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The adolescent brain and age-related behavioral manifestations

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Abstract

To successfully negotiate the developmental transition between youth and adulthood, adolescents must maneuver this often stressful period while acquiring skills necessary for independence. Certain behavioral features, including age-related increases in social behavior and risk-taking/novelty-seeking, are common among adolescents of diverse mammalian species and may aid in this process. Reduced positive incentive values from stimuli may lead adolescents to pursue new appetitive reinforcers through drug use and other risk-taking behaviors, with their relative insensitivity to drugs supporting comparatively greater per occasion use. Pubertal increases in gonadal hormones are a hallmark of adolescence, although there is little evidence for a simple association of these hormones with behavioral change during adolescence. Prominent developmental transformations are seen in prefrontal cortex and limbic brain regions of adolescents across a variety of species, alterations that include an apparent shift in the balance between mesocortical and mesolimbic dopamine systems. Developmental changes in these stressor-sensitive regions, which are critical for attributing incentive salience to drugs and other stimuli, likely contribute to the unique characteristics of adolescence.

Keywords: Adolescence; Brain; Behavior; Stress; Hormones; Mesocorticolimbic dopamine; Prefrontal cortex; Risk taking; Social behavior; Puberty; Drug abuse; Alcohol

1. Introduction

The central thesis of this review is that maturational changes in brain contribute to the age-specific behavioral characteristics of adolescence, including an increase in propensity to use drugs. Certain behavioral features common among adolescents of a variety of species may have evolved to promote attainment of the necessary skills for independence; these age-related behaviors, such as an adolescent-associated increase in risk taking, may be promoted less by increases in pubertal hormones than by developmental events occurring in brain during adolescence. These age-related neural alterations provide a partial biological basis for the unique behavioral strategies of adolescence, although they are not deterministic. Rather, these transient neuronal features may predispose adolescents to behave in particular ways, and make them particularly likely to initiate use of alcohol and other drugs relative to individuals at other ages.

1.1. Adolescence versus puberty

The focus of this review is on adolescence rather than the more temporally restricted phase of puberty. Although the timing of these periods overlap, the terms are not synonymous. Puberty refers to the attainment of sexual maturation (i.e. gonadarche) [210]. In contrast, adolescence is the gradual period of transition from childhood to adulthood, and thus is a process or series of "soft events" [422] rather being defined by a discrete event or events. As such, it is difficult to characterize the precise onset and offset of adolescence. Although "one may define puberty in specific neuroendocrinological terms,…adolescence is, of its essence, a period of transitions rather than a moment of attainment" ([468], p. 63). Puberty is but one of these adolescent transitions. In humans, the onset of the biological changes associated with puberty often has been considered to signal the onset of adolescence (e.g. Ref. [409]), although the timing of puberty within the adolescent period varies notably among human adolescents (e.g. Ref. [144]). Indeed, the timing and tempo of puberty may be of considerably psychosocial significance for adolescent humans, with early maturation advantageous in several respects for boys but associated with several negative outcomes for girls (see Ref. [212] for review and references).

1.2. Animal models of adolescence

Developing mammals of many species undergo an

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ontogenetic transition from the dependence of youth to the (relative) independence of adulthood. During this transition, individuals across a variety of species undergo puberty and are faced with similar developmental challenges of acquiring the necessary skills to permit survival away from parental caretakers. As discussed later in this review, human adolescents and many of their counterparts in other species exhibit certain characteristic behaviors, including increases in peer-directed social interactions and elevations in novelty-seeking and risk-taking behaviors. These transient behavioral features may represent ontogenetic adaptations [391] to help adolescents survive in the limbo between childhood and adulthood, while also serving to assist them in acquiring the necessary skills to permit survival away from parental caretakers. Increased affiliation with peers and the taking of risks via exploring novel areas, behaviors and reinforcers may also help facilitate the dispersal of adolescents away from the natal family unit. Such an age-related emigration is common among mammalian species (even humans in pre-industrial societies—see Ref. [518]) and may have been evolutionarily adaptive as a means to avoid inbreeding [484].

Although there are many gaps in our knowledge of ontogenetic changes in brain function during adolescence, the data that are available suggest that prominent neural alterations in brain regions such as prefrontal cortex (PFC) occur during adolescence not only in humans, but across species ranging from rodents to nonhuman primates (see later discussion). Given these across-species similarities in neurobehavioral features of adolescence, the question arises as to whether nonhuman animals undergoing this developmental transition can be used as models of human adolescence.

Some researchers have argued that adolescence is uniquely human and hence cannot be modeled in animals (e.g. Ref. [50]). For instance, Bogin [50] maintains that only humans undergo adolescence based on the conclusion that only human adolescents show a growth spurt [571]. Yet, developmental hyperphagia and accelerated growth rates are evident during adolescence even in adolescent rodents (e.g. Ref. [283]). Indeed, others have concluded that pubertal growth spurts are common across mammalian species, and it is the relatively long period of slowed growth during the preadolescent childhood/early juvenile period that is unique to humans and other primates [587]. Reasoning for the exclusivity of human adolescence based on growth criteria alone can also be challenged by questioning whether the global attribute of adolescence should be affirmed or dismissed solely on the basis of any single characteristic.

There are many different processes unfolding during adolescence, and what one identifies as essential feature(s) of adolescence determine the appropriateness of any given animal model. Traditionally, animal models have been extensively used for the purposes of modeling human psychopathology, with each given animal model typically emulating only a few psychopathological features thought to be central to the target disorder. Certainly no animal model can be similar in all respects to the complexity of human psychopathology or of human behavior during adolescence (or at any time in life, for that matter). Indeed, there are numerous areas of adolescent functioning in humans that seemingly cannot be addressed using animal models, including issues ranging from peer pressure and self esteem, impact of parenting styles on parent/adolescent conflict, obsessions with thinness in adolescent females in some Western cultures, and cultural differences in perception of adolescence as a life stage, to mention but a few.

Thus, as with animal models of psychopathology in humans, to answer the question of the appropriateness of animal models of adolescence, it is necessary to first consider what aspect of human adolescence is to be modeled. For instance, the increases in adrenal androgens/neuroactive steroids seen during adrenarche in humans (see later section of this review) are generally not evident in other mammalian (or even primate) species. Chimpanzees are an exception (e.g. Ref. [111]), and hence may provide a useful model to examine effects of adrenarche on subsequent neurobehavioral and endocrine function during adolescence. As another example, given that much information about neural substrates and hormonal factors modulating drug self-administration has been obtained in rodent studies, work in rodents may provide a cost-effective model to examine neurobehavioral characteristics underlying the rewarding effects of drugs, social stimuli and their environmental modulation during adolescence. Yet, forebrain systems of rodents are substantially less prominent than in humans and other primates, their social organization considerably less complicated, and the time course of their adolescence brief; these and other limitations add constraints to the use of rodent models. The more protracted development of nonhuman primates and their generally more complex social structure relative to other laboratory animals may prove useful for long-term studies of pharmacological and social environmental influences on drug self-administration during adolescence, although more needs to be understood regarding the time course of adolescence in nonhuman primates, particularly among seasonal breeders where the onset of puberty per se is often tightly synchronized with the mating season (e.g. Refs. [95,427]).

The validity of animal models is typically assessed using three evaluation criteria borrowed from the psychological testing literature [361,592] and adapted for assessing the validity of animal models of human psychopathology (e.g. Ref. [595]). Face validity asks whether there are similarities between the model and what is being modeled in terms of etiology, symptomology, treatment, or physiological bases. Predictive validity examines whether the model successfully forecasts future findings (typically regarding efficacy of drug treatments). Construct validity addresses whether the model is homologous to the clinical syndrome being modeled in terms of physiological determinants, precipitating psychosocial environment and other factors theorized to

influence its occurrence [595]. As discussed later in this review, there are similarities between human adolescents and various animal models of adolescence in terms of developmental history, behavioral symptomology as well as neural and hormonal characteristics. These resemblances provide some measure of face and construct validity that are sufficiently promising to support further development of these animal models as tools for the study of adolescence. Assessment of validity is an ongoing process; as more data is generated, stronger tests of these forms of validity as well as that of predictive validity will be possible. Ultimately the validity of animal models is determined by their usefulness in expanding understanding of the phenomena under investigation, propagating further testable hypotheses, and generating data to refine the model and further assess its validity.

1.3. What is the age span of adolescence?

Adolescence eludes precise characterization of its ontogenetic time course, with no single event signalling its onset or termination. There are numerous physiological and sociobehavioral transitions that occur during the age span between childhood to adulthood, with the timing of these transitions varying with nutritional status [181,284] as well as sociocultural values and economic conditions in humans [155]. For the purposes of this review, adolescence in humans will be considered to be the age range from roughly 12 to 18 years, ages commonly considered to be within the adolescent age span in humans. There is less consensus as one approaches the "gray zones" at the margins of this age range. The entire second decade is not infrequently considered adolescence (e.g. Ref. [412]), and even ages up to 25 years have been considered as late adolescence by some researchers [35]. Conclusions reached regarding the boundaries of adolescence may vary depending not only on the adolescent transition of focus, but also gender, with females across mammalian species generally maturing more rapidly than males (e.g. Ref. [483]).

When assessing the time frame of adolescence in nonhuman animals such as the rat, it likewise is difficult to characterize absolute boundaries during which the first transition of adolescence begins to emerge and the last remnant still persists. Even among the handful of researchers who study adolescence in rats, opinions somewhat differ. Not only may the boundaries vary with gender, the transition under examination, and the growth rate of animals derived from different suppliers, but the problem is further magnified by the limited amount of research that has focused on adolescence in laboratory animals. Although much research in nonhuman animals has been directed toward the neuroendocrinology of puberty and potential triggers of these changes, relatively little animal research has been intentionally directed toward examination of biosociobehavioral function during the broader age range of adolescence. For instance, in developmental work with rats, researchers have often tested animals up until the conventional age of weaning and again in adulthood, drawing a straight line between these points. Adolescence in nonhuman primates is even less explored territory [407,408].

Rather than engaging in a questionable and premature attempt to define the absolute margins of adolescence, the strategy used in this review will be to characterize prototypic adolescence in rats using a conservative age range during which animals of both genders and most breeding stock would be expected to exhibit adolescent-typical neurobehavioral characteristics. This age range from approximately postnatal days 28–42 (P28–42) was originally derived by considering the age range during which age-specific behavioral discontinuities from younger and older animals were evident (e.g. Ref. [510]), but is also supported by measures as diverse as the timing of the growth spurt (peak at 4–5 weeks of age—e.g. Ref. [283]; Silveri and Spear, unpublished observations), the loss of excitatory amino acid overshoot to PFC (developmental peak in *N*-methyl-D-aspartate [NMDA] receptor binding at P28 at levels that are substantially higher than at P60 [253]), and the timing of emergence of rats from the protected nest burrow in the wild (beginning at P28— Ref. [186]). During this interval, vaginal opening occurs in females [137] and marked increases are seen in the number of maturing spermatids in the seminiferous tubules in males [93].

Use of this conservative age range is not meant to imply, however, that animals in the gray zone slightly younger or older than this prototypic age range might not also be undergoing some adolescent transition(s). Indeed, some ontogenetic changes signalling the early onset of adolescence in female rats may begin to emerge as early as 20 days, with later changes lasting until 55 days or so in males [387,390]. The latter is important to recognize, given that 250–275 g male rats are sometimes used in work presumed to examine neurobehavioral function in adults, although males in this weight range may fall within the gray zone between adolescence and adulthood. Under some experimental circumstances, inclusion of a broader age range of adolescence (e.g. from shortly after weaning until 60 days or so) may be prudent if the intent is to expose animals to a particular treatment throughout the entire ontogenetic window from the emergence of early harbingers of puberty in females through the disappearance of the last of these changes in males. With additional research examining adolescence in rodent models, new findings regarding the timing of particular developmental transitions within the adolescent period may help to further characterize the limiting boundaries of this stage of life.

If anything, the timing of adolescence in nonhuman primates is even less established, with some primate researchers even avoiding use of the term. Those that do typically consider adolescence to be the time between puberty and mature reproductive function [405,406] or the time from first external signs of impending sexual maturity to the cessation of linear growth [582]. Dentation and hormone levels have also been used to accurately determine

adolescent stage, although these measures require more invasive assessments than are typically available in naturalistic settings [300].

More commonly employed than the term "adolescence" in studies with nonhuman primates is the term "juvenile" that has been varyingly used to refer to the age span from weaning until puberty [404], until sexual maturity (typically defined by successfully carrying offspring to term) [105] or until physical growth rate begins to slow [259]. Researchers using puberty as a stage discriminator typically also include a "sub-adult" period consisting of postpubertal but prereproductive individuals (e.g. Ref. [150]). The distinction between puberty and sexual maturity is important here; following menarche, female primates typically undergo a period of "adolescent sterility" before beginning to ovulate regularly (e.g. Refs. [46,459]). High teen pregnancy rates not withstanding, human females also typically show depressed fertility during early adolescence [257], with as much as 5 years being required after menses begin for mature rates of ovulatory frequency to be reached [601]. As is the case with their female counterparts, nonhuman primate males typically do not father young at puberty, but first must attain a certain status via emigration and/or attainment of high rank among conspecifics (see Ref. [408] for discussion).

Researchers do not always agree on the timing of the juvenile and adolescent stages among specific primate species (e.g. compare the timing of adolescence in rhesus monkeys presented by Ehardt and Bernstein [150], with that of Paule [399]), perhaps in part because of variations in the indices used to reflect maturational state, and sensitivity of maturational rate to environmental quality. The latter includes variables such as nutrition, social context, stress, energy drains and other factors that may vary among primate populations [601], particularly those studied in captivity versus in the wild [259,366]. The rather long time span characterizing the juvenile period as typically defined in primate research corresponds in humans to roughly the interval from 2 years of age until 13–25 years—i.e. childhood and much or all of adolescence [601]. Thus, what appears to be comparable to the adolescent period in humans encompasses latter portions of the juvenile period in primates (classified as "older juveniles" by some) as well as part of the subadult period when included as a separate stage. These time periods will be referred to as "adolescence" for the purposes of this review, whether or not so-referred in the material cited.

2. Adolescent behavioral changes

For successful negotiation of the developmental transition from childhood to adulthood, developing organisms must attain the necessary skills for independence. Behavioral characteristics of adolescents that bear similarity across diverse species may have adaptive value [483] and may represent ontogenetic adaptations to meet the needs of this age-specific niche [391] as well as the means by which necessary adult skills are acquired. An adolescent-associated increase in risk taking is seen in a variety of species and may provide the opportunity to explore new behaviors, situations, and reinforcers. Increases in the value attributed to social interactions with individuals outside the natal family unit likewise may serve to promote independence.

2.1. Social behavior

Social interactions and affiliation with peers take on particular importance during human adolescence. During an average week during the academic year, adolescents have been reported to spend close to one-third of normal waking hours talking with peers, but only 8% of this time talking with adults [108]. Peers provide a significant source of positive experiences for adolescents, with adolescents reporting that they are most happy when talking with peers [108]. Social interactions with peers may help develop social skills away from the home environment during adolescence (for an extreme view, see Ref. [228]), with these outside-the-home relationships helping to ease the transition toward independence from the family. Such interactions may also in some cases facilitate antisocial behavior, with peer conformity to antisocial behaviors (including cheating, stealing, trespassing and minor property destruction) peaking in early- to mid-adolescence [41].

Along with this shift in social orientation from adults to peers, adolescence is also frequently characterized by an increase in the perceived number of conflicts between the adolescent and his/her parents [518]. Interestingly, similar elevations in conflict during the pubertal period are evident in monogamous family groups of nonhuman primates as well [518].

Indeed, like human adolescents, adolescents of other species also show alterations in social behavior. For instance, adolescent rodents spend more time in social interactions [437] and exhibit peak levels of play behavior (e.g. Ref. [169]). Not only the quantity but the quality of these social interactions changes during adolescence, perhaps in part to inhibit aggression by adult males with whom the adolescents come in contact (see Ref. [186] for discussion). For example, although by P20, weanling rat pups exhibit the adult-typical repertoire of defensive strategies, these strategies are temporarily replaced by more juvenile tactics of play fighting during adolescence (P30–40) [402] that then diminish as sexual maturity is reached [401]. Social interactions in adolescent rodents help guide their food choices [185] and seemingly also allow for the practice of behaviors in mock form that will later form part of the adult behavioral repertoire (e.g. sexual and aggressive behaviors) [163,504].

Primate adolescence is likewise associated with age-related alterations in social behavior. Yet, in contrast to rodents, primates play most during the late infancy and early juvenile periods, with play behavior declining

progressively thereafter through adolescence and into adulthood [162]. As conspecific-directed play behavior declines, the form of social behavior among adolescent-age primates switches to higher levels of affiliative behavior (huddling, grooming, pair-sitting) [150] and increased association with same-sexed adults (see Ref. [166] for review). Such changing strategies of social behavior may be critical for adolescent survival as the tolerance generally shown by adults toward young is replaced by more competitive behaviors directed towards the adolescent [130,406]. Indeed, adolescent primates not only receive, but also engage in substantial amounts of aggressive behavior, with aggressive behavior peaking during adolescence in a number of primate species [406]. Although the risks associated with aggressing against bigger adults may be high, in some cases such aggression may be necessary for the adolescent to avoid reproductive suppression and/or eviction [405]. Aggression is not incompatible with social bonding [130], and indeed adolescent primates often engage in affiliative, reconciliatory, and other social behaviors that may serve to appease adults and encourage acceptance [101]. During adolescence in some species of primates, animals seem to further their future prospects by developing alliances with adults that could later help them rise in social rank [165,581]. Even when emigrating from their natal group, adolescent primates sometimes emigrate with peers with whom they have formed alliances [408] and typically must establish new "affiliative, cooperative relationships with strangers" to effectively terminate their emigration via entering or forming a new troop [105].

In addition to showing alterations in peer- and adult-directed social interactions, adolescents (particularly female adolescents) of a variety of species focus increasing attention on infants. During adolescence, females' interest in infants ("allomaternal behavior") increases substantially in humans (e.g. Ref. [183]), nonhuman primates [386,586] and even rodents [348,383]. This behavior is sexually dimorphic, with males generally across a variety of species showing lower levels of interest in infants than females [383,586].

