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The International Society for Developmental Psychobiology Sackler Symposium: Early adversity and the maturation of emotion circuits - a cross-species analysis

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Abstract

Early-life caregiving shapes the architecture and function of the developing brain. The fact that the infant-caregiver relationship is critically important for infant functioning across all altricial species, and that the anatomical circuits supporting emotional functioning are highly preserved across different species, suggests that the results of studies examining the role of early adversity and emotional functioning should be translatable across species. Here we present findings from 4 different research laboratories, using 3 different species, which have converged on a similar finding: adversity accelerates the developmental trajectory of amygdala-prefrontal cortex (PFC) development and modifies emotional behaviors. First, a rodent model of attachment learning associated with adversity is presented showing precocial disruption of attachment learning and emergence of heightened fear learning and emotionality. Second, a model of infant-mother separation is presented in which early adversity is shown to accelerate the developmental emergence of adult-like fear retention and extinction. Third, a model of early life adversity in Rhesus monkeys is presented in which a naturally occurring variation in maternal-care (abuse) is shown to alter the functioning of emotion circuits. Finally, a human model of maternal deprivation is presented in which children born into orphanages and then adopted abroad exhibit aberrant development of emotion circuits. The convergence of these cross-species studies on early life adversity suggests that adversity targets the amygdala and PFC and has immediate impact on infant behaviour with the caregiver, and emotional reactions to the world. These results provide insight into mechanisms responsible for caregiver induced mental health trajectory alterations.

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About the symposium

The findings discussed in this paper were presented at the Sackler Special Interest Symposium at the Internatio0nal Society for Developmental Psychobiology annual meeting in 2012. The symposium documented emerging data from the following labs across the world: Regina Sullivan at New York University School of Medicine; Bridget Callaghan (who was a PhD candidate in the laboratory of Professor Rick Richardson at The University of New South Wales in Australia at the time of the symposium and presented a complement of studies from her doctoral thesis); Brittany Howell (who was a PhD candidate in the laboratory of Dr. Mar Sanchez in the Department of Psychiatry and Behavioral Sciences, School of Medicine, Emory University and the Yerkes National Primate Research Center, Atlanta, GA at the time of the symposium and presented a combination of previous results from Dr. Sanchez's group and preliminary results from her dissertation research); Nim Tottenham from the Department of Psychology at the University of California, Los Angeles (who presented data from both from her work at UCLA as well as findings from her dissertation research with Dr. BJ Casey's laboratory in the Sackler Institute for Developmental Psychobiology at Weill Cornell Medical College in New York City).

Introduction

Early-life experiences shape the architecture and function of the developing brain (Levine, 1962; Suomi et al., 1970). Amongst the most important of early-life experiences is the relationship between the primary caregiver and the infant. In both human and non-human primates, as well as other mammals, the quality of the infant-caregiver relationship plays an important role in the development of behavior and the brain (Callaghan & Richardson, 2013; Kuhn & Schanberg, 1998; Ladd et al., 2004; Plotsky & Meaney, 1993; Plotsky et al., 2005; Raineki et al., 2010; Ruppenthal et al., 1976; Sanchez et al., 2001a; Tottenham & Sheridan, 2009). For example, individuals reared in institutional settings characterized by high child to caregiver ratios have been shown to exhibit deficits in emotion regulation, attachment to primary caregivers, and cognitive development (Kreppner et al., 2007; see Nelson, 2007, for a review of these findings; O'Conner et al., 2003; Rutter, 1998; Rutter et al., 2001; Tottenham et al., 2010; Zeanah et al., 2009).

While the importance of early experiences on an individual's emotional and cognitive functioning has been recognized for some time, many of the models which have been created to probe this link are underutilized because they do not focus on early developmental time points (Thompson & Levitt, 2010). It is well accepted that many mental health problems have their onset early in life (e.g., Bradley et al., 2008; Cartwright-Hatton et al., 2006; Caspi et al., 2003; Juster et al., 2011; Polanczyk et al., 2009; Spataro et al., 2004; Taylor et al., 2011). Indeed, in one cohort, over 70% of individuals with a diagnosable anxiety disorder at age 21 had first received a diagnosis in childhood or adolescence (Newman et al., 1996). Also, for adult onset disorders (e.g., schizophrenia) the developmental trajectory eventually leading to end-state functioning is established in early life (Lewis & Levitt, 2002). For these reasons it has been suggested that clinical advances in the understanding and treatment of mental health problems will emerge from research which attempts to link the timing of adverse events to the onset of circuit disruption (Thompson & Levitt, 2010). Hence, studies investigating the outcomes of stress at *early* developmental time points will be critical in determining the initial steps in developmental trajectories which are established by stress and adversity, as well as how its early emerging manifestations might accumulate across the lifespan of an individual to result in end-state mental health dysfunction.

Models of disrupted infant-caregiver relationship have already shown much promise in uncovering some of the factors linking early adversity to poor mental health in adulthood, with similar findings being observed across species. For example, in infant rats, low levels of active maternal care are associated with greater methylation of a glucocorticoid receptor (GR) gene promoter in the hippocampus of adult offspring (Weaver et al., 2004). Similar epigenetic changes to GR gene promoters were recently found in the hippocampus of adult suicide victims that had been abused early in life; these changes were not observed in adult suicide victims not exposed to such early abuse (McGowan et al., 2009). These studies clearly demonstrate the benefits of utilising a 'translational' approach in investigating the effects of early-life adversity, with many findings in rodents appearing to be applicable to primates. Continuing with that approach, here we present findings from 4 different research laboratories, using 3 different species, which have converged on a similar finding: adversity

alters the early trajectory of emotion regulation behaviors and the neural circuits which support those behaviors. These findings provide strong support for the view that translational models of disrupted infant-caregiver relationship are critical in our understanding of the establishment of mental health trajectories. We start this review by briefly outlining the development of the stress response system in rodents, primates and humans, contrasting this against the maturation of emotion behaviors to suggest that early postnatal life may be an especially sensitive period for the input of stress signals to regulate emotional development.

