Exposure to juvenile stress exacerbates the behavioural consequences of exposure to stress in the adult rat

Avi Avital and Gal Richter-Levin
Department of Psychology and The Brain & Behavior Research Center, University of Haifa, Mount Carmel, Haifa, Israel

Abstract
To examine the effects of exposure to post-weaning pre-puberty (juvenile) stress on the emotional and cognitive abilities in response to exposure to stress in adulthood, we first exposed rats to a platform stress at the age of 28 d. Two months later the rats were exposed to acute swim stress. Rats exposed to both stressors showed a higher level of anxiety (as measured both in open-field and startle response tests) than controls or rats exposed to either the juvenile or the adulthood stressor. In the Morris water-maze, rats that were exposed to both juvenile and adulthood stress performed better than the other groups. In a second experiment we verified that the effect of the juvenile stress was indeed age-dependent. One group was exposed at the age of 26–28 d and again at the age of 60 d (juvenile + adulthood stress); the other group was exposed to the first stressor at the age of 60–62 d and to the second at the age of 90 d [adulthood (60) + adulthood (90) stress]. Juvenile + adulthood stress had a significantly greater effect than exposure to stress twice in adulthood, on anxiety level and on the performance in the water-maze. Finally, in a third experiment we found that the juvenile + adulthood stress group swam faster and tended to explore the central area more than the other groups – a finding that could explain their better performance on the first trial of the spatial task. These results indicate that an exposure to a relatively brief juvenile stressful experience has profound and long-lasting effects on the ability to cope with stress in adulthood.

Received 10 February 2004; Reviewed 7 July 2004; Revised 28 July 2004; Accepted 1 August 2004

Key words: Anxiety, juvenile, PTSD, rat, spatial learning.

Introduction
The degree of subsequently experienced trauma may be related to the child’s age at the onset of abuse, although controversial views have been noted in the literature (Browne and Finkelhor, 1986). Some researchers claim that younger children are more vulnerable to trauma due to their impressionability (Browne and Finkelhor, 1986) and show greater symptomology as a result of abuse (Beitchman et al., 1991). Others claim that young children’s naivety serves as a protective device, especially if the children are unaware of the social stigma associated with the type of victimization they have suffered (Browne and Finkelhor, 1986). Still others (e.g. Kiser et al., 1991) argue that the age of onset of the abuse has no systematic relationship with the degree of disturbance. A possible explanation for these controversial findings is that new symptoms may emerge as a child matures, even though the full extent of detrimental effects may not be evident (Beitchman et al., 1991).

The vast majority of the animal research into early life trauma effects on affective symptoms in adulthood has focused on maternal deprivation paradigms. In this very early postnatal period, the rodent brain is remarkably different from the post-weaning pre-puberty and the post-puberty brain, both in structure and function (Vazquez, 1998). For example, in the rodent the early postnatal limbic hypothalamic–pituitary–adrenal (HPA) axis is remarkably different from that in the adult, both in structure and function (Vazquez, 1998). The HPA axis in the developing animal has a limited response to acute challenges between days 3 and 14 of life. These first 2 wk of pre-weaning are characterized by a ‘silent period’ during which the animal is hyporesponsive to stress [stress hyporesponsive period (SHRP)]. This may in fact lead...
under extreme conditions to a far more significant stress response when the animal fails to swiftly terminate glucocorticoid secretion. Several hypotheses have been proposed to explain the quiescent state; common explanations being immaturity of brain, pituitary and adrenal elements, or excessive feedback inhibition (Vazquez et al., 1996).

The period of postnatal development, for which most early experience research has been conducted with rat pups (i.e. 3–14 d postnatal), has been suggested to correspond approximately to week 23 of gestation in humans (Fitzgerald and Anand, 1993).

Here we focused on the effects of exposure to post-weaning pre-puberty (named ‘juvenile’) stress on rats’ ability to cope with stress in adulthood. At this age the pups already present a more independent behaviour and are not yet sexually mature. Furthermore, the post-weaning pre-puberty period in the rat, a life period not widely targeted before, may also resemble human childhood in that the HPA axis is fully developed but key brain areas such as the hippocampus are not.

