

FEATURE REVIEW

A role for synaptic plasticity in the adolescent development of executive function

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Adolescent brain maturation is characterized by the emergence of executive function mediated by the prefrontal cortex, e.g., goal planning, inhibition of impulsive behavior and set shifting. Synaptic pruning of excitatory contacts is the signature morphologic event of late brain maturation during adolescence. Mounting evidence suggests that glutamate receptor-mediated synaptic plasticity, in particular long term depression (LTD), is important for elimination of synaptic contacts in brain development. This review examines the possibility (1) that LTD mechanisms are enhanced in the prefrontal cortex during adolescence due to ongoing synaptic pruning in this late developing cortex and (2) that enhanced synaptic plasticity in the prefrontal cortex represents a key molecular substrate underlying the critical period for maturation of executive function. Molecular sites of interaction between environmental factors, such as alcohol and stress, and glutamate receptor mediated plasticity are considered. The accentuated negative impact of these factors during adolescence may be due in part to interference with LTD mechanisms that refine prefrontal cortical circuitry and when disrupted derail normal maturation of executive function. Diminished prefrontal cortical control over risk-taking behavior could further exacerbate negative outcomes associated with these behaviors, as for example addiction and depression. Greater insight into the neurobiology of the adolescent brain is needed to fully understand the molecular basis for heightened vulnerability during adolescence to the injurious effects of substance abuse and stress.

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Adolescent development of executive function

Adolescence is rather inexactly defined as the period beginning with the onset of puberty and ending with the shouldering of adult responsibilities.¹ It is a time of increased propensity to engage in risky behaviors that include experimentation with alcohol, tobacco, drugs and sexual behavior. Dahl¹ has called the adolescent brain a 'natural tinderbox' because gonadal hormones are actively stimulating affective and appetitive behaviors, such as sexual drive, increased emotional intensity, and risk taking, yet the brain systems that regulate and moderate these emotional and appetitive urges are not yet mature.

The prefrontal cortex (PFC) mediates executive functions, i.e., internally guided behavior, goal planning, and impulse control, that form the essence of rational thinking and serve to counter appetitive urges and check risk-taking behavior.^{2,3} The PFC is the last brain region to mature,⁴⁻⁷ and therefore not surprisingly the frontal lobe capacity for internally guided behavior, working memory, and organizational skills do not reach full adult functional capacity until mid to late adolescence.⁸⁻¹²

Crews *et al.*¹³ have drawn parallels between adolescence and early sensory critical periods, which are dependent on plasticity of developing sensory connectivity and allow for environmental (sensory) modulation of maturing sensory connections. Specifically, they have suggested that in

adolescence PFC circuitry may be endowed with similar plasticity and responsiveness to environmental factors, and as a consequence with heightened vulnerability to the detrimental effects of substance abuse and stress.¹³

This review examines the literature on adolescent development across species and focuses on the role that glutamate-receptor mediated plasticity may play in maturation of PFC circuitry in adolescence. It is postulated that adolescence represents a phase of increased activity of long term depression (LTD) mechanisms that predispose to synaptic elimination and further that termination of this LTD-permissive phase marks the transition to adulthood. Finally, consideration is given to the possibility that greater vulnerability to substances of abuse and stress may represent an interaction between these environmental factors and the LTD mechanisms of plasticity that are accentuated during adolescence. The hypothesis put forward in this review, while speculative, is intended to spark further research into possible molecular mechanisms associated with adolescent development of the PFC. Certainly synaptic plasticity has been studied much less extensively in the PFC than in the hippocampus; nonetheless, mounting evidence suggests that both long term potentiation (LTP) and LTD play an important role in cognitive functioning mediated by the PFC and perhaps when disturbed in diseases related to malfunction of this cortex.¹⁴

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Preadolescent development and sensory critical periods

The specificity and topography of brain wiring are not entirely genetically preprogrammed but instead established via dynamic processes occurring in the developing brain. Adolescence represents the final epoch in a series of developmental stages that transform the immature brain into its adult form. In order to fully understand adolescent development, it is important to appreciate how it differs from earlier preadolescent maturation.

