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Trajectories of brain development: point of vulnerability or window of opportunity?

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Abstract

Brain development is a remarkable process. Progenitor cells are born, differentiate, and migrate to their final locations. Axons and dendrites branch and form important synaptic connections that set the stage for encoding information potentially for the rest of life. In the mammalian brain, synapses and receptors within most regions are overproduced and eliminated by as much as 50% during two phases of life: immediately before birth and during the transitions from childhood, adolescence, to adulthood. This process results in different critical and sensitive periods of brain development. Since Hebb (1949) first postulated that the strengthening of synaptic elements occurs through functional validation, researchers have applied this approach to understanding the sculpting of the immature brain. In this manner, the brain becomes wired to match the needs of the environment. Extensions of this hypothesis posit that exposure to both positive and negative elements before adolescence can imprint on the final adult topography in a manner that differs from exposure to the same elements after adolescence. This review endeavors to provide an overview of key components of mammalian brain development while simultaneously providing a framework for how perturbations during these changes uniquely impinge on the final outcome.
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1. Background and theoretical framework

Nearly 22.1% of the adult population of the United States has a diagnosable mental illness. Differences in diagnostic issues may slightly influence this statistic, but the World Health Organization estimates that mental disorders are on the rise [94]. Depression, for example, is projected to become the second leading disorder by 2020 [94]. Despite the complete mapping of the human genome, the genetic culprits that underlie the most prevalent psychiatric disorders in our society remain elusive. Concordance rates between monozygotic twins fall significantly short of 100% for most disorders, suggesting a strong role for the environment for the etiology or expression. For example, data from twin studies suggests that the heritability index for schizophrenia is 75%, depression 70%, hyperactivity 81%, and personality disorders 42%, although no single gene has been identified [154]. In an age full of great technological advances in genotyping with microarray analyses [156], the importance of the environment on the final phenotypic expression still cannot be minimized [64].

This review endeavors to provide a framework of brain development with an emphasis on the transitions between childhood, adolescence, and adulthood as it relates to psychopathology. Once the framework is established, the influence of intrinsic and extrinsic factors on development will be discussed. Though this window of observation, it is hoped that new insights into the unique aspects of the phenotypic expression of various disorders following environmental challenges will be provided.

1.1. The maturation of psychopathology

The illnesses of attention deficit hyperactivity disorder (ADHD), Tourette's syndrome (TS), schizophrenia, and depression have a very strong tie that binds them together. Symptoms in all of these disorders change markedly across lifespan periods that coincide with hormonal changes [54]. Disorders that begin in childhood, such as ADHD and TS,

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become significantly worse during puberty, but then symptoms wane in the majority of cases [129]. Schizophrenia typically appears post-pubertally, but symptoms, including dystonias, increase during the postpartum and menopausal periods [189]. Depression typically emerges post-pubertally, with an average age of onset of 20 years [17]. The prevalence of substance use disorder (SUD) also follows a similar course. For example, stimulant abuse rises sharply between the ages of 12 and 16, increasing from 2.9 to 16.4%, respectively, [183]. Taken together, these data suggest that puberty is a key maturational period that sets the stage for potentially a lifetime free from or full of psychopathology.

Without debate, development should be full of successful achievements of each and every milestone. Information about brain development, complete with its points of vulnerability or windows of opportunity, provides a starting point to understanding the emergence, course, and severity of psychopathology in general. Given that mental illness is polygenic in nature, multiple approaches are needed to understand its basis. At the very least, knowledge on how genetics, sex, and risk factors interact with normal ontogeny will provide a framework to guide research on the phenotypic expression of neuropsychiatric disorders [139]. At its greatest, this knowledge may offer novel insights into how to make this transition smooth for individuals at risk for psychopathology and may lead to new therapeutic approaches for treatment.

1.2. Sex differences in the psychopathology

One of the most puzzling aspects of psychiatric illnesses is the occurrence of dramatic sex differences in prevalence rates and course without obvious anatomical differences between males and females (although subtle differences are observed). Early childhood disorders, such as ADHD and TS, preferentially affect males over females (ADHD: 2–9-fold more prevalent in males; [16,29]; TS: 3–4-fold more prevalent in males than females; [129]). Differences in the onset of psychotic symptoms in schizophrenia are also subject to sex differences, but in this case, it is the age of onset that is delayed by an average of 4–5 years in females, rather than gender differences in prevalence rate [86,134]. However, a second peak of onset of schizophrenia is observed between 45 and 49 years of age that coincides with menopause [83,86]. Even within the diagnosis of schizophrenia, gender differences in psychotropic treatment response are also apparent whereby women fare better [78,189], but are also more prone to adverse, dystonic side effects, especially with the onset of menopause [37,185]. SUD also affects men more than women. At least in terms of dopamine-related disorders, being female seems to offer some advantage or protection over males in terms of risk or severity of these illnesses. Depression, in contrast, afflicts females to a much greater extent [17].

Numerous hypotheses have been proposed to explain gender differences in symptomatology and prevalence rates for these and other disorders [189]. For example, estrogen is hypothesized to have neuromodulatory and neurotrophic effects that buffer the expression of pathology [83,87]. Alternatively, differences in social pressures [188] and sex differences in stress reactivity [42], which may be part and parcel of the same process, have been proposed. To date, no one unifying theory has emerged, which is not to underscore its importance for understanding the implications for etiology or treatment.

2. Normal brain development

The trajectory of brain development occurs in multiple stages as reviewed below. Schematically, this timeline is found in Fig. 1. Within the timeline, different brain regions have a unique course of ontogeny. Late developing structures, including the cortex, hippocampus and the cerebellum [77,103,107], set the stage for differential periods of vulnerability in a regionally specific manner.

