Is Adolescence a Sensitive Period for Depression? Behavioral and Neuroanatomical Findings From a Social Stress Model

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KEY WORDS amygdala; anxiety; hippocampus; learned helplessness; myelin; prefrontal cortex

ABSTRACT Objectives: Sex differences in depressive symptoms emerge during adolescence, with females more at risk than males. However, adverse life events during development have greater impact on males. An animal model that incorporates behavioral and anatomical changes following adolescent stress is needed. Experimental Design: Sprague-Dawley rats were exposed to social stress (SS; isolation housing during P30–35) or remained group-housed (GRP) and tested in the forced swim test (FST), the triadic learned helplessness model (LH), and the elevated plus maze. Western immunoblots of myelin basic protein (MBP) and synaptophysin (SVP) and spino- phillin indexed synaptic and dendritic plasticity, respectively. Principal Observations: At P36, SS increased climbing behavior in both sexes, and decreased the latency to immobility in females following a 15 min inescapable swim in the FST. Depressive-like behaviors were differentially elevated in both sexes 24 h later. GRP females exhibited higher levels of depression-related behaviors than GRP males in both FST and LH paradigms. SS significantly increased depressive behaviors in the FST in males, and impaired their ability to escape shock previously conditioned to be controllable. SS decreased open arm time in females only. The greatest reductions in synaptic plasticity proteins were observed in the prefrontal cortex: spinophillin (19.1%), SVP (7.9%), and MBP (48.7%, males only). Smaller reductions in spinophillin were observed in the hippocampus and amygdala. Conclusions: Adolescent separation produces both behavioral and neural changes associated with stress-related depression and anxiety. Additional work is needed to improve our understanding of stress as it relates to depression during this vulnerable period of development. Synapse 62:22–30, 2008. ©2007 Wiley-Liss, Inc.

INTRODUCTION
Adolescence is a significant period of development, characterized by increased social interactions (Spear, 2000), responses to stressors (Lyss et al., 1999; Romeo and McEwen, 2006; Romeo et al., 2004), and neuroanatomical rearrangements (Andersen and Teicher, 2004; Kalsbeek et al., 1988; Zehr et al., 2006). These changes are believed to increase vulnerability to psychiatric disorders (Andersen, 2003; McEwen, 2003; Thompson et al., 2004). Beginning in adolescence, females become more susceptible to clinical depression than males (Nolen-Hoeksema and Girgus, 1994). While hormonal changes are a likely culprit, they minimally influence depression when compared with social factors such as negative life events (Brooks-Gunn and Warren, 1989). Prior exposure to chronic stress alters an individual's behavioral, neurochemical, and neuroendocrine response to acute stressors (Bhatnagar and Meaney, 1995; Weiss et al., 2004). In clinical studies that have examined sex differences, early adverse events have a greater neuroanatomical

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impact on males than females (De Bellis and Keshavan, 2003; Teicher et al., 2004).

One possibility that has not been explored in sufficient detail is whether the timing of stress exposure during the course of maturation produces regionally-specific effects on brain development (Andersen, 2003). Brain regions undergoing periods of rapid change or rearrangements may be more susceptible to the effects of stress (Andersen et al., in press; Brunson et al., 2001). For example, a history of childhood sexual abuse is associated with hippocampal volumetric loss (Bremner et al., 2003; Stein et al., 1997). In an analysis designed to determine if a sensitive period for child abuse exists, we recently found that abuse between 3–5 years of age was associated with a volumetric reduction in the hippocampus (Andersen et al., in press). However, abuse during this period had little effect on prefrontal cortex (PFC) gray matter. Abuse between 14–16 years of age was associated with reduced gray matter in the PFC, with little effect on hippocampal size. Maternal separation, designed to impact early postnatal development in the rat, reduces synaptophysin (a marker for gray matter) in the hippocampus but not the PFC (Andersen and Teicher, 2004). Together, these findings suggest that the PFC may be selectively vulnerable to stress during adolescence (Andersen, 2003; Andersen et al., in press). This, in turn, may increase depression, which is a cortically-mediated process (Amat et al., 2005).

