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Postpartum scarcity-adversity disrupts maternal behavior and induces a hypodopaminergic state in the rat dam and adult female offspring

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Postpartum adversity is among the strongest predictors for the emergence of postpartum depression (PPD) in humans and a translational risk factor employed in rodent models. Parental care is disturbed under conditions of environmental adversity, including low resource environments, and in PPD. Nonetheless, the neural changes associated with these adversity-induced maladaptive behavioral states remain poorly understood. Postpartum scarcity-adversity can be modeled in rats by providing the dam with limited bedding and nesting (LBN) materials, which mimics the effects of a stressful low resource environment in potentiating maltreatment/neglect in humans. Indeed, LBN exposure from postpartum days (PD) 2–9 increased adverse maternal behaviors, impaired pup retrieval, and increased passive stress coping responses. Since mesolimbic dopamine (DA) activity is an important mechanism for motivated maternal behavior and is implicated in PPD, we assessed the impact of postpartum scarcity-adversity on *in vivo* electrophysiological properties of ventral tegmental area (VTA) DA neurons at two timepoints. We found reduced numbers of active VTA DA neurons in LBN dams at PD 9–10 but not PD-21, suggesting a transient impact on VTA population activity in LBN dams. Finally, we assessed the impact of early life scarcity-adversity on VTA DA function by conducting VTA recordings in adult female offspring and found a long-lasting attenuation in DA activity. These findings highlight a link between adversity-induced deficits in DA function and disrupted maternal behavior, suggesting the VTA/mesolimbic DA system as a potential mechanism by which postpartum scarcity-adversity drives aberrant maternal behavior, and early postnatal programming of adult VTA function in the offspring.

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INTRODUCTION

Exposure to chronic stress or adversity shortly after giving birth is one of the strongest predictors for the emergence of postpartum depression (PPD) in humans [1–3] and a translational risk factor widely employed in relevant rodent models [4–7]. Postpartum stressors (chronic social stress, learned helplessness) impair maternal care, disrupt mother–infant interactions, and increase negative affect (i.e., anxiety and depressive-like behaviors) in rat dams [8–11]. This is consistent with clinical literature indicating that postpartum adversity compromises the quality of mother–infant interactions and that depressed mothers have difficulty caring for and are less responsive to their infant’s needs [12–15]. Thus, postpartum adversity drives aberrant maternal behaviors and disrupted mother–infant interactions, which are hallmark features of PPD.

Parental care is disturbed under conditions of adversity and/or chronic stress, which can take a variety of forms in both humans and rodents. In humans, low socioeconomic status (SES) or poverty is associated with higher levels of physiological and psychological stress in the mother–infant dyad due to unpredictable circumstances, restricted resources in their environment [16–18] as well as disrupted mother–child interactions, which negatively influence growth and development in the offspring [19–21]. Indeed, growing

up in a low SES environment is linked to substantially worse health outcomes in the offspring, including impaired emotional development and higher rates of mood disorders [16, 18, 22–26]. Low SES can be modeled in rodents by depriving the rat dam of adequate nesting materials during the early postpartum period, which results in an impoverished nesting environment, thereby representing a form of scarcity-adversity for the dam and pups [27, 28]. Since bedding type and volume are important components of the dam’s nesting environment, limited bedding and nesting (LBN) constitutes a continuous stressor and results in higher corticosterone (CORT) levels as well as unpredictable, adverse maternal caregiving of pups (i.e., roughhousing, maltreatment) [28–31]. Most studies have employed LBN within the context of early life adversity and focused on long-term effects in the male offspring, which exhibit increased depression-related behaviors such as: passive coping, social withdrawal, blunted reward-related responses (i.e., anhedonia) and compromised cortical and limbic function and connectivity [32–38]. However, the offspring effects of early life scarcity-adversity are thought to be mediated by disrupted caregiving behaviors in the dam/mother [19, 27, 39, 40], suggesting maladaptive maternal behaviors as the behavioral mechanism by which postpartum scarcity-adversity programs offspring development. Yet, there is no data on the neural changes induced by LBN

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exposure in the dam that coexist with aberrant maternal behavior. This underscores the need to understand neural processes by which scarcity-adversity influences maternal brain function to drive maladaptive behavioral states.

Maternal behaviors including pup contact and nipple attachment activate the mesolimbic dopamine (DA) system and increase DA release, suggesting high reward value of these pup-dam interactions [41–44]. This is consistent with the VTA's role as part of the maternal caregiving neuronal network, which is highly sensitive to interactions occurring between dams and their offspring [44–47]. Importantly, lesions of the ventral tegmental area (VTA) disrupt maternal behavior in postpartum rats [48]. Moreover, structural and functional deficits within the mesolimbic DA system have also been reported in PPD, and these are linked to impaired maternal care and responses to infants among women [7, 14]. Thus, compromised activity of VTA DA neurons induced by postpartum adversity could not only contribute to postpartum negative affect (depressive-like behavior) but may also interfere with reward-related processes necessary for maternal motivation and responsiveness.