2.1. Prenatal brain development

Neuronal progenitor cells are born, differentiate, and laid down in an inside-out pattern. Larger cells, like pyramidal cells, typically arrive earlier than smaller cells (i.e. granule cells) and adhere to some degree of a phylogeny in which older regions are established first [103]. Proper innervation patterns are guided by radial glia or target-derived neurotrophic factors [174]. Once neurons reach their final destination at about the 16th fetal week, they arborize and branch in an attempt to establish appropriate connections [192]. Axon collaterals connect to numerous regions in the brain before the neuron finishes migrating to its target location [105]. Brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), glia-derived GF (GDNF), CNTF, and IGF-1 [104] influence the migration or retraction of neurons. Concentrations of ephrins guide neurons further by establishing a chemical gradient to follow [116].

Growth factors continue to play an integral role in dendritic branching once neurons reach their target. The expression of growth factors reaches its highest level during the prenatal period as neurons first establish synaptic contacts, and rises again in a regionally specific manner during postnatal development in the rat [106,213]. For example, mRNA for BDNF reaches an adult level in hippocampus by 7 days and remains elevated throughout juvenile development. In contrast, cortical levels peak at approximately 14 days of age and then gradually decline. Growth factors continue to play a role in synaptic plasticity throughout the lifespan, and are integral for neuronal changes associated with learning [80], drug exposure [58, 84], and neuronal repair following injury or transplantation [115]. Whether it is the amount of growth factors that is
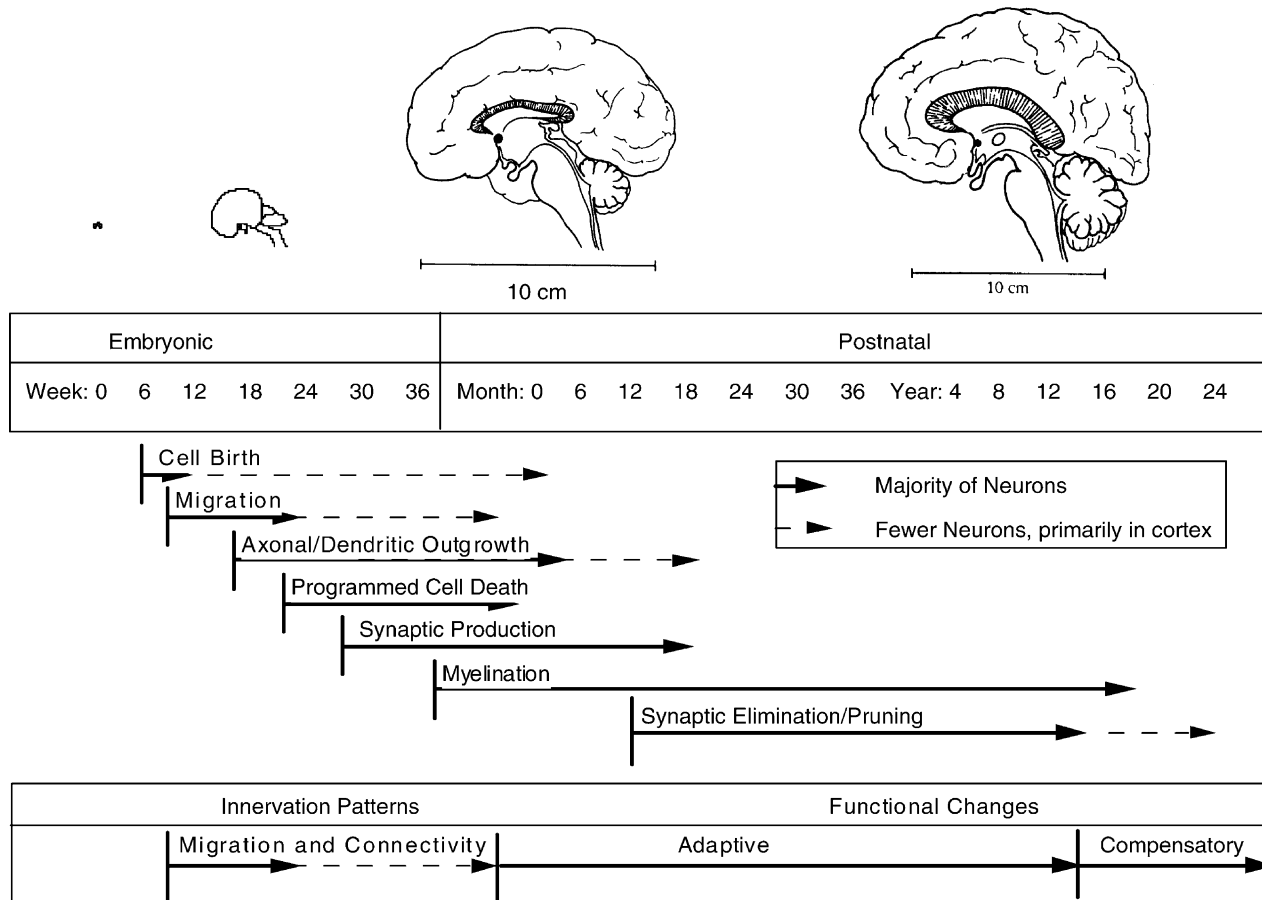
Fig. 1. The stages of brain development (top) and different windows of vulnerability (bottom). Developmental processes occur in phases, setting the stage for potential periods of vulnerability. Insults early in life (bottom) will be assimilated into innervation patterns, whereas a later pre-pubertal insult will cause functional changes that are more adaptive.

expressed or their interaction with other factors, harnessing these important mediators of brain development may offer a novel mechanism to alter trajectories following an insult.

Once the initial phase of innervation has occurred, approximately 50% of all neurons are eliminated during the period immediately before birth, in a process known as programmed cell death or apoptosis [102,124]. During this period, dramatic morphological rearrangements occur with the hypothesized goal to increase efficiency of synaptic transmission [40,100,172]. A second wave of overproduction and elimination occurs later in life during periadolescence.