To investigate whether a significant stressor during a discrete period of adolescent development influences both behavior and neuroanatomy in a sex-dependent manner, the following animal model was developed. Rats were isolated from peers (postnatal days, P30–35) during a peak interval of social development (Panksepp, 1981), elevated corticosterone responses to stress (Romeo et al., 2004), and the emergence of stress-induced activity in the PFC (Lyss et al., 1999). This interval of P30–35 differs from other social isolation paradigms when rats are individually housed from weaning until testing, 30–60 days or more (Hall, 1998; Weiss et al., 2004). As stress-associated brain regions in mammalian species are undergoing significant rearrangements in synaptic density (Andersen and Teicher, 2004; Giedd et al., 1999; Zehr et al., 2006), it is difficult to link when stress exposure affects anatomy.

We hypothesize that social stress (SS) will have selective effects on the adolescent PFC, with little effect on the hippocampus. The effects will be more dramatic in males than females, consistent with the clinical literature (De Bellis and Keshavan, 2003; Teicher et al., 2004). The impact of SS on the onset of depressive-like symptoms in adolescent rats will be evaluated using the behavioral despair paradigms of forced swim test (FST) (Porsolt et al., 1977) or learned helplessness (LH) (Maier and Watkins, 2005).

METHODS AND MATERIALS

Subjects

Sprague-Dawley rats were bred at McLean Hospital (breeders from Charles River Laboratories; Wilmington, MA). Male and females rats were weaned at P21 and housed with same-sex littermates in groups of three. Rats were randomly assigned to the SS or group (GRP) condition, with one pup per litter per condition. From P30–35, SS rats were housed in isolation while control rats remained group-housed during this period. At P35, SS rats were rehoused with their preisolation cagemates. These ages were chosen as pubertal onset (marked by vaginal opening or descent of the testes) occurs, on average, at P38 in our colony. Previous research suggests that estrous cycle has negligible effects on stress response at this stage (Hodes and Shors, 2005), and less than 25% exhibited vaginal opening at testing. Food and water were available ad libitum throughout the experiment, except during behavioral testing. At P36, animals were tested in the elevated plus maze (EPM), followed by either the FST (n = 5–7/condition) or LH (n = 6–8 triads/condition) paradigms. For Western blot analysis, rats were sacrificed at P36 and not subject to any behavioral testing.

FST

On Day 1 of the FST (P36–37), rats were placed in a clear 25-cm-diameter cylinder filled with 25°C water to a depth of 40 cm. After 15 min of forced swimming, the subject was removed from the water, dried, and warmed for 20 min before returning to the home cage. Twenty-four hours later, rats were retested for 5 min under the same conditions. The training and test sessions were videotaped from the side of the cylinder, and scored by raters blind to treatment condition.

Two scoring methods were used: latency to become immobile (Carlezon et al., 2003) and behavioral sampling (Detke et al., 1995). Latency to become immobile was defined as the time the rat initiates a stationary posture for ≥2.0 s that does not reflect attempts to escape. For behavioral sampling, rats were rated at 5 s intervals throughout the training/testing session. At each interval, the predominant behavior was assigned to one of four categories: immobility, swimming, climbing, or diving, as defined previously (Carlezon et al., 2003; Detke et al., 1995). Diving data are not presented, as it was only rarely observed.

LH

Rats were tested in the LH paradigm between P36 and P38. The triadic LH protocol was used to assess the role of controllability of stress on behavior (Maier...
and Watkins, 2005). On Day 1, rats are assigned to a triad consisting of (1) an inescapable shock (IS) subject; (2) an escapable shock (ES) subject; and (3) a no shock (NS) control subject. Subjects from the SS or GRP conditions were counterbalanced within the triad to avoid possible differences in shock exposure on Day 1 as a result of condition (Drugan, 2001). Rats were given 100 trials of a tail shock (1.0 mA for trials 1–30, 1.3 mA for trials 31–60, and 1.6 mA for trials 61–100) in a wheel-turn box (Drugan, 2001). The shocks were unsignaled, and delivered on a variable time 45-s schedule (range 30–60 s). The ES subject could turn a wheel to terminate the shock. The IS subject was yoked to the ES subject, receiving the same amount of shock as the ES subject, but without the ability to terminate the shock. The shock lasted until the ES rat completed the wheel-turn response, or a maximum of 30 s. The NS rat was restrained in a wheel-turn box but received NS and is used to assess generalized deficits in learning or responding on Day 2. On Day 2, each subject was placed into a shuttlebox (Med Associates, St Albans, VT). Rats from all three conditions could terminate a 1 mA foot-shock by shutting to the other side for trials 1–5, or by shutting to the other side and back again for trials 6–30. This response was cued by a tone that preceded the shock by 2 s. The shock remained on for 30 s, or until terminated by the appropriate behavioral response. Consistent with previous studies (Drugan, 2001), data from the first five trials were not used in the analyses as subjects were learning the appropriate behavioral response. The number of escape failures and the mean latency to escape was recorded for trials 6–30.

