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Research report

Withdrawal emotional-regulation in infant rats from genetic animal models of depression

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ABSTRACT

Children of depressed parents exhibit high rates of emotion-dysregulation, characterized by excessive withdrawal or approach strategies toward the mother in infancy. The understanding of factors affecting the establishment of these behavioral deficits is limited. The current study utilized two genetic animal models of depression, the Wistar–Kyoto (WKY) and Flinders Sensitive Line (FSL) rat strains. In addition, in order to assess the interactive effects of depressive vulnerability and exposure to early life stress, the subjects were raised either in a standard rearing condition or exposed to mild chronic-stress on postnatal days (PND) 2–9. On PND 10–11, an isolation test examined the pups’ emotion-regulation. WKY pups produced less separation-induced ultrasonic vocalizations (USV) and proximity-seeking behaviors, compared to controls. In addition, WKY pups did not show the expected potentiation effect that was evident in control pups (an increase in USV and pivoting behavior after a short reunion with the dam). FSL pups exhibited less proximity-seeking behaviors compared to controls while showing levels of USV, potentiation of USV, and change in proximity-seeking behaviors that were similar to controls. No differences between the strains were found in self-grooming. The early life chronic-stress paradigm had no effect on the behaviors of the pups, indicating either stress-resilience or a limited effect of the paradigm. Overall, the results tentatively imply a tendency of the WKY and FSL pups towards withdrawal behavior instead of approach-behavior when regulating emotion, with a more pronounced pattern in WKY pups. This behavioral profile is reminiscent of avoidant attachment, a characteristic of many children of depressed parents.

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1. Introduction

Emotional-regulation, “extrinsic and intrinsic processes involved in monitoring, facilitating and inhibiting heightened levels of positive and negative affect” [1,2], received in the past years increasing research attention [3–8]. Emotional-regulation is comprised of a multitude of physiological, cognitive, and behavioral overlapping processes, and follows a developmental trajectory of increasing reliance on self-regulation by the infant [2,9–11]. The maturation of these emotion-regulation capacities is considered central to the organism’s growing abilities to handle stress, develop coping skills, mediate attentional and learning processes and achieve optimal functioning [10,12,13].

Parental depression has been shown to adversely affect the development of the offspring’s emotion-regulation, along with effects on their social and cognitive development [14–17]. Children of depressed parents exhibit emotional, social, and cognitive deficits and are at risk for psychiatric disorders [15,18–20]. These infants are typically described as withdrawn and exhibit “depressed-like” behavior [21].

Animal models of depression are used in order to understand the neurobiological basis of the disorder and to predict successful treatment strategies [22,23]. Genetic animal models of depression are a relatively new type of models, exhibiting hereditary vulnerability similar to that found in depressed humans. The present research utilized two well-studied genetic animal models, the Flinder’s Sensitive Line (FSL) and the Wistar–Kyoto (WKY) rats [24–26]. The FSL model was created by selectively breeding Sprague–Dawley (SD) rats to exhibit hyper-sensitivity to cholinergic agonists, as found in depressed humans [27,28]. FSL rats exhibit abnormalities in central neurochemical systems associated with depression (e.g., dopaminergic, serotonergic and HPA axis) and behavioral deficits resembling those of depressed humans [24,29–32]. The second animal model, the WKY strain, was inbred from the Wistar strain

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and exhibits characteristic depressive-like behavior and sensitivity to stress [25,33,34]. In addition, WKY rats exhibit neurochemical abnormalities in several systems (e.g., dopaminergic and noradrenergic), as well as in peripheral hormones (e.g., HPA axis and TSH) [35–37].