The hippocampus is rich with corticosteroid receptors that play a role in modulating the basal tone of the HPA and in the magnitude and duration of stress responses (Vazquez et al., 1996). Moreover, the rat hippocampal formation continues to develop until the rat is sexually mature (Martin and Berthoz, 2002). The delayed anatomical development of the hippocampus appears to influence the physiological properties of its neurons, in particular the efficacy of inhibitory synaptic transmission. Using paired pulses, Michelson and Lothman (1989) found that excitatory transmission between CA3 and CA1 reached adult levels by 14 d postnatal, while full inhibitory responses were not seen until 28 d postnatal. Nurse and Lacaille (1999) further state that the GABA(B)-mediated inhibitory transmission is not fully developed until 35–45 d postnatal.

Comparing between the consequences of the exposure to stress in adulthood as a function of whether or not the animals were previously exposed to stress at the proposed age may enable us to suggest that exposure to juvenile trauma may contribute to increased vulnerability to stress-related disorders in adulthood.

In Expt 1 we tested the effects of exposure to a stressor in adulthood on the rats’ ability to perform in a spatial learning task in the Morris water-maze, as a function of whether or not they were exposed to a stressor early in their life. As a juvenile stress we applied the elevated platform stress (PL), which is similar to a protocol named small platform stress (Pokk and Vali, 2001; Pokk and Zharkovsky, 1998). The PL protocol comprises several factors of stress like novelty, restraint, uncontrollability, and unpredictability. As adulthood stress we utilized the acute swim stress (ASS) which is a commonly used stress protocol in the adult rat (Burjing et al., 1996; Avital et al., 2001). In addition, we used the open-field and startle response tests to assess anxiety level alterations.

In Expt 2 we aimed to examine whether the effects observed in Expt 1 were qualitative (developmental) or quantitative. Explicitly, was the impact of exposure to juvenile stress due to the developmental period within which it was applied, or were the effects due to repeated exposure to the stressor? Therefore, in this experiment we compared the juvenile + adulthood stress to a double exposure to stress during adulthood. To facilitate direct comparison between the two exposure protocols, the same stressor (PL) was applied in all stages of this experiment.

Finally, in Expt 3 we attempted to evaluate potential mechanisms that may contribute to the better performance of the juvenile + adulthood stress group in the first trial of the spatial task, compared to controls.

Materials and methods

Animals

Eighty-eight Male Wistar rats (eight rats per group in both experiments) weighing between 45 and 49 g (age 24 d) were purchased from Harlan (Jerusalem, Israel) and were given 4 d acclimation. Rats were housed four per cage in 75.0 x 55.0 x 15.0 cm Plexiglas cages in temperature-controlled (23±1°C) animal quarters on a 12:12 h light–dark cycle (lights on 07:00–19:00 hours). They had ad-libitum access to standard Purina Rat Chow pellets and water. All rats were weighed once a week.

General procedure

The general procedure of Expt 1 is detailed in Figure 1a. In Expt 2 (Figure 1b) several modifications were introduced compared to the first experiment. In addition to the groups we examined in the first experiment, we examined the effects of double exposure to stress in adulthood in Expt 2. Moreover, we intensified the juvenile stress protocol: exposure to the platform stress was repeated for three consecutive days (at the age of 26–28 d). Furthermore, in Expt 2 rats were trained in a massed training protocol (see below: massed spatial training – Expt 2). Finally, in Expt 3 (Figure 1c) we focused on the better performance on the first trial of the spatial learning task, observed in the juvenile + adulthood stress group. Therefore, we
recorded the swim pattern and speed of the juvenile + adulthood stress and the control groups.

**Behaviour**

**Elevated-platform stress (PL)**

Following 4 d of habituation to the housing conditions, individual rats (age 28 d) in the juvenile and the juvenile + adulthood stress groups were placed for 30 min on an elevated black platform (12.0 × 12.0 cm), located in the middle of a water pool, with its top 10.0 cm above the water’s surface. Rats were subjected to this stress three times, separated by 1 h in a resting cage, before being returned to their home cage. In Expts 2 and 3, rats were subjected to this stress during three consecutive days (age 26–28 d).

**Acute swim stress (ASS)**

Individual rats (age 12 wk) exposed to adulthood stress were made to swim for 15 min in a circular water tank (diameter 0.5 m, height 0.5 m). Water depth was 40.0 cm, and temperature was maintained at 23 ± 1°C. Following exposure to the ASS, rats were allowed to dry (for 1 h) in a resting cage prior to commencing the post-stress tests (Avital et al., 2001).