2.2. Postnatal brain development

Monoamine neurons are detectable by embryonic ages 13–18 days in the rat [161]. At birth, dopaminergic markers, including tyrosine hydroxylase activity, dopamine uptake sites, and dopamine content, are approximately 10% of levels in the adult rat [34,43]. These markers increase monotonically and attain adult levels between 28 and 35 days in the rat. Monoamine oxidase (MAO) increases, and accordingly, turnover ratios (metabolite to transmitter)

decrease with age [110,210]. Firing rates of nigrostriatal neurons increase gradually [167,212]. Dopamine D1 and D2 receptor density increases in a linear fashion during the first 4 weeks of life and reach their adult-like density at this stage [159,163,176].

During the periadolescent period, the second wave of neuronal rearrangements occurs. This wave witnesses a tremendous overshoot of synapses and receptors during periadolescence, followed by their pruning or competitive elimination. (For a comparison of ages and stages of rat versus human developmental periods, see Fig. 2.) This fundamental developmental strategy is common to most regions of the mammalian central nervous system and has been observed in humans [72,98,190], primates [138,175, 179], and rats [13,71,209]. Between 7 and 15 years of age in humans, synaptic density in the frontal cortex decreases by approximately 40% [98,174]. Comparable changes occur in the human receptors for dopamine [190], glutamate [20], and neurotensin [147].

Huttenlocher [98] was the first to demonstrate that the timing of synaptic production and elimination of the postnatal human brain differed across different regions of the cortex. The density of synapses in the primary visual
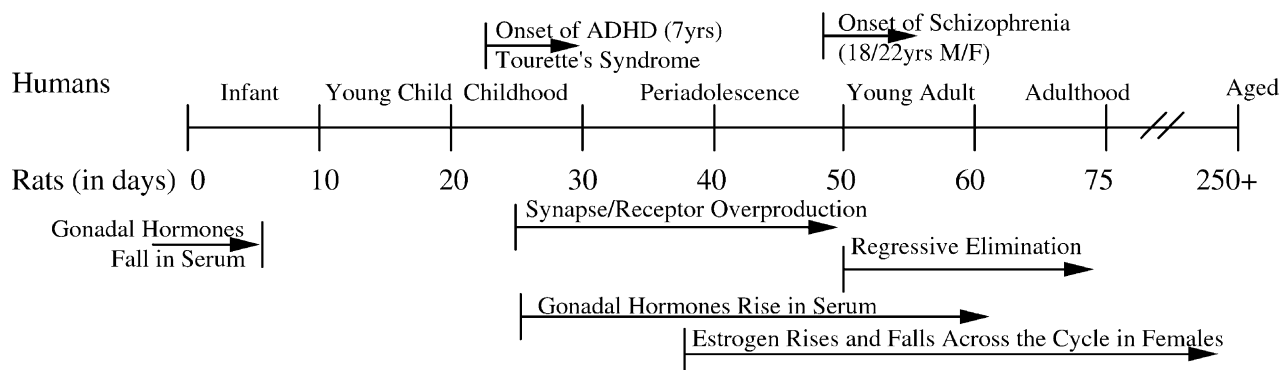
Fig. 2. A relative comparison of ages and stages of human versus rat development [12].

cortex peaks at 6 months of age [99], but peaks at 2 years of age in the prefrontal cortex [98]. Similarly, Lewis and colleagues [16,179] demonstrated differences in the magnitude of change in tyrosine hydroxylase immunoreactivity for different cortical areas; laminar changes exist within regions as well [135]. Comparable results are reported with magnetic resonance imaging (MRI) of gray matter in humans [72,74, 75]. Finally, cortical changes occur later than subcortical changes in overproduction and elimination [15].

These anatomical changes parallel the functional development of each region, with marked differences in time course for cortical and subcortical regions [15,209]. For example, changes in the morphology of dopaminergic neurons occur with a similar time course as the peak of dopamine content in the cortex [77]. Similarly, alterations in synaptic density parallel density changes in receptor density for a number of neurotransmitter systems [138]. Functionally, motor development occurs earlier than cognitive development and parallels the ontogeny of the striatum and cortex, respectively [15,224].

One of the greatest transitions during adolescence, however, is in the development of abstract reasoning and affect and its regulation [19,195]. Here, the clinical knowledge has surpassed our preclinical knowledge, in part because of the difficulties of modeling such complex behaviors in animals. To date, information based on longitudinal fMRI studies have led Casey et al. [38] to hypothesize that the maturation of cognition parallels the synaptic elimination phase. Future longitudinal fMRI studies will yield important information about the development of the amygdala, hippocampus, and cingulate gyrus as it relates to affect. To conclude, the maturation of motor behavior, cognition and affect is integrally related to synaptic remodeling or enhanced connectivity that occurs before adulthood.

3. Intrinsic factors of brain development

A number of functional changes occur during the maturation of the brain that serve as important regulators or stabilizers of programmed development [101].

In addition to the structure–function relationships described above, age-dependent changes in intrinsic factors are integral for determining set points in synaptic activity that further define a developmental trajectory. Four categories exist: (1) neurotransmitters serve as trophic factors that directly guide innervation; (2) neurotransmitters work indirectly by altering the transient expression of certain markers; (3) pharmacological sensitivity varies dramatically across age; and (4) underlying sex differences. Thus, alterations within any of these categories during the titration of a set point of function could modify function later in life in a way that would differ from a similar insult during adulthood.

3.1. Neurotransmitters themselves serve trophic functions in the brain

Changes in neurotransmitter levels produce regional-selective changes indirectly via their trophic actions during development. Appropriate stimulation during a critical period of development is necessary for normal maturation, while inappropriate stimulation during these transitions causes abnormal development [227]. For example, dopamine [70,107,125,203,216] and serotonin [123,126,228] have trophic roles early in development (including neuroblast division, cell migration, and synapse formation). Dopamine increases neuronal branching and outgrowth [216] via the D2 receptor family [202]. Furthermore, activation of D1 dopamine receptors inhibits growth cone motility [125]. These plastic effects are found only during a pre-pubertal window of opportunity [203].