Earlier studies indicated physiological and behavioral abnormalities of FSL pups at PND 1 and reduced approach–behavior toward the dam in both FSL and WKY strains, at PND 17–19 [38,39]. In addition, research in our laboratory of older (pre-pubertal) WKY and FSL rats indicated that these rats exhibit heightened depressive-like behaviors, such as greater immobility in the swim-test compared to controls [35,40]. The two strains presented opposite profiles of social play and of basal corticosterone and ACTH hormonal levels [35]. WKY rats further exhibited anhedonic and anxious-like profiles too [40,41]. In the current study we aimed to elaborate upon these previous findings, focusing on emotion-regulation in these animal models. This is important in light of the high rates of comorbid emotion-disregulation and depression; in clinical samples the rate of comorbid anxiety disorders is also high. Moreover, healthy youth up to age 20 can run as high as 70%, and in community samples the average is 25–50% [42–45]. Comorbidity is also associated with increased severity of depression [46–48], and may even exert a potentiating effect [45,49].

In the current study, emotion-regulation was analyzed in a series of two separations from the dam, an extended version of the isolation-test [50]. Both separation–protest and proximity-seeking behaviors were assessed. Ultrasonic-vocalization (USV), whistle like sounds in frequencies of 40–70 kHz produced by rat pups, were used as indicators of separation–protest [51–53]. USV production plays an ethologically important role in mother–offspring communication, promptly stimulating maternal behavior [54–56]. In addition, “Potentiation of USV” was assessed during a subsequent separation from the dam (after a previous separation) [57]. Finally, proximity-seeking behaviors, active behaviors through which an infant achieves proximity or maintains contact with the dam, were assessed [58]. We hypothesized that WKY and FSL pups will exhibit abnormal USV production and potentiation in light of the susceptibility of these behaviors to earlier parental behavior [59,60]. More broadly, we hypothesized that WKY/FSL pups will exhibit emotion-regulation compared to their control strains.

The second aim of the study was the investigation of the effect of early life stress on the establishment of emotion-regulation in the two animal models. In humans, early life stress constitutes a major risk factor for the development and persistence of mental disorders [54–56]. According to diathesis-stress theories, stress interacts with hereditary vulnerability in the establishment of these mental disorders [63]. In order to assess these interactive effects, the subjects were tested either in a standard rearing condition or after exposure to mild chronic-stress (PND 2–9) [64]. The stress paradigm is chosen based on the finding that limiting the amount of available bedding material in the cage constitutes a persistent stressor for dam and pups [65]. This paradigm is unique in that it constitutes a handling manipulation with long-term effects, while avoiding the use of stress-arousing manipulations alien to the world of the rat. We hypothesized that differences between the ‘depressed-like’ and control strains will be more pronounced after exposure to the early life mild chronic-stress paradigm.

2. Method

2.1. Subjects

WKY, Wistar, FSL, and SD pups at post-natal day 10/11 participated in the study (N = 196). There were a total of 8 experimental groups (4 strains × 2 growing conditions), with N = 24–25 pups per group. Two siblings per litter were tested in order to achieve litter representation while controlling for litter effects [66]. Their results were averaged and entered as single datum to the analyses, resulting in N = 12–13 per group. The animals were reared in the Developmental Psychobiological Laboratory in Bar-Ilan University. Cages of pregnant dams were transferred daily before noon and parturition day was noted as post-natal day 0 (PND 0). Dam and pups were maintained in individual polycarbonate cages (26 cm × 42 cm × 30 cm), in our colony with temperatures of 22 ± 2 °C and a light–dark cycle of 14:10 (lights on between 5:00 and 19:00). The animals had food and water ad lib. On PND 2 litter size was culled to 6 (with equal sex distribution when possible) and the litters were divided randomly to 2 groups, as described in the procedure section [in accordance to; 64]. The study protocol was approved by the Institutional Animal Care and Use Committee in Bar-Ilan University and adhered to the guidelines of the Society for Neuroscience and the American Psychological Association.

2.2. Materials

2.2.1. Pup observation cage

A transparent plastic cage (12.5 cm diameter, 13.5 cm high), used for recording USV and other relevant behaviors of the pup.

2.2.2. Dam-pups observation cage

Identical to the home cage (26 cm × 42 cm × 30 cm). The dam was kept in the cage and it was used for dam–pup reunions.

