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## Developing a neurobehavioral animal model of poverty: drawing cross-species connections between environments of scarcity-adversity, parenting quality, and infant outcome

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### Abstract

Children reared in impoverished environments are at risk for enduring psychological and physical health problems. Mechanisms by which poverty affects development, however, remain unclear. To explore one potential mechanism of poverty's impact on social-emotional and cognitive development, an experimental examination of a rodent model of scarcity-adversity was conducted and compared to results from a longitudinal study of human infants and families followed from birth (N=1292), who faced high levels of poverty-related scarcity-adversity. Cross-species results supported the hypothesis that altered caregiving is one pathway by which poverty adversely impacts development. Rodent mothers assigned to the scarcity-adversity condition exhibited decreased sensitive parenting and increased negative parenting relative to mothers assigned to the control condition. Furthermore, scarcity-adversity reared pups exhibited decreased developmental competence as indicated by disrupted nipple attachment, distress vocalization when in physical contact with an anesthetized mother, and reduced preference for maternal odor with corresponding changes in brain activation. Similarly, human results indicated that scarcity-adversity was inversely correlated with sensitive parenting, positively correlated with negative parenting, and that parenting fully mediated the association of poverty-related risk with infant indicators of developmental competence. Findings are discussed from the perspective of the usefulness of bidirectional-translational research to inform interventions for at-risk families.

### Keywords

Poverty; parenting; development; regulation; brain

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## Introduction

Socioeconomic status (SES), often measured by income, occupation, and education, is a matter of access to and distribution of resources, with low SES, or poverty, equating to low access to and availability of resources (Hackman, Farah, & Meaney, 2010; Vidyasagar, 2006). According to recent reporting from the U.S. Census Bureau, nearly 20% of families with children under the age of 18 are living below the federal poverty threshold (U.S. Census Bureau, 2015). Children living in poverty are more likely to experience a scarcity of material resources, less parental nurturance, greater family instability, more crowded homes, elevated stress levels, increased exposure to violence, and less cognitive stimulation (Evans, 2004). Impoverished children are also at greater risk for exposure to poorer quality diets, as well as air and water pollution (Darmon & Drewnowski, 2008). Thus, poverty greatly increases the potential for children and families to experience a host of adverse exposures. In turn, exposure to these poverty-related risk factors increases the likelihood of poor neurobehavioral development, including cognitive and social-emotional, behavioral, and physical health problems (Yoshikawa, Aber, & Beardslee, 2012). Such developmental outcomes ultimately contribute to greater risk of poor academic achievement and worse employment outcomes throughout life (Barnett, 1998; Brooks-Gunn & Duncan, 1997; Duncan, Ziol-Guest, & Kalil, 2010).

Human studies have established a general association between poverty and brain development, with developmental imaging studies providing great insights into the potential neural consequences of poverty in early-life (for review see Johnson, Riis, & Noble, 2016). On average, findings provide evidence of slower trajectories of brain growth and lower volumes of gray matter in children living in poverty (Hanson et al., 2013). Additionally, low SES is associated with smaller hippocampi (Staff et al., 2012), and less regulated prefrontal cortex and amygdala activation during emotion processing tasks (Kim et al., 2013). Thus, infants may be particularly vulnerable to the effects of low SES, perhaps due to their heightened, rapid brain development and the role of early-life experience in sculpting brain structure and function (Hanson et al., 2013; Johnson, 2001; Noble, Houston, Kan & Sowell, 2012). However, further research is needed to understand the mechanisms by which poverty can influence brain development, particularly in infancy, and to connect brain development with behavioral development. Identifying neurobehavioral phenotypes in the earliest stages of development can potentially provide invaluable insight into the mechanisms by which poverty can affect development.

The specific mechanisms by which poverty affects neurobehavioral development remain unclear and are challenging to disentangle given the variety of poverty-related risks ranging from psychosocial to ecological factors (Evans, 2004). However, thus far, a majority of studies exploring possible pathways by which poverty impacts development have focused on family psychosocial characteristics, and parenting quality in particular (Blair & Raver, 2016). Results of these studies largely support a mediating role of parenting quality as it relates to the influence of environmental scarcity-adversity and early-life indicators of later-life social-emotional and cognitive competence (Gee, 2016; Perry, Blair & Sullivan, 2017; Tang, Reeb-Sutherland, Romeo & McEwen, 2014; Tottenham, 2015). Specifically, stressful rearing environments place parents at risk for less sensitive caregiving (Asok, Bernard, Roth,

Rosen & Dozier, 2013; Finegood et al., 2016; McLoyd, 1998). In turn, this lower caregiving quality has been shown to mediate the effects of adversity on child outcomes, including emotion dysregulation, behavioral problems, and executive function (Blair et al., 2011; Mills-Koonce et al., 2016; Raver, Roy, Pressler, Ursache, & McCoy, 2016).

On a physiological level, adversity is associated with disrupted regulation in both parents and infants. This includes altered regulation of the physiological response to threat, primarily as indicated by activity in the hypothalamic-pituitary-adrenal (HPA) axis (Berry et al., 2017; Blair et al., 2008) and connectivity among brain areas important for physiological and behavioral regulation (Jedd et al., 2015; Luby et al., 2013). Furthermore, regulation of infant physiology by way of sensitive caregiving has been proposed to provide early-life programming which guides appropriate socio-emotional and cognitive development (Perry et al., 2017). Together, these findings suggest that the quality of parental care is critical for guiding optimal socio-emotional and cognitive development. Indeed, improving parenting quality despite environmental adversity has become the central goal of many intervention efforts for low SES families, such as the Attachment and Biobehavioral Catch-up (ABC; Bernard, Meade & Dozier, 2013) and Play and Learning Strategies (PALS) interventions (Landry, Smith, Swank, & Guttentag, 2008). Further research is needed, however, to understand the neurobiological mechanisms by which parenting quality guides infant development.

Overall, while human studies have provided strong support for the hypothesis that parenting quality is at least one pathway by which socioeconomic adversity influences infant development, these studies are primarily observational, or correlational. Some intervention studies have utilized randomized controlled trials to assess relationships between caregiver interventions and outcomes (Bernard et al., 2012; Nelson et al., 2007). Even in these studies, however, experimenters could not control the initial selection process of research participants into poverty conditions, nor the participants' histories or other potentially confounding variables. Thus, human studies are fundamentally limited in establishing causation to inform mechanisms by which poverty-related adversity influences development. Human researchers also face technical challenges when it comes to the assessment of neurobiological correlates of poverty in young infants. Lastly, human research studies primarily employ a "cumulative risk" approach to studying low SES, by assessing the cumulative influence of poverty-related risk factors (ranging from ecological to psychosocial) on development. More specifically, a cumulative risk approach creates a risk score by totaling exposure to a range of distinct adverse experiences. Even with its strengths, this approach is unlikely to disentangle specific mechanisms by which different aspects of poverty-related adversity influence development (Evans, Li, & Whipple, 2013).

To address these challenges, our field has increasingly turned to animal models of early-life adversity. While there are limitations to animal models (such as the inability to fully model social and cultural phenomena), their use in conjunction with human research can isolate candidate mechanisms for cause-effect relationships between poverty-related variables and neurobehavioral development (Hackman et al., 2010; Poldrack & Farah, 2015; Thapar et al., 2015). Animal models allow for the controlled manipulation of poverty-related variables in a way that cannot be achieved with humans. Furthermore, they allow for random assignment

of subjects into group conditions, giving experimenters the ability to control the selection process into poverty-like conditions. Based on this, the experimenter has the ability to rule out potential confounding variables related to subjects' histories and timing of exposure to adversity leading up to testing, which pose challenges to the study of poverty in human samples. Animal models also provide technical advantages when it comes to assessing neurobiological, genetic, and epigenetic mechanisms by which early-life adversity influences parenting style and infant development. Understanding such mechanisms is central to disentangling the directionality and cause-effect nature of relationships between exposure to poverty, an individual's attributes (i.e. genetics), and experience-driven and/or intergenerational changes (i.e. epigenetics). Lastly, through the use of animal models, researchers can create and experimentally test taxonomies of early-life adversity in order to understand how different dimensions of adversity influence different aspects of development (Sheridan & McLaughlin, 2014). For example, our field recently witnessed a renewed effort to create animal models that will allow for the study of effects of early-life deprivation separately from the effects of early-life threat on neurobehavioral development (McLaughlin & Sheridan, 2016). Notably, while poverty is commonly categorized as a form of deprivation, it is increasingly recognized as an indicator of exposure to threat as well (Blair & Raver, 2016; McLaughlin, Sheridan, & Lambert, 2014). Thus, the strict orthogonalization of deprivation and threat using animal models may not be ideal for modeling poverty-related adversity in a translationally meaningful way. Altogether, the comparative strengths and weaknesses of human and animal research underscore the need for animal models of poverty-related adversity that maintain high translational validity, while permitting assessment of causal mechanisms using multiple levels of analyses.

Thus far, animal researchers have failed to develop animal models that are optimized to inform mechanisms by which poverty affects neurobehavioral development. Therefore, the present study tested a novel application of a previously developed animal model to evaluate its appropriateness for studying developmental processes as a function of poverty-related adversity exposure. Specifically, we leveraged a "limited bedding" rodent protocol, which was originally developed as a model of chronic early-life stress (Raineke, Moriceau, & Sullivan, 2010; Walker et al., 2017). In this model rodent families (the dam and her offspring) are supplied with insufficient nesting materials, so that the mother cannot build a proper nest for her pups (Perry & Sullivan, 2014). In keeping with current efforts to create taxonomies appropriate for measuring the effects of specific dimensions of adversity on development, this study utilized a domain-specific approach by modeling resource depletion to create conditions of scarcity-adversity. Following random assignment of rodent dams and her pups into control vs. scarcity-adversity rearing environments we measured the impact of resource depletion on caregiving quality, and pup neurobehavioral development which was determined using early-life neurobehavioral indicators of later-life social-emotional and cognitive competence (Landers & Sullivan, 2012). Furthermore, we assessed the ecological validity of this rodent model by considering our rodent findings to a parallel set of analyses that we conducted with a large sample of children and families (N=1,292) followed longitudinally from birth in predominantly low-income and non-urban communities in the U.S. (Vernon-Feagans & Cox, 2013). In this human study, we adopted a similar "cumulative risk" approach to what has been previously used. However, we created a targeted "scarcity-

adversity” risk index related to indicators of resource depletion only, with the aim of identifying a domain-specific mechanism through which poverty-related risk affects child development. Furthermore, we assessed the extent to which this cumulative risk index significantly predicted parenting quality, and through parenting quality we tested key measures of infant social-emotional and cognitive competence. Thus this cross-species approach allows for the assessment of process-level similarities and differences between species as it relates to scarcity-adversity exposure, parenting quality, and infant social-emotional and cognitive development. Through the use of cross-species research, we explore the potential for scientifically advancing the understanding of mechanisms by which poverty impacts development.

