

Stress and the Adolescent Brain

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ABSTRACT: During adolescence the brain shows remarkable changes in both structure and function. The plasticity exhibited by the brain during this pubertal period may make individuals more vulnerable to perturbations, such as stress. Although much is known about how exposure to stress and stress hormones during perinatal development and adulthood affect the structure and function of the brain, relatively little is known about how the pubertal brain responds to stress. Furthermore, it is not clear whether stressors experienced during adolescence lead to altered physiological and behavioral potentials in adulthood, as has been shown for perinatal development. The purpose of this review is to present what is currently known about the pubertal maturation of the hypothalamic-pituitary-adrenal (HPA) axis, the neuroendocrine axis that mediates the stress response, and discuss what is currently known about how stressors affect the adolescent brain. Our dearth of knowledge regarding the effects of stress on the pubertal brain will be discussed in the context of our accumulating knowledge regarding stress-induced neuronal remodeling in the adult. Finally, as the adolescent brain is capable of such profound plasticity during this developmental stage, we will also explore the possibility of adolescence as a period of interventions and opportunities to mitigate negative consequences from earlier developmental insults.

KEYWORDS: adolescence; adrenocorticotrophic hormone (ACTH); *amygdale*; hippocampus; hypothalamic-pituitary-adrenal (HPA); axis neuroendocrine; stress

INTRODUCTION

Adolescence is increasingly being viewed as a significant period of developmental vulnerabilities.⁵⁻⁷ For instance, puberty is marked by an increase in the morbidity and susceptibility to various psychological disorders, such as anxiety and depression.^{8,9} However, it is presently unclear what central mechanisms may mediate the pubertal increase in these events. Interestingly, stressors in adulthood can lead to the onset and exacerbation of psychological disorders.¹⁰ Furthermore, brain regions implicated in stress reactivity and

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emotionality, such as the hippocampus, medial prefrontal cortex (mPFC), and amygdala (AMY) undergo profound changes in both structure and function in response to stress.⁴ Thus, stress-induced alterations in the pubertal nervous system may contribute to an individual's vulnerability to the onset of psychopathologies during adolescence. There is presently a paucity of knowledge regarding how stressors may affect the brain during adolescence. This is quite surprising for two reasons. First, stress reactivity changes dramatically depending on both the pubertal development and experience of an individual (see below). Second, brain regions that are highly sensitive to stress hormones play an important role in regulating emotionality and stress responsiveness (i.e., hippocampus, mPFC, AMY) continue to mature during the peripubertal period.^{1-3,6,11-13} It is our hope that this review will provide a point of departure for future experiments elucidating the role of stress on the developing pubertal brain.

Pubertal Maturation of the Hypothalamic-Pituitary-Adrenal (HPA) Axis

The release of stress hormones by the HPA axis is driven by the release of corticotropin-releasing hormone (CRH) and vasopressin (AVP) from the medial parvocellular division of the paraventricular hypothalamic nucleus (PVN). CRH and AVP are released into the portal system of the pituitary, which in turn causes the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary. ACTH then stimulates the secretion of the glucocorticoids (e.g., cortisol in primates and corticosterone in most rodent species) from the adrenal cortex. The stress hormones secreted by the HPA axis indirectly control their own secretion through a classic neuroendocrine negative feedback loop. That is, the glucocorticoids feedback on the PVN and many other extrahypothalamic sites, in particular, the hippocampus and mPFC, to inhibit further release of CRH¹⁴ (FIG. 1). In addition to extrahypothalamic sites of negative feedback on the PVN, projections from the central nucleus of the amygdala (CeA) can activate the PVN and modulate stress reactive behaviors¹⁴ (FIG. 1).

Studies that have examined stress responsiveness in juvenile animals have demonstrated that although basal and stress-induced ACTH and corticosterone secretion are similar in prepubertal and adult animals, prepubertal animals have a much more prolonged ACTH and corticosterone stress response compared to adults. For example, in males exposed to either intermittent foot shock,¹⁵ ether vapors,¹⁶ or restraint,¹⁷ corticosterone levels of prepubertal males take at least 45 to 60 min longer to return to baseline compared to adults (FIG. 2). It is important to note that this extended response exhibited by prepubertal animals is to both total and free corticosterone,¹⁸ indicating that corticotropin-binding globulin (CBG) is not upregulated to "buffer" the prepubertal animal from this prolonged exposure to corticosterone.