EPM

Rats were tested in the EPM at P36. The maze consisted of two open and two closed arms (each 10 × 50 cm²) attached to a central platform, and raised 50 cm above the floor. Each rat’s behavior was examined over a 5-min period, and included measures of time in the open arms, total entries into the open and closed arms, and the number of rears.

Western blots

At P36, SS, and GRP rats were rapidly decapitated, their brains removed and flash frozen in isopentane, then stored at −80°C. For the infralimbic (IL) and cingulate gyrus (CG3) regions of the PFC, the central and basolateral nuclei of the amygdala (CeA and BLA, respectively), and the dorsal and ventral CA3 region of the hippocampus (HCd and HCV), bilateral punches (0.98-mm diameter) were obtained (Paxinos and Watson, 1986). Each brain region was specifically chosen due to its contribution to the stress response and relation to depression.

We examined the plasticity-related proteins spinophilin, a protein involved in the regulation of dendritic spine structure and function (Sarrouilhe et al., 2006); SVP, a presynaptic protein (Glantz and Lewis, 1997); tyrosine hydroxylase (TH), a dopaminergic marker (Lewis et al., 1988); and myelin basic protein (MBP), a marker for oligodendrocytes (De Groot, 1988).

Proteins were prepared from tissue homogenization in cold 1X SDS and quantified with the Bradford method. Fifteen micrograms of protein were used for western immunoblot and all markers, treatment condition, and sex were run together on each blot. Proteins were separated on a 10% PAGE (BioRad, Hercules, CA) and transferred overnight to a nitrocellulose membrane (Osmonics, Minnetonka, MN) at 40V. After block in TBS-T buffer with 5% milk for 60 min, the membrane was incubated overnight in primary antibodies: SVP (produced in mouse; 1:20,000; Sigma), spinophilin (1:1000; Chemicon; Temicula, CA), TH (1:5000; Chemicon), MBP (1:1000; Chemicon), and actin as the control (1:20,000; MP Biomedical; Akron, OH). Membranes were incubated in TBS-T buffer with 5% milk and secondary antibodies (goat anti-mouse, 1:20,000; goat anti-rabbit, 1:10,000, Chemicon), rinsed, placed in ECL detection buffer (SuperSignal, Pierce, Rockford, IL), and developed on film. All proteins were identified by molecular weight using a Rainbow marker (BioRad, Hercules, CA).

Statistical analysis

FST and EPM data were analyzed by 2-way ANOVA with treatment and sex as variables, followed by Fisher’s LSD post-hoc comparisons for the EPM (SPSS, v11.0.4). In the FST test, Day 1 and Day 2 were analyzed independently. Differences between GRP males and females were analyzed by t-test, based on a priori hypotheses for the FST test data. Day 2 LH data were analyzed by three-way ANOVA with treatment, sex, and LH condition (IS, ES, NS) as variables, followed by Fisher’s LSD post-hoc comparisons. Analysis of western blot data was completed separately for each brain region of interest following correction by individual actin values. As each immunoblot was repeated 2–3 times, a mixed within-between ANOVA was utilized, with run considered the within-subjects factor and treatment and sex between-subjects factors. Fisher’s LSD post-hoc comparisons determined individual group differences following a significant main effect or interaction.

RESULTS

FST

Sex differences were evident in the FST in GRP conditions, but not during Day 1 (Fig. 1A). Significant
sex differences in GRP animals emerged 24 h later on Day 2 (Fig. 1B). Relative to GRP males, GRP females exhibited a shorter latency to immobility \( (t(11) = 2.42, P < 0.05) \), more intervals of immobility \( (t(11) = -2.54, P < 0.05) \), and fewer intervals of swimming \( (t(11) = 2.56, P < 0.05) \), suggesting that normal adolescent females are more susceptible to depression-induction than males in this test.