## Methods

### Rodent

**Subjects**—Male and female Long-Evans rats (originally from Harlan, Indiana) were born and bred in our colony using multiparous mothers, which are preferred because they increase the consistency of maternal care relative to primiparous mothers (Walker et al., 2017). On the day of birth, infants were considered postnatal day (PN) 0, and litters were culled to 12 infants each (6 male, 6 female) on PN1. Infants were housed in a light and temperature controlled room ( $20 \pm 1$  °C, 12 h light/dark cycle) in polypropylene cages ( $34 \times 29 \times 17$  cm) with their mother. Animals had ad libitum access to food (Purina LabDiet #5001) and water.

**Scarcity-adversity Treatment**—Litters were randomly assigned to control or scarcity-adversity conditions a week after birth. In control conditions, mothers were provided with abundant wood shavings materials (4 cm layer), so that they were able to build nests for their pups, which served as a secure base for the pups and the center for caregiving. In scarcity-adversity conditions mothers were provided with scarce amounts of wood shavings materials (100 mL shavings, < 1 cm layer), so that the mothers could not build a proper nest for their pups (Fig 1A). Litters were exposed to scarcity-adversity conditions from PN8–12. This age of exposure was based on prior research which tested this model over a variety of different intervals in early development (i.e. PN1–7, 2–9, 3–8, 8–12, or 10–14) and demonstrated that the scarcity-adversity model produces the greatest impact on neurobehavioral development from PN8–12 (for review see Walker et al., 2017). This age range begins during the rodent pup’s sensitive period for attachment (before PN10), and continues into an age range when the mother has significant effects on regulation of pups’ neurobehavioral function (after PN10) (Moriceau & Sullivan, 2006; Sarro, Wilson, & Sullivan, 2014). Scarcity-adversity exposure was terminated at the end of PN12, because pups then enter an age range of reduced impact by maternal care. However, terminating scarcity-adversity conditions also allowed for the experimenter to be blind to early-life rearing conditions during testing at PN14 ( $\pm 1$  day). Each subject was tested only once. All procedures were approved by our institute’s Animal Care and Use Committee, in accordance to the National Institutes of Health’s guidelines.

**Mother-infant Interaction: Caregiving Behaviors**—Interactions between the rodent mothers and pups were observed in a 30-minute non-structured assessment of behavior

within the home cage during control and scarcity-adversity conditions. The interaction was video recorded and later coded by trained coders to assess levels of caregiving behaviors. Maternal behavior was scored for 30 min observation periods on 3 days (PN8; PN9, 10 or 11; PN12) by experienced researchers using Cowlog software ([www.cowlog.org](http://www.cowlog.org)). Nurturing caregiver behaviors that ensure survival of offspring and attachment formation were categorized as “sensitive,” and included the mother’s presence in the nest with her pups, keeping pups together in the nest, nursing, and grooming (Rilling & Young, 2014; Table 1). Caregiver behaviors categorized as “negative” included behaviors that placed the pup at increased risk of threat (rough transport of pups, stepping on pups) or deprivation (pups scattered throughout home cage, mother self-grooming; Drury, Sanchez, & Gonzalez, 2016; Table 1). While self-grooming is a common animal behavior serving the primary purpose of hygiene and thermoregulation (Sprujit, van Hooff, & Gispen, 1992), increased self-grooming occurs as a result of increased stress hormones (D’Aquila, Peana, Carboni, & Serra, 2000; Dunn, Berridge, Lai, & Yachabach, 1987). Thus, we coded mother self-grooming to allow for the assessment of altered levels of self-grooming as a function of scarcity-adversity exposure, where heightened self-grooming reflects a negative caregiving style indicative of increased stress and decreased time interacting with pups.

To assess caregiving behaviors in undisturbed conditions within the home cage, coders could not be blinded to control vs. scarcity-adversity conditions (home cage wood shavings levels were visible in the video recording). However, the mother’s presence in the nest was verified using automated tracking software (Ethovision, Noldus). Further assessment of pup interactions with the mothers (described below) were conducted in semi-structured and structured environments, outside of the home cages, by experimenters blind to rearing conditions.

**Nipple Attachment Test**—Infant rat pups require maternal odor to attach to their mother’s nipples for nursing. Without maternal odor, nipple attachment does not occur (Hofer, Shair, & Singh, 1976; Teicher & Blass, 1977). Here we tested the ability of maternal odor to guide nipple attachment following control and scarcity-adversity rearing, through the use of a semi-structured nipple attachment test conducted by experimenters blind to rearing conditions. Mothers were anesthetized with urethane (2 g/kg, intraperitoneally) prior to testing, to prevent milk letdown. For this test, the natural maternal odor was eliminated from the mother’s ventrum and reintroduced into the testing environment via an airstream infused from underneath a mesh floor supporting the mother and pup. To remove the natural maternal odor, the ventrum of the mother was washed with acetone, alcohol, and water, (Hofer et al., 1976; Teicher & Blass, 1977). The washed mother was then placed on her side in the testing cage (25 × 40 × 20 cm), so that the pups had access to her nipples, and the odor from a separate lactating female was delivered via a flow dilution olfactometer (2 L/min flow rate, 1:10 odor:air, 4 min ITI) from under the mesh floor. The pup was then placed on the opposite side of the chamber, and latency to attach to a nipple and time spent attached to the nipple was recorded during the 3 minute test, by a researcher blind to experimental conditions (Rainecki, Moriceau et al., 2010; Rincón-Cortés et al., 2015; Sarro et al., 2014). Maternal odor is diet-dependent, thus pups cannot distinguish between the odor of

their own mother or another mother on the same diet (Leon, 1975, 1980; Sullivan, Wilson, Wong, Correa, & Leon, 1990).

**Y-maze Testing of Approach/Avoidance**—In a structured test of pup behavior, a Y-maze test was used to assess infant preference or aversion to maternal odor. The subject was placed in a start box ( $10 \times 8.5 \times 8$  cm), which was separated from two equal length arms ( $24 \times 8.5 \times 8$  cm) by sliding doors. The end of one arm contained maternal odor (from a lactating female), while the end of the second arm contained a control odor (clean wood shavings). The biological maternal odor was delivered via a flow dilution olfactometer (2 L/min flow rate, 1:10 odor:air, 4 min ITI), and the control odor was a familiar odor of clean wood shavings (20 mL) in a petri dish. Maternal odor is diet-dependent, thus pups will approach any lactating mother on the same diet as their own mother (Leon, 1975, 1980; Sullivan et al. 1990). Following a 5-second holding period in the start box, the sliding doors were lifted and the pup was given 1 minute to make a choice. It was considered a choice when the entire body of the subject entered the alleyway of an arm. The subject was given a total of 5 trials to select between maternal odor and the control odor, and all trials were conducted by a researcher blind to experimental conditions (Moriceau, Shionoya, Jakubs, & Sullivan, 2009; Raineke, Moriceau et al., 2010; Raineke et al., 2015; Sullivan & Wilson, 1991).

**Ultrasonic Vocalizations (USVs)**—Similar to human crying, infant ultrasonic vocalization (USV) is a valid measure of pup distress, and serves an important communicative role in eliciting caregiving behaviors (Branchi, Santucci, & Alleva, 2001). In this structured assessment of infant USVs outside of the nest, USVs were recorded for 1 minute while pups were isolated in a beaker (2000 mL), and then for an additional 1 minute once being placed with an anesthetized mother, with all testing occurring in a temperature regulated room ( $32^\circ\text{C}$ ) by an experimenter blind to experimental conditions. The mother was anesthetized with urethane (2 g/kg, intraperitoneally), and placed with her abdomen against the bottom and side of the testing cage to prevent the possibility of pups attaching to her nipples during the test (Hofer & Shair, 1978). All recordings were made following a 1 minute habituation period, using an Ultramic 200k USB microphone (Dodotronic), with a 200 kHz sampling rate, and USVs were visualized using SeaWave (CIBRA) software. Spectral analysis of USV data was performed using the Spectral Analysis Toolbox from the open source code repository Chronux (chronux.org). The code was implemented using MATLAB (MathWorks) and utilized a moving window, multi-taper spectral analysis. A detailed description and validation of these specific procedures is provided elsewhere (Bokil, Andrews, Kulkarni, Mehta, & Mitra, 2010; Mitra & Bokil, 2008). Moving windows were set to 300 ms and 100 ms. Sampling frequency of the USV data was 200 kHz, meaning that the Nyquist frequency of the computation (100 kHz) was well above the target frequency band of 30–60 kHz, which is the frequency at which pups elicit “distress” calls, such as when socially isolated (Cacioppo, Hawkey, Norman, & Berntson, 2011; Hofer, 1996; Insel, Hill, & Mayor, 1986; Shair, 2007). Following computation of the spectral analysis, data in the 30–60 kHz band were isolated during the second minute of data recording under all four conditions. Total spectral power in the frequency band was calculated in decibels (dB). The mother’s ability to reduce infant USV emission was calculated as the percent reduction of

USV power (dB) from the socially isolated condition to the anesthetized mother condition [(dB alone – dB with mom) / dB alone \* 100]. All recordings and data processing were conducted by experimenters blind to rearing conditions