Development of the hypothalamic-pituitary-adrenal (HPA) axis

The hypothalamic-pituitary-adrenal (HPA) neuroaxis is one of the main systems activated by stress and is thought to mediate some of the alterations that have been reported in studies of early adversity. Briefly, when a stressor is detected specific pathways are activated, resulting in parvocellular neurons of the paraventricular nucleus of the hypothalamus (PVN) being activated and releasing corticotropin-releasing hormone (CRH), and other neuropeptides, such as arginine vasopressin (AVP), into the portal vasculature of the median eminence, which then act on the anterior pituitary to cause release of adrenocorticotropic hormone (ACTH) into the general circulation. ACTH acts upon cells in the adrenal cortex to cause the synthesis and release of glucocorticoids (GCs), cortisol in primates and corticosterone in rodents (together referred to as CORT; Charmandari et al., 2005; Levine, 2001). CORT is a highly catabolic steroid hormone whose main function is to mobilize energy substrates to provide fuel to organs such as the heart and skeletal musculature to respond to threat. The HPA axis has a negative feedback mechanism to shut down its activity via GCs, so that CORT, for example, turns off axis activation by inhibiting ACTH synthesis at the level of the pituitary, and CRH at the level of the hypothalamus, and also by acting on extrahypothalamic structures, including limbic regulatory regions such as the hippocampus and PFC, that inhibit the axis (Charmandari et al., 2005; Herman & Cullinan, 1997; Ulrich-Lai & Herman, 2009). Stress-induced increases in circulating CORT levels are superimposed on circadian rhythms of cortisol, with the highest levels occurring in the morning around waking, and the lowest occurring at night around the onset of sleep, a result of changes in pulsatile release of CRH and AVP from the hypothalamus (Charmandari et al., 2005). Although CORT can have fast, nongenomic effects (Dallman, 2005), glucocorticoids are mainly slow-acting and act via two types of intracellular receptors: (1) glucocorticoid receptors (GR) which have low affinity for GCs and are primarily responsible for negative feedback of the HPA axis in both basal circadian function and the stress response, and (2) mineralocorticoid receptors (MR) which have high affinity for GCs and are primarily responsible for maintaining basal HPA axis activity (Sanchez, 2006). Both of these receptors translocate to the nuclei of cells once CORT is bound, affecting gene transcription by acting as transcription factors (Charmandari et al., 2005; Ulrich-Lai & Herman, 2009).

The HPA neuroaxis undergoes dramatic development across the early postnatal period in both rodents as well as non-human and human primates. One of the distinguishing features of this period is the relative quiescence of the HPA axis, either at baseline or in response to parental presence. In rodents, few stressors are capable of mounting a strong release of CORT early in development, leading to the characterisation of this developmental period as the ‘stress hyporesponsive period’ (Dallman, 2000). In rodents the SHRP extends from

about postnatal day (P) 4–14. At the termination of the SHRP, P14 rats can mount a corticosterone response to stress, however, other components of the HPA axis continue to develop after this time, e.g., diurnal patterns of corticosterone do not mature until approximately P26 (Levin & Levine, 1975). In humans, activity of the developing HPA axis is strongly socially buffered, particularly by maternal cues in securely attached dyads (Hostinar et al., 2014). For example, compared to insecurely attached infants, children with secure attachments to the mother exhibited lower cortisol levels when mothers accompanied them to the first few days of childcare (Ahnert et al., 2004). In older children too, even access to maternal vocalisations have a powerful cortisol buffering effect. Specifically, 7–12 year old girls exposed to the Trier Social Stress Test for children and then given physical or telephone access to their mother exhibited a much faster return of cortisol to baseline levels than girls not given any access to the mother (Seltzer et al., 2010). Another important feature of HPA axis development in humans is the rise in baseline cortisol levels at the transition from childhood to adolescence, which corresponds with pubertal status (Kiess et al., 1995). Similar, to studies demonstrating social buffering of the HPA axis in humans, parental care also appears to buffer the developing HPA system in rhesus monkeys, with absence of parental care leading to increases in CORT (Sanchez, 2006).

Neurodevelopment of amygdala-prefrontal circuitry and fear

Interestingly, the time course of maturation for many fear behaviors (e.g., conditioned fear responses in the rat and separation anxiety in the human), and the neural circuitry which supports those behaviours, appears to map very well on to the trajectory of HPA axis maturation. For example, infant rats are markedly different from adults both in how fear is learned and expressed: amygdala dependent cued fear learning and innate fear to predator odor does not functionally emerge until P10 (Camp & Rudy, 2004; Haroutunian & Campbell, 1979; Sullivan et al., 2000; Takahashi et al., 2005). The delayed emergence of fear is not atypical. Indeed, for many altricial species, fear expression is developmentally delayed, presumably emerging when it becomes ecologically significant and beneficial for survival. For rodents, fear emerges at a time when pups begin to leave the protection of the nest by taking brief trips outside the nest. We suggest that the emergence of the neural circuits supporting fear provides animals with a nervous system and behavioral repertoire adapted to their changing ecological niche as they transition from the nest to independence, which occurs over a brief 3 week period from birth to weaning.

