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Short communication

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

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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

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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,