. Eur J Neurosci. 2009; 29:997–1014. [PubMed: 19291226]

McDonald AJ, Pearson JC. Coexistence of GABA and peptide immunoreactivity in non-pyramidal neurons of the basolateral amygdala. Neurosci Lett. 1989; 100:53–8. [PubMed: 2569703]

Milad MR, Quirk GJ. Neurons in medial prefrontal cortex signal memory for fear extinction. Nature. 2002; 420:70–4. [PubMed: 12422216]

Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annu Rev Neurosci. 2001; 24:167–202. [PubMed: 11283309]

Mink JW. The basal ganglia: focused selection and inhibition of competing motor programs. Prog Neurobiol. 1996; 50:381–425. [PubMed: 9004351]

Moll GH, Mehnert C, Wicker M, Bock N, Rothenberger A, Ruther E, Huether G. Age-associated changes in the densities of presynaptic monoamine transporters in different regions of the rat brain from early juvenile life to late adulthood. Brain Res Dev Brain Res. 2000; 119:251–7.

Morris RW, Fung SJ, Rothmond DA, Richards B, Ward S, Noble PL, Woodward RA, Weickert CS, Winslow JT. The effect of gonadectomy on prepulse inhibition and fear-potentiated startle in adolescent rhesus macaques. Psychoneuroendocrinology. 2010; 35:896–905. [PubMed: 20042297]

Nuñez JL, Juraska JM. The size of the splenium of the rat corpus callosum: influence of hormones, sex ratio, and neonatal cryoanesthesia. Dev Psychobiol. 1998; 1998; 33:295–303. [PubMed: 9846233]

Nuñez JL, Sodhi J, Juraska JM. Ovarian hormones after postnatal day 20 reduce neuron number in the rat primary visual cortex. J Neurobiol. 2002; 52:312–21. [PubMed: 12210098]

O'Donnell P. Adolescent Maturation of Cortical Dopamine. Neurotox Res. 2010

Panksepp J. The ontogeny of play in rats. Dev Psychobiol. 1981; 14:327–332. [PubMed: 7250521]

Paus T. Growth of white matter in the adolescent brain: myelin or axon? Brain Cogn. 2010; 72:26–35. [PubMed: 19595493]

Paus T. Mapping brain maturation and cognitive development during adolescence. Trends Cogn Sci. 2005; 9:60–8. [PubMed: 15668098]

Paus T, Keshavan M, Giedd JN. Why do many psychiatric disorders emerge during adolescence? Nat Rev Neurosci. 2008; 9:947–57. [PubMed: 19002191]

Paus T, Tomaiuolo F, Otaky N, MacDonald D, Petrides M, Atlas J, Morris R, Evans AC. Human cingulate and paracingulate sulci: pattern, variability, asymmetry, and probabilistic map. Cereb Cortex. 1996; 6:207–14. [PubMed: 8670651]

Paus T, Toro R. Could Sex Differences in White Matter be Explained by g ratio? Front Neuroanat. 2009; 3:14. [PubMed: 19753325]

Paus T, Zijdenbos A, Worsley K, Collins DL, Blumenthal J, Giedd JN, Rapoport JL, Evans AC. Structural maturation of neural pathways in children and adolescents: in vivo study. Science. 1999; 283:1908–11. [PubMed: 10082463]

Peper JS, Brouwer RM, Schnack HG, van Baal GC, van Leeuwen M, van den Berg SM, Delemarre-Van de Waal HA, Boomsma DI, Kahn RS, Hulshoff Pol HE. Sex steroids and brain structure in pubertal boys and girls. Psychoneuroendocrinology. 2009; 34:332–42. [PubMed: 18980810]

Perlman WR, Webster MJ, Herman MM, Kleinman JE, Weickert CS. Age-related differences in glucocorticoid receptor mRNA levels in the human brain. Neurobiol Aging. 2007; 28:447–58. [PubMed: 16540204]

Perrin JS, Herve PY, Leonard G, Perron M, Pike GB, Pitiot A, Richer L, Veillette S, Pausova Z, Paus T. Growth of white matter in the adolescent brain: role of testosterone and androgen receptor. J Neurosci. 2008; 28:9519–24. [PubMed: 18799683]