**Neurobiology**—Infant brain activity in response to maternal odor presentations was assessed using  $^{14}\text{C}$  2-deoxyglucose (2-DG) autoradiography (Boulanger Bertolus et al., 2014; Debiec & Sullivan, 2014; Landers & Sullivan, 1999; Moriceau et al., 2009; Sullivan, Landers, Yeaman, & Wilson, 2000; Sullivan & Wilson, 1995), which provides data that permits functional assessment of the brain that is similar to PET and fMRI (Casquero-Veiga et al., 2016; Yan et al., 2017). Five minutes prior to maternal odor presentations, pups were injected with  $^{14}\text{C}$  2-DG (20  $\mu\text{Ci}/100\text{g}$ , subcutaneous injection), which allows labeling of cells via  $^{14}\text{C}$  2-DG uptake into active cells. Pups were then placed individually into beakers (2000 mL), where they received 11 maternal odor presentations delivered via a flow dilution olfactometer (2 L/min flow rate, 1:10 odor:air, 4 min ITI) controlled by Ethovision software (Noldus). The natural maternal odor was sourced from two anesthetized mothers that were placed in an airtight chamber connected to the flow dilution olfactometer (Perry, Al Aïn, Rainecki, Sullivan, & Wilson, 2016). Brains were dissected following the end of odor presentations, and stored in a  $-80\text{ }^{\circ}\text{C}$  freezer before being sectioned in a cryostat (20  $\mu\text{m}$ ) at  $-20\text{ }^{\circ}\text{C}$ . Every other brain section was collected onto a cover slip and exposed to X-ray film (Kodak) for 5 days with  $^{14}\text{C}$  standards (10  $\times$  0.02 mCi, American Radiolabeled Chemicals Inc.; Coopersmith, Henderson, & Leon, 1986; Sullivan & Wilson, 1995). ImageJ software (National Institutes of Health [NIH]), which is a computer-based system for quantitative optical densitometry, was used to compute levels of brain activity in brain regions of interest (ROI). To compute 2-DG uptake, autoradiographic density was measured in both hemispheres of the brain within each ROI (described below), and then averaged across both hemispheres. All 2-DG uptake measures were expressed relative to 2-DG uptake in the corpus callosum to control for differences in section thickness or exposure levels (Sullivan et al., 2000). A total of four brain sections per ROI were analyzed per animal, and the reported results reflect an average of relative 2-DG uptake across all four sections. An increase in autoradiographic density indicates increased neural activation, but does not differentiate between inhibitory and excitatory activity. All experiments and analyses were conducted by a data collector blind to experimental conditions. Our neurobiological assessment focused on developing olfactory-limbic brain regions underlying attachment learning and social-emotional and cognitive development in humans and rodents (Callaghan, Sullivan, Howell, & Tottenham, 2014; Landers & Sullivan, 2012; Perry et al., 2017; Tottenham, 2015), as well as areas thought to be vulnerable to impact from scarcity rearing (Hanson et al., 2013; Johnson, 2001; Noble et al., 2012; Rincón-Cortés & Sullivan, 2016). All odor presentations and image analysis were conducted by experimenters blind to rearing conditions.

**Anterior Piriform Cortex (aPCX):** NIH ImageJ software was used to measure 2-DG uptake within the olfactory cortex (anterior piriform cortex; aPCX), by using a stereotaxic atlas (Paxinos & Watson, 1986) to outline the region. Anatomical landmarks within aPCX were visible in the autoradiographs, thus no cresyl violet staining was required for analysis.



**Amygdala and Hippocampus:** Anatomical landmarks within the amygdala and hippocampus were not visible in the autoradiographs. Therefore, specific nuclei and anatomical landmarks were identified by staining brain sections with cresyl violet following exposure, which were used to make template overlays for the autoradiographs (Debiec & Sullivan, 2014; Moriceau, Shionoya, Jakubs, & Sullivan, 2009; Raineki, Holman, et al., 2010). Analyses within the amygdala and hippocampus included medial (MeA), basolateral (BLA), central (CeA), and cortical (CoA) nuclei of the amygdala, as well as CA1, CA3, and dentate gyrus (DG) of the dorsal hippocampus.

**Prefrontal Cortex (PFC):** Cresyl violet staining was not used for analysis of the PFC because anatomical landmarks were visible in the autoradiographs. Rather, brain areas were outlined with the aid of a stereotaxic atlas (Paxinos & Watson, 1986). Analyses within the PFC included the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), prelimbic cortex (PL), and infralimbic cortex (IL).

**Functional Connectivity Network Analyses:** Relative 2-DG uptake data across individual animals was calculated for the aPCX, amygdala (average of BLA, MeA, CeA, CoA), hippocampus (average of CA1, CA3, DG), and PFC (average of ACC, PL, IL, OFC). Pairwise Pearson correlation coefficients were then calculated for all possible combinations of brain regions for each animal, and transformed into Fisher  $z$ -values to allow quantitative analyses of functional connectivity (Perry, Al Ain, Raineki, Sullivan, & Wilson, 2016). Fisher  $z$ -values greater than 0.5 were considered to be meaningful measures of functional connectivity between brain regions of interest.

**Statistical Analyses—**Behavioral and 2-DG ROI data were analyzed by ANOVA, followed by Fisher's post hoc tests between individual groups, or Student's  $t$  tests in cases with only two experimental groups. For functional connectivity network analyses, Pearson correlation coefficients ( $r$ ) were converted to  $z$  score values using Fisher's  $r$ -to- $z$  transformation, and  $z$  scores were compared and analyzed for statistical significance by calculating the observed  $z$  test statistic formula:  $[z_{observed} = (z_1 + z_2) / \text{square root of } ((1/N_1 - 3) + (1/N_2 - 3))]$ . All differences were considered significant when  $p < 0.05$ .

## Human

**Participants—**Data were from the Family Life Project (FLP), a population-based, longitudinal study of 1,292 children and their primary caregivers (99.61% biological mothers) living in low-income rural communities in eastern North Carolina (NC) and central Pennsylvania (PA). Families were recruited in local hospitals shortly after the birth of the target child, oversampling low-income families in both states and African American families in NC. A detailed description of the sampling plan and recruitment procedures has been published elsewhere (Vernon-Feagans & Cox, 2013). The data presented here come from a series of data collected in families' homes when infants were approximately 2, 6, and 15 months of age. Home visits were completed by two trained home visitors, lasting 2–3 hours and included self-reported measures and semi-structured interviews assessing household characteristics, family demographics, and infant behavior, as well as a mother-infant interaction task.

For this sample, 59.8% of families resided in NC, and 40.2% resided in PA, with 57% of the study population being Caucasian, the remaining 43% African American. At 6 months postpartum, mothers were on average 26.37 years of age ( $\pm 6.12$  years), and infants were on average 0.64 years old ( $\pm 0.12$ ), and near evenly split as male (49.10%) and female (50.9%). On average, families lived approximately 192% above the poverty level (income-to-needs ratio [INR] = 1.92) with 34% of families living in poverty (INR  $\leq 1.0$ ) and half of those families, 17%, in deep poverty (INR  $\leq .50$ ).

**Scarcity-Adversity Exposure**—Scarcity-adversity exposure was assessed by creating a composite poverty-related risk index. As with prior analyses of the FLP (Vernon-Feagans & Cox, 2013), we computed a cumulative risk composite of six variables measured at 6 months: family income-to-needs ratio, economic strain, household density, neighborhood noise/safety, maternal education, and consistent partnership of a spouse/partner living in the home. A continuous cumulative risk index was generated by reverse-scoring the positively framed indicators, standardizing each risk measure, and averaging the standardized variables. Correlation coefficients among the six indicators included in the cumulative risk index ranged from  $r = .13$  to  $.53$ ,  $p < 0.001$ .

**Parent-Infant Interaction: Parenting Behaviors**—Interactions between primary caregivers and their infants were observed in a 10-minute semi-structured, free-play task during the 15-month home visit. In this task, primary caregivers were instructed to play with their infant using a provided set of standardized toys. The interaction was video recorded and later coded by highly trained coders to assess levels of primary caregivers' sensitivity (responses to infant's signals of physical and emotional needs), detachment (emotional involvement and level of physical activity with infant, e.g., rarely making eye contact), intrusiveness (degree to which the caregiver imposed their agenda on their infant), stimulation (cognitive stimulation of infant), positive regard (expression of positive affect and delight in interacting with infant), negative regard (expression of negative affect), and animation (enthusiasm for infant; Cox & Crnic, 2002; National Institute of Child Health and Human Development Early Child Care Research Network, 1999). Each behavioral dimension was coded using a scale from 1 ("not at all characteristic") to 5 ("highly characteristic") by a team of coders, which included a master coder. Coders underwent training with their master coder until acceptable reliability was established, as determined by intra-class correlation coefficients (ICC  $> 0.80$ ). Once acceptable reliability was established, coders coded in pairs while continuing to complete at least 30% of the videos with their master coder. Each coding pair met biweekly to reconcile scoring discrepancies, and the scores used in analysis were the final scores arrived at after reconciling.

Two distinct dimensions of parenting behavior emerged from principle factor analyses of parenting measures conducted with an oblique rotation (i.e., Promax) at each time point. These dimensions included sensitive parenting, (the average of sensitivity, stimulation, positive regard, detachment (reversed), and animation) and negative parenting (the average of detachment, intrusiveness, and negative regard) (Mills-Koonce et al., 2011; Vernon-Feagans & Cox, 2013).

**Infant Affect**—Interactions between primary caregivers and their infant were observed in a 10-minute semi-structured, free-play task during the 15-month home visit, as described above. Videos were coded for infant positive affect (infant satisfied, content, or pleased with overall situation) and negative affect (infant fussing, frowning, tensed body, discontent). Each behavioral dimension was coded using a scale from 1 (“not at all characteristic”) to 5 (“highly characteristic”) by a team of 4 to 5 coders. Coders were trained by a master coder, before formally coding in pairs as described above. Each coder maintained an ICC of .80 or higher to their master coder and completed at least 30% of the videos with their master coder.

**Infant Mental Development**—The Mental Development Index (MDI) was measured using the Bayley Scales of Infant Development-II (BSID-II; Bayley, 1993), which was administered at the 15-month time point. The BSID-II is the most widely used measure of cognitive developmental status for children in the first 2 years of life. The MDI is a standard series of developmental tasks that measures children’s cognitive skills in infancy. These scores are norm-referenced standard scores ( $M = 100$ ,  $SD = 15$ ).