We assessed the effects of postpartum environmental adversity (i.e., scarcity-adversity via LBN) on mother-infant interactions, motivated maternal behavior, stress coping and VTA DA neuron activity in the rat dam. We hypothesized that LBN would have a negative impact on these parameters. To evaluate intergenerational effects of postpartum scarcity-adversity on VTA activity in females, a subset of female pups was retained until adulthood and underwent electrophysiological recordings. We focused on females to evaluate the intergenerational impact of scarcity-adversity on the female DA system by studying early postpartum adversity effects (dams) and early life adversity effects (F1- pups) and because most LBN studies have emphasized long-term effects in male offspring, although LBN dams more often maltreat female pups [49]. Consistent with prior studies showing early life LBN rearing results in long-term changes in offspring reward- and depression-related behaviors suggesting mesolimbic DA system dysfunction (i.e., anhedonia) [32, 37, 38, 50], we hypothesized that early life LBN rearing would program an enduring attenuation of VTA DA activity in females.

MATERIALS AND METHODS

Animals

Primiparous timed-pregnant Sprague-Dawley rat dams were obtained from Envigo (Indianapolis, IN) on gestational day 13, housed individually and maintained in a quiet, temperature-controlled room on a 12-h light/dark cycle (7 PM lights off/7 AM lights on) with unlimited access to food and water. Parturition was verified daily; the day of birth was designated as postpartum day (PD) 0. Dams were randomly assigned to experimental conditions on PD 2 and remained in their condition until VTA recording (PD 9–10). A separate cohort of dams were used for behavioral testing, and a subset of female offspring were weaned at PD 23 and used for electrophysiological recordings during adulthood (+PD 90; Fig. 1). All experiments were carried out according to NIH guidelines and were approved by the University of Pittsburgh Institutional Animal Care and Use Committee.

LBN and maternal behavior observations. On PD 2, litters were culled to 10 pups with equal sex distribution (5 male, 5 female) and dams were randomly assigned to LBN (scarcity-adversity: 500 mL, 0.5" layer) or control bedding cages (2500 mL, ~4" layer), where they remained until the end of PD9. Naturalistic maternal behavior observations were conducted within the home cage and recorded three times a day (daily, PD 2–6) in 30-min sessions (morning/afternoon/night), as described previously [29, 36, 38]. The rationale for selecting these days was based on a prior study in LBN dams which identified the most marked behavioral effects within this range (PD2-5) [29]. We focused on adverse caregiving behaviors, which refer to aggressive behavior of the dam towards the pup, including behaviors that place pups at increased risk of threat or deprivation such as: rough/improper transport (carrying pup by limbs), dragging pups, stepping on pups, shoving pups away, trampling the nest, as these are

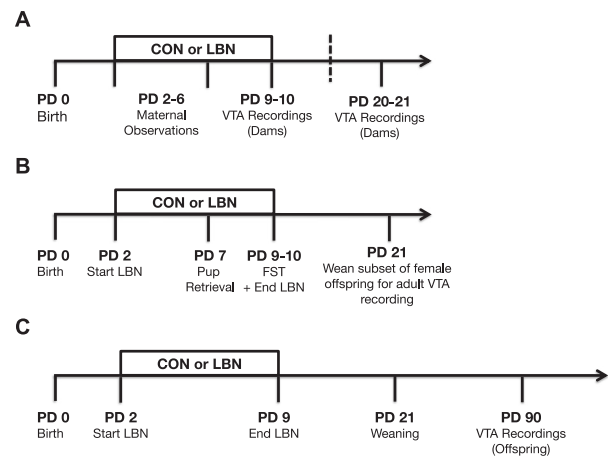


Fig. 1 Schematic depiction of the timeline and experimental design. **A** Dams gave birth (PD 0) and were assigned to control (CON) or postpartum scarcity-adversity (LBN) conditions from PD 2–9. Home cage observations were conducted 3× per day, daily from PD 2–6 during both light/dark cycle periods. Dams underwent electrophysiological recordings of the VTA during the last days of LBN (PD 9–10) using an acute, terminal procedure. A separate cohort of dams underwent LBN from PD 2–9 and VTA recordings at PD 20–21 to test for duration of effects. **B** A separate cohort of dams were housed in a CON or LBN cage from PD 2–9 and were tested for pup retrieval at PD7 and in the FST at PD 9. LBN was ended on the afternoon of PD 9 and dams were kept in normal bedding conditions until weaning of pups. A subset of female pups was kept for assessing long-term effects of early postnatal scarcity-adversity in the adult offspring. **C** Female pups were born and reared with a CON or LBN mother from PD 2–9 and weaned at PD 21. Rats were kept in pairs and undisturbed (except for weekly animal care) until they reached adulthood, at which point they were used for VTA DA neuron recordings. PD postpartum day, CON control, LBN limited bedding and nesting, VTA ventral tegmental area, FST forced swim test, DA dopamine.

consistently disrupted by adversity [27, 51, 52]. Each 30-min observation period was divided into 5-min segments during which behaviors were scored as occurring or not. Percentages of behaviors were obtained by dividing the number of segments in which a particular behavior was scored over the total number of observation segments on all days. Observation sessions conducted during light cycle (morning/afternoon) were grouped together and scored separately from those occurring during the dark cycle (night).