Perrin JS, Leonard G, Perron M, Pike GB, Pitiot A, Richer L, Veillette S, Pausova Z, Paus T. Sex differences in the growth of white matter during adolescence. Neuroimage. 2009; 45:1055–66. [PubMed: 19349224]

Pezze MA, Bast T, Feldon J. Significance of dopamine transmission in the rat medial prefrontal cortex for conditioned fear. Cereb Cortex. 2003; 13:371–80. [PubMed: 12631566]

Price JL. Prefrontal cortical networks related to visceral function and mood. Ann N Y Acad Sci. 1999; 877:383–96. [PubMed: 10415660]

Pryce CR. Postnatal ontogeny of expression of the corticosteroid receptor genes in mammalian brains: inter-species and intra-species differences. Brain Res Rev. 2008; 57:596–605. [PubMed: 17916381]

Purves D, Lichtman JW. Elimination of synapses in the developing nervous system. Science. 1980; 210:153–7. [PubMed: 7414326]

Putnam FW. Ten-year research update review: child sexual abuse. J Am Acad Child Adolesc Psychiatry. 2003; 42:269–78. [PubMed: 12595779]

Qiu D, Tan LH, Zhou K, Khong PL. Diffusion tensor imaging of normal white matter maturation from late childhood to young adulthood: voxel-wise evaluation of mean diffusivity, fractional anisotropy, radial and axial diffusivities, and correlation with reading development. Neuroimage. 2008; 41:223–32. [PubMed: 18395471]

Rakic P, Bourgeois JP, Eckenhoff MF, Zecevic N, Goldman-Rakic PS. Concurrent overproduction of synapses in diverse regions of the primate cerebral cortex. Science. 1986; 232:232–5. [PubMed: 3952506]

Rapoport JL, Giedd JN, Blumenthal J, Hamburger S, Jeffries N, Fernandez T, Nicolson R, Bedwell J, Lenane M, Zijdenbos A, Paus T, Evans A. Progressive cortical change during adolescence in childhood-onset schizophrenia. A longitudinal magnetic resonance imaging study. Arch Gen Psychiatry. 1999; 56:649–54. [PubMed: 10401513]

Rebec GV, Sun W. Neuronal substrates of relapse to cocaine-seeking behavior: role of prefrontal cortex. J Exp Anal Behav. 2005; 84:653–66. [PubMed: 16596984]

Reid SN, Juraska JM. Sex differences in the gross size of the rat neocortex. J Comp Neurol. 1992; 321:442–7. [PubMed: 1506479]

Rios O, Villalobos J. Postnatal development of the afferent projections from the dorsomedial thalamic nucleus to the frontal cortex in mice. Brain Res Dev Brain Res. 2004; 150:47–50.

Robbins TW. Shifting and stopping: fronto-striatal substrates, neurochemical modulation and clinical implications. Philos Trans R Soc Lond B Biol Sci. 2007; 362:917–32. [PubMed: 17412678]

Rosenberg DR, Lewis DA. Postnatal maturation of the dopaminergic innervation of monkey prefrontal and motor cortices: a tyrosine hydroxylase immunohistochemical analysis. J Comp Neurol. 1995; 358:383–400. [PubMed: 7560293]

Rosenkranz JA, Moore H, Grace AA. The prefrontal cortex regulates lateral amygdala neuronal plasticity and responses to previously conditioned stimuli. J Neurosci. 2003; 23:11054–64. [PubMed: 14657162]

Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SC, Simmons A, Andrew C, Bullmore ET. Functional frontalisation with age: mapping neurodevelopmental trajectories with fMRI. Neurosci Biobehav Rev. 2000; 24:13–9. [PubMed: 10654655]

Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SC, Simmons A, Bullmore ET. Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. Am J Psychiatry. 1999; 156:891–6. [PubMed: 10360128]

Salimi K, Glantz LA, Hamer RM, German TT, Gilmore JH, Jarskog LF. Regulation of complexin 1 and complexin 2 in the developing human prefrontal cortex. Synapse. 2008; 62:273–82. [PubMed: 18240322]