**Infant Attention**—At the 15-month home visit, infant attention was assessed using a subscale from an adaptation of the Infant Behavior Record (IBR; Bayley, 1969). The IBR was applied to behavior observed globally across the entire home visit (Stifter & Corey, 2001). Ratings were completed independently by both home visitors whose scores were averaged. Alpha for the Attention subscale was 0.88.

**Covariates**—To control for site differences in study variables, state of residence (PA = 0, NC = 1) was included as a covariate. Additional demographic covariates included the primary caregiver’s report of the sex (Male = 0, Female = 1), and race (African American = 1, not African American = 0) of their infant during the 2 month home visit, as well as the reported age of the primary caregiver and their infant at the time of the 6 month visit.

**Missing Data**—The full sample of the Family Life Project consisted of 1,292 families at the time of study entry, with 1,204 families seen at 6 months postpartum and 1,169 families seen at 15 months postpartum. To assess possible differential attrition in the sample at each time point we examined a number of variables for which we had complete information collected at infant age of approximately 2 months. Few variables indicated differences between families who were present and those who were missing at each time point. Complete information on missing data is available from the first author upon request.

Participants were included in the analysis if they had non-missing data on at least one or more assessments of parenting, infant affect, infant mental development, or infant attention, resulting in an analytic sample of  $N=1,169$ , which was used in all analyses. All models were specified and fitted using full information maximum likelihood (FIML) estimation, to reduce potential bias in estimates related to missing data (Enders, 2010).

**Statistical Analyses**—Descriptive analyses and bivariate correlations were computed for study variables in IBM SPSS Statistics Version 21. Mediation analyses were conducted in Mplus 7 software (Muthén & Muthén, 1998–2012) using the bootstrapping (resampling)

procedure, a method developed to assess multiple mediator effects simultaneously (Preacher & Hayes, 2008). To quantify effect size, we report the completely standardized indirect effects (Table 4; Preacher & Kelley, 2011). These standardized coefficients ( $\beta$ ) for the indirect effects indicate how much the dependent variable would be expected to change for a single standard deviation change in the predictor variable, and are therefore expressed on the metric of standard deviations.

## Results

### Rodent

**Resource Scarcity Impairs Parenting**—Using our rodent model of scarcity-adversity, we first demonstrated that resource conditions experienced by rodent mothers and their pups directly influence maternal interactions with pups. Rodent mothers randomly assigned to the scarcity-adversity environment showed a significant decrease in time spent displaying sensitive caregiving behaviors toward their pups (Fig 1B). This included a significant decrease in time the mothers spent in the nest ( $t_{(19)} = 2.253, p = 0.0362$ ), decreased time that all pups spent huddled together in the home cage ( $t_{(19)} = 3.045, p = 0.0073$ ), and decreased time the mothers spent nursing pups ( $t_{(19)} = 4.721, p = 0.0001$ ), relative to mothers in control conditions. Despite decreased time spent nursing, pups gained weight normally as indicated by no significant group difference in weights measured at PN14 (control  $M \pm SEM: 28.790 \text{ g} \pm 0.846$ ; scarcity-adversity  $M \pm SEM: 29.220 \text{ g} \pm 0.679$ ;  $t_{(19)} = 0.397, p = 0.6940$ ). Interestingly, no significant group difference was found in time spent by the mothers grooming their pups ( $t_{(19)} = 0.569, p = 0.5761$ ).

Additionally, in the scarcity-adversity conditions, mothers spent increased time displaying negative caregiving behaviors toward their pups (Fig 1C). This included increased time spent roughly transporting their pups (Fig 1A;  $t_{(19)} = 2.406, p = 0.0317$ ), and stepping on pups (Fig 1A;  $t_{(19)} = 8.496, p < 0.0001$ ). Furthermore, mothers in scarcity-adversity conditions showed a significant increase in time spent grooming themselves ( $t_{(19)} = 2.607, p = 0.0178$ ). Lastly, pups in scarcity-adversity conditions spent a significantly higher amount of time scattered throughout the home cage, relative to pups in control conditions ( $t_{(19)} = 3.357, p = 0.0035$ ).

**Scarcity-Adversity Rearing Impairs Maternal Regulation of Infant Behavior**—Next we demonstrated that scarcity-adversity rearing negatively impacts the effect of maternal odor on pup behavior (Fig 2). Pups reared in the scarcity-adversity condition were significantly less likely to approach maternal odor relative to a control odor in a Y-maze odor choice test (Fig 2A;  $t_{(14)} = 3.480, p = 0.0041$ ). However, both control and scarcity-adversity reared pups displayed a preference to maternal odor, as indicated by choices toward the odor at levels significantly greater than chance (control:  $t_{(7)} = 10.250, p < 0.0001$ ; scarcity-adversity:  $t_{(7)} = 4.596, p = 0.0037$ ). Furthermore, in a maternal odor-guided nipple attachment test, pups reared in scarcity-adversity conditions showed a significant decrease in time spent nipple attached to an anesthetized mother ( $t_{(14)} = 4.522, p = 0.0007$ ), and a significant increase in the latency to attach to a nipple, relative to control reared pups (Fig 2B;  $t_{(14)} = 7.281, p < 0.0001$ ). Lastly, scarcity-adversity exposure significantly impacted the

mother's ability to reduce infant distress USV emissions (30–60 kHz) following a brief period of social isolation (Fig 2C; Cacioppo et al., 2011; Hofer, 1996; Insel et al., 1986; Shair, 2007). Specifically, following a brief period of social isolation, presentation of an anesthetized mother almost completely reduced USV emissions in control reared pups, but led to a significantly decreased reduction of USV emissions in scarcity-adversity reared pups ( $t_{(10)} = 2.112, p = 0.0304$ ). When in the presence of an anesthetized mother, all pups remained in physical contact with the mother throughout the duration of USV recordings (SEM = 0). Together, these findings display impaired maternal regulation of infant behavior from scarcity-adversity rearing. When infant behaviors were analyzed with sex as a variable, no significant sex differences were found.

### **Scarcity-Adversity Rearing Alters Infant Brain Processing of Maternal Cues—**

Lastly, we demonstrated that rearing in the scarcity-adversity condition altered the processing of maternal odor in the infant's brain. Relative 2-DG uptake measures across individual animals were used to compute Pearson correlation coefficients ( $r$ ) for all pair-wise combinations of brain regions of interest in response to maternal odor (Fig 3A). Pearson correlation coefficients were then transformed to Fisher  $z$ -values to allow for the determination of the significance of difference between the correlation coefficients between groups (Fig 3A), and visual depiction of functional connectivity within each group (Fig 3B).  $Z$  scores indicated greater network activity in scarcity-adversity reared pups in response to maternal odor presentations. Overall, more instances of significant functional connectivity between the aPCX, hippocampus, amygdala, and PFC were observed in the scarcity-adversity group ( $z$  score  $> 0.5$ ). Specifically, statistical analyses revealed a significant increase in functional connectivity between the aPCX and PFC in scarcity-reared pups, relative to control reared pups ( $z_{observed} = -2.290, p = 0.022$ ). No significant group differences were found for aPCX-amygdala ( $z_{observed} = -1.340, p = 0.1802$ ), aPCX-hippocampus ( $z_{observed} = 1.520, p = 0.1285$ ), amygdala-hippocampus ( $z_{observed} = -0.290, p = 0.7718$ ), amygdala-PFC ( $z_{observed} = -0.67, p = 0.5029$ ), or hippocampus-PFC ( $z_{observed} = -0.630, p = 0.5287$ ) modules of network activity. No significant sex differences were found when 2-DG responses to maternal odor were analyzed with sex as an analysis variable.

## **Human**

In order to assess translational validity of our rodent model of scarcity-adversity, we considered our rodent results in relation to a longitudinal study of human children and families followed from birth in predominantly low-income and non-urban communities in the U.S. (Vernon-Feagans & Cox, 2013).

**Descriptive Statistics and Correlations—**Descriptive statistics for demographic variables and analysis variables from the human longitudinal data are presented in Table 2. Correlations among study variables are presented in Table 3. Poverty-related scarcity-adversity exposure at 6 months was significantly related to parenting quality at 15 months, such that higher scarcity-adversity exposure was associated with decreased sensitive caregiving ( $r = -0.50, p < 0.01$ ), and increased negative caregiving ( $r = 0.32, p < 0.01$ ). Furthermore, poverty-related scarcity-adversity at 6 months was significantly associated with infant positive affect during the parent-infant interaction, as well as measures of infant

mental development and attention, such that greater adversity was associated with decreased positive affect ( $r = -0.13, p < 0.01$ ), decreased mental development ( $r = -0.24, p < 0.01$ ), and decreased attention ( $r = -0.07, p < 0.05$ ). Parenting quality was also associated with infant affect, mental development, and attention. Specifically, sensitive parenting positively correlated with infant positive affect ( $r = 0.31, p < 0.01$ ), mental development ( $r = 0.25, p < 0.01$ ), and attention ( $r = 0.12, p < 0.01$ ). Conversely, negative parenting positively correlated with infant negative affect ( $r = 0.29, p < 0.01$ ), and was associated with lower scores on measures of mental development in infancy ( $r = 0.19, p < 0.01$ ). Together, this pattern of statistically significant pathways lent support to a mediating model of scarcity-adversity for infant outcomes, which is empirically tested below.

## Mediation

**Infant Affect**—Next, we tested the hypothesis that parenting quality mediates the association between poverty-related scarcity-adversity and infant affect in the presence of the primary caregiver. Specifically, two potential aspects of parenting at 15 months (sensitive parenting and negative parenting), were assessed as potential mediators of the association between scarcity-adversity at 6 months and infant positive and negative affect at 15 months (Fig 4).

After controlling for our covariates (state of residence, race, infant sex and age, caregiver age), we found that the association between scarcity-adversity and infant affect was statistically mediated by parenting quality, with sensitive parenting mediating the predictive role of scarcity-adversity for positive infant affect ( $\beta = -0.14, p < 0.0001$ ) and negative parenting mediating the predictive role of scarcity-adversity for negative child affect ( $\beta = 0.08, p < 0.0001$ ). These indirect pathways are also listed in Table 4. The model is depicted (without covariates) in Figure 4.