Indeed, the first few weeks of life in the rodent also represent a period of developmental change in retention and extinction of conditioned fear. Specifically, while adult rats exhibit excellent memory retention following just a single conditioning episode (Gale et al., 2004; Paschall & Davis, 2002), infant rats rapidly forget fear associations across intervals as short as one week (a phenomenon known as infantile amnesia; Campbell & Campbell, 1962; Campbell & Spear, 1972). In addition, adult rats use an extinction system which is prone to fear relapse (e.g., Bouton, 2002; Bouton & Bolles, 1979), yet extinction in infancy is relapse-resistant (for a review see Kim & Richardson, 2010). In other words, after extinction training in adulthood, rats will exhibit fear again if the context changes (renewal), if they are given a brief reminder treatment (reinstatement), or merely following the passage of time (spontaneous recovery). On the other hand, fear that is extinguished in infancy is

permanently suppressed, regardless of the post-extinction manipulation (Kim & Richardson, 2007a; 2007b; Yap & Richardson, 2007). In addition to these behavioral dissociations in fear expression and extinction, there are also developmental changes in the neural circuits which support these behaviors. For example, the expression of fear in adult rats is dependent upon neural activity in the prelimbic prefrontal cortex (PL-PFC; Burgos-Robles et al., 2009; Corcoran & Quirk, 2007; Quirk et al., 2003; Sierra-Mercado et al., 2010; Vidal-Gonzalez et al., 2006). However, fear expression in infancy is PL-PFC independent (Li et al., 2012) and it was recently suggested that the exaggerated forgetting seen in young rats may be due to the apparent lack of coordinated activity between the mPFC and basolateral amygdala (BLA) early in life (Kim et al., 2012). Similar, to fear expression, infant rats also use a different neural circuit to adults when fear is extinguished. While extinction in adult rats is dependent upon the infralimbic (IL) region of the PFC (Milad & Quirk, 2002), infant extinction is IL independent (Kim et al., 2009). Taken together these data suggest that fear conditioning and extinction in infancy are likely supported by a very simple circuit, involving only the amygdala and probably downstream targets involved in the expression of specific fear responses (e.g., the periaqueductal gray).

Non-human primates also exhibit substantial change in emotion circuits across the infancy to juvenile period of development. For example in rhesus monkeys amygdala afferents from portions of temporal cortex that relay visual information mature at week 3 when an animal first begins to respond appropriately to social cues, while efferents from these same temporal regions to orbital PFC do not become mature until 2 months when curiosity and frustration become apparent (Machado & Bachevalier, 2003). It is also during this time that the amygdala undergoes the fastest changes in volume (Chareyron et al., 2012; Payne et al., 2010). PFC development occurs over a much longer period, not becoming mature until approximately 3–4 years (Machado & Bachevalier, 2003). An example of how maturation and myelination of the PFC is reflected behaviorally is in the transition from infancy to early childhood, when the capacity for effortful behavioral control becomes apparent (Dawson et al., 1992; Maestripieri & Carroll, 1998).

Finally, significant maturation of emotional networks also occurs over the childhood to adolescent period in humans. Specifically, typically raised children show an immature pattern of task-based connectivity between amygdala and mPFC (Gee et al., 2013b; i.e., positive coupling, such that when activity of the amygdala increased, so did activity of the mPFC). This immature pattern was paralleled by high amygdala reactivity and immature fear behaviors (i.e., developmentally normative high separation anxiety). This amygdala-mPFC connectivity phenotype switched to an adult-like phenotype around 10 years old, such that like adults, adolescents showed the mature pattern of amygdala-mPFC connectivity (i.e., negative coupling, such that when mPFC activity increased, amygdala reactivity decreased). The mature pattern was paralleled by decreased amygdala reactivity and lower levels of separation anxiety.

Together these data suggest that there exist both immature and mature patterns of fear responding and neural connectivity in emotion circuits and that the natural developmental transition between such behaviours/circuits may correspond with maturation of the HPA axis. Specifically, as the animal ages and maternal care decreases, HPA axis activity matures

and there is a corresponding development of fear behaviours and supporting neural circuitry. Considering that the caregiver is a species-expected stimulus in altricial species, such as rodents and primates, then premature separation or near complete deprivation in the infant period should have enormous consequences on the developmental trajectory of systems that require maternal presence. In fact, it can be hypothesised that in the presence of early adversity the transition from immature to mature fear/stress circuitry would be accelerated. The following sections outline recently collected data supporting that hypothesis in rodent, monkey and human models of early adversity.

Rat models of early life adversity within attachment and the developmental trajectory of affiliation and fear

As mentioned earlier, amygdala dependent fear learning and innate fear to predator odor does not functionally emerge until P10 (Camp & Rudy, 2004; Haroutunian & Campbell, 1979; Sullivan et al., 2000; Takahashi et al., 2005). Here we briefly review the initial developmental emergence of cue (odor) fear learning in rodents. In very young rats, cue fear (the stimulus that predicts the shock) is not expressed or learned until around P10, which corresponds with the functional emergence of the amygdala, a brain area well-documented as critical for fear. Hippocampal-dependent fear learning does not functionally emerge until pups are weaning age (Sullivan & Holman, 2010). Second, we describe how early life fear cue learning and expression is uniquely dependent on the presence of amygdala CORT and the important role of the mother in controlling her pups' CORT levels, thus controlling her pups' fear. Finally, we describe the benefits of a reduced fear system in early infancy when considered within the context of attachment to the mother.

