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Rat pup social motivation: A critical component of early psychological development

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Abstract

Examining the role of the offspring in early social dynamics is especially difficult. Human developmental psychology has found infant behavior to be a vital part of the early environmental setting. In the rodent model, the different ways that a rodent neonate or pup can influence social dynamics are not well known. Typically, litters of neonates or pups offer complex social interactions dominated by behavior seemingly initiated and maintained by the primary caregiver (e.g., the dam). Despite this strong role for the caregiver, the young most likely influence the litter dynamics in many powerful ways including communication signals, discrimination abilities and early approach behavior. Nelson and Panksepp (1996) developed a preference task to examine early rodent pup social motivation. We have used the same task to examine how variations in maternal care or different environmental perturbations could alter the rat pup preferences for social-related stimuli. Rat pups receiving low levels of maternal licking and grooming were impaired in maternal odor cue learning and emitted lower levels of 22 kHz ultrasounds compared to pups from the high licking and grooming cohort. Prenatal stress or early exposure to a toxicant (polychlorinated biphenyl) altered early social preferences in the rat pup in different ways indicating that diverse strategies are expressed and specific to the type of perturbation exposure. A greater focus on the offspring motivation following early ‘stressors’ will allow for more complete understanding of the dynamics in behavior during early social development.

Keywords

Attachment emotion; epigenetics; stress; toxicology

Early social development involves dynamic interactions

The idea that there is a continuous interaction between individuals during early development is not new (Bishop and Merrill, 1951; Sander, 1962; Wolff, 1963). Bowlby emphasized this fact throughout his writings (1973 (1982) and a significant amount of child developmental work has focused on different aspects of this dynamic social environment (Courage and Howe, 2002; Pelaez et al., 2008; Repacholi, 2009). This has included work on joint attention (Grossberg and Vladusich, 2010), interactive speech and learning (Gogate et al., 2000) and the gradual development of theory of mind (Wellman and Brandone, 2009). These different

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crucial abilities depend upon both caregiver and care-seeker and how each of these interactive participants learn and respond from one another. There is little doubt in the present developmental field of psychology and behavior that the infant can strongly influence the responses of the primary caregiver and is an active part of its own psychological development (Ham and Tronick, 2009). Vocalizations and related facial and body movements are major contributing factors in this influence (Volker, 2005; Fuertes et al., 2006).

Bowlby's work originated out of studies on animal social behavior and the important, groundbreaking work of ethologists (Lorenz, 1935; Tinbergen, 1951) that focused on innate behavior in natural contexts (Bowlby 1973; 1982). Behavioral neuroscience using animal models to study early social development have not incorporated the dynamic aspects of the interactions as well as the human research fields. The work using animal models have focused more on the caregiver and the quality of care. A large body of work examines the impact of deprivation, a situation in which the developing offspring has lost the power to influence another's actions and psychological state (Lovic et al., 2001; Oitzl et al., 2000). A very interesting avenue of research examines maternal potentiation of pup isolation calls (Shair, 2007) uncovering important neurochemical mediation of early social bond formation (Muller et al., 2009; Shair et al., 2009). Other important work has identified the hormonal and neural basis for pup associative learning as it matures to enable appetitive and aversive associations following the stress hyporesponsive period (Moriceau et al., 2010). Much is now known about the powerful influence of maternal care in the rodent model (Champagne et al., 2003; Menard and Hakvoort, 2007). Dams can influence diverse array of neurochemical and hormonal systems by performing care behaviors such as licking and grooming at high or low levels (Zhang et al., 2002; Champagne and Curley, 2008; Cameron et al., 2008). Pups receiving low levels of care have an enhanced stress response and show abnormalities in neurochemical systems related to emotional behavior (Champagne et al., 2004; Zhang et al., 2006). Additionally, these same pups demonstrate a behavioral profile of high anxiety and fear and these behavioral effects appear to be long-term (Zhang et al., 2004; 2005). Amazingly, these experiences in the early environment produce shifts in gene expression that can be transmitted from one generation to the next (Champagne and Meaney, 2007). For example, a female rat pup who has received low levels of maternal care is likely to express this same level of care to her own offspring. In order to form a complete understanding for the psychological processes involved in social dynamics, future work could include indicators of gene expression and related historical patterns of genome activation or suppression (Meaney and Szyf, 2005; Darnaudery and Maccari, 2008).