examined from the age of 90 d in a battery of tests including the open-field, the water-maze, and finally, the startle response test. (b) Expt 2 – Rats were exposed to two stressors, 1 month apart. They were exposed either to a juvenile + adulthood or to adulthood (60)+ adulthood (90) stress. Other groups were exposed only to those stages indicated below. The following groups were compared. (1) Control: naive rats (n = 8). (2) Juvenile stress: rats were exposed to PL at the age of 26–28 d (n = 8). (3) Adulthood (60) stress: rats were exposed to PL at the age of 60 d (n = 8). (4) Juvenile + adulthood stress: rats were exposed to PL both at the age of 26–28 and at the age of 60 d (n = 8). (5) Adulthood (90) stress: rats were exposed to PL at the age of 90 d (n = 8). (6) Adulthood (60) + (90) stress: rats were exposed to PL at the age of 60–62 d and again at the age of 90 d (n = 8). The following groups were examined at the age of 60 d: juvenile, adulthood (60) and juvenile + adulthood stress groups. The following groups were examined at the age of 90 d: adulthood (90) and adulthood (60) + (90) stress groups. The control group included four control (60) (examined at the age of 60 d) and four control (90) (examined at the age of 90 d) rats. Previous verification indicated that there was no differences between those groups, therefore they were grouped together. (c) Expt 3 – The following groups were compared. (1) Control: naive rats (n = 4). (2) Juvenile + adulthood stress: rats were exposed to PL at the age of 26–28 d and then to ASS at the age of 60 d (n = 4).
Open-field test

The open-field test may be seen as a non-conditioned anxiety test based on the creation of a conflict between the exploratory drive of the rat and its innate fear of exposure to an open area (Angrini et al., 1998; Broadhurst, 1975).

One hour post-adulthood stress (Expt 1 – following ASS; Expt 2 – following PL stress), the open-field test was carried out according to methods described previously (Carli et al., 1989; Lemoine et al., 1990). Briefly, the open-field test consists of a wooden box 90.0 x 90.0 x 38.0 cm positioned in a dimly lit room. The walls are black, and the floor is white divided by 1-cm-wide black lines into 25 squares 17.0 x 17.0 cm. Rats are placed at the corner of the open field. For the following 3 min, the number of line crossings in the central and the peripheral areas are manually recorded. The total line crossings represent the activity level of the rat, whereas the ratio between line crossings in the peripheral area and the total line crossings represents an anxiety index (Avital et al., 2001). All rats were tested between 11:00 and 17:00 hours by the same experimenter.

The water-maze task

The water-maze (Morris, 1984) consists of a circular pool of water (1.7 m in diameter with a rim 0.5 m high) painted black. The water depth was 30.0 cm, and temperature was maintained at 23 ± 1°C. The only obvious landmarks are those outside the water-maze, in the surrounding environment. Rats were placed in the maze and allowed to swim freely for a maximum of 1 min or until they reached the hidden platform. At the end of each trial rats were either led to or left on the platform for 15 s. Each trial began from a different starting point in random order. The experimenter measured the escape latency with a stopwatch. All rats were tested between 11:00 and 17:00 hours by the same experimenter.

Water-maze massed spatial training (Expt 2)

The difference in water-maze performance in Expt 1 was mainly during the first training day. To focus on this difference in performance in Expt 2 we employed a more intensive, single-day protocol, as described previously (Akirav et al., 2001). In the massed spatial learning task conducted 1 d after the open-field test, rats were given a total of 12 trials with inter-trial intervals of 1 and 4 min, alternately. A criterion for good performance (>15 s to locate the escape platform) was defined, as described previously (Akirav et al., 2001) based on the maze size and the average swim speed.

Tracing system (Expt 3)

To analyse the differences in path length and swim speed, we used the Water-maze 31, which is a computer-based system for the analysis of Morris water-maze trials online (Grossmann and Skinner, 1996).

The startle response test

The acoustic startle response test is used extensively to index fear and anxiety in rodents (e.g. Faraday and Grunberg, 2000) and humans (e.g. Riba et al., 2001). Previous studies have shown that the amplitude of the acoustic startle response is increased by the presentation of aversive stimuli, e.g. noise (Vazquez et al., 1996), and by corticotropin releasing factor (CRF) infusion (Lee and Davis, 1997; Liang et al., 1992).

The startle response (Patrick, 1994) was measured by an automated JR Startle box (Hamilton-Kinder, USA) that was positioned in a dimly lit room. Immediately after exposure to the water-maze spatial learning, rats were habituated for 30 min to the startle test room before being placed in the chamber. All rats were tested between 11:00 and 17:00 hours by the same experimenter. Rats were subjected to eight tones (40.0 ms 115 dB noise stimulus), separated by 1 min. The maximum startle response for each tone was measured.