The developmental mechanisms that account for major remodeling of connectivity occur before the onset of adolescence, i.e., before postnatal day 28 (PD28) in rodents, 9 months in cats, and 3 years in non-human primates^{15–17} and include prominent degeneration of neurons and axons.^{18,19} Indeed, the immature mammalian brain is distinguished from its adult counterpart by the presence of connections between brain areas that are not interconnected in the mature brain and by overlap of terminal fields that are segregated in the adult brain. For example, in the newborn hamsters and rats, uncrossed retinocollicular projections, i.e. from the retina to the ipsilateral superior colliculus (SC), not only occupy a much expanded territory in the SC relative to that of the adult brain but also originate from nasal as well as temporal retinal ganglion cells.^{20–22} Retraction of the terminal projections is associated with loss of these nasal, ipsilaterally-projecting ganglion cells.²² More generally, in the central nervous system overproduction of neurons with ensuing neuronal death is a common mechanism employed by the developing brain to ensure that the appropriate balance of projection and receptive neurons is attained.^{19,23–25}

A second, pervasive form of degeneration in the developing brain is degeneration limited to axonal connections leaving the neurons of origin intact. For instance, in the central nervous system, cortical callosal projections that are widespread in kittens and young rats are constricted to the adult patterning by retraction of callosal axons without cell loss.^{26–28} Quantitative analysis of axon number in major tracts underscores the magnitude of this form of degeneration as the number of axons in the young non-human primate brain ranges from twice (optic tract) to 3.5 times (corpus callosum) the number in the adult brain.^{29–31} Both forms of degeneration, involving loss of neurons or loss of axons, necessarily are associated with dissolution of established synapses.³² However, these early developmental events are occurring at a time when, overall, synapses are increasing in density.^{33–38} The classic example or early connective remodeling, that of reduction of polyneuronal input on a single muscle fiber to a single axon, illustrates how synaptic number may increase as the surviving single axon sprouts a much more elaborate terminal plexus.^{18,39} Likewise, in the central nervous system regression of inappropriate synapses is more than compensated by growth and expansion of appropriate terminal fields.⁴⁰

A wealth of evidence has established that reorganization of connections throughout the brain is activity dependent and therefore mediated by a Hebbian mechanism.^{41–45} Although normal regression of connections in the visual system can proceed in the absence of visual input⁴¹ there exists a period of plasticity during postnatal development that permits rewiring in response to altered sensory environments.^{43,46,47}

It is noteworthy that critical periods for sensory plasticity occur in the same preadolescent period in which remodeling of connectivity occurs.^{34,48,49}

Adolescence: synaptic elimination and excitatory/inhibitory balance

The maturational event most consistently linked to the adolescent stage of development is reduction of synaptic density or 'synaptic pruning.' Quantitative analyses of synapses in the non-human primate uncovered a synchronous increase in synaptic density in multiple cortical areas that peaks during the postnatal 3rd month, declines slowly (10%) until ~2 years of age with a steeper decline (40%) occurring between 2.7 and 5 years (adulthood).^{35–38} In the human cortex the timing of peak synaptic density is staggered in different regions, but the basic pattern of peak synaptic density in early childhood followed by robust synapse elimination throughout early (auditory cortex) or mid-adolescence (PFC) is in basic agreement with non-human primate studies.^{4,50} More recent data have established that synapse elimination in humans does not end in adolescence but continues at a lower rate into early adulthood.⁵¹ In addition, in human cortex the synaptic related proteins synaptophysin and postsynaptic density protein-95 (PSD-95) show similar patterns of peak in childhood and decline through adolescence,⁵² though it should be noted that a recent study found increasing concentrations of synaptic-related molecules throughout the adolescent epoch.⁵³ Nonetheless, most evidence points to synaptic pruning as the signature late maturational process associated with adolescence. Other species have been studied less extensively but exhibit a comparable pattern. Peak synaptic density was observed by the 7th postnatal week in the cat.³⁴ In rat, recent data suggest that peak spine density in the PFC is present at PD31 with spine density decreasing thereafter until PD 57 or PD60, i.e., early adulthood.³³

