

Review

The impact of stress on the structure of the adolescent brain: Implications for adolescent mental health



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ABSTRACT

Adolescent development is associated with major changes in emotional and cognitive functions, as well as a rise in stress-related psychological disorders such as anxiety and depression. It is also a time of significant maturation of the brain, marked by structural alterations in many limbic and cortical regions. Though many elegant human neuroimaging studies have described the adolescent-related changes in these regions, relatively little is known about these changes in non-human animals. Moreover, both human and non-human data are lacking on how exposure to chronic stress may disrupt this structural maturation. Given the fundamental structure-function relationship in the nervous system, it will be important to understand how these normative and stress-induced structural alterations during adolescence influence psychological function, which in turn can modify future neural development. The purpose of this brief review is to describe the impact of stress on the structure of brain regions that continue to show structural maturation during adolescence and are highly sensitive to the effects of chronic stress exposure. Specifically, this review will focus on the amygdala, hippocampal formation, and prefrontal cortex, particularly from a morphological perspective. As many unanswered questions remain in this area of investigation, potential future lines of research are also discussed. A deeper appreciation of how stress affects adolescent brain development will be needed if we are to gain a better understanding of the mechanisms that mediate the increase in stress-related psychological dysfunctions often observed during this stage of development.

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1. Introduction

Since the seminal reports on longitudinal magnetic resonance

imaging (MRI) studies were published in the late 1990s (Giedd et al., 1999; Paus et al., 1999; Sowell et al., 1999), increased attention has been focused on the structural maturation of the teenage brain. As structure in part dictates function (Miller and Jacobs, 1984), the adolescent-related morphological changes in cortical and limbic brain regions have been posited to contribute

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to the significant shifts in cognitive abilities and emotional control observed during adolescence (Giedd et al., 2015). Along with the growing interest in the normative development of the adolescent brain, researchers have begun to study factors that may disturb this development and the short- and long-term ramifications of these perturbations (Giedd and Rapoport, 2010). Animal studies have provided a more mechanistic view of how certain elements disrupt adolescent brain maturation, due to their increased experimental control and cellular resolution. One such factor that appears to have a widespread and pervasive impact on the developing adolescent brain is exposure to prolonged periods of stress or stress-related hormones (Eiland and Romeo, 2013).

The purpose of this brief review is to highlight the studies that have examined the influence of stress on the adolescent brain from a neuroanatomical perspective. More specifically, this review will focus on the effects of stress on the morphology of neurons and markers of structural plasticity in three brain regions that are highly sensitive to stress and exhibit unique developmental profiles during adolescence, namely the amygdala, hippocampus, and prefrontal cortex. The last section of this review will suggest potential future lines of research that may help further our understanding of how stress shapes the adolescent brain.

2. Stress and the adolescent brain: enhanced vulnerability?

Accumulating research has begun to show negative effects of chronic stress exposure during adolescence on various neurobehavioral outcomes, particularly in regards to emotionality (Eiland and Romeo, 2013; Hollis et al., 2013; McCormick, 2010; McCormick and Mathews, 2010; McCormick et al., 2010; McCormick and Green, 2013). It should be noted here that the ages that span adolescent development in rodents, such as mice and rats, range approximately from 30 to 60 days of age, while in humans this stage would roughly span between 10 and 18 years of age (Eiland and Romeo, 2013). The convergence of several factors during adolescence may result in a unique vulnerability of the brain to stress and stress-related adrenal hormones, such as the glucocorticoids (i.e., cortisol in primates and corticosterone in many rodent species; Romeo, 2013). First, studies in rats and mice have indicated that prepubertal animals (25–30 days of age) exhibit prolonged stress-induced corticosterone responses compared to adults, particularly in response to stressors with both physical and psychological attributes (≥ 65 days of age; Romeo, 2010a, 2010b; Romeo et al., 2013). Second, the adolescent brain may be more sensitive to corticosterone, as a study reported that mid-adolescent (42 days of age) and adult (67 days of age) rats treated with similar levels of corticosterone show different gene expression profiles. In particular, this study showed that corticosterone-induced expression for glutamate receptor subunits was greater in the mid-adolescent compared to adult hippocampus (Lee et al., 2003). Third, brain areas that continue to develop during adolescence, such as the amygdala, hippocampus, and prefrontal cortex (Giedd and Rapoport, 2010), show relatively high levels of the glucocorticoid receptors throughout adolescent development (Dziedzic et al., 2014; Pryce, 2008; Romeo et al., 2013; Vazquez, 1998). Thus, the interaction between protracted hormonal responses and the continued maturation of stress-sensitive brain areas could lead to an adolescent brain being highly susceptible to stress (Fig. 1). Though it is unclear if this increased susceptibility is a reality, the adolescent brain does display structural changes in response to chronic stress exposure and some of these effects are different in adolescent compared to adult animals.

