Behavioural Brain Research 226 (2012) 345–350

Contents lists available at SciVerse ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Short communication

Functional specificity in the modulation of novelty exposure effects by reliability of maternal care

Bethany C. Reeb-Sutherland[a,1], Akaysha C. Tang[a,b,*]

[a] Department of Psychology, University of New Mexico, Albuquerque, NM 87131, United States
[b] Department of Neurosciences, University of New Mexico, Albuquerque, NM 87131, United States

ARTICLE INFO

Article history:
Received 24 June 2011
Received in revised form 28 August 2011
Accepted 31 August 2011
Available online 6 September 2011

Keywords:
Maternal care
Maternal mediation
Maternal modulation
Post-natal handling
Neonatal handling
Neonatal novelty exposure
Early experience
Open field
Emotionality
Morris water task
Watermaze
Social recognition memory

ABSTRACT

Using the within-litter neonatal novelty exposure procedure, we manipulated newborn pups' environmental novelty independently from natural variations in maternal care. To better translate animal models to human development studies, we introduce a measure for maternal care reliability. We examined how this reliability modulates novelty-exposure-induced effects on offspring cognitive, social, and emotional development and show that maternal care reliability acts in a function-specific manner. We discuss our results within the framework of a maternal reliability-based modulation model.

The mother plays an important role during infant development since she is typically the main source of necessary nutrients and physical security [1,2]. Scientific evidence based on animal studies supporting the mother's role in offspring's development comes in several basic forms. In the most popular form, infants are shown to suffer negative physical and psychological consequences when they are deprived of maternal presence for a prolonged duration [3–6]. In another, infants are shown to experience both negative and positive consequences when non-maternal aspects of the environment are directly manipulated along with side effects on their mothers, including a change in the quantity of maternal care [7–14]. The latter form of studies produced many correlated changes in the infants and the mothers [see summary provide in [13]] which confirms to the common sense model that more maternal care is generally better for the developing infant but does not necessarily support a causal relation between variations in the quantity of maternal care and offspring outcome measures. This presumed causal relation between maternal care quantity and offspring functional outcomes has been challenged by a third type of studies where the mothers' environment was directly manipulated and the offspring maternal environment was indirectly affected via an influence on the mother [15–18]. These studies provided evidence for a dissociation between maternal care quantity and offspring outcome measures, joining others in questioning the common sense model regarding the role of maternal care [19–24].

While animal studies have continued to primarily and almost exclusively focus on the quantity of maternal care received by offspring [11–13,15–18], one of the focuses in human infant development studies has been on maternal care quality, particularly consistency in maternal care, known to influence attachment security [1,25]. For example, it is maternal care sensitivity and consistency, i.e. reliability, but not the average amount of care that has predictive power for infant development [26–29], particularly when the behavioral outcomes were observed during times of infant distress [30,31]. Therefore, we speculate that in the rat, maternal care consistency or reliability may also play a role in offspring development. The recent interest in developing

* Corresponding author at: University of New Mexico, Albuquerque, NM 87131, United States. Tel.: +1 505 610 9077; fax: +1 505 277 1394.
E-mail address: akaysha@unm.edu (A.C. Tang).
URL: http://atlab.unm.edu (A.C. Tang).
[1] Present address: Department of Human Development, Child Development Lab, University of Maryland, College Park, MD 20742, United States.

0166-4328/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbr.2011.08.047

rodent models for understanding early experience effects on human development [32] particularly motivates us to explore this hypothesis.

To this end, we developed a novel measure for characterizing maternal care reliability, which we call post-novelty-exposure maternal care (PNE care) [33]. The essence of this new measure is its focus on maternal care immediately after the pups are exposed to a novel non-home environment and on quantification that captures day-to-day consistency or reliability of maternal care. In principle, compared to round-the-clock maternal care observations, this PNE care measure should better characterize how the mother copes with her pups' and her own stress following an environmental stressor, thus potentially offering a more sensitive measure for capturing maternal individual differences in care. This choice over the popular round-the-clock observation is supported by the finding that little variability in average maternal care based on such round-the-clock observation was observed in the non-disturbed home cage [13].