Behavioral testing

Testing occurred between 11:00 AM and 4:00 PM. Behavioral tests were videotaped and scored by a blind experimenter.

Pup retrieval. Cages were moved into the testing room for a 30-min acclimation period. The dam was placed in a testing apparatus (56 × 43 × 44 cm, made of opaque black Plexiglas) for a 5-min habituation period that also served as a short separation from pups. After 5 min, each of the 4 pups were placed in a Petri dish (1 per dish) containing a handful of home cage bedding in each corner of the apparatus (1 dish × corner). Latency to retrieve at least 75% of the pups was scored over a 10-min test period. This criterion was selected given that some dams in both groups retrieved 3 pups to the same corner (already containing a pup).

Forced swim test (FST). Rats underwent the FST using a standard procedure consisting of 15-min swimming session on day 1 and a 5-min test on the following day in a cylinder filled with water (25 ± 1 °C) up to 38 cm, as described previously [53–55].

In vivo electrophysiology of VTA DA neurons

Electrophysiological recordings were conducted in rat dams at PD 9–10 or PD 20–21 (no behavioral testing exposure) and in a subset of adult female offspring as described previously [53–55]. Briefly, rats were anesthetized

with chloral hydrate (400 mg/kg, i.p.; Sigma), mounted on a stereotaxic frame (Kopf, Tujunga, CA) and glass electrodes were lowered through 6–9 vertical tracks in a predetermined pattern within the VTA [AP: 5.4–5.7 mm; ML: 0.6–1.0 mm from bregma, and dorsoventral (DV): 6.5–9.0 mm from dura]. Only animals with a minimum of 6 tracks within 0.4 mm of target coordinates were included. All DA neurons recorded were found between 5.0 and 6.1 mm AP from bregma, and primarily from rostral VTA [56, 57], which is consistent with our prior work regarding stress effects on VTA population activity [53, 55, 58, 59]. Spontaneously active DA neurons were identified based on well-established criteria [60]. See Supplementary Methods for details.

Statistical analysis

Behavioral and electrophysiological data with a normal distribution were analyzed using unpaired *t*-tests; data sets deviating from the normal distribution were analyzed using Mann–Whitney *U* tests. Electrophysiological data of DA neurons was collected with Powerlab Lab Chart (AD Instruments) to identify spike time courses and exported to Neuroexplorer (NEX Technologies, NexTech Systems) software to calculate firing rate and burst firing. Statistics were calculated using GraphPad Prism 9.0 and differences were considered significant at $p < 0.05$. Statistical outliers were identified using QuickCalcs Grubbs test (GraphPad) and excluded from analysis.

RESULTS

Postpartum scarcity-adversity, as modeled by LBN from PD 2–9, increases adverse maternal behavior

LBN dams exhibited increases in negative maternal behaviors directed at pups and nest-building compared to control dams ($n = 7$ /group) across the light/dark cycle (Fig. 2). LBN dams exhibited increased percentages of time stepping on pups ($U = 1.5$, $p = 0.0017$), dragging pups ($t_{12} = 4.268$, $p = 0.0011$), transporting pups ($U = 0$, $p = 0.0006$), and shoving pups away ($t_{12} = 3.859$, $p = 0.0023$) during the daytime observation sessions (Fig. 1A–D). LBN dams also spent greater percentages of time nest-building ($t_{12} = 3.077$, $p = 0.0096$) and with pups scattered throughout the cage ($U = 2.5$, $p = 0.0029$), (Fig. 1E, F). LBN dams exhibited greater percentages of time stepping on pups ($U = 0$; $p = 0.0006$), dragging pups ($t_{12} = 3.742$, $p = 0.0028$), transporting pups ($t_{12} = 4.596$, $p = 0.0006$), pushing/shoving pups away ($t_{12} = 2.274$, $p = 0.0422$), nest-building ($U = 0.5$, $p = 0.0012$) and with a scattered litter ($t_{12} = 2.307$, $p = 0.0397$) during nighttime observation sessions (Fig. 1G–L). These data are summarized in Supplementary Table 1.

LBN dams exhibit impaired pup retrieval and passive FST coping

A separate cohort of dams (CON: $n = 7$, LBN: $n = 9$) was used to determine the effects of postpartum scarcity-adversity on pup retrieval (PD 7) and the FST (PD 9) (Fig. 1C). Compared to controls, LBN dams exhibited longer latencies to retrieve pups (Mann–Whitney: $U = 8$, $p = 0.0107$) (Fig. 3A) and exhibited increased FST immobility compared to CON dams (*t*-test: $t_{14} = 2.684$, $p = 0.0178$) (Fig. 3B).