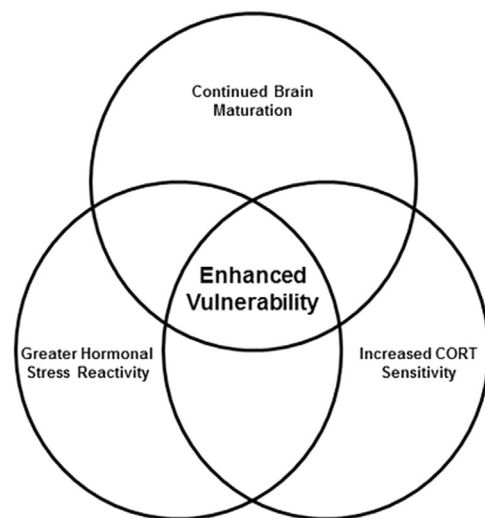


Fig. 1. A schematic representation of interacting variables, including continued adolescent brain maturation, greater stress-induced hormonal reactivity, and increased sensitivity to corticosterone (CORT), which may contribute to the enhanced stress-related vulnerabilities observed during adolescence.

3. Stress and the adolescent amygdala

The amygdala plays a major role in mediating fear learning, reward, aggression, and sexual behavior and is composed of several subnuclei, including the basolateral, central, and medial nuclei (LeDoux, 2007). Human MRI studies have shown that overall amygdalar volumes increase in both males and females from childhood to early adolescence, peaking around 12 and 14 years of age for boys and girls, respectively (Goddings et al., 2014; Hu et al., 2013). Though these trajectories are further shaped by the pubertal status of the individual and show hemispheric differences, it is important to note that following these peaks in expansion boys continue to show minor increases in amygdalar volume until young adulthood, while girls exhibit slight volumetric decreases (Goddings et al., 2014; Hu et al., 2013). Thus, sex appears to modulate the adolescent maturation of this brain region and suggest that gonadal hormones may influence this developmental process.

In parallel with these human studies, animal experiments in rodents, namely rats and hamsters, also show pubertal-related volumetric increases in subnuclei of the amygdala, such as the basolateral and medial nuclei (Cooke, 2010; Romeo and Sisk, 2001; Rubinow and Juraska, 2009). These changes may be in part be regulated by alterations in circulating gonadal hormone levels (Cooke, 2010; Romeo and Sisk, 2001). In the basolateral nucleus, the volumetric increase appears to be mediated by expansion of the neuropil, with the early stages of adolescence in both male and female rats marked by increases in dendritic length and complexity of neurons in the basolateral nucleus (Koss et al., 2014), while increases in the volume of the medial nucleus in hamsters is likely mediated by the pubertal increase in cell body size noted in this region, an effect that may influence membrane excitability (Romeo and Sisk, 2001). Taken together, the human and non-human animal studies indicate there are adolescent-related increases in amygdalar volume and that these changes occur relatively early in the transition to adulthood. It should be noted, however, that the exact age during which these changes occur in either males or females are unknown, as studies sampling these morphological changes at multiple ages in both sexes across adolescence are currently lacking.