Independent from the empirically demonstrated predictive power of a reliability-based measure in human infant studies [1,25,34] and in our own initial animal study [33], it has been hypothesized [23] that if the pattern of maternal care over time is consistent or reliable, then the home environment for the developing infant will be more predictable. Such an environment may serve to facilitate the recovery of any physiological and psychological stress response, evoked by the novelty of the non-home environment, upon the infant's return to the home environment. Conversely, if the pattern of maternal care is unreliable, therefore unpredictable, then the infant that experiences the same non-home environment may have a longer stress response recovery time. By modulating the infants' early life responses to each of the cumulative stressful events, maternal care reliability may serve to shape the offspring's stress response profile. Initial evidence appears to support this maternal care reliability-based modulation hypothesis because greater reliability in day-to-day PNE care received by the offspring led to greater neonatal novelty-induced enhancement of plasticity in the adult offspring's corticosterone stress response [33].

Having established this initial evidence for the modulation of novelty effects on offspring stress *physiology* by maternal care reliability does not necessarily mean that this modulatory role can be automatically generalized to offspring *behavior*. Furthermore, demonstration of maternal modulation of environmental impact on a behavioral measure of a specific brain function, for example, spatial memory, does not necessarily mean that a similar modulatory role applies to another functional measure, such as social memory. Here we hypothesized that maternal care reliability-based modulation of early experience effects on the offspring may show functional specificity. Demonstration of functional specificity would serve to stress the currently understated need for an active avoidance of the over-generalization of a developmental finding, based on the evaluation of a single or even a few behavioral or physiological endpoint measures, to a multitude of brain and behavioral functions.

In a recent report on one part of a large longitudinal study, we documented that novelty exposure of infant pups during the first weeks of life leads to enhanced spatial working memory performance, enhanced 24-h social memory performance, increased open field disinhibition to novelty, and reduced aggression independent of preferential maternal care differences [35]. Here we conducted a follow-up study of the same cohort of animals in an attempt to answer three additional and qualitatively distinctive questions: (1) How does PNE care affect litter-to-litter variations in novelty effect? (2) Does the relation between PNE care and offspring functional measures differ between Novel and Home offspring? (3) Do these relations hold across different functional measures?

In a single cohort of animals, neonatal novelty exposure (postnatal day, PND, 1–21), observation of subsequent maternal care (PND1–10), and assessment of offspring emotional reactivity to a novel environment (PND24), spatial (PND32) and social memory (PND100), and aggression (PND100) were carried out (Fig. 1a). Twenty-two litters born of Long–Evans hooded dams (Harlan, Indianapolis, IN) were each culled to eight pups shortly after birth, keeping as many males as possible. A 12-h light/dark cycle was used with lights on at 0800 and food and water were *ad libitum*. Pups were weaned on postnatal day (PND) 21 and housed separately in translucent plastic cages (51 cm × 25 cm × 22 cm). Only male offspring ($N = 106$) were used in this study. All experimental procedures were approved by the Institutional Animal Care and Use Committee at the University of New Mexico.

Neonatal novelty exposure [23,36–38] and the subsequent post-novelty-exposure maternal care observation (PNE care) took place daily from PND1–21 between 10:00 and 15:00 h (Fig. 1b). Two halves of each litter was pseudo-randomly assigned to the Novel and Home groups respectively (split-litter design). The dam was first removed from the home cage and then the Novel pups were placed in a new cage (30 cm × 19 cm × 13 cm) lined with fresh bedding for 3-min daily while the Home pups remained in the home cage. Following the 3-min exposure, all pups were reunited in the home cage and then the dam was returned to the litter. Novel and Home pups received a matching amount of experimenter contact at approximately the same time.

Consistency or reliability of post-novelty-exposure maternal care from day to day was characterized based on maternal care behavior observed within the 10 min immediately after each daily neonatal novelty exposure on PND 1-10. After the initial retrieval of pups into a nesting area upon dam-pup reunion, which has been analyzed elsewhere [35], the licking behavior was the only frequently occurring pup-directed caregiving behavior observed and nursing of the pups was rarely observed during this initial PNE period. We therefore focused the PNE care analysis on licking behavior. Licking-based maternal care was recorded without reference to individual pups because reliable identification of individual pups during maternal licking via daily re-marking [13] could not be achieved due to the dams' tendency to lick off sufficient markings necessary for identification. Video-recorded licking behavior was coded offline and for each 5-s epoch, an occurrence of one was counted if licking was present anytime during the epoch. Sound inter-rater reliability between two independent coders ($r = .80$) was obtained on 10% of the data. Observations of litters took place sequentially between 10:00 and 15:00 h and upon examination, we found no statistically significant time of day effects on any of the measures. To index post-novelty-exposure (PNE) maternal care reliability, we provided a measure we call maternal care variability (Var) which is inversely related to maternal care reliability—the more variable the day-to-day PNE care is, the less reliable the maternal care. As all dams displayed a systematic increasing trend in licking due to habituation to the novelty exposure procedure across the observation days, we first removed this trend from the data and then used the standard deviations of the residuals as an index for maternal care variability as detailed in [33].