LBN dams exhibit attenuated VTA population activity on PD 9–10 but not PD 20–21

Electrophysiological recordings were conducted on PD 9–10 (last LBN day) (Fig. 4A, B) in the same cohort of CON/LBN dams monitored previously for maternal behavior (CON: $n = 5$, 47 neurons; LBN: $n = 5$, 17 neurons; Fig. 1A). LBN dams exhibited attenuated VTA population activity, as indexed by lower numbers of spontaneously active DA neurons compared to CON dams ($t_8 = 5.419$, $p = 0.0006$; Fig. 4C). No differences were detected for average firing rate ($t_{62} = 0.1844$, $p = 0.8543$; Fig. 4D) or percentage of spikes fired in bursts ($U = 388$, $p = 0.8683$; Fig. 4E).

To determine whether there are distinct short- and long-term effects of postpartum adversity on maternal VTA function, a separate cohort of dams underwent CON/LBN from PD 2–9 and

recordings on PD 20–21, ~11–12 days post-LBN exposure (CON: $n = 5$, 25 neurons; LBN: $n = 5$; 25 neurons; Fig. 4A, B). No differences were found between CON and LBN dams for VTA population activity ($t_8 = 0.6439$, $p = 0.5377$; Fig. 4F), basal firing rate ($t_{48} = 0.9620$, $p = 0.3409$; Fig. 4G) or percentage of spikes fired in bursts ($U = 310$, $p = 0.9693$; Fig. 4H), suggesting that LBN-induced attenuation of VTA population activity is transient and likely confined to the duration of scarcity-adversity exposure. A summary of electrophysiological results in CON and LBN dams at both timepoints are summarized in Supplementary Table 2.

Adult female offspring of LBN dams exhibit long-lasting attenuation in VTA DA activity

Electrophysiological recordings were conducted in a subset of adult female offspring (CON: $n = 8$, 55 neurons; LBN: $n = 8$; 36 neurons; Fig. 5). Adult female rats reared with an LBN dam from PD 2–9 exhibited 75% fewer active VTA DA cells (blunted VTA population activity) compared to rats reared with CON dams (Mann–Whitney: $U = 4.5$, $p = 0.0022$; Fig. 5A), 26% increased basal firing rate ($U = 486$, $p = 0.0091$; Fig. 5B) but no change in percentage of spikes firing in burst ($U = 775$, $p = 0.0785$; Fig. 5C). These data are summarized in Supplementary Table 3.

DISCUSSION

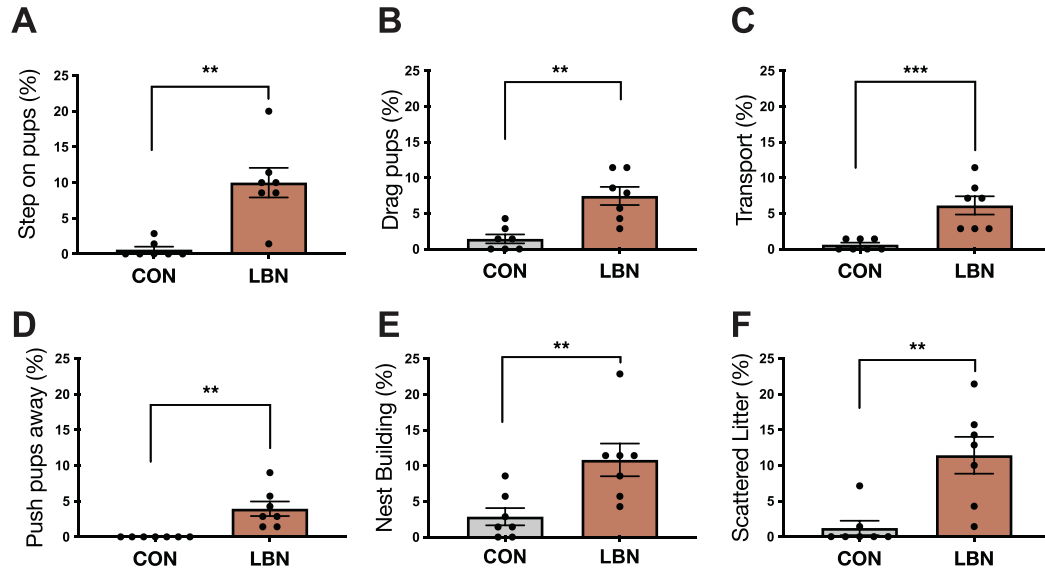
In humans, low SES environments constitute a form of scarcity-adversity that places parents at greater risk for disrupted caregiving, including increased negative parenting behaviors [21, 61]. We show that scarcity-adversity can be modeled in rodents by depriving the dam of adequate nesting materials during the early postpartum (i.e., LBN PD 2–9), which increased negative maternal behaviors directed at pups and impaired maternal responses, thereby mimicking the effects of adverse environments (low SES) in potentiating negative parenting behaviors such as maltreatment and neglect in humans [27, 61, 62].