Schmithorst VJ, Holland SK, Dardzinski BJ. Developmental differences in white matter architecture between boys and girls. Hum Brain Mapp. 2008; 29:696–710. [PubMed: 17598163]

Schmithorst VJ, Wilke M, Dardzinski BJ, Holland SK. Cognitive functions correlate with white matter architecture in a normal pediatric population: a diffusion tensor MRI study. Hum Brain Mapp. 2005; 26:139–47. [PubMed: 15858815]

Schoenbaum G. Affect, action, and ambiguity and the amygdala-orbitofrontal circuit. Focus on “combined unilateral lesions of the amygdala and orbital prefrontal cortex impair affective processing in rhesus monkeys”. J Neurophysiol. 2004; 91:1938–9. [PubMed: 15069091]

Schultz W. Predictive reward signal of dopamine neurons. J Neurophysiol. 1998; 80:1–27. [PubMed: 9658025]

Schulz KP, Fan J, Tang CY, Newcorn JH, Buchsbaum MS, Cheung AM, Halperin JM. Response inhibition in adolescents diagnosed with attention deficit hyperactivity disorder during childhood: an event-related FMRI study. Am J Psychiatry. 2004; 161:1650–7. [PubMed: 15337656]

Schwandt ML, Barr CS, Suomi SJ, Higley JD. Age-dependent variation in behavior following acute ethanol administration in male and female adolescent rhesus macaques (Macaca mulatta). Alcohol Clin Exp Res. 2007; 31:228–237. [PubMed: 17250614]

See RE, Fuchs RA, Ledford CC, McLaughlin J. Drug addiction, relapse, and the amygdala. Ann N Y Acad Sci. 2003; 985:294–307. [PubMed: 12724166]

Seeman P, Bzowej NH, Guan HC, Bergeron C, Becker LE, Reynolds GP, Bird ED, Riederer P, Jellinger K, Watanabe S, et al. Human brain dopamine receptors in children and aging adults. Synapse. 1987; 1:399–404. [PubMed: 3505371]

Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, Clasen L, Evans A, Giedd J, Rapoport JL. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc Natl Acad Sci U S A. 2007; 104:19649–54. [PubMed: 18024590]

Shepherd, GM. The synaptic organization of the brain. Oxford University Press, Oxford University Press; 1990.

Sinclair D, Webster MJ, Wong J, Weickert CS. Dynamic molecular and anatomical changes in the glucocorticoid receptor in human cortical development. Mol Psychiatry.

Sisk CL, Foster DL. The neural basis of puberty and adolescence. Nat Neurosci. 2004; 7:1040–1047. [PubMed: 15452575]

Slotkin TA, Seidler FJ, Ryde IT, Yanai J. Developmental neurotoxic effects of chlorpyrifos on acetylcholine and serotonin pathways in an avian model. Neurotoxicol Teratol. 2008; 30:433–9. [PubMed: 18436430]

Somel M, Franz H, Yan Z, Lorenc A, Guo S, Giger T, Kelso J, Nickel B, Dannemann M, Bahn S, Webster MJ, Weickert CS, Lachmann M, Paabo S, Khaitovich P. Transcriptional neoteny in the human brain. Proc Natl Acad Sci U S A. 2009; 106:5743–8. [PubMed: 19307592]

Somerville LH, Casey BJ. Developmental neurobiology of cognitive control and motivational systems. Curr Opin Neurobiol. 2010; 20:236–41. [PubMed: 20167473]

Sowell ER, Thompson PM, Rex D, Kornsand D, Tessner KD, Jernigan TL, Toga AW. Mapping sulcal pattern asymmetry and local cortical surface gray matter distribution in vivo: maturation in perisylvian cortices. Cereb Cortex. 2002; 12:17–26. [PubMed: 11734529]

Sowell ER, Thompson PM, Tessner KD, Toga AW. Mapping continued brain growth and gray matter density reduction in dorsal frontal cortex: Inverse relationships during postadolescent brain maturation. J Neurosci. 2001; 21:8819–29. [PubMed: 11698594]

Sowell ER, Thompson PM, Toga AW. Mapping changes in the human cortex throughout the span of life. Neuroscientist. 2004; 10:372–92. [PubMed: 15271264]

Spear L. The adolescent brain and age-related behavioral manifestations. Neuroscience and Biobehavioral Reviews. 2000; 24:417–463.