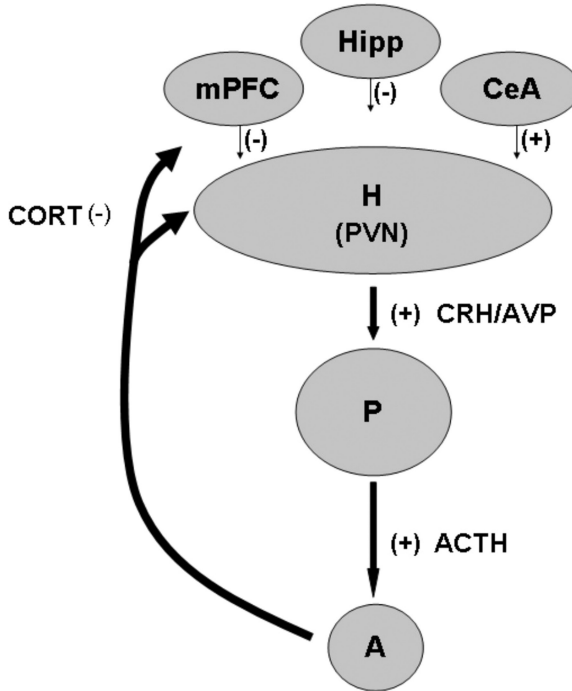


FIGURE 1. A diagram of the HPA axis and various extrahypothalamic sites that play a role in modulating stress hormone secretion. Abbreviations, A = adrenal; ACTH = adrenocorticotropic hormone; AVP = vasopressin; CeA = central nucleus of the amygdala; CORT = corticosterone; CRH = corticotropin-releasing hormone; Hipp = hippocampus; H = hypothalamus; mPFC = medial prefrontal cortex; P = pituitary; PVN = paraventricular nucleus; (+), positive drive; and (-), negative feedback.

The above-mentioned studies examined the hormonal stress response in prepubertal and adult animals only in the context of a single, acute stressor. However, it is well documented that experience with a stressor can also influence stress reactivity. For instance, in adults, repeated exposure to a stressor leads to habituation of the stress response, such that peak stress hormone levels are blunted.^{19–22} Interestingly, we found that experience and pubertal maturation interact to affect HPA axis plasticity.¹⁸ Specifically, we showed that, in contrast to the extended response observed after acute stress, chronic stress resulted in prepubertal males exhibiting a higher peak ACTH and corticosterone (free and total) response immediately following the stressor, but a faster return to baseline, compared to adults (FIG. 3).

In addition to these endocrine differences in stress reactivity, we have also found that this differential response to acute and chronic stress is associated with differential neuronal activation in the PVN of prepubertal and adult

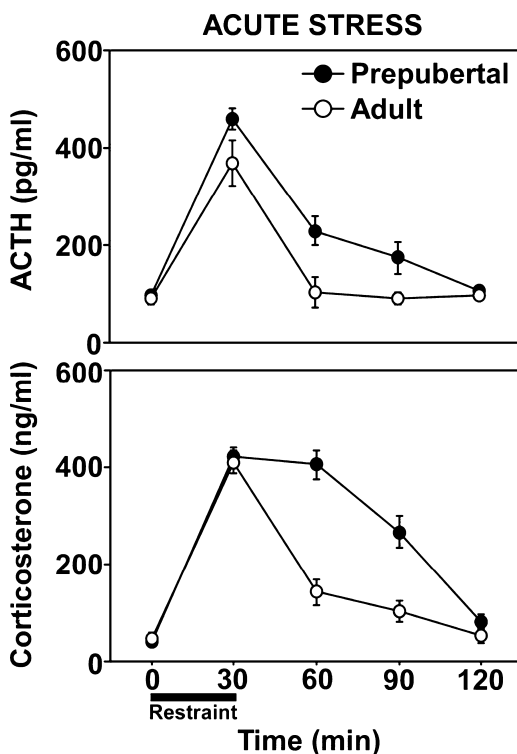


FIGURE 2. Plasma ACTH and corticosterone concentrations in prepubertal and adult males before and after a 30-min session of restraint stress.¹⁷

animals.¹⁸ Moreover, we have established that a significantly larger proportion of CRH, but not AVP, cells are activated in the PVN in response to both acute and chronic stress in prepubertal compared to adult animals.¹⁸ Together, these data indicate that experience-dependent plasticity of the HPA axis is markedly influenced by pubertal development, and that CRH neurons of the PVN are at least one neural locus involved in these changes.