Postpartum scarcity-adversity increases negative maternal behaviors and impairs goal-directed and stress-related responses in the dam

Compared to CON dams, LBN dams exhibited increased adverse maternal behaviors that are disruptive to pups: stepping, dragging, shoving away, and improper transport. Similar results were obtained during the dark cycle, suggesting that the LBN-induced expression of negative pup-directed maternal behaviors is present throughout the circadian cycle. These findings are consistent with prior reports indicating that dams exposed to LBN during PD 8–12 spent higher percentages of time stepping on pups, transporting, and dragging of pups, which coexisted with an increase in nest-building by the dam and a fragmented, unpredictable nest environment for pups (scattered litter) [27, 36, 51, 63, 64]. Thus, the effects of LBN exposure during the first 2 weeks postpartum on maternal behavior parallel the clinical literature showing that children living in low SES or poverty conditions are more likely to experience increased exposure to negative parenting behaviors such as maltreatment and/or neglect [61, 62].

We also examined the impact of postpartum scarcity-adversity on goal-directed maternal responses and coping responses to an acute uncontrollable stressor. When tested for pup retrieval in a novel environment, LBN dams exhibited longer latencies compared to CON dams. Similarly, dams or adult female offspring (F1) exposed to chronic social stress from PD 2–16 also take longer to gather/retrieve their pups on PD 9 [10, 65], suggesting that postpartum stressors converge in impairing pup retrieval behavior. LBN dams also exhibited greater FST immobility at PD 9, suggesting a passive coping response which has previously been interpreted as higher depressive-like behavior [66–68]. Early postpartum dams exposed to

Negative Maternal Behaviors PD2-6 Morning/Afternoon



Negative Maternal Behaviors PD 2-6 Night

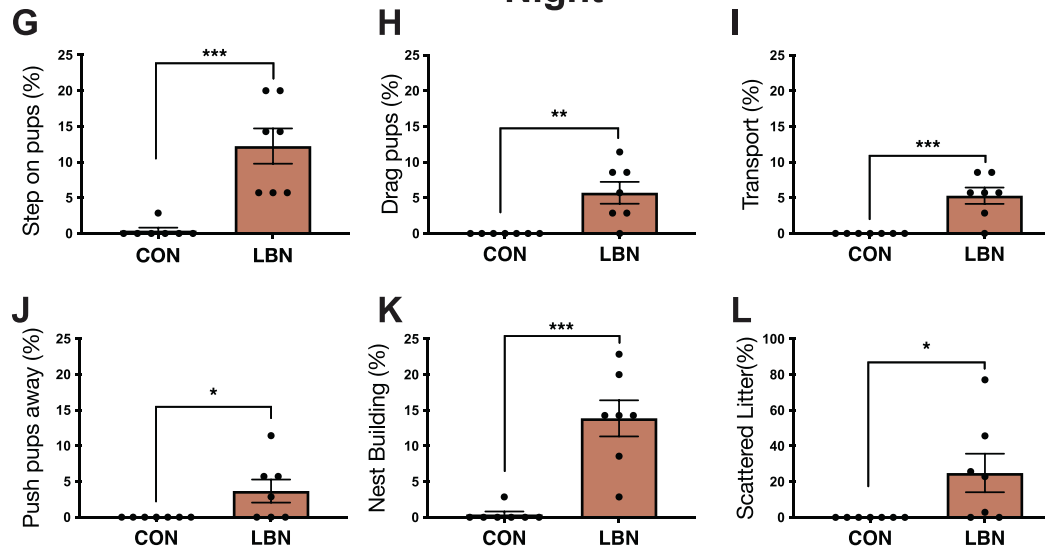


Fig. 2 LBN exposure increases negative maternal behaviors directed at pups and produces a fragmented nest environment. During the light cycle observation sessions, LBN dams exhibited increased percentages of **A** stepping ($p = 0.0017$), **B** dragging ($p = 0.0011$), **C** transporting pups ($p = 0.0006$), and **D** shoving pups away ($p = 0.0023$) ($n = 7/\text{group}$). LBN dams also spent more time nest-building ($p = 0.0096$) and with scattered litter ($p = 0.0029$). LBN dams also spent greater percentages of time **G** stepping pups ($p = 0.0006$), **H** dragging pups ($p = 0.0028$), **I** transporting pups ($p = 0.0006$), **J** pushing or shoving pups away ($p = 0.04$), **K** nest-building ($p = 0.0012$) and **L** with a scattered litter ($p = 0.04$) during nighttime observation sessions ($n = 7/\text{group}$). Error bars represent mean \pm SEM. Gray bars represent control dams (CON), pink bars represent dams that underwent scarcity-adversity (LBN). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

gestational restraint stress also spend more time immobile in the FST [69, 70], suggesting that psychosocial stressors during pregnancy/postpartum converge in augmenting passive FST coping responses. Furthermore, increased FST immobility is commonly observed after chronic stress exposure and in preclinical models useful for the study of depression and postpartum mood disorders ([5, 6, 55, 71–74]). Collectively, these data show that postpartum scarcity-adversity impairs maternal goal-directed pup responses and

produces divergent (i.e., passive) stress coping strategies. This is in agreement with prior reports indicating both deficits in maternal behavior and passive FST coping as common behavioral endpoints in a variety of preclinical rodent models relevant for the study of PPD, including non-stress based (e.g., genetic, hormone) models [72, 75–78]. Thus, our findings recapitulate the link between disrupted maternal behaviors and increased depression-related phenotypes in rodent models of PPD.

