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This paper presents my conceptual model of threat and deprivation as dimensions of early experience that have distinct influences on children's emotional, cognitive, and neural development. This model has guided much of the empirical work in my lab over the past five years, and has also stimulated research by other groups.

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Review

Childhood adversity and neural development: Deprivation and threat as distinct dimensions of early experience☆

Katie A. McLaughlin[a,*,1], Margaret A. Sheridan[b,1], Hilary K. Lambert[a]

[a] Department of Psychology, University of Washington, Seattle, WA, United States
[b] Division of Developmental Medicine, Boston Children's Hospital, Harvard Medical School Boston, MA, United States

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ABSTRACT

A growing body of research has examined the impact of childhood adversity on neural structure and function. Advances in our understanding of the neurodevelopmental consequences of adverse early environments require the identification of dimensions of environmental experience that influence neural development differently and mechanisms other than the frequently-invoked stress pathways. We propose a novel conceptual framework that differentiates between *deprivation* (absence of expected environmental inputs and complexity) and *threat* (presence of experiences that represent a threat to one's physical integrity) and make predictions grounded in basic neuroscience principles about their distinct effects on neural development. We review animal research on fear learning and sensory deprivation as well as human research on childhood adversity and neural development to support these predictions. We argue that these previously undifferentiated dimensions of experience exert strong and distinct influences on neural development that cannot be fully explained by prevailing models focusing only on stress pathways. Our aim is not to exhaustively review existing evidence on childhood adversity and neural development, but to provide a novel framework to guide future research.

Contents

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* Corresponding author. Tel.: +1 206 616 7863.
E-mail address: mclaughk@uw.edu (K.A. McLaughlin).
[1] Please note that these authors contributed equally to this work.

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There has been a veritable explosion of research in the last decade into the long-term consequences of exposure to childhood adversity. The terms 'childhood adversity', 'adverse childhood experience', and 'early life stress' have been used to refer to a broad set of negative exposures during childhood, ranging from physical and sexual abuse to institutional rearing and chronic poverty (Anda et al., 2006; Burghy et al., 2012; Cohen et al., 2013). Evidence from population-based epidemiological studies indicates that childhood adversity is common and associated strongly with the subsequent onset of psychopathology not only in childhood, but also in adolescence and adulthood (Cohen et al., 2001; Green et al., 2010; Kessler et al., 1997; McLaughlin et al., 2012). Individuals who have been exposed to adverse childhood experiences are at elevated risk of developing a wide range of mental disorders, including mood, anxiety, behavior, and substance use disorders. Importantly, exposure to childhood adversity has been shown to explain more than 30% of mental disorders in the U.S. population (Green et al., 2010; McLaughlin et al., 2012), underscoring the significance of these experiences in shaping population-level mental health.

The strong and pervasive relationship between adverse childhood experiences and psychopathology has generated considerable interest in identifying the underlying mechanisms that explain these associations. However, identifying central mechanisms has proved difficult, because different types of adverse experiences frequently co-occur, meaning that most individuals exposed to childhood adversity have experienced multiple adverse experiences (Dong et al., 2004; Finkelhor et al., 2007; Green et al., 2010; McLaughlin et al., 2012). Recognition of the co-occurring nature of adverse childhood experiences has resulted in a shift from focusing on single types of adversity, such as parental death, divorce, abuse, and neglect (Chase-Lansdale et al., 1995; Dubowitz et al., 2002; Fristad et al., 1993; Mullen et al., 1993; Wolfe et al., 1994), to examining the associations between *number* of adverse childhood experiences and psychopathology (Arata et al., 2007; Dube et al., 2003; Edwards et al., 2003; but see also Humphreys and Zeanah, 2014 for a recent alternative approach). The fundamental lesson from this research has been that as childhood adversities increase, the likelihood of psychopathology increases. While this has proved valuable for identifying children in need of intervention, it has led to an oversimplification of the boundaries between distinct types of environmental experience and has done little to uncover the core underlying mechanisms through which adversity increases risk for psychopathology.

Here we propose that cognitive neuroscience provides a powerful set of tools that will allow us to most fruitfully identify the developmental pathways linking childhood adversity to psychopathology and that examining the imprint of environmental experience on neural structure and function will help to resolve some of the challenges inherent in studying complex and co-occurring exposures. Indeed, one of the basic principals of neuroscience, developed and elaborated over the last half century, is that early experience shapes the structure and subsequent function of the brain. A small but rapidly growing body of work has begun to examine the impact of childhood adversity on neural development (Hackman and Farah, 2009; Hart and Rubia, 2012). However, to date most existing work has conceptualized adverse childhood experiences purely within a stress perspective, which has hindered the identification underlying dimensions of environmental experience that might influence neural structure and function in distinct ways (but see Rao et al., 2011 for a counter example). Here we argue that the distinct neural effects of different dimensions of experience have often been oversimplified or ignored. Extant research has almost universally defined childhood adversity according to broad descriptive categories (i.e., abuse, neglect, institutionalization, poverty) or has examined even broader constructs that combine diverse forms of adversity together, often referred to as 'early life stress' (Burghy et al., 2012; Cohen et al., 2006; Gatt et al., 2009). This term has been used to refer to such disparate experiences as parental psychopathology, abuse, poverty, marital conflict, and institutional rearing. This approach not only obscures meaningful differences between these types of experiences that are likely to have important implications for understanding their effects on neural development but also implicitly suggests that very different types of environmental experiences influence brain development through the same underlying mechanisms. This lack of specificity both with regard to the measurement of environmental experience and the impacts on brain development constitutes a critical barrier to identifying the pathways through which childhood adversity impacts neural development and, ultimately, psychopathology.