Important questions remain unanswered and involve the details of the dynamic interaction between the caregiver and care-seeker in generating these important effects on emotional expression and regulation. For instance, pups that receive low licking and grooming could respond less to maternal cues (e.g., olfactory, auditory or somatosensory) and provide behavioral and emotional feedback that guides and maintains a particular level of care. This type of interaction could either provide positive feedback in terms guiding care in its original direction or negative feedback that overrides the original care and redirects in an opponent fashion. A case in which the pups redirect care could occur if the litter becomes exposed to an environmental toxicant altering pup arousal or responsiveness. This altered pup behavioral and physiological development could potentially trigger a caregiver to provide greater levels of maternal care and thus shift the care behavior level from one of less maternal licking and grooming to one of more maternal licking and grooming. Previous work has shown that exposure to stressors during gestation can shift a previously high maternal licking and grooming dam into a low-licking maternal caregiver (Champagne and Meaney, 2006). How important is the impact of the prenatal stress on the pup's social motivation in this scenario? One would have to examine the early pup behavior and

responsiveness in detail to answer questions such as this one. We have used a set of behavioral tests to investigate the early pup behavior and motivation toward the dam and have found that the pup's activities and responses can vary significantly depending upon the different factors that are altered in the early environmental setting.

Asking the pup: Conditioned odor preference tests and maternal cues

Nelson and Panksepp (1996) devised a novel method to examine early pup preferences related to social experience. It was based on the well established conditioned place preference task used to examine drug and food reward (Tzschentke, 2007). The standard task uses a place conditioning process in which a location is paired with a positive (or negative) unconditioned stimulus. The unconditioned stimuli have included pharmacological agents, footshock or food items (Beninger and Banasikowski, 2008; McBride et al., 1999; Schechter and Calcagnetti, 1993). Panksepp has made several novel and effective modifications of this classical conditioning paradigm over time. In one set of studies, he has shown rats prefer locations in which they have previously experienced 'tickling' stimulation from the experimenter (Panksepp and Burgdorf, 2000). In another set of studies, experience with rough and tumble play behavior was demonstrated to be a potent unconditioned stimulus leading to place preference (Panksepp et al., 1984). Utilizing the appropriate unconditioned stimulus is crucial for strong associations to guide behavioral responses. Several research groups have utilized maternal odors as cues leading to strong conditioning effects (Raineke et al., 2010; Alberts and May, 1980; Sevelinges et al., 2009; Sanchez-Andrade, 2009). Designing a paradigm to use with rat pups was innovative in that it utilized an odorant paired with maternal exposure after acute isolation as the unconditioned stimulus (Nelson and Panksepp, 1996). The odorant was applied by coating the dam on her ventral surface with a lemon extract solution. The pups were isolated from the dam for three hours prior to a reunion in which the odorant was experienced. Then, the pups were tested for the odor preference 24 hr after a set of three pairings between the dam and the odor in a smaller sized version of the conditioned place preference apparatus (Figure 1). Typically, the pups demonstrate a robust preference for the odor. We have replicated the experiment multiple times since the initial demonstration and shown that pups will express the odor preference during a broader window within early development and this supports the idea that pups can demonstrate an earlier expression of this discrimination ability, even prior to the onset of basic sensory (non-olfactory) and motor abilities (Cromwell et al., 2007; Harmon et al., 2008; 2009).