Delayed development of olfactory fear learning and its ecological significance

Prior to the emergence of amygdala-dependent fear, pairing an odor and pain (moderate intensity shock, tailpinch, or rough handling by the caregiver) in rat pups results in a strong learned approach to the odor present during the pain (Camp & Rudy, 2004; Sullivan et al., 2000). The paradoxical odor preference learning induced by odor-pain pairings (i.e. a fear conditioning paradigm) occurs despite pups' robust response to pain and minor changes in pain threshold (Barr, 1995). Young pups fail to show odor avoidance learning due to their suppressed fear system, and particularly, the failure of the young amygdala to exhibit learning-associated plasticity. We have demonstrated this phenomenon in controlled classical fear conditioning outside the nest and within natural learning paradigms where an abusive mother delivers aversive stimuli within the nest, with all manipulations resulting in a failure to recruit the amygdala and preference learning (Raineki et al., 2012)

The suppression of fear learning and the production of preference learning by odor shock conditioning appears paradoxical. However, when these results are placed within the context of the pup's ecological niche, a cohesive picture of ecological significance emerges. The main function of odor learning in rat pups is to learn the maternal odor, which the deaf and blind pup relies on to support feeding and huddling with the mother. Finally, the maternal odor changes its characteristics as the mother eats new foods, suggesting pups are required to learn and relearn the maternal odor. Decades of research has shown us that pups readily

learn new maternal odors simply by pairing a novel odor with presumably pleasant stimuli (i.e. milk, warmth, tactile stimulation – called stroking) but also painful stimuli (0.5mA shock, tail pinch) (Camp & Rudy, 2004; Haroutunian & Campbell, 1979; Roth & Sullivan, 2005; Sullivan et al., 2000; Takahashi et al., 2005; Upton & Sullivan, 2010). Within the nest, mothers frequently interact with their pups in a gentle manner, but also inflict pain through stepping on them when entering or leaving the nest. We speculate that, since pups in the sensitive period for attachment are confined to the nest and the mother remains with her pups about 80% of the time, a broad system to support odor preference learning and suppress fear learning could optimize pups learning to approach the mother, rather than avoid the mother (Sullivan & Holman, 2010).

It should be noted that pups can learn to avoid odors if that odor is paired with malaise, such as that produced by a LiCl injection or strong 1.0 mA shock, although this learning does not depend upon the amygdala, unlike the adult, (Shionoya et al., 2006; Smotherman, 1982) and does not produce paradoxical approach/preference learning, despite pups experiencing endogenous malaise and pain.

Maternal control of the newly emerging fear system

After amygdala-dependent fear learning functionally emerges, this system has the unique function of being turned off if the mother is present. As is discussed here, it is the mother's ability to suppress pups' shock induced CORT release via social buffering, combined with the infant amygdala's unique dependence on CORT plasticity, that appears to underlie the maternal effect on fear at this age. Clues to the importance of the stress hormone CORT's critical role in fear have been known for decades. As previously stated, pups' fear expression to predator odor emerges at P10, yet increasing CORT in younger pups permits the precocious expression of fear, while reducing CORT in older pups prevents fear expression (Takahashi, 1994). Our pharmacological manipulations of pups' CORT levels also demonstrated its critical role in fear learning and its ability to switch on amygdala plasticity to support fear learning (Moriceau et al., 2006).

As noted above, CORT has a unique function in early life: it controls fear to predator odor and learned fear (Sullivan & Holman, 2010; Takahashi et al., 2005). Specifically, at about P10, shock begins to increase pups' CORT levels sufficiently to provide enough CORT to support fear expression and amygdala plasticity required for fear learning. Microinfusions of amygdala CORT can rapidly permit amygdala plasticity in pups during the SHRP, while infusions of receptor blockers prevent amygdala plasticity in post-SHRP pups. There is ecological significance to the ability of CORT to control pups' fear learning: mothers can alter pups' CORT levels though her milk or through rough handling of pups. Specifically, stress-induced rough maternal care (induced by providing insufficient bedding for nest building) produces a premature elevation in pups' CORT (Gilles et al., 1996; Raineki et al., 2012). The source of CORT seems to be a combination of that delivered through the mother's milk and pups' premature activation of the adrenal gland, which releases CORT (Raineki et al., 2012). Prematurely increasing pups' CORT, produces premature emergence of fear learning and termination of the sensitive period for attachment. Mothers can also suppress pups' cortiocsterone levels, although this only occurs after the SHRP has

terminated and pups can mount a CORT response to stressors, which more recent data suggests occurs around P10 (VanOers et al., 1998). Indeed, when pups receive shock during the 'Transitional Sensitive Period', maternal presence "socially buffers" their CORT response, by completely blocking the shock-induced CORT response. Maternal presence suppresses the infant CORT response by blocking norepinephrine release, which is typically induced by shock, and which is necessary to activate the hypothalamic-piuitary-adrenal axis, causing the release of CORT from the adrenal gland (Shionoya et al., 2006). As maternal presence blocks pups' CORT, pups' amygdala plasticity and fear learning is blocked, allowing the reinstatement of pups' attachment learning (Moriceau & Sullivan, 2006; Shionoya et al., 2006).

Taken together, these data support an acceleration hypothesis of emotion learning by early life stress, suggesting that adult-like fear behaviours and the underlying neural circuitry which produces those behaviours can be elicited prematurely by adversity which causes early HPA stimulation. Further, they highlight the important role of the mother in buffering the infants cortisol response and regulating the expression of fear in transitional periods of development.