Current conceptualization of the impact of childhood adversity on neural development has focused almost exclusively on stress pathways and allostatic load (Burghy et al., 2012; Cohen et al., 2013). The stress model has been described in detail in numerous previous papers (see McEwen, 2012). Briefly, activation of the hypothalamic–pituitary–adrenal (HPA) axis results in the release of glucocorticoids, which can lead to structural and functional changes in brain regions with high concentrations of glucocorticoid receptors, including the hippocampus, amygdala, and prefrontal cortex (PFC) (McEwen, 2012). The HPA axis is a plastic system and exposure to extreme or chronic stress can lead to changes in the functioning of this system, resulting in excessive or blunted glucocorticoid release and related downstream structural consequences in the brain (McEwen, 1998, 2012). Extensive evidence suggests that early exposure to adverse environments can disrupt the development and functioning of the HPA axis (Gunnar and Quevedo, 2007), and this is the primary mechanism through which it is often argued that adverse experiences shape neural structure and function. Focusing only on this mechanism is problematic, however, as adversity sometimes appears to have a remarkably broad impact on neurodevelopment. For example, children exposed to institutional rearing exhibit widespread cortical thinning in the superior and inferior parietal cortex (McLaughlin et al., 2014), and children exposed to neglect and poverty often have deficits in language abilities (Farah et al., 2006; Hildyard and Wolfe, 2002) and accompanying differences in neural function supporting language function (Raizada et al., 2008). Neither of these patterns is an obvious consequence of HPA axis activation or cortisol.

However, this evidence is by no means conclusive. Glucocorticoids are only one of many mediators that work together to modulate brain development following stress. The coordinated actions of these mediators are dependent on the state of differentiation of each brain region and are highly region and cell type specific when stress occurs. Indeed, a host of mechanisms of hormone action reveal that the whole brain is a target for the modulatory effects of stress and other hormones via genomic and non-genomic receptors (Liston et al., 2013; McEwen, 2010; Popoli et al., 2012) As such, it is important to acknowledge that the effects of stress are not fully mediated by cortisol (the most common marker of HPA axis activation in human research) and that cortisol actions on their own do not explain how stress affects gene expression or neuronal plasticity (Gray et al., 2013). Thus, although it is possible, given the potentially wide variety of effects that stress can have on the brain, that the changes described above are the downstream effect of stress exposure, it is also possible – and we argue, likely – that alternative mechanisms explain these effects of childhood adversity on neural development. Investigating these mechanisms first requires a novel method of describing and measuring different forms of childhood adversity.

We argue here that the field must move beyond the prevailing approach to one that attempts to distill complex adverse experiences into their core underlying dimensions, and we propose a conceptual framework for doing so. Specifically, our model

differentiates between experiences of *deprivation* (i.e., the absence of expected environmental inputs and complexity) and *threat* (i.e., the presence of experiences that represent a threat to one's physical integrity) and provides predictions and preliminary evidence grounded in basic neuroscience principles and mechanisms drawn from animal research on sensory deprivation and fear learning about the expected effects of each of these dimensions of experience on neural structure and function. Our aim is not to exhaustively review existing evidence on early adversity and neural development in humans or animals, but to provide a novel conceptual framework to guide future research.

Importantly, we do not propose that deprivation and threat are the *only* dimensions of early experience that are important or that all types of childhood adversity can be conceptualized solely along these dimensions. For example, institutional rearing involves the complete absence of an attachment figure early in development, (Tottenham, 2012). This lack of species-typical expectations of the presence of an attachment figure in early development is a dimension not fully captured by either deprivation or threat. Rather, we propose that these are two dimensions of experience that have not previously been clearly differentiated or explained by prevailing models focused on stress pathways and argue that these dimensions of experience exert strong and distinct influences on neural development.

1. Distinguishing between deprivation and threat

The framework we propose here distinguishes between core dimensions of environmental experience that underlie different forms of childhood adversity and describes their distinct impacts on neural development. The central distinction we make is between experiences of *deprivation* and experiences of *threat.* We suggest that these dimensions of experience can be assessed across different forms of childhood adversity (e.g., physical and sexual abuse, domestic violence, institutionalization, neglect) and will differentially predict aspects of neurodevelopment and ultimately behavior. Experiences of deprivation involve the absence of expected cognitive and social inputs as well as the absence of species- and age-typical complexity in environmental stimuli. The impact of low environmental complexity on cortical development has been well studied in animal models of sensory and global deprivation and is conserved across species (Diamond et al., 1972; Leporé et al., 2010; O'Kusky, 1985). The dimension of deprivation is central for children exposed to institutionalization, neglect, and poverty (Fig. 1). In contrast, experiences of threat include events that involve actual or threatened death, serious injury, sexual violation, or other harm to one's physical integrity. Threat experiences are conceptually similar to events defined as traumatic in the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013). Events involving threat of serious harm result in strong learning mediated by emotional learning networks that have been well characterized in animals and are conserved across species (Johansen et al., 2011; LeDoux, 2003). Threat is a primary dimension of experience for children exposed to physical and sexual abuse, domestic violence, and other types of interpersonal violence (Fig. 1). Critically, we do not propose that exposure to deprivation and threat experiences *occurs* independently for children, as most of the exposures described above co-occur. Instead we propose that they can be *measured* separately and have unique effects on neurodevelopment.