Offspring's emotional reactivity in a novel environment was characterized by their initial changes in open field activity [35,39]. On PND24, animals were exposed to a novel open field (60 cm × 60 cm × 20 cm) during eight 20-s trials. Activity level was coded and defined as the number of squares traversed. To quantify the rapid initial change in behavioral inhibition upon entering the open field, we used a disinhibition score (Disinh), defined as the difference in open field activity between Trial 2 and Trial 1 [T2 − T1; [35,39]]. Although unconventional, this measure is more sensitive than activity measures over more trials or trials of longer durations, to relatively subtle early life environmental manipulations,

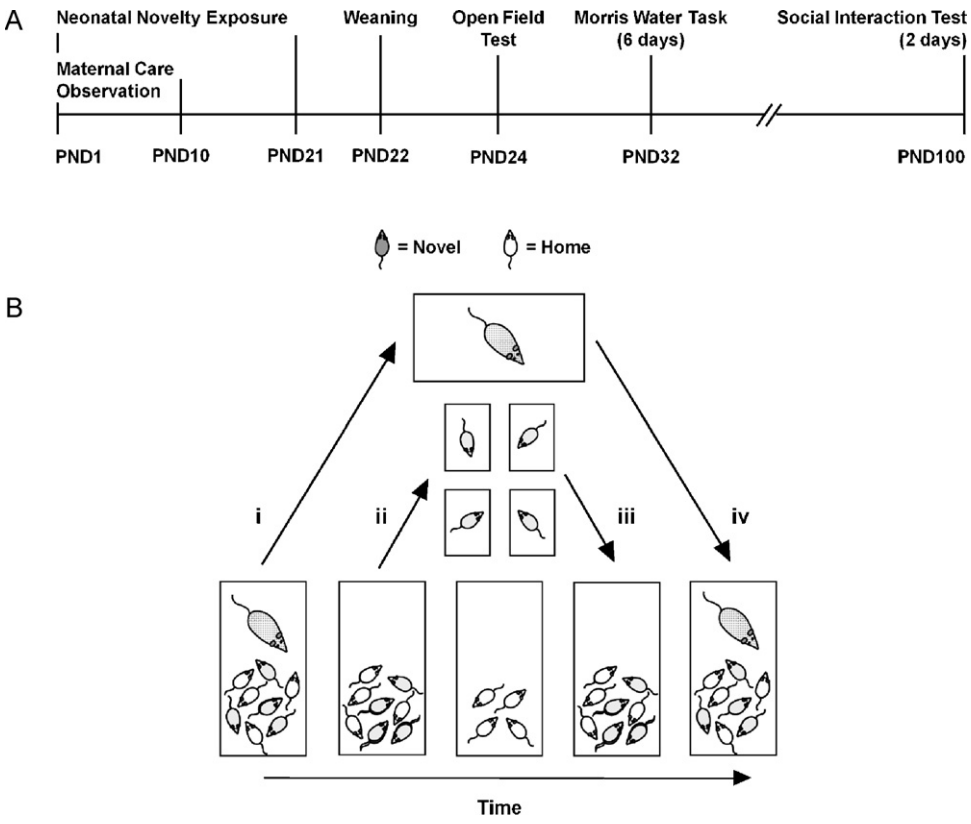

Fig. 1. Experimental methods. (A) Timeline. (B) Sequential steps in neonatal novelty exposure using a split-litter design. For each litter: (i) Removal of dam from home cage. (ii) Transfer of Novel pups (solid color) to individual non-home cages (small rectangles). (iii) Return of Novel pups to home cage after a 3-min exposure to non-home cages. (iv) Return of the dam to the entire litter in the home cage.

such as the 3 min daily trip away from the home cage, in comparison to neonatal handling which consists of additional maternal separation, maternal stress, experimenter handling, in addition to the time away from home cage [40,41].