The effects of SS, however, were evident on Day 1 of testing. Relative to GRP controls, males and female SS subjects had an increase in climbing \( (F_{1,23} = 11.85, P < 0.001, \text{Fig. 1A}) \) and a decrease in swimming behavior \( (F_{1,23} = 5.17, P < 0.05) \), although the effect on swimming was driven by the males. A trend-level decrease in latency to immobility was observed for SS females \( (P = 0.06) \) relative to the GRP females. Within the SS group itself, females had significantly lower latencies to immobility than males \( (t(9) = 2.54, P < 0.05) \). A treatment \( \times \) sex interaction \( (F_{1,19} = 6.04, P < 0.05) \) on Day 2 of FST suggested that SS males exhibited significantly lower latencies to immobility than GRP males, with no change in SS females (Fig. 1B). A similar observation was made for intervals of immobility and swimming (treatment \( \times \) sex interaction: \( F_{1,19} = 2.25, P < 0.05 \) and \( F_{1,19} = 6.34, P < 0.02 \), respectively). Male SS rats exhibited more immobility and less swimming than GRP males, with no difference between SS and GRP females (Fig. 1B).

**Learned helplessness**

In the LH paradigm, the latency to escape varied significantly according to LH condition, ES, IS, or NS \( (F_{2,72} = 23.58, P < 0.001; \text{Fig. 2A}) \), as did the number of escape failures \( (F_{2,72} = 24.23, P < 0.001; \text{Fig. 2B}) \). IS animals had the highest latencies to escape and greatest number of escape failures when collapsed across all groups. Further, there was a three-way interaction between LH condition, treatment, and sex \( (F_{2,72} = 4.38, P < 0.02) \). Only the IS-exposed animals...
were helpless in GRP males and females. Similar to the findings in the FST, male GRP rats were less susceptible to helplessness following IS than females, as evidenced by their lower latency to escape on Day 2 compared to females ($P < 0.05$).

SS exposure produced helplessness in males following ES or IS ($P < 0.001$ and $P < 0.001$ vs. NS, respectively), but only following IS in SS females ($P < 0.01$ and $P < 0.05$ vs. ES or NS, respectively). Importantly, ES rats from all groups learned the wheel-turn response on Day 1 (unpublished observation), suggesting the helplessness of SS-ES males does not stem from differences in responding to the ES on Day 1.

**EPM**

A significant treatment × sex interaction was observed for time spent in the open arms ($F(1,28) = 4.18, P < 0.05$) (Fig. 3). Among males, both GRP and SS rats spent equal amounts of time in the open arms ($P > 0.1$). In contrast, SS reduced the amount of time spent in the open arms relative to GRP females ($P < 0.01$). Treatment effects on rearing ($P > 0.9$) or total number of arm entries ($P > 0.5$) were not observed. Normal GRP females exhibit lower levels of anxiety than males in the EPM ($P < 0.05$), as previously shown (Johnston and File, 1991).

**Western blot**

**PFC**

In the IL region of the PFC, spinophilin decreased 19.1% ± 7.6% following SS ($F(1,15) = 4.92, P < 0.05$; Fig. 4A). SVP decreased in the IL region following SS, though by a more modest, yet significant 7.9% ± 3.2% ($F(1,12) = 5.68, P = 0.035$; Fig. 5). There was no overall sex effect ($P > 0.1$), and no treatment × sex interaction ($P > 0.1$). SS did not affect TH ($P > 0.1$) or MBP ($P > 0.1$) in this region of the PFC (Table I).

Spinophilin levels in the CG3 of the PFC were not altered by SS ($P > 0.1$; Fig. 4B) or sex ($P > 0.1$). Neither SVP ($P > 0.1$) nor TH ($P > 0.1$) were affected by SS (Table I). However, a treatment × sex interaction ($F(1,7) = 10.65, P < 0.02$) in MBP expression shows a 48.7% ± 5.5% decrease in males following SS ($P < 0.001$), with no change in females ($P > 0.1$; Fig. 6). Finally, females exhibited lower levels of MBP than males, when collapsed across treatment condition ($F(1,7) = 33.85, P < 0.001$).
Amygdala

In the CeA, spinophilin was decreased 25.5% ± 7.5% following SS ($F(1,12) = 7.79, P < 0.02$; Fig. 4C), independent of sex ($P > 0.1$). No differences were observed in SVP ($P > 0.1$), TH ($P > 0.1$), or MBP ($P > 0.1$) in the CeA following SS (Table I).