Below we separately describe deprivation and threat and their distinct impact on neural structure and function. Within each section we first review mechanisms of neural development from animal neuroscience (see Table 1 for a summary of animal paradigms included), describe how neuroimaging and neuropsychological measures in humans may reflect these processes, and review how exposure to deprivation and threat may shape these aspects of neural development in light of evidence from animal studies and emerging human research. Throughout we identify plausible mechanisms through which commonly studied forms of adversity (e.g., maltreatment, institutionalization) may come to affect neural development, leading to our novel model of environmental experience. We end by proposing directions for future research into the impact of adversity on neural development that will confirm or disprove these hypothesized pathways.

2. Deprivation

2.1. Predictions based on animal literature

One of the areas where the impact of experience on neural development has been most clearly documented is in the pruning of synaptic connections during development in the central nervous system. These principals were first examined in studies employing sensory deprivation (Wiesel and Hubel, 1965b). Studies of deprived or anomalous sensory input during development illustrated that one of the primary mechanisms through which early experience shapes neural structure and function is by pruning initially over-produced synaptic connections (Huttenlocher et al., 1982), described more than three decades ago as the selective-elimination hypothesis (Changeux and Danchin, 1976; Petanjek et al., 2011; Purves and Lichtman, 1980). Here we propose that the same mechanisms through which sensory deprivation or anomalous sensory environments shape primary sensory cortex in animals may also be the mechanism through which broader social-cognitive deprivation shapes association cortex in humans. We argue that we can use basic principals of sensory deprivation to make predictions about the way that decreased exposure to cognitive and social stimulation affects neural development. Specifically, we suggest that an early environment without cognitive enrichment will yield a neural structure designed to deal with low complexity environments. We predict that exposure to cognitive and social deprivation in children results in (a) age-specific reductions in thickness and volume of association cortex, as measured in vivo using MRI, due in part to early or over-pruning of synaptic connections, lower numbers of synaptic connections, and reduced dendritic branching; and (b) reduced performance on tasks that depend on these areas (e.g., complex cognitive tasks). We expect that reductions in cortical thickness should be most pronounced in regions of association cortex that are recruited for processing complex social and cognitive inputs, including prefrontal cortex (PFC), superior and inferior parietal cortex, and superior temporal cortex.

We limit our argument to the development of association cortex simply because association cortex has a prolonged developmental trajectory relative to most areas of primary sensory cortex (Gogtay et al., 2004; Huttenlocher, 1979) and because social and cognitive inputs likely shape areas of cortex involved in complex social and cognitive processing. The term association cortex refers to lateral and medial prefrontal, parietal, and temporal areas of cortex that are not primarily involved in processing sensory stimuli or motoric responding but instead are activated in response stimuli that require cognitive processing (Goldman-Rakic, 1988; Mountcastle et al., 1975). These regions are considered amodal in that they respond to and process stimuli across multiple sensory modalities. While association cortex is likely to be organized along governing principals (Badre and D'Esposito, 2009), these principals continue to be investigated and are thought to be different to the organizational principals of primary sensory cortex (e.g., retinotopy). Generally it is understood that association cortex is necessary for higher-level cognitive processes such as executive function, language, and spatial navigation as well as social cognition. We acknowledge that association cortex refers to a large area of cortex,