**Mental Development and Attention**—To further examine the potential mediation of scarcity-adversity on infant development through parenting quality, we next examined measures of infant cognitive ability at age 15 months, specifically the MDI of the Bayley Scales and an observational rating of infant attentiveness during the approximately 2 hour data collection period at 15 months. Findings are presented in Table 5 and indicate that the association between scarcity-adversity exposure and child attention was also statistically mediated by parenting quality. Sensitive parenting served as a significant mediator for the role of scarcity-adversity in predicting infant attention ( $\beta = -0.05, p < 0.0001$ ) and mental development ( $\beta = -0.05, p < 0.0001$ ), while negative parenting mediated the predictive role of scarcity-adversity for infant mental development ( $\beta = -0.02, p < 0.05$ ). The model is depicted (without covariates) in Figure 5.

**Alternative Models**—In addition to testing the hypothesized model described above, in which the predictive role of scarcity-adversity for infant affect was mediated by parenting quality, we also evaluated an alternative model in which the pathways were reversed (i.e. the role of scarcity-adversity on parenting quality would be mediated by infant affect). Our results yielded some support for this alternative model, with significant direct effects of scarcity-adversity on sensitive parenting ( $\beta = -0.36, SE = 0.04, p < 0.0001$ ) and negative

parenting ( $\beta = 0.24$ ,  $SE = 0.04$ ,  $p < 0.0001$ ), as well as a statistically significant mediating predictive role of infant positive affect for sensitive parenting ( $\beta = -0.03$ ,  $SE = 0.009$ ,  $p = 0.005$ ). We next evaluated an alternative model in which scarcity-adversity exposure on parenting quality would be mediated by child cognitive abilities. Our results provided some support for this alternative model, with significant direct effects of scarcity-adversity on sensitive parenting ( $\beta = -0.36$ ,  $SE = 0.04$ ,  $p < 0.0001$ ) and negative parenting ( $\beta = 0.22$ ,  $SE = 0.04$ ,  $p < 0.0001$ ), as well as a statistically significant mediating predictive role of infant mental development for sensitive parenting ( $\beta = 0.02$ ,  $SE = 0.01$ ,  $p = 0.011$ ), and infant mental development for negative parenting ( $\beta = 0.01$ ,  $SE = 0.01$ ,  $p = 0.021$ ).

## Discussion

Children raised in poverty are at increased risk for a host of negative physical and mental health outcomes (Blair & Raver, 2012, 2016; Duncan et al., 2010; Hackman et al., 2010; Johnson et al., 2016; Yoshikawa et al., 2012). However, specific mechanisms by which this occurs remain unclear, and understanding them is of critical public health importance. Over the past decades, a growing number of studies on children have identified parenting quality as one likely mechanism through which poverty affects child development (Blair & Raver, 2012; Brooks-Gunn & Duncan, 1997; McLoyd, 1998; Perry et al., 2017). Additionally, recent evidence has suggested that parenting quality is at least one mediator of poverty on child brain as well as behavioral development in humans (Granero, Louwaars, & Ezpeleta, 2015; Hackman, Gallop, Evans, & Farah, 2015; Holochwost et al., 2016; Luby et al., 2013). As noted in the introduction, however, research on the effect of poverty on child development is necessarily correlational. While human research provides valuable insight into relationships among poverty, parenting, and child development, one limitation is that most studies cannot control the selection process into poverty, and thus are potentially confounded by the host of factors that co-vary with poverty status and are potential 'third variable' explanations for observed associations among poverty, parenting, and child outcomes. Thus, in order to allow for more strongly controlled experiments and the study of causal mechanisms related to poverty, parenting, and neurobehavioral development, the present study assessed the appropriateness of modeling domain-specific aspects of poverty through the use of a rodent model.

### Operationalizing the Impact of Poverty on Development: Threat vs. Deprivation

Operationalizing poverty in a way that allows for controlled experiments (e.g., via animal models) is challenging given the variety of poverty-related risks ranging from psychosocial to ecological factors (Evans, 2004). Thus, as a first approach to modeling poverty using a rodent model, the current study took a domain-specific approach by manipulating only one poverty-related factor: resource levels. This procedure has high face validity in that rodent mothers randomly assigned to the treatment condition were provided with limited quantities of an essential parenting resource, namely wood shavings with which to build the nest. Mothers in the control condition were similar in all respects other than the amount of material available to build a proper nest. Resource-depleted mothers were less sensitive in the care that they provided to their offspring as demonstrated by a number of well-established indicators of caregiving competence, including time spent with pups in the nest

and nursing, as well as pup transport, rough handling, and placement within the home cage (for review see Drury et al., 2016).

These results mirror the present study's human findings. Specifically, scarcity-adversity as indicated by cumulative scarcity-related risk indicators was inversely correlated with sensitive parenting, positively correlated with negative parenting, and parenting fully mediated the association of poverty-related risk with infant affect and cognitive abilities. While parenting is only one potential pathway of many by which poverty can influence child development (Evans, 2004), the current findings support the idea that altered parenting is at least one point of commonality for cross-species mammalian research. Thus, future rodent research with our scarcity-adversity rodent model may be leveraged for discovering specific mechanisms by which poverty influences development via altered parenting quality.

Interestingly, our rodent model impacted caregiving behaviors by exposing scarcity-adversity reared pups to increased maternal neglect (i.e. decreased time spent in nest, with pups, and nursing) as well as increased threat from the mother (i.e. increased rough transport and stepping on pups). This finding is in agreement with growing evidence from human research studies indicating that poverty shapes neurodevelopment by depriving the brain of vital input (e.g., maternal neglect, decreased cognitive stimulation, compromised nutrition), while increasing its exposure to negative input (e.g., heightened stress, environmental toxins, adverse parenting behaviors; for reviews see Blair & Raver, 2016; Johnson et al., 2016). Together, these findings are of particular interest due to current efforts to study early-life adversity along core dimensions of deprivation (the absence of expected positive input) versus threat (the presence of aversive input), which are argued to have distinct influences on neural development (McLaughlin & Sheridan, 2016; McLaughlin et al., 2014; Sheridan & McLaughlin, 2014). This orthogonalization is important for discerning distinct mechanisms by which threat versus deprivation influences neurobehavioral development. However, our findings suggest that animal models that study the interaction of deprivation and threat may be the most optimal for informing mechanisms by which poverty-related adversity affects development.

The foregoing stands in contrast to models of early-life adversity that prevailingly conceptualize adverse childhood experiences within a stress perspective focused on either deprivation or threat (Brett, Humphreys, Fleming, Kraemer, & Drury, 2015; Howell et al., 2017; McLaughlin et al., 2014; Szyf, Weaver, & Meaney, 2007). In fact, other laboratories are even using a rodent model of resource depletion similar to the one used for the present study, for the purpose of studying early-life stress or abuse (i.e. threat; Molet et al., 2016; Molet, Maras, Avishai-Eliner, & Baram, 2014; Blaze, Asok, & Roth, 2015). However, these models have not been leveraged for informing poverty-related research. To the best of our knowledge, we are the first to integrate an animal model alongside human developmental research related to poverty, in order to maximize translational validity of the animal model and allow for multiple levels of analyses. By leveraging the ecological validity of our rodent model, continued research may determine mechanisms by which the interaction of deprivation and threat shape infant neurobehavioral development.



## Scarcity-adversity and Developmental Competence

A major goal of this study was to explore cross-species developmental impacts as a result of scarcity-adversity in very early life, a vulnerable period due to heightened and rapid brain development (Perry et al., 2017). In order to assess infant outcomes related to social-emotional and cognitive developmental competence, we chose well-established species-specific indicators. For rodent pups, such indicators encompassed pup responses to maternal olfactory and somatosensory stimuli as measures of healthy, typical development. Rodent pups rely on chemosensory and somatosensory systems for survival in early-life, as infant auditory and visual systems only begin to emerge around PN15 (Ehret, 1976; Weber & Olsson, 2008). For example, maternal odor and somatosensory cues regulate mother-infant social behavior, nipple attachment, infant USVs in the presence of threat, and infant amygdala activity to permit maternal social buffering of pups' stress hormones (Al Ain et al., 2016; Hill & Almlil, 1981; Hofer et al., 1976; Hostinar, Sullivan & Gunnar, 2014; Moriceau & Sullivan, 2006; Oswalt & Wilson, 1979; Perry et al., 2016; Rainecki, Pickenhagen, et al., 2010; Singh & Tobach, 1975; Takahashi, 1992; Teicher & Blass, 1977).

In the present study, scarcity-adversity rearing produced profound neurobehavioral impacts on the developing infant rat pup's response to maternal olfactory and somatosensory stimuli. We interpret these effects as indicative of the extent to which maternal caregiving behaviors function to regulate and foster ongoing behavior and development. This view is consistent with Hofer's (1994) concept that maternal sensory cues function as "hidden regulators of development." For example, within this framework, maternal tactile stimulation regulates levels of growth hormone, and warmth from the mother regulates overall activity levels. Maternal odor is a particularly powerful regulator for pups; it evokes approach to the mother and permits nipple attachment, which is needed for pup survival (Perry et al., 2016). It is important to note that maternal odor-guided behaviors are dependent on pups first learning about the maternal odor, which occurs via their exposure and experiences with the maternal odor (beginning in the womb; Logan et al, 2012; Perry et al, 2016). That is, the infant rat pup's response to maternal odor is not innate. Young pups learn to approach maternal odor regardless of the quality of maternal care, presumably to ensure survival (Perry & Sullivan, 2014). However, our present results demonstrate that scarcity-adversity exposure in early-life impacts the strength of maternal odor's ability to regulate the pup's neurobehavioral responses. Importantly, the failure of maternal cues to optimally regulate infant pup behavior has been shown to precede social-emotional and cognitive deficits throughout development, including into adulthood (Al Ain et al., 2016; Perry & Sullivan, 2014; Perry et al., 2016; Rainecki, Moriceau et al., 2010; Rainecki et al., 2015; Rincón-Cortés & Sullivan, 2014; Sullivan & Perry, 2015; Walker et al., 2017). Furthermore, across species, maternal regulation of infant behavior and physiology has been proposed as vital to the early-life programming of brain areas underlying life-long emotionality and developmental competence, although the neural mechanisms by which this occurs remain to be elucidated (for reviews see Gee et al., 2014; Tottenham, 2015).