2.2. Risk taking

> "By definition, a transition period such as adolescence is disequilibrating and disrupting and thus replete with opportunities that are both dangerous and growth enhancing" ([35], p. 98).

Adolescents are risk takers. Relative to individuals at other ages, human adolescents as a group exhibit a disproportionate amount of reckless behavior, sensation seeking and risk taking (e.g. Ref. [560]) (note: these terms are not completely synonymous [24], although their distinctions are not critical for the purpose of discussion here). In one report of $11\frac{1}{2}$–15 year-olds, 80% exhibited one or more problem behaviors during the previous month; these behaviors included disobeying parents, school misconduct, substance use and antisocial behaviors (including theft or fighting) [342]. Indeed, with half or more of adolescents exhibiting drunk driving, sex without contraception, use of illegal drugs, and minor criminal activities, "reckless behavior becomes virtually a normative characteristic of adolescent development" ([24], p. 344). Similarly, Moffitt [369] concludes from a review of antisocial behavior in adolescence that it is statistically aberrant to refrain from such behavior during adolescence, with "actual rates of illegal behavior soar(ing) so high during adolescence that participation in delinquency appears to be a normal part of teen life" (p. 675).

Unfortunately, risk taking by definition carries with it some potential for negative outcome. Along with increases in adolescent risk taking is a sizeable increase in mortality rate from early to late adolescence [255,256], with homicides, suicides and accidents collectively accounting for more than 85% of all adolescent deaths [254]. Other potential negative outcomes from adolescent risk taking include incarceration, AIDS infection, unwanted pregnancy, and alcohol or drug dependence. Risk taking escalates in some instances into a deviant lifestyle characterized by continued involvement in criminal activities and problem behaviors in adulthood [318]. Fortunately, however, adolescent experimentation in risk taking is transient for most individuals, with the vast majority of adolescents surviving the lottery for negative outcome they enter by engaging in risk taking.

Albeit hazardous, risk taking during adolescence may have some benefits. Risk taking may allow the adolescent to explore adult behavior and privileges [495], to accomplish normal developmental tasks [377], and to develop and express mastery of hierarchal challenges associated with certain risky behaviors [107]. Risk taking has sometimes [495] but not always [351] been linked to gains in self-esteem, perhaps via reinforcement provided for such behavior among peers engaged in similar activities [271]. Risk takers report that they feel more accepted by peers, and view risk taking as reinforcing ("fun") [342]. Interestingly, adolescents experimenting with drug use were found to be more socially competent both in childhood as well as in adolescence than either frequent users or abstainers [493], data that prompted Shedler and Block [493] to suggest that occasional drug use during adolescence may be a manifestation of "developmentally appropriate experimentation." Abstainers were characterized as anxious, overcontrolled, emotionally constricted, and lacking in social skills, while frequent users were characterized as alienated, distressed and deficient in impulse control [493]. Thus, some degree of adolescent risk taking is normative, and perhaps adaptive—assuming that the adolescent moderates the amount of these activities and is fortunate in avoiding potential long-lasting negative consequences.

There is some question as to whether adolescents specialize in particular forms of deviant behavior, or whether the nature of the social situation and environment

influence whether antisocial behavior is exhibited, and the form that behavior may take (for review, see Refs. [24,369]). Analogous to Spearman's "g", a single factor proposed to underlie variation in IQ, Rowe and Rodgers [471] postulated a "d" factor to reflect a single trait that can be expressed by a diversity of deviant behaviors ranging from vandalism to illicit drug use. Donovan and colleagues likewise conclude that there is a syndrome of problem behavior in adolescence consisting of a constellation of high-risk behaviors and an associated decrease in health maintaining behaviors [139,140]. Others suggest that deviant/risk-taking behaviors may not be best represented as a single factor, but as a variety of behaviors with unique characteristics [16,556]. For instance, Anderson and colleagues [16] drew a distinction between reactive and active risk taking, with the latter representing a means of developmental experimentation that may lead to positive adaptations, successes and resourcefulness.

Individuals engaging in risk taking may do so to attain the positive arousal produced by the sensations of novelty, complexity, change or intensity of experience [611]. Indeed, the most frequent reason given for the initiation of drug use is to satisfy curiosity or to experience something new or different [611]. Perceived risks of risk taking decline with age during adolescence [255], so it is possible that the level of risk taking necessary to attain an "adrenaline rush" of danger may rise as well, perhaps leading to an escalation of risk-taking behaviors in certain individuals, particularly those with poor prospects for attaining other reinforcers [599]. Yet, for some adolescents risk taking may not reflect so much the seeking of positive outcomes from novel or intense stimuli, but rather as a means of reducing dysphoria or coping with stress [256,352].

Indeed, there appear to be multiple distal and proximal determinants of risk taking and other problem behaviors in adolescence that range widely from individual disposition, social influences and environmental stressors [261] to perceived maturational rate [460]. Gardner [191] used decision making theory to explore risk taking in adolescence, basing his calculations on merely two underlying assumptions: (a) income increases with age, and (b) individuals have "positive time preferences" (i.e. that they attribute less value to a good when its receipt is delayed). From his analysis, he concluded that risk taking during adolescence represents "an optimal life-span pattern for a rational decision maker who must gain knowledge of self and environment through experience" ([191], p. 79).

Risk-taking behavior during adolescence may have potential evolutionary antecedents. And indeed, adolescents of other species also seem to seek out novel and potentially risky aspects of their environment. Adolescent mice are hyperactive in a novel environment [114], and exhibit higher levels of novelty seeking than their adult counterparts [4]. Rats in the age range from around P28–42 are often hyperactive and exhibit greater exploration in novel situations than other aged rats (e.g. Ref. [513]). They also frequently appear hyper-reactive to stimuli, displaying substantially greater startle response amplitude than adults (S. Brasser, personal communication). These specific age-related increases in exploration and novelty-seeking, together with the adolescent-associated elevations in social interactions (discussed earlier) may help adolescent rodents successfully negotiate the developmental transition from dependence to independence. It is during adolescence that young rats in the wild first emerge from the burrow and confront the unknowns and challenges of the outside world (see Ref. [186] for review). Although they begin to wean from their dam and eat solid food around 18 days of age, developing rats in the wild do not leave the protective surrounds of the burrow until around the start of adolescence at 28 days of age. By the time they are 34 days old, these adolescents are successful in exploring some distance from the nest site, acquiring food outside the burrow, and interacting with rats other than their own mother and siblings [186]. Thus, reminiscent of the behavior of human adolescents, the age-related modifications in behavior of adolescents from this quite different species also are consistent with the need of the adolescent to explore novel and often risky domains and establish new social relationships during the process of achieving independence.

Adolescence in nonhuman primates is also an inherently risky business. As the tolerance for young shown by adults is gradually replaced by competition (e.g. Ref. [130]), primate adolescents may be compelled to emigrate from their natal group [105] or "forced to fit into an ecological niche determined by conspecific adults when (they have) neither the size nor the experience to do so easily" ([259], p. 57). Emigration is common among primates, with males or females or both (depending on the species) emigrating from their natal groups, typically during adolescence [406]. Sometimes animals are evicted from their natal troop, while in other instances the emigration seems voluntary and "begs explanation" given that it is associated with considerable risk [105,568] and even in some cases with apparently lower than average reproductive success [105]. Emigration is associated with a dramatic increase in mortality rate; life-threatening risks of emigration include not only predation and intraspecific aggression, but also malnourishment as the emigrant moves into unfamiliar territory [105,449]. To be successful, emigrants must cautiously but boldly explore novel areas. This movement may be enhanced by age-specific alterations in activity levels, with activity peaking in at least some primate species during adolescence (see Ref. [300]), as in their rodent counterparts. New potential food sources must be located as well; it has been estimated that emigrating howler monkey adolescents find less than 40% of the plant species in common with those of their natal habitat ([104]; cited by Crockett and Pope [105]). Indeed, juvenile primates are often considerably more likely to explore new food sources than adults ([70]; see also discussion of candy eating by 2–3 year-old Japanese macaques in article by Kawamura [275]), although in some species the

tendency to explore novel foods may be even greater in infants than in juveniles (e.g. Ref. [580]). While emigrating, adolescents are unlikely to survive if fearful of novelty, or if such brazen risk takers that they relax vigilance of their surroundings.

Evolutionarily, adolescent-associated increases in novelty seeking and risk taking may have facilitated adolescent emigration from the natal group by providing the impetus to explore novel and broader areas away from the home. Inbreeding would thereby be avoided via dispersal of male (and sometimes female) offspring to new territories away from the natal family unit as sexual maturation is reached [484]. Such increases in risk taking may also provide the opportunity to explore new behaviors and reinforcers, perhaps facilitating the relinquishing of juvenile patterns of behavior as well as the acquisition of behaviors essential for adult functioning. Expression of risk-taking behaviors in maturing males may also increase the probability of reproductive success in a competitive reproductive environment (see Ref. [598] for discussion of the ethology of adolescent risk taking). Thus, behaviors associated with risk taking "may be—or at least once were—means of securing physical resources, attracting mates, and denying mating opportunities to competitors" ([519], p.117).

2.3. Cognitive development

Physical growth is generally related to growth in mental abilities (e.g. Ref. [292]), with increases in most cognitive abilities occurring during adolescence in humans and other animals (e.g. Refs. [211,320]). Although detailed discussion of this topic is beyond the scope of this presentation and is available in other reviews (e.g. Refs. [211,276]), several pertinent points will be briefly mentioned here.

A primary focus in studies assessing the impact of adolescent development on cognitive ability in humans has been to compare early maturers with their more delayed counterparts on particular cognitive tests during adolescence. A reliable finding from these studies is that early maturers score slightly higher on intelligence (IQ) tests than their later maturing counterparts, a small IQ advantage that seems to persist into adulthood [381]. Interestingly, this effect is also present before puberty [380], and hence may not reflect an adolescent-specific maturational effect, but rather an effect related more to the overall "tempo" of growth (see Ref. [543] for discussion), with a particular pacing of growth seen throughout development that generally characterizes each individual (although there are some exceptions—Ref. [323]).

Early adolescence in humans is associated with a major transformation of cognitive thought leading to abstract reasoning (see Ref. [211] for review). This cognitive acquisition is not absolute. The developmental emergence of formal reasoning emerges earlier when addressing problems associated with the physical world than with interpersonal issues, and even in adulthood some individuals do not consistently function at the formal reasoning stage [277]. Given the only small differences in decision making capacity between individuals from mid-adolescence onward, the question arises as to why the decision making efforts of adolescents result in substantially more risk-taking behavior than is characteristic of adults. Although there are a number of potential reasons why this may be the case (see Ref. [44] for discussion), one little explored possibility is that the decision making capacity of adolescents may be more vulnerable to disruption by the stresses and strains of everyday living than that of adults. That is, unlike adults, adolescents may exhibit considerably poorer cognitive performance under circumstances involving everyday stress and time-limited situations than under optimal test conditions [276].

Indeed, there is some, albeit limited evidence that adolescent rats may perform more poorly than other aged animals in stressful and complex conditioning tasks. For example, adolescent rats often exhibit impaired performance relative to other aged animals on complex avoidance tasks (such as discriminated escape and Sidman avoidance tasks), perhaps as a function of increased distractibility and difficulties in focusing attention on salient cues and reward contingencies under the stressful conditions of training and testing (see Ref. [510] for review and references). Yet, on less cognitively challenging tasks, performance of adolescent rats may occasionally be enhanced relative to other aged animals, particularly in situations where their tendencies to show increases in activity and exploration might result in improved performance—such as in the radial arm maze [77] and in active avoidance testing [34].

At least in studies in laboratory animals, performance of adolescents also may be influenced by their unusual responses to reward contingencies. Adolescent rats exhibit less persistence during extinction of appetitive operant responding on an intermittent reward schedule (the so-called "partial reinforcement extinction effect") (e.g. Ref. [56]), but more persistence during extinction of a one-way active avoidance task [378]. They also seem to be slower to acquire a discrimination task for food reward, and to drop and ignore food when reaching the goal box in a simple runway task (see Ref. [510] for discussion), despite evidence that animals of this age are generally hyperphagic and eat more than their younger or older counterparts ([379]; see below). The significance of these potentially telling, but piecemeal observations remains to be determined; likewise, it has yet to be firmly established whether human adolescents also exhibit age-related alterations in the way they respond to reinforcers and their absence (see further discussion in Section 6.7).

2.4. Restorative behaviors: eating and sleeping

Associated with an adolescent spurt of growth is a notably enhanced rate of consummatory behavior. Adolescent rats consume the greatest caloric intake relative to their body

weight of any time in the life span [379]. Adolescent humans likewise exhibit elevated metabolic activity and (aside from recent cultural trends for dieting in female adolescents) show developmental hyperphagia as well [189,432]. In species where developing animals choose or are forced to leave natal territories during adolescence, adolescence may not be associated with a notable elevation in body weight gain, although these newly independent individuals spend large amounts of their time foraging for food. For instance, newly independent juncos who are evicted from their family territory spend more than 90% of their time foraging for food and eating to maintain a positive energy balance, while mature, non-nesting adult juncos spend only about 30% of their time foraging and eating food [524]. In primates as well, juveniles and adolescents typically spend more time feeding [300] and foraging for food to meet their needs than adults, in part because of potentially lower foraging success [259] as well as the substantial caloric demands of the adolescent-associated growth spurt [46].

Potential physiological mechanisms that might support an adolescent-associated focus on consummatory behavior have not been explored, but may potentially be related to adolescent-related alterations in forebrain dopaminergic systems (see later section). Given the similarities in the neural substrates presumed to modulate the reward value of drugs of abuse with those underlying other motivational stimuli such as food and water (e.g. Ref. [267]), it is an intriguing possibility that the physiological mechanisms contributing to the increase in consumption of these natural reinforcers during adolescence might also extend to intake of drug reinforcers as well during this ontogenetic transition.

Adolescents not only eat more, but they sleep less. In addition to a decrease in the total amount of time spent sleeping [321] and in the amount of time spent in slow wave sleep [112], human adolescents also demonstrate a phase delay—i.e. a preference for waking and going to bed later than their younger counterparts [75]. This phase delay may not be entirely psychosocially based. The magnitude of the phase delays is not associated with whether or not the adolescents are in school with younger or older peers or have older siblings present at home [75]. This adolescent phase delay has been suggested to have been of adaptive significance during evolution [113] and indeed is apparent in other species. For instance, adolescent (P40) rats stay awake longer before falling asleep than younger (P23 and P29) animals following the transition from the dark to light phase—that is, when going from the period of predominant waking to that of predominant sleep in these nocturnal animals [9]. Thus, adolescent humans may not be unique among their counterparts in other species in their predisposition to stay up late.

3. Adolescent drug use

High levels of novelty/sensation-seeking are powerful predictors of drug and alcohol use [17,35,597]. Hence, it perhaps should not be surprising that along with increases in sensation and novelty seeking during adolescence [24,342,369], an increase in drug use is seen as well.

3.1. Prevalence of alcohol and other drug use during adolescence

Like sensation and novelty seeking behaviors, some exploratory drug use is normative during adolescence (e.g. Ref. [493]). According to the National Institute of Drug Abuse 1996 Monitoring the Future Study, by the time that adolescents reach their senior year in high school, approximately 50% have used marijuana/hashish, 65% have smoked cigarettes, and 82% have tried alcohol. This drug use begins relatively early in adolescence, with 26% of 8th graders, 40% of 10th graders and 51% of high school seniors reporting use of alcohol in the past month; comparable percentages for prior month use of illicit drugs were 15, 23 and 25%, respectively. Some of this use is excessive. For example, 10% of 8th graders, 21% of 10th graders, and 31% of 12th graders in the 1996 Monitoring the Future survey reported getting drunk on one or more occasions during the past month. Clearly, many adolescents at least explore use of alcohol, cigarettes and illicit drugs. And, although drug experimentation differs from drug misuse and should not be so construed [106], evidence of excessive drug use does emerge in some adolescents.

Indeed, adolescents are not immune to the development of dependence on alcohol, cigarettes and other drugs. Adolescents who use substantial amounts of alcohol may exhibit a variety of alcohol dependence symptoms, including evidence of ethanol tolerance, escalating patterns of use, and difficulty in cutting down or quitting [431]. Once adolescents become addicted to alcohol, their rates of relapse approximate those of alcoholic adults, despite the much shorter chronicity of the adolescent alcohol abusers [64]. Lifetime prevalence rate of alcohol abuse/dependence was reported to be about 1 in 3 among older adolescents from a working class community sample; about 1/10 were diagnosed with abuse/dependence of other drugs (overwhelmingly marijuana) [457]. Via studying cigarette use patterns over years in the Monitoring the Future data, Bachman and colleagues [27] concluded that these use patterns provide evidence for nicotine addiction even in early- to mid-adolescence, with physical addiction playing a strong role in the very high stability in cigarette use over time [27]. Within a year of beginning to smoke cigarettes, most adolescent smokers report trying to quit, but adverse effects from abstinence; 97% of these adolescent smokers are still smoking 2 years later, with most reporting that they are dependent [356].

Not only may adolescents become dependent on drugs and alcohol, but there is also some limited evidence to suggest that their rate of progression to alcohol/drug dependence may be unusually rapid. Escalation of cocaine use

appears more rapid among adolescent than adult users, suggesting a greater addictive potential of cocaine during adolescence than in adulthood [159]. Compared with individuals initiating drug use in adulthood, adolescent-onset individuals had "accelerated dependency courses, with shorter times from first exposure to dependence for alcohol and cannabis and shorter times between their first and second dependencies" ([92], p. 120).

Adolescents using drugs are typically polydrug users and this may contribute to observed adverse effects. Adolescent withdrawal is greater than predicted for the length of use of a single drug, and indeed most adolescents met criteria of dependence on more than one drug [521]. Approximately 85% of the adolescents entering alcohol and drug treatment also smoke cigarettes [64], with heavy use of alcohol and cigarettes exacerbating withdrawal symptoms from other drugs by adolescents [521].