The paper by Nelson and Panksepp examined the effects of the administration of oxytocin or an oxytocin antagonist, [d(CH₂)⁵(Tyr(Me)₂, Thr₄, Tyr(NH₂)₉)₂] orinithine vasotocin (OTA) into the third ventricle on the odor cue preferences on postnatal day 14. The injection of OTA prior to testing the odor conditioning eliminated the preference in the group exposed to the odor-dam pairing schedule. These experimental pups are compared with control pups who experience the odor in a neutral setting (i.e., paired with cotton balls). This eliminates any basic odor and familiarity effects. The paper included interesting findings on general odor approach, dam approach and general aversive odor learning. It was found that general learning was spared in the same OTA injection group suggesting oxytocin antagonism selectively effects social learning/motivation and not learning or motivation in general. Interestingly, injections of oxytocin at 14 days PN did not enhance the social learning or responsivity. Nelson and Panksepp (1996) noted that the basal levels of this neuropeptide may be already at an optimal level and any greater enhancement using pharmacological administration may not be effective. These previous findings and implications were prescient to the recent emphasis on oxytocin for social learning and motivation (Carter et al., 2008). The implications of these results include the idea that oxytocin levels in the rat pups are important in mediating early social learning and expression of that learning. Possible

perturbations of these neuropeptides levels could alter the pups' social motivation (Shahrokh et al., 2010).

Maternal odor preference and USVs in pups from low or high maternal care litters

Our recent work used this identical conditioned odor paradigm to examine early pup social motivation in pups that had received either low or high levels of maternal care (McFarland et al., 2008). We delineated levels of low and high maternal licking and grooming by noting the different maternal care behaviors for a 10 hour observation period during the first 8 days postpartum. The methods were derived from Champagne et al., (2003) and resulted in clear differences in maternal care behaviors between groups. We then examined the conditioned odor preference in pups from the different maternal care groups and found that animals that had received low levels of MLG (at least 1 standard deviation below the average) showed a significant reduction in the maternal cue preference (McFarland et al., 2008). This finding was similar to the previous result using the oxytocin antagonist injection (Nelson and Panksepp, 1996) and fit with the findings that oxytocin synthesis and receptor function are altered in rats that have received low levels of MLG (Shahrokh et al., 2010). The animals that received high levels of MLG did not show enhanced preference compared to the medium MLG group. This indicates that higher levels of MLG may not significantly enhance early pup social learning and could be related to the early ceiling effect of neuropeptides such as oxytocin. We also examined ultrasonic vocalizations (USVs) in these different groups at two different developmental time periods. The first test was the standard isolation test at postnatal day 10 and we found that the animals receiving the highest levels of MLG produced higher numbers of USVs while the low licking group produced the lowest levels of calls. We also examined the USV production during the odor preference test and found an even greater difference with significantly higher calls emitted by the pups who had received the highest levels of MLG. These results could reflect the dynamic interactions that occur during the early care environment. Pups that receive low levels of maternal care are not as frequently exposed to cues related to the dam and to care behaviors. This less frequent exposure would dampen the strength of any cues to direct approach behavior. In addition, USV emission may not be effective in influencing the dam and obtaining greater levels of care. Previous work has shown that rat pup USVs at 22 kHz are effective in influencing dam approach behavior (Noirot, 1968; 1972; Hofer et al., 2002; Hahn and LaVooy, 2005). Conversely, the higher levels of calls by the rat pups receiving high levels of licking and grooming could arise from the effective nature of the calls in eliciting care. These results suggest that the variations in maternal care during the early environment may be in part due to the actions of the pup as well as the dam. A next step in investigating this influence was to examine the pup maternal cue preference in groups of animals that received early exposure to stress. We have examined rat pups exposed to variable prenatal stress and pups exposed to the xenobiotic polychlorinated biphenyl (PCB).