Our rodent research findings are similar to the present study's human findings demonstrating that scarcity-adversity is associated with altered early-life indicators of social-emotional and cognitive competence, namely infant affect during a mother-infant interaction test and

indices of infant attention and mental development. However, our rodent findings extend these human findings by providing experimental evidence that random assignment into scarcity-adversity conditions produces alterations in indicators of developmental competence as early as in infancy. Lastly, the comparable nature of these cross-species findings provides ecological support for the use of our rodent model for studying developmental aspects of poverty-related adversity exposure. Thus, our rodent model may be further leveraged to study potentially translationally-relevant neurobehavioral mechanisms by which scarcity-adversity influences development.

### Exploring Neural Phenotypes of Scarcity-adversity

Lastly, in search of candidate neural mechanisms by which scarcity-adversity may impact key brain areas related to later-life social-emotional and cognitive abilities, we assessed the effects of scarcity-adversity on infant brain activity in response to the primary regulatory cue of infant rat pup behavior: maternal odor. Using a measure of glucose uptake into brain cells ( $^{14}\text{C}$  2-DG), which is an indicator of neural activity, we found scarcity-adversity-induced functional connectivity differences between brain regions of interest in young pups in response to presentations of maternal odor. These regions of interest included brain areas previously identified in the human literature as impacted by early-life adversity, including the PFC and amygdala (for reviews see Gee et al., 2014; Tottenham, 2015 ). Functional connectivity is a sensitive indicator in both rodents and humans of circuit function, and disruptions (increases or decreases) of functional connectivity are associated with an increased risk for a variety of pathologies during development (Di Martino et al., 2013; Scheinost et al., 2017; Sheffield & Barch, 2016; Wilson, Peterson, Basavaraj, & Saito, 2011; Yan et al., 2017).

Here we found enhanced functional connectivity within the olfactory-limbic network, with a greater number of significantly connected brain areas in the scarcity-adversity group. Specifically, functional connectivity between the cortical region for odor processing (aPCX) and the PFC was statistically significantly greater in the scarcity-adversity group than the control group. The aPCX is critical for supporting mother-infant interactions and keeping pups within the nest, via an OB/aPCX-dependent circuit that supports strong odor preference learning (Landers & Sullivan, 2012; Moriceau, Roth, & Sullivan, 2010; Moriceau & Sullivan, 2004; Morrison, Fontaine, Harley, & Yuan, 2013). The PFC, which has been implicated in executive function and emotion regulation processes, shows protracted development continuing through adolescence (Hackman & Farah, 2009). Thus, it is unclear if the PFC is functionally developed and contributing to rat behavior at this young age (Andersen, Lyss, Dumont, & Teicher, 1999; Andersen, LeBlanc, & Lyss, 2001; Bertolino et al., 1997; Cunningham, Bhattacharyya, & Benes, 2002; Seminowicz et al., 2004; Sripanidkulchai, Sripanidkulchai, & Wyss, 2004; Sturrock, 1978; Zhang, 2004). Taken together, our findings suggest that the basic olfactory network that is important for maternal odor responses in infant pups has altered functional interactions with a brain area important for cognitive and emotional regulation across species (Landers & Sullivan, 2012; Tottenham, 2015).

Because data were collected only following maternal odor presentations, it is not possible to discern if the pattern of altered functional connectivity between aPCX and PFC observed in scarcity-adversity reared pups is specific to differences in processing maternal odor or differences in overall brain development and function. However, a recent study explored systems-level brain activation to odors of varying hedonic values (e.g., appetitive, aversive) relative to “no odor” control conditions across early development (Perry et al., 2016). Perry et al. (2016) found evidence that while aPCX activity is similarly elevated in response to both appetitive (i.e. maternal odor) and aversive odor (i.e. predator odor) stimuli relative to no odor controls, it is the functional connectivity between olfactory cortex (e.g., aPCX) and limbic/cortical brain regions (e.g., PFC, hippocampus, amygdala) that varies as a function of an odor’s hedonic value. Furthermore, this study demonstrated that the assignment of a hedonic value to an odor stimulus is highly plastic in early life, and is based on the pup’s prior experiences with the odor. For example, altering the smell of rat mothers’ natural odor via manipulation of their diet led to a devaluation of the natural maternal odor as assessed by behavioral indicators of odor preference as well as corresponding changes in olfactory cortex-limbic/cortical brain functional connectivity, following two weeks of rearing with these “newly scented” mothers. Therefore, one possible interpretation of the present study’s findings is that the altered functional connectivity between aPCX and limbic/cortical brain regions reflects a change in the hedonic value of maternal odor as a function of scarcity-adversity rearing, such that the odor becomes less appetitive, perhaps due to the pairing of maternal odor with negative caregiver-infant interactions in scarcity-adversity rearing conditions. Indeed, while scarcity-adversity reared pups still displayed a preference for maternal odor in the Y-maze test, they showed a significant reduction in approach to maternal odor relative to control reared pups, indicative of a reduced preference for maternal odor following scarcity-adversity rearing.

It should be noted, however, that these functional connectivity changes may also be reflective of overall differences in brain function following scarcity-adversity rearing, rather than being specific to maternal odor presentations. There has been extensive work on early-life experience and brain programming, which indicates that early-life adversity, and even prenatal adversity (Posner et al, 2017), alters the developmental trajectory of limbic areas such as the PFC and amygdala (for review see Callaghan et al, 2014). For example, a pattern of functional connectivity that is similar to the present findings was found in previously institutionalized youth who had faced caregiver adversity (Silvers et al., 2016). Specifically, previously institutionalized youth displayed significantly increased prefrontal-amygdala/hippocampal functional connectivity during an aversive learning task involving non-odor stimuli. Furthermore, increased prefrontal amygdala/hippocampal functional connectivity was associated with resilience against anxiety, suggesting that these neural changes may provide some adaptive advantages (Silvers et al, 2016). However, findings regarding the adaptive nature of adversity-induced changes in cortico-limbic structure and activity have been mixed. For example, poverty-related changes in the PFC have been associated with difficulties in executive functions, such as planning, attentional control, and impulse control following exposure to early-life adversity (Hackman & Farah, 2009). Understanding the causal role of adversity-induced PFC alterations, particularly as it relates to the emergence of psychopathologies versus resilience should be the focus of future mechanistic research.

Together, we suggest that the neural phenotype observed in our rodent model of scarcity-adversity is likely reflective of differences in the learned value of the maternal odor, combined with overall differences in the brain's developmental trajectory.

## Limitations and Future Directions

The present findings should be considered alongside the limitations of this study. Discerning the mechanisms that underlie links between poverty and child outcomes is difficult, due largely to technical limitations faced by researchers, particularly when dealing with infants and children. For example, participants of the Family Life Project were not randomly assigned to conditions of poverty in infancy. Therefore, the effects of scarcity-adversity environments versus "control" environments could not be clearly discerned. Thus, the observed correlational relationships between scarcity-adversity and the measured outcomes could have occurred due to a variable other than early-life experience. However, an advantage of the present study is the comparison of these human findings to an experimentally-controlled rodent model of scarcity-adversity. Our rodent model produced findings similar to our human findings, such that altered caregiving quality and infant outcomes occurred as a function of early-life experience. Furthermore, our rodent findings suggest that scarcity-adversity rearing may produce a learned devaluation of maternal odor and changes in the developmental trajectory of the brain. The extent to which findings from experimental manipulations with rodents generalize to human populations, however, is an open question, for animal models cannot fully encompass the rich complexity of the human condition. Taken together, our rodent findings provide experimental support to our human findings, and likewise, the human findings provide translational support for the continued use of this animal model to study the impact of poverty-related adversity on development. Thus, in this study and beyond, we promote the use of a bidirectional translational framework for developmental research, in which human and animal research is conducted in close conjunction to maximize translational comparisons and levels of analysis.

Continued use of this animal model of scarcity-adversity will be particularly beneficial for studying mechanisms by which scarcity-adversity impacts development. Indeed, by drawing on mechanistic findings from our animal model, we have identified next steps for human researchers. This includes, but is not limited to, identifying salient cues from parents that guide human infant behavior, exploring how poverty affects the infant neurobehavioral responses to those cues, and exploring the usefulness of early-life assessments of infant responses to parental cues in screening for at-risk children and families. Overall, the notion that learned regulatory cues from the caregiver might contribute to altered neurobehavioral development in the rodent presents a novel line of research to explore in human children.

Future rodent research efforts should also be made to develop additional animal models of poverty-related adversity, by going beyond manipulation of resource levels, by manipulating other poverty-related factors (e.g., air/water pollution, food quality). Furthermore, future rodent research should extend the results of the current findings by exploring cause-effect relationships between specific maternal behaviors and pup outcomes. For instance, developmental science has highlighted the bidirectional nature of parenting quality and children's outcome (Mills-Koonce, Garipey, et al., 2007; Mills-Koonce, Propper, et al.,

2007), which was partially supported in our follow-up analyses of our longitudinal human data indicating statistically significant mediation of infant positive affect and mental development on parenting quality. Disentangling the directionality of effects as it relates to parenting and infant outcomes in scarcity-adversity conditions, as well as corresponding neurobiological mechanisms, would be of great translational importance. Lastly, future experiments should also look at the neurobehavioral effects of extending scarcity-adversity exposure beyond infancy, to explore effects of chronic exposure across the lifespan.