Indeed, alcohol and cigarettes have often been considered "gateway" drugs, with most individuals progressing through the use of these drugs before initiating use of marijuana and other illicit drugs. This sequence of use, however, should not be construed to reflect a causal association between the use of these drugs and later use of illicit drugs, and may reflect a variety of other factors such as age-associated differences in drug accessibility or sensitivity (e.g. see Ref. [363]).

Before exploring age differences in sensitivity to drugs, animal models of drug self-administration during adolescence will be considered, albeit briefly as scant data are available. Preliminary evidence supports the suggestion that adolescent rats may display 2–3 times higher levels of ethanol intake relative to their body weights than do more mature animals ([307]; Bannoura and colleagues, unpublished observations), reminiscent of findings that heavy alcohol use in humans is likewise often "adolescence-limited" (e.g. Ref. [33]). Yet, ethanol preference per se in rats does not peak until well into adulthood (around 5 months of age: [206,396]). The notably different ontogenetic conclusions reached when using g/kg intake versus proportion of overall fluid consumption to index ethanol consumption may reflect the developmental hyperphagia of adolescence [379], with elevated consummatory behaviors of adolescence contributing to high levels of ethanol intake by these growing individuals relative to their body weight. Self-administration of other drugs during adolescence in laboratory animals has yet to be explored.

3.2. Ontogeny of drug sensitivity

3.2.1. Studies in nonhuman animals

Adolescents of a variety of species differ in their psychopharmacological sensitivity to various drugs relative to their adult and sometimes younger counterparts. Considering first studies in laboratory animals, adolescent rats and mice are less sensitive than younger animals or adults to the psychomotor stimulants such as amphetamine and cocaine when indexed in terms of acute locomotor stimulation and stereotypy [51,308,312,313,355,507,511]. This reduced sensitivity to amphetamine during adolescence does not appear to be simply related to an age-related alteration in drug levels in brain [510], and is also evident when examining amphetamine-induced conditioned taste aversions [252]. In contrast to the ontogenetic dissociation seen to these indirect dopamine (DA) agonists, only a progressively declining pattern of locomotor activation was reported during ontogeny following administration of the direct DA receptor agonist quinpirole, with less apomorphine-induced activation seen in adult rats than in adolescents, and in adolescents than in weanlings [176]. Like their rodent counterparts, adolescent rhesus monkeys also have been reported to be considerably less sensitive than adults to stimulants such as amphetamine and cocaine, although in this case sensitivity is even lower in younger juveniles than in adolescents [400]. Interestingly, although the attenuated responsivity to cocaine in adolescent rats is evident both following acute administration (e.g. Ref. [511]) and when expressing previously sensitized responses to cocaine induced by chronic exposure prior to adolescence [507], adolescent animals are capable of developing sensitization to the locomotor (but not stereotypy) effects of cocaine following chronic drug exposure during adolescence [4,313].

In contrast to the attenuated behavioral responsiveness to acute administration of stimulants often evident during adolescence, adolescent rats conversely are more sensitive to the cataleptic-inducing behavioral effects [72,513] and neurochemical consequences [551] of the DA antagonist haloperidol than younger animals or adults. This adolescent accentuation in responsiveness is not restricted to the neuroleptic haloperidol in that it is also evident with the structurally and pharmacologically dissimilar neuroleptic perphenazine [72]. Accentuations in neuroleptic sensitivity during adolescence were also apparent when both neuroleptics were directly administered in the brain, suggesting that this age-related change reflects developmental differences in brain responsiveness to the drugs [72].

Ontogenetic differences in psychopharmacological sensitivity during adolescence are not only evident when examining drugs interacting with the DA system. Adolescent rats are also more sensitive to the locomotor stimulant effects of morphine than are adults, although morphine-induced stereotypy does not vary across these ages [512]. Adolescent rats are relatively insensitive to diazepam, failing to show the adult-typical, diazepam-induced reversal of the suppression in social interactions seen following placement in an unfamiliar environment [438].

Alcohol sensitivity likewise varies during ontogeny. Studies using a variety of measures in laboratory animals have observed increases in ethanol sensitivity from infancy, with further increases in sensitivity during the aging process (e.g. Ref. [605]). This early attenuation in ethanol sensitivity is evident despite slower rates of ethanol metabolism in younger animals [498,610] and is evident using measures

such as assessment of lethal doses [246], tilting-plane performance [245], ethanol-induced hypnosis [158,334,496] and hypothermia [498,514], although these findings are not ubiquitous [279]. The relative insensitivity of adolescents to these alcohol effects may be related in part to their greater propensity for developing acute [496] and chronic [219,539] tolerance to these effects of alcohol than adult animals. This relative insensitivity may permit adolescents to sustain comparatively large ethanol intakes when compared with their more mature counterparts.

Yet, in some respects, young rats may be unusually sensitive to ethanol. Swartzwelder and his group found that hippocampal slices from preadolescent (P15–25) and adolescent (P30) rats were more sensitive than adult slices to ethanol disruption of hippocampal long-term potentiation [443,540,541]. Behaviorally, P30 adolescents were found to be more impaired than adult rats by ethanol in a spatial memory task in the Morris maze, whereas non-spatial performance was unaffected by ethanol at either age [344]. Somewhat similar age-related memory disruptions by ethanol have been reported in humans, with early post-adolescent (21–24 year-old) adults showing more ethanol-induced disruption of memory acquisition on both semantic and figural memory tasks than slightly older (25–29 year-old) individuals [2]. Thus, whereas a reduced sensitivity to the motor impairing and sedative consequences of ethanol (discussed above) may permit adolescents to consume greater amounts of ethanol, this exposure might have more adverse effects on hippocampally related memory processing than later in life.

3.2.2. Human data

There are few ontogenetic comparisons of sensitivity to psychoactive drugs across age in studies with humans, but the studies that are available are reminiscent of the findings from animal studies. For instance, in a study comparing hyperactive juvenile boys and normal men, euphoria was reported by adults following stimulant exposure, whereas the juveniles only reported feeling tired or “different” after taking the stimulant [455]. In a number of other instances as well, juveniles and adolescents have been reported to differ in their sensitivity to psychoactive drugs from adults. In contrast to the effective use of tricyclic antidepressants for treatment of adult depression, depressed children and adolescents were found not to differ significantly in their response to tricyclic antidepressants from their response to placebos alone (see meta-analysis of Ref. [233]). In contrast to these more catecholaminergically acting tricyclics (that predominantly block reuptake of norepinephrine [NE] and to some extent DA), when a more selective inhibitor of the reuptake of serotonin (5HT), fluoxetine, was used, significant improvement over placebo has been reported in the treatment of depressive disorders in childhood and adolescence [154]. The NMDA antagonists phencyclidine and ketamine do not produce hallucinations in prepubertal children, although this is a typical reaction to these drugs in adulthood [242]. The older the near daily marijuana user, the lower the average number of joints smoked on each occasion [270]. Finally, akin to the findings of enhanced sensitivity to neuroleptics seen in adolescent rats relative to their adult counterparts [72,513], children and adolescent humans likewise respond to lower doses of neuroleptics than adults and may be more sensitive to neuroleptic-induced extrapyramidal side effects [217,278].

3.2.3. Pharmacokinetic considerations

Taken together, the evidence to date shows that adolescents differ in their response to a variety of drugs from adults. These ontogenetic variations in drug responsivity may be related in part to age-associated differences in pharmacokinetics. Changes in body composition and organ function associated with the adolescent growth spurt and rising gonadal steroid titers may alter the volume of drug distribution and drug metabolism and excretion rates [238]. The nature of these ontogenetic differences are drug-specific and depend on many factors, including the relative affinity of the drug for fat versus water compartments (i.e. its lipid–water partition coefficient) as well as the ontogeny of drug-binding proteins and enzymes for drug metabolism [238]. Developmental differences in psychopharmacological responsiveness between adolescents and adults may also be related to ontogenetic changes in functioning of the neural substrates upon which these drugs act. Indeed, as discussed in later sections, the brain of the adolescent differs considerably from the adult in a number of neural systems prominent in the action of these drugs.

Regardless of underlying mechanisms, these ontogenetic differences in drug responsiveness may have significant consequences for the adolescent. To the extent that adolescents exhibit a reduced sensitivity to various drugs of abuse, this insensitivity could promote greater use per occasion relative to more mature individuals. Moreover, given these age-associated alterations in drug sensitivity and in the neural mechanisms upon which these drugs act (see later section), it remains to be determined whether factors precipitating drug use in adults will bear resemblance to those contributing to the initiation of drug use in adolescence. Although the vast majority of drug use is initiated during adolescence, basic research examining contributors to drug use initiation has exclusively focused to date on assessment of animals in adulthood.

3.3. The early exposure effect: early alcohol/drug use as a predictor of later abuse

Early onset of alcohol use has been shown in both prospective and retrospective studies to be a powerful predictor of later alcohol abuse and dependence [132,171,179,214,231,436,447]. In a study of 27,616 current and former drinkers interviewed for the 1992 National Longitudinal Alcohol Epidemiological Survey, the rate of lifetime alcohol dependence was found to be

40% when individuals started drinking at or before 14 years of age, but only 10% when drinking was not initiated until 20 years or later [214]. Overall, with each year of delay in onset of alcohol use, the odds of dependence decreased by 14% while the odds of abuse decreased by 8%. Early experience effects were evident with exposures occurring as early as 6 years of age [171].

This early exposure effect has been suggested to be one of the strongest predictors of subsequent alcohol abuse [32,231,466], and is seen in relation to other drugs as well. Early alcohol exposure is correlated with increased later use and abuse of other substances [132,465,466,604], while early exposure to illicit drugs is associated with increased later abuse of alcohol [466] as well as other drugs of abuse [270,466,604]. Chronicity of alcohol use during adolescence has even been associated with non-drug-related adjustment problems and illegal behaviors (including aggression and theft) in young adulthood [146]. There is even some suggestion that early elicitation of delinquent behavior per se may predict extent of subsequent delinquency in adulthood [555]; this study, however, did not distinguish among different forms of early delinquent behavior, and hence it is possible that this effect might be mediated by the inclusion of early drug/alcohol use within the delinquent behavior category.

Using survival data analysis techniques and a retrospective data base, Anthony and Petronis [20] observed that the increased risks associated with early drug use do "not become crystallized and stable until more than 4 years after drug use began" (p. 13). Their analyses also showed that the increased risk of later drug problems associated with early onset of use is not merely because early users have accumulated more years during which to experience drug problems.

There are at least two possible explanations of this powerful early exposure effect. First, exposure to alcohol and other drugs during adolescence may alter critical ongoing processes of neural development occurring at that time, with long-term effects on neurobehavioral function that increase the propensity for later abuse. Indirect support for this possibility was obtained via path analysis of data from 10–11 year-old children collected prospectively for 7 years; in this study, effects of all significant risk factors for alcohol misuse were found to be mediated through age of alcohol initiation, other than a modest independent influence of gender [231].

An alternative interpretation of the early exposure effect is that early use of alcohol or other drugs might independently predict later problem use, regardless of prior drug history; according to this view, early alcohol/drug use serves as a marker, not a precursor, of a later abuse disorder. For instance, high novelty seeking in preteens was predictive of ethanol abuse at 27 years of age [94]; high novelty seeking is one of a number of traits that seem to facilitate initiation of alcohol and other drug use [35]. These two perspectives regarding the significance of the early exposure effect are not necessarily mutually exclusive. For instance, presence of conduct problems predicts both early drug use and later drug abuse, although there is an interaction between conduct disorder and age of first use, with each found to contribute to a later increase in drug abuse [465].

In animal studies, genetic differences in alcohol intake among inbred lines of rats have been observed not only in adulthood, but in adolescence as well [355], raising the possibility that similar genetic factors might influence not only problem drinking in adulthood, but also the emergence of alcohol drinking during ontogeny. Indeed, Prescott and Kendler [436] recently concluded from study of human twins that age of initiation of alcohol use was not a direct risk factor for alcoholism, but an "alternative manifestation of vulnerability to problematic alcohol involvement" (p. 106). Causality was inferred in this self-report study using structural modeling statistical approaches, and was based on the assumptions that for early drinking to be causally related to later alcohol dependence, the age of initiation of use must be solely related to individual-specific sources of variation and not associated with additive genetic factors or even any shared environmental influences between twins. Not surprisingly given these assumptions, the association between drinking onset and later alcohol dependence was found to reflect not merely individual-specific variation, but also shared genetic and environmental factors between twins. The authors thus concluded that the association between drinking onset and alcohol dependence was noncausal [436].

There is also at least one case where early exposure to abusable drugs does not increase later abuse potential, and indeed may protect individuals from later drug abuse. Children with attentional deficit/hyperactivity disorder (ADHD) treated with stimulant medication do not have an elevated risk for later substance abuse disorders relative to other individuals and indeed have a lower risk than individuals with ADHD who were not on such medication [45]. In this instance, the drug exposure typically begins well prior to adolescence and in individuals labelled with a disorder that in itself is a vulnerability factor for later alcoholism and substance abuse (e.g. see Ref. [547] for review and references). It remains to be determined how relevant data obtained in this population—which is typically dysfunctional in multiple domains and often has comorbid psychopathology—are with regard to long-term outcome following early adolescent drug exposure in other populations.

Animal models could help determine whether there is a causal relationship between early exposure and later substance abuse problems, and in exploring the mechanisms underlying this possible association. Although little investigated, there is some evidence that drug exposure during adolescence can have a long-term influence on later neurobehavioral function. For instance, voluntary ethanol consumption [494] and chronic cocaine exposure [229] during adolescence both were found to significantly

increase later aggressive behavior in male Golden hamsters. Chronic exposure of adolescent rodents to alcohol has been reported to induce later alterations in emotionality [474] and cognitive functioning [393] as well as to disrupt puberty-associated increases in reproductive endocrinology in both males [89] and females [118]. In most cases, it is not clear, however, as to whether exposure during adolescence is critical for these effects or whether similar effects would be evident with comparable drug exposure in adulthood. Critical postadolescent exposure groups were included by Barnes and Fried [31] in a study examining chronic administration of Δ^9-tetrahydrocannabinol (THC). In that experiment, rats given THC chronically during and after adolescence (from P28–69) had smaller brain weights and developed tolerance more rapidly upon THC challenge in adulthood relative to both control animals not exposed to THC, as well as animals exposed to THC for equivalent period in adulthood [31].

Of particular relevance for understanding the early exposure effect is the little explored question of whether adolescent drug exposure alters later drug sensitivity or intake. Weaning through adolescent cocaine exposure has been reported to alter subsequent cocaine-induced open field behavior [505] and to increase the later reinforcing efficacy of cocaine as indexed by greater cocaine-induced conditioned place preferences [506]. In terms of adolescent alcohol exposure, reports that pre- [232] or postweaning [243] exposure to ethanol can increase later ethanol preference are contrasted by data from several groups showing no increase in later consumption following periods of ethanol exposure that include adolescence [266,396,557]. In the development of animal models of the early exposure effect, it may prove useful to consider the intriguing suggestion of Tolliver and Samson [557] that stress may serve to unmask effects of early exposure on later patterns of drug use.

4. Stress and adolescence

Given the large number of transitions faced by adolescents, they have been viewed to be "…in a chronic state of threatened homeostasis," with "their adaptive responses during this period (being) crucial" ([141], p. 685). Stress likewise has been characterized as a state of threatened homeostasis that requires adaptive processes to restore and sustain this equilibrium. Thus, almost by definition adolescence could be considered to be a stressful life stage. Indeed, Denver [122] has postulated that neurohormonal stress responses to ontogenetically driven environmental changes serve as a cue for facilitating developmental transitions from one habitat to another. He supports this suggestion using examples such as the corticotropin-releasing hormone (CRH) facilitation of metamorphosis in desert amphibian tadpoles as well as the promotion of parturition in human preterm births precipitated by fetal distress. In mammals, adolescence is second only to the neonatal period in terms of both rapid biopsychosocial growth as well as changing environmental characteristics and demands, although it is not known whether a stress-activated regulatory system might function to facilitate these adolescent transitions. Yet, as discussed below, there is evidence that the perception of events as stressful, if not also the incidence of stressful events per se, may be elevated in human adolescents. At least some aspects of the neurobehavioral and hormonal responses to stressors may also vary in adolescents relative to younger or older organisms.

4.1. Stress and human adolescents

There are a number of potential sources of adolescent stress. During the adolescent transition, the adolescent is confronted with numerous developmental changes and challenges associated with puberty, changing socio-environmental contexts and the gradual move toward independence. Seeking out and learning from novel stressors and challenges is "pivotal for emotional and intellectual growth and development" ([84], p. 312); yet, in addition to these positive responses, these challenges also have the potential to overwhelm the adolescent and lead to significant stress [413]. Some investigators have viewed human adolescence as a time of "storm and stress", while others have concluded that most adolescents "negotiate this time of transition with emotional ease rather than with emotional turmoil" ([388], p. 1152) (see Refs. [25,458] for brief historical reviews). These varying views seem to depend on the type of data from which conclusions are drawn.

Most individuals traverse adolescence without significant psychological problems, leading some researchers to conclude that adolescence is not a time of storm and stress. Only a minority of adolescents exhibit overt psychopathology such as clinical depression; the 20% incidence of psychopathology in adolescence is similar to rates observed in adults [388]. Given that these emotional and behavioral disorders appear to be in part precipitated by stress, to the extent that adolescence is an unusually stressful time period, incidence of psychopathology might be expected to increase during adolescence and reach levels greater than in adulthood. Yet, while the prevalence rates of depression [99] and schizophrenia (see later discussion) notably increase during adolescence, the rates reached are similar to incidence rates reported in adulthood. While it is possible that a potential increase in the stress of adolescence could contribute to the ontogenetic increase in incidence of psychopathology seen at this time, ontogenetic changes in brain function occurring between childhood and adolescence could certainly play an important role. Likewise, the consistency in prevalence of psychopathology between adolescents and adults may not necessarily imply similarity in environmental stressors across age, but rather could reflect maturational changes in brain function acting in conjunction with potential age differences in the stressfulness of these life stages. Clearly, there are serious problems with interpretation when using

the incidence of psychopathology to index the relative stressfulness of adolescence.