Animal models of impaired social abilities and the conditioned odor preference test

Examining how perturbing the early environment changes measures of rat pup motivation and emotion could be highly valuable in producing a more complete picture for the diverse factors leading to long-term psychological impairment in these animals. It is well known that offspring exposed to stress demonstrate a broad set of behavioral and physiological impairments (Lee et al., 2007; Moore and Power, 1986; Moriceau et al., 2009; Patin et al., 2005; Rice et al., 2007). It is unknown how or when early impairments commence in these animal models of behavior pathology. We exposed pups to a regimen of variable and

moderate stressors (handling, injection, novel environment and acute (10 min) restraint) during the 3rd week of gestation and found significant deficits in maternal odor conditioning using the previously described maternal-odor conditioning procedure (Harmon et al., 2009). The deficit was found as an over-generalization of preference to the odor regardless of conditioning history. The PNS exposed pups equally preferred the scent cue after pairing with the CS+ (dam) or with the neutral CS (cotton balls) (Figure 2). This atypical preference may be based on an over reliance upon mere exposure or basic familiarity. This type of over-generalization in preference in these animals could be a mechanism whereby learning remains less discriminatory and less specific. Animals exposed to stressors have been shown to express similar types of impairments in discrimination abilities (Aleksandrov et al., 2001; Nishio et al., 2001). Previous human basic and clinical studies have found overgeneralization related to psychological processes of negative valence, stress, anxiety or panic (Hearst, 1960; Dunsmoor et al., 2009; Lissek et al., 2010; Schechtman et al., 2010). In the young rat study, learning per se does not seem to be significantly impaired because both groups (CS+ and Neutral CS) demonstrate a clear preference over the no-odor location. This type of impairment could influence how the pups respond during separation periods and the types of stimuli that evoke care-seeking. Previous studies have found impaired learning following prenatal stress exposure (Lemaire et al., 2000). Restraint stress during gestation produces spatial learning impairments in adult male rats. Another possibility is enhanced neophobia and associated changes in arousal. Other related work has demonstrated that rats exposed to PNS have a hypersensitive hypothalamic-adrenal-pituitary (HPA) circuit and increases in anxiety in response to novel situations (Fride et al., 1988; Deminiere et al., 1992). Our work as well as other studies have not dissociated very well between learning and expression deficits. These issues and possible explanations are important to pursue because they could be a part of the changing dynamics in interactions between the young rat pup and the caregiver.

USVs were also examined in rats exposed to PNS and were found to be significantly enhanced in the experimental group compared to the control group (Harmon et al., 2009). These USVs may be indicators of motivational states related to social behavior; however, this issue is still controversial. One idea is that ultrasounds particularly in young rodents (22 kHz calls) could arise as byproducts of an abdominal compression reaction (ACR) (Blumberg et al., 2000; Blumberg et al., 1999). A recent review argues that even if the USVs have evolved as ACRs, they most likely have acquired, as an exaptation, communicatory importance (Arch and Narins, 2008). Other research groups have found similar relationships between ultrasounds and gestational stress exposure (Williams et al., 1998). The possibility exists that these pups are 'excessively needy' and drive maternal care in directions of enhanced care at certain times. A comparison between rat pups exposed to PNS and pups at the low end of licking grooming point to a dramatic divergence in social motivation. Pups exposed to PNS show generalized preference and high USV levels which is quite different from the reduced lack of preference and low levels of distress USVs emitted by the low licking and grooming animals. In terms of attempting to understand how maternal care might be related, one would have to posit that the PNS exposed animals might be more similar to the pups from high licking and grooming litters. Given that much of the previous work on PNS has shown that maternal care is reduced (Smith et al., 2004; Baker et al., 2008; Darnaudery et al., 2004; Bosch et al., 2007), this was an unexpected result and most likely reflects a qualitative dissociation between the 'abnormal' situation of gestational stress exposure and the natural situation characterized by a range of care behaviors. However, several groups have not found a significant difference after PNS when measuring certain indicators of care (Patin et al., 2005; Moore and Power, 1986). An important point worth considering is that a shift in the level of stress during a critical time period does not simply shift animals along the spectrum of natural care behaviors but could produce a qualitative shift in the type of care expressed. Possibilities to explore include shifts in ways that alter

the pattern of care interactions between the care-giver and care-seeker. Additional basic information in regards to the ordering or sequential integrity of care behaviors has not been well characterized. These predictable sequences of care could be an important part of the early social environment and when they are disrupted, problems in emotional and motivational systems could arise.