Rat models of early-life stress: Maternal-separation and the developmental trajectory of fear and extinction systems

The developmental transition in attachment learning is not the only change to take place in the fear system across early life. As mentioned earlier fear conditioning and extinction in rats have each been shown to function differently in infancy than in adulthood (infants exhibit infantile amnesia and relapse resistant extinction whereas adults exhibit good fear retention and relapse-prone extinction learning). Importantly, Pavlovian fear conditioning and extinction are two aspects of emotional learning that have high cross-species validity and clinical relevance. For example, there is high convergence between rats and humans in the neural structures which support fear and extinction learning. Also, disruptions in the processes of fear and extinction learning are believed to underlie numerous anxiety disorders (e.g., post-traumatic stress disorder [PTSD] and specific phobias; Coles & Heimberg, 2002; Milad et al., 2008; Milad et al., 2009; Monk et al., 2008). Further, the cognitive and behavioral treatments for anxiety disorders (i.e., exposure therapy) are modeled on the process of extinction (Milad et al., 2006). Hence, understanding the processes of fear learning and fear inhibition in animals across development, as well as how these processes are affected by early-life stress, will be critical for enhancing our understanding of the establishment and progression of anxiety disorders, as well as how such disorders can be avoided through preventative intervention and treatment across the lifespan.

Much of the research which has examined the effects of early adversity on fear and extinction learning has focused on adult outcomes. For example, disruptions in the infant-caregiver relationship have been shown to lead to impaired context and cued fear conditioning (Kosten et al., 2006; Kosten et al., 2005; Stevenson et al., 2009) as well as extinction recall (Wilber et al., 2009) in adult rodents. Until very recently, only a small number of studies had investigated the early-life outcomes of infant-caregiver disruption on

fear and extinction learning, however, both of those studies support an acceleration hypothesis. Specifically, parental separation was reported to enhance active avoidance learning in juvenile rodents (Abraham & Gruss, 2010) and early-life handling enhanced contextual conditioning in P18 rats (Beane et al., 2002); both those types of fear learning are typically impaired early in development. We recently investigated the effect of early adversity on cued fear and extinction learning in infancy.

Consistent with previous studies examining the effect of stress on developmental trajectories in fear behaviour we also found that early stress accelerated the emergence of adult-like forms of cued fear retention and extinction. Specifically, we exposed rats to maternal separation (MS) rearing and then examined fear retention and extinction behaviours following conditioning in infancy. Maternal-separation is a potent stressor which typically involves removal of the pups from the mother for a moderate period of time (usually three hours), every day, across the first two weeks of life (e.g., Sanchez et al., 2001a). The procedure has been designed to model abnormal disruptions in maternal-infant contact, based upon the observation that dams often leave the nest to forage for food for periods of only 15–30 minutes (Sanchez et al., 2001a). In addition, MS is sufficient to evoke a CORT response in pups within the SHRP (Huot et al., 2002), and appears to disrupt maternal behaviors, with MS dams exhibiting delays in retrieving the pups as well as initiating licking and grooming upon reunion (Sanchez et al., 2001a). In the first demonstration that MS affected emotional learning in infant rats, Callaghan and Richardson (2011) exposed pups to 3 hour bouts of MS from post-natal days (P) 2–14. These rats were then trained, extinguished, and tested for extinction retention on consecutive days in infancy (i.e., beginning at P17). MS rats were compared to standard reared (SR) rats of the same age. Across three experiments it was shown that MS had no effect on the initial amount of fear learned or the rate of within-session extinction, with both MS and SR infant rats showing high levels of fear at the start of extinction and low levels of fear by the end of extinction. However, when MS rats were tested for their fear to the CS in a different context than extinction-training, or when rats were tested the day after a brief reminder of conditioning (a single mild footshock), their fear responses returned. Standard-reared infant rats, on the other hand, exhibited low levels of fear regardless of these post-extinction manipulations. In other words, similar to adult rats, P17 MS rats exhibited the renewal and reinstatement effects, whereas SR infant rats did not. In addition, those experiments showed that the expression of extinction at test was dependent upon activity of the neurotransmitter GABA (gamma amino butyric acid) in MS infants but not in SR infants; GABA is critical for the expression of extinction memories in adult rats but not in typically developing infant rats (Harris & Westbrook, 1998; Kim & Richardson, 2007b). Together, the results reported by Callaghan and Richardson (2011) show that disrupting the infant-caregiver relationship through maternal-separation results in an early transition from the infant to the adult extinction systems. That is, after MS, rats appear to exhibit adult-like extinction earlier in development.

Because early-life stress has been shown to cause early developmental transitions in both the extinction system and in the fear learning system, we recently asked whether early life stress would also cause an early transition in a different component of the fear system – retention (Callaghan & Richardson, 2012). In those experiments rats were exposed either to MS or SR

and were then trained in infancy (P17). Using a between-subjects design rats were tested for their fear to the CS at one of two intervals, either 1 day later (an interval where young rats would normally remember) or 10 days later (an interval where young rats would normally forget; Callaghan & Richardson, 2012). The performance of the SR animals was consistent with the typical profile of infantile amnesia – memory was good one day after training but was dramatically reduced 10 days after training. The performance of the MS animals on the other hand was surprising because memory expression was high at both the one and 10 day intervals, suggesting that no forgetting had occurred across that time period. In a follow-up experiment we examined how long infant MS rats could retain a memory before it was forgotten. In that experiment the performance of MS paired rats was compared to a control group of MS rats that was given unpaired presentations of the CS and US at intervals 7, 14, 30, or 55 days after training. While MS unpaired rats expressed low freezing to the CS at all intervals, MS paired rats expressed fear to the CS for as long as 30 days post conditioning. In a final experiment of that study, we examined whether the effects of MS could be mimicked by exposing mothers to the stress hormone CORT in their drinking water, rather than putting them through an MS procedure. In that experiment, pups that were nursed by CORT-treated dams (CORT-nursed) exhibited the same enhanced retention of fear associations as did the MS pups in the earlier experiments. On the other hand, pups nursed by vehicle-treated mothers exhibited infantile amnesia. Those results suggest that exposure to a stress hormone alone was sufficient to cause the early transition in fear retention systems.