The physiological and behavioral implications of these differential stress responses in prepubertal compared to adult animals are currently unknown. However, two factors may render the prepubertal brain especially vulnerable to stress. First, the prepubertal brain may be more sensitive to corticosterone, as a recent study showed an equivalent dose of corticosterone increased hippocampal N-methyl-D-aspartate (NMDA) receptor subunit expression (e.g., NR2A and NR2B) to a greater degree in prepubertal than adult males.²³ Second, brain regions that continue to mature during adolescence, such as hippocampus,²⁴⁻²⁶ PFC,^{1,11,27} and AMY,^{12,28} are also the most sensitive to corticosterone.⁴ Thus, upon encountering a similar stressor, the immature, and possibly more

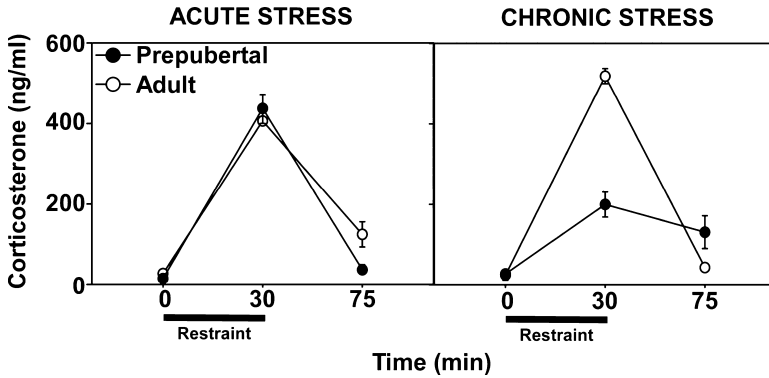


FIGURE 3. Plasma corticosterone concentrations in prepubertal and adult males exposed to a single 30-min session of restraint (acute stress) or a daily 30-min session of restraint for 1 week (chronic stress).¹⁸

sensitive, prepubertal brain experiences differential exposure to corticosterone compared to the more fully developed adult brain.

Stress and the Adolescent Brain: What We Can Learn from the Adult Brain

Though few experiments have examined the effects of stress on the structure of the pubertal brain, it is widely recognized that stressors experienced during adolescence can have long-lasting and profound consequences for the future behavioral and psychological function of an individual. For instance, human studies clearly demonstrate that stress burden during adolescence is strongly correlated with the subsequent onset of depressive and/or anxiety disorders in adulthood.²⁹ Similarly, studies in rodents indicate that animals exposed to stress during puberty show increases in basal and stress-induced anxiety-like behaviors upon reaching adulthood.^{30,31} The neural correlates associated with these long-lasting changes in emotionality and behavior remain unknown. However, the effects of stress on the structural remodeling of the adult brain have been relatively well studied.⁴ Thus, we will next discuss stress and structural remodeling of the adult brain, namely in the hippocampus, PFC, and AMY, to highlight current and future directions regarding the influence of stress on the adolescent brain.

Hippocampus

The hippocampus is critically important in learning and memory,³² and continues to develop well into adolescence.^{24,33} In adult male rats, chronic restraint (6-h per day of restraint stress for 3 weeks) or social stress significantly

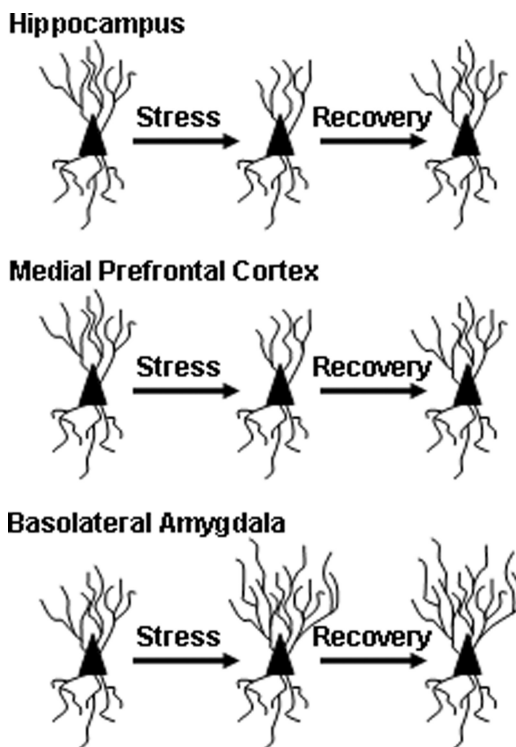


FIGURE 4. Schematic diagrams of dendritic remodeling in the adult hippocampus (*top*), mPFC (*middle*), and basolateral amygdala (*bottom*). Note that the dendritic remodeling of both the hippocampus and mPFC are reversible, while basolateral amygdala dendritic hypertrophy is longer lasting.