Exposure to stress in adulthood has been reported to significantly affect the structure of amygdalar neurons (McEwen

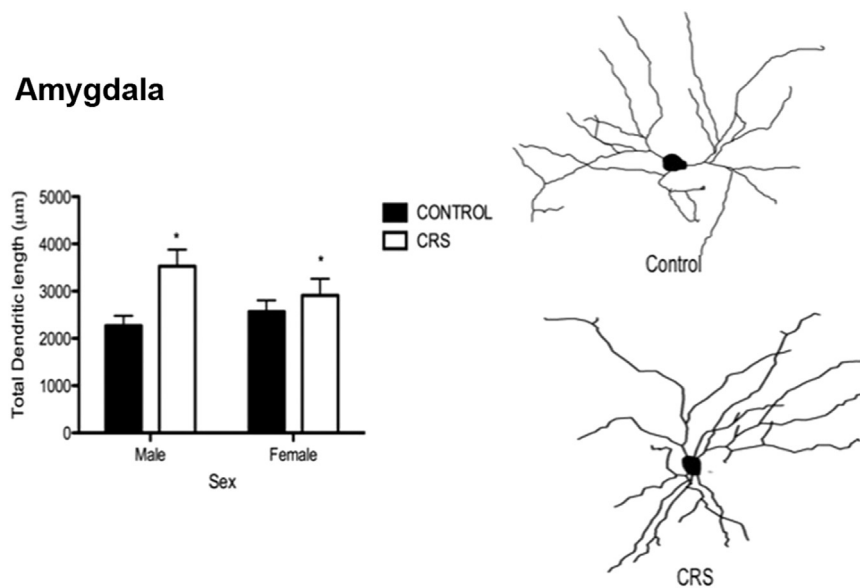


Fig. 2. The effects of chronic restraint stress (CRS) during adolescence on dendritic remodeling in the amygdala of male and female rats. Representative tracings are from Golgi-stained basolateral amygdalar neurons. Note the stress-induced dendritic hypertrophy in the amygdala. Adapted from Eiland et al. (2012) and Eiland and Romeo (2013).

et al., 2016). Specifically, adult male rats chronically exposed to restraint stress show increases in dendritic complexity as well as increased dendritic spine density, particularly in the neurons of the basolateral nucleus (Vyas et al., 2002, 2006). A similar effect of chronic restraint stress in early pubertal development is also noted in the basolateral nucleus of male and female rats (Eiland et al., 2012; Padival et al., 2015; Fig. 2). However, this stress-induced increase in dendritic length of adolescent animals is accompanied by a decrease in dendritic spine density in these neurons (Padival et al., 2015). Another study that investigated social isolation stress showed decreases in spinophilin, a protein marker of dendritic spines, in the basolateral and central nuclei of the amygdala in male and female rats (Leussis and Andersen, 2008). Thus, presuming decreases in spinophilin would be associated with decreased spine density (Allen et al., 1997), these results would suggest that stress leads to decreased spine density during adolescence, but increased spine density during adulthood. These data indicate that chronic stress exposure during early adolescence leads to morphological changes both similar and different from those observed in the amygdala of adult animals. Moreover, these stress-induced changes may be dependent on the type of stressor experienced, as chronic restraint and social isolation lead to different neurobiological outcomes in the amygdala (Table 1).

Although the implications of these structural changes in either adolescent or adult rodents are far from clear, these studies show

significant effects of stress on the structure of the amygdala both before and after adolescence. It should also be noted that both adolescent and adult animals exposed to chronic stress show enhanced anxiety-like behaviors (Padival et al., 2015; Vyas and Chattarji, 2004). Thus, it will be interesting for future studies to investigate which structural changes in the amygdala are important for these behavioral changes and whether structure and function relationships are different if the chronic stress exposure occurs early in adolescent development or later in adulthood.