3.2. Transient receptor expression guides innervation

Transient expression of receptors and/or function during early postnatal life is believed to play a guiding/trophic role for innervation. These receptors/functions are expressed for a discrete period developmentally and then become virtually absent from the adult brain [46]. For example, the serotonergic 5-HT7 receptor is transiently expressed in striatum before 15 days and is virtually absent by 21 days and adulthood [221]. Almost in parallel, serotonin

immunoreactive varicosities increase synaptic formation between birth and 14 days of age, fall at 21 days, but subsequently increase to adult levels [53]. In the late-developing cortex [77], serotonin innervation prunes to adult levels after puberty. At this stage it is not clear, however, whether these changes in serotonin serve a guiding/trophic function in brain development, or whether marked neuronal overproduction has its own functional adaptations. Furthermore, transient expression of receptors is not limited to membrane-bound receptors. Nuclear estrogen receptors are detectable in layer V of the rat auditory cortex between 7 and 15 days of age in the rat, and other cortical areas as well [232]. Furthermore, transient neuronal projections exist [90].

Transient pharmacological function also occurs during development. A transient synthesis-modulating autoreceptor in the prefrontal cortex is present pre-pubertally, but absent post-pubertally [8,207,211]. Furthermore, experiments utilizing tetrodotoxin in cortical slices suggest the presence of a stimulatory interneuron that wanes during adolescence [207]. This transient functional activity may be indicative of an underlying trophic role of dopamine into this region, but this is not known with certainty yet. Retention or stabilization of these factors can program a given brain region along a different developmental trajectory; this is discussed further in Sections 4 and 5.

3.3. Age-dependent differences in pharmacological sensitivity to drugs

Pharmacological profiles change dramatically with age, and allow neurotransmitters greater or lesser range to influence their own development. The determination of set points for future regulation and pharmacological sensitivity occurs pre-pubertally and influences the overall tone of the mature neurotransmitter system. For example, dopamine pharmacology changes during the transitions from pre-weaning to puberty to adulthood in the rat [8,11,146].

Pharmacological sensitivity changes with different maturational states for some, but not all, regulatory processes. Surprisingly, the sensitivity of the release modulating autoreceptor that regulates this process does not change appreciably in response to dopamine agonists [9, 10,48,69]. However, maturational differences in dopamine release modulation appear under conditions of elevated activity [10], and in response to dopamine antagonists [11]. The ED50s for the disinhibitory autoreceptor response (i.e. an increase in dopamine release) to either the D2 antagonist sulpiride [11] or haloperidol [36] decline as much as 75 times with maturation [35]. However, under depolarized conditions, dopamine release is actually inhibited at 21 days and adulthood, but not at 5, 10, or 15 days following D2 receptor antagonism [11]. We have hypothesized that this phenomenon is akin to depolarization block as theorized by Grace [81], and may provide an additional protective

mechanism against pathological stimulation in older animals that is not present earlier.

Synthesis regulation also shows an idiosyncratic profile of maturation, with an abrupt loss of function in adolescence. Synthesis autoreceptors have exquisite sensitivity in the striatum, accumbens and the prefrontal cortex as early as 10 days of age [8] that wanes dramatically during the onset of adolescence (at approximately 40 days) and becomes adult-like in the accumbens and striatum [30]. To illustrate this point, estimates of the Inhibitory Dose of 50% of the maximum effect (ID50) are found in Table 1. Cortical synthesis regulation is absent by adulthood [211].

Pharmacological transitions are another distinct characteristic of adolescence relative to other ages. Extracellular levels of dopamine are significantly reduced at this stage of development relative to younger and older ages [9]. Pinnacle levels of locomotor activity during adolescence [200] parallel changes in cyclic AMP levels [4] more closely than changes in dopamine receptor density or levels [13]. Furthermore, blunted behavioral responses to stimulants reported during the adolescent period [128,196] are mirrored in blunted pharmacological response to D1 and D2 agonists at the level of cAMP [4]. One possibility for this blunting of pharmacological responsiveness may be related to increases in gonadal hormones during adolescence. These hormonal changes, in turn, may shift subcortical to cortical dopamine hyperactivity during adolescence and adulthood [4].

Stress responsiveness also dramatically changes during development. Stress-mediated changes within the dopamine system have a wider magnitude of effect during development than adulthood. Before puberty, the beta-carboline FG-7142, an agent that has stress-like effects on dopamine [31,50], increases neuronal activation (indicated by c-fos immunoreactivity changes) in accumbens to a greater extent than the adult-typical response of predominant prefrontal cortex activation [146]; these data are shown in Fig. 3. We have used this finding to possibly explain developmental differences in how children handle stress (an increase in activity) compared with adults (a much more 'cognitive' event). Mechanistically, the stress-effectors also change dramatically early in postnatal life. Fetal rats have high basal blood levels of corticosterone that respond to multiple stressors [186]. Between 2 and 14 days of age,

Table 1

ID50s (mg/kg) for synthesis inhibition in vivo by ±7-OH-DPAT in striatum, nucleus accumbens, and prefrontal cortex of developing rats (from Ref. [8])

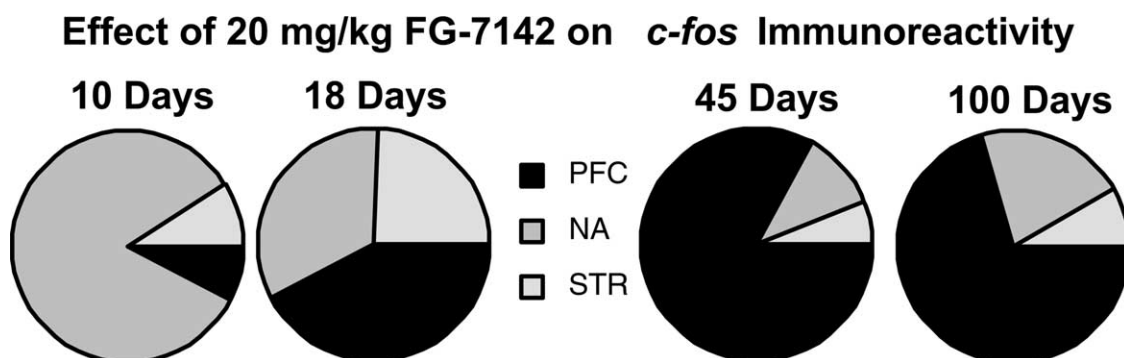| Age (days)	Striatum	Nucleus accumbens	Prefrontal cortex
10	$\ll 0.1$	0.267 ± 0.20	$\ll 0.1$
15	0.488 ± 0.32	1.415 ± 0.46	0.794 ± 0.43
20	0.405 ± 0.14	0.953 ± 0.21	2.969 ± 0.12
40	2.460 ± 0.25	3.533 ± 0.64	–