Offspring's spatial working memory was characterized by their performance in the working memory version of the Morris water task [42–45]. On PND32–38, rats were trained to escape cold water (21 °C) by finding a square platform (15 cm × 15 cm) hidden underneath the surface of the water in a circular tank (170 cm diameter). Platform location was changed daily beginning on Day 2 of testing therefore requiring the animal to use its working memory capacity to guide the animal's behavior in reaching the new platform location using recently updated information. Working memory was indexed by a normalized one-trial learning score [Norm_OTL; [35,46]] defined as the difference in latency to reach the platform between Trial 1 and Trial 2 normalized by Trial 1 latency (Norm_OTL = (T1 − T2)/T1 × 100). Based on previous findings, such a one-trial learning measure is particularly sensitive to the neonatal novelty manipulation on the first of these testing days that require working memory, i.e. testing Day 2 [35,46]. Lack of difference in asymptotic performance reached over the additional days of testing served to confirm that the two groups did not differ in their motor, sensory, and motivational functions.

Offspring's social recognition memory was characterized during several sessions of social dyadic interactions using a habituation paradigm [37,47]. Offspring's aggression was characterized by making observations of biting behavior during these interaction sessions [35]. On PND100, in a neutral testing cage, social investigation was observed between non-sibling age- and weight-matched Novel-Home pairs on two consecutive days during four 5-min sessions, three sessions on day 1 and one session on day 2 [37]. Each session was divided into sixty 5-s epochs and an occurrence of one was counted if the social investigation behavior was present any time during the epoch. Frequency of social investigation and biting was recorded for each session. Twenty-four-hour social recognition memory was indexed by a long-term habituation (LTH) score defined as (Day 1 S1 − Day 2 S1)/Day 1 S1 × 100.

To examine how PNE care may differentially influence previously reported novelty exposure effects across multiple psychological functions [35], repeated measures analysis of covariance (ANCOVA) was performed with type of behavioral outcome measure (Type) and novelty exposure treatment (Novelty) as within factors, scores on the four behavioral measures as dependent variables, and two PNE care measures of amount (Avg) and reliability (Var) used as separate covariates. Litter average scores for Disinh, Norm_OTL, LTH, and Biting were computed separately for Novel and Home rats. Scores were standardized (z-scores) within each measure type. Prior to analysis, raw data was examined for violation of normality and equal variance assumptions. If detected, outliers were removed prior to computing litter averages. One Home and 2 Novel rats were removed from Disinh, 4 Home and 2 Novel rats were removed from Norm_OTL, 1 Home rat was removed from LTH, and 2 Novel rats were removed from Biting resulting in the removal 2 litters from the current data set.

In testing the functional specificity hypothesis of maternal *modulation* by the reliability of care, we found a significant Novelty × Type × Var interaction effect ($F(1,18) = 5.718$, $p = .028$, $f = .564$)) showing that maternal care variability can influence the novelty exposure effect differently depending on the specific function being examined. In the case of LTH (Fig. 2a), novelty-induced enhancement in social recognition memory was observed when PNE care is reliable (low variability), but not when care is unreliable (high variability), indicated by the two regression lines converging on the right. In contrast, in the case of Biting (Fig. 2b),

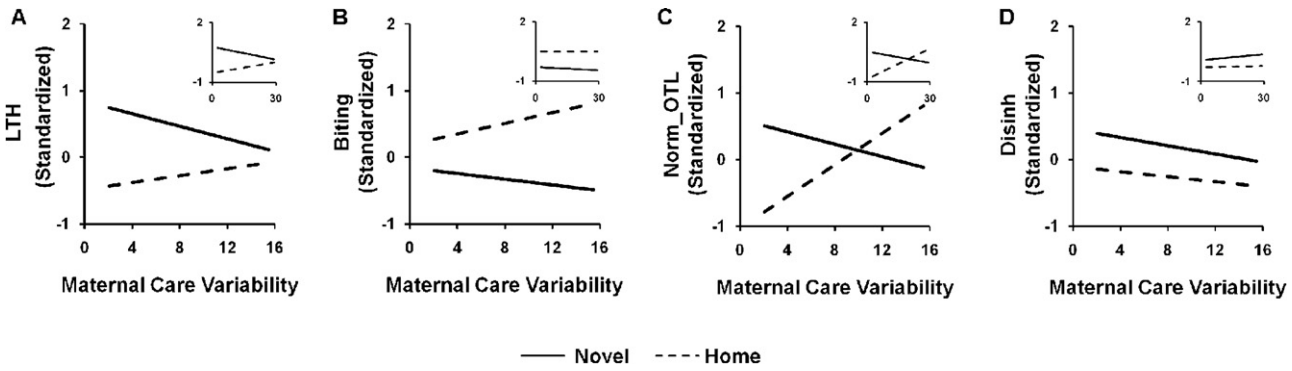

Fig. 2. Modulation of novelty exposure effects on multiple behavioral outcomes is function-specific as indicated by the distinct patterns across the four measures (A–D). Main graphs: maternal care variability (Var) as a predictor; insets: maternal care quantity (Avg) as a predictor. Home: dashed line; Novel: solid line. (A) 24-h social recognition memory (LTH); (B) aggression (Biting); (C) spatial working memory (Norm_OTL); (D) disinhibition to novelty (Disinh). Novelty effect is indicated by the vertical distance between the trend lines for Novel and Home offspring.