2.2.3. USV measurement and data analysis system

USV measurement was conducted using a QMC mini bat detector set to frequencies of 40–45 KHz [67]. USV’s were recorded using a mini-disc recorder and counted later by pressing a button that activated a silent electronic counter. Reliability tests showed an inter-observer correlation of 0.97 with this method [68] and 0.86 in our laboratory on the current data set (using the ‘Ultravox’ automatic acoustic monitoring device, designed for USV detection; Noldus Information Technology b.v., Wageningen, The Netherlands). Pup behavior and dam–pup interactions were analyzed using the Observer 5.0, a software package for the collection, analysis and presentation of observational data (Noldus Information Technology).

2.3. Procedure

Pups from each strain were divided into two groups on PND 2/3: (1) standard growing conditions; litters and dams were transferred to standard growing cages (with bedding from wood shavings). Bedding was replaced at PND 4/5. (2) ‘limited-bedding’ condition (simulating mild chronic-stress): litters and dams were transferred to standard cages equipped with a steel grid (2.5 cm above the cages floor); the grid served as the cage floor while allowing the passage of excrements. The only bedding materials available were paper towels (total: 112.5 cm × 22.5 cm), towels that the dam shreds and uses to make a nest [64]. The paper towels were replaced at PND 4/5. Overall, the procedure created 8 groups (4 rat strains, 2 growing-conditions), with two independent variables; strain (WKY pups compared to Wistar or FSL compared to SD) and growing-condition (chronic-stress compared to the control, standard housing-condition).

At PND 8/9 all litters and dams were returned to standard housing-conditions for two days until the start of the experiment. At PND 10/11 between 7:00 and 9:00 a litter was taken out of the home cage and placed in a temporary cage (20 cm × 26 cm × 22 cm). Cages of preg-nant dams were transferred to this cage to maintain original cage scent) in a humid incubator at 33 °C. At the same time, the dam was transferred, in the home cage, to the next room. Next, the isolation-test procedure was conducted as follows: (a) first separation from dam: a pup was taken out of the incubator 2 min after being placed there with its litter, and put in the ‘pup observation cage’ for 5 min. USV production was detected using a QMC mini bat detector and the pup’s behavior was video taped for later analysis. (b) Reunion with dam: the pup was moved to the dams’ cage for 5 min. (c) Second separation: the pup was put back into the ‘pup observation cage’. USV and relevant behaviors were recorded for 5 min. (d) Afterwards a second pup underwent an identical procedure, using a new clean ‘pup observation cage’ (as described in a–c, above). The onset of this second pups’ test was about 17 min from placement in the incubator.

3. Data analysis

All analyses were performed separately for the two different progenitor strains. Thus, one set of analyses compared pups from the WKY ‘depressed-like’ strain to their control strain, Wistar. Another set of analyses compared FSL rats to SD controls. USV and pup behavior analyses: USV data were analyzed using repeated-measures ANOVA with strain and growing-condition as between-subject measures and potentiation (difference between USV in the first isolation and the second, after a 5 min reunion with dam) as a within-subject repeated-measure. Pups’ behaviors (pivoting, supported rearing [wall-climbing] and self-grooming,
modified from 69] were analyzed using two separate MANOVAs and one ANOVA. In each MANOVA data on number and duration of behavior were entered; the ANOVA for self-grooming only included duration, because of a large correlation with number; \( r = 0.851 \). Significant MANOVAs were followed by one-way ANOVA’s to ascertain source of significance. Since no significant growing-condition effects were found, these results are not presented.

4. Results

4.1. WKY pups’ behavior compared to Wistar controls

4.1.1. Ultra-Sonic Vocalizations (USV)

There was a significant strain main-effect with WKY pups emitting less USV compared to controls \([F(1,45) = 64.84, p < .001]\). The effect was accompanied by a significant potentiation main-effect and a strain × potentiation interaction \([F(1,45) = 44.25, p < .001; F(1,45) = 40.90, p < .001\]; respectively); WKY pups showed similar USV levels before and after the reunion with the dam, while control pups showed higher USV in the second separation (a potentiation effect). There were no additional significant potentiation interactions. See Fig. 1A.