Effect of 20 mg/kg FG-7142 on *c-fos* Immunoreactivity

Fig. 3. The percentage of c-fos immunopositive neurons that respond to FG-7142 during development in the rat[146]. Immature and mature rats were administered 20 mg/kg FG-7142, a pharmacological stressor, and the number of c-fos immunopositive neurons were quantified in the prefrontal cortex, nucleus accumbens, and the striatum.

corticosterone levels decline and are paralleled by a decrease in responsiveness to some [186], but not all [121, 132,166,168], stressors within the hypothalamic–pituitary adrenal (HPA) axis. This period is known as the stress hypo-responsive period (SHRP). These changes are believed to be vitally important for programming the HPA axis [168], and possibly the dopamine system, to stress-related events in the environment.

Taken together, differences in neuroanatomy and pharmacological sensitivity during maturation set the stage for different periods of vulnerability to insult. The dramatic rearrangements in structure and function that characterize adolescence represent a turning point in how the brain deals with exogenous or pathological stimulation. That is, pre-pubertal influences are incorporated into the maturation of anatomy and function as it determines set points for adult function. Stress, for example, would potentially have a greater impact on the development of sub-cortical rather than cortical structures and set the stage for schizophrenia [224].

3.4. Sex differences in brain development

Aside from regional-dependent changes in synapse/receptor overproduction and elimination, sex-dependent changes are also observed during development. We first reported that D1 and D2 receptors are overproduced and eliminated by as much as 40% in the striatum of male, but not female, rats during adolescence [13]. D1 and D2 receptor density was not different across sexes by adulthood in the striatum, but D1 receptor density in the accumbens was significantly higher in males than females. The observed overproduction of receptors is not controlled by the pubertal surge in gonadal hormones, as neither castration nor oviarectomy influenced their expression [6]. These data point to the importance of early hormonal experience in determining maturational changes in the dopamine system.

Behaviorally, animal studies show that females are significantly more active in open-field experiments than

males [23,199,201,229]. After the periadolescent period, activity levels decline by half in the males, but only a mere 10% in females [199,201]. Running wheel activity is cyclical in females, reaching its pinnacle when estrogen levels are low and its nadir when estrogen levels are elevated [225]. This increased activity in adolescent females is attributed to the postnatal organizing effects of gonadal steroid exposure that are activated around puberty [193,200].

Similar sex differences in overproduction and elimination of gray and white matter in the human brain are reported [72, 75]. Girls reach peak levels of gray matter earlier than males (11.6 versus 12.8 years, respectively), but again, regionally specific changes are noted. Males have an overall 8–9% larger total cerebral and cerebellar volume than females [47, 74]. Volume of the left amygdala increases significantly in males, whereas the right hippocampus increases significantly in females [75]. The relative volume of the putamen and the globus pallidum is larger in males, but the caudate is larger in females. The size of the caudate and the putamen subsequently decrease with age in males only. Many of these sex differences persist into adulthood [79].

Age and sex differences in myelination are also observed, in which the development of white matter is inversely related to gray matter [73]. Myelination of the corpus callosum [170] and other structures [27] continues well into the third decade of life, with males often lagging behind females in this process. This sex differences appears in childhood, where developmentally, the *rate* of myelination within the corpus callosum is greatest during childhood and decreases thereafter [111]. By adulthood, however, males have larger corpus callosum subregions in the genu and anterior body than females [230]. Once formed, myelin does not appear to fine-tune, as it is not pruned at any age that we know.

3.5. Clinical implications of age and sex related changes in brain development

Overproduction and elimination of synapses, receptors, and function is the mechanism by which the brain fine-tunes itself in order to achieve its adult topography.

The overproduction phase is hypothesized to maximize the information-carrying capacity of the immature brain. With the onset of puberty, and thus pruning, synaptic efficacy is streamlined [63,224] in a regionally specific manner. Similarly, pharmacological sensitivity stabilizes after puberty, but pre-pubertal transitions aid in the determination of proper physiological set points that match the demands of the environment. Hormonal changes are hypothesized to aid in the transition of subcortical hyperactivity/cortical hypoactivity during childhood to the reverse during adolescence and young adulthood and could explain the appearance of primarily motoric symptoms during childhood, followed by more psychotic sympomotology in adolescence and adulthood [224]. Thus aberrancies in this mechanism have been proposed to result in schizophrenia [63,93,112], and more recently, TS and ADHD [14,208,209].

Taken together, differences in neuroanatomy, pharmacological sensitivity, and sex during maturation set the stage for unique periods of vulnerability to insult. The dramatic rearrangements in structure and function that characterize adolescence represent a turning point in how the brain deals with exogenous or pathological stimulation. That is, pre-pubertal influences are incorporated into the maturation of anatomy and function as it determines set points of physiological function. Pertubations during this process will subsequently reveal themselves after the initiation of puberty or adrenarche as hormone levels rise [164].

4. Extrinsic factors of brain development

The sculpting of the immature brain is an interactive process between genetic programming, cell function, and the environment. The result of this process is an *endophenotype*, which refers to heritable traits that increase the risk to develop or manifest a given disease [39], and offers a new approach to elucidating the underlying mechanisms of action of common symptoms across disorders [3]. For example, the endophenotypes of ADHD consist of aberrancies in temporal processing or delay gradients [39]. As a result of such categorization, hypotheses about the 'input' (the underlying brain mechanisms that are involved) as well as the 'output' (the behavioral manifestation) permit a broader evaluation of relevant risk factors. At this juncture, we have already discussed normal developmental trajectories (part of the input). The remaining portion of this review will present available evidence for how various known risk factors impact this process to produce a behavioral phenotype (part of the output). Taken together, evidence for how the same etiological risk factors produce different phenotypes will illustrate the importance of points of vulnerability (or windows of opportunity) of brain development.