## Conclusion

In conclusion, the present results provide species-specific process similarities between humans and rodents in regards to relationships among scarcity-adversity, parenting, and infant development. Thus, we provide a rodent protocol with translational validity which allows for assessment of causal mechanisms related to poverty, parenting quality, and development. Additionally, our rodent model supports that scarcity-related adversity lays at the intersection of exposure to both deprivation and threat. This finding offers important direction regarding how to operationalize poverty for research purposes, and will help direct how future interventions should be constructed to address exposure to both deprivation and threat for low SES populations. Lastly, our rodent model revealed novel evidence for a neural phenotype in response to the caregiver's sensory cues following scarcity-adversity rearing, which could be relevant to the potential development of subsequent psychopathologies. As with all animal models, we do not purport that our animal model encompasses the complexity of poverty in humans. Rather, we highlight our model's ability to provide strong experimental control and manipulation of variables of interest, which allows for determination of cause-effect relationships between specific variables, and their corresponding neurobiological mechanisms. Furthermore, we promote a bidirectional translational approach that leverages the strengths of both human and animal research. In doing so, we encourage increased cross-disciplinary collaboration between neuroscientists and developmental psychologists, in order to enable the most rapid advancement of specific and powerful interventions to prevent and remediate potential effects of poverty on child development.

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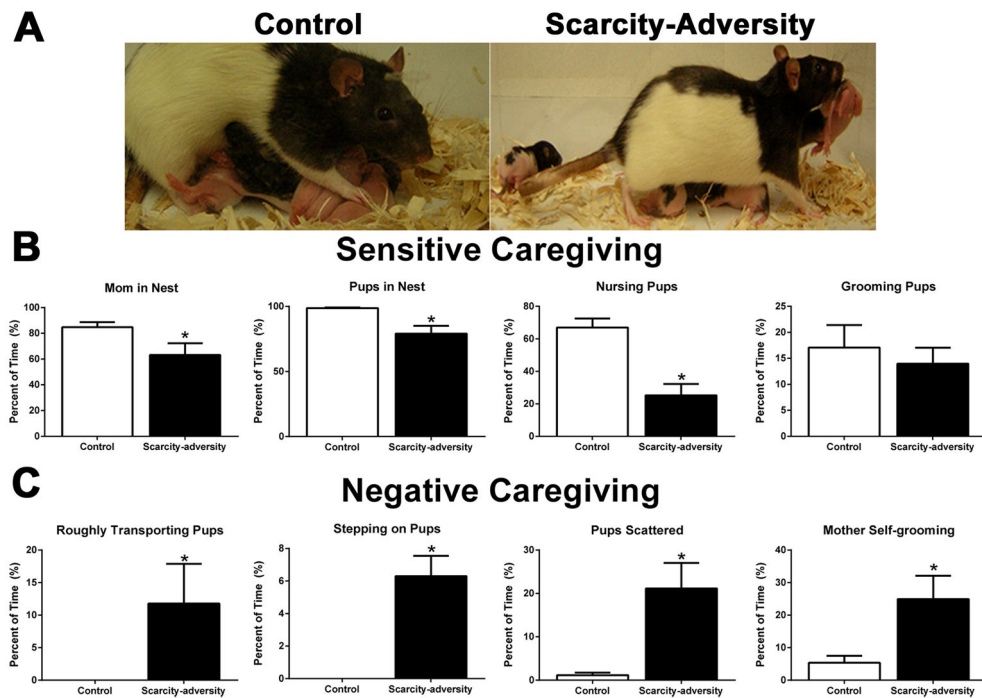
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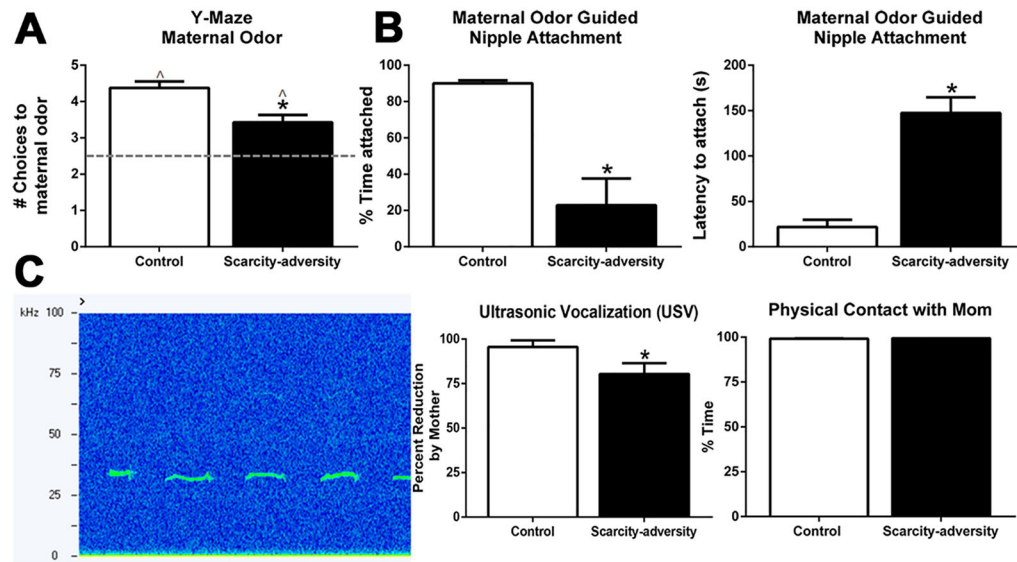
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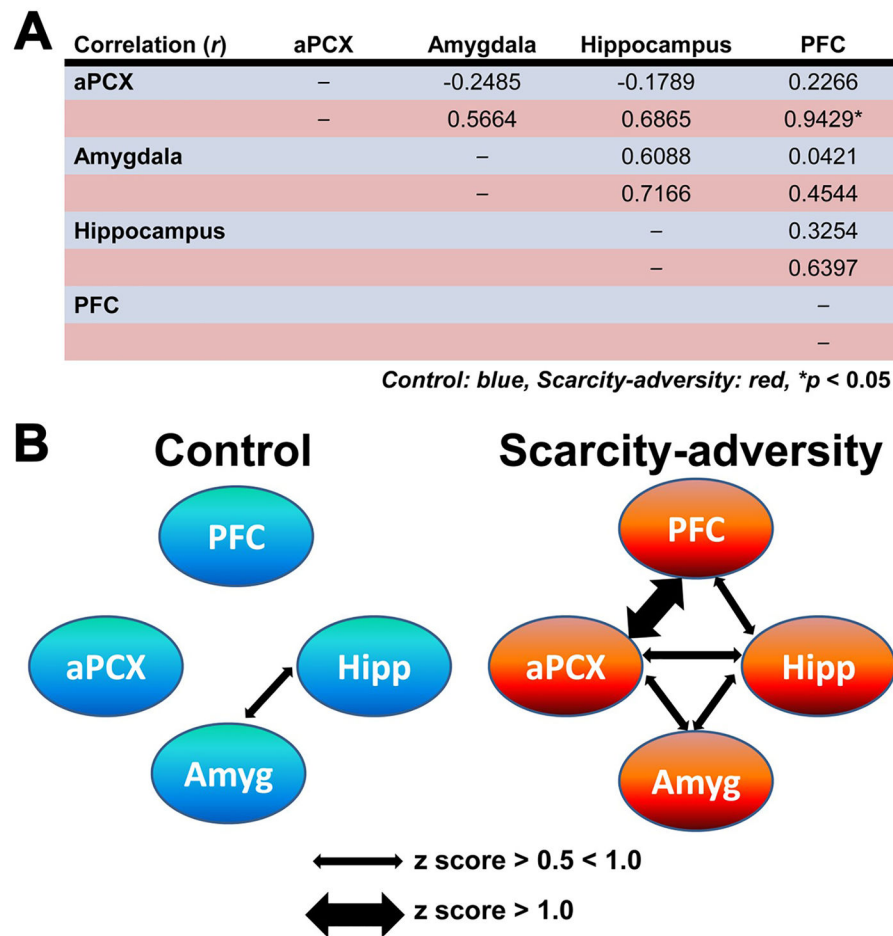
**Figure 1.**

A rodent model of scarcity-adversity decreased sensitive caregiving and increased negative caregiving. A) Using a rodent model, litters were randomly assigned to control conditions (left), with ample bedding needed by the mother for nest-building, or to scarcity-adversity conditions (right), where mothers were provided with insufficient nest-building materials. These environmental conditions directly influenced maternal behavior. For example, in the image on the left, a mother is shown nursing her pups in an arch-back position, which applies the least amount of pressure on her pups. In the image on the right, a mother is depicted stepping on her pups while carrying a pup in her mouth by its limb. B) Scarcity-adversity conditions caused a decrease in multiple measures of sensitive caregiving, relative to control conditions, as indicated by the percent of time mothers spend in the nest with their pups, nursing their pups, as well as the percent of time all pups are present in the nest ( $n = 10-11/\text{group}$ ,  $*p < 0.05$ ). C) Scarcity-adversity conditions caused an increase in measures of negative caregiving, relative to control conditions. These measures include the percent of time mothers spent roughly transporting their pups (i.e. carrying pup by limb), stepping on pups, and self-grooming, as well as the percent of time pups were scattered throughout the home cage ( $n = 10-11/\text{group}$ ,  $*p < 0.05$ ).