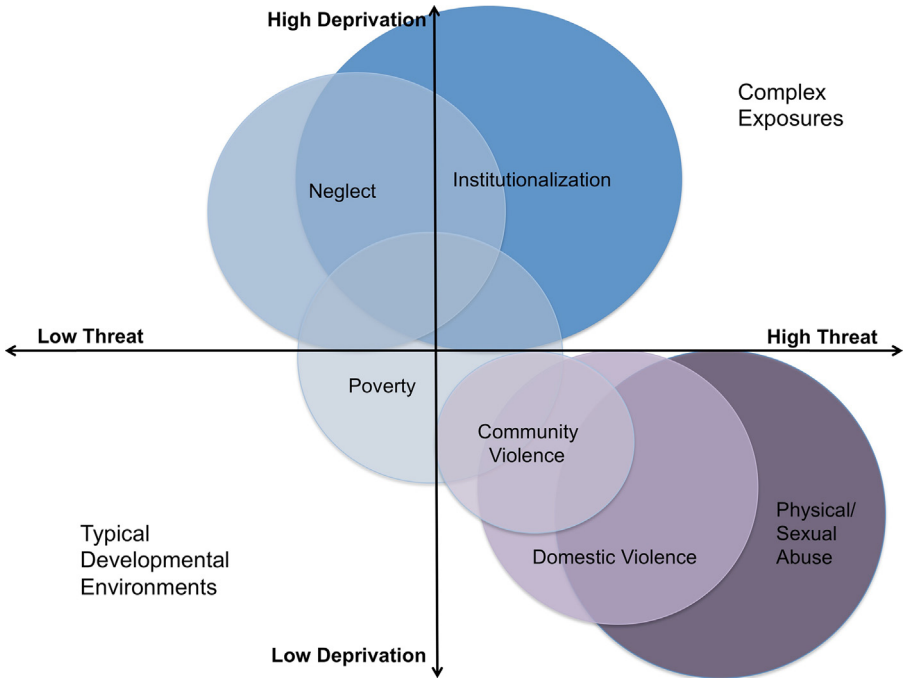

Fig. 1. *Dimensions of threat and deprivation associated with commonly occurring adverse childhood experiences (ACEs).* Importantly, we argue that threat and deprivation are *dimensions* of experience that can be measured among children exposed to a wide ranges of ACEs, both those that occur in isolation (e.g., a single incident of community violence exposure) and those that are co-occurring (e.g., physical abuse and physical neglect). We use the term complex exposures to refer to experiences that in most cases involve aspects of both threat and deprivation. Institutionalization is one such exposure, which involves deprivation in both cognitive and social inputs – consistent with our definition of deprivation – as well as the absence of a primary attachment figure, which is an atypical experience that can represent a significant threat to safety and survival for an infant in the extreme absence of care. Note that institutional rearing also involves lack of species-typical expectations of the presence of an attachment figure in early development (Tottenham, 2012), a dimension not fully captured by either deprivation and threat. Poverty differs in fundamental ways from the other exposures we describe. Critically, poverty does not inherently involve dimensions of either threat or deprivation (i.e., it is possible to be poor and to have no exposure to threatening experiences and typical exposure to cognitive, social, and environmental complexity). However, poverty is often a *marker* of exposure to both threat and deprivation, particularly deprivation in exposure to enriching and cognitively complex environments. Because the degree of threat and deprivation exposure associated with poverty is heterogeneous, this could be one reason that the findings with regard to poverty and neural development have been inconsistent across studies. Figure reproduced, with permission, from Sheridan and McLaughlin (2014).

making our predictions relatively non-specific. However, greater specificity in these predictions requires improvements in our measurement of deprivation in both animal and human models, and greater understanding of the specific types of social and cognitive inputs that are required for diverse regions of association cortex to develop normally. As we review below, the hypothesis that exposure to deprivation preferentially affects association cortex is born out in the current data on the association between exposure to environments characterized by deprivation and neural structure and function in humans.

2.1.1. Proliferation and pruning

Early in the study of neural structure, it was hypothesized that synaptic connections emerged following a genetic blue print

Table 1
Dimensions of deprivation and threat associated with commonly used animal paradigms of early adversity.

Paradigm	Description	Primary dimension
Dark Rearing	Animals that typically develop ocular dominance columns (e.g., cats) are deprived of visual input via rearing in complete darkness. Animals are not deprived of other forms of sensory input (sound, tactile, taste, smell) but are raised without visual input until they are post-pubertal	Deprivation
Individual rearing	Rodents are single-housed after weaning to reduce visual, auditory, and olfactory communication and to prevent physical interactions with littermates housed in separate cages in the same room	Deprivation
Repetitive foot shock[1]	Rodents are exposed to a series of aversive foot shocks in a closed chamber. The series of shocks is repeated daily for a number of consecutive days.	Threat
Chronic restraint	Rodents are physically restrained for a specified number of hours. Restraint is repeated daily for a number of consecutive days.	Threat
Predator odor	Rodents are exposed to a natural predator odor in a closed chamber for a specified number of hours. Exposure is repeated daily for a number of consecutive days	Threat
Minimal bedding	Rodent dam and litter are housed with a minimal amount of nesting and bedding materials for a specified number of days prior to weaning. Minimal bedding is associated with rough handling of and stepping on pups as well as inconsistent and fragmented dam-pup interactions (Raineki et al., 2012)	Threat
Chronic maternal separation	Litter is removed from rodent dam and placed in an incubator for a specified number of hours. Separation is repeated daily for a number of consecutive days prior to weaning	Deprivation and Threat

[1] Foot shock is the most commonly used stimulus in fear conditioning rodent models, which can also be used as models of early adversity (Raineki et al., 2010; Raineki et al., 2012; Sarro et al., 2014; Sevelinges et al., 2011).