Synaptic elimination in adolescence is widely thought to account for the decline in gray matter volume detected via longitudinal magnetic resonance imaging (MRI) of human subjects. Although reduction of synaptic connectivity might be accompanied by retraction of glial and neuronal processes, elimination of neuronal cell bodies occurs much earlier in development.⁵⁴ One of the first longitudinal MRI studies of human subjects detected divergent developmental growth patterns in gray and white matter volumes: white matter volume increased linearly until approximately age 22 whereas cortical gray matter volume in the frontal and parietal lobes peaked just prior to adolescence (~10–12 years) and then declined to adult volumes.⁵ Cross-sectional studies of children and adolescents, including one recent large multi-center study, also show opposing patterns for gray and white matter.^{55–57} Interestingly, changing cortical volumes over this age range are most prominent in the frontal and parietal lobes.^{8,58,59} Indeed, a recent study indicates that there is a progression in which higher cortical association areas like the PFC are last to show reduction of gray matter volume.⁷

The functional significance of synaptic elimination during adolescence, though still enigmatic, probably involves adjustment of the excitatory/inhibitory balance on individual neurons

and within networks. The main argument in support of this hypothesis stems from the specificity of the loss: excitatory synapses are selectively degenerated whereas inhibitory synapses are spared.^{35,37} Even loss of chandelier axon boutons in the PFC, a finding that was originally interpreted as loss of inhibitory synapses,⁶⁰ now supports the elimination of excitatory input in light of new physiologic data.⁶¹ Furthermore, recent evidence has established that D2 dopamine receptors on interneurons undergo a profound maturational change during adolescence.^{62–64} Prior to adolescence, D2 stimulation elicits either no effect or only weak inhibition on interneurons. However, in adult animals stimulation of D2 receptors is strongly excitatory and therefore results in robust firing of interneurons and potent inhibition of their pyramidal cell targets. As a result, inhibition gains a position of ascendancy in adolescence via increased dopamine-mediated firing of interneurons as well as a relative gain in inhibitory/excitatory synapse ratio. In the PFC, neurophysiologic studies have established a critical role for inhibitory synapses in mediating information flow through local networks.^{65,66} Moreover, fast-spiking interneurons mediate gamma oscillations which are essential to cortical computation in many areas of the cortex and to cognitive processing in the PFC.^{67,68} Thus, the correct balance of inhibition and excitation seems to be critical for normative executive function, and conversely, disturbance of this balance is thought to be a fundamental component of psychiatric illness.^{69,70}

Molecular mechanisms associated with synaptic stabilization and synaptic pruning

Synapse stabilization and synapse elimination are primary players in the maturational processes associated with preadolescent and adolescent development. The transition of nascent synapses into mature synapses represents the first step in synapse stabilization. N-methyl-D-aspartate receptors (NMDAR) are localized very early to the postsynaptic membrane, but transition to a more mature synapse state is characterized by recruitment of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPA) to the synapse.^{71–74} Expression of AMPARs on the postsynaptic membrane is induced by NMDAR-mediated long term potentiation (LTP), the same mechanism originally described in hippocampus for learning and memory.^{73–76} A second NMDAR-mediated process, LTD, results when afferent stimulation fails to activate a target neuron.⁷⁶ In many respects LTP and LTD are opposite processes although they engage distinct intracellular signaling mechanisms.^{77–80} Essentially stimulation of NMDARs can induce activity-dependent strengthening of synapses via LTP or weakening via LTD, and AMPAR insertion or removal from the postsynaptic membrane is the conduit for this change in synaptic strength.^{81,82} Importantly, LTP and LTD do not just strengthen or weaken synaptic connections (short term plasticity) but actually trigger the addition or loss of synapses (long term plasticity) even in the adult brain.^{83–92}