reduces branching of the apical dendrites of the CA3 region of hippocampus³⁴⁻³⁶ (FIG. 4). The apical dendrites of CA3 neurons receive inputs from the granule neurons of the dentate gyrus.³⁷ The stress-induced remodeling in the hippocampus is dependent on corticosterone as cyanoketone, a corticosterone synthesis inhibitor, blocks the stress-induced atrophy of the CA3 dendrites,¹⁹ while chronic injections of corticosterone mimic the stress-induced atrophy.³⁸ Interestingly, these effects of stress on hippocampal structure are reversible such that 10 days after the last stress session dendritic branching reverts to prestress levels³⁹ (FIG. 4).

Parallel to these morphological studies, it was found that chronic stress results in spatial memory impairment.⁴⁰ Furthermore, chronically stressed animals pretreated with tianeptine, an antidepressant that blocks stress-induced CA3 dendritic atrophy,⁴¹ showed spatial abilities similar to nonstressed control animals.⁴⁰ Together, these data indicated that stress potently affects the adult hippocampus and suggests that the stress-induced dendritic atrophy

demonstrated by the CA3 pyramidal cells adversely affects spatial cognition. It is important to note, however, that these effects of stress are reversible.

A recent study aimed at understanding stress and puberty showed that male rats exposed to variable physical and social stressors throughout adolescence exhibited volumetric deficits in CA1 and CA3 pyramidal cell layers as well as the dentate gyrus of the hippocampus.²⁵ The authors suggested that the reduction in hippocampal volume was due to stress blocking the normal maturational increase in hippocampal volume.²⁵ Interestingly, these effects on the hippocampus were not observed until 3 weeks after the stress sessions were terminated, indicating these effects of chronic stress on the developing adolescent hippocampus are delayed. Furthermore, the decrease in hippocampal volume was associated with deficits on the Morris water maze, a commonly used task to assess spatial memory.²⁵ Thus, these data indicate that, similar to the adult, the pubertal hippocampus is sensitive to stress. However, unlike the reversibility of the effect of stressors on the adult hippocampus, it appears that the effects of pubertal stress may be long-lasting, and perhaps permanent. Future studies will need to assess whether pubertal stress affects the structure and function of the hippocampus months after the stressors have been terminated, and whether behavioral effects persist into adulthood and aging. It will also be interesting to examine whether various pharmacological interventions shown to block stress-induced remodeling of the adult hippocampus, such as tianeptine,⁴¹ phenytoin,⁴² or lithium,⁴³ mitigate stress-induced changes in the pubertal hippocampus.

Prefrontal Cortex

The PFC is a key brain region involved in the regulation of emotional behaviors, executive function, and fear extinction.⁴⁴ In adults, chronic restraint stress (6-h per day of restraint stress for 3 weeks) results in reductions in both apical dendritic branching and spine density of medial prefrontal cortical pyramidal neurons in layer II/III of the anterior cingulate cortex and prelimbic area^{45,46} (FIG. 4). As chronic injections of corticosterone mimic the effects of chronic stress on the prefrontal cortex it appears that stress-induced release of corticosterone is involved in the mechanism for these morphological changes.⁴⁷ The remodeling of the mPFC in response to stress is reversible such that animals allowed to recover for 3 weeks after exposure to chronic stress show dendritic branching similar to nonstress controls⁴⁸ (FIG. 4). The stress-induced remodeling in the PFC is associated with impairment of attention set-shifting,⁴⁹ an adaptive behavior that is also impaired by lesions of the mPFC.⁵⁰ Moreover, whereas mPFC neurons show atrophy with chronic stress, neurons in the orbitofrontal cortex show growth as a result of repeated stress.⁴⁹ These data indicate the structure of the prefrontal cortex is sensitive to the remodeling effects of stress and these morphological changes may mediate, at least in part, the changes in emotionality after prolonged exposure to stress.⁴

Similar to the hippocampus, the prefrontal cortex continues to mature throughout adolescence.^{1,11} However, it is presently unknown whether exposure to stress during puberty affects the structure and function of the prefrontal cortex. Given that the pubertal mPFC expresses glucocorticoid receptors (R. D. Romeo, unpublished observation), it seems likely that this brain area would be sensitive to stress. Based on the accumulating evidence that exposure to stressors during adolescence can lead to an increased propensity to develop emotional and psychological disorders (i.e., depression and anxiety),²⁹ it is imperative to understand the influence of stress and stress hormones on such an important node in the neuronal circuitry of emotional regulation.