In the BLA, SS significantly decreased the levels of spinophilin by 20.9% ± 4.9% ($F(1,9) = 11.488, P < 0.05$), with no effect in females ($P > 0.1$; Table I).

MBP and actin are presented. *$P < 0.05$. 

Fig. 5. Adolescent social stress decreases synaptophysin in the PFC. A) Social stress (SS) significantly decreased synaptophysin (SVP) protein levels in the infralimbic (IL) region of the PFC when compared to group-housed (GRP) animals. Values represent mean (+SEM) optical density for SVP levels, after correcting for actin levels. B) Representative immunoblots for SVP and actin are presented. *$P < 0.05$.

TABLE I. Mean (±SEM) optical density (OD) values for synaptophysin (SVP), tyrosine hydroxylase (TH), and myelin basic protein (MBP) in the IL and CG3 regions of the PFC, BLA, and CeA regions of the amygdala, and ventral (HCv) and dorsal (HCD) CA3 regions of the hippocampus (average n = 5–6 per condition).

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<th>CeA</th>
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TH values within the hippocampus were not detectable. Total values represent mean values for GRP and SS treatments when collapsed across sex. OD values are relative to actin levels, to control for differences in total protein.

* $P < 0.05$ GRP total versus SS total; ** $P < 0.05$ for treatment × sex interaction.

Fig. 6. Social stress decreases myelin basic protein in the PFC of males. A) Adolescent social stress (SS) significantly decreased myelin basic protein (MBP) protein levels in the CG3 region of the PFC in males, when compared to group-housed (GRP) males. MBP levels did not change in females following SS, although levels in GRP females were significantly lower than in GRP males to begin with. Values represent mean (+SEM) optical density for MBP levels, after correcting for actin levels. B) Representative immunoblots for MBP and actin are presented. *$P < 0.05$. 

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Hippocampus

In the ventral hippocampus (HCv), a treatment x sex interaction for spinophilin ($F(1,13) = 8.28, P < 0.02$; Fig. 4E) revealed an increase in male spinophilin levels by 16.3% ± 7.5% ($P < 0.05$; relative to GRP), while SS lowered spinophilin in males by 11.9% ± 6.2% relative to GRP ($P < 0.001$). Sex also exerted a significant effect overall ($F(1,13) = 17.69, P < 0.001$), with females exhibiting lower spinophilin levels in the HCv when collapsed across treatment. SS did not affect the levels of SVP ($P > 0.1$) or MBP ($P > 0.1$) in the HCv (Table I). In the dorsal hippocampus (HCD), no significant differences in the levels of spinophilin were observed ($P > 0.1$; Fig. 4F). SVP ($P > 0.1$), or MBP ($P > 0.1$) (Table I).

DISCUSSION

The present study is the first to provide evidence of adolescent onset of sex differences in depressive behaviors in an animal model. This effect is similar to the clinical condition, where adolescent females are more susceptible to depression than males (Kessler et al., 1993; Nolen-Hoeksema and Girgus, 1994). Here, normal (GRP) female rats were more susceptible to depression-induction than GRP males in situations of uncontrollable stress during adolescence. Females exhibit significantly more intervals of immobility, fewer intervals of swimming, and a shorter latency to go immobile than males in the FST on Day 2, with no sex difference observed on Day 1. Such a demonstration of sex differences in the FST has eluded researchers in adults (Kalynchuk et al., 2004; Yang et al., 2007), although recently observed under modified testing conditions (Sun and Alkon, 2006). Similar sex differences were also observed in the LH paradigm with GRP females exhibiting a longer latency to escape and more escape failures than males under the inescapable (IS) condition. However, comparisons of the IS group to the NS group suggest that both males and females have increased helplessness in the LH paradigm, without evidence of learning deficits (subjects escaped readily in the NS condition).

Moreover, SS increased depressive behaviors when compared with the GRP controls. Day 1 FST data shows that SS subjects, independent of sex, had increased climbing behavior relative to GRP subjects. Previous research has related this behavior to increased norepinephrine levels (Cryan et al., 2002), suggesting that SS heightens awareness to the environment. SS females had lower latency to become immobile than SS males, indicating an increased sensitivity to uncontrollable stress initially. In contrast, SS had little additive effect on depressive-like behaviors in the FST or the LH test in females on Day 2. High levels of depressive-like behaviors in GRP females in both paradigms on Day 2 may have obscured the effects of SS in females. However, SS females had higher latencies to immobility relative to GRP males ($P < 0.05$). In the LH model, SS females demonstrated improved (but not significant) performance relative to GRP females in the IS condition. It is possible that the cessation of the stressor (i.e., rehousing of the SS subjects with cagemates) may have reduced the impact of LH testing in females.