4.1.2. Pivoting

There was a significant strain main-effect \([F(2,43) = 6.18, p < .01]\; Fig. 1B]; post hoc one-way ANOVA’s showed that WKY pups made less pivots compared to controls \([F(1,44) = 10.39, p < .01]\). There was also a significant potentiation main-effect and potentiation × strain interaction \([F(2,43) = 33.90, p < .001; F(2,43) = 15.41, p < .001\]; respectively); WKY pups showed similar pivoting in the first separation and second separation from the dam, while Wistar pups showed a decrease both in number and duration \([F(1,44) = 24.65, p < .001; F(1,44) = 27.34, p < .001\]; for number and duration of pivoting, respectively, Table 1). There were no other significant potentiation interactions.

4.1.3. Supported rearing

There was a significant strain main-effect \([F(2,43) = 3.34, p < .05\; Fig. 1B]; WKY pups performed less rearings and had shorter duration of rearing, compared to controls \([F(1,44) = 4.44, p < .05; F(1,44) = 5.21, p < .05\]; respectively). There was a significant potentiation main-effect without an accompanying potentiation × strain interaction \([F(2,43) = 46.07, p < .001\; Table 1\). There were no other significant potentiation interactions.

4.1.4. Self-grooming

There was no strain effect \([F(1,44) = 0.28, n.s.; not presented\). There was a significant potentiation main-effect with pups performing fewer self-groomings after reunion with the dam \([F(1,44) = 4.60, p < .05\; Table 1\]. There were no significant potentiation interactions.

4.2. FSL pups’ behavior compared to SD controls

4.2.1. Ultra-Sonic Vocalizations (USV)

There was no significant main-effect for strain \([F(1,45) = 1.12, n.s.; Fig. 2A]\). A significant potentiation main-effect was found, indicating that more USV were produced after a short reunion with the dam, compared to USV in the initial separation from dam \([F(1,45) = 36.71, p < .001\). There were no significant potentiation interactions.
Table 1
Mean ± S.E.M. of frequency and duration (in seconds) of pups’ behaviors in the isolation test (beyond growing conditions), during the 1st and 2nd periods of maternal separation

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Frequency (number)</th>
<th>Duration (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WKY</td>
<td>FSL</td>
</tr>
<tr>
<td>Pivoting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st separation</td>
<td>4.77 ± 0.50</td>
<td>2.71 ± 0.55</td>
</tr>
<tr>
<td>2nd separation</td>
<td>6.38 ± 0.43</td>
<td>5.42 ± 0.47</td>
</tr>
<tr>
<td>Supported rearing</td>
<td>22.31 ± 1.21</td>
<td>25.10 ± 1.24</td>
</tr>
<tr>
<td>Self-grooming</td>
<td>5.87 ± 0.35</td>
<td>6.29 ± 0.31</td>
</tr>
<tr>
<td>USV</td>
<td>8.04 ± 0.71</td>
<td>8.19 ± 0.70</td>
</tr>
<tr>
<td>Proximity-seeking</td>
<td>7.41 ± 0.66</td>
<td>7.69 ± 0.70</td>
</tr>
<tr>
<td>Active behaviors</td>
<td>10.34 ± 0.71</td>
<td>11.20 ± 0.68</td>
</tr>
</tbody>
</table>

Note: see also Figs. 1B and 2B for overall frequency data (averaging both separation periods).

4.2.2. Pivoting

There was a significant strain main-effect \(F(2,44) = 19.13, p < .001; \text{Fig. 2B}\); FSL pups made less pivots and had a shorter duration of pivoting \(F(1,45) = 3.67, p < .001; F(1,45) = 4.43, p < .05\), respectively. There was a significant potentiation main-effect \(F(2,44) = 13.51, p < .001\); pups made fewer pivots and had a shorter duration of pivoting after reunion with the dam, \(F(1,45) = 13.96, p < .001; F(1,45) = 27.50, p < .001\); respectively, Table 1]. There were no significant potentiation interactions.