Taken together, the studies reviewed here suggest that experiences which occur in the first few weeks of the rats' life are vital in establishing the developmental trajectory of emotion regulation systems. While adult-like forms of fear retention and fear extinction are typically slow to develop, these forms of emotion learning come online much faster following exposure to stress and stress hormones. These findings contribute to the burgeoning literature which points to stress as a general developmental switch, stimulating developmental transitions in many forms of emotional learning.

Rhesus monkey models of early life stress: phylogenetic bridge between rodents and humans

As demonstrated by the extensive work described above, rodents are indispensable translational models of the effects of early life stress on the development of fear and emotion systems. However, due to their phylogenetic distance to humans, it is difficult to know how these findings translate to primates. Non-human primate models are crucial when studying the neural mechanisms of the developmental effects of early life stress because they help to bridge the phylogenetic gap between rodents and humans (Gibbs et al., 2007). Rhesus monkeys, an Old World species, in particular have been widely used to study outcomes following disruption of the mother-infant relationship in early life due to their similarity to humans in both behavioral and neural development. Rhesus monkeys show complex social behaviors and mother-infant relationships that develop in ways similar to humans. For example, rhesus monkeys have single offspring and infants spend the first month of life in close physical contact with their mothers, who limits the infant's social interactions to

immediate family members (Hinde & Spencer-Booth, 1967), much like the infant phase in humans. Another example are the rapid changes in the mother-infant relationship that occur between 3 and 6 months of age, a time of increased infant independence, exploration and social interactions, when social fear emerges, corresponding to the toddler age in humans. Rhesus monkeys have been instrumental in providing evidence of the neurodevelopmental changes that parallel these behavioral changes in primates, both under species typical conditions and during disruption of the mother-infant relationship.

Several rhesus monkey models of mother-infant relationship disruption have been used to study the effects of this experience on the brain and behavior (Sanchez et al., 2001b). Rearing monkeys without a mother in partial social isolation (as done by Dr. Harry Harlow and colleagues in the 1960's and 70's) resulted in severe behavioral and social deficits including stereotypies, self-injurious behavior, inability to read social cues or develop normal social relationships, and hyper aggressiveness, while rearing in complete social isolation led to similar outcomes, but with increased severity, and also included increased fear and anxiety (Seay & Gottfried, 1975; Suomi et al., 1971). Maternal separation has also been used in non-human primates to model early life stress and its effects on the brain. Separation from the mother is a potent stressor in infant monkeys, just as in rodents, that leads to increased motor activity, vocalizations, and increased HPA axis function (Bayart et al., 1990; Harlow et al., 1971). Increased acoustic startle reactivity and alterations in HPA axis function have been reported in maternally separated monkeys (Sanchez et al., 2005), effects thought to be mediated by exposure to elevated levels of stress hormones (Sanchez et al., 2001a).

These alterations parallel those discussed above in rodents and are thought to be due to underlying alterations in the brain, particularly regions involved in fear and emotion such as PFC-amygdala circuits. It is important to highlight that rhesus monkeys have well-developed brains that closely resemble humans' in respect to organization and neurochemistry (Barbas, 2000; Croxson et al., 2005; Reep, 1984; Thiebaut de Schotten et al., 2012), particularly regarding the PFC, which is very different in primates versus rodents (Öngür & Price, 2000; Preuss, 1995; Preuss & Goldman-Rakic, 1991a; 1991b), making them strong model organisms to study developmental effects of experience on PFC-amygdala circuits. The rhesus brain also develops in similar temporal and anatomical patterns as in humans, i.e. maturational processes occur in similar region specific patterns during development, although over a condensed time period in the case of monkeys (approximately 1:4 years, monkey to human time; Diamond, 1991; Gibson, 1991; Huttenlocher & Dabholkar, 1997).

As mentioned earlier, PFC-amygdala circuits undergo rapid developmental changes early in life in both humans and rhesus monkeys, one of the primary reasons these regions are thought to be especially vulnerable to early life stress. For example in rhesus monkeys afferents and efferents between the amygdala and portions of temporal cortex continue to mature across the first 2 months of life (Machado & Bachevalier, 2003) and amygdala volume increases dramatically across this time (Chareyron et al., 2012; Payne et al., 2010). On the other hand, maturation and myelination of the PFC occurs over a much longer period, not becoming mature until approximately 3–4 years (Machado & Bachevalier, 2003).

Evidence in rhesus monkeys corroborates the role of cortisol in the alterations of PFC-amygdala circuits. In primates glucocorticoid and mineralocorticoid receptors (the two main types of receptors to which cortisol binds) are expressed in most cortical regions, including the PFC (Sanchez, 2006; Sanchez et al., 2000). It is through these receptors that stress-induced elevations of GCs can affect the PFC and other emotion regulatory regions, particularly during development. Functional changes in metabolism in PFC that correlate with cortisol have been demonstrated in juvenile rhesus monkeys during maternal separations (Rilling et al., 2001). Interestingly, enlargement of these stress sensitive areas, including the dorsomedial PFC and dorsal anterior cingulate cortex, has been reported in juvenile monkeys reared in partial social isolation (Spinelli et al., 2009), which, given that volumes of these regions increase during and beyond the juvenile period (Knickmeyer et al., 2010) is consistent with the hypothesis that this adverse early experience increases the rate of maturation in these regions. Alterations in the HPA axis have also been reported in non-human primate models of social isolation (Boyce et al., 1995; Ladd et al., 2005). It is difficult to determine whether or not these changes are consistent with an increase in maturational rate of the HPA axis because this system is one of the primary responses to stressors, and may change its function in response to stress, especially during development. It is also important to recognize the role of heritable factors in the complex interplay of early experience and development of these systems. Recently several studies provided evidence for several gene x environment interactions and epigenetic mechanisms for the effects of early adversity (Barr et al., 2004; Provençal et al., 2012), highlighting the importance of genetic contributions to the effects of early experience.