(Sperry, 1963). However, the "preformist" theory rapidly gave way to evidence in favor of the selective-elimination hypothesis that emphasized the critical role that environmental inputs played in shaping neural structure (Changeux and Danchin, 1976). Since that time, decades of work have documented that central and peripheral nervous system development contains two distinct phases of synaptic growth, which ultimately shape adult neural structure and function: proliferation and pruning. Synaptic proliferation occurs in a period beginning during the third trimester, peaking about three months after birth, and ending before the second year of life (Huttenlocher and Dabholkar, 1997; Petanjek et al., 2011). During this period, there are rapid increases in the ratio of asymmetrical to symmetrical synapses (an index of newly formed synaptic connections), synaptic density, and total number of synapses (Huttenlocher and de Courten, 1987; Rakic et al., 1986). Following synaptic proliferation, a period of pruning of synaptic connections occurs and continues for an extended period through childhood and adolescence. In humans, this synaptic elimination occurs earlier for primary sensory cortex and later for association cortex, although the final density of synapses in adulthood across areas of cortex is not different (Huttenlocher, 1979; Huttenlocher and Dabholkar, 1997; Huttenlocher and de Courten, 1987).

Pruning of synaptic connections occurs in all six layers of cortex, but occurs primarily for synaptic connections on dendritic spines as compared to other classes of synapses on dendritic shafts or cell somas (Rakic et al., 1986). This is likely a corollary of the finding that presynaptic neurons rely on trophic factors released from their post-synaptic targets, and thus co-activation, for survival (Purves and Lichtman, 1980). That is, as two cells co-activate, the association between the cells strengthens, trophic factors are transmitted, and it becomes more likely that this synaptic connection will survive. In contrast, if a synaptic connection is infrequently activated, this connection becomes weaker over time and is likely to be pruned. Conceptually, the emergent system reflects the relative effectiveness of various pathways, theoretically yielding the most efficient system where only the most effective and environmentally relevant connections remain. Thus, through the interaction of pre and post-synaptic cell interactions, the elimination of synapses during development gives rise to the adult organization of the peripheral and central nervous system.

2.1.2. Visual deprivation as early experience

Much of the early work concerning the effect of experience on neural structure and function comes from investigations of the effect of visual deprivation on visual cortex structure and function. In animals this has been observed through experimental manipulation of visual input during development. In initial studies of monocular deprivation, kittens were deprived of visual input to one eye during development, leading to irreversible changes in ocular dominance columns. In contrast, monocular deprivation in adult cats leads to no such irreversible effects (Wiesel and Hubel, 1965a,b). Importantly, where early monocular deprivation leads to changes in visual cortex organization, complete visual deprivation, or "dark rearing" leads to radical reductions in synapses in primary visual cortex (V1) and irreversible decreases in visual acuity (O'Kusky, 1985). These and other findings ultimately led to the concept of developmental plasticity: the understanding that early experience has a preferentially permanent impact on neural structure, in particular during specific periods termed sensitive or critical periods when environmental stimuli have a more pronounced impact on neural structure and function (Hensch, 2005; Morishita and Hensch, 2008; O'Kusky, 1985).

In humans, the impact of sensory deprivation on neural development has been studied in individuals with congenital and late-onset blindness. Congenital blindness is associated with increased use of visual cortex to process auditory stimuli and the spatial relationships between auditory stimuli (Voss et al., 2008). In addition, congenitally blind individuals activate these cortical areas during tasks requiring the processing of auditory or tactile stimuli and when performing complex cognitive tasks (Collignon et al., 2013). This pattern of re-organization appears to reflect the fact that congenitally blind individuals may be able to use the inherent organizational structure of extrastriate cortex to process complex perceptual stimuli in other sensory modalities. Moreover, congenitally blind individuals have thinner primary visual cortex compared to sighted or late-blind participants (Collignon et al., 2013; Leporé et al., 2010), indicating that the reduction of inputs into primary visual cortex results in reductions in cortex and thus reduced processing capacity.

Thus it appears in humans and rodents that, (a) reduction in sensory inputs during periods of developmental plasticity leads to thinner cortex in primary sensory areas, due at least in part to increased synaptic pruning; and (b) non-primary sensory areas, such as extra-striate cortex, can be 'colonized' by other sensory and cognitive processes when typical inputs are absent. In humans, this appears to result in more diffuse patterns of activation in response to task demands. However, even in the context of cortical 'colonization', cortical thinning occurs within primary sensory areas, indicating that the synaptic connections associated with reduced or absent environmental input may be observable using neuroimaging techniques.

2.1.3. Global deprivation in animal models

A second literature in rodents has investigated the impact of a more general developmental experience, that of global deprivation and enrichment. It has been amply demonstrated in animal models that global deprivation due to single rodent housing results in widespread decreases in dendritic arborization, spines, and overall brain volume (Bennett et al., 1996, 1974; Diamond et al., 1966, 1972; Globus et al., 1973). This change in cortical structure has been observed following random assignment to individual housing with decreased visual, auditory, and social inputs for pre-pubertal and peri-pubertal animals (Bennett et al., 1996). Changes in dendritic morphology are marked throughout cortex (Diamond et al., 1975), are stronger and more persistent if the duration of exposure is longer (Bennett et al., 1974), and decline slowly following a transition to a new environment. These changes appear to be at least partially reversible through exposure to enriching, cognitively stimulating environments following deprivation (Diamond et al., 1972). Because the current evidence from rodent models of deprivation and enrichment are not tied specifically to the developmental stage at which exposures occur, it is difficult to know if such exposures would have a larger and less malleable impact if they occurred earlier or if they would have a smaller and more reversible impact if they occurred later.