4.2.3. Supported rearing

There was a significant strain main-effect \(F(2,44) = 19.77, p < .001 \text{Fig. 2B}\); FSL pups performed less rearings and had a shorter duration of rearing compared to controls \(F(1,45) = 34.07, p < .001; F(1,45) = 17.45, p < .001\), respectively. There was also a significant potentiation main-effect \(F(2,44) = 24.90, p < .001\); pups made fewer rearings and had a shorter duration of rearing after a reunion with the dam \(F(1,45) = 24.31, p < .001; F(1,45) = 41.38, p < .001\); respectively, Table 1]. There were no significant potentiation interactions.

4.2.4. Self-grooming

There was no significant strain main-effect \(F(1,45) = 1.05, \text{n.s.; not presented}\), as well as no significant potentiation main-effect or interactions (Table 1).

In summary, WKY pups produced less distress-vocalization and proximity-seeking behaviors, compared to controls. In addition, WKY pups did not show the expected potentiation effect that was evident in control pups (an increase in USV and proximity-seeking behaviors after a short reunion with the dam). FSL pups exhibited less proximity-seeking behaviors compared to controls indicating a similar although less pronounced behavioral profile to that of the WKY pups. No differences between the strains was found in self-grooming, a self-comforting behavior that was used as a behavioral control measure. Finally, the early life chronic-stress paradigm had no effect on the behaviors of the pups.

5. Discussion

The current study utilized genetic animal models of depression in order to increase our understanding of emotion-regulation in children with a hereditary tendency towards depressive-like behavior. The study utilized a mild chronic-stress paradigm ("limited-bedding") to test the possible interaction between depressive vulnerability and exposure to early life stress [65]. The study's overall findings indicate that emotion-regulation deficits were evident in both animal models when compared to their respective control strains.

Compared to controls, WKY pups reacted to separation from their dam with markedly low rates of USV. This abnormal separation-protest behavior was accompanied by low rates of proximity-seeking behaviors (active behaviors that could, in principle, increase proximity to the dam if she was in the testing arena). The pups’ behavior was additionally assessed after a short exposure to the dam, conditions in which the pups tend to increase their USV compared to their vocalization in the first separation [57]. This phenomenon, potentiation of USV, was found to be affected by earlier experiences of the pup [50,60,69]. In the current study, WKY pups did not exhibit the expected potentiation effect. Similarly, WKY pups did not alter their pivoting (an additional proximity-seeking behavior) after an exposure to the dam. Pups belonging to the second animal model (FSL) exhibited certain similarities to the WKY strain, with a less pronounced overall behavioral profile. These pups exhibited less proximity-seeking behaviors compared to controls.
At the same time, FSL pups did not differ from controls in their separation-protest and exhibited potentiation of USV.

Earlier studies [38,39] indicated physiological and behavioral abnormalities of FSL pups (PND 1) and reduced approach–behavior toward the dam in both FSL and WKY strains (PND 17–19). The current study elaborates upon these earlier findings and points toward behavioral alterations in WKY and FSL pups, alterations that are already evident at PND 10–11. WKY and FSL pups exhibit a tendency toward excessive withdrawal behaviors from the dam, with WKY pups exhibiting a more pronounced profile. This observed profile is reminiscent of avoidant attachment common in children to depressed parents [70], with subsequent increased developmental risk [71,72]. Thus, these behaviors can be speculatively conceptualized as components of an abnormally developing attachment system, a motivational system that develops at an early age [73]. Future studies may address this possibility. The use of USV measurements for this aim presents a valid paradigm for the assessment of attachment bonds. In this regard, the markedly low rates of USV evident in WKY pups warrant special attention in order to elucidate their underpinnings.

One pathway through which the pup can ultimately affect its own development is by alterations in its interactions with the dam. Reductions in proximity-seeking behaviors are likely to lead to reduced treatment and contact by the dam [for example, USV stimulates maternal responses such as pup retrieval, maternal licking and inhibition of biting; 54,55,74]. A vicious cycle can thus be created, in which altered dam–pup interactions impair the physiology and behavior of the pup later in life [75–77]. Beside the contribution of the pups’ genotype, its behavioral phenotype may also be influenced by the prenatal environment and pattern of maternal care received from their similar-genotype dam and from subject-siblings-dam interactions. In fact, our research team found differences in maternal behavior patterns between WKY/FSL and control strains [78–80]. Thus, the role of these environmental sources needs to be elucidated by future studies.