In another related set of studies we have completed a series of studies examining the influence of perinatal exposure to a toxicant, polychlorinated biphenyl (PCB) on social motivation and social learning (Cromwell et al., 2007; Joulous-Jamshidi, 2010). Using the similar conditioned odor preference test, we uncovered a significant alteration in the expression of maternal cue preference (Cromwell et al., 2007). Pups exposed to PCB during the perinatal period (gestation up to the day of testing or PND 12–14) did not express a preference for the lemon scent regardless of conditioning history (Figure 3). This result appears quite similar to the finding observed in pups from low-licking maternal care groups. Surprisingly, other research has examined maternal care in dams exposed to PCB during gestation and found some elements of care enhanced (Simmons et al., 2005). Maternal actions such as licking and grooming were increased in dams exposed to the toxicant during gestation. In an elegant cross-fostering design, the same research group examined the role of the pup exposure in producing these effects and found altered care in both cross-fostered groups (*Group 1*: exposed dam and unexposed pups and *Group 2*: unexposed dam and exposed pups) (Cummings et al., 2005). This type of result adds to the support for the idea that young offspring play a very important role in the quality of social actions within the early environment because altered care was obtained without the dam being directly exposed to the toxicant. It was enough for the pups to be exposed in order for the early caregiver reactions to shift in subtle but important ways. Enhanced maternal care following exposure to a toxicant during gestation may be one way that the caregiver attempts to ameliorate detrimental effects of exposure (Champagne et al., 2003). The result of poor maternal-odor conditioning may signify an alteration in pup basic social functions and related physiology which cannot easily be restored by the shifts in maternal care. Exposure to PCB leads to a plethora of hormonal, neurochemical and morphological changes in the brain and other organs (Meserve et al., 1992; Khan et al., 2002; Donohue et al., 2004; Goldey et al., 1995). Early alterations caused by certain environmental or chemical stressors may not be reversible or take a more prolonged period during development to subside (Domingo and Bocio, 2007; Colbert et al., 2005). In addition early alterations can reverse due to compensation by behavioral or physiological means. Perinatal lead exposure causes a significant decrease in USVs in 7 day old rat pups but a significant increase later in 14 day old pups (DeMarco et al., 2005). This type of reversal can be related mainly to direct compensatory mechanisms or maturation of activation hormonal and neural systems during development. These examples provide novel insight into the potential role of offspring responses during early development and how dynamic interactions likely continuously interplay and feedback onto one another.

Conclusions: Learning from the offspring

The study of early social dynamics is complex; however, it will be crucial to study the joint interactions and influences in order to fully comprehend how behavior, emotion and motivation develop adaptively and how different environments and experiences widen or constrict the window of behavioral flexibility involved. Rats are probably not the best model for the examination of maternal-offspring interactions involved in attachment and bonding because the rat pup does not seem to be affiliated with the specific dam and recognition is a general process for the most part (Jolous-Jamashidi et al., 2010; Thor and Holloway, 1982). Other animal models are now being explored to examine early social interactions and the development of social learning (Young et al., 2010; Panksepp, this volume). It will be very