In sum, evidence from the animal literature indicates that decreases in environmental input within a single modality (e.g., vision) during development can disrupt cortical organization and decrease dendritic arborization and number of synapses within corresponding sensory cortex regions. In animals exposed to multifaceted deprivation, a general lack of stimulation, general decreases in cortical thickness are observed due to decreases in dendritic arborization, neuronal depth, and glia cells. An obvious next step is to determine whether similar patterns of neural outcome are observed in children exposed to social and cognitive deprivation.

2.2. Consistency with evidence from human studies

We next review evidence from studies of children exposed to diverse environments that share the characteristic of lacking complexity in social and cognitive inputs. These include institutionalization, low socio-economic status (SES), and neglect, each of

which are characterized by deprivation in social stimulation, cognitive inputs (e.g., language), and in the case of institutionalization, the absence of a primary attachment figure (Hart and Risley, 1995; Hildyard and Wolfe, 2002; Smyke et al., 2007). Given observed neural changes following sensory and global deprivation in rodents, it is likely that these forms of social and cognitive deprivation will result in changes in thickness and volume in humans, as measured using MRI. We predict that exposure to these diverse forms of deprivation will be associated with age-specific reductions in cortical thickness as a result of decreases in dendritic arborization, spines, and density. Moreover, we expect that reductions in cortical thickness will be most pronounced in regions of association cortex that are recruited for processing complex social and cognitive inputs, including the PFC, superior parietal cortex, and superior temporal cortex. As shown below, existing evidence supports these predictions. Critically, however, because fine-grained measurement of the dimensions of deprivation and threat have not typically been undertaken in human studies of neurodevelopment and because prior studies have often focused on specific types of exposure (e.g., abuse) without measuring or reporting co-occurring exposures (e.g., neglect), any conclusions regarding the consistency of existing human work with our proposed framework are necessarily tentative.

Institutionalization in early childhood is a well-studied phenomenon involving exposure to profoundly deprived environments in early childhood. This exposure is complex and heterogeneous. However, most children in institutions are clearly deprived of species-expectant early experiences of two types. First, both the ratio of caregivers-to-children and caregiver investment in children are low (McCall et al., 2012; Zeanah et al., 2003). This lack of an early attachment figure, a central feature of early human experience, has been investigated and reviewed extensively by Tottenham and colleagues (Gee et al., 2013; Tottenham, 2012; Tottenham et al., 2010), and as such we do not review these effects in depth. However, briefly, lack of an early attachment figure results in increased susceptibility to anxiety that appear to be mediated by changes in amygdala structure and function (Tottenham, 2012). These findings are consistent with animal studies investigating deprivation of early maternal care (Eiland and McEwen, 2012; Tottenham and Sheridan, 2009).

Second, institutional rearing is associated with decreased social and cognitive inputs of numerous kinds. Children raised in institutions are less likely than children raised in families to be exposed to all forms of language, interactions with adults, variation in daily routines and experiences, novel and age-appropriate enriching cognitive stimuli (e.g., books, toys), opportunities for peer interaction, and a wide range of other types of environmental stimulation (Nelson et al., 2009; Smyke et al., 2007; Zeanah et al., 2003). Likely as a result of this profound social and cognitive deprivation, children raised in institutions are more likely than children raised in families to have deficits in cognitive function (Nelson et al., 2007; O'Connor et al., 2000) and in language production and comprehension (Albers et al., 1997; Windsor et al., 2011). Relatedly, children reared in institutional settings have a wide range of developmental problems including markedly elevated rates of attention-deficit/hyperactivity disorder (ADHD) (Kreppner et al., 2001; Zeanah et al., 2009). Several recent studies document associations between institutionalization and grey matter volume and thickness. In addition to being associated with global changes in cortical function (Chugani et al., 2001; Marshall et al., 2008; McLaughlin et al., 2010), institutionalization is associated with overall decreases in grey matter volume and thickness (McLaughlin et al., 2014; Mehta et al., 2009; Sheridan et al., 2012a), with the most pronounced reductions in areas of association cortex supporting complex cognitive and social processing including the PFC, superior and inferior parietal cortex, and superior temporal cortex (McLaughlin et al., 2014). In some areas of cortex these decreases in thickness mediate the association between institutionalization and atypical cognition function (e.g., ADHD symptoms; McLaughlin et al., 2014).