Amygdala

The AMY plays a central role in emotional memory and fear conditioning.⁵¹ Unlike the stress-induced dendritic atrophy exhibited by the adult hippocampus and mPFC, adults show dendritic hypertrophy in the basolateral, but not central nucleus, of the amygdala after chronic immobilization stress (2-h per day of immobilization stress for 10 days; FIG. 4).^{52,53} This chronic immobilization stress paradigm also results in elevated anxiety-like behaviors, suggesting that the dendritic hypertrophy influences anxiety levels.⁵⁴ Dissimilar to the reversibility of dendritic atrophy of the hippocampus³⁹ and mPFC,⁴⁸ stress-induced dendritic hypertrophy in the amygdala and increased levels of anxiety-like behaviors remain even after 3 weeks of stress-free recovery⁵⁵ (FIG. 4). It is presently unknown whether these effects of stress on amygdalar morphology are dependent upon stress-induced release of corticosterone. However, as glucocorticoid receptors are expressed in the amygdala,⁵⁶ it would appear likely that the effects of stress on the amygdala are, at least in part, due to the actions of corticosterone.

Pubertal development is marked by changes in the structure and function of the AMY.^{28,33} However, the effects of stress on AMY during pubertal development remain unknown. Like the mPFC, the adolescent amygdala expresses abundant glucocorticoid receptors (R. D. Romeo, unpublished observation), indicating corticosterone sensitivity in this area. Future studies will need to examine the impact of stress on the developing AMY during puberty, and whether any effects on the structure and function of this brain region are transient or permanent.

Adolescence as a Period of Interventions and Opportunities

Puberty is marked by profound changes in an individual's nervous system, physiology, and behavior.^{12,57,58} Although this may render an individual especially vulnerable to harm during this period, it may also allow for interventions to mitigate earlier or concurrent emotional and/or physical trauma.⁵

A stunning example of puberty as a period of opportunity to diminish the impact of an earlier, negative trauma comes from a classic paper by Twiggs, Popolow, and Gerall.⁵⁹ In this study, prepubertal males were housed alone (solitary) or in groups (social) and then given lesions of the medial preoptic nucleus of the anterior hypothalamus (MPN), an area of the brain critical for the display of male reproductive behavior.⁶⁰ Although MPN lesions in adulthood lead to irreversible deficits in male mating, males receiving a lesion prior to puberty were able to show copulatory behaviors upon reaching adulthood.⁵⁹ Interestingly, however, only the animals raised in the social groups during adolescence demonstrated substantial behavioral reversal of the effects of MPN lesions.⁵⁹ These data indicate that pubertal development and the social environment can interact to diminish or even reverse prior brain damage.

Recent studies have also explored the ability of environmental enrichment during adolescence to offset the negative influences of perinatal stress. For instance, animals derived from stressful pregnancies show increases in anxiety-related behaviors and HPA reactivity and depressed play behavior later in life.^{61,62} However, animals raised in an enriched environment (larger housing, toys, running wheel) during puberty do not show these negative physiological and behavioral effects of prenatal stress compared to prenatally stressed offspring raised under normal laboratory conditions.^{61,62} In addition to prenatal stress, postnatal stress in the form of suboptimal maternal care and maternal separation leads to increased HPA reactivity and emotionality and reduced cognitive function in adulthood.^{63,64} Similar to the studies mentioned above, animals exposed to postnatal stress, but raised in enriched environments during puberty, show less HPA reactivity and emotionality and greater cognitive abilities compared to their postnatally stressed counterparts that were raised in standard laboratory environments.⁶⁵⁻⁶⁷ Taken together, these studies clearly demonstrate that the pubertal period of development can serve as a time of interventions and opportunities to reduce or reverse the adverse effects accumulated from earlier insults.

CONCLUSIONS

The literature reviewed above indicates that stress reactivity is markedly influenced by both the pubertal maturation and the experience of the individual. Furthermore, although stress affects key regulatory nuclei related to stress responsiveness, emotional behavior, and cognitive function in adulthood, scant information exist about the effects of stress on the pubertal nervous system. Finally, it is important to note that despite the possible vulnerabilities of the pubertal brain to stress, adolescence may also provide opportunities to alleviate adverse effects of stress experienced earlier in development. Although much research remains to be done regarding the effects of stress on the structure and function of the adolescent brain, the vast body of stress research on adults

may aid in honing our potential hypothesis and provide a point of departure for future experiments.