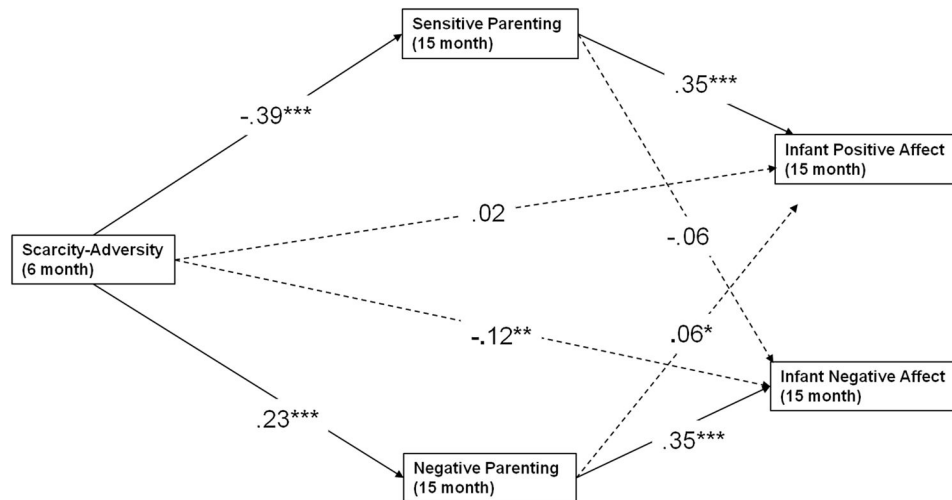
**Figure 2.**

Scarcity-adversity rearing reduced maternal regulation of infant behavior. A) Maternal odor regulates infant proximity to the caregiver to guide attachment formation via odor-preference learning. Following scarcity-adversity rearing, pups showed a significant decrease in choices toward the maternal odor in a Y-maze test ( $n = 8/\text{group}$ ,  $*p < 0.05$ ). However, both control and scarcity-adversity reared pups displayed a preference to maternal odor, as indicated by choices toward the odor at levels significantly greater than chance ( $^{\wedge}p < 0.05$ ). B) Infant rat pups require maternal odor to nipple attach to the mother. Pups reared in scarcity-adversity conditions showed a significant decrease in the percent of time spent attached to the nipple of an anesthetized mother during a nipple attachment test. Furthermore, scarcity-adversity reared pups showed a significant increase in the latency to attach to a nipple during the nipple attachment test ( $n = 8/\text{group}$ ,  $*p < 0.05$ ). C) Maternal presence regulates infant reactivity in times of distress. Infant rat pups emit USVs (30–60kHz) when socially isolated, as indicated by the representative spectrogram on the left. Following social isolation, presenting control pups with an anesthetized dam led to almost a complete reduction of USVs. Presenting scarcity-adversity reared pups with an anesthetized dam led to a significantly decreased reduction in USVs, relative to control pups (middle,  $n = 6/\text{group}$ ,  $*p < 0.05$ ). In both rearing conditions, pups remained in physical contact with the anesthetized dam during the entire duration of the USV recording (right).

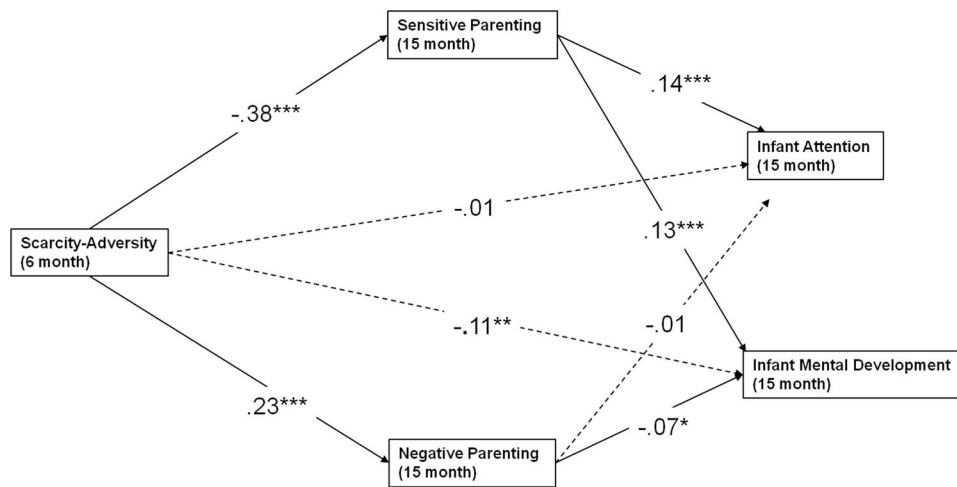


**Figure 3.** Scarcity-adversity rearing increases olfactory-limbic network functional connectivity in response to maternal odor. A) Pearson correlation coefficients (*r*) were calculated from relative 2-DG uptake in brain regions of interest and displayed here in blue rows for control reared animals and red rows for scarcity-adversity reared animals. Scarcity-adversity reared pups showed overall greater functional connectivity, with a significant increase in functional connectivity between the anterior piriform cortex (aPCX) and prefrontal cortex (PFC), relative to control reared pups (*n* = 7–8/group, \*denotes significant difference between groups, *p* < 0.05). B) Within each rearing condition, functional connectivity between the aPCX, PFC, hippocampus (Hipp), and amygdala (Amyg) are visually depicted here, based on *z* score values calculated from *r*. Normally weighted arrows indicate a *z* score value between 0.5 and 1.0. Bolded arrows indicate stronger functional connectivity between brain regions, with a *z* score greater than 1.0.





**Figure 4.** Multiple mediation model exploring mediation of parenting quality on infant affect. The statistically significant directional paths are depicted here (bolded) with standardized coefficients ( $\beta$ ). Sensitive parenting mediates the predictive role of early-life scarcity-adversity exposure for infant positive affect, while negative parenting mediates the predictive role of early-life scarcity-adversity exposure for infant negative affect. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.0001$ .



**Figure 5.**

Multiple mediation model exploring mediation of parenting quality on early-life measures of cognitive abilities. The statistically significant directional paths are depicted here (bolded) with standardized coefficients ( $\beta$ ). Sensitive parenting mediates the predictive role of early-life scarcity-adversity exposure for infant attention and mental development, while negative parenting mediates the predictive role of early-life scarcity-adversity exposure for infant mental development. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.0001$ .

**Table 1**

Rodent caregiving behaviors.

	<b>Behavior</b>	<b>Description</b>
<i>Sensitive caregiving</i>	Mom in nest	Mother is in physical contact with one or more pups in the nest.
	Pups in nest	All pups are huddled together in the home cage.
	Nursing pups	At least one pup is nipple attached to the mother.
	Grooming pups	Mother is licking and grooming at least one pup. This includes licking of the pup's paws, body, head, genitals and/or tail.
<i>Negative caregiving</i>	Roughly transporting pups	Mother is carrying pup by any body part other than the nape of neck (i.e hind limb).
	Stepping on pups	Mother steps on at least one pup when navigating the home cage.
	Pups scattered	A quarter of the litter or more (3+ pups) is located outside of the nest.
	Mother self-grooming	Mother is licking and grooming herself. This includes face wiping and/or licking of paws, body, genitals or tail.

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**Table 2**

Demographics and descriptive statistics for all study variables.

<b>Variable</b>	<b>Mean/%</b>	<b>SD</b>	<b>Minimum</b>	<b>Maximum</b>	<b>N</b>
Male (infant)	49.10%				635
Caucasian	57.00%				736
African American	43.00%				556
Resides in North Carolina	59.80%				773
Primary Caregiver Age (6 month)	26.37	6.12	14.70	69.91	1195
Infant Age (6 month)	0.64	0.12	0.42	1.28	1204
Scarcity-Adversity (6 month)	0.005	0.64	-2.51	2.17	1204
Income-to-Needs Ratio	1.92	1.70	0.00	16.49	1102
Economic Strain	11.57	3.66	1.00	22.00	1194
Maternal Education	14.44	2.82	6.00	22.00	1204
Consistent Partnership	57.1%				1204
Neighborhood Safety	2.99	0.58	1.00	4.00	1195
Household Density	0.88	0.36	0.36	3.33	1092
Sensitive Parenting (15 month)	2.79	0.80	1.00	5.00	1108
Negative Parenting (15 month)	2.27	0.69	1.00	5.00	1108
Infant Positive Affect (15 month)	2.88	0.87	1.00	5.00	1108
Infant Negative Affect (15 month)	1.92	1.06	1.00	5.00	1108
Infant Mental Development (15 month)	96.37	10.16	66.00	122.00	1081
Infant Attention (15 month)	17.91	2.35	11.00	23.50	1130

Table 3

Correlations among analysis variables.

	1 SA	2 SP	3 NP	4 CP	5 CN	6 CM	7 CA
1 Scarcity-adversity (6 month)	–						
2 Sensitive Parenting (15 month)	–0.50 <sup>***</sup>	–					
3 Negative Parenting (15 month)	0.32 <sup>***</sup>	–0.31 <sup>***</sup>	–				
4 Infant Positive Affect (15 month)	–0.13 <sup>***</sup>	0.31 <sup>***</sup>	–0.03	–			
5 Infant Negative Affect (15 month)	–0.04	–0.06	0.29 <sup>***</sup>	–0.11 <sup>**</sup>	–		
6 Infant Mental Development (15 month)	–0.24 <sup>***</sup>	0.25 <sup>***</sup>	–0.19 <sup>***</sup>	0.07 <sup>*</sup>	–0.01	–	
7 Infant Attention (15 month)	–0.07 <sup>*</sup>	0.12 <sup>***</sup>	–0.03	0.18 <sup>***</sup>	–0.22 <sup>***</sup>	0.13 <sup>***</sup>	–

*Note.*<sup>\*\*\*</sup>  $p < 0.01$ ,<sup>\*</sup>  $p < 0.05$

Mediation analysis: Direct and indirect effects of poverty-related scarcity-adversity on infant affect in caregiver's presence.

**Table 4**

Predictor	Dependent Variable					
	Infant Positive Affect			Infant Negative Affect		
	B	SE	$\beta$	B	SE	$\beta$
Scarcity-Adversity (Direct Effect)	0.03	0.05	0.02	-0.19	0.06**	-0.12
Specific Indirect Effects						
SA → Sensitive Parenting	-0.19	0.02***	-0.14	0.04	0.02	0.02
SA → Negative Parenting	0.02	0.01	0.01	0.13	0.02***	0.08

Note. B = unstandardized coefficient; SE = standard error;  $\beta$  = standardized coefficient; SA = Scarcity-Adversity;

\*\*  $p < 0.01$ ;

\*\*\*  $p < 0.0001$ .

Mediation analysis: Direct and indirect effects of poverty-related scarcity-adversity on infant cognitive abilities.

**Table 5**

Predictor	Dependent Variable					
	Infant Mental Development		Infant Attention			
	B	SE	$\beta$	SE	$\beta$	
Scarcity-Adversity (Direct Effect)	-1.69	0.58**	-0.11	-0.05	0.14	-0.01
Specific Indirect Effects						
SA → Sensitive Parenting	-0.79	0.23***	-0.05	-0.20	0.05***	-0.05
SA → Negative Parenting	-0.25	0.12*	-0.02	-0.01	0.03	-0.002

Note. B = unstandardized coefficient; SE = standard error;  $\beta$  = standardized coefficient; SA = Scarcity-Adversity;

\*\*  $p < 0.01$ ;

\*\*\*  $p < 0.0001$ .