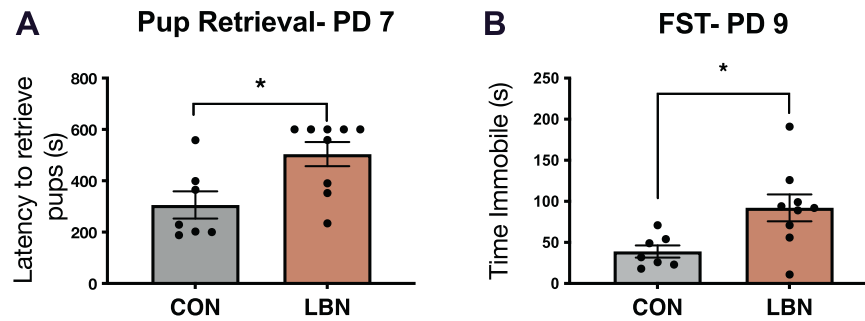


Fig. 3 Postpartum scarcity-adversity impairs pup retrieval and enhances passive FST coping. **A** Compared to controls, LBN dams exhibited longer latencies to retrieve pups (Mann–Whitney: $U = 8$, $p = 0.01$) at PD 7 ($n = 7$ –9/group). **B** When tested in the FST at PD 9, these same dams (i.e., LBN) also exhibited increased immobility duration compared to CON (t -test: $t_{14} = 2.684$, $p = 0.02$; $n = 7$ –9/group), suggesting an enhanced passive coping response induced by postpartum adversity. Error bars represent mean \pm SEM. $*p < 0.05$.

Postpartum scarcity-adversity induces a transient hypodopaminergic state in the rat dam

This study extends the current knowledge regarding adversity-induced changes in the maternal brain by demonstrating that early postpartum scarcity-adversity (LBN PD 2–9) compromises in vivo maternal mesolimbic DA function in the dam and induces distinct short- versus long-term effects. This was characterized by an hypodopaminergic state in LBN dams compared to CON dams at PD 9–10 but not PD 20–21, as indexed by a reduction in the number of active DA neurons within the VTA (i.e., blunted population activity = lower numbers of cells per track). This finding is in accordance with our prior studies on stress-induced plasticity of VTA DA neurons showing that adult male and female rats exposed to learned helplessness or chronic mild stress exhibit a selective attenuation in VTA population activity indicative of DA system downregulation, particularly in the medial reward-related population [53, 58, 73, 79–82]. Moreover, reduced VTA population activity in LBN dams is also consistent with our recent study showing a hypodopaminergic state in a novel rodent model useful for the study of PPD based on social adversity (permanent pup removal at PD1) [55]. Thus, postpartum scarcity-adversity mimics the effects of adult stress paradigms on VTA DA neuron function previously reported by our group and is consistent with stress-induced VTA plasticity in preclinical rodent models of depression [83, 84]. This is significant because the LBN paradigm is used by >15 groups as a model of early life stress, but this model's effectiveness is dependent on adversity-induced changes in maternal caregiving behaviors, which negatively impact offspring development [28]. Within this context, our study is the first to show that postpartum scarcity-adversity (LBN) compromises maternal mesolimbic DA function by decreasing the number of active VTA DA neurons, thereby resulting in attenuation of DA neuron response to stimuli that we propose drives negative affect, anhedonia (e.g., depression-like states) and aberrant maternal behavior in postpartum females [44, 85]. Importantly, our findings of increased negative maternal behaviors towards pups, impaired pup retrieval, and VTA DA deficit in LBN dams are consistent with prior studies reporting disruptions in rat maternal behavior, including deficits in pup retrieval, following temporary pharmacological VTA inactivation [86, 87], 6-OHDA VTA lesions [88] or systemic DA signaling blockade via DA receptor antagonism [88–91]. Taken together, these data highlight the importance of mesolimbic DA system integrity, particularly within the VTA, for the adequate expression of maternal behaviors and suggest compromised VTA function (i.e., VTA hypoactivity leading to mesolimbic DA downregulation) as a mechanism by which LBN disrupts mother-infant interactions and drives maladaptive behavioral states in the dam.

Our prior work has shown normative, time-dependent effects of parturition on immobility behavior and VTA DA neuron activity, in

which early postpartum dams (PD 1–3) exhibit increased immobility and blunted VTA population activity compared to virgins [54, 74]. Thus, early postpartum rodents exhibit a transient, normative negative affect state shortly after giving birth, which is analogous to the postpartum blues commonly reported in human mothers [92–94]. Within the context of this work, early postpartum LBN exposure (PD 2–9) appears to prolong depression-related neurobehavioral phenotypes (e.g., FST immobility, hypodopaminergic state), as suggested by our finding of higher immobility duration and reduced VTA DA activity during PD 9–10 in LBN dams. In accordance, postpartum adversity is a risk factor that can interact with postpartum blues and lead to PPD in human mothers [3, 15], suggesting translational relevance of early postpartum LBN exposure and usefulness for modeling constructs relevant to the study of PPD.

