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Implications of newborn amygdala connectivity for fear and cognitive development at 6-months-of-age

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ABSTRACT

The first year of life is an important period for emergence of fear in humans. While animal models have revealed developmental changes in amygdala circuitry accompanying emerging fear, human neural systems involved in early fear development remain poorly understood. To increase understanding of the neural foundations of human fear, it is important to consider parallel cognitive development, which may modulate associations between typical development of early fear and subsequent risk for fear-related psychopathology. We, therefore, examined amygdala functional connectivity with rs-fcMRI in 48 neonates ($M = 3.65$ weeks, SD = 1.72), and measured fear and cognitive development at 6-months-of-age. Stronger, positive neonatal amygdala connectivity to several regions, including bilateral anterior insula and ventral striatum, was prospectively associated with higher fear at 6-months. Stronger amygdala connectivity to ventral anterior cingulate/anterior medial prefrontal cortex predicted a specific phenotype of higher fear combined with more advanced cognitive development. Overall, findings demonstrate unique profiles of neonatal amygdala functional connectivity related to emerging fear and cognitive development, which may have implications for normative and pathological fear in later years. Consideration of infant fear in the context of cognitive development will likely contribute to a more nuanced understanding of fear, its neural bases, and its implications for future mental health.

1. Introduction

1.1. Typical development of fear in infancy

Fear is a basic emotion involving perception of potential danger. The importance of fear for survival and adaptive functioning is highlighted by the conservation of fear-based learning and behavior, and the underlying neural circuitry across species (Milad and Quirk, 2012; Phelps and LeDoux, 2005). The developmental trajectory of fear in human infants is typically characterized by increasing fearfulness over the first year of life (Carranza Carnicero et al., 2000; Gartstein and Rothbart, 2003; Gartstein et al., 2010). In particular, a steep increase in fearfulness has been observed beginning at approximately 6-months-of-age (Braungart-Rieker et al., 2010) when a fear of strangers (Brooker et al., 2013; Waters et al., 1975), and increased allocation of attention to human facial expressions indicative of danger (Nelson and Dolgin, 1985; Peltola et al., 2009a,b) begin to emerge.

While a large part of the child and adult literature focus on pathologic aspects of fear, the increase in fear around 6 months of age in infants has been interpreted as supporting infants' ability to successfully navigate the environment (as it coincides with increased capacity to independently navigate and explore surroundings, Leppanen and Nelson, 2012). At the same time, infant fear plays an important role in facilitating attachment with caregivers, as the presence of caregivers regulates fear and reduces distress (Ainsworth and Bell, 1970; Hofer, 1994; Landers and Sullivan, 2012). In fact, higher levels of fear during infancy have been associated with increased capacity to benefit from supportive

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caregiving (Belsky et al., 2007; Belsky and Pluess, 2013). Moreover, early fearfulness is also associated with subsequent development of prosocial emotions (Baker et al., 2012; Kochanska et al., 2002), and lower levels of aggression and disruptive behavior problems (Biederman et al., 2001; Rothbart and Bates, 2006).

1.2. Links between early fear and subsequent pathological fear

Although fear is adaptive, and typical developmental trajectories involve increasing fear during the first year of life, high levels of fearfulness during early development have also been associated with development of anxiety disorders. Higher levels of fearful temperament (and particularly a well characterized type of fearful temperament termed behavioral inhibition) during infancy and early childhood have been linked to the subsequent emergence of anxiety symptoms (Gartstein et al., 2010; Kagan and Snidman, 1999), and increased frequency of anxiety disorders in childhood and adolescence (Clauss and Blackford, 2012). Consistently high levels of fearfulness over time during toddlerhood and early childhood (Chronis-Tuscano et al., 2009; Hirshfeld et al., 1992), and extremes of fearful temperament during infancy and toddlerhood (Pérez-Edgar and Fox, 2005; Schwartz et al., 1999), are particularly strong predictors of emerging anxiety in adolescence. However, despite these findings, the association between early temperamental fear and subsequent anxiety is modest (Degnan and Fox, 2007; Nigg, 2006).