4. Stress and the adolescent hippocampal formation

The hippocampal formation, composed of the hippocampus and dentate gyrus, is a critical brain region involved in mediating many forms of learning and memory, as well as aspects of emotional function and stress reactivity (Fanselow and Dong, 2010). Similar to the amygdala, neuroimaging studies indicate that hippocampal volumes exhibit linear growth early in adolescence in both males and females, after which females begin to show a volumetric loss in this region, while the increase in males continues into late adolescence (Goddings et al., 2014). Non-human animal studies also report adolescent-related structural changes in the hippocampal formation, with female rats showing increased dendritic branching between 44 and 51 days of age, followed by decreased dendritic branching between 51 and 55 days of age (Chowdhury et al., 2014). Moreover, though dendritic spine density remains relatively constant during these ages, the frequency of more stable, mature-like spines (i.e., mushroom-shaped spines) increase across these ages (Chowdhury et al., 2014). Studies in prepubertal male mice, on the other hand, show increased spine densities on the dendrites of hippocampal pyramidal and granular cells, but these changes are curvilinear, such that spine densities increase during the early portion of puberty followed by a decrease during the transition into young adulthood (Meyer et al., 1978). Thus, both the human and non-human animal studies indicate that there are significant hippocampal structural changes associated with adolescence, but as in the amygdala, these changes show some differences between the sexes and the time at which they occur.

In adults, a fair amount of research has been conducted on the

Table 1

Studies examining the effects of chronic stress exposure during adolescence on morphological parameters of the amygdala. Note all of these studies were conducted on rats.

Sex	Stressor	Age of stress	Outcome	Reference
M&F	Chronic restraint	20–41 days	↑Dendritic length	Eiland et al. (2012)
M	Chronic restraint	32–40 days	↑Dendritic length	Padival et al. (2015)
M	Chronic restraint	32–40 days	↓Dendritic spines	Padival et al. (2015)
M&F	Social isolation	30–35 days	↓Spinophilin ^a	Leussis and Andersen (2008)

^a Spinophilin is a protein marker for dendritic spines.

impact of stress and stress-related hormones on the size of the hippocampal formation and the morphology of its neurons (McEwen et al., 2016). Specifically, in postmenopausal women, hippocampal volume was negatively correlated with levels of perceived stress (Gianaros et al., 2007). It is interesting to note that reduced hippocampal volumes are also observed in patients that have Cushing's syndrome (Starkman et al., 1999a), a disorder marked by hypercortisolemia. Due to limitations in the spatial resolution of neuroimaging, the cellular basis of these structural changes is still unknown; however, non-human animal studies would suggest that these volumetric alterations might be mediated by reductions in dendritic branching of hippocampal neurons. For instance, studies in adult rats have shown significant dendritic atrophy in cells of both the hippocampus and dentate gyrus following chronic restraint stress or prolonged exposure to relatively high levels of glucocorticoids (McEwen et al., 2016). These effects of stress on neuronal morphology are reversible, such that neuronal branching patterns can return to pre-stress levels within 10 days after the stressor has been terminated (Conrad et al., 1999). Along these lines, hippocampal volumes return to normal after successful treatment of patients with Cushing's syndrome, which reduces the abnormally high levels of cortisol (Starkman et al., 1999b). Taken together, these studies indicate the hippocampal formation is sensitive to chronic exposure to stress and stress-related hormones, but that these effects are reversible if given enough time to recovery.

Reductions in dendritic branching following prolonged exposure to restraint stress have been noted in the hippocampus of adolescent male and female rats (Eiland et al., 2012; Fig. 3). Moreover, chronic variable physical stress, but not social stress, during adolescence has also been reported to slow the normal increase in the volume of the hippocampal pyramidal and granular cell layers during the transition from late adolescence to early adulthood (between 56 and 77 days of age; Isgor et al., 2004; Table 2). Similar to these results in rodents, boys and girls (between 8 and 14 years of age) presenting with post-traumatic stress symptoms, which are associated with relatively high levels of circulating cortisol, show decreased hippocampal volume

Table 2

Studies examining the effects of chronic stress exposure during adolescence on morphological parameters of the hippocampal formation. Note all of these studies were conducted on rats.