Since the WKY and FSL strains are considered genetic animal models of depression, this allows the investigation of environmental factors hypothesized to affect the establishment of emotion-regulation [22,81]. The current study addressed this possibility by exposing the pups to different early life stress levels. The overall findings indicate that the behavior of the pups was not affected by the stress paradigm. Most of the earlier studies focused on the physiological effects of the mild chronic-stress paradigm used in the study (‘limited bedding’) and did not assess its effect on behavior [see review; 82]. An exception in this regard is a study by Brunson et al. [83] who found that this stress paradigm causes delayed, progressive impairments of synaptic and behavioral measures of hippocampal function (with deficits evident in middle-age, but not young adult rats). This presents an interesting possibility that is in line with findings in our laboratory [indicating that this chronic-stress paradigm has limited behavioral effects in young-age rats; 41]. Overall, it is possible that either the stress paradigm is too mild to have a clear behavioral impact, or that deficits will be evident only in later stages of rats’ life. Two possible lines of future research follow: (1) manipulation of variables in the stress paradigm (e.g., the amount of towel available for the dam), (2) conducting behavioral tests at later stages of the rats’ life-cycle.

In addition, two factors limit our ability to strongly conclude from our measurements of USV that we exclusively assessed separation-protest. First, the USV separation manipulation was performed in room temperature. Although ambient temperature in the test arena was monitored and was similar in all experimental groups, it is still very likely that a portion of the USV were elicited by the change in temperature (from the incubator to the testing arena). We note that this situation has ecological validity – when separated from the nest and dam, a pup would naturally be concomitantly exposed to cooler, external ambient temperatures. Second, the analysis of ultrasonic vocalization was performed solely on PND 10/11. Though the differences found between the experimental groups are clear, our analysis does not allow us to ascertain whether the differences are due only to deviations from the normal range of responding or also to changes in the time of “emergence” of normal response patterns. Since USV emission follows a specific ontogenetic profile, analysis at several time-points would have been more informative.

The lack of effect of the mild chronic-stress condition and the fact that isolation-induced patterns were already altered at an early age, point toward a strong hereditary influence on the strains’ behavioral phenotype. Such a conclusion fits findings of strong hereditary transmission of emotional-regulation patterns to children of depressed parents [84,85]. More studies are clearly needed to untangle emotion-regulation transmission pathways. For this aim, future research can also use additional methods such as cross-fostering and it should be noted, though, that cross-fostering has an inherent limitation, as some studies demonstrate that fostering itself has an impact on maternal behavior. The use of dams belonging to genetic animal models of depression presents a additional complication; the fostering itself can be viewed as stress-arousing and it may alter the dams’ behavior [in accordance with diathesis-stress theories; 23,63,86]. FSL and WKY dams may therefore react differentially to the adoption compared to controls, adding a major confound to such a study. An additional issue to note regards the possible testing of HPA axis activity; measurement of corticosterone levels at this age could potentially have strengthened the pattern of results. However, the neuroendocrine stress response of the immature rat, specifically on days 4–14 of life, is characterized by attenuated hormonal responses and altered gene regulation in response to stress as compared to the adult situation [87–90]. Thus, at the age of the current study, it was not preferable to assess HPA hormones, in our opinion. Instead, we have assessed ACTH and corticosterone following the current manipulations, in older, pre-weaning rats beyond the hyporesponsive age range, and published the pattern of results [39].

Gotlib and Goodman [91] describe a shift from examination of the deficits of children to depressed parents to the identification of factors that are associated with this risk. However, despite this shift in focus we do not have an adequate understanding of the mechanisms that underlie the risk for these adverse outcomes. Animal models offer the opportunity increase our knowledge on the intergenerational transmission of emotion-regulation disturbances in children of depressed parents. Future studies in the current models may further unravel the underlying physiological mechanisms.

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