Well before the role of NMDAR-mediated LTP in establishing mature synaptic connections was recognized, Constantine-Paton *et al.*⁴⁴ postulated that activity-dependent remodeling of connectivity in the developing brain might be

mediated by NMDARs because these receptors are perfectly suited to detection of synchronized pre- and postsynaptic activation. Growing evidence now supports the idea that LTP and LTD are required for generation of whisker barrel field maps in the primary somatosensory cortex and ocular dominance columns in the primary visual cortex, both involving reorganization of thalamic inputs to layer 4.^{49,93–96} In development, as in learning and memory, plasticity is bidirectional, i.e., synchronized activity of afferent inputs may trigger LTP and resulting synapse maturation and stabilization; conversely, asynchronous activity may diminish synaptic strength via LTD and predispose the synapse to elimination.⁹⁷

Recently, changes in the NMDAR have been linked to critical periods of early developmental plasticity. NMDAR subunit composition shifts from NR2B predominant to NR2A prevalent forms in early development in the visual and somatosensory cortices.^{98–100} Moreover, the shift in NR2B to NR2A shows a rough correspondence to critical periods for sensory plasticity: the beginning of the critical period is marked by an increase in NR2A expression, and the end of the critical period is associated with a decrease in NR2B expression.^{100,101} Importantly, the switch is not locked to a specific age but in fact can be delayed by sensory deprivation, suggesting that it is controlled by activity.^{93,102–105} In turn, the changeover from NR2B to NR2A receptor subtypes controls the sensitivity of these connections to stimulation by NMDARs. For example, in the primary visual cortex of the ferret, NR2B levels are already high at eye opening and decline in layer 4 at the end of the critical period for plasticity of ocular dominance columns but remain high in layer 2/3.¹⁰⁶ Correspondingly, physiologic studies in the cat visual cortex have shown that cortical layer 4 neurons, but not layer 2/3 cells, exhibit reduced sensitivity of visual and spontaneous activity to an NMDAR antagonist at the end of the critical period.¹⁰⁷ Together these findings suggest that the switch from NR2B to NR2A dominated receptors terminates the critical period of experience-dependent plasticity for establishment of ocular dominance columns in the visual cortex.

NMDAR-mediated LTP and LTD may also constitute the molecular underpinnings for adolescent synaptic pruning, albeit with greater emphasis on LTD and synaptic elimination. How could the same mechanism account for two very different developmental processes? Perhaps the period of adolescence corresponds to a widespread shift in the balance of LTP/LTD mechanisms and a corresponding prevalence of synaptic elimination over synaptic addition. In rat hippocampal slices, an increased NR2A/NR2B ratio has been linked to decreased spine motility and increased synaptic stabilization, suggesting a role in the NMDAR subunit composition in halting synaptogenesis.¹⁰⁸ Furthermore, the NR2A state is less conducive to LTP. This is because calcium/calmodulin-dependent protein kinase II (CaMKII), which has a well established role in LTP,^{109,110} binds preferentially to the NR2B subunit.^{110–112} Accordingly, NR2B expression on the postsynaptic membrane has been shown to be necessary for LTP induction, while a role for NR2A in LTP is not well established.^{113–115} Moreover, NR2A expression is enhanced by ligand binding to NMDARs and therefore is activity-modulated whereas NR2B expression is not dependent on previous activity.¹¹⁶ The NR2A subunit is therefore thought to

be responsible for metaplasticity of synapses, i.e., a change in the likelihood of subsequent synaptic plasticity.^{117,118} With age and activity, NR2A subunits become incorporated into the postsynaptic membrane, replacing NR2B subunits.¹¹⁶ The resulting increased NR2A/NR2B ratio translates into a higher threshold for induction of LTP and conversely a state that is more favorable for induction of LTD.^{118,119}