When relative stressfulness of the adolescent transition is estimated through ontogenetic assessments of affective behavior, a different perspective emerges. For instance, while only a small minority of adolescents meet criteria for clinical depression, about one-third to one-half of adolescents at any point in time report significant depressed mood or affective disturbances which could be described as "inner turmoil" or feeling miserable [97,472]. Incidence of depressed mood increases notably from childhood to adolescence [472] to reach rates during adolescence that are often higher than in adulthood (e.g. see Ref. [410] for review). Indeed, adolescents exhibit higher prevalence rates of depressed mood as well as of sleep problems than their mothers do (comparable data for fathers were not available) [472]. Adolescents also tend to show greater extremes in mood than adults ([310]; see Ref. [25] for review); in addition to this emotional volatility, anxiety and self-consciousness also appear to peak at this time (see Ref. [66] for extensive review). While it may seem paradoxical that adolescence is associated with increases in emotionality/anxiety as well as risk taking, these attributes are not mutually exclusive. Indeed, evolutionarily speaking, greater anxiety and emotional reactivity in the face of considerable risk taking could have proved adaptive for our adolescent ancestral predecessors by serving to increase their vigilance to potential predators during the considerable risks of emigrating from natal territories.

The greater prevalence of depressed mood in adolescents may be in part related to an increase in the overall number of stressful life events during this developmental transition (especially during early adolescence—see Refs. [60,62,143]) than earlier or later in life [194]. Larson and Asmussen [309] observed a substantial increase in both the number of negative life events as well as the experience of negative emotions in adolescence relative to the preadolescent period. These findings are not ubiquitous, however (see Ref. [572]), and direct comparisons of the number and significance of stressors across age can be problematic. Situations viewed as significant life events in adolescence (e.g. changing schools, rapid growth and change in body shape) may differ from those occurring in adulthood (e.g. being promoted within or fired from one's job) or childhood (e.g. loss of a championship game), and even similar situations (e.g. social exclusion, parental divorce or death) may be viewed differently across age. For instance, preadolescents and adolescents differ in the types of situations that typically precipitate negative experiences for them, with preadolescents exhibiting a greater proportion of negative events yoked with family matters and activities in the immediate surroundings, early adolescents being more likely to experience negative events in association with peers, and older adolescents viewing academic issues as particularly stressful [309,572]. The most likely domain of emergent problems may also vary with age, with parental conflicts particularly likely in young adolescents (see meta-analysis by Laursen et al. [311], mood disruptions in mid-adolescence, and risk behavior in late adolescence (see Ref. [25] for review). There may be gender differences as well. During early adolescence, females may be unusually vulnerable to stress, perceiving events to be more stressful than at other ages and than as perceived by males ([194,572]; see Ref. [570] for further discussion of gender differences in perceived stressfulness during adolescence).

Simmons and colleagues [499] observed that greater numbers of life changes co-occurring during adolescence were associated with an escalation in problem behavior along with decreases in grades and diminished involvement in extramural activities; for females a decrease in self-esteem was also evident [499]. A majority of the potentially stressful life events scored in the Simmons and colleagues [499] study were normative (school change, change in pubertal status, dating), although others were not (geographic mobility, major family change). Indeed, buildup of daily stressors/hassles has been reported to be more important than major life events as sources of risk for emotional/behavioral problems in adolescence [98], with the number of negative life events and not their nature linked to depression in adolescent females [58]. Many simultaneous changes (that individually may not necessarily be particularly stressful) may exceed the capacity of the adolescent to cope, leading to more negative outcomes than sequential changes [315,411]. In these studies, however, it should not be assumed that the relationship between stressors and negative outcome is necessarily causal. Indeed, this relationship may well be bidirectional [309], with negative events not only predicting later problems, but problem behaviors also predicting later increases in the number of perceived negative events [98].

Undergoing adolescent-associated developmental transitions—particularly those associated with puberty—at a time that is unusually early or late relative to other adolescents may add additional pressure, with this timing shown to correlate with behavioral and emotional problems in a gender-specific manner (see Ref. [212] for review of the extensive literature on this topic). Although deviations from average timing in either direction may be correlated with adolescent emotional or behavioral problems (e.g. Ref. [305]), early maturation has been more consistently so associated, particularly in girls. For instance, early pubertal maturation in girls is associated with emotional difficulties, depression, and problems in self-image, as well an increase in risk-taking behaviors (including early sexual intercourse); although early maturing boys also exhibit increased risk-taking behaviors, their early physical maturation is associated with greater involvement in athletics and as a result, increased popularity and confidence (see Ref. [519] for review).

An additional potential contributor to the stressfulness of adolescence is the age-associated transformation in sleep discussed earlier in this review. The adolescent phase

delay in sleep onset may lead to some amount of sleep deprivation—at least during the school week when adolescents are typically (albeit paradoxically) required to start school earlier than their younger counterparts [75]. Not only may sleep deprivation itself be stressful (see Ref. [25] for discussion), but it also has been speculated that this loss of sleep may itself alter stress recovery processes, increasing the amount of time taken for increases in levels of the stress-related hormone, cortisol, to return to baseline following stressor exposure [3].

Together these findings suggest that not only incidence of stressful events, but also perception of occurrences as stressful may be increased in adolescents relative to children and adults. There is limited but intriguing evidence that adolescents may also show an increased physiological responsivity to stressors, at least when indexed in terms of cardiac measures. Adolescents show a greater blood pressure (BP) and cardiac output response to various laboratory test procedures than do children, a pattern of findings consistent with an increase in β-noradrenergic reactivity during adolescence, with little evidence of alterations in α-noradrenergic or parasympathetic nervous system activation [10].

Individual differences in basal heart rates have been shown to predict problem behavior in adolescence as in other stages of life. Low resting heart rates have been correlated with increases in aggression in children [426], aggression (see Ref. [364] for review) and high-risk behavior [324] in adolescents, and violence in adults ([168]; but see Ref. [338] for negative findings). Whether or not this potential physiological predisposition is expressed in problem behavior may be dependent on other individual or environmental factors. For instance, Liang and colleagues [324] reported that neither life events or cardiovascular reactivity (indexed by BP) alone predicted risk behavior in adolescent boys, although the interaction of elevated BP and positive life events were associated with a lower probability of exhibiting risk behavior. Similarly, from his work with high and low cardiovascular reactive individuals, Boyce [55] concluded that "both extreme vulnerability and uncommon resilience can be found in the same highly reactive children depending on the basic stressfulness or supportiveness of the surrounding social context" (p. 53). For instance, highly reactive individuals exhibited elevated risk taking when exposed to few positive life events, but lower levels of risk taking when exposed to many positive life events; in contrast, the risk taking of low reactivity individuals was little influenced by environmental events [55].

4.2. Stress and adolescence in nonhuman animals

Reminiscent of the findings in experiments with human adolescents, behavioral experiments in laboratory animals have likewise hinted that adolescents may sometimes be more disrupted by stressors than younger or older animals. In terms of acute stress responses, adolescent rats show more stress-induced immobility than adults during forced swim testing [575] or when tested in the presence of intermittent footshock [73]. Tail-pinch-induced feeding also has been reported to peak in "juvenile" rats [239], although the precise ontogeny of this response has apparently not been well characterized. Digging in novel or other mildly stressful situations is another response that appears to peak in adolescence in gerbils [591] as well as rats (Barron, personal communication). Akin to the heightened anxiety reported during adolescence in humans (see Ref. [66] for review), young adolescent (4 week-old) mice were reported to be more anxious than both younger and older animals in a light/dark box [230]. Adult-typical environmental inhibition of social behavior emerges in adolescence, with an unfamiliar environment decreasing social interactions in adult (P60) and mid-adolescent (P35), but not early adolescent (P28) male rats [437].

Adolescent rats have been reported to habituate relatively rapidly to the behavioral and hormonal consequences of repeated stress [492]. Nevertheless, a number of studies have shown that repeated exposure to stressors during adolescence may have long-term consequences. Periodic exposure to a varying set of stressors over an extended period including much of adolescence (P31–73) was observed to blunt later hormonal stress responses in rats, with males being particularly sensitive to this effect [204]; other treatment periods were not examined however, so it is not clear whether exposure during adolescence is necessary or sufficient for this effect. When other treatment periods are included for comparison, exposure to stressors during adolescence has often (albeit not always—see Ref. [461]) been reported to produce more pronounced long-term effects than exposure at other ages. Stone and Quartermain [522] reported that chronic social stress (placement in the cage of an isolated adult male for 5 min daily for 5 days) had a greater impact on adolescent (P28–32) than adult male mice, suppressing food intake, body weight gain and time spent on open arms of a plus maze in adolescents but not adults. Chronic restraint stress also suppressed body weight gain in adolescents but not adults [522]. Housing in isolation has likewise been reported to have more pronounced and long-lasting effects on object exploration in an open field when the social isolation stress occurred between P25 and P45 than when the rats were isolated between P16 and P25 or after P45 [152]. Greater effects of social isolation during adolescence were also reported in terms of water intake, with the stress of single housing increasing fluid intake of adolescent but not adult animals [354].

In terms of neural responsivity and other physiological measures, adolescent rats also differ from their counterparts at other ages. For instance, young adolescent (P28) rats were found to be insensitive to effects of an unfamiliar environment on the benzodiazepine/gamma-aminobutyric-acid [GABA] receptor complex, context sensitivity that was evident in adults [440]. They likewise showed less widespread stress-induced FOS immunoreactivity than adult rats, exhibiting little activation in a number of brain regions such

as the anterior olfactory nucleus, anterior cingulate cortex and medial and cortical amygdaloid nuclei that showed notable stress-induced increases in FOS immunoreactivity in adults [281]. In marked contrast, when examining the ontogeny of c-fos activation by the anxiogenic (and presumably stress-inducing) anxiogenic β-carboline FG-7142, Lyss and colleagues [341] concluded that immature rat brain showed more diffuse c-fos activation than adult brain, with PFC becoming preferentially activated by FG-7142 by P45.

Choi and Kellogg [82] observed greater stress-related increases in NE utilization in rat hypothalamus early in adolescence; this response was blunted later in adolescence (P42), a transition toward the decreases in stress-related NE utilization in hypothalamus seen in adulthood. A similar adolescent transitional period was seen in terms of autonomic reactivity to stressor stimuli; whereas preweanling rat pups exhibit heart rate bradycardia to an aversive stimulus, heart rate tachycardia emerges by adolescence, with this increased heart rate mediated by parasympathetic withdrawal in adolescents but primarily by sympathetic activation in adults [301]. Taken together, these data illustrate that adolescent rodents, reminiscent of their human counterparts, may differ behaviorally and physiologically in the way they respond to stressors when compared to animals at other ages.

4.3. Hormonal response to stressors in adolescence

Exposure to a stressor activates the hypothalamo–pituitary–adrenal (HPA) axis, resulting in a cascading sequence of hormone release from the hypothalamus (CRH) and pituitary (adrenocorticotropic hormone [ACTH]), with increases in plasma ACTH inducing the adrenals to release glucocorticoids (corticosterone in rats; cortisol in humans) into the blood stream. Rodent studies have shown significant stress-induced activation of the HPA axis in neonatal rat pups, although sensitivity to stressors is reduced considerably after the first several postnatal days, with this stress hyporesponsive period (SHRP) lasting for most of the first 2 weeks of postnatal life [481]. While similar peak corticosterone responses to stressors have occasionally been observed in weanlings, adolescent and adult rats [23,82,202], stress-induced HPA activation has more consistently been reported to increase ontogenetically following the SHRP in rats to reach an asymptote around adolescence, at least in males [29,357,452,463,569,574]. In recent work using mice, however, adolescents were observed to have lower corticosterone levels than adults following the mild stress of saline injection [312]. Gender differences in the corticosterone response to stress begin to emerge late in adolescence, with elevated levels in female rats when compared with males as well as prepubescent females [91,184,451].

Whether similar ontogenetic increases in stress-induced cortisol levels are evident in humans is unclear, although several investigators have suggested that adolescence may be a period when individuals are more responsive hormonally and physiologically to stressors [212,576]. Challenges associated with examining the ontogeny of the HPA response to stress in humans include constraints involving the administration of experimental stressors to human subjects and in obtaining true basal samples in experimental settings that sometimes include intravenous (iv) catherization or other potentially stressful procedures or situations.

In adolescents as well as other aged individuals, individual differences in HPA responsivity have been suggested to be related to ongoing or subsequent problem behavior. For instance, adolescents showing increased cortisol reactivity during the experimental procedures exhibited more behavior problems and symptoms of depression when examined 1 year later [528]. In general, Ryan [473] concluded that individuals with externalizing disorders (conduct disorder in adolescence; antisocial behavior and aggressiveness in adults) exhibit lower cortisol levels, while those with internalizing disorders (social withdrawal, depression) exhibit cortisol hypersecretion after stressors, especially social stressors. Lower basal cortisol levels in individuals with externalizing disorders may reflect underarousal, with such underarousal perhaps reflecting an adaptation to chronic prior stress which serves to increase the probability of engaging in problem behaviors such as substance abuse [375]. Indeed, Susman and Ponirakis [534] concluded that "hyporesponsivity of the HPA axis may be a significant risk factor for antisocial…and aggressive behavior in children, adolescents and adults" (p. 265). As with the cardiovascular measures discussed earlier, it is likely that responsivity of the HPA axis interacts with environmental context and individual differences in stimulus and response expectancies in predicting subsequent problem behavior [157]. Turning to basal cortisol levels, increases in basal salivary cortisol have been reported with increases in pubertal status [287] and with increasing age across age spans from 4 to 14 years [188] or from 10 to 18 years [585]; increases in cortisol production have likewise been reported across this age range [285]. These findings, however, are tempered by other data reporting no notable age differences in cortisol levels among children and adolescents ([291]; see Ref. [602] for discussion).

Interestingly, while lower socioeconomic status (SES) children exhibit higher basal salivary cortisol levels than do children from higher SES groups, this association is lost during adolescence [340]. These findings mirror numerous other instances of health inequities associated with social class that are evident during childhood, but shift to relative equality from approximately 12 to 19 years of age, before reemerging in adulthood [589]. Somewhat akin to these findings, adolescent behavior has been shown in a number of instances to correlate less well with adult outcome than childhood behavior—the so-called "sleeper effect" of Kagan and Moss [265] (see Ref. [335] for discussion). What causes this period of adolescent equity rather

than progressively cascading effects with age (as sometimes reported in the competency/resiliency literature—e.g. Ref. [345]) is unknown. In this regard, however, it is interesting to note that the adolescent abatement of the SES difference in basal cortisol levels seemed to be associated with an elevation in basal cortisol levels in the higher SES up to levels characteristic of the lower SES group. Could it be that the stresses of adolescence contribute to the adolescent equity in health? More data will be needed to address this point.

Activity within the HPA axis is under close negative feedback regulation, with glucocorticoids released by stress-induced activation of the HPA axis acting on glucocorticoid receptors in brain regions such as the hippocampus to terminate continued activation of this axis (e.g. Refs. [357,358,482]). Positive feedback systems exist as well, with evidence for both positive and negative feedback systems regulating activity of the HPA axis obtained in hippocampus and other mesolimbic and mesocortical brain regions including the PFC, amygdala, lateral septum and ventral subiculum (see Ref. [240] for review), although some inconsistencies have been reported (with, for instance, reports of the PFC exerting either negative [136] or positive [525] feedback on the HPA axis). Based on the finding that adolescents with depression are less likely to exhibit hypercortisolism than depressed adults [441], Dorn and Chrousos [141] hypothesized that negative feedback loops within the HPA system may function better in adolescents than adults. This hypothesis is contrary to results obtained in animal studies where it appears that the delayed post-stress return to basal corticosterone levels seen in juvenile rats [202] may extend into the early- to mid-adolescent period [82,482]. This apparent prolongation of the stress-induced increase in corticosterone in adolescents relative to adults may reflect a variety of factors, including slower ACTH metabolism, delayed adrenal secretion of corticosterone, immature negative feedback regulation mediated at least in part by glucocorticoid receptors in hippocampus, or perhaps even transiently enhanced positive feedback.

It is not the case, however, that the apparent immaturity in negative feedback regulation reflects insufficient numbers of glucocorticoid receptors. Glucocorticoid receptor binding increases ontogenetically to reach at least adult-typical levels during the preweanling period in hippocampus, septum and amygdala, with binding in hippocampus reported in several studies to peak in adolescent (P35) rats at levels greater than those seen in adulthood ([357,569]; however, see also Ref. [358]). The expression of these glucocorticoid receptors seems relatively resistant to up- [569] and down-regulation [482] by corticoids during mid-adolescence. For instance, corticosterone administration has been shown to reduce corticosterone receptor binding in both hippocampus and amygdala of adult rats [480], but to only down-regulate corticosterone receptors in hippocampus and not amygdala, septum or hypothalamus of their adolescent counterparts [482]. Mid-adolescent (P35) animals are also remarkably unresponsive to the receptor up-regulating effects of corticosterone depletion, with adrenalectomy rapidly increasing glucocorticoid receptor mRNA in CA1 of adult rats and throughout hippocampus in P18 and P28 rats, effects that were not evident in P35 adolescents where expression of these receptors was uninfluenced by adrenalectomy [569]. Underlying substrates and consequences of this receptor insensitivity to corticoid feedback regulation in adolescence have not been explored.