1.3. Disentangling maladaptive versus adaptive fear development by considering parallel cognitive development

In light of somewhat conflicting evidence regarding the implications of early fear development, investigators have sought to examine factors that interact with early fearfulness to determine healthy versus maladaptive developmental trajectories (Degnan et al., 2010). One fruitful approach that has emerged for disentangling maladaptive versus adaptive fear development is examination of fear in parallel with cognitive development. Patterns of negative emotional reactivity, including fearfulness, have generally been conceptualized as strong risk factors for psychopathology in the context of low cognitive capacity to regulate emotional and behavioral responses (Nigg, 2006; Rothbart and Bates, 2006). In line with this idea, children with high levels of fearful or inhibited temperament accompanied by higher cognitive skills, and particularly ability to shift attention, are less likely to develop anxiety symptoms compared to fearful children with lower cognitive skills (Degnan and Fox, 2007; Fox and Pine, 2012; White et al., 2011). This pattern extends to infancy. During the first year of life, higher levels of negative affect (including fear) predict subsequent internalizing symptoms only for infants with poor capacity to orient attention and regulate emotions (Gartstein et al., 2012). Thus development of cognitive skills may mitigate the chances of normative fear development leading to fear-related psychopathology.

Other research goes further and suggests that the combination of higher fear and early emerging cognitive skills during infancy may be associated with more optimal emotional and cognitive outcomes. For example, Crockenberg and Leerkes (2006) reported that in the context of good attentional control at 6 months, high distress to novelty at 6 months predicted lower levels of anxiety symptoms at 2.5 years (Crockenberg and Leerkes, 2006). A combination of both high negative reactivity and high frequency of regulatory behaviors (including attention orienting, seeking comfort, and avoidance) in response to a frightening stimulus at 15 months, has been found to predict the highest levels of executive functioning at 4-years compared to all other combinations of reactivity and regulation (Ursache et al., 2013). Taken together these results suggest that parallel examination of cognitive development is an important starting point for understanding the implications of fear during infancy for ongoing development and behavioral health.

1.4. Early brain connectivity as a predictor of fear development

In the current study we attempt to determine whether markers of functional brain organization in the neonatal period precede and relate to the emergence of fear at 6 months-of-age. Importantly, we do this in the context of variation in cognitive development to contribute to a more nuanced understanding of fear development. We focus on amygdala connectivity due to the animal literature indicating an important role for the amygdala in the early development of fear (Barr et al., 2009; Bauman et al., 2004; Bliss-Moreau et al., 2010; Moriceau and Sullivan, 2006; Moriceau et al., 2006; Raper et al., 2013). In humans, the amygdala functions in a coordinated manner with multiple subcortical and cortical brain regions including sensorimotor, emotion, memory and higher order attention centers (Das et al., 2005; Gabard-Durnam et al., 2014; Gee et al., 2013a,b; Qin et al., 2014, 2012; Roy et al., 2009; Stein et al., 2007). Previous work in children and adults has highlighted coordinated functioning of the amygdala with several of these brain regions, including the anterior insula (aI) and medial prefrontal cortex (MPFC), as particularly important for understanding the neural basis of typical and pathological fear (Callaghan et al., 2014; Etkin et al., 2011; Etkin and Wager, 2007; Milad and Quirk, 2012; Qin et al., 2014; Rabinak et al., 2011; Sripada et al., 2012). However, the role of amygdala connectivity in the emergence of fear during infancy has not been investigated.

1.5. The role of the caregiving environment

In examining neonatal amygdala connectivity as a precursor of emerging fear and cognitive development during infancy, it is imperative to consider the role of the caregiving environment. Evidence suggests that early developmental trajectories of fear are influenced by levels of positive and responsive caregiving (Braungart-Rieker et al., 2010; Gartstein et al., 2010). Work in animal models and with human children indicates that caregiving influences emerging fear via effects on developing amygdala circuitry (Gee et al., 2013a; Landers and Sullivan, 2012; Tottenham, 2014). An emerging body of work also suggests that certain early biological phenotypes (in the form of combinations of certain genes or aspects of nervous system functioning) confer sensitivity to the caregiving environment, such that negative environments will be associated with more detrimental outcomes, and positive environments will be associated with more gains (Belsky, 1997; Boyce and Ellis, 2005). Patterns of amygdala functioning (and associated physiological and behavioral measures) are posited to be a potentially important biological phenotype in determining sensitivity to the caregiving environment (Belsky and Pluess, 2013; Obradović and Boyce, 2009).

1.6. Present study

The present study therefore has the following aims. First, we aim to identify whether patterns of neonatal amygdala functional connectivity precede and relate to emerging fear at 6-months-of-age, an important time for typical development of fear behaviors. Second, we aim to establish whether patterns of amygdala connectivity at birth provide information relevant not only to development of fear, but to a more nuanced understanding of fear that incorporates cognitive development. Third, we aim to identify the extent to which functional brain connectivity at birth is relevant for emerging fear and cognition after accounting