REFERENCES

1. GIEDD, J.N. 2004. Structural magnetic resonance imaging of the adolescent brain. *Ann. N.Y. Acad. Sci.* **1021**: 77–85.
2. BLAKEMORE, S.-J. & S. CHOUDHURY. 2006. Development of the adolescent brain: implications for executive function and social cognition. *J. Child Psychol. Psychiatry* **47**: 296–312.
3. MACCARI, S. *et al.* 2003. Prenatal stress and long-term consequences: implications of glucocorticoid hormones. *Neurosci. Biobehav. Rev.* **27**: 119–127.
4. McEWEN, B.S. 2005. Glucocorticoids, depression, and mood disorders: structural remodeling in the brain. *Metabolism* **54**: 20–23.
5. ANDERSEN, S.L. 2003. Trajectories of brain development: point of vulnerability or window of opportunity. *Neurosci. Biobehav. Rev.* **27**: 3–18.
6. SPEAR, L.P. 2000. The adolescent brain and age-related behavioral manifestations. *Neurosci. Biobehav. Rev.* **24**: 417–463.
7. DAHL, R.E. 2004. Adolescent brain development: a period of vulnerabilities and opportunities. *Ann. N.Y. Acad. Sci.* **1021**: 1–22.
8. CONGER, J. & A. PETERSEN. 1984. *Adolescence and Youth: Psychological Development in a Changing World*. Harper and Row. New York.
9. MASTEN, A. 1987. Toward a developmental psychopathology of early adolescence. *In* *Early Adolescent Transitions*. M. Levin & E. McArnary, Eds.: 261–278. Heath. Lexington, KY.
10. McEWEN, B.S. 2003. Mood disorders and allostatic load. *Biol. Psychiatry*. **54**: 200–207.
11. GOGTAY, N. *et al.* 2004. Dynamic mapping of human cortical development during childhood through early adulthood. *Proc. Natl. Acad. Sci. USA* **101**: 8174–8179.
12. ROMEO, R.D. 2003. Puberty: a period of both organizational and activational effects of steroid hormones on neurobehavioral development. *J. Neuroendocrinol.* **15**: 1185–1192.
13. SUZUKI, M. *et al.* 2005. Male-specific volume expansion of the human hippocampus during adolescence. *Cerebral Cortex* **15**: 187–193.
14. HERMAN, J.P. *et al.* 2003. Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamic-pituitary-adrenocortical responsiveness. *Front Neuroendocrinol.* **24**: 151–180.
15. GOLDMAN, L. *et al.* 1973. Postweaning development of negative feedback in the pituitary-adrenal system of the rat. *Neuroendocrinology* **12**: 199–211.
16. VAZQUEZ, D.M. & H. AKIL. 1993. Pituitary-adrenal response to ether vapor in the weanling animal: characterization of the inhibitory effect of glucocorticoids on adrenocorticotropin secretion. *Pediatric Res.* **34**: 646–653.
17. ROMEO, R.D. *et al.* 2004. Testosterone cannot activate an adult-like stress response in prepubertal male rats. *Neuroendocrinology* **79**: 125–132.
18. ROMEO, R.D. *et al.* 2006. Stress history and pubertal development interact to shape hypothalamic pituitary adrenal axis plasticity. *Endocrinology* **147**: 1664–1674.
19. MAGARINOS, A.M. & B.S. McEWEN. 1995. Stress-induced atrophy of apical dendrites of hippocampal CA3c neurons: involvement of glucocorticoid secretion and excitatory amino acid receptors. *Neuroscience* **69**: 89–98.