Key risk factors for the expression or modulation of psychopathology include exposure to drugs, stress, hypoxia/ischemia, viral infection, and gonadal steroids. The action of some of these factors will be discussed as they influence trajectories of brain development via direct or indirect actions on the development of their own systems [227].

4.1. Experience-expectant and experience-dependent development

The terms 'experience-expectancy' and 'experience-dependency' first were presented by Black and Greenough [82]. In this seminal paper, they articulated how the environment can have differential effects on the final adult topography as it relates to the development of the normal trajectory of brain development. Both qualitative and quantitative differences in environmental stimuli can alter brain maturation depending on the timing of the insult, the stage of assessment, and the brain region of interest. Keeping in mind that development is full of abrupt transitions (e.g. the overproduction and elimination of synapses and receptors, functional changes, and transient effects of transmitters and hormones), it is easier to understand how the timing of numerous insults is instrumental for the unique expression of a deficit or injury later in life.

4.1.1. Experience-expectant development

Experience-expectant development incorporates environmental stimuli into the normal pattern of neuronal development. This process involves a *critical period*, when appropriate stimulation is required for normal development [149,171,233]. Developmental critical periods refer to events earlier in life that have a significantly greater impact than the same event later in life [171] rather than an 'all-or-none' process as previously conceptualized. The classic example is the necessity of visual stimulation on the development of ocular dominance columns [97], which has provided a body of information about how synaptic activity sculpts brain morphology by its influence on neuronal survival. Three crucial components for activity-dependent plasticity exist: (1) a critical period for neuroanatomical rearrangements [66,96,97]; (2) 'use it or lose it', in which the remaining inputs expand into enucleated projection sites [76,173,198]; and (3) the necessity of a number of factors, including the n-methyl-D-aspartate (NMDA) receptor system [65], the neurotrophin BDNF [89], GABA [61], class I major histocompatability (I MHC) genes [41], and modulatory neurotransmitter systems, especially serotonin [218]. Disruption of any of these components during key periods demonstrates their involvement in an experience-expectant manner.

4.1.2. Experience-dependent development

Experience-dependent development involves the incorporation of unique information into neuronal patterns. This process involves a *sensitive period*, when stimuli may

impinge on development to produce a characteristic effect specific to the maturational stage of insult. Such stimuli include drugs, stress, toxins, infection, or hypoxia/ischemia. Interference of the immature neuronal milieu during a sensitive period alters future neuronal function and will be discussed in depth in Section 5.

4.2. Imprinting and epigenetic factors

Imprinting describes the long-lasting effects that endure well after the removal of the originating agent [91,130]. On a molecular level, imprinting of epigenetic factors, i.e. those that have a heritable influence on chromosome or gene function without changes in gene structure [136], occurs at various levels of structure and function. Epigenetic factors undoubtedly play a large role in the expression of a number of neuropsychiatric illnesses, given that concordance rates do not reach 100% in monozygotic twin studies. Epigenetic factors can serve as the original impetus for a disorder, as in fetal alcohol syndrome, or play a permissive role in the expression of a disorder [62,217].

Early in life, genomic imprinting is the process by which epigenetic influences alter the expression of an allele [21]. Genomic imprinting occurs during two main stages of development: during the differentiation of germ cells and in post-implantation of the embryo, thus influencing the function of cell types during different periods of development [178]. The process works by either DNA methylation or by histone acetylation or methylation and regulates gene expression by blocking transcription regulatory factors, repressing gene expression, or regulating transcription activity [136]. As a result of genomic imprinting, any one of approximately 50 genes associated with either paternal (androngenetic) or maternal (parthogenetic) transmission can be silenced [21] and influence the development of psychopathology [113]. Genes that are maternally influenced are found in the cortex, striatum, and hippocampus and are involved in increasing brain growth; genes that are paternally influenced are found primarily in the hypothalamus, septum, preoptic area, and the bed nuclei of the stria terminalis and are involved in retarding brain growth [114]. Allele-specific changes in expression can be polymorphic, incomplete, or tissue-specific. As a result, penetrance for these genes can vary.

Later in life, gene and environmental interactions play themselves out more directly than discussed above, and is encompassed in the field of epigenomics [162]. However, it is often the case that phenotypic expression is delayed for psychiatric illnesses [45,148,204]. For example, prominent theories for schizophrenia include a combination of structurally unstable DNA that is vulnerable to either acquired or inherited epigenetic influences [108,165]. Similarly, underlying genetic vulnerability is proposed for drug addiction [160]. The environmental factor of stress can cause the genetic liability of both disorders to come to light,

with earlier stress exposure resulting in a greater likelihood of expression. Therefore, it is often the unique combination of genetic vulnerability and the maturational stage of exposure that differentially determines the enduring impact of similar environmental factors (discussed below in Section 5) on developmental trajectories [177].

5. Extrinsic factors known to influence the vulnerability to insult

This section will highlight supportive data regarding the importance of a number of factors that influence the appearance of any early insult.

5.1. The importance of timing

The enduring impact of an early insult depends on the maturational stage of exposure such that perturbations in the synaptic milieu redirect the normal developmental trajectory. Specifically, the immature organism adapts by *incorporating* environmental information permanently into the mature structure and function (Fig. 1). In contrast, the mature organism *compensates* to accommodate changes in the environment. Despite a burgeoning literature documenting age-dependent changes following exposure to various epigenetic factors (reviewed below), we are now beginning to appreciate the potentially enhanced vulnerability of the pre-pubertal brain to the long-lasting effects of early insult [7]. Alternatively, the time before puberty may represent a window of opportunity to redirect aberrant development back onto a normal trajectory.