Postpartum scarcity-adversity induces an enduring hypodopaminergic state in adult female offspring

Exposure to early life adversity results in later-life changes in reward-related behaviors, which likely reflect long-term alterations in mesolimbic DA function [50]. For example, adolescent and adult rats exposed to early life LBN exhibit decreases in sucrose consumption and palatable food preference, reduced social play, and attenuated social motivation [32, 35, 37, 38, 95]. Furthermore, adolescent rats exposed to early life LBN display blunted social motivation that is linked to reduced Fos activation within mesolimbic DA targets, including the nucleus accumbens, in response to typically rewarding (social) stimuli [37]. Thus, early life LBN exposure induces persistent anhedonia in the offspring, as indexed by decreases in reward-related behaviors throughout the lifetime.

Although previous studies using LBN have identified long-term reward-related deficits in LBN offspring, little is known regarding the impact of early life LBN exposure on adult mesolimbic DA function. Therefore, we assessed long-term effects of LBN exposure on VTA function in the adult female offspring. We focused on females to evaluate the intergenerational impact of scarcity-adversity on the female DA system by comparing early postpartum adversity effects (dams) and early life adversity effects (F1- pups) and because female LBN dams more often maltreat female pups [49]. Early life scarcity-adversity induced an enduring attenuation in VTA population activity and increased firing rate, although the increase in firing rate was small in magnitude compared to the decreased responsiveness engendered by a 75% decrease in population activity. The effect on population activity in adult female offspring was comparable to LBN dams at PD 9–10, which also exhibited VTA DA neuron hypoactivity, but divergent from those observed after the cessation of LBN exposure (PD 20–21) in which there was no difference in VTA activity between CON and