Thus, the mechanisms of adaptation within glucocorticoid receptive regions of the limbic system of adolescents may vary from those employed in the mature brain. As previously reviewed, there is also reasonable evidence for a greater overall corticoid response to acute stressors in adolescence as characterized by stress-induced increases that may be elevated relative to younger organisms and prolonged relative to adults (e.g. Ref. [569]), although these findings are not ubiquitous [312]. To the extent that the overall HPA response to stressors is indeed more pronounced during adolescence, this presents an interesting paradox when viewed within the broader context of glucocorticoid effects, given that elevated levels of glucocorticoids mobilize energy stores and inhibit activity in numerous systems involved in the physiological changes of puberty and adolescence. Growth hormone release is inhibited as is activity of the hypothalamo–pituitary–gonadal (HPG) axis, whereas activation of these hormonal systems is central to the adolescent growth spurt and the physiological changes associated with sexual maturation [85,142]. Interestingly, cross-cultural studies have shown that males from cultures with stressful maturational rituals during late childhood and adolescence are significantly shorter as adults than males from cultures without such rituals. Although of course it is not possible to determine from these studies alone whether the rituals are causal in this association nor the role of HPA axis activation per se in this growth suppression (see Ref. [479] for discussion), a similar inhibition of growth was recently reported in adolescent (but not adult) mice exposed chronically to stressors [522]. In contrast to these findings, however, some researchers have suggested that stressors occurring prior to adolescence (including parent/child conflict, sexual abuse, and the absence of the father) may in some instances lead to early puberty in humans [519,526,559].

No clear resolution is apparent to the paradox that adolescence may be associated with a somewhat elevated glucocorticoid burden despite presumed inhibitory influences of these glucocorticoids on physiological changes of adolescence. Physiological outcomes associated with chronic perturbation in glucocorticoids may vary considerably, however, from consequences of acute exposure [69,392,475], potentially contributing in part to this apparent paradox. It is also possible that glucocorticoid inhibition of growth and the HPG axis may be less effective during adolescence due to a partial uncoupling of glucocorticoid feedback effects on these systems (Sapolsky, personal communication), akin to a similar uncoupling seen in

males of some species of marsupial rodents that allows these animals to procreate during a rapid glucocorticoid-induced aging process culminating in death [353]. Congruent with this suggestion, corticosterone has been reported to be less effective in impairing brain growth of adolescent (P27–46) rats than their young adult (P46–65) counterparts [128]. The "neuroendocrine context" has been shown to be critical for determining cellular reactions to glucocorticoids across a variety of species [392], and hence the notable hormonal alterations of puberty could potentially provide the impetus for altering the cellular response to corticosteroids during the adolescent age period. It is also possible that some of the metabolic cost associated with a stress-associated mobilization of energy stores by glucocorticoids in adolescence could potentially be paid in part by the marked hyperphagia of adolescence. These speculations aside, it remains virtually unknown territory as to how growth and maturation occurs during adolescence despite the presumed stresses associated with the transitions of this life stage.

4.4. Stress and drug abuse in adolescents

Perceived level of stress is one of a number of factors that predicts use and abuse of alcohol and other drugs by human adolescents ([28,131,132,262,561,596]; but see also Ref. [224]). In her review of the literature on stress effects on alcohol consumption in humans, Pohorecky [430] concluded that stress is most convincingly associated with alcohol consumption in adolescence, with more mixed findings evident in studies conducted in adults. After peer substance use, the next most powerful predictor of adolescent alcohol and drug use was found by Wagner [573] to be levels of perceived stress, with the appraisal of events as being stressful of more importance than the absolute number of such events. Attribution of cause and effect, however, may be difficult when examining stress and drug use associations. These two variables may be bidirectionally related [570]; for example, although stress may lead to increased ethanol consumption, ethanol itself may serve as a stressor and precipitate negative life events [263]. Several prospective and retrospective studies have obtained evidence that stress or emotional distress (indexed by negative affect) may in some instances predate initiation of adolescent substance use, suggesting that perceived levels of stress may exacerbate the already elevated propensity of human adolescents to exhibit alcohol use and other drug-taking behavior [131,561,596]. Indeed, in studies conducted using a variety of animal models, stress has been shown to increase alcohol and drug self-administration in adulthood [419]. In this work, both physical as well as psychological stressors have been shown to enhance acquisition of drug self-administration [316,453] and increase drug reinforcing efficacy (as indexed by the number of operant responses animals are willing to emit before they terminate responding under an escalating response requirement [i.e. progressive ratio schedule]—[489]). Animal models of ethanol ingestion have likewise reported a stress-induced facilitation of ethanol consumption [54], although the interaction of stress and ethanol intake is complex, with increases in ethanol consumption often becoming evident during the recovery period following chronic stressor exposure (see Ref. [429] for review).

As reviewed later, many of the neural systems known to undergo developmental alterations in adolescence are sensitively activated by stressors, including DA projections to PFC as well as to mesolimbic brain regions thought to be critical in modulating the reward value of drugs [1,109,148,251,554]. Receptors for glucocorticoids have been identified in rodent brain on dopaminergic neurons in the ventral tegmental area (VTA) and substantia nigra (SN) as well as in DA terminal regions including the nucleus accumbens (ACC) and PFC [6,90,136,225]. Stress-induced elevations in corticosterone may play a critical role in activation of DA transmission, with corticosterone treatment increasing, and adrenalectomy decreasing extracellular DA levels in ACC [416,421] and PFC [251] of rodents. Likewise, adrenalectomy or pharmacologically induced blockade of glucocorticoid synthesis suppresses alcohol consumption [164] and self-administration of other drugs [200] in laboratory animals. The results of this basic research suggest that stress-induced increases in glucocorticoids may interact with mesocorticolimbic brain regions to facilitate drug taking behavior.

Rewarding stimuli, including alcohol and other drugs of abuse, increase plasma corticosterone levels in laboratory animals (e.g. Ref. [153]) and humans (e.g. Ref. [486]). Corticosterone itself has been shown to be reinforcing, and is intravenously and orally self-administered by rodents [125,417]. Indeed, Piazza and Le Moal [418] view corticosterone as an endogenous, state-dependent psychostimulant that shares many neurochemical and physiological effects with psychostimulant drugs such as cocaine and amphetamine. In this regard, it may be highly significant that several studies have incidentally noted that adolescent rats exhibit lower drug-induced increases in plasma corticosterone levels than do their more mature counterparts. This paradoxically attenuated corticosterone response to drug exposure has been seen in adolescent rats following challenge with morphine [29], cocaine [313] as well as ethanol [497], and in adolescent mice following amphetamine [312]. To the extent that elevations in corticosterone contribute to the reward value of drugs, higher levels of adolescent drug exposure may be necessary to attain the reinforcing value that these drugs have in more mature individuals. This notion implies, however, that reward values would be progressively increased with increasing elevations in corticosterone levels, which may not be the case—at least in studies conducted in adult animals (where increases beyond a threshold level of corticosterone necessary to support drug self-administration may not necessarily lead to greater drug intake; [201]). Thus, it remains to be determined whether adolescent attenuations in drug-induced corticosterone

release reported in laboratory animals [29,312,313,497] contribute to the high per occasion level of use of alcohol [33,346] and potentially other drugs [270] seen in human adolescents relative to their more mature counterparts.

5. Hormonal changes of adolescence

In addition to developmental alterations in stress-induced HPA activity discussed previously, two characteristic types of hormonal changes are associated with adolescence: adrenarche, the increase in output of adrenal hormones that begins to occur prior to other signs of impending adolescence; and gonadarche, the pubertal increase in gonadal hormones associated with the process of sexual maturation. These hormonal changes and their behavioral implications will be briefly reviewed prior to addressing the extensively investigated but as of yet unresolved mystery of what triggers the developmental increase in pubertal hormones.

5.1. Adrenarche

The earliest sign of upcoming puberty in humans is an increase in secretion of androgens from the adrenal. This process, called adrenarche, is associated with increased adrenal secretion of a variety of androgens, particularly androstenedione (Δ4A), dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) (see Ref. [397] for review). The onset of adrenarche typically begins well before adolescence (i.e. between 6 and 8 years of age), with levels of these androgens continuing to increase for about 10 years until asymptotic levels are reached well into puberty. Although adrenarche precedes gonadarche, it does not appear to be necessary for gonadal activation at puberty, given that adrenarche and gonadarche are often dissociated in individuals with clinical disorders of gonadal or adrenal maturation [103,502]. Moreover, gonadarche is a common characteristic of all mammalian species, whereas many species do not appear to show a clear adrenarche. Cutler and colleagues [111] surveyed across a variety of primates and other mammals and found clear evidence for adrenarche only in chimpanzees, and not in rodents, domestic animals, or even rhesus monkeys. Indeed, Δ4-A does not appear to be released from rat adrenals, with radioimmunoassay-detectable plasma levels largely driven by gonadal production [37].

The increased release of androgens during adrenarche is not associated with an increase in adrenal secretion of corticoids, nor in greater release of ACTH from the pituitary (e.g. Refs. [22,454]). Given that ACTH stimulates adrenal production of androgens as well as cortisol, some other factor is presumably involved in the selective stimulation of adrenal androgen activity at adrenarche. Adrenal activation by the sympathetic nervous system may prove to be critical [151]. One possible regulator of the adrenarche-specific stimulation of adrenal androgen production may be the polypeptide diazepam binding inhibitor (DBI), a presumed endogenous $GABA_A$ modulator that has been shown to facilitate ACTH-stimulated steroidogenesis in the adrenals of laboratory animals [43,53]. The ontogeny of DBI and its potential relationship to adrenarche in humans, however, have yet to be explored.

Increases in adrenal androgens during adrenarche are associated in humans with development of pubic and axillary hair, and with a slight acceleration in rate of bone maturation and skeletal growth [110]. Other physiological consequences of these androgens are few, although (as discussed later) levels of these androgens have been occasionally linked to adjustment and behavior problems. Indeed, adrenal androgens have been found to influence brain function in laboratory animals, and hence are included in the large group of steroids called neuroactive steroids (e.g. Ref. [442]). Neuroactive steroids fall into two classes (see Refs. [374,398] for review): (a) inhibitory neuroactive steroids that are positive modulators of $GABA_A$ receptors; and (b) excitatory neuroactive steroids that appear to increase overall brain excitability by antagonizing GABA receptors and possibly by potentiating NMDA receptors [117]. The adrenarche-prominent steroids DHEA and DHEAS fall into this latter group. DHEA has recently been reported to reduce energy intake and intake of fats in rodent studies through action at the hypothalamic level [226], raising the speculation that levels of adrenal steroids asymptoting late in adolescence could potentially contribute to the post-growth-spurt decline in food intake. The rapid progress being made in the study of neuroactive steroids in the field of neuroscience may lead to important clues regarding functional implications of the adrenarche-associated increase in excitatory neuroactive steroids.

5.2. Gonadarche

The increase in release of gonadal hormones at puberty that is seen across a wide variety of species ranging from rats [36], nonhuman primates [71] and humans [523] represents a reinstatement of patterns of hormone release that were evident much earlier in ontogeny. After a prolonged period of suppression during the childhood/juvenile period, puberty is associated with the reestablishment of pulsatile release of gonadotropin-releasing hormone (GnRH) that was evident perinatally. This pubertal reinstatement of pulsatile patterns of GnRH release promotes increased release of both follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which in turn stimulate release of gonadal hormones (e.g. testosterone in males and estrogen in females) (see Ref. [63] for review). Release of growth hormone (GH) also increases substantially during the growth spurt of adolescence in humans [336] as in other species [184]. Increases in gonadal hormones stimulate the emergence of many secondary sexual characteristics in human adolescents [40], while increases in both GH and the sex steroids stimulate growth and contribute to the pubertal growth spurt [336].

5.3. How closely are these hormonal alterations associated with behavioral change during adolescence?

Developmental changes in gonadal hormones have customarily been thought to exert two types of influences on behavior: "organizational" and "activational" effects. Organizational effects have been attributed to the influence of hormones on sex-typical structural differentiation of the nervous system during the pre- and early postnatal period (see Ref. [527] for review and references). Activation influences, on the other hand, are typically thought to be exerted by the presence of gonadal hormones at the time that behavior is being assessed in adolescence or adulthood (e.g. see Ref. [66]). Yet, some of these later hormonal influences may also have an "organizational" component, in the sense that alterations in hormone levels in adulthood can be accompanied by significant structural change in brain, as illustrated by work in the avian nervous system by Gould and colleagues [208].

Because of the rapid rise in gonadal steroids during adolescence and the often pronounced behavioral changes occurring at that time, substantial interest has been directed toward examining potential relationships between these hormones and behavior during adolescence. A number of studies have demonstrated the importance of gonadal hormones for neurobehavioral maturation during adolescence in laboratory animals. For instance, Primus and Kellogg [437,438,439] showed that the emergence of novelty-suppression of social interactions in rats depends on gonadal hormones, as does the effect of diazepam in reducing this suppression. Neurochemical measures of responsiveness of the GABA/benzodiazepine (BDP) receptor complex in cortex to environmental challenge were likewise shown to be dependent on the presence of gonadal hormones during adolescence [440]. In other instances, however, adolescent-typical behaviors emerge without typical pubertal-associated increases in gonadal hormones. For instance, the sex differences that emerge during adolescence in squirrel monkeys were observed to be largely independent of hormonal state at puberty, appearing to follow a maturational clock set by organizational influences of gonadal hormones exerted pre- or perinatally [96]. As another example, the temporary switch in adolescent rats from adult-typical defense strategies to more juvenile tactics of play fighting (discussed earlier) is not influenced by castration at weaning [503] but is blocked by neonatal decortication [403]. Thus, even in laboratory animals, with their arguably stronger relationship between hormone levels and behavior than that seen in humans (e.g. see Refs. [59,96]), behavioral changes during adolescence may not be necessarily dependent on increases in pubertal hormones.

Likewise, in initial work with human adolescents, few reliable relationships were observed between gonadal hormones and adolescent brain function [362] or behavior, the latter prompting Susman and colleagues [530] to assert: "at a folk-wisdom level, hormonal changes are associated with behavior change in adolescents. The empirical evidence confirming this link is almost nonexistent." (p. 1114). More recent research, however, has provided evidence for some reliable (albeit modest) associations between gonadal hormones and adolescent behavior/mood in humans (e.g. see Ref. [209] for review). Such evidence includes, for instance, reports of weak relationships between aggression and estrogen in female adolescents and between aggression and testosterone or its binding globulin in males (see Refs. [333,533] for review). Moving beyond correlational studies, convincing empirical evidence for an association of gonadal hormones with human behavior has been recently obtained in a randomized, blinded clinical trial that examined hormonally deficit (pubertally deficient) adolescent-aged individuals under hormonally replete and deplete conditions [172]. Administration of gonadal steroids was associated with increases in physical aggression and aggressive impulses, evidence for causal effects of hormones on behavior—at least in this clinical population.

In correlational studies comparing hormone levels and behavior in normal adolescents undergoing puberty, only a small portion of the variance in behavior is generally attributable to gonadal hormone levels. For instance, gonadal steroids typically account for about only 4% of the variance in negative affect among adolescents, whereas 8–18% of this variance is attributed to social events [61]. There are a number of possibilities for this weak association between specific gonadal hormones and behavior. Reliable assessment of hormone levels is a challenge given substantial day-to-day variability in these levels [529]. Moreover, although hormone and behavior data are typically collected contemporaneously, the appropriateness of this approach is debatable in that it is not known how long it takes for hormones to influence behavior [66,567].

In addition to these methodological problems, it is possible that only weak associations between gonadal hormones and adolescent behavior have been obtained because the notion of a direct relationship between a particular gonadal hormone and a specific behavior may be too simplistic. Behaviors occur in social and environmental contexts that vary in stressfulness, and both the behaviors and the impact of those contexts may influence (and be influenced by) hormone levels. These complex interrelationships challenge the appropriateness of models based on simple hormone/behavior relationships. Thus, recent research has emphasized potential complex bidirectional associations between gonadal hormones and behavior, and has considered the social environment and psychological factors as additional potential modulatory/mediating variables [61,535].

It is also likely that hormones other than, or in addition to, gonadal hormones may contribute to adolescent behavior. Of particular interest are the adrenal androgens. For instance, increases in adrenal androgens along with decreases in gonadal hormones have been associated with antisocial behavior and other behavior problems in adolescents (e.g. Refs. [531,534]). Different adrenal hormones

may vary in the nature of their association with adolescent behavior. For example, higher levels of Δ4A, sometimes in association with not only lower levels of testosterone but also DHEA-S, have been correlated with adjustment problems in both boys and girls during the pre- and early adolescent years [384,530,532]. Given that chronic stress has been reported to elevate Δ4-A levels while lowering levels of the Δ5-adrenal androgens DHEA and DHEA-S (e.g. Ref. [446]), stress-induced alterations in the balance of Δ4-A to DHEA-S could contribute to the association between these hormones and adjustment/behavior problems during adolescence. Interestingly, Δ4-A has recently been shown to decrease cortisol negative feedback efficacy on subsequent ACTH release [477], delaying post-stress recovery of the HPA axis.

Taken together, the evidence thus far suggests that, although developmental increases in neurosteroids of adrenal origin may be of behavioral significance (e.g. Ref. [533]), gonadal hormones per se have been shown to account for only a small amount of the variance in behavior during adolescence, contrary to what is implied by the folklore notion of the "raging hormones" of adolescence.

5.4. "Triggers" of puberty

Biological changes other than alterations in hormone levels may contribute to behavioral change during adolescence. Particularly likely suspects are age-associated transformations in brain function. Before turning to a broad discussion of maturational changes occurring in adolescent brain, we will first consider a specific subset of these neural alterations—those suggested to play a role in triggering the hormonal alterations of puberty.

It is likely that a variety of both neural and non-neural mechanisms collaborate in the reawakening of the HPG axis. Somehow the body must signal the HPG axis that is it ready for puberty, and evidence is mounting that a protein produced by fat cells, leptin, may provide one such metabolic signal. The pubertal activation of GnRH release appears to be associated with both a weakening of inhibitory tone (mediated by GABA and possibly opiate peptides) as well as an increase in excitatory tone (involving NE and excitatory amino acids such as glutamate) on hypothalamic neurons releasing GnRH. Neuropeptide Y (NPY) may be another modulator, although the directionality of this influence is controversial and may depend on other factors such as levels of gonadal hormones. Other suggested contributors to the pubertal activation of the HPG axis include hormones such as prolactin [337] and insulin growth factor 1 [241].