Steinberg L. A behavioral scientist looks at the science of adolescent brain development. Brain Cogn. 2010; 72:160–4. [PubMed: 19963311]

Steinberg L. A dual systems model of adolescent risk-taking. Dev Psychobiol. 2010; 52:216–24. [PubMed: 20213754]

Stevens MC, Pearlson GD, Calhoun VD. Changes in the interaction of resting-state neural networks from adolescence to adulthood. Hum Brain Mapp. 2009; 30:2356–66. [PubMed: 19172655]

Stinear CM, Coxon JP, Byblow WD. Primary motor cortex and movement prevention: where Stop meets Go. Neurosci Biobehav Rev. 2009; 33:662–73. [PubMed: 18789963]

Supekar K, Musen M, Menon V. Development of large-scale functional brain networks in children. PLoS Biol. 2009; 7:e1000157. [PubMed: 19621066]

Supekar K, Uddin LQ, Prater K, Amin H, Greicius MD, Menon V. Development of functional and structural connectivity within the default mode network in young children. Neuroimage. 2010; 52:290–301. [PubMed: 20385244]

Swann N, Tandon N, Canolty R, Ellmore TM, McEvoy LK, Dreyer S, DiSano M, Aron AR. Intracranial EEG reveals a time- and frequency-specific role for the right inferior frontal gyrus and primary motor cortex in stopping initiated responses. J Neurosci. 2009; 29:12675–85. [PubMed: 19812342]

Tarazi FI, Baldessarini RJ. Comparative postnatal development of dopamine D(1), D(2) and D(4) receptors in rat forebrain. Int J Dev Neurosci. 2000; 18:29–37. [PubMed: 10708903]

Tau GZ, Peterson BS. Normal development of brain circuits. Neuropsychopharmacology. 35:147–68. [PubMed: 19794405]

Teicher MH, Andersen SL, Hostetter JC Jr. Evidence for dopamine receptor pruning between adolescence and adulthood in striatum but not nucleus accumbens. Brain Res Dev Brain Res. 1995; 89:167–72.

Teicher MH, Dumont NL, Ito Y, Vaituzis C, Giedd JN, Andersen SL. Childhood neglect is associated with reduced corpus callosum area. Biol Psychiatry. 2004; 56:80–5. [PubMed: 15231439]

Thomason ME, Race E, Burrows B, Whitfield-Gabrieli S, Glover GH, Gabrieli JD. Development of spatial and verbal working memory capacity in the human brain. J Cogn Neurosci. 2009; 21:316–32. [PubMed: 18510448]

Todd RD. Neural development is regulated by classical neurotransmitters: dopamine D2 receptor stimulation enhances neurite outgrowth. Biol Psychiatry. 1992; 31:794–807. [PubMed: 1643194]

Toran-Allerand CD. The estrogen/neurotrophin connection during neural development: is co-localization of estrogen receptors with the neurotrophins and their receptors biologically relevant? Dev Neurosci. 1996; 18:36–48. [PubMed: 8840085]

Tseng KY, Amin F, Lewis BL, O'Donnell P. Altered prefrontal cortical metabolic response to mesocortical activation in adult animals with a neonatal ventral hippocampal lesion. Biol Psychiatry. 2006; 60:585–90. [PubMed: 16780812]

Tseng KY, O'Donnell P. Dopamine modulation of prefrontal cortical interneurons changes during adolescence. Cereb Cortex. 2007; 17:1235–40. [PubMed: 16818475]

Ventura R, Morrone C, Puglisi-Allegra S. Prefrontal/accumbal catecholamine system determines motivational salience attribution to both reward- and aversion-related stimuli. Proc Natl Acad Sci U S A. 2007; 104:5181–6. [PubMed: 17360372]

Vernadakis A. Neuronal--glial interactions during development and aging. Fed Proc. 1975; 34:89–95. [PubMed: 162799]