In contrast to females, additional stress by Day 2 FST or LH testing further degraded the performance of SS males. SS males exhibited a shorter latency to immobility, fewer intervals of swimming, and greater immobility when compared with GRP males. The triadic LH model differentiates between controllable and uncontrollable stress (Maier and Watkins, 2005) and demonstrated that SS males in the IS and ES conditions are helpless. The ability to experience some degree of control over stress is an important strategy the brain uses to protect itself from depression (Robbins, 2005). As such, the LH paradigm revealed additional sex differences between SS subjects that were not possible to characterize with the FST paradigm. These data suggest that SS diminishes the ability to cognitively modulate the effects of a controllable stressor in males, but not females. The finding that males are more vulnerable than females to the loss of controllability has been observed in adult rats (Shors et al., 2007).

Anatomically, the data suggest that SS during adolescence has regionally-selective effects on the PFC. SS reduced spinophilin and SVP in the male and female PFC, and produced no change in SVP in the hippocampus. These data are consistent with clinical evidence of a sensitive period for adolescent effects of abuse on gray matter in the PFC (Andersen et al., in press). SS effects on SVP endure into adulthood, but
were assessed with immunohistochemistry in a separate study and thus not presented here (Leussis and Andersen, submitted). Given the observed synaptic loss in the cortex, SS is likely to increase vulnerability to depressive-like symptoms through its effects on the PFC (Amat et al., 2005).

The enhanced vulnerability of males to SS, while predicted from clinical studies (De Bellis and Keshavan, 2003; Teicher et al., 2004), suggests that anatomiical changes in myelination of the PFC play an important role in affect control and responsiveness to stressors. In vitro studies show corticosterone metabolites reduce MBP in oligodendrocytes (Melcangi et al., 1997). Moreover, oligodendrocytes are overproduced in major myelinated areas of the rat brain during adolescence in males, but not females (Cerghet et al., 2006). Females compensate for a 40% lower density with a higher turnover rate of these cells. A 48.7% reduction in MBP in the PFC was observed in SS males, but not females, suggesting that an adolescent sensitive period exists for the effects of stress on oligodendrocytes. No current studies in humans have reported data that would corroborate the hypothesis that adolescent stress reduces myelin in the male PFC. However, postmortem data show reductions in cortical myelin in bipolar disorder and major depressive disorder patients (Ongur et al., 1998). Such a loss of MBP, which regulates glutamate levels (Fressinaud et al., 1991), could increase activity in the CG. Previous clinical studies with PET imaging have linked increased activity of area 25 of the CG in human patients to depression (Mayberg et al., 2005). This hypothesized overactivity of the CG may further be related to a loss of cognitive control in SS male adolescents.

This is not to say, however, that males are more impaired than females following adolescent stress exposure. SS decreased spinophilin in the amygdala of both sexes; only SS females had elevated anxiety scores. The dendritic marker spinophilin undergoes pruning in the amygdala between P21 and P49 (Zehr et al., 2006), and this process is vulnerable to SS. The loss of cortical modulation following SS could exacerbate anxiety-related behavior, as IL PFC projections to the brain during adolescence in males, but not females, which is similar to changes in adult hippocampal CA1 region following acute stress (restraint plus footshock) using Golgi staining (Shors et al., 2001). Both techniques provide a similar characterization of modest, sex-dependent dentritic change in the hippocampus. We note that SS did not produce the striking alterations in SVP that are observed with the early life, maternal separation stress (Andersen and Teicher, 2004).

These studies provide evidence of sex-dependent emergence of depressive-like behaviors during adolescence in an animal model. Through the use of a developmentally-appropriate social stressor, the results suggest that adolescent males are more vulnerable to the loss of controllability that leads to hopelessness (Robbins, 2005). While additional studies are needed to clarify the specific role of observed anatomical changes produced in this model, these data clearly suggest that the PFC is particularly vulnerable during adolescence. Loss of myelin in males may render them especially susceptible to the effects of stress at this age. Animal models such as this will improve our understanding of the unique profile of adolescent depression, and may help identify more effective antidepressant treatments for this population.

REFERENCES


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