In conclusion, nonhuman primate models have been invaluable in the study of development of the brain and behaviour in response to early life stress. To best understand the effects of mother-infant relationship disruption in primates we need to first understand normative development in primates. There is still much to learn about normative brain development before we can accurately interpret and understand the many findings described above. It is also important to recognize the importance of rodent studies in informing nonhuman primate research on both typical and atypical development. In order to further our understanding of alterations in human development, studies in monkeys can be designed using information gained from the important work being done in rodents. An example are the current studies being undertaken in the laboratory of Dr. Mar Sanchez, in which the role of the experience of maternal infant maltreatment is being investigated using a cross-fostering design in rhesus monkeys, much like the studies done by Michael Meaney and others in rodents (Caldji et al., 2011). Using this design we hope to disentangle the role of the experience, independent of heritable factors, on the brain and behavior in primates, with the ultimate goal being to apply this knowledge to humans.

Early-life adversity in the human: Developmental trajectory of amygdala circuits in previously institutionalised children

Despite the many important differences between humans and the other non-human species discussed in this paper, there are nonetheless important early-life processes that share an ecological similarity across rodents and primates. For example, although the species differ in

the duration of gestation and subsequent age at birth, the regulatory needs of the infant are highly similar regardless of species. The infant is born in an altricial state; that is, the infant could not survive without caregiving (as discussed in Tottenham, 2012). The critical value of this relationship for survival qualifies the caregiver as a species-expected stimulus for the infant. Therefore, the infant, regardless of rodent, non-human primate, or human, has the same goal, which is to ensure proximity to the caregiver (Ainsworth, 1969; Bowlby, 1982; Moriceau & Roth, 2010).

If the caregiver is a species-expected stimulus, then premature separation or near complete deprivation in the infant period should have devastating consequences on the developmental trajectory of systems that require maternal presence. As is discussed in this paper, the amygdala and prefrontal cortex have shown aberrant developmental trajectories following early caregiving adversity in the monkey and the rodent. In particular, the rodent findings provide evidence that maternal absence acts to accelerate amygdala and prefrontal development. This acceleration may be a developmental adaptation of the infant to meet the unexpected needs elicited by a severely altered caregiving environment. This section discusses development of the human amygdala following early maternal deprivation.

The hypotheses driving research with human samples have been largely motivated and constrained by the animal findings, such as those presented in this paper. Until the advent of functional magnetic resonance imaging (fMRI) technology, a non-invasive technique that provides both structural information and an indirect measure of neural activity, there was very little opportunity to address neurodevelopment in healthy and awake humans. Structural or functional MRI is a particularly valuable technique for examining the development of deep structures in the brain, such as the amygdala. With the advent of fMRI, the field of research on human brain development has exploded. For the first time in history, scientists are able to obtain information about normative brain development in awake and performing child and adolescent participants. The first fMRI study on normative brain development was published by Dr. BJ Casey (1995), and since then, the field has grown rapidly.

Early-life stress exposure is an experimental variable that can be controlled in many animal models. That is, to make claims about the timing of early-life stress, researchers can restrict the timing and duration of adversity to a particular developmental period (e.g., the early post-natal period). However, this temporal specificity is not commonly available in most human populations, where adversity tends to remain a fairly stable characteristic across the lifetime (e.g., psychosocial adversity at one age has a high likelihood of being followed by subsequent adversity/ies). Therefore, making claims about the effects of early adversity on human amygdala development is typically not possible. The sample that we have been closely following is a very special group of children and adolescents who experienced maternal deprivation (in the form of institutional rearing, such as orphanages abroad) and were subsequently adopted (via international adoption) into families in the United States. Families that adopt internationally tend to come from very high socio-economic backgrounds. As demonstrated by their efforts to adopt internationally (which is arduous), families that adopt internationally have a great desire to provide care, a critical characteristic in children’s mental health outcomes (Hodges & Tizard, 1989). Therefore, this population of children provide two unusual factors: the environment of early-life (pre-adoption) and that

after adoption contrast starkly; and the end-date of the maternally deprived environment is known.

Consistent with animal models that have shown alterations in amygdala development following early-life stress, examination of human amygdala development has also demonstrated altered phenotypes. In a group of children (mean age = 8 years old), those with a history of institutional care (previously-institutionalized; PI) exhibited larger amygdala volumes relative to a typically-raised comparison group of peers (Tottenham et al., 2010). Longer stays in the institutional care setting (i.e., later age of adoption) were associated with larger amygdala volumes. Similar findings have been observed in a group of children adopted from Romania into the United Kingdom (Mehta & Golembo, 2009; although see Sheridan & Fox, 2012). Larger amygdala volumes have been observed in less extreme forms of maternal deprivation as well; namely, children of depressed mothers also exhibit enlarged amygdala volumes and elevated levels of glucocorticoids (Lupien & Parent, 2011). These findings suggest that the human amygdala may be particularly sensitive to variations in maternal care early in life. We have observed behavioral correlates of amygdala phenotype such that larger amygdala volumes were associated with more errors on a behavioral regulation task in the context of highly arousing emotional information and greater parent reported internalizing problems and trait anxiety (Tottenham et al., 2010), phenotypes commonly identified in this sample of children (Goff et al., 2012; Wiik & Loman, 2011; Zeanah et al., 2009). It is unclear what larger volume as assessed by structural MRI reflects at the cellular level, but rodent work has shown that early weaning results in premature myelination of cells in the basolateral amygdala (Ono et al., 2008). If the same occurs in humans, structural differences measured at the level of MRI may reflect increased speed and efficiency within the amygdala following early caregiving adversity.