novelty-induced reduction in aggression was observed when PNE care is unreliable, but not when care is reliable, indicated by the two regression lines converging on the left. In the case of Norm_OTL (Fig. 2c), novelty-induced enhancement in spatial working memory was observed when PNE care is reliable, but impaired when care is unreliable, indicated by the two regression lines converging in the middle. Lastly, in the case of Disinh (Fig. 2d), novelty-induced enhancement in disinhibition is independent from PNE care variability indicated by the two parallel regression lines. We suspect that this lack of sensitivity to maternal care variability may be due to the low stress level involved in open field exposure in comparison to the stress levels involved during social encounter with a novel conspecific or during the spatial memory tests conducted in cold water.

Follow-up 2-way ANCOVAs were computed separately for each of the four types of behavioral measures. A significant interaction effect between novelty exposure and maternal care variability on Norm_OTL ($F(1,18) = 4.377$, $p = .045$; $f = .493$; Fig. 2c) shows that when maternal care is reliable (low variability), novelty exposure increases one-trial learning (left side: solid line over the dashed lined) and when maternal care is unreliable, the same novelty exposure treatment decreases one-trial learning (right side: dashed line over the solid line). This result indicates that both the direction and magnitude of novelty exposure effects are influenced by maternal care reliability. In contrast, similar 2-way ANCOVAs for the other outcome measures were not significant ($ps > .20$). Together, the above findings support the functional-specificity hypothesis of maternal modulation showing that maternal modulation demonstrated for one function does not necessarily generalize to another. Therefore, caution should be exercised when making general statements regarding the mother's role in offspring development.

To examine whether the average amount of PNE maternal care can similarly influence novelty exposure effects, we performed the same ANCOVA with average PNE maternal care (Avg) as the covariate. As average maternal care and variability are positively correlated as shown in a previous [33] as well as the present study ($r_{20} = .824$, $p < .001$), it is not surprising that we found a marginally significant Novelty × Type × Avg interaction effect ($F(1,18) = 4.288$, $p = .053$, $f = .488$). Follow-up 2-way ANCOVAs revealed a marginally significant interaction effect between novelty exposure and average amount of maternal care on Norm_OTL ($F(1,18) = 3.086$, $p = .090$, $f = .414$). Most interesting is the direction of this effect—*high* average care was associated with a novelty exposure-induced *reduction* in one-trial learning (right side of Fig. 2c), i.e. higher average PNE care is associated with a negative effect of novelty exposure (inset: solid line below dashed line) and *low* average PNE care is associated with a novelty-induced *increase* in one-trial learning (left side of Fig. 2c inset: dashed line below solid line). Therefore, there is no evidence that high average PNE care is associated with any positive novelty exposure effects on offspring social, cognitive, and emotional function.

Taking advantage of the within-litter design used in the present study, we are able to show separately for the Novel and Home offspring, how average PNE care (Avg) relates to spatial memory (Fig. 2c inset). Interestingly, only among the Home rats, average amount of maternal care is positively correlated (though marginal) with spatial working memory performance ($r_{20} = .436$, $p = .055$, Fig. 2c inset, dashed line). Therefore, our finding here using a *working* memory measure is consistent with Meaney and colleagues' finding using a spatial *reference* memory measure [48]—both showing a positive association between more maternal care and better memory performance. It could be safely concluded that at least infants raised in a relatively impoverished environment lacking environmental novelty can do better in spatial memory tests if their mothers supply a greater amount of care.

Particularly noteworthy are the conditions under which this positive association holds and ceases to exist. When siblings experienced little novelty (Home rats), maternal care measures are found to correlate positively with those sibling's spatial memory. In contrast, when siblings are exposed to brief exposures of environmental novelty systematically (3 min/day for the first 3 weeks), such influence by maternal care no longer holds (Fig. 2c inset, solid line). Therefore, Novel offspring's spatial memory function appeared to have become independent from the influence of maternal care shortly after weaning while the Home rats' spatial memory function appears to remain under such maternal influence. These results revealed that the association between maternal care quantity and offspring spatial memory function has limited external validity because it fails to generalize when the pups' neonatal life deviated from the impoverished rearing environment by a mere 3 min daily time away from the home cage prior to weaning.