The cast of potential modulators of adolescence is large, and the influences exerted are sometimes complex, with the directionality of the effect of a particular modulator perhaps determined by levels of another. Concentrations of many hormones and neuromodulators are changing nearly concomitantly during puberty, making it challenging to dissect which systems may play particularly prominent roles in the initiation of puberty via facilitating pulsatile GnRH release. A full discussion of this topic is beyond the scope of this review, although evidence for the importance of these systems in the processes contributing to pubertal onset will be briefly detailed below.

5.4.1. Body weight, metabolism and leptin

Body weight or composition (i.e. proportion of body fat) has been more strongly linked to the timing of puberty than chronological age in species ranging from rodents [284] to humans [180,181]. In humans, delays in puberty are associated with protein calorie malnutrition, anorexia nervosa and the extensive dieting and physical exertion of ballet dancing, while an early onset of puberty is evident in mildly obese girls (see Refs. [181,395,520] for discussion and references). Sufficient body fat is accumulated in females by the time of puberty for caloric support of a pregnancy and several months of lactation [182], although some have questioned whether reaching a critical weight/percent body fat is actually causal or permissive, or whether it reflects merely a manifestation of puberty (e.g. Ref. [414]).

For body weight/composition to "trigger" or permit puberty to proceed, this information somehow must be transmitted to CNS regions involved in initiating gonadarche. One metabolic signal proposed as a possible "metabolic gate" for the onset of puberty [80] is leptin, a protein product of the *ob* gene released by fat cells that is thought to serve as a satiety signal regulating appetite and weight [48] as well as a regulator of energy balance and growth processes [288]. Leptin stimulates growth hormone [236] and hormones critical for reproductive function [48], while inhibiting the HPA axis [236,434]. Leptin levels have often although not always (e.g. Ref. [5]) been reported to increase during the prepubertal to early pubertal period in both rats ([26], cited by Kiess et al. [286]) and humans [304,343]. Leptin is capable of inducing reproductive function in otherwise sterile ob/ob mice [78] and accelerating the onset of puberty in female mice [5,79], even at a dose that suppressed body weight gain (consistent with leptin's action as a satiety signal). Leptin did not, however, accelerate the onset of puberty beyond that seen in normally fed rats, nor did it completely reverse pubertal delays associated with severe food restriction, leading Cheung and colleagues [80] to conclude that "leptin is not the primary signal that initiates the onset of puberty but that instead, it acts in a permissive fashion, as a metabolic gate, to allow pubertal maturation to proceed—if and when metabolic resources are deemed adequate" (p. 855). Urbanski and Pau [564] have likewise concluded that leptin does not serve to trigger the onset of puberty in primates. Recent evidence for ontogenetic changes in levels of activity of binding proteins for leptin in circulation may help link leptin to the progression of puberty [445].

5.4.2. Attenuation of inhibitory tone

Leptin or any other signal of the body's readiness to enter

puberty must ultimately provoke the hypothalamus to release GnRH, thereby initiating the cascade of events leading to increases in gonadal hormones. Activity in these critical hypothalamic brain regions may be facilitated during puberty by a weakening of inhibitory influences (as well as an increase in excitatory tone as discussed in the next section).

During the early postnatal period (including the first several months of life in human infants), the HPG axis is clearly active, with pulsatile release of GnRH, LH and FSH, and associated high levels of gonadal hormones. Thus, the quiescence of the HPG axis evident in childhood presumably involves active inhibition of this precociously functioning system rather than immaturity in the neural systems responsible for its activation. Reawakening of the HPG axis at puberty is seemingly at least in part related to a reduction in this inhibitory tone. Gonadal hormones themselves may play a role in maintaining the quiescent period of childhood via strong feedback inhibition of GnRH neurons, with an attenuation in hypothalamic sensitivity to this feedback occurring during puberty (e.g. Ref. [196]). Yet, initiation of puberty does not rely on alterations in sensitivity to gonadal steroid feedback; there are species differences in these feedback systems [428], and pubertal activation of pulsatile GnRH release is evident even in patients with gonadal agenesis [21].

Research conducted primarily with rodents has shown that weakening of inhibitory tone derived from a number of neural sources may contribute to the reawakening of the HPG axis at puberty. Puberty is associated with a decline in GABA inhibition of GnRH release [368]. There is likewise evidence for a pubertal-associated desensitization of hypothalamic DA receptors, thereby reducing the inhibitory influences of this catechol on GnRH release [303,306,603]. Leptin inhibits release of DA and NE in rat hypothalamus [65] and rising levels of leptin during adolescence (see Section 5.4.1) may further reduce levels of dopamine inhibition on GnRH release. While opiates inhibit GnRH in intact adults, their role in the pubertal process requires further characterization, with evidence for a pubertal-associated reduction in sensitivity of the hypothalamic gonadostat to opiate inhibition [347] countered by other work reporting an emergence of opiate inhibition at this time [196].

The data are likewise mixed regarding the role of neuropeptide Y (NPY), a peptide that stimulates food intake and whose synthesis is potently suppressed by leptin (see Ref. [48] for review). While chronic administration of NPY has been reported to delay sexual maturation in rats [222,424], other research has shown that levels of NPY increase during the prepubertal to pubertal period in rats and rhesus monkeys [207,537], with NPY antiserum decreasing the magnitude of the GnRH surge in pubertal rats [367] and monkeys, but not prepubertal monkeys [207]. Part of the complexity of studying the interaction of NPY (as well as opiates) with the hypothalamic gonadostat around the time of puberty is that these peptides may exert opposite influences on GnRH release depending on gonadal hormone levels [222], with levels of these gonadal steroids (and potentially the receptor systems responsive to these steroids) changing substantially during the course of puberty.

5.4.3. Increases in excitatory tone

Activation of hypothalamic GnRH release during puberty may be facilitated not only by a weakening of inhibitory tone, but also by an increase in excitatory influences on the hypothalamus. Maturational changes are seen in NE release in the hypothalamus of adolescent rats [81,83], and noradrenergic influences on GnRH release may switch from being largely inhibitory during the prepubertal period in rats to a predominance of NE stimulatory effects at puberty [456]. Puberty is also convincingly associated with increases in levels of the excitatory neurotransmitter glutamate. Administration of the glutamate agonist NMDA induces precocious puberty in rats and nonhuman primates [57,428], while the antagonists MK-801 [563] and phencyclidine [501] delay puberty. Opinions differ as to whether this effect is mediated by kainate [161], NMDA, or DL-α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) [607] forms of the glutamate receptor [57], although stimulation of each receptor type has been shown to facilitate GnRH release [74,425]. Glutamate may not only stimulate GnRH release directly, but also indirectly via stimulating the release of the prostaglandin PGE_2 by local astrocytes, with this PGE_2 also facilitating GnRH release [389].

5.4.4. Potential amygdala involvement

Although exploration of the neural instigators of puberty has largely focused to date on influences exerted at the level of the hypothalamic gonadostat, the hypothalamus receives afferent input from a variety of forebrain regions, including PFC and limbic regions such as the ACC and extended amygdala [237,433,462,478], brain areas that undergo notable ontogenetic alterations during adolescence (see below). Adolescent-associated alterations in these forebrain regions could potentially influence the onset of puberty via these hypothalamic afferents. For instance, there is evidence for immaturity of hypothalamic interconnections with forebrain regions such as the amygdala during adolescence [281]. Indeed, there is old and complex literature implicating the amygdala complex in the timing of puberty. The directionality of this influence, however, is controversial, with evidence that the amygdala (particularly the corticomedial and basolateral nuclei) exerts a strong restraining influence on the onset of puberty through hypothalamic inhibition countered by other data supporting an opposite conclusion (see Ref. [371] for extensive review). These dissenting findings are perhaps not surprising when considering the diversity among, and sometimes opposing actions of, nuclei traditionally included within the amygdala complex (e.g. Refs. [149,538]). Given the evidence outlined below for

maturational changes in limbic regions during adolescence, perhaps it is time to revisit the notion that ontogenetic changes in the amygdala and other limbic brain regions may promote hypothalamic events leading to puberty.

6. Neural alterations during adolescence

Impetus for assessment of neural development during adolescence has largely arisen from two quarters, one of which was just reviewed. In addition to these studies that have largely focused on hypothalamic areas and puberty, interest in forebrain regions during adolescence was precipitated by observations that the symptomology of psychological disorders including depression (e.g. see Ref. [302]) and schizophrenia (see Ref. [584] for review) typically increases substantially during adolescence. In other respects, however, the topic of adolescent brain function has received relatively little emphasis in the literature in developmental psychology over the past several decades. Rather, the strategy has been to focus on hormonal changes, an approach that (as discussed earlier in this review) has yielded evidence for at best only modest associations between gonadal hormones and particular behaviors during adolescence.

Back in 1974, Epstein suggested that "fairly abrupt changes in behavior are likely to reflect associated changes in the biophysical properties of brains" ([156], p. 208). Although his view that successive stages of cognitive development are attained via spurts in whole brain growth has been convincingly disputed [218], it nevertheless seems time to re-explore the notion that behavioral and cognitive changes occurring during adolescence may be related to maturational events in brain. Indeed, the adolescent brain is a brain in flux, undergoing numerous regressive and progressive changes in mesocorticolimbic regions. Before detailing these adolescent-associated alterations, we will first turn to a brief discussion of adolescence and schizophrenia, a topic that historically has provided much of the impetus behind studies of forebrain function in adolescence.

6.1. Adolescence, schizophrenia and neural development

Symptomology of schizophrenia typically only emerges during adolescence, although evidence is rapidly accumulating that schizophrenia is a disorder of fetal development that is not fully expressed until at least adolescence (see Ref. [67] for review). In schizophrenic brain, neurons are abnormally located in the innermost cortical layers, findings consistent with a disruption in neuronal migration to neocortex during the second fetal trimester [8,258]; evidence for similar disruptions in migration also have been reported in other brain regions, including hippocampus [100,299]. Among the chromosomal loci with linkage to schizophrenia are regions coding for genes regulating retinoids and retinoic acids, substances that modulate transcription of numerous target genes critical for neural development (see Ref. [205]). Prenatal nutritional deprivation [536] as well as fetal exposure to influenza during the second trimester of pregnancy [360,542] also have been associated with a modest increase in risk of developing schizophrenia (see Ref. [584] for review, including discussion of negative findings). Genetic and environmental factors may interact to increase the probability for later development of schizophrenia, with a genetic deficit perhaps predisposing the developing nervous system to be adversely affected by viruses, nutritional deficiencies, birth traumas, or drug/toxin exposure occurring early in life [332,359].

Although not sufficiently outside the normal range to be diagnostically useful, children that will eventually develop schizophrenia differ in a number of respects from other children, showing transitory neuromotor abnormalities [577] and developmental delays [264], and being anxious and socially withdrawn relative to other children [138,264]. Yet, overt symptomology of schizophrenia typically emerges only during adolescence. This delayed emergence is opposite the more typical situation of greater recovery following early brain damage—the so-called "Kennard Principle". Yet, there is some precedent in the animal literature for delayed emergence of lesion effects. For instance, deterioration of function emerges over time following early lesions of the PFC in rats [173] and nonhuman primates [203]. Deficits following excitotoxic lesions of the ventral hippocampus in infant rats become evident only during the adolescent period, effects that are more pronounced than after presumably comparable damage sustained in adulthood [329,330,332].

Researchers have surmised that relatively late maturational events occurring during puberty in the PFC, hippocampus, or other limbic regions somehow trigger symptoms of early brain damage such as the onset of overt schizophrenia (e.g. Ref. [331]). Specific maturational events have yet to be definitively linked, however, with symptom emergence. Stress has been postulated to play an important role. Stressors have often been reported to exacerbate if not precipitate episodes of heightened schizophrenic symptomology [49], with stress-precipitated neurochemical sensitization postulated to contribute to the pathophysiology of schizophrenia [327]. Early brain dysfunction may predispose certain individuals for the later development of schizophrenia by increasing their sensitivity to stressors during the vulnerable stage of adolescence [49,331]. Indeed, among the neural regions undergoing developmental alterations during adolescence are stress-sensitive forebrain regions (e.g. Ref. [147]), including regions involved in glucocorticoid negative feedback inhibition of stress-related HPA activation [136,482] as well as those critical for the expression of sensitization to stressors and drugs [268,273,423].

6.2. Cortical synapse elimination and "developmental hypermetabolism"

Globally speaking, there is a massive loss of synapses in

neocortical brain regions during adolescence. The magnitude of this loss is difficult to fathom, with Rakic and colleagues [450] estimating that as many as 30,000 synapses may be lost per second over the entire cortex during the pubertal/adolescent period in primate brain, leading to an ultimate loss of almost one-half of the average number of synapses per cortical neuron that was evident in the preadolescent period. Similar overproduction and pruning has been reported in human neocortex (e.g. Ref. [249]). The scarcity of postmortem brains from human children and young adults, however, makes it difficult to determine the precise ontogenetic time course of this pruning which appears to occur largely after 7 years and prior to 16 years of age [248].

The functional significance of this presumed synaptic down-sizing in the neocortex of adolescents is not known, although it is speculated that such pruning is an example of developmental plasticity whereby the brain is ontogenetically sculpted on the basis of experience to effectively accommodate environmental needs [450]. Keeping in mind that correlated developmental events cannot be used to infer causality, it is nevertheless interesting that along with this developmental loss in synapses is an increase in focal activation of the brain, with less widespread activation of brain function during task performance as development proceeds through childhood and adolescence [76]; see also Ref. [52] for discussion). Adolescence in humans is also associated with a marked increase in the degree to which the two cerebral hemispheres can process information independently [362] and in the amount of hemispheric asymmetry evident in the EEG [19]; independent growth trajectories for different cortical regions likewise emerge at this time [247]. Age-related changes are also evident during adolescence in magnetic resonance imaging (MRI) of cortex [260], with this imaging not approximating average adult levels until 20 years of age [517]. Increases in EEG dimensional complexity are also seen through adolescence in humans, along with an adolescent-associated decrease in beta power which is especially pronounced in frontal regions, findings attributed to an overall decline in EEG amplitude at this age [18].

Receptors of a variety of different neurotransmitter systems (including DA, 5HT, acetylcholine (ACh), and GABA) are overproduced and undergo pruning during infancy and adolescence in primate cortex [325,326]. Yet, most of the synapses undergoing developmental pruning during adolescence are asymmetrical and presumed to be excitatory in nature; thus, this synaptic pruning presumably results in a major decline in the amount of excitatory stimulation reaching cortex [450]. Substantial amounts of energy are required for neural activity in brain, brain activity that can be roughly estimated from rates of glucose metabolism, oxygen utilization and blood flow. Not surprisingly given the apparent adolescent-associated curtailment of excitatory input to cortex, these measures of brain activity likewise show developmental declines during adolescence. For instance, brain rates of glucose metabolism increase ontogenetically to reach a plateau well above adult levels by 3–4 years of age; this plateau is sustained until the beginning of the second decade at which time metabolic rates begin to decline, reaching adult levels by the end of that decade [88]. Such “developmental hypermetabolism” is particularly evident in neocortex and forebrain regions [86] and is also evident when examining blood flow and oxygen utilization, with these rates likewise declining during adolescence until adult levels are reached (see Refs. [87] and [170] for review and references). Interestingly, similar developmental hypermetabolism is evident in other species as well, with rates of oxygen consumption and glucose utilization greater in 4–7 week-old (adolescent) rats than adult rats [562] and glucose metabolic rates elevated above adult levels in cats until after sexual maturation [86].

6.3. Alterations in prefrontal cortex and limbic brain regions

Because of the hypothesized importance of maturational changes in PFC or closely related limbic regions for the emergence of overt schizophrenic symptomology in late adolescence [331], particular interest has been directed toward this brain region in the adolescent. This focus has been productive. PFC is prominently remodelled during adolescence across a variety of species, with the volume of PFC declining around adolescence not only in humans [197,260,508] but also in rats [565]. Density of spines on pyramidal cells in human PFC declines between adolescence and adulthood [376]. As in other cortical regions (see Section 6.2), substantial synapse elimination of presumed glutaminergic excitatory input occurs during adolescence in PFC of humans [249] and nonhuman primates [608]. This synapse elimination may have functional consequences; preadolescent (7–12 year-old) human youth exhibit greater prefrontal activation during a go/no-go task than the volume of prefrontal activation seen in young adults (21–24 years of age) [76] and performance on a number of neuropsychological tasks purportedly involving PFC function continues to improve into adolescence [320,588]. In rats, cortical binding to NMDA receptors peaks during early adolescence (P28), with a loss of about 1/3 of these cortical glutamate receptors by P60 [253]. Complementary to this adolescent decline in NMDA receptors, sensitivity to neurotoxicity induced by antagonists to these NMDA receptors increases considerably in late adolescence (around P45) and becomes maximal in early adulthood [167].

In contrast to the adolescent-associated loss of excitatory drive to cortex [608], DA input to PFC increases during adolescence in nonhuman primates to peak at levels notably higher than those seen earlier or later in life ([469,470]; see Ref. [322] for review). Increases in DA input to PFC are also evident during adolescence in rats as indexed by PFC DA fiber density (increasing until P35 in superficial layers and continuing to P60 in other layers) [269], as well as by

neurochemical assessments of DA concentrations in the frontal pole (where marked increases are evident between 4 and 6 weeks postnatal) [319]. Density of DA transporters (often used as an index of innervation density—e.g. see Ref. [7]) likewise appears to increase into adolescence. Weanling rats exhibit only about 70% of adult levels of the DA transporter in PFC, ACC, and olfactory tubercles [102], while binding to the DA and 5HT transporters reach levels not significantly different from adults by early-mid adolescence (P28–35) [545]. Cholinergic innervation of PFC also increases to reach mature levels in adolescence in rats [208] and humans [298]. Further evidence for delayed development of prefrontal regions continuing through adolescence has been obtained in lesion work, with bilateral lesions of the sulcal PFC in rats at 60 days of age and older resulting in aphagia and adipsia, effects that were not evident when the animals were lesioned before or at 40 days of age [294].