Statistical analysis

Results are presented as means ± standard error of the means (s.e.m.). Two-way mixed analysis of variance (ANOVA) as well as one-way ANOVA followed by Tukey post-hoc multiple comparison tests were used as indicated. In addition, a Student’s t test for unpaired samples and Pearson’s correlation coefficient were calculated. All tests were two-tailed and a p value of less than 0.05 was considered statistically significant. All tests were done with SPSS version 11.0 (SPSS Inc., Chicago, IL, USA).
Approval

The experiments were approved by the institutional Animal Care and Use Committee, and adequate measures were taken to minimize pain or discomfort, in accordance with the guidelines laid down by the NIH in the USA regarding the care and the use of animals for experimental procedures.

Results

Expt 1

Activity level was measured as the total line crossings in the open field (Figure 2a). One-way ANOVA revealed a significant treatment effect \([F(3, 28) = 15.54, p < 0.0001]\). Post-hoc Tukey test revealed a significant decrease in activity level of the juvenile stress group \((p < 0.01)\), the adulthood stress group \((p < 0.001)\), and the juvenile + adulthood stress group \((p < 0.001)\), compared with the control group.

The ratio between the number of line crossings in the peripheral part of the open field and the total line crossings is considered a measure of anxiety (Figure 2b). One-way ANOVA revealed a significant treatment effect \([F(3, 28) = 21.72, p < 0.0001]\). Post-hoc Tukey test revealed that exposure to stress in adulthood significantly increased anxiety level compared with the control group \((p < 0.001)\) and the juvenile stress group \((p < 0.01)\). Juvenile + adulthood exposure to stress increased anxiety levels further, and the anxiety index was significantly higher than in the control group \((p < 0.001)\), the juvenile stress group \((p < 0.001)\), and the adulthood stress group \((p < 0.05)\).

Beginning 24 h after exposure to stress in adulthood, all groups were trained for 6 d on a spatial learning task (platform was positioned in q1) in the Morris water-maze (Figure 3). Two-way mixed ANOVA with group as a between-subjects factor and days as a within-subjects factor revealed a significant main effect of days \([F(3, 101) = 145.69, p < 0.0001]\), group \([F(3, 28) = 27.27, p < 0.0001]\), and the interaction between the two factors \([F(10, 101) = 3.36, p < 0.001]\). Importantly, post-hoc Tukey test revealed that the juvenile + adulthood stress group performed significantly better than the other groups \((p < 0.0001)\) across the first 4 d of training. However, this difference tended to disappear over days (on days 5 and 6), when rats from the other groups improved their performance.

On day 7, and for 3 d thereafter, the escape platform was positioned in a new location (q3) and the rats were trained to find the new platform location (Figure 4). One-way ANOVA revealed a significant treatment effect of the first day’s performance \([F(3, 28) = 13.488, p < 0.0001]\). The juvenile + adulthood and the juvenile stress groups performed significantly better than either the controls \((p < 0.001)\) or the adulthood stress group \((p < 0.05)\). The adulthood stress group performed significantly better than the control group \((p < 0.01)\).

Rats were then tested for startle response (Figure 5). One-way ANOVA revealed a significant treatment

Figure 2. In the open-field test (Expt 1) (a) a significant decrease in the total number of crossings was observed in all experimental groups compared to controls. (b) The juvenile + adulthood stress group showed the highest anxiety index (**p < 0.01, ***p < 0.001).

Figure 3. In a spaced spatial learning task (Expt 1), the juvenile + adulthood stress group learned the location of the hidden platform better than the other groups. This difference tended to disappear over days (*p < 0.0001).
ANOVA revealed a significant treatment effect $[F(3, 28) = 17.686, p < 0.0001]$. Post-hoc Tukey test revealed that exposure to stress in adulthood significantly increased startle response compared to the control group ($p < 0.01$). However, the combination of juvenile and adulthood exposure to stress significantly increased startle response compared with all groups ($p < 0.001$).

Finally, to assess the relationship between the differences observed in the first trial performance in the water-maze and the anxiety level measured in the startle response test, we calculated a Pearson correlation. A significant negative correlation was found between these two factors $[r_p = -0.623, p < 0.0001]$, i.e. better performance in the first trial was associated with higher anxiety level.

Expt 2

The activity level was measured as the total line crossings in the open field (Figure 6a). One-way ANOVA revealed a significant treatment effect $[F(5, 42) = 20.58, p < 0.0001]$. Post-hoc Tukey test revealed a significant decrease in activity level in all experimental groups compared with the control group ($p < 0.001$).