20. MARTI, O. & A. ARMARIO. 1997. Influence of regularity of exposure to chronic stress on the pattern of habituation of pituitary-adrenal hormones, prolactin and glucose. *Stress* **1**: 179–189.
21. HELMREICH, D.L. *et al.* 1997. Correlation between changes in stress-induced corticosterone secretion and GR mRNA levels. *Stress* **2**: 101–112.
22. HARRIS, R.B.S. *et al.* 2004. Increased glucocorticoid response to a novel stress in rats that have been restrained. *Physiol. Behav.* **81**: 557–568.
23. LEE, P.R., D. BRANDY & J.I. KOENIG. 2003. Corticosterone alters N-methyl-D-aspartate receptor subunit mRNA expression before puberty. *Mol. Brain Res.* **115**: 55–62.
24. MEYER, G., R. FERRES-TORRES & M. MAS. 1978. The effects of puberty and castration on hippocampal dendritic spines of mice. A Golgi study. *Brain Res.* **155**: 108–112.
25. ISGOR, C. *et al.* 2004. Delayed effects of chronic variable stress during peripubertal-juvenile period of hippocampal morphology and on cognitive and stress axis function in rats. *Hippocampus* **14**: 636–648.
26. ANDERSEN, S.L. & M.H. TEICHER. 2004. Delayed effects of early stress on hippocampal development. *Neuropsychopharmacol* **29**: 1988–1993.
27. GIEDD, J.N. *et al.* 1999. Brain development during childhood and adolescence: a longitudinal MRI study. *Nat. Neurosci.* **2**: 861–863.
28. ROMEO, R.D. & C.L. SISK. 2001. Pubertal and seasonal plasticity in the amygdala. *Brain Res.* **889**: 71–77.
29. TURNER, R.J. & D.A. LLOYD. 2004. Stress burden and the lifetime incidence of psychiatric disorder in young adults. *Arch. Gen. Psychiatry* **61**: 481–488.
30. AVITAL, A. *et al.* 2006. Effects of early-life stress on behavior and neurosteroid levels in the rat hypothalamus and entorhinal cortex. *Brain Res. Bull.* **68**: 419–424.
31. AVITAL, A. & G. RICHTER-LEVIN. 2004. Exposure of juvenile stress exacerbates the behavioural consequences of exposure to stress in the adult rat. *Int. J. Neuropsychopharmacol.* **8**: 1–11.
32. EICHENBAUM, H. 1997. Declarative memory: insights from cognitive neurobiology. *Ann. Rev. Neurosci.* **48**: 547–572.
33. GIEDD, J.N. *et al.* 1996. Quantitative MRI of the temporal lobe, amygdala, and hippocampus in normal human development: ages 4–18 years. *J. Comp. Neurol.* **366**: 223–230.
34. WATANABE, Y., E. GOULD & B.S. MCEWEN. 1992. Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. *Brain Res.* **588**: 341–345.
35. MCEWEN, B.S. 1999. Stress and hippocampal synaptic plasticity. *Ann. Rev. Neurosci.* **22**: 105–122.
36. MCKITTRICK, C.R. *et al.* 2000. Chronic social stress reduces dendritic arbors in CA3 hippocampus and decreases binding to serotonin transporter sites. *Synapse* **36**: 85–94.
37. BLACKSTAD, T.W. & A. KJAERHEIM. 1961. Special axo-dendritic synapses in the hippocampal cortex: electron and light microscopic studies on the layer of mossy fibers. *J. Comp. Neurol.* **117**: 133–159.
38. WOOLLEY, C.S., E. GOULD & B.S. MCEWEN. 1990. Exposure to excess glucocorticoids alters dendritic morphology of adult hippocampal pyramidal neurons. *Brain Res.* **531**: 225–231.