The present data set further revealed a paradoxical pattern in the influence of maternal care reliability on the home-staying rats—*less reliable* (more variable) maternal care predicted *better* spatial memory performance ($r_{20} = .488$, $p = .029$, Fig. 2c, dashed line, right-end of line). That is, if a pup is reared with little environmental novelty as in the case of the Home rats, then offspring's spatial working memory performance appeared to benefit from high maternal care variability. Such a paradoxical finding can be explained by the stress inoculation hypothesis [22,49] which states that early exposure to small amounts of stress can lead to positive developmental outcomes. In the absence of exposure to salient novelty in the environment, variations in maternal care may well be the only such source of stress activation needed for positive developmental

outcomes. However, as maternal care variability and average quantity are positively correlated, we are unable to discriminate between these explanations given the design of the current study. Based on the stress inoculation hypothesis, we suspect that the aforementioned correlation between average maternal care and offspring spatial memory performance among the Home rats is actually an epiphenomenon and that the true cause of Home rats' individual difference in spatial memory performance is maternal care variability.

To summarize, we found that: (1) the precise pattern of influence of maternal care reliability on early novelty exposure effects was function-specific, with different functions showing different patterns of maternal modulation; (2) for spatial working memory, high *reliability* in maternal care set the condition for novelty-induced enhancement while low reliability set the condition for novelty-induced impairment; (3) a high *quantity* of maternal care was, paradoxically, associated with novelty-induced impairment suggesting that increased maternal care may *not necessarily* facilitate offspring development; and (4) among only the subset of offspring with little or no other source of stress activation, low maternal care *reliability* was, also paradoxically, associated with improved spatial memory performance. Together these results demonstrate that the role of the mother in offspring development is complex and cannot be captured by a simple common sense model of "more is better", and instead, temporal pattern in maternal care, specifically, maternal care reliability plays an important role. Furthermore, such maternal care reliability-based modulation is function-specific. Similar to the role of maternal self-stress regulation [38,50], maternal care reliability can create distinct family-specific experience even though the initial trigger, i.e. the novelty exposure, is the same.

To explain the current set of findings, we adopt a maternal modulation-based theoretical framework [23] that assumes that the programming of offspring stress regulation requires an immunizing dose of stress that activates the stress response system [22,49] and that being a potential source of stress, maternal variables can set the context for the same environmental stimulation to produce differential stress activation and post-stress recovery [33,38,50–55]. Within this framework, systematic exposures to novelty and maternal care variability are viewed as two potential sources of stress and the interaction between these two sources can generate a wide range of effects including the seemingly paradoxical findings reported in the present study. Individual differences in both maternal behavioral (PNE care reliability) and physiological (circulating corticosterone measures) variables can affect the developing stress response system of the offspring, with the former facilitating the rate of rise and recovery of the stress response and the latter affecting the maternal circulating stress hormones available to the offspring through the maternal milk supply [24,56].

Finally, these findings have significant practical implications. Observations of maternal care modulation of novelty effects tell us who would benefit from novelty exposure and who would not. The correlation between maternal care measures and the offspring's spatial working memory measure tells us which mother would be more likely to have offspring with better performance *if the early environment is derived of novelty*. The functional specificity of maternal care reliability-based measure informs us that one cannot necessarily generalize a finding made regarding physiology to behavior and from one function to another.