Sex	Stressor	Age of stress	Outcome	Reference
M&F	Chronic restraint	20–41 days	↓Dendritic length	Eiland et al. (2012)
M	Chronic physical stress	28–55 days	↓Hippocampal growth	Isgor et al. (2004)
M	Chronic social stress	28–55 days	ns	Isgor et al. (2004)

ns=nonsignificant

compared to healthy controls (Carrion and Wong, 2012). Therefore, it appears that both human and non-human adolescents exhibited stress-induced hippocampal remodeling similar to that observed in adults. These changes may be a mediating factor in the decreased learning and memory abilities and increased emotional reactivity seen in adolescents exposed to chronic stress (McCormick and Mathews, 2010; McCormick et al., 2010; McCormick and Green, 2013), yet a direct link has not been established.

5. Stress and the adolescent prefrontal cortex

The prefrontal cortex shows remarkable structural changes during adolescence, with increased volumes observed from childhood to the onset of puberty, followed by a period of cortical thinning into young adulthood (Giedd et al., 1999; Gogtay et al., 2004; Sowell et al., 1999). Along with the neuroimaging data, histological studies in postmortem human and non-human adolescent brain tissue suggest that synaptic pruning and programmed cell death are partially responsible for the phase of cortical thinning associated with adolescence (Huttenlocher, 1979; Juraska and Markham, 2004; Markham et al., 2007). Given that the prefrontal cortex is integral in the regulation of emotional

Hippocampus

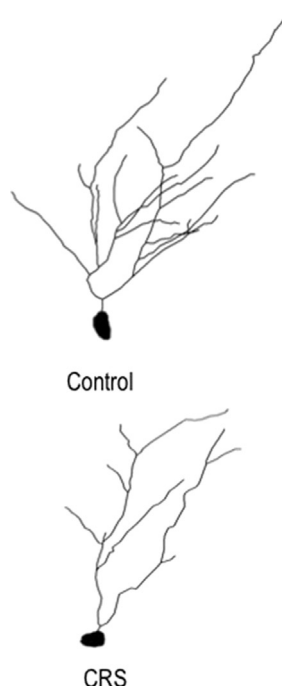
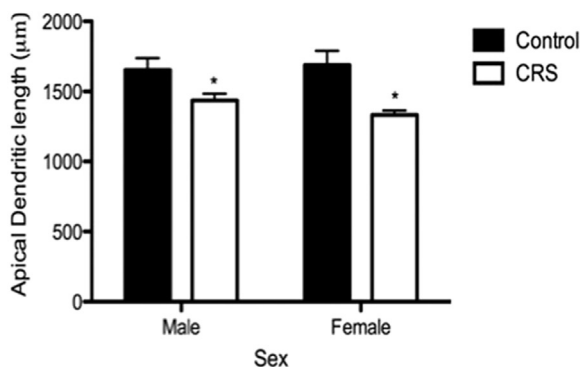


Fig. 3. The effects of chronic restraint stress (CRS) during adolescence on dendritic remodeling in the hippocampus of male and female rats. Representative tracings are from Golgi-stained hippocampal CA3 neurons. Note the stress-induced dendritic atrophy in the hippocampus. Adapted from Eiland et al. (2012) and Eiland and Romeo (2013).

behaviors, executive function, and fear extinction (Sotres-Bayon et al., 2006), these structural alterations have been posited to moderate some of the adolescent-related changes in psychological function (Blakemore and Choudhury, 2006; Casey et al., 2010; Ernst and Mueller, 2008; Giedd and Rapoport, 2010; Somerville and Casey, 2010; Yurgelun-Todd, 2007).