Using the ratio between the number of line crossings in the peripheral part of the open field and the total line crossings as a measure of anxiety (Figure 6b), one-way ANOVA revealed a significant treatment effect $[F(5, 42) = 97.57, p < 0.0001]$. Post-hoc Tukey test revealed that exposure to juvenile stress significantly increased the anxiety level compared with the control group ($p < 0.001$). In addition, exposure to stress in adulthood significantly increased the anxiety level compared with the control group ($p < 0.001$) and the juvenile stress group ($p < 0.001$). Juvenile + adulthood exposure to stress increased anxiety levels further, and the anxiety index was significantly higher than in the control group ($p < 0.001$), the juvenile stress group ($p < 0.001$), the adulthood stress group ($p < 0.001$), double exposure to adulthood stress ($p < 0.001$), and adulthood (90) stress group ($p < 0.01$).

Twenty-four hours after exposure to stress in adulthood, all groups were trained for a massed spatial learning task in the Morris water-maze (Figure 7). Two-way ANOVA with group as a between-subjects factor and trials as a within-subjects factor revealed a significant main effect of trials $[F(7, 307) = 101.97, p < 0.0001]$, group $[F(5, 41) = 14.08, p < 0.0001]$, and the interaction between the two factors $[F(37, 307) = 3.36, p < 0.001]$. Interestingly, post-hoc Tukey test revealed that the juvenile + adulthood stress group performed significantly better than all other experimental groups ($p < 0.0001$) across all trials.

Rats were then tested for startle response (Figure 8). One-way ANOVA revealed a significant treatment effect $[F(5, 42) = 137.93, p < 0.0001]$. Post-hoc Tukey test revealed that exposure to stress in adulthood significantly increased startle response compared with the control group ($p < 0.001$) and the juvenile stress group ($p < 0.001$). However, juvenile + adulthood exposure to stress further increased the startle response. It was significantly higher than in the control ($p < 0.001$), the
juvenile stress ($p < 0.001$), the adulthood stress ($p < 0.001$), double exposure to adulthood stress ($p < 0.001$), and the adulthood (90) stress ($p < 0.001$) groups.

**Expt 3**

Twenty-four hours after exposure to stress in adulthood, the rat’s path length and average swim speed were recorded during a 1-min swim trial (without a platform) in the water-maze.

A $t$ test for independent samples revealed a significant increase in both the path length and average swim speed (Figure 9a) of the juvenile + adulthood stress group compared with controls ($t(6) = 4.96, p < 0.01$), on the first trial performance. There was no significant difference in the maximal swim speed between the control and the juvenile + adulthood stress groups (15.01 ± 3.6 and 16.18 ± 3.39 respectively).

The representative exploration patterns of the control and the juvenile + adulthood stress groups, with reference to peripheral vs. central areas of the water-maze, are given in Figure 9b, c.

**Discussion**

The results of the present study demonstrate that even a brief exposure to juvenile stress can modulate the ability to cope with stress in adulthood, as was observed up to 2 months later.

The emotional consequence of exposure to juvenile stress was examined in both the open-field and the
startle response tests. Single or double exposure to stress in adulthood increased anxiety level, but the exposure to the combination of juvenile and adulthood stress increased anxiety further. The activity level of all stress groups significantly decreased compared with the control group, a finding that excludes the possibility that the differential increase in anxiety level in the adulthood and juvenile + adulthood stress groups may be related to differences in general activity. Similar findings were reported for chronic isolation-reared rats (21–77 d) that showed increased startle reactivity measured at the end of the isolation period (Varty et al., 2000). Recently, Maslova et al. (2002) found that exposure to chronic variable stress (CVS) during the pre-pubertal period of life (21–32 d) produced long-lasting effects on the startle response, comparable to that seen in our juvenile stress group. The long-lasting effects of CVS experienced in pre-pubertal life appears to produce startle response changes similar to those seen in patients with PTSD. Similar to our finding in the open field, male rats that were exposed to chronic variable social stress for 28 d at the onset of adolescence showed low locomotor activity in a novel environment in adulthood, compared with controls (Kabbaj et al., 2002). Previously, Marks-Kaufman and Lewis (1984)

**Figure 7.** In a massed spatial learning task (Expt 2), the juvenile stress group showed poor learning, whereas the juvenile + adulthood stress group reached the criterion of good performance (>15 s to reach the escape platform, dotted line) faster than all other experimental groups.