Activity of the amygdala and its connections with medial prefrontal cortex (mPFC) are also altered following institutional rearing. We have observed amygdala hyperactivity in PI youth across two separate samples (Weill Cornell Medical College & UCLA) in response to highly arousing emotional faces (Tottenham et al., 2011). Amygdala hyperactivity was associated with poorer social competence with peers as reported by parents, and hyperactivity also mediated group differences in laboratory-measured social behaviors. Specifically, children in the post-institutionalized group exhibited decreased eye-contact relative to typically-raised peers, and this decreased contact was mediated by heightened amygdala response during the scanning session.

We also observed a pattern of functional connections between amygdala and mPFC that was highly consistent with the rat models presented above. Typically raised children show an immature pattern of task-based connectivity between amygdala and mPFC (Gee et al., 2013) (i.e., positive coupling, such that when activity of the amygdala increased, so did activity of the mPFC). This immature pattern was paralleled by high amygdala reactivity and immature fear behaviors (i.e., developmentally normative high separation anxiety). This amygdala-mPFC connectivity phenotype switched to an adult-like phenotype around 10 years old, such that like adults, adolescents showed the mature pattern of amygdala-mPFC connectivity (i.e., negative coupling, such that when mPFC activity increased, amygdala reactivity decreased). The mature pattern was paralleled by decreased amygdala reactivity and lower levels of

separation anxiety. In contrast to the typical group, PI children showed evidence of the mature amygdala-mPFC connectivity phenotype such that their connectivity resembled an adolescent's (Gee et al., 2013a). These group differences between typically raised and PI children were mediated by group differences in cortisol production, consistent with the notion that stress can accelerate amygdala-mPFC circuit development. One interpretation of this timing effect is that the shift in connectivity towards the adult-state is the cascading result of early and/or elevated amygdala activity, which could have instantiated this change in connections with mPFC.

It is unclear at this point whether aberrant amygdala development in the post-institutionalized group reflects accelerated development of the human amygdala as it does in the rodent. To make this claim, much more needs to be understood about the normative course of human amygdala development. The age of human amygdala functional onset is not yet known, and this information is critical for understanding the timing effects of early adversity. In the rodent, the amygdala remains functionally dormant for a period (e.g., approximately 10 days) after birth. This level of specific knowledge has not been established in the human, although it is a goal in the human research and progress is being made. We have shown that the human amygdala is responsive to fear-relevant stimuli by 4 years old (Gee et al., 2013b). The amygdala was highly reactive at this young age and showed attenuated responses in older ages. This finding suggests that amygdala functional onset emerges earlier than early childhood and may occur in the preschool period (if not earlier). Until those data are collected, it is not possible to know whether heightened amygdala response following early life caregiving adversity reflects acceleration or not. In fact, the heightened amygdala reactivity to fear faces observed in typically developing groups may mask any group differences in amygdala hyperactivity during early childhood. Therefore, a prerequisite for understanding the effects of early caregiving adversity is to characterize normative development of the human amygdala.

Conclusions

The models of early-life stress discussed here (maternal-deprivation/separation, abuse) are frequently used, across species, to empirically examine the effect of exposure to adverse events on early emotional functioning. The fact that many emotional disorders emerge during development and are associated with early-life adversity affords high clinical importance to the research being done in this area and support the use of a translational approach. Indeed, there are many features of early stress models that make them amenable to translation across species. Specifically, neural circuits that are affected by early stress, and those which support fear learning and attachment, are highly preserved across different species (e.g., rodents and primates; Lissek et al., 2005; Milad et al., 2008; Milad et al., 2009; Monk et al., 2008). Also, the infant-caregiver relationship is critical for infant survival in all altricial mammals (due to complete dependence upon the caregiver at birth), suggesting that maternal-deprivation/separation and abuse represent ecologically valid models of disruption in exposure to a species-expected stimulus.

In the symposium, and now in this review, we have highlighted the remarkable similarity in research findings to emerge from current models of early-life adversity across 3 different

species – rodent, monkey, and human. The four research groups that contributed to this symposium had reported that early-life adversity affected the maturation of fear circuitry (e.g., amygdala and prefrontal cortex), as well as associated behaviours of the fear network (e.g., attachment learning, fear conditioning, extinction, and anxiety). It is striking that many of these outcomes appear to reflect accelerated maturation of emotion circuits and behaviours following early-life stress. Indeed, early maturation of fear systems following adversity could be advantageous, promoting independent survival at an earlier than expected time point. However, the interpretation of these findings as either accelerated maturation, or aberrant development, will be greatly enhanced by further studies which map typical development of emotion networks in the brain, especially in monkeys and humans (see Gee et al., 2013b; Qin et al., 2012, for examples). If these outcomes are indeed reflective of accelerated maturation it will be interesting for future studies to determine the functional 'cost' of such premature development in emotional systems as well as the short-term benefits and the likely evolutionary significance of this effect. We hope that these findings will encourage greater research into the development of fear circuits and the environmental cues which regulate their maturation across species.

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