39. CONRAD, C.D. *et al.* 1999. Repeated restraint stress facilitates fear conditioning independently of causing hippocampal CA3 dendritic atrophy. *Behav. Neurosci.* **113**: 902–913.
40. CONRAD, C.D. *et al.* 1996. Chronic stress impairs rat spatial memory on the Y maze, and this effect is blocked by tianeptine pretreatment. *Behav. Neurosci.* **110**: 1321–1334.
41. WATANABE, Y. *et al.* 1992. Tianeptine attenuates stress-induced morphological changes in the hippocampus. *Eur. J. Pharmacol.* **222**: 157–162.
42. WATANABE, Y. *et al.* 1992. Phenytoin prevents stress- and corticosterone-induced atrophy of CA3 pyramidal neurons. *Hippocampus* **2**: 431–435.
43. WOOD, G.E. *et al.* 2004. Stress-induced structural remodeling in hippocampus: prevention by lithium treatment. *Proc. Natl. Acad. Sci. USA* **101**: 3973–3978.
44. SOTRES-BAYON, F., C.K. CAIN & J.E. LEDOUX. 2006. Brain mechanisms of fear extinction: historical perspectives on the contribution of prefrontal cortex. *Biol. Psychiatry.* **60**: 329–336.
45. RADLEY, J.J. *et al.* 2006. Repeated stress induces dendritic spine loss in the rat medial prefrontal cortex. *Cerebral Cortex* **16**: 313–320.
46. RADLEY, J.J. *et al.* 2004. Chronic behavioral stress induces apical dendritic reorganization of pyramidal neurons of the medial prefrontal cortex. *Neuroscience* **125**: 1–6.
47. WELLMAN, C.L. 2001. Dendritic reorganization in pyramidal neurons in medial prefrontal cortex after chronic corticosterone administration. *J. Neurobiol.* **49**: 245–253.
48. RADLEY, J.J. *et al.* 2005. Reversibility of apical dendritic retraction in the rat medial prefrontal cortex following repeated stress. *Exp. Neurol.* **196**: 199–203.
49. LISTON, C. *et al.* 2006. In review. Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. *J. Neurosci.* **26**: 7870–7874.
50. BIRRELL, J.M. & V.J. BROWN. 2000. Medial frontal cortex mediates perceptual attentional set shifting in the rat. *J. Neurosci.* **20**: 4320–4324.
51. LEDOUX, J.E. 2000. Emotion circuits in the brain. *Ann. Rev. Neurosci.* **23**: 155–184.
52. VYAS, A. *et al.* 2002. Chronic stress induces contrasting patterns of dendritic remodeling in hippocampus and amygdala neurons. *J. Neurosci.* **22**: 6810–6818.
53. VYAS, A., S. BERNAL & S. CHATTARJI. 2003. Effects of chronic stress on dendritic arborization in the central and extended amygdala. *Brain Res.* **965**: 290–294.
54. VYAS, A. & S. CHATTARJI. 2004. Modulation of different states of anxiety-like behavior by chronic stress. *Behav. Neurosci.* **118**: 1450–1454.
55. VYAS, A., A.G. PILLAI & S. CHATTARJI. 2004. Recovery after chronic stress fails to reverse amygdaloid neuronal hypertrophy and enhanced anxiety-like behavior. *Neuroscience* **128**: 667–673.
56. VAN EEKELLEN, J.A., M.C. BOHN & E. R. DE KLOET. 1991. Postnatal ontogeny of mineralocorticoid and glucocorticoid receptor gene expression in regions of the rat tel- and diencephalon. *Dev. Brain Res.* **61**: 33–43.
57. ROMEO, R.D. 2005. Neuroendocrine and behavioral development during puberty: a tale of two axes. *Vitam. Horm.* **71**: 1–25.
58. ROMEO, R.D., H.N. RICHARDSON & C.L. SISK. 2002. Puberty and the maturation of the male brain and sexual behavior: recasting a behavioral potential. *Neurosci. Biobehav. Rev.* **26**: 379–389.

59. TWIGGS, D.G., H.B. POPOLOW & A.A. GERALL. 1978. Medial preoptic lesions and male sexual behavior: age and environmental interactions. *Science* **200**: 1414–1415.
60. HEIMER, L. & K. LARSSON. 1966/1967. Impairment of mating behavior on male rats following lesions of the preoptic-anterior hypothalamic continuum. *Brain Res.* **3**: 248–263.
61. MORLEY-FLETCHER, S. *et al.* 2003. Environmental enrichment during adolescence reverses the effects of prenatal stress on play behaviour and HPA axis reactivity in rats. *Eur. J. Neurosci.* **18**: 3367–3374.
62. LAVIOLA, G. *et al.* 2004. Beneficial effects of enriched environment on adolescent rats from stressed pregnancies. *Eur. J. Neurosci.* **20**: 1655–1664.
63. MEANEY, M.J. 2001. Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Ann. Rev. Neurosci.* **24**: 1161–1192.
64. PRYCE, C.R. *et al.* 2005. Long-term effects of early-life environmental manipulations in rodents and primates: potential animal models in depression research. *Neurosci. Biobehav. Rev.* **29**: 649–674.
65. BREDY, T.W. *et al.* 2004. Peripubertal environmental enrichment reverses the effects of maternal care on hippocampal development and glutamate receptor subunit expression. *Eur. J. Neurosci.* **20**: 1355–1362.
66. BREDY, T.W. *et al.* 2003. Partial reversal of the effect of maternal care on cognitive function through environmental enrichment. *Neuroscience* **118**: 571–576.
67. FRANCIS, D.D. *et al.* 2002. Environmental enrichment reverses the effects of maternal separation on stress reactivity. *J. Neurosci.* **22**: 7840–7843.