The full imprinted effect of early drug exposure transitions through development, with the long-term effects often opposite to those observed following adult drug exposure. These transitions are illustrated in a simple model in Fig. 4. Drugs like neuroleptics [180], marijuana and nicotine [67], alcohol, and stimulants [7] have delayed effects that are not apparent until adolescence or later [118]. The adaptive processes underlying these changes is not necessarily qualitatively different than that proposed in the allostasis model of drug abuse [117]. However, quantitatively, these adaptations are far more reaching and permanent following early exposure compared with later exposure to the same drug.

The expression of monoamine receptors and function are programmable, meaning that it follows the adage use it or lose it, and demonstrates how the timing of extrinsic factors can be expressed in a developmentally dependent manner. For example, prenatal and postnatal D2 receptor antagonism with haloperidol decreases D2 expression, behavioral responsiveness to apomorphine and amphetamine, auto-receptor sensitivity, and adenylate cyclase activity [131, 180,187,197]. These findings are opposite to what is found following adult chronic neuroleptic exposure [181]. Similarly, early manipulations of dopamine levels can reduce D1
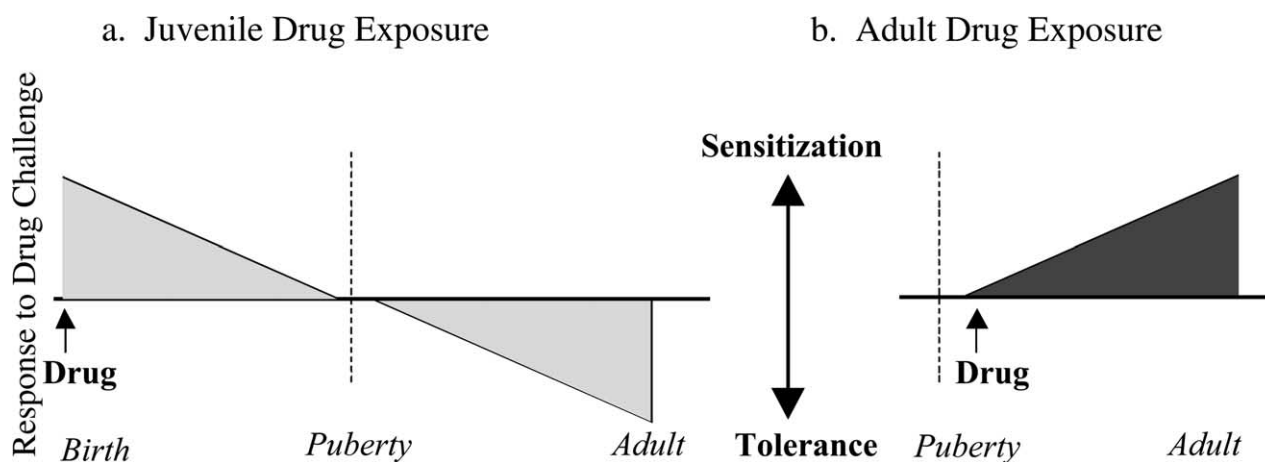
Fig. 4. Diagram of different trajectories of stimulant responsiveness depending on the maturational stage of exposure: (a) pre-pubertal drug exposure (left) may (or may not) produce an initial sensitized response [128] that wanes with time and manifests as decreased sensitivity (tolerance) after puberty (b) post-pubertal drug exposure (right) produces sensitization that increases with time.

and D2 receptor expression [119] in a reversible manner [70]. Again, these developmental findings are completely opposite to the well-known effects of these agents during adulthood, and receptor antagonism leads to receptor up-regulation or supersensitivity [44].

Very little data is available on the developmental effects of chronic administration of agonists (the 'use it too much' phenomenon) during early development. Prenatal exposure to cocaine permanently alters neuronal migration and innervation patterns [133,137] that in turn, may underlie functional changes [194]. Postnatal exposure to cocaine (25 mg/kg; between 1 and 10 days of age) elevates extracellular dopamine levels at 10 and 21 days that return to control values by 35 days [95]. These changes are accompanied by an abnormal distribution of striatal D2 receptor mRNA.

The most dramatic changes following postnatal drug exposure are delayed in their expression and appear after puberty. Chronic administration of the stimulant methyl-phenidate (Ritalin™) before puberty (between 20 and 35 days) or after puberty (between 50 and 65 days) produces different responses to cocaine challenge following a 25-day withdrawal period [7]. Pre-pubertal exposure to methylphe-nidate increases the aversive properties to cocaine and reduces locomotor responsiveness to cocaine. Dow-Edwards and colleagues report similar behavioral results following pre-pubertal exposure to cocaine [55–57]. More-over, methylphenidate-induced behavioral changes were accompanied by an increase in the transcription-regulating factor, cyclic AMP regulating binding protein (CREB), and suggest a long-term genetic modification [7]. In contrast, it is well known that post-pubertal [32] or adult exposure to stimulants increases responsiveness to later challenge [68, 120,127,157,158,206]. Clinically, these results support the observation by Biederman et al. [28] of reduced SUD in adolescents with ADHD that had received pharmacotherapy during childhood relative to untreated adolescents with ADHD. Taken together, these results suggest that dopamine tone set prior to adolescence determines the fate of the synaptic milieu during adulthood—but in this case, these data suggest that a window of opportunity exists for reducing risk later in life.

Serotonin is also vulnerable to environmental insults during development. The most extensive literature that documents postnatal exposure to increased serotonin levels is found in the clomipramine model of depression [222]. By name alone, this model is associated with behavioral changes, including decreased latency for the forced swim test [219], circadian rhythm blunting [223], increased anxiety [5], as well as neurochemical changes [5] that are consistent with clinical symptoms of depression later in life. Taken together, pre-pubertal drug exposure produces behavioral, neurochemical, and molecular alterations that differ from the alterations observed following post-pubertal drug exposure.