The role of plasticity in the neocortex is not as well established as in the hippocampus. However, NMDAR-mediated LTP and LTD have been described in the visual neocortex¹²⁰ and at multiple synapses in the PFC.^{121–123} Notably, LTD mediated through metabotropic glutamate receptors (mGluRs) has emerged as a major alternative to NMDAR-mediated LTD in widespread areas of the brain^{124–126} and therefore deserves consideration as a possible molecular basis for synaptic pruning in the PFC. In this regard, mGluR plasticity has been described at the thalamocortical synapse in the somatosensory cortex,¹²⁷ perhaps indicating that this form of plasticity is also present at the mediodorsal thalamic synapses in the PFC. However, at the thalamocortical synapse, mGluR LTD acts presynaptically to decrease transmitter release and depress synaptic activity.¹²⁷ Such a mechanism would be unlikely to result in synapse loss and spine involution and therefore would not be a strong candidate for LTD-facilitated synaptic pruning during adolescence. Furthermore, mGluR LTD at postsynaptic sites in the hippocampus has been associated with large spines containing an abundance of AMPAR.¹²⁸ Unlike the hippocampus where large mushroom spines are in the majority, thin, filopodial spines predominate in the PFC.¹²⁹ Thus, strong evidence for mGluR in plasticity related to PFC synaptic pruning is presently lacking; nonetheless, possible involvement of mGluR-mediated LTD in prefrontal adolescent maturation cannot be discounted.

Many questions remain to be answered about the role of metaplasticity in the PFC as well. As the NR2A subtype promotes a LTD-receptive state in the synapse and LTD is associated with synaptic elimination, it would be interesting to know whether and when the NR2B to NR2A switch occurs in the PFC and how it relates to the synaptic pruning that refines connectivity associated with cognitive control of behavior. If the LTD-receptive state is a hallmark of adolescent development, a reasonable presumption is that there exists an additional molecular switch that greatly curtails the LTD-receptive state of adolescence into the much less receptive state of adulthood. This switch, although presently unidentified, would transform the synapse into a state that is less receptive to alterations in AMPAR expression on the postsynaptic membrane. Given that synaptic pruning continues into early adulthood albeit at a lower level than that of adolescence,^{33,51} it seems likely that the transition phase is gradual rather than abrupt resulting in a much less plastic state by the end of the third decade in humans.

Adolescence development of cognitive function and synaptic plasticity

Executive functions governed by the PFC exhibit a prolonged period of maturation reaching fulfillment only in late adolescence.^{11,130} Volumetric changes occurring during adolescence have been correlated with improved cognitive performance, e.g., verbal and spatial memory performance is

positively correlated with gray matter thinning in the frontal lobes.⁶ General intelligence has also been shown to bear a relationship to the trajectory of frontal cortical gray matter thinning, such that subjects with superior intelligence show a robust early adolescent increase in gray matter volume followed by equally robust thinning during later adolescence.¹³¹ However, too much cortical thinning during adolescence has been associated with diseased states such as Attention Deficit Hyperactivity Disorder (ADHD).¹³² Thus, there is an optimal level of synaptic pruning that is essential to normal development of adult cognitive function.

One recent study addressed the role of AMPAR expression and LTD in the development of PFC function in the mouse. Vazdarjanova *et al.*¹³³ utilized a transgenic mouse that over-expresses calcyon, a protein which mediates activity-dependent AMPAR internalization, and found that calcyon over-expression over the lifetime of the mouse resulted in marked impairment of contextual fear extinction (CFE) and working memory capacity, both dependent on normal PFC function. Most relevant to this discussion, adolescence was the critical period for production of these deficits. When over-expression was silenced specifically during the adolescent epoch, normal CFE function was rescued.¹³³ One possible explanation for these findings is that AMPAR internalization and associated functions like LTD are more sensitive to regulation during adolescence and this regulation is turned off, or at least greatly diminished, in the adult brain. Whether overactive LTD during adolescence translates into altered synaptic number in the PFC or elsewhere is currently not known. However, it is interesting that upregulated calcyon expression has been found in schizophrenia, a neurodevelopmental disease in which PFC gray matter deficits are prominent.^{134–136}

In the PFC, synaptic plasticity is highly modulated by dopamine receptor, especially the D1 receptor.^{14,122,137} This is not surprising since D1 receptor stimulation has been shown to trigger phosphorylation of AMPAR, which in turn promotes trafficking of these receptors to the external membrane.^{138,139} The D1 receptor is therefore strategically positioned to effect changes in AMPAR synaptic expression and ultimately in synaptic strength and/or number. In the adult non-human primate, long term sensitizing regimens of amphetamine decrease spine density on pyramidal cells in the PFC and have detrimental effects on working memory performance.¹⁴⁰ Moreover, these effects seem to be due to changes at the D1 receptor because both cognitive and morphologic effects on PFC pyramidal neurons can be reversed by long term treatment with a D1 antagonist.¹⁴¹ If AMPAR-mediated LTD expression is in a state of greater sensitivity to modulation in adolescence, then D1 receptor-stimulated interference with this mechanism could be magnified during adolescence resulting in exaggerated consequences at the synapse. Other known modulators of synaptic plasticity, e.g. D2,¹³⁹ muscarinic,¹⁴² and cannabinoid¹⁴³ receptors, might have similarly increased potency during the adolescent period.