Maturational changes are also evident during adolescence in other limbic regions such as the hippocampus of rodents [145,600] as well as humans [39]. As in PFC, glutamate receptors in hippocampus undergo substantial pruning during adolescence, with a loss of about 1/4 of the NMDA receptors in hippocampal pyramidal regions between P28 and P60 in rats [253]. Sensitivity of the hippocampus to novelty-induced increases in c-fos activation only emerges during adolescence, being evident in P30 rats but not those tested at P16 or P23 [578]. Hippocampal lesions in weanling-age rats restore sensitivity to amphetamine in adolescent animals that normally exhibit little locomotor response to the drug [308]. Cannabinoid binding sites in limbic forebrain of rats peak between P30 and P40 before declining to reach adult levels [467], while oxytocin receptor binding in olfactory tubercles and ventral pallidum increases markedly between P40 and P45 [558].

The adolescent amygdala is also of interest in humans and other animals. Rats from P26 to P40 are markedly more sensitive to seizures induced by electrical stimulation of the amygdala than are younger or older rats [553]. Young adolescent (P28) rats have been reported to exhibit less stress-induced c-fos activity in certain amygdala nuclei than P60 rats [281]. Age-specific differences in amygdala activity in human adolescents versus adults were reported in a recent functional MRI study [606]. In this intriguing preliminary report, adolescents were reported to exhibit greater brain activity in the amygdala than in the frontal lobe when engaged in a task requiring the subjects to identify emotional state from facial expressions, while adults conversely exhibited greater activation in frontal lobe than amygdala when engaged in the same task.

6.4. Alterations in DA systems

In addition to the notable adolescent-associated increase in DA concentration and fiber density in PFC discussed above, there are other indications that DA systems undergo substantial reorganization during adolescence. Analogous to the often inverse relationship between DA terminal density and levels of DA activity seen following collateral sprouting of DA terminals in mesocortical brain regions of adult animals (e.g. Ref. [548]), the developmental increase in DA fiber density in PFC during adolescence may be at least partially compensated later in adolescence by a developmental decline in DA synthesis and/or turnover in this region. Levels of basal DA synthesis in PFC of rats increase to considerably elevated levels at P30 before declining to lower levels by later in adolescence (P40) [11], with estimates of basal DA turnover in PFC likewise greater at P30 than in adulthood [551]. Conversely, estimates of basal DA synthesis in ACC are lower early (P30) than later (P40) in adolescence, with estimates of DA turnover likewise being lower in young adolescent rats (P30) than adult animals [11]. Similar developmental increases in estimates of DA turnover are also evident in rat striatum, although estimates of DA synthesis remain relatively constant throughout this ontogenetic period [11,551]. A somewhat different ontogenetic pattern was reported by Leslie and colleagues [319] who observed that in both the frontal pole and in the remainder of forebrain, estimates of DA turnover were considerably lower in adolescent (4–6 week-old) than younger (1–3 week) rats, although postadolescent age groups were not included for comparison.

Developmental overproduction followed by pruning of DA receptors during time periods subsuming adolescence has been reported in both humans and rodents. Seeman and colleagues [488] observed notable changes in DA receptor populations in human striatum during the juvenile-to-adult period, with one-third to one-half or more of the DA D_1-like and D_2-like receptors present in the striatum of juveniles being lost by adulthood [488]. Although some work has failed to reveal ontogenetic alterations in the D_2 receptor, developmental declines in D_1 receptors from infancy to adulthood in humans have been confirmed by others [372,394]. In rats as well, D_1 and D_2 receptor binding in striatum have been reported to undergo a developmental decline, peaking in adolescence (P40) at levels that are about 30–45% greater than those seen in adulthood ([544,546,550]; see also Ref. [195]). Evidence is mixed as to whether similar ontogenetic alterations are evident in rat ACC, with work reporting notably less pronounced overproduction and pruning in this brain region than in striatum [550] contrasting with other data showing a clear peak in both D_1 and D_2 receptors in ACC during early adolescence (P28) followed by a loss of about one-third of that binding between P35 and P60 [544,546]. Findings of DA receptor overproduction and pruning in mesolimbic brain regions during adolescence are not ubiquitous; Leslie and colleagues [319] reported only a gradual ontogenetic increase in D_1 binding in striatum and ACC, although the oldest rats examined in that study were adolescents (6 weeks of age) and inclusion of an adult comparator group may have revealed broader ontogenetic patterns.

In contrast to the ontogeny of D_1 and D_2 binding in subcortical (striatal and mesolimbic) brain regions, no comparable adolescent peak and subsequent decline in D_1 and D_2 receptors have been observed in PFC of rats [544,546], although reports disagree as to whether [319] or not [546] there may be an early, preweanling peak in PFC D_1 receptors to reach levels significantly above those seen in older animals. Moreover, whereas ontogenetic patterns of D_4-like binding have been reported to be similar to those of D_2 receptors [544], D_3 receptor ontogeny does not appear to be characterized by a period of overproduction followed by pruning (other than a transient developmental expression of D_3 receptors during the preweanling period in somatosensory cortex that is not evident in weanling and older animals; [121]). Only monotonic increases in D_3 receptors have been reported in rat ACC, striatum, olfactory tubercles, although there is some disagreement as to the time course of these increases, with reports of DA D_3 binding at weaning approaching adult levels [121] versus being only 40% of adult levels [516].

In these ontogenetic binding studies, gender of animals examined may be critical. D_1 and D_2 receptor overproduction and subsequent pruning are more evident in male than female rats [13], although interestingly these ontogenetic alterations are not influenced by gonadectomy of either males or females prior to adolescence [15]. Another potentially important consideration when examining receptor ontogeny is the extent to which data reflect autoreceptors versus heteroreceptors. Low dose suppressant effects of DA agonists emerge during adolescence (e.g. Refs. [235,491,566]), neurochemical and behavioral findings originally postulated to reflect a delayed maturation of inhibitory DA autoreceptors in mesolimbic brain regions [490,510]. This suggestion, however, has not been supported by more recent work [11,175], and the significance of the late ontogenetic emergence of low dose behavioral and neurochemical suppressant effects remain to be determined.

When pondering the significance of ontogenetic changes in DA receptor binding, it is important to consider the functional consequences of activation of these receptors, such as the coupling of these systems to second messenger systems. Andersen and Teicher [14] recently examined the ontogeny of DA agonist-stimulated adenylyl cyclase activity in ACC, striatum and PFC. Basal and forskolin-stimulated cAMP levels were generally greater in P40 adolescents than in P100 adult rats, whereas D_1 stimulatory and D_2 inhibitory effects on adenylyl cyclase production were typically less evident in adolescence than in adulthood (although there were some exceptions to these generalities, with less forskolin-stimulated cAMP in PFC and greater D_1 stimulation in striatum of adolescents than adults). These results were interpreted to suggest differences in DA tone between adolescents and adults [14]. Using another approach to assess functional consequences of DA receptor activation, Bolanos and colleagues [51] examined drug-induced inhibition of ACh overflow in rat striatal slices as an index of extracellular DA activity following administration of indirect DA agonists. They observed that adolescents were more sensitive to the DA uptake inhibitors cocaine and nomifensine (but not the DA receptor agonist apomorphine) than adults, opposite the attenuated behavioral responsivity to these indirect DA agonists during adolescence which they [51] and others (e.g. Ref. [510]) have observed. A similar dissociation between behavioral and neurochemical responses to amphetamine has been reported following PFC lesions in adulthood, with lesioned animals exhibiting less amphetamine-stimulated DA release in caudate but a greater behavioral response to amphetamine [594]. As a possible explanation of the lesion-induced dissociation, down-regulation of caudate DA release was postulated to be associated with a functional up-regulation at other sites that may serve to enhance the amphetamine-induced behavioral response. Indeed, there is substantial evidence for reciprocal relationships among various forebrain DA terminal regions (e.g. see Ref. [500]), with "expressed behavior (being) the result of the summed outcome of competing systems" ([590], p. 9). We will return later to this notion when discussing a potential developmental shift in the balance among different forebrain DA terminal regions during adolescence.

A final bit of confirming evidence for DA maturation through adolescence can be obtained from examining consequences of DA depletion during ontogeny. While extensive depletion of DA induced by the neurotoxin 6-hydroxydopamine (6-OHDA) results in Parkinsonian-like sensorimotor deficits and supersensitivity to antagonists in rats following neurotoxin treatment in adulthood, substantial functional recovery is seen when such damage is incurred early in ontogeny, with adult-typical lesion effects only emerging during adolescence [476,583].

Collectively the available data, albeit sometimes sparse, limited in across-species comparisons and occasionally inconsistent across laboratories, provide considerable evidence for the continued development of mesolimbic and mesocortical DA systems and their terminal regions through adolescence. These adolescent-associated transformations are not exclusive, however, given evidence for alterations in other neural systems during adolescence, as outlined below.

6.5. Alterations in other neural systems

With the attention focused on alterations in DA systems and associated mesolimbic and mesocortical brain areas during adolescence, other regions have received less emphasis. Nevertheless, the research available to date illustrates that adolescent-associated transformations in neural function are not restricted to forebrain DA projections and associated frontal and limbic brain regions.

6.5.1. Adolescence, glutamate NMDA receptors and the GABA/BDP receptor complex

Levels of glutamate and binding to the NMDA subtype of glutamate receptors peak at 2–3 weeks in rat pups, and decline significantly thereafter (see Ref. [223] for review and references). Reminiscent of this ontogenetic time-course, locomotor responses to intra-accumbens infusion of the noncompetitive NMDA antagonist, MK-801, were found to peak in rats at P21 and to decline significantly by P31, suggesting possible synaptic pruning of excitatory glutamate input to ACC or a reduction in accumbal NMDA receptors between weaning and the early adolescent period [174]—findings akin to those discussed previously for PFC.

$GABA_B$ synaptic transmission in hippocampus develops relatively late, gradually maturing between P35 and P45 [385]. Notable maturational changes also occur in the cortical GABA/BDP receptor complex during adolescence, including the emergence of the sensitivity of this system to environmental challenges and stressors. In general, responsiveness of the cortical $GABA_A$ system decreases from adolescence to adulthood, with basal levels of $GABA_A$ receptor mediated chloride uptake greater in cortex from P35 adolescent than adult rats [282]. In contrast, responsiveness of the GABA/BDP receptor complex to stressors and environmental challenges emerges over adolescent development when such responsivity is indexed both in terms of stress-induced alterations in binding to the BDP receptor site as well as with respect to $GABA_A$ receptor mediated Cl^- uptake (e.g. see Refs. [280,282,440] for review and discussion).

6.5.2. Serotonergic alterations during adolescence

Widely scattered evidence supports the suggestion that 5HT systems undergo developmental alterations during time periods that may in some cases include adolescence. For instance, Darmani and colleagues [114] examined ontogeny of psychopharmacological sensitivity to the $5HT_{2A}$ agonist, (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) in mice and observed that DOI-induced head twitches and ear scratching increased developmentally to peak at P28 and between P22 and P35, respectively, with the incidence of both behaviors declining thereafter; DOI-induced increases in locomotor activity were only evident in mice up to 28 days of age and not thereafter. Serotonergic innervation of basal forebrain in rats also shows considerably ontogenetic change, with the number of serotonergic synapses reaching adult levels by P14 prior to dropping to levels considerably below adult levels by weaning at P21 [135]; unfortunately no ages were examined between weaning and adulthood, and hence the relevance of these changes in basal forebrain 5HT systems for adolescent neurobehavioral function are unknown.

Ontogeny of 5HT binding in human adolescents undergoes a developmental decline through ontogenetic periods that may include adolescence. Dillon and colleagues [134] reported a significant negative correlation between age and binding to the $5HT_{1A}$ receptor in male human postmortem brains; although sample sizes were small, the most dramatic decline appeared to occur during the adolescent period (see Fig. 2 from Ref. [134]). Psychopharmacologically, however, developmental declines in responsivity to the indirect 5HT agonist fenfluramine were not seen in humans until after adolescence, with individuals in their twenties showing greater fenfluramine-induced prolactin release than those 30 years or age or older [349].

Estimates of 5HT turnover in ACC have been reported to be approximately 4-fold lower in adolescent (P30–40) rats relative to younger (P10–15) and adult (P60,80) animals, a developmental discontinuity that was not evident in striatum [549]. These findings are provocative, given the often reciprocally modulatory interactions between 5HT and DA systems in the modulation of behavior (e.g. Refs. [464,515]) and similarities between age-associated characteristics often attributed to adolescents and the postulated "traits" associated with predispositions to low 5HT activity (including hyperresponsivity to mild stressors, negative affect, hyperdipsia, increased alcohol drinking, attenuated sleep, and anxiety—[124]).

6.5.3. Endogenous cannabinoid systems in adolescence

Receptors for endogenous cannabinoids mature slowly during the postnatal period [38,467], with binding peaking during adolescence at higher than adult levels in hippocampus [467]. Psychopharmacological data suggest that these endogenous cannabinoid systems may reach functional maturity around adolescence [177,178]. In these studies, administration of anandamide (an endogenous ligand of the cannabinoid receptor) or THC was found to decrease locomotion and induce analgesia in rats examined shortly after the adolescent period (P45) or in adulthood, but not when the animals were tested as preweanlings (P6–20) or weanlings (P23) [177,178]; unfortunately, intervening ages between P23 and P45 were not examined. These findings suggesting the potential functional maturity of cannabinoid systems around adolescence are enticing when considered within the context of postulated alterations in the balance between striatal/mesolimbic and mesocortical DA systems during adolescence (as discussed later in Section 6.6.2). Emergence of an endogenous cannabinoid system during adolescence could potentially facilitate this developmental shift in balance, given evidence (in adult animals at least) for cannabinoid activation of mesocortical DA systems [133] contrasting with indications of negative feedback suppression of DA-induced activation in striatal regions [198].

6.6. Mesocorticolimbic DA regions, motivational states and adolescence

6.6.1. Mesocorticolimbic DA regions and the linkage of motivational states and motor outputs

Developmental alterations in mesocorticolimbic brain

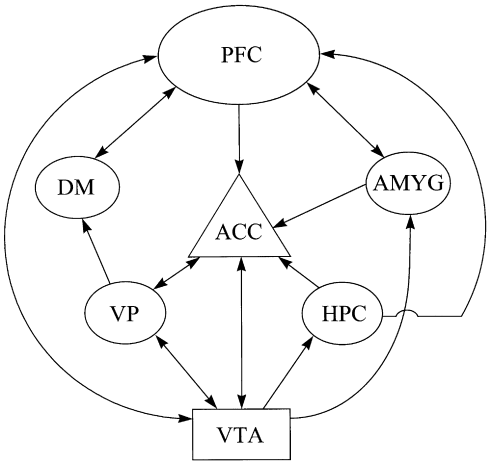

Fig. 1. Highly simplified schematic diagram depicting major interconnections of the accumbens (ACC) and dopamine neurons from the ventral tegmental area (VTA) with mesocorticolimbic brain regions including the prefrontal cortex (PFC), amygdala (AMYG) and hippocampus (HPC). DM, dorsomedial nucleus of the thalamus; VP, ventral pallidum.

regions may have considerable functional relevance for the adolescent. These regions form part of the circuitry implicated in drug reward processes [295,297], attributing appetitive value [487] or incentive salience to stimuli [42], translating motivational stimuli into adaptive behaviors [267], and integrating sensory and motor systems to facilitate flexible approach responses [250]. The shell portion of the ACC has been suggested to play a particularly important role, forming a central component of the "motive circuit" (VTA/ACC/ventral pallidum) serving to integrate input regarding motivational state from diverse limbic structures and convey this information to motor systems [267], as well as of the circuitry of the extended amygdala thought to play a critical role in the activating and associative components of drug reinforcement [297]. The ACC is thought to serve as an interface between the limbic systems and motor systems [123], and may ultimately influence cortical processing of sensory stimuli as well [215]. The ACC largely receives excitatory input, with much of this input being derived from the PFC as well as from various limbic brain regions that modulate basic biological drives and motivational states [370] (see Fig. 1). Limbic input from regions such as the amygdala and hippocampus may serve to "gate" responsiveness of the ACC to input from afferent regions such as the PFC [221]. The ACC also receives dense DA inhibitory input from the VTA that may also provide a critical filtering influence on limbic input to ACC [370], with increases in this DA transmission presumedly increasing the gain of information through the "motive circuit" so that this information becomes more motivationally relevant [267]. All of this ACC activity is presumably subject to the "overarching control of the prefrontal cortex" ([123], p. 470).

As in ACC, DA input to PFC is likewise functionally inhibitory, presumably via direct DA inhibition of pyramidal cells as well as perhaps indirectly via GABA interneurons [220]. The net effect is thus DA inhibition of these pyramidal cells, reducing glutamatergic excitatory output from the projections of these pyramidal cells to brain regions including the ACC as well as to DA neurons in the VTA and SN (see Ref. [267]). DA projections to PFC are very sensitive to activation by even relatively mild stressors, while mesolimbic DA projections require greater stressor levels for mobilization, with only intense stressors recruiting DA activity in striatum as well (e.g. Ref. [147]).

DA projections to PFC affect subcortical DA neurotransmission, with levels of DA activity in PFC generally being inversely related to DA release in subcortical regions, a conclusion based on work with rats (see Refs. [126,331] for review) as well as nonhuman primates [293,593]. This characterization of an inverse relationship between DA activity in these two brain regions is undoubtedly overly simplistic to explain the full range of functional interactions (e.g. see Refs. [593,594]) and ignores, for example, the important distinction between tonic and phasic DA release in subcortical DA terminal regions [213,373]. Nevertheless, DA depletion in PFC is often associated with increases in DA utilization in subcortical sites. This increase in DA utilization in ACC is sometimes [227,444] but not necessarily [127] evident in terms of increases in basal DA utilization rates, but is more typically characterized by a notable increase in the sensitivity of DA terminals in ACC to stressors [127,290]. Increases in DA stimulation of PFC conversely attenuate DA activity in striatal and limbic terminal regions [274,293] and attenuate motor stimulatory effects of systemically administered stimulants such as amphetamine and cocaine [272]. Manipulations of limbic activity have been reported to exert opposite effects on DA metabolism in PFC versus ACC, with hippocampal lesions decreasing DA metabolism in PFC but increasing it in ACC [328], while the converse is seen following amygdala kindling [448].