References

[1] Bowlby J. Attachment and loss. New York: Basic Books; 1969.
[2] Rutter M. Maternal deprivation reassessed. 2nd ed. England: Penguin books; 1981.
[3] Harlow HF, Zimmerman R. Affectional responses in the infant monkey. Science 1959;130:421–32.
[4] Harlow HF, Dodsworth RO, Harlow MK. Total social isolation in monkeys. Proc Natl Acad Sci USA 1965;54:90–7.
[5] Sanchez MM, Ladd CO, Plotsky PM. Early adverse experience as a developmental risk factor for later psychopathology: evidence from rodent and primate models. Dev Psychopathol 2001;13:419–49.
[6] Stevens HE, Leckman JF, Coplan JD, Suomi SJ. Risk and resilience: early manipulation of macaque social experience and persistent behavioral and neurophysiological outcomes. J Am Acad Child Adolesc Psychiatry 2009;48:114–27.
[7] Levine S. The effects of differential infantile stimulation on emotionality at weaning. Can J Psychol 1959;13:243–7.
[8] Barnett SA, Burn J. Early stimulation and maternal behavior. Nature 1967;213:150–2.
[9] Lee MHS, Williams DI. Changes in licking behavior of rat mother following handling of young. Anim Behav 1974;22:679–81.
[10] Smotherman WP, Bell RW. Maternal mediation of early experience. In: Bell RW, Smotherman WP, editors. Maternal influences and early behavior. New York: Spectrum; 1980. p. 201–10.
[11] Liu D, Diorio J, Tannenbaum B, Caldji C, Francis D, Freedman A, et al. Maternal care, hippocampal glucocorticoid receptor gene expression and hypothalamic-pituitary-adrenal responses to stress. Science 1997;277:1659–62.
[12] Francis D, Diorio J, Liu D, Meaney MJ. Nongenomic transmission across generations of maternal behavior and stress responses in the rat. Science 1999;286:1155–8.
[13] Champagne FC, Francis DD, Mar A, Meaney MJ. Variations in maternal care in the rat as a mediating influence for the effects of environment on development. Physiol Behav 2003;79:359–71.
[14] Buchen L. In their nurture. Nature 2010;467:146–8.
[15] Macrì S, Würbel H. Effects of variation in postnatal maternal environment on maternal behaviour and fear and stress responses in rats. Anim Behav 2007;73:171–84.
[16] Coutellier L, Würbel H. Early environmental cues affect object recognition memory in adult female but not male C57BL/6 mice. Behav Brain Res 2009;203:312–5.
[17] Coutellier L, Friedrich A-C, Failing K, Marashi V, Würbel H. Effects of foraging demand on maternal behaviour and adult offspring anxiety and stress response in C57BL/6 mice. Behav Brain Res 2009;196:192–9.
[18] Mashoodh R, Sinal CJ, Perrot-Sinal TS. Predation threat exerts specific effects on rat maternal behaviour and anxiety-related behaviour of male and female offspring. Physiol Behav 2009;96:693–702.
[19] Denenberg VH. Commentary: is maternal stimulation the mediator of the handling effect in infancy? Dev Psychobiol 1999;34:1–3.
[20] Pryce CR, Feldon J. Long-term neurobehavioral impact of the postnatal environment in rats: manipulations, effects, and mediating mechanisms. Neurosci Biobehav Rev 2003;27:57–71.
[21] Macrì S, Würbel H. Developmental plasticity of HPA and fear responses in rats: a critical review of the maternal mediation hypothesis. Horm Behav 2006;50:667–80.
[22] Parker KJ, Buckmaster CL, Sundlass K, Schatzberg AF, Lyons DM. Maternal mediation, stress inoculation, and the development of neuroendocrine stress resistance in primates. Proc Natl Acad Sci USA 2006;103:3000–5.
[23] Tang AC, Akers KG, Reeb BC, Romeo RD, McEwen BS. Programming social, cognitive, and neuroendocrine development by early exposure to novelty. Proc Natl Acad Sci USA 2006;103:15716–21.
[24] Macrì S, Zoratto F, Laviola G. Early-stress regulates resilience, vulnerability and experimental validity in laboratory rodents through mother-offspring hormonal transfer. Neurosci Biobehav Rev 2011;35:1534–43.
[25] Ainsworth MDS, Blehar MC, Waters E, Wall S. Patterns of attachment: a psychological study of the strange situation. Hillsdale, NJ: Lawrence Erlbaum; 1978.
[26] van IJzendoorn MH, Dijkstra J, Bus AG. Attachment, intelligence, and language: a meta-analysis. Soc Dev 1995;4:115–28.
[27] Gunnar MR, Brodersen L, Nachmias M, Buss K, Rigatuso J. Stress reactivity and attachment security. Dev Psychobiol 1996;28:191–204.
[28] Nachmias M, Gunnar M, Mangelsdorf S, Parritz RH, Buss K. Behavioral inhibition and stress reactivity: the moderating role of attachment security. Child Dev 1996;67:508–22.
[29] Moss E, St-Laurent D. Attachment at school age and academic performance. Dev Psychol 2001;37:863–74.
[30] Behrens KY, Parker AC, Haltigan JD. Maternal sensitivity assessed during the Strange Situation Procedure predicts child's attachment quality and reunion behaviors. Infant Behav Dev 2011;34:378–81.
[31] Leerkes EM. Maternal sensitivity during distressing tasks: a unique predictor of attachment security. Infant Behav Dev 2011;34:443–6.
[32] Cicchetti D, Gunnar MR. Integrating biological measures into the design and evaluation of preventive interventions. Dev Psychopathol 2008;20:737–43.
[33] Akers KG, Yang Z, DelVecchio DP, Reeb BC, Romeo RD, McEwen BS, et al. Social competitiveness and plasticity of neuroendocrine function in old age: influence of neonatal novelty exposure and maternal care reliability. PLoS ONE 2008;7:e2840.
[34] de Woolf MS, van IJzendoorn MH. Sensitivity and attachment: a meta-analysis on parental antecedents of infant attachment. Child Dev 1997;68:571–91.
[35] Reeb-Sutherland BC, Tang AC. Dissociation between neonatal novelty-induced preferential maternal care and enhancement in cognitive, social, and emotional functions. Behav Brain Res 2011;224:318–25.