Adolescence vulnerability to environmental factors

Adolescence has been described as a period of accentuated opportunity and of enhanced vulnerability.¹ It has long been recognized that early onset of substance abuse is associated

with greater propensity for problem drug use later in life.^{144–147} In recent years, the period of adolescent plasticity has been shown to temporally correlate with the time of greatest vulnerability to addiction.¹⁴⁸ Some have postulated that addiction constricts the learning and memory pathways in a maladaptive fashion,^{149,150} but the question of why addiction is more devastating in adolescence than in adulthood remains unanswered. Adolescence is also associated with onset of mental illness, as for example depression rates rise in adolescence especially for females,¹⁵¹ and the prodromal phase of psychosis, including early onset schizophrenia, surfaces during the adolescent window.¹⁵² Despite the fact that adolescents are bigger and stronger than younger children, mortality rates increase more than 200% from childhood mainly due to accidents, suicide, substance abuse, and eating disorders.¹

One of the most studied environmental effects in adolescence is alcohol abuse. In adults, brain toxicity has been documented as a consequence of chronic alcohol abuse: cortical gray matter thinning is most prominent in the PFC¹⁵³ and associated with changes in neuronal and glia density in both the orbitofrontal¹⁵⁴ and superior frontal cortices.¹⁵⁵ Alarming, the detrimental effects of alcohol consumption seem to be magnified in adolescence. Studies in human subjects have shown that impairment of memory function is more pronounced following even acute exposure to alcohol in younger (ages 21–24) than in older (ages 25–29) subjects.¹⁵⁶ In adolescent rats, ethanol administration selectively impairs spatial memory whereas adult rats are unaffected by the same doses.¹⁵⁷ Moreover, ethanol consumption in rats that simulates binge drinking results in more widespread pathology in adolescent animals than in adults.¹⁵⁸

The basis of the enhanced vulnerability to alcohol in adolescence is undoubtedly complex and involves interaction with multiple neurotransmitter systems.¹⁵⁹ With regard to neuroplasticity, there are well documented effects of alcohol on the glutamate system. Acutely, ethanol inhibits NMDAR neurotransmission whereas long term exposure results in homeostatic upregulation of NMDAR signaling.^{159,160} There is also growing evidence to suggest that ethanol has a greater effect on glutamate neurotransmission during adolescence than in later life. Ethanol exposure at low doses in adolescent rats is associated with inhibition of NMDAR-mediated EPSCs in the CA1 region of the hippocampus while high doses are required to inhibit EPSCs in adults.¹⁶¹ Ethanol also blocks LTP in CA1 neurons of the hippocampus in adolescent but not adult rats.¹⁶² Thus, even acute alcohol consumption in adolescence could disrupt mechanisms of Hebbian plasticity, and more chronic alcohol consumption in adolescence may induce homeostatic upregulation of glutamate neurotransmission that could result in long term changes in synapse number and dendritic spine morphology.¹⁶⁰ Homeostatic regulation of synaptic activity, i.e., increases or decreases synaptic scaling across the whole population of synapses, is also thought to be mediated by increased or decreased expression of AMPAR receptors on the post-synaptic membrane.¹⁶³ This suggests a potential site of interaction between developmental plasticity and homeostatic plasticity since both involve trafficking of AMPARs. Furthermore, sites of homeostatic plasticity correlate with lamina that exhibit plasticity during critical periods in the visual and somatosensory cortices, suggesting a possible

mechanism for heightened vulnerability of selected circuitry during different phases of development.¹⁶³ If synaptic plasticity in adolescence is primarily occurring in the neural circuitry that mediates executive processing, then disruption of synaptic plasticity at this time might result in enduring deficits in control of emotion, logical thinking and inhibition of impulsivity. In turn this lack of executive control could exacerbate the addictive tendencies and result in more severe alcoholism.