Verney C, Grzanna R, Farkas E. Distribution of dopamine-beta-hydroxylase-like immunoreactive fibers in the rat cerebellar cortex during ontogeny. Dev Neurosci. 1982; 5:369–74. [PubMed: 6754334]

Vincent SL, Pabreza L, Benes FM. Postnatal maturation of GABA-immunoreactive neurons of rat medial prefrontal cortex. J Comp Neurol. 1995; 355:81–92. [PubMed: 7636016]

Viveros M-P, Marco EM, Lopex-Gallardo M, Garcia-Segura LM, Wagner EJ. Framework for sex differences in adolescent neurobiology: a focus on cannabinoids. Neurosci Bio Rev. 2010 in press.

Vizuete ML, Venero JL, Traiffort E, Vargas C, Machado A, Cano J. Expression of 5-HT7 receptor mRNA in rat brain during postnatal development. Neurosci Lett. 1997; 227:53–6. [PubMed: 9178857]

Volkow ND. What do we know about drug addiction? Am J Psychiatry. 2005; 162:1401–2. [PubMed: 16055760]

Voorn P, Vanderschuren LJ, Groenewegen HJ, Robbins TW, Pennartz CM. Putting a spin on the dorsal-ventral divide of the striatum. Trends Neurosci. 2004; 27:468–74. [PubMed: 15271494]

Wang DD, Kriegstein AR. Blocking Early GABA Depolarization with Bumetanide Results in Permanent Alterations in Cortical Circuits and Sensorimotor Gating Deficits. Cereb Cortex. 2011

Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry. 1987; 44:660–9. [PubMed: 3606332]

Whitaker-Azmitia PM, Azmitia EC. Autoregulation of fetal serotonergic neuronal development: role of high affinity serotonin receptors. Neurosci Lett. 1986; 67:307–12. [PubMed: 3461314]

Wong DF, Wagner HN Jr, Dannals RF, Links JM, Frost JJ, Ravert HT, Wilson AA, Rosenbaum AE, Gjedde A, Douglass KH, et al. Effects of age on dopamine and serotonin receptors measured by positron tomography in the living human brain. Science 21. 1984; 226(4681):1393–6.

Woo TU, Pucak ML, Kye CH, Matus CV, Lewis DA. Peripubertal refinement of the intrinsic and associational circuitry in monkey prefrontal cortex. Neuroscience. 1997; 80:1149–58. [PubMed: 9284067]

Yates MA, Juraska JM. Pubertal ovarian hormone exposure reduces the number of myelinated axons in the splenium of the rat corpus callosum. Exp Neurol. 2008; 209:284–7. [PubMed: 17963756]

Yin X, Crawford TO, Griffin JW, Tu P, Lee VM, Li C, Roder J, Trapp BD. Myelin-associated glycoprotein is a myelin signal that modulates the caliber of myelinated axons. J Neurosci. 1998; 18:1953–62. [PubMed: 9482781]

Zavitsanou K, Wang H, Dalton VS, Nguyen V. Cannabinoid administration increases 5HT1A receptor binding and mRNA expression in the hippocampus of adult but not adolescent rats. Neuroscience. 2010; 169:315–24. [PubMed: 20438810]

Zecevic N, Bourgeois JP, Rakic P. Changes in synaptic density in motor cortex of rhesus monkey during fetal and postnatal life. Brain Res Dev Brain Res. 1989; 50:11–32.

Zehr JL, Todd BJ, Schulz KM, McCarthy MM, Sisk CL. Dendritic pruning of the medial amygdala during pubertal development of the male Syrian hamster. J Neurobiol. 2006; 66:578–90. [PubMed: 16555234]

Zhang LI, Poo MM. Electrical activity and development of neural circuits. Nat Neurosci. 2001; 4(Suppl):1207–14. [PubMed: 11687831]

Zhou FC, Sari Y, Zhang JK. Expression of serotonin transporter protein in developing rat brain. Brain Res Dev Brain Res. 2000; 119:33–45.