important to keep in mind that the pup can guide and maintain behavior of peers and caregiver in direct and indirect ways and that these are important determinants of long-lasting 'traits' in these animals. It might be expected that in animal models with more specific recognition capabilities the extent of interactions might be greater and the degree of control over actions more intense. An important conclusion related to this previous work is that the alterations in maternal care along the natural spectrum of variation may not lead necessarily to predict that offspring reared within the range of this spectrum are experiencing a form of 'impaired' maternal care. A better way of describing the shifts is along a quantitative continuum of 'typical' care. When animal experience a significant shift in the environment from a stressor, then care not only shifts in terms of quantity but it could shift in a certain qualitative ways as well. As previously mentioned this area of study is open to investigation in terms of examining in detail how care changes after certain exposure to stressors during early development. Current work in our laboratory is examining how action sequences related to maternal might shift. Ordered sequences of care behaviors transitioning from active care to quiet nursing behaviors seems to take place in a consistent manner. Dams who diverge from these sequences could be causing more stress to the pups and create an unpredictable environment of care. Action sequences are important in rodent sensorimotor functions and even social abilities (Bursten et al., 2000). They depend on higher forebrain and midbrain regions to be implemented in appropriate ways (Cromwell et al., 1996; 1998). These midbrain regions such as the dopamine cell groups may be especially susceptible to early stress exposure and lead to changes in the reinforcing effects as well as the syntactical efficacy of movement production (Seegal et al., 2005).

Finally, focusing on the social dynamics and the impact of stress on these interactions will benefit the study for how behavioral and social impairments in developmental disorders arises. Presently, the primary focus has been on the caregiver in animal models and measures of alterations in adult organisms have been attributed to the behaviors produced by the caregiver (Zhang et al., 2004; Zhang et al., 2005). Treatment regimens and new therapies will use this information to examine how care-giving proceeds and focus on the unidirectional process of reception of care in different contexts (Tremblay, 2010; Szyf et al., 2008). This way of proceeding could be remiss in lacking important elements of bidirectional interactions between the social partners. Animal models incorporating dynamics of interactions would be more accurate and better enabling science to tease apart the important contributions such as the timing and the details for how behavioral and psychological processes come to persist in individuals over time. Several research groups now examine animal models of autism or attention deficit disorder and many either do not examine early environmental social interactions or do so in a limited fashion. The early work of Panksepp in social learning and expression of social emotion was pivotal in directing this research in the direction of more holistic and novel ways (Nelson and Panksepp, 1998; Sahley and Panksepp, 1987; Panksepp et al., 1984). This rich tradition of social inquiry at the basic affective neuroscience level (Scott, 1944; Scott and Marston, 1950; Scott et al., 1974) should continue and enable a more thorough understanding for the highly complex and dynamic influences of early care-giving and care-seeking.

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importance of the early environment in everything we do and as a causal factor for debilitating emotional disorders, and I am finding it extremely daunting yet critically essential for all of psychology.

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Figure 1.

Schematic of Conditioned Odor Preference Apparatus. A smaller version of the adult-sized conditioned place preference apparatus has been found to be effective. Rat pups are placed in the center of the chamber and the time spent in the left or right halves is measured. An additional measure of 'entry numbers' provides an index of general activity level and arousal.

Figure 2.

COP Chamber Preference for Each Experimental and Conditioning Group. Rat pups exposed to prenatal variable stressors display a unique general preference in that the pup paired with the scent and neutral situation (cotton balls) show a preference similar to the positive conditioning group (scent + dam). White bars = time in the lemon-side of the apparatus while black bars = time in the non-scented side. * = $p < 0.05$; ** = $p < 0.01$ and *** = $p < 0.001$ significance levels.

Figure 3.

Impaired odor conditioning in rats exposed to PCBs. These findings are significantly different from the PNS exposure. Rat pups exposed to PCB at two different doses (12.5 ppm or 25 ppm) both showed deficits in conditioned odor preference and demonstrated an actual aversion to the lemon scent in CS+ group for the 12.5ppm subgroup and the neutral CS group in the 25 ppm subgroup. In both PCB subgroups the normal preference was not expressed. Lem = lemon-side of the apparatus and No = no scent side of the apparatus. Dam = those animals exposed to the scent + dam pairing and Cot = those animals exposed to the scent + cotton balls. Significance levels are identical to Figure 2.