The adolescent brain is also more responsive to stress than the adult brain¹⁶⁴ and as a consequence may be more vulnerable to depression.¹⁵¹ Analogous to the manner in which alcohol has age-specific effects that may depend on which regions of the brain are most plastic, a recent study has shown that the effects of sexual abuse, presumably the stress associated with the abuse, produces different brain pathology at childhood and adolescent ages.¹⁶⁵ Notably, frontal gray matter volume deficits were most pronounced in adult subjects who experienced sexual abuse at ages 14–16.¹⁶⁵

The neural pathways that mediate and modulate the stressful effects on cognitive function in the PFC involve monoamine signaling.¹⁶⁴ Given the prominence of dopamine neurotransmission in mediating stress, the development of dopamine innervation of the PFC during late maturation might provide insight into the enhanced sensitivity to stress at this age. In the non-human primate, dopamine innervation of the middle PFC layers peaks near the onset of puberty and then decreases rapidly to adult levels while innervation of other layers is stable throughout the postnatal period.¹⁶⁶ D1 receptor levels also peak and decline to adult levels around the beginning of puberty.¹⁶⁷ These findings which indicate that the adult D1 receptor pattern is reached early do not appear to support a role for dopamine in adolescent enhancement of plasticity. However, in rodent prefrontal cortex, cell specificity has been observed in the distribution of D1 receptors with pyramidal cell neurons, but not interneurons, expressing higher levels of D1 receptors in adolescence than in adulthood.¹⁶⁸ These rodent data suggest that changes in D1 receptor expression might accentuate dopamine signaling in adolescence and thereby account for greater plasticity during this critical period. However, a credible alternative explanation is that the LTD-receptive state of adolescence is more sensitive to modulators like dopamine and that critical differences might be found in the mechanisms of glutamate receptor-mediated synaptic plasticity in the adolescent brain compared its adult counterpart.

Clinical considerations

Identifying the molecular basis for synaptic pruning in adolescence could have wide ranging clinical ramifications. If NMDA-mediated LTD were proved to underlie reduction of connectivity, then the intracellular pathways associated with LTD processes, including those that mediate AMPAR internalization, could be targeted to curtail excessive synaptic pruning in diseases such as schizophrenia and ADHD. Because the D1 receptor is a key modulator of synaptic plasticity in the PFC and can even determine polarity of plasticity, i.e. high dopamine levels can predispose prefrontal synapses to LTD over LTP,¹³⁷ treatment with dopaminergic

antagonists or drugs that target intracellular dopamine signaling might also be useful in decreasing overactive LTD mechanisms. Along these same lines, drugs that impact the D1 receptor or its signaling pathways could ameliorate the impact of stress on the adolescent brain of individuals at risk for depression. Likewise, the involvement of glutamate receptors, including mGluRs,¹²⁶ in drug and alcohol addiction raises the possibility that pharmacologic targeting of glutamate signaling might have the potential to diminish the long term consequences of substance abuse in adolescence. In the same manner that the discovery of aberrant mGluR5 mechanisms in Fragile X syndrome has spawned new therapeutic approaches for treating this disease,^{169–171} greater insight into the molecular substrates of adolescent maturation of the prefrontal cortex might lead to similar novel drug development for disorders and environmental exposures linked to abnormal adolescent development.

Conclusions

The adolescent epoch is a time when refinement of connectivity establishes the proper excitatory/inhibitory balance in the PFC, and it is a critical period for normal maturation of executive functioning. Adolescence is postulated to be a time when LTD-driven synaptic pruning is occurring at a high rate in regions that govern higher cognitive function like the PFC. Further, the transition to adulthood is hypothesized to be marked by changes in the synapse that make the mature neuron less sensitive to AMPAR internalization, less likely to undergo LTD and thus less likely to undergo retraction of synaptic contacts.

Conflict of interest

The author declares no conflict of interest.

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