As with the amygdala and hippocampal formation, the adult medial prefrontal cortex also shows significant changes in structure following chronic exposure to either stress or glucocorticoids (McEwen et al., 2016). In particular, pyramidal cells in layer II/III of the prefrontal cortex exhibit decreased dendritic branching (Cook and Wellman, 2004; Liston et al., 2006) as well as decreased spine density (Radley et al., 2006). This structural remodeling of the prefrontal cortex is associated with impairment of attention set-shifting (Liston et al., 2006), a cognitive ability compromised by lesions of the prefrontal cortex (Birrell and Brown, 2000), suggesting a link between these morphological changes and changes in frontal-mediated behaviors. Like those seen in the hippocampus, these stress-induced morphological changes in the prefrontal cortex are reversible, such that animals allowed to recover for three weeks after stress exposure show dendritic branching similar to unstressed, controls (Radley et al., 2005). It is presently unknown whether changes in prefrontal-mediated behaviors, such as attention set-shifting, show reversibility similar to the structural remodeling.

Prefrontal cortical neurons also show dendritic atrophy following chronic restraint stress in adolescent male and female rats (Eiland et al., 2012; Fig. 4). Moreover, protein markers of synaptic plasticity, including spinophilin and synaptophysin, exhibit significant reductions in the prefrontal cortex in response to social isolation stress early in adolescent development (Leussis and Andersen, 2008; Table 3). It is important to note that these changes were reported to persist for over three weeks after cessation of the isolation stress (Leussis et al., 2008), suggesting that stress-induced structural alterations in the adolescent prefrontal cortex may be longer lasting than those exhibited by adults (Radley et al., 2005). Though it is currently unknown whether attention tasks are compromised in adolescent animals exposed to chronic restraint or social isolation stress, it appears that chronic stress exposure during either adolescence or adulthood can result in structural changes of prefrontal cortical neurons.

Table 3

Studies examining the effects of chronic stress exposure during adolescence on morphological parameters of the prefrontal cortex. Note all of these studies were conducted on rats.

Sex	Stressor	Age of stress	Outcome	Reference
M&F	Chronic restraint	20–41 days	↓Dendritic length	Eiland et al. (2012)
M&F	Social isolation	30–35 days	↓Spinophilin ^a	Leussis and Andersen (2008)
M&F	Social isolation	30–35 days	↓Synaptophysin ^b	Leussis and Andersen (2008)
M&F	Social isolation	30–35 days	↓Synaptophysin ^b	Leussis et al. (2008)

^a Spinophilin is a protein marker for dendritic spines.

^b Synaptophysin is a presynaptic protein marker.

6. Directions for future research

Though clear progress has been made delineating the effects of chronic stress exposure on the structure of the adolescent brain, many unanswered questions remain. As the field moves forward, there are at least three areas of research that will be important to pursue if we are to arrive at a broader understanding of the relationship between stress and adolescent brain morphology.

First, experiments will need to directly compare the effects of chronic stress on the adolescent and adult brain. To date, studies have examined the effects of stress on the neuronal structure in the adolescent amygdala, hippocampus, and prefrontal cortex and show that these effects of stress are similar to those observed in adulthood. What is currently unknown, however, is whether these stress-induced structural changes are similar in magnitude between the adolescent and adult brain. For instance, if the decrease in dendritic complexity and length are quantitatively the same in adolescent and adult prefrontal cortical neurons, then these data would suggest that the brain is similarly sensitive to chronic stress-induced morphological changes before and after adolescence. Conversely, if the adolescent brain shows greater or lesser changes than the adult following exposure to the same bout of chronic stress, this would suggest developmental shifts in the sensitivity to stress-induced plasticity. With the lack of direct comparisons between adolescent subjects and subjects at different