[36] Tang AC. Neonatal exposure to novel environment enhances hippocampal-dependent memory function during infancy and adulthood. Learn Mem 2001;8:257–64.
[37] Tang AC, Reeb BC, Romeo RD, McEwen BS. Modification of social memory, hypothalamic-pituitary-adrenal axis, and brain asymmetry by neonatal novelty exposure. J Neurosci 2003;23:8254–60.
[38] Tang AC, Reeb-Sutherland BC, Yang Z, Romeo RD, McEwen BS. Neonatal novelty-induced persistent enhancement in offspring spatial memory and the modulatory role of maternal self-stress regulation. J Neurosci 2011;31:5348–52.
[39] Tang AC, Nakazawa M, Reeb BC. Neonatal novelty exposure affects sex difference in open field disinhibition. Neuroreport 2003;14:1553–6.
[40] Levine S. Infantile experience and resistance to physiological stress. Science 1957;126:405.
[41] Denenberg VH. Critical periods, stimulus input, and emotional reactivity: a theory of infantile stimulation. Psychol Rev 1964;71:335–51.
[42] Morris RG. An attempt to dissociate 'spatial mapping' and 'working-memory' theories of hippocampal function. In: Siefert W, editor. Neurobiology of the hippocampus. London: Academic Press; 1983.
[43] Panakhova E, Buresova O, Bures J. Persistence of spatial memory in the Morris water tank task. Int J Psychophysiol 1984;2:5–10.
[44] Whishaw IQ. Formation of a place learning-set by the rat: a new paradigm for neurobehavioral studies. Physiol Behav 1985;35:139–43.
[45] Steele RJ, Morris RG. Delay-dependent impairment of a matching-to-place task with chronic and intrahippocampal infusion of the NMDA-antagonist D-AP5. Hippocampus 1999;9:118–36.
[46] Yang Z, Tang AC. Novelty-induced enhancement in spatial memory: is infancy a critical period? Behav Brain Res 2011;219:47–54.
[47] Thor D, Holloway W. Social memory in the male laboratory rat. J Comp Physiol Psychol 1982;96:1000–6.
[48] Liu D, Diorio J, Day JC, Francis DD, Meaney MJ. Maternal care, hippocampal synaptogenesis and cognitive development in rats. Nat Neurosci 2000;3:799–806.
[49] Levine S. A further study of infantile handling and adult avoidance learning. J Pers 1956;25:70–80.
[50] Tang AC, Jiang H, Yang Z, Zhang Y, Romeo RD, McEwen BS. Converging influence of neonatal novelty experience and maternal self-stress regulation on the plasticity of offspring acoustic startle response latency. Behav Brain Res 2011;221:253–60.
[51] Smotherman WP. Mother-infant interaction and the modulation of pituitary-adrenal activity in rat pups after early stimulation. Dev Psychobiol 1983;16:169–76.
[52] Stanton ME, Wallstrom J, Levine S. Maternal contact inhibits pituitary-adrenal stress responses in preweanling rats. Dev Psychobiol 1987;20:131–45.
[53] Stanton ME, Levine S. Maternal modulation of infant glucocorticoid stress response: role of age and maternal deprivation. Psychobiology 1988;16:223–8.
[54] Stanton ME, Levine S. Inhibition of infant glucocorticoid stress response: specific role of maternal cues. Dev Psychobiol 1990;23:411–26.
[55] Moriceau S, Sullivan RM. Maternal presence serves as a switch between learning fear and attraction in infancy. Nat Neurosci 2006;9:1004–6.
[56] Catalani A, Alemà GS, Cinque C, Zuena AR, Casolini P. Maternal corticosterone effects on hypothalamus-pituitary-adrenal axis regulation and behavior of the offspring in rodents. Neurosci Biobehav Rev 2011;35:1502–17.