Zink CF, Pagnoni G, Martin-Skurski ME, Chappelow JC, Berns GS. Human striatal responses to monetary reward depend on saliency. Neuron. 2004; 42:509–17. [PubMed: 15134646]

Zisook S, Rush AJ, Lesser I, Wisniewski SR, Trivedi M, Husain MM, Balasubramani GK, Alpert JE, Fava M. Preadult onset vs. adult onset of major depressive disorder: a replication study. Acta Psychiatr Scand. 2007; 115:196–205. [PubMed: 17302619]

Zuo XN, Kelly C, Adelstein JS, Klein DF, Castellanos FX, Milham MP. Reliable intrinsic connectivity networks: test-retest evaluation using ICA and dual regression approach. Neuroimage. 2010; 49:2163–77. [PubMed: 19896537]

Highlights

- We review adolescence as a heterogeneous developmental stage.
- Neuroanatomical changes are juxtaposed with environmental influences and demands.
- Developmental trajectories interact with sex-dependent changes.
- We discuss the evolution of understanding with increasingly sensitive research tools.

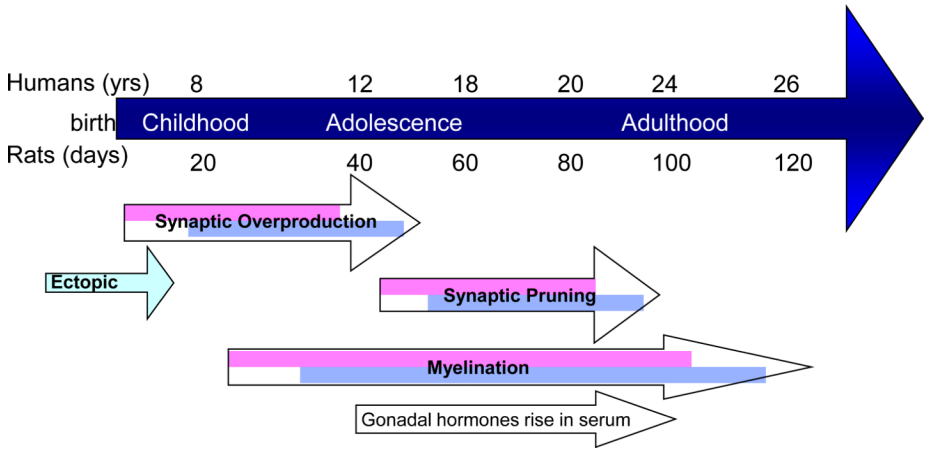

Figure 1.

Timeline of developmental processes across humans and rodents. Pink bars represent the timeline for females, which precedes that of males, represented in blue bars. Transient expression of receptors ("ectopic") occurs early in life and expression is no longer observed later in life. Ectopic expression differs from continued receptor expression within other brain regions.

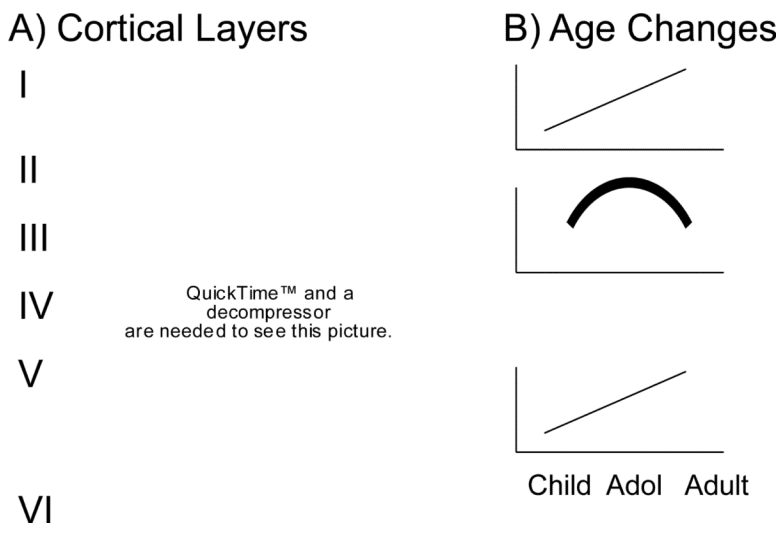

Figure 2.

a) Drawings of cortical lamination in vertical cross-section by Santiago Ramon y Cajal following Nissl (left, middle) in an adult and Golgi staining (right) in a 1½ month old infant. B) patterns of synaptic changes that occur during the transitions between childhood and adulthood in Layers I (the molecular layer), III (the external pyramidal layer; predominantly corticocortical efferents), and V (the internal pyramidal layer V; predominantly subcortical efferents).