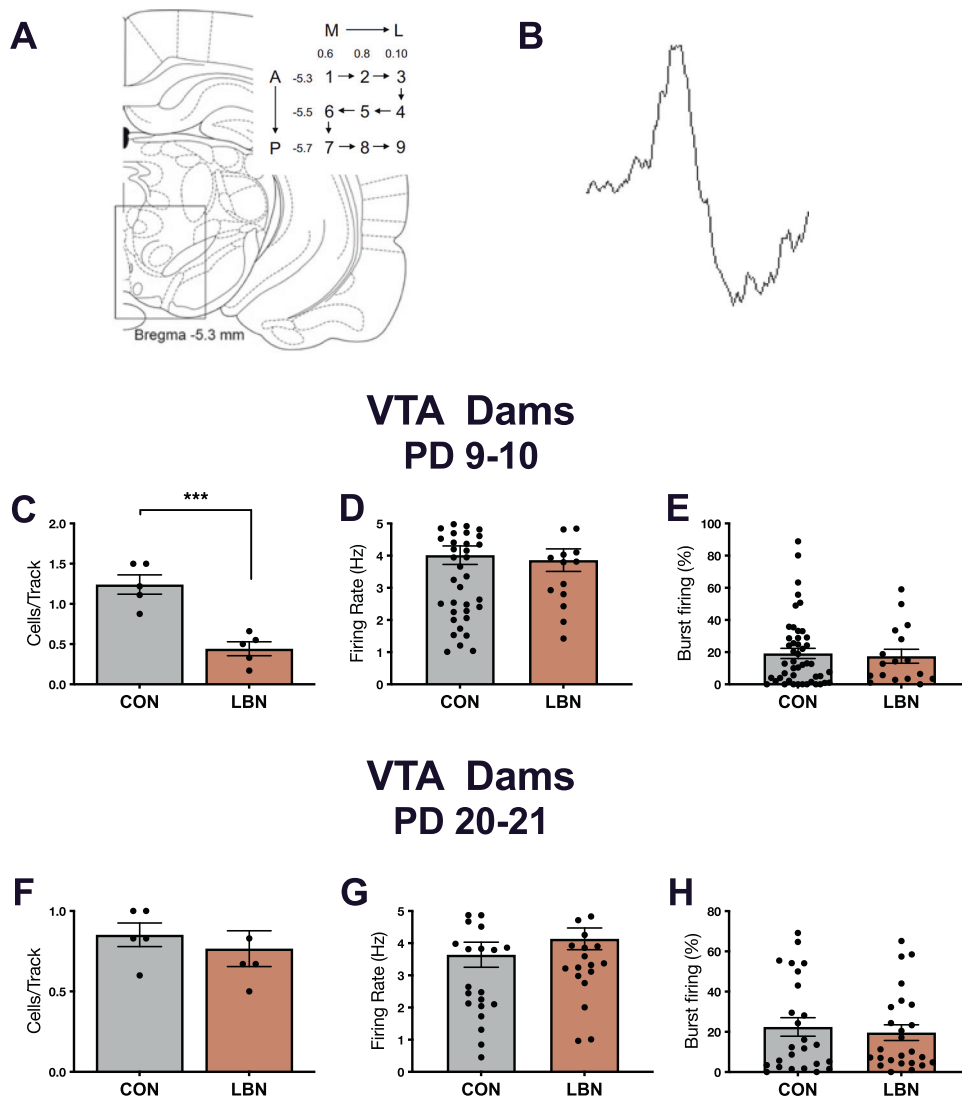


Fig. 4 Postpartum scarcity-adversity induces a time-dependent attenuation in VTA population activity. **A** VTA DA neuron sampling: population activity was assessed by passing the electrode through the VTA in a predetermined grid pattern (3×3) of 9 tracks separated by 0.2 mm. **B** A representative dopaminergic neuron waveform. **C** At PD 9–10, LBN dams exhibited attenuated VTA population activity, as indexed by a reduction in the number of spontaneously active DA neurons found, compared to CON dams (t -test: $p = 0.0006$, $n = 5/\text{group}$). **D** No effect of LBN on DA neuron firing rate ($p = 0.85$) at PD 9–10. **E** No effect of LBN was found for percentage of spikes firing in burst ($p = 0.87$) at PD 9–10. **F** When assessed at PD 20–21, no differences in VTA population were found between CON and LBN dams for VTA population activity ($p = 0.54$; $n = 5/\text{group}$). **G** At PD 20–21, LBN and CON dams exhibited comparable DA neuron firing rate ($p = 0.34$). **H** No difference between LBN and CON dams in percentage of spikes firing in burst ($p = 0.97$) at PD 20–21. Error bars represent mean \pm SEM. *** $p < 0.001$.

LBN dams. This finding is significant because it highlights: (i) the intergenerational impact of scarcity-adversity in VTA function of female rats (dam + pup), and (ii) that the impact of scarcity-adversity on female VTA function is dependent on the developmental stage at which it occurs: postpartum LBN exposure induces a transient hypodopaminergic state observed at PD 9–10 but not PD 20–21 in the rat dam, whereas early life LBN exposure (via rearing with an LBN dam) induces a long-lasting hypodopaminergic state (>PD90) in the adult offspring. In accordance, a recent study conducted by our group in female rats showed no long-term impact of adolescent stress exposure on adult VTA population activity [96]. Collectively, these data suggest that early postnatal life (PD 2–9) may constitute a sensitive period for scarcity-adversity induced programming of an adult hypodopaminergic state in female rats.

In sum, postpartum scarcity-adversity induced aberrant (i.e., adverse) maternal behaviors in the dam, impaired pup retrieval

responses and increased passive FST coping. These results overlap with those observed in rodent models relevant to PPD, in which deficits in maternal care and FST immobility are common behavioral outputs. These behavioral changes were accompanied by blunted VTA DA neuron activity at PD 9–10 but not PD 20–21, indicating temporary DA downregulation (i.e., hypodopaminergic state) in LBN dams that recovers after LBN cessation. In contrast, long-lasting VTA effects were observed in adult female offspring reared by LBN dams, suggesting early life programming of adult VTA function by scarcity-adversity and an intergenerational impact of scarcity-adversity on mesolimbic DA function. These findings highlight a link between adversity-induced deficits in DA function and disrupted maternal behavior, suggesting the VTA/mesolimbic system as a potential mechanism by which postpartum scarcity-adversity drives disrupted maternal behavior and therapeutic target for ameliorating impairments in maternal care induced by stress exposure and/or PPD.

VTA Adult Female Offspring (+PD90)

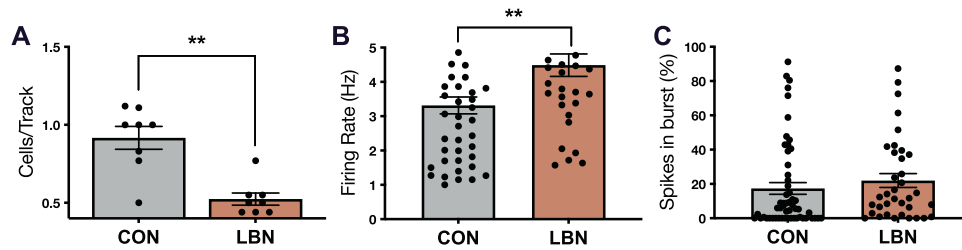


Fig. 5 Long-lasting effects of LBN exposure on VTA DA neuron activity in adult female offspring. **A** Adult female rats that were reared under early life scarcity-adversity conditions (i.e., LBN dam PD 2–9) had a reduced number of active VA DA neurons compared to adult female rats reared with CON dams (Mann–Whitney: $U = 4.5$, $p = 0.0022$; $n = 8$ /group). **B** Adult female rats reared with LBN dams exhibited increased basal DA neuron firing rate ($U = 486$, $p = 0.0091$). **C** No difference between CON and LBN offspring in percentage of spikes firing in burst ($p = 0.08$). Error bars represent mean \pm SEM. ** $p < 0.01$.

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AUTHOR CONTRIBUTIONS

Millie Rincón-Cortés: Conceptualization, methodology, software, validation, formal analysis, investigation, resources, writing—original draft, writing—review and editing, visualization, supervision, project administration, funding acquisition. Antony A. Grace: Resources, writing—review and editing, supervision, funding acquisition.

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COMPETING INTERESTS

Dr. Rincón-Cortés declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict

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