Although low parental SES is not as clear-cut or extreme an exposure as institutionalization, it similarly confers risk for less complex cognitive inputs during childhood. Low parental SES is associated with decreased complexity and amount of linguistic inputs (Hart and Risley, 1995), lower exposure to enriching cognitive experiences in the home (Bradley et al., 2001a,b) and in the school environment (Sirin, 2005), including decreased access to books and extracurricular experiences. Unsurprisingly, given this difference in exposure to complex cognitive stimuli, low SES is associated with decreased performance on complex cognitive tasks, including those tapping executive function and long-term memory (Evans and Schamberg, 2009; Farah et al., 2006; Hackman et al., 2010; Kishiyama et al., 2009; Noble et al., 2007), language ability (Fernald et al., 2013; Weisleder and Fernald, 2013), and overall cognitive and academic achievement (Brooks-Gunn and Duncan, 1997; Duncan et al., 1998; Jokela et al., 2009; Sirin, 2005). These differences in developmental outcomes are mediated by lack of exposure to complex and enriching activities in childhood (Bradley et al., 2001a,b; Linver et al., 2002; Yeung et al., 2002). In addition to the well-documented associations between low SES and cognitive function, low SES is additionally associated with decreased volume and volume by age in association cortex, particularly the PFC (Noble et al., 2012; Sheridan et al., in prep). Additionally, low SES is associated with increased levels and more diffuse patterns of activation in association cortex to support performance on language and executive functioning tasks in both children (Raizada and Kishiyama, 2010; Raizada et al., 2008; Sheridan et al., 2012b) and adults (Gianaros et al., 2008; Gianaros and Manuck, 2010; Gianaros et al., 2011). Further, in at least one instance the impact of low SES on neural function was explained by lack exposure to complex cognitive experiences, including language (Sheridan et al., 2012b).

Neglect refers to inadequate care on the part of parents for their offspring. This can include a lack of provision for basic needs such as food, shelter, and clothing or a lack of provision for the emotional needs of a child. Because neglect inherently involves a lack of parental care, it constitutes an obvious form of early deprivation. When neglect is directly compared to abuse, children exposed to neglect are at greater risk for cognitive deficits than children exposed to abuse (Hildyard and Wolfe, 2002) and these deficits are similar to those observed in severe poverty and institutionalization (Dubowitz et al., 2002; Spratt et al., 2012), consistent with our conceptualization of neglect as a form of deprivation. Moreover, childhood emotional neglect predicts poor performance on a cognitive control task and a more widespread pattern of dorsolateral PFC activation during trials requiring inhibitory control (Mueller et al., 2010).

3. Threat

3.1. Predictions based on animal literature

Evidence from animal and human studies demonstrates consistently that early exposure to threat is associated with long-term changes in neural circuits that underlie emotional learning. Based on this evidence, we argue that early threat exposure impacts the structure, function, and coupling of the hippocampus, amygdala, and ventromedial prefrontal cortex (vmPFC). First, we predict that early threat exposure leads to changes in hippocampal morphology and function, including reduced dendritic spines and arborization and poor function in hippocampus-dependent learning and memory tasks. These predictions are based on extensive evidence

that potential threats activate the hypothalamic–pituitary–adrenal (HPA) axis, leading to enhanced expression of corticotropin releasing hormone (CRH) in the hippocampus and damage to hippocampal neurons (Brunson et al., 2001; Ivy et al., 2010).

Second, we argue that early exposure to threat leads to changes in amygdala function. The amygdala detects and processes salient environmental stimuli, particularly stimuli that have emotional significance, such as facial displays of emotion (Adolphs, 2010; Davis and Whalen, 2001; Fitzgerald et al., 2006; Liberzon et al., 2003). Although the amygdala responds to both positive and negative emotional stimuli (Somerville et al., 2004), evidence suggests that it is centrally involved in detection of potential threats (Isenberg et al., 1999; Ohman, 2005) and required for the acquisition and expression of learned fear (Johansen et al., 2011; LeDoux, 2003). We suggest that early threat exposure leads to novel learning, resulting in the pairing of threat cues with previous neutral stimuli, a reduced threshold for experiencing fear, and heightened vigilance to detect other potential threats (van Marle et al., 2009), all of which are adaptive responses to potential danger. Together, these changes result in elevated amygdala activation to emotional stimuli due to the increased salience of such information, and potentially as a result of up-regulation of CRH receptors in the amygdala (Hatalski et al., 1998). Behaviorally, this results in heightened attention to threat-related cues, generalization of learned fear to previously neutral stimuli, and elevated emotional responses to a wide range of emotional cues. For a review of how institutionalization, a specific form of childhood adversity associated with high degrees of both threat and deprivation, influences amygdala development, please see Tottenham (2012).

Finally, we propose that chronic experiences of threat have additional influences on neural systems involved in modulating the amygdala and hippocampus. As a result of fear extinction mechanisms, exposure to consistently safe environments following early threats will result in new learning that inhibits previously acquired fear responses to threatening cues, termed extinction learning. The vmPFC is activated during retrieval of extinction learning and down-regulates the amygdala (Milad and Quirk, 2012; Milad et al., 2007; Quirk et al., 2003; Quirk et al., 2000). The vmPFC is thus essential for retention of extinction learning and inhibition of fear (Phelps et al., 2004; Quirk et al., 2000). However, learned fear continues to be represented in the amygdala and hippocampus, and previously extinguished fear can be re-activated following exposure to situations where fear learning initially occurred or to other threatening contexts (Bouton, 2002; Bouton et al., 2006; Rescorla, 2004). As such, we predict that chronic threat exposure will result in stronger representations of conditioned fear than extinction memories, lowering recruitment of the vmPFC in multiple forms of emotional processing. Over time, this reduced vmPFC recruitment will lead to accelerated pruning, resulting in reduced vmPFC thickness, and poor vmPFC-amygdala coupling (i.e., low structural and functional connectivity between these regions).