Prefrontal Cortex

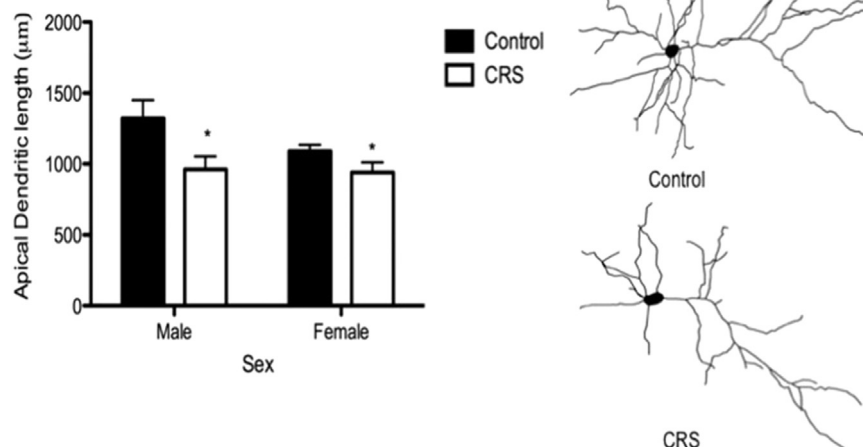


Fig. 4. The effects of chronic restraint stress (CRS) during adolescence on dendritic remodeling in the prefrontal cortex of male and female rats. Representative tracings are from Golgi-stained prelimbic neurons. Note the stress-induced dendritic atrophy in the prefrontal cortex. Adapted from Eiland et al. (2012) and Eiland and Romeo (2013).

developmental stages, such as childhood or adulthood, it is difficult to determine whether adolescence marks a unique period of stress sensitivity in the context of brain structure.

Second, it will be critical for future experiments to determine the reversibility of these effects of stress on the adolescent brain. As noted above, stress-induced structural changes in adult hippocampal and prefrontal cortical neurons have been reported to return to their pre-stress morphology following sufficient recovery times (Conrad et al., 1999; Radley et al., 2005). It will be important to establish whether the adolescent brain shows similar elasticity or whether stress-induced changes are longer lasting than those observed in the adult brain, such as that reported for synaptophysin levels in the prefrontal cortex following social isolation during adolescence (Leussis et al., 2008). Thus, stress may lead to more prolonged, or perhaps permanent, structural alterations in the adolescent brain, which would have implications for recovery of function and future sensitivity to additional periods of chronic stress.

Finally, most studies that investigate the effects of chronic stress on brain structure have employed only male subjects, yet notable sex difference have been reported on the effects of stress on the adult brain (Bangasser and Valentino, 2012; Farrell et al., 2015; Galea et al., 1997). Moving forward, it will be vital for experimental designs to included females subjects to assess potential sex differences in how the adolescent brain responds to stress and whether these effects are different between adolescent and adult males and females. Given the role of gonadal hormones on structural changes in the amygdala, hippocampal formation, and prefrontal cortex (Romeo and McEwen, 2004), future studies will need to address whether any sex-dependent effects of stress on the adolescent brain are apparent before the secretion of significant levels of gonadal hormones.

7. Conclusions

The literature reviewed above clearly indicates that structural components of the adolescent amygdala, hippocampal formation, and prefrontal cortex are significantly affected by exposure to chronic stress. Though many of these stress-induced morphological effects appear to be similar to those reported in adults, no direct comparisons have been made between adolescent and adult cohorts. Thus, it is currently unknown whether chronic stress exposure during adolescence may be particularly damaging to the developing brain. Given the increase in stress-related psychological vulnerabilities during this crucial stage of development (Andersen, 2003; Dahl and Gunnar, 2009; Eiland and Romeo, 2013; McCormick and Green, 2013), it will be necessary for future lines of research to examine both the short- and long-term influence of stress on adolescent brain structure. It will also be imperative to establish the exact role of stress-induced structural changes in the mental health and well-being of adolescent individuals as they transition into young adulthood and beyond.

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