6.6.2. Possible alterations in the balance between the mesocortical and mesolimbic DA terminal regions during adolescence

The limited neurochemical and anatomical evidence available to date supports the suggestion that there is a shift in the relative balance between subcortical and cortical DA systems during adolescence toward a greater predominance of cortical DA in early adolescence. Mesocortical DA influence appears to peak at this time, based on adolescent-associated increases in DA concentrations and fiber density in PFC [269,319,469,470] along with evidence that basal DA synthesis and turnover peaks early in adolescence in PFC [11,551]. Activity in this DA projection system might be further enhanced during adolescence by the ontogenetic disappearance of an early DA autoreceptor-like modulation of DA synthesis that functioned to inhibit DA synthesis in this brain region prior to adolescence [11,552]. These factors may work together to ensure that DA inhibitory input to PFC is at its highest level early in adolescence,

with an adolescent-associated loss in excitatory drive to cortex (e.g. Ref. [608]; see discussion above) perhaps further amplifying the inhibitory impact of this DA input. Associated with evidence for enhanced DA tone in PFC during adolescence, there is some, albeit more limited, support for the suggestion that DA activity in ACC and other subcortical DA terminal regions is lower in adolescents than adults. For instance, basal extracellular DA levels in dialysates from adolescent striatum are lower than from the striatum of adult rats [12]. Young adolescent (P30) rats also display lower estimates of DA synthesis in ACC relative to older adolescent (P40) animals and lower ACC DA turnover rates relative to adults, opposite the ontogenetic profile seen for these measures in PFC ([11,551]; but see also Ref. [319]).

The proposed shift in the balance between mesocortical and mesolimbic brain regions during adolescence might become even more pronounced by stressors. Mesocortical DA projections are more sensitive to activation by stressors than mesolimbic (and striatal) DA systems (e.g. Ref. [147]), and hence any preponderance of mesocortical over subcortical DA transmission during adolescence would be expected to be further exacerbated by stressors [69].

6.6.3. Behavioral correlates, theoretical considerations and some caveats

While the limited available neurochemical and anatomical data are generally consistent with the notion of some shift toward greater predominance of DA activity in PFC over that in ACC early in adolescence, this suggestion must be tempered by consideration of potentially relevant pharmacological and lesion data. To the extent that adolescence is associated with a shift in balance of DA function toward greater PFC than ACC activity, adolescents might be expected to resemble in some respects adult animals with elevated DA activity in PFC or with attenuated DA function in ACC. Indeed, acute intracortical injection of DA into frontal regions of adult rats has been reported to attenuate responsiveness to systemically administered stimulants [272] as well as to disrupt expression of sensitization to cocaine [435], data reminiscent of the similarly reduced response of adolescent rats to acute stimulant exposure [51,308,313,491,507,510,511] and attenuated expression of cocaine sensitization [507]. Likewise, adult rats with 6-OHDA lesions of DA input to ACC, like their normal adolescent counterparts (as discussed earlier), are hyperphagic [160,296], less sensitive to locomotor activating effects of psychomotor stimulant drugs [296], and exhibit problems adjusting to alterations in reward contingencies (see Ref. [317] for review and references). Yet, in other respects the behavior of adult lesioned animals and normal adolescents vary. Adult animals with extensive lesion-induced depletions of ACC DA are not hyperactive and often exhibit attenuated exploratory behavior, opposite that generally seen in adolescents; lesioned adults also exhibit reduced self-administration of psychomotor stimulants [317], opposite the predicted increase in drug use propensity in adolescence. It is uncertain, however, how relevant the behavioral consequences of extensive lesion-induced depletions of DA in adult brain are for functional modifications seen following the more modest alterations in neural function projected to occur in normal adolescents.

Even within physiological ranges of DA function, there is some controversy as to whether increases in drug seeking behavior are related to elevations or reductions in mesolimbic DA activity (or perhaps even to deviations in either direction, if the relationship between DA activity and drug intake is non-monotonic, as often the case in psychopharmacology with its high prevalence of inverted U-shaped relationships). According to the traditional DA hypothesis of reward, activity in mesolimbic DA systems should be positively related to drug seeking behavior (see Ref. [509] for review), a hypothesis supported by the lesion data mentioned above. Also congruent with this perspective are data from the Le Moal, Piazza and Simon groups showing that animals labelled as high responders (HR) in terms of their elevated locomotor response to a novel environment not only exhibited increased novelty seeking and an enhanced probability of self-administering a low dose of amphetamine, but also exhibited greater DA activity in ACC and lower DA activity in PFC than animals characterized as lower responders (LR) in their response to the novel environment [420].

Yet, others have suggested that enhanced vulnerability to drug use and abuse is associated with a reward deficiency syndrome [47,190]. Due presumably to functional deficits in mesolimbic DA reward systems, individuals with this reward deficiency may find reinforcing stimuli less pleasurable than others do, leading them to "actively seek out not only addicting drugs but also environmental novelty and sensation as a type of behavioral remediation of reward deficiency" ([190], p. 82). The range of functional DA deficiencies potentially associated with such a reward deficiency syndrome remains to be completely characterized; among the possibilities are lower extracellular DA levels [190] and/or lower DA D_2 receptor levels (due to expression of the A_1 allele of the D_2 receptor gene; [47]).

A variety of types of evidence supports the notion that increased propensity for drug use and abuse is associated with a reward deficiency syndrome perhaps resulting from functional deficits in DA reward systems. To give but a few examples (see Ref. [190] for more extensive review), rodents selectively bred for high ethanol consumption typically exhibit low levels of DA (and sometimes 5HT) in ACC (e.g. Ref. [350]), while abstinence from drug use in human addicts is associated with hypofunctional DA systems (see Ref. [509] for review and references), with the withdrawal phase characterized not only by cravings, but anxiety, lack of motivation, boredom and anhedonia [193]. Individuals with increased genetic risk of alcohol dependence are less sensitive to ethanol's intoxicating (as well as motor impairing) effects (e.g. Ref. [234]), a reduced sensitivity that

significantly increases the risk of future alcoholism ([485]; see, however, Ref. [382] for an alternative view).

When attempting to relate drug seeking behavior to either elevated [317] or attenuated [190] activity in mesolimbic DA "reward" systems, it may be useful to consider the issue of tonic (resting levels) versus phasic (impulse dependent) release of DA in ACC. As detailed by Grace [213], glutaminergic afferents arriving from PFC regulate steady state levels of "tonic" DA release in ACC, while these tonic levels in turn regulate the magnitude of "phasic" DA release in ACC induced by DA neuronal firing. This tonic regulation is homeostatically driven, with high tonic levels serving to reduce (and low tonic levels increasing) intensity of impulse-driven, phasic DA release. Given this inverse relationship between tonic and phasic DA release, conclusions regarding the nature of the relationship between mesolimbic DA activity and reward may well be influenced by the nature of the assessments used and the degree to which they reflect tonic or phasic release and their associated homeostatic processes.

Thus, while there is reasonable evidence for developmental alterations in mesocorticolimbic DA systems and related circuitry that process incentive stimuli during adolescence, the precise nature of these maturational events seemingly defies easy categorization and will require further exploration. This perhaps should not be surprising, given that the "precise mechanisms through which changes in corticostriatal function may impact on subcortical DA release, and the precise sites at which such transsynaptic regulation occurs, remains to be elucidated" even in the adult organism ([68], p. 658), let alone one that is undergoing developmental change. One serious complication is the difficulty in distinguishing whether particular neurochemical and anatomical characteristics of adolescence reflect primary developmental changes or compensatory reactions to other developmental events. Alterations in DA function typically precipitate homeostatic regulatory responses within other portions of the DA system (e.g. see Refs. [548,609]). Distinguishing between primary neural alterations and their often conversely directed, partial compensations may thus be of considerable theoretical as well as pragmatic importance in determining potential developmental shifts in the balance among various DA terminal regions.

Also remaining for future investigation is the critical issue of how well these developmental alterations in mesocorticolimbic brain regions largely derived from work with rodents represent developmental events occurring in the brains of human adolescents. Despite continuing advances in brain imaging techniques, exploration of subtle compensatory interactions among mesocorticolimbic DA systems and their relation to other related neural systems in human brain still represents a considerable challenge.

As an additional caveat, it is likely that reciprocal relationships among forebrain DA terminal regions may extend beyond the PFC/ACC comparisons emphasized here [500], although the dearth of pertinent adolescent data for other regions constrains their consideration at present. Adolescent-associated alterations in non-dopaminergic systems may likewise contribute to the functional characteristics of this age span. Thus clearly the notion of a simple static shift in the balance of DA activity between PFC and ACC during adolescence, although potentially of transient heuristic usefulness, is unlikely to ultimately provide a sufficient model of the full dynamics of the adolescent brain in flux.

Promising terrain for future exploration is the adolescent amygdala and its DA input [289]. From studies conducted in laboratory animals, nuclei within the amygdala have been suggested to form a critical part of the circuitry modulating emotional reactivity [187,216], the set point for hedonic tone [190], attentional and representational processes [244], and behavioral responses to stressors and other incentive stimuli [297,314]. DA activity in the ACC is under inhibitory control of the amygdalar DA system [339], with 6-OHDA lesions of DA input to the amygdala facilitating acquisition of amphetamine self-administration in rats [120]. The amygdala has been suggested to be tonically inhibited by PFC activity [116]; indeed, metabolic activity in the amygdala of humans is inversely related to activity in the PFC and is correlated with levels of negative affect and anxiety [115]. Recent preliminary findings suggesting greater involvement of the amygdala in processing of emotional stimuli in human adolescents than adults [606] when combined with evidence that the amygdala complex is one of the few forebrain areas shown to notably influence the timing of puberty (see Ref. [371]) provide appreciable rationale for further exploration of the amygdala of the adolescent.

6.7. Adolescent-associated shifts in the value of incentive stimuli: adolescent anhedonia?

To the extent that the ACC and related brain regions are critical for integrating the motivational value provided by different limbic inputs, developmental alterations in these regions and the balance within the mesocorticolimbic DA systems might well alter the incentive value attributed to different types of motivationally relevant information. Indeed, given clear differences between adolescents and adults in mesocorticolimbic function, it would be surprising if adolescents did not differ from adults in various aspects of their motivated behavior. Recalling the behavioral characteristics of human adolescents discussed previously provides some evidence consistent with the notion that adolescents exhibit age-related shifts in the incentive value which they attribute to stimuli. Adolescence across a variety of species is typically associated with an increase in importance attributed to social reinforcers outside the family unit. Adolescents also generally seek out new stimuli (novelty seeking; risk taking). Increases in consummatory behavior for appetitive reinforcers such as food (hyperphagia) is also evident in both human and nonhuman animals and, importantly, this may extend to drugs of abuse as well.

Whether such increases in consummatory behavior are related to increases or decreases in the incentive value attributed to these stimuli is not intrinsically obvious: consumption could be increased because the reinforcer is viewed as more appetitively salient, or alternatively because more must be consumed to obtain its limited reinforcing consequences. This issue has likewise haunted the adult literature (e.g. see Ref. [30] for discussion). Yet, in certain respects, there appears to be some degree of adolescent anhedonia. Human adolescents exhibit an increase in negative affect/affective disturbances/depressed mood relative to younger or older individuals [309,415,472]. Although high negative affectivity does not necessarily imply a lack of ability to experience pleasurable experiences [579], in addition to greater negative affect adolescents also appear to experience and expect to experience positive situations as less pleasurable than other aged individuals. Between late childhood and early adolescence (5th to 7th grade), the number of reports of feeling "very happy" drops by 50%, a "falling from grace" documented by Larson and Richards [310]. Even when engaged in the same activities, adolescents find them less pleasurable than do adults [310]. In terms of their expectations for future rewards, adolescents (12–18 years of age) are less optimistically biased when compared with either college students or adults (18–65 years of age) [365]. A final example considers a recent study exploring ontogenetic differences in preference for sweet tastes in human children, adolescents and adults [119], findings potentially relevant here given the frequent use of taste preferences to index hedonic capacity. Sensitivity to sugar was generally found to increase ontogenetically, whereas optimal preferred sugar level declined with age. Interestingly, when examining Fig. 3 of the report [119], adolescents seemed to find low concentrations of sucrose less pleasant than children and adults and to demonstrate a relatively flat curve between these variables, not showing the decline in pleasantness seen at higher concentrations in adults. This apparent relative indifference to sweetness intensity in adolescents was not explored by the authors, however, and hence its reliability is uncertain.

Together these bits of evidence raise the tentative speculation that adolescents may generally attain less positive impact from stimuli with moderate to low incentive value, and may pursue new appetitive reinforcers through increases in risk taking/novelty seeking and via engaging in deviant behaviors such as drug taking. The suggestion is thus that adolescents display a mini-"reward deficiency syndrome" which is similar, albeit typically transient and of lesser intensity, to that hypothesized to be associated in adults with DA hypofunctioning in reward circuitry including the ACC [190]. Such a transient reward deficiency syndrome is consistent with the proposed adolescence-associated shift in DA balance toward PFC predominance, resulting in net DA hypofunctioning in ACC at this time.

When considering this notion, it is interesting to reflect upon our earlier discussion that adolescent rats are less sensitive than their adult counterparts to many of the effects of psychomotor stimulants [308] and alcohol [334,496]), which at least in the latter case may be associated with increases in consumption capacities and relatively high levels of "binge" alcohol use [346]. Furthermore, given evidence that corticosterone contributes to the rewarding value of drugs [199,201], earlier discussed findings that adolescent rodents exhibit lower drug-induced increases in plasma corticosterone than adults [29,312,313,497] may likewise be of relevance. Rats during adolescence also exhibit numerous age-specific peculiarities in the way they respond to reward contingencies, showing delayed extinction in an aversive task [378], but more rapid extinction and reduced partial reinforcement extinction effects for appetitive reinforcers (e.g., [56]). Moreover, although generally hyperphagic [379], adolescent rats within the context of appetitive conditioning studies "tended to…often drop and ignore food in the goalbox" ([510], p. 99). Thus, adolescent rats, seemingly like their human counterparts, may exhibit a shift in the incentive value they receive from appetitive and aversive stimuli, although this possibility has yet to receive systematic experimental examination.

7. Summary and final comments

Over the past several decades, research in developmental psychology has placed surprisingly little emphasis on adolescent brain in the quest for determinants of adolescent-typical behavioral propensities. Yet the adolescent brain is a brain in transition, and differs anatomically and neurochemically from that of the adult. Although the data in some cases are still limited, this remodelling of brain during adolescence appears highly conserved across species and may involve age-specific modifications in the balance between DA in PFC and in mesolimbic brain regions such as the ACC. These stressor-sensitive brain regions play important roles in gating the flow of motivationally relevant information associated with a broad variety of stimuli ranging from novel objects or social stimuli to psychoactive drugs. Given the neural transformations occurring during adolescence in these brain regions, it would be remarkable if adolescents did not differ from individuals of other ages in their motivated behavior toward these and other reinforcing stimuli.

Indeed, adolescents appear to show some signs of attaining less appetitive value from a variety of stimuli relative to individuals at other ages, perhaps leading them to seek additional appetitive reinforcers via pursuit of new social interactions and engagement in risk taking or novelty seeking behaviors. Such adolescent-typical features may have been adaptive evolutionarily in helping adolescents to disperse from the natal unit and to negotiate with success the developmental transition from dependence to independence. In

the human adolescent, these propensities may be expressed, however, in alcohol and drug use, as well as a variety of other problem behaviors.

Despite the appealing ontogenetic associations between adolescent-typical behavioral characteristics and brain function in relevant brain regions during adolescence, causality of course cannot be inferred. The rather piecemeal observations of adolescent brain to date need to be integrated within a broader characterization of adolescent brain function, with the relationship of these neural alterations to adolescent-typical behavior patterns substantiated using experimental approaches. In this work, it may be important to consider that some of the neural changes occurring during adolescence could potentially serve to protect consistency in behavior as the individual progresses through the hormonal, neural and physical upheaval of this transition. This perspective is akin to that reached by De Vries and Boyle [129] in their work examining sex differences in brain, where they concluded that some sex-specific neural characteristics contribute to sex differences in function, while others prevent functional sex differences despite considerable physiological and hormonal differences between the sexes.

To the extent that transformations occurring in adolescent brain contribute to the characteristic behavioral predispositions of adolescence, adolescent behavior is in part biologically determined. Yet, biology is not destiny, and is modifiable by social behavior and other experiences. As Gariéty and colleagues [192] concluded from their assessment of the contribution of genetics, neurobiology and social behavior to aggressive behavior, "behavior should be viewed as the leading edge of biological adaptation"(p. 57). There are likely to be complex multidirectional influences among environmental context, behavior, hormones and brain function during the transitions of adolescence. Whether the normal adolescent brain in transition is unusually sensitive to these influences relative to the more mature brain is unknown territory, and an important area for future inquiry.

Throughout this review, similarities in brain function and continuity of adolescent behavior across species have been emphasized. Yet, species-specific adaptations to adolescence are also evident (see Ref. [408] for examples of some adolescent variations across primate species). As anthropological studies of human adolescents have shown, cultural differences may also exist, with adolescence being less likely to be viewed as a difficult period when the socioculture context is such that adolescent-typical behavioral characteristics are minimally disruptive [484]. Even within a species, there are individual differences in the extent to which adolescent-typical behavioral characteristics are exhibited, with some individuals showing only limited age-related change and the behavior of others representing the extreme (e.g. see Ref. [493]). Thus, although neural factors potentially contributing to continuity across species in adolescent neurobehavioral function have been emphasized in this review, future work could also profitably be directed toward exploring mechanisms underlying species, cultural and individual differences in the functioning of adolescents as well.

Multiple research approaches and study populations are needed when exploring the relationship between adolescent brain and behavior function. Although some aspects of adolescence can be effectively modeled in nonhuman animals, others clearly cannot and will require studies in human adolescents. Recent advances in imaging have made the human brain more accessible for study, yet many questions about adolescent brain in relation to age-related behavioral characteristics require experimental manipulations that necessitate the use of research animals. Studies conducted across multiple levels of analysis will ultimately be needed to relate the unique behavioral features of this critical developmental transition to functioning of the adolescent brain.

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