**Figure 8.** Adulthood exposure to stress significantly increased startle response (Expt 2). However, exposure to juvenile + adulthood stress further increased startle response in comparison with all other groups (**p < 0.001, *p < 0.01, *p < 0.05).
reported that rats that were raised in isolation (from weaning until the age of 60 d) were less active in the open field than animals raised in groups. Early housing experience was also found to modify later morphine consumption and physical dependence. Animals raised in isolation exhibited a trend to start drinking morphine sooner and experienced less severe withdrawal symptoms following naloxone administration than group-raised animals (Marks-Kaufman and Lewis, 1984). The present results indicate that even a relatively brief exposure to juvenile stress may lead to long-lasting impairments in coping abilities in adulthood.

The effects of exposure to stress in adulthood on the performance of rats in a spatial learning task in the Morris water-maze, as a function of exposure to juvenile stress was also tested. There is abundant evidence that depending on the severity and context, stress can either improve or impair performance in the water-maze task. Intense arousal and corticosterone were reported to enhance performance on a spatial learning task in the Morris water-maze (Vázquez, 1998). Similarly, in Expt 1, the adulthood stress group performed significantly better than the juvenile stress group and the control group on the first day. Interestingly, rats exposed to the combination of juvenile + adulthood stress performed significantly better than all other groups. This difference tended to disappear over days, when rats from the other groups improved their performance. A significant negative correlation was found between the performance on day 1 in the water-maze and the anxiety level measured in the startle response test. Therefore, the differences in performance observed on day 1 may be related to the differences in anxiety level. Furthermore, during the first day of a reversal-learning task in Expt 1, the control group exhibited the worst level of performance, whereas rats exposed to juvenile or juvenile + adulthood stress performed significantly better than both the control and the adulthood stress groups. This result may be an indication that spatial memory for the previous location of the platform (learned during the first phase of the experiment) was most efficient in the control group compared with all stress groups. Retaining the memory of the previous location of the platform can be expected to interfere at first with the shift to learning the new platform location.

To focus on the difference in performance during the first day, in Expt 2 we employed a single-day, 1-h massed training protocol. In both Expts 1 and 2 rats exposed to juvenile + adulthood stress performed better mainly during the first trial of the water-maze task.

Figure 9. During the first trial in the Morris water-maze, (a) rats exposed to juvenile + adulthood stress swam faster than controls (*p < 0.01), and (b) tended to explore the central part of the water-maze more than (c) controls.
Therefore in Expt 3 we examined the path length and the averaged swim speed on a single (first) trial and found that both measures were increased following exposure to juvenile + adulthood stress. Interestingly, it seems that the stressed rats tended to swim more in the central part than in the peripheral part of the water-maze, compared with controls. Such a pattern of behaviour during the first trial could explain the faster level of acquisition of the water-maze task, observed in these animals, since this pattern of behaviour increases the chance of locating the hidden platform. The different swim patterns of control and juvenile + adulthood stress rats in the water-maze are opposite to those observed in the open-field and may be explained by the different nature of these two tests: compared to the water-maze, the open-field is considered as a non-conditioned anxiety test based on the creation of a conflict between the exploratory drive of the rat and its innate fear of exposure to an open area (Angrini et al., 1998; Broadhurst, 1975).

A repeated exposure to adulthood stress yielded a higher startle response compared to a single adulthood exposure. However, it should be noted that the exposure to juvenile + adulthood stress yielded a significantly more robust increase in startle response, a significantly higher anxiety index in the open-field test, as well as an effect on water-maze performance, thus supporting the notion that the juvenile period is a particularly sensitive period and that an exposure to stress during this period may lead to adverse consequences in adulthood.

In sum, exposure to juvenile stress enhanced anxiety level in response to exposure to stress in adulthood, as measured both in an open-field and a startle box. Similarly, exposure to juvenile stress accentuated the effects of the adulthood stress on performance in a spatial learning task in the Morris water-maze. These results indicate that exposure to a relatively brief stressful experience during the post-weaning pre-puberty period has profound and long-lasting effects on the ability to cope with stress in adulthood.

This model may now be used to enhance the search for the neurobiological and endocrine mechanisms associated with stress-related syndromes.

Acknowledgments
This work was supported by a grant from The Israel Foundation Trustees (2000) to G.R-L.

Statement of Interest
None.

References


Nurse S, Lacaille JC (1999). Late maturation of GABA(B) synaptic transmission in area CA1 of the rat hippocampus. Neuropharmacology 38, 1733–1742.