5.2. The age of assessment

The expression of imprinted effects of an early insult depends on the stage of maturation that they are assessed [7, 197]. For example, prenatal exposure to haloperidol results in a hyposensitive, no change, or a hypersensitive locomotor response to amphetamine when assessed in weanlings, adolescent, and adult rats, repectively [197]. Stimulants produce an initial sensitization response immediately following exposure [128], but reverse sensitization later in life [7]. Reduced serotonin levels between 10 and 20 days of age in the rat decreases hippocampal innervation at 30 days that reverses by 62 days [150]. Thus, the timing of assessment is vitally important to our understanding of early insult.

The effects of early insults are often delayed after the onset of puberty, suggesting an interactive process between deficit and development [25,26,33,226]. For example, direct

lesions of the hippocampus early in life produce post-pubertal symptoms that are consonant with schizophrenia [141]. Specifically, deficits in pre-pulse inhibition [143], enhanced sensitivity to stress [142], and pharmacological responsiveness [144] are not apparent until after day 56 in this animal model.

5.3. Regional selectivity of insult

The effect of an early insult is an interactive process between location of neurotransmitters and receptors and their functional state for their given stage of maturation. As reviewed above in Sections 2 and 3, age-related fluxes within the target of the insult could dramatically impact the expression of the insult in ways that are not predictable from what we know from adult studies. For example, it is well accepted that the high density of glucocorticoid receptors in the hippocampus and cerebellum is integrally important for enhanced vulnerability to stress in these regions. However, as described in Section 3.3 above, stress has more widespread effects earlier in development (Fig. 3) [146]. As a result, early stress can imprint on the subcortical dopamine systems to a greater extent within this pre-pubertal window than post-pubertal exposure to stress.

5.4. Dose-dependency issues of early insults

Most drugs exert their effects in a dose-dependent manner. At this stage, we know little about long-term exposure to most medications primarily because it is difficult to dissect disease process from medication effects. Preclinical studies suggest a non-linear relationship between drug exposure and enduring effects on structure and function. For example, low concentrations, 5-methoxytryramine ($0.1-100\ \mu M$) inhibits serotonin uptake binding, whereas higher concentrations augment binding [191,228]. In culture, reduced serotonin increases dendritic branching at distal, but not proximal branch points, while augmented serotonin decreases neuronal branching [51].

The effects of stress can be dose-dependent as well. Exposure to stress within a normal physiological range promotes synaptic plasticity, whereas pathological levels lead to impaired development of structure and function [18]. Evidence from the preclinical literature on the effects of early maternal separation as a species-relevant stressor (reviewed in Refs. [49,220]) suggest that glucocorticoids and corticotrophin releasing hormone (CRH) are integrally involved in programming HPA activity for life [140,184].

5.5. The influence of sex as an important variable for the expression of early insult

An important, and often overlooked, facet of environmental influences is the relationship between sex and early insult. Steroid hormones can have two main effects. The first

role occurs early in life and directs the differentiation of the brain. Specifically, cells are born, differentiate, migrate, or die depending on the hormonal environment in a sex-dependent manner [151,215]. This hormonal environment can have dramatic (take the sexual dimorphic nucleus as an example), or subtle (differential isoform expression of $D_{2\ long}$ versus the $D_{2\ short}$ dopamine receptor messenger RNA [85,122]) influences on overall neuronal function. Such sex-dependent differences can, in turn, underlie sex-dependent differences in the expression of an illness or medication effects.

The second role of steroid hormones appears during puberty when gonadal and adrenal hormones increase [92]. Behavioral transitions parallel changes in gonadal and adrenal hormone changes during adrenarche [164,182]. Gonadal hormones influence behavior directly for reproduction [1] or indirectly via their interactions with neurotransmitter systems [22,24,152]. Gonadal hormones modulate neurotransmitter effectiveness via membrane-bound estrogen receptors [152,155,214], which exert their effects non-genomically to alter G protein activity [52,145, 231]. It is at this stage that the functional expression of an earlier insult emerges as hormonal changes influence the pharmacological sensitivity in such a way so as to unmask any deficit. As noted above, the waning or emergence of various psychiatric illnesses parallels these pubertal changes.

In summary, we do not know how early insult interacts with sex and gonadal hormones to produce sex-dependent effects. Yet, we know that sex differences are observed in a number of clinically relevant animal models, including drug exposure [5,57] and hypoxia/ischemia (Boksa, this journal; [60,169,205]. It is possible that early insult alters gonadal hormone expression or function [59,153], or alternatively, hormones alter the nature of the insult [2].

6. Conclusions

The relationship between early insult and resulting psychopathology is still in its infancy. Waves of over-production and elimination of synapses, receptors, and function may serve as a neural guide or stabilization mechanism during adolescence [101]. Thus, the key to understanding the impact of various risk factors on the emergence of psychopathology is the time course of development of the underlying brain structures and function. In this regard, we know very little about how the brain matures from childhood to adolescence. Clearly, the pre-pubertal brain is extremely plastic, but with this enhanced plasticity, comes enhanced vulnerability that is not fully observable until well after the time of insult during adolescence or adulthood. Whether the onset of puberty signifies the closing of a window of opportunity for altering trajectories has yet to be determined. Literature from the effects of early stress exposure [88] and stimulant exposure

[7,55–57] imply that this may indeed be the case, but a more refined time course is needed to make this assertion.

The potential clinical implications for treatment, including long-term exposure to medications or early intervention during abuse, during childhood need to be considered. Clinicians treating young children with psychotropic drugs need to make a difficult decision weighing the potential benefits of treatment versus unknown consequences of exposure of the immature brain to drugs that may exert enduring effects on brain development. While not reviewed comprehensively here, stress also significantly impacts developmental trajectories that are involved in various psychiatric disorders [2], including schizophrenia, depression, drug abuse, and a myriad of other psychiatric disorders [109]. New frontiers in early intervention need to embrace the fact that the immature brain incorporates information into its structure and function differently than the mature brain. Novel treatment strategies should be directed at restoring the disordered trajectory along a normal course, rather than treating symptoms. Based on the review provided here, an increased appreciation of both intrinsic and extrinsic factors during the developmental process and its response to insult should be used to guide future understanding of the nature of illness and insult and its future treatment.

Acknowledgements

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