Table 1

Paper	Species	NT	Subunit	Region	Measure	Age and Level/Change			Notes
						Young	Adolescent	Adult	
Seeman et al (1987)	human	DA			RB (pmol/g)	3 y	10 y	20 y	
			D1	STR		40	37	20	
			D2	STR		34	14	14	
Teicher et al (1995),	rat	DA			RB (fmol/mg)	25 d	40 d	80d	
			D1	STR		1010	1686	1112	
			D1	NA		500	1250	997	
			D2	STR		480	1150	600	
			D2	NA		375	750	650	
Tarazi (1997, 2006)	rat	DA			RB (fmol/mg)		42 d	60 d	
			D3	STR			15.2	6.4	
			D3	NA			25.9	21.5	
			D3	PFC			NA		
			D4	STR			41.1	19.4	
			D4	NA			32.3	17.3	
			D4	PFC			19.3	3.7	
Duncan et al. (2010) J. Psych Research	human	GABA			qPCR (% change)	0.1y	10y	50y	% change from first timepoint
			a1	dlPFC		100	200	150	
			a2	dlPFC		100	62	57	
			a4	dlPFC		100	125	100	
Hashimoto et al (2009) Biol. Pschiatry	monkey	GABA			ISH (OD)	1–12w	16–46m	93–108m	
			a1	dlPFC		200	275	325	
			a2	dlPFC		250	150	150	
Davis et al. (2000) Dev Br Res	rat	GABA			IHC *	5d	45+d		*Est values expressed as region/surro unding density
						1.5	2.75		
			a1	AMYG		(no data)	lowered (no data)		
			a2	HIP (CA1)		2.5	3		

Paper	Species	NT	Subunit	Region	Measure	Age and Level/Change			Notes
						Young	Adolescent	Adult	
			a2	AMYG		(no data)	lowered (no data)		
Verdurand etal. (2010) Brain Res.		GABA			RB (fmol/mg)		46 d	100 d	
			GABA A	PFC (Cing)			29.3	28.2	
			GABA A	STR			14.7	15.4	
			GABA A	NA			17.6	19.1	
			GABA A	HIP			22.2	22	
			GABA A	AMY			23.4	26.1	
Henson et al. (2008) Cerebral Cortex	human	glu			WB	<1y 1y	15y	21–25y	% of max
			NR3A	dlPFC		1 100		50	
			NR1	dlPFC		50	100	50	
Law et al (2003) Eur. J. Neurosc.	human	glu			ISH (OD)	0–3m	14–18y	20–55y	
			NR2A/NR2B	HIP		1	2	1.5	
						0–12m	14–18y	20–50y	
			NR2A	HIP (DG)		85	108	87–94	
			NR2A	HIP (CA1)		64	61	46–52	
Zavitsanou et al (2010) Neuroscienc e	rat	5HT					35 d	70 d	
			5HT1a	PFC (cing)	RB (fmol/mg)		28.1	32.6	
			5HT1a	CA1			90.5	63.8	
			5HT1a	AMY			25.1	17.7	
Slotkin et al (2008) Brain Res Bull	rat	5HT			RB (fmol/mg)		30d	60–100d	
			5HT1a	PFC			104.5	56–68	
			5HT2	PFC			125	88	
Werling et al (2009) Int. J. Neurosci.	rat	CB			RB(nCi/mg)		37d	67d	
			CB	PFC (Cg3)			18.5	32	
			CB	CA1			5.2	5.3	

IHC: immunohistochemistry

AMY: Amygdala

ISH: in situ hybridization

CA1: Hippocampus

OD: optical density

NA: Nucleus Accumbens

RB: receptor binding

PFC: Prefrontal Cortex

WB: western blotting

STR: Striatum