To justify our predictions regarding early threat and emotional learning networks, we review evidence from the animal literature on mechanisms underlying fear learning and extinction given substantial existing knowledge of the neural circuitry underlying these mechanisms and the consistency of that circuitry across species. Importantly, some (i.e., effects on hippocampus), but not all (i.e., effects on vmPFC), of the predictions outlined above have previously been articulated within the literature on stress and neural development (Tottenham and Sheridan, 2009). Indeed, the pathways we describe with regard to the hippocampus and amygdala have frequently been invoked as mechanisms through which stress influences the brain. We review this literature nonetheless as we expand upon prior predictions, identify other mechanisms (i.e., fear learning) that might alter hippocampus and amygdala development following threatening or traumatic experiences, and highlight the distinction between neural systems influenced by threat as compared to deprivation.

3.1.1. Fear learning

Fear is a defensive mechanism that activates behavioral and neurobiological responses to danger that promote survival, including freezing and activation of sympathetic nervous system and HPA axis, generating downstream hormonal and metabolic changes (LeDoux, 2003). An extensive literature in rodents has characterized the neural circuitry that underlies fear learning using Pavlovian fear conditioning tasks (Johansen et al., 2011; Kim and Jung, 2006; LeDoux, 2003). In Pavlovian conditioning a previously innocuous stimulus (conditioned stimulus, CS) is paired with an aversive or threatening unconditioned stimulus (US). After repeated contingent pairings, the CS begins to elicit the behavioral and neurobiological responses associated with the US. Fear conditioning happens without effort, allowing threats to quickly elicit defensive responses that promote safety. In the animal literature, the amygdala and hippocampus contribute differentially to aspects of fear learning. The amygdala is necessary for both the acquisition and expression of conditioned fear in paradigms involving a cued CS (i.e., a simple sensory stimulus, like a tone or light) and a contextual CS (i.e., a more complex polymodal stimulus, such as the place where cue conditioning occurs; (Phillips and LeDoux, 1992). In contrast, the hippocampus is involved only in the acquisition of conditioned fear to complex contextual stimuli (Phillips and LeDoux, 1992). Lesions of the amygdala prevent fear acquisition and expression to both cued and contextual CS, while hippocampal lesions prevent fear acquisition only to contextual CS (Anagnostaras et al., 1999; Cousens and Otto, 1998; Hitchcock and Davis, 1986; Phillips and LeDoux, 1994).

Learned fear is not immutable; conditioned fear generally abates with the passage of time as a result of extinction processes. Extensive evidence suggests that fear extinction involves novel learning of an association between the CS and absence of the US, rather than a loss of the initial CS-US association (Quirk, 2002). Because the CS-US pairing remains intact, extinguished fear can be re-activated through a variety of processes, including spontaneous recovery, exposure to novel threats, exposure to the CS in novel contexts, or re-exposure to the US, highlighting the context-dependent nature of extinction learning (Bouton, 2002, 2004; Bouton and King, 1983; Rescorla, 2004). Extinction of conditioned fear initially requires the amygdala, whereas retrieval of extinction memory on subsequent days additionally requires the vmPFC (Falls et al., 1992; Morgan et al., 1993; Quirk et al., 2000), which has direct projections to the amygdala (Hurley et al., 1991). vmPFC activation during recall of extinction memory inhibits the amygdala and dampens fear expression (Knapska and Maren, 2009; Milad and Quirk, 2002). Thus, successful fear extinction requires functional coupling of the vmPFC and amygdala (Quirk et al., 2003).

3.1.2. Effects of early threat on fear learning circuits

Exposure to threatening stimuli early in development has consistently been shown to alter the neural circuitry underlying fear conditioning and extinction. Here we focus on paradigms that specifically elicit fear, including repeated foot shock, physical stress (e.g., restraint), and predator odor (see Table 1). We also highlight findings from minimal bedding paradigms that result in erratic, inconsistent maternal care provided to pups (Rice et al., 2008), as well as increases in rough handling of pups by the dam (Raineki et al., 2012; Roth and Sullivan, 2005). In the service of focusing explicitly on models of threat, we do not review paradigms that elicit more complex emotional and neural responses, including early maternal separation (Liu et al., 1997), which involves both high threat as well as high degrees of deprivation resulting from

isolation and lack of both social and cognitive inputs during separation.

An extensive literature documents that acute and uncontrollable stressors in adulthood result in reduced dendritic length and branching as well as lower plasticity and long-term potentiation in the hippocampus, and impairments in hippocampus-dependent learning and memory (Kim et al., 2006; McEwen, 1999). Early threat exposure results in similar shifts in adult hippocampal structure and function in studies using a wide range of paradigms. Chronic restraint stress during pre-adolescence is associated with reduced apical dendritic length and branching of pyramidal neurons in the hippocampus and mPFC (Eiland et al., 2012). Dendritic atrophy, reduced long-term potentiation in the hippocampus, and deficits in hippocampus-dependent learning and memory have also been observed in adult rats following early exposure to minimal bedding (Brunson et al., 2005; Ivy et al., 2010; Rice et al., 2008). Notably, some evidence suggests that the effects of early threat exposure on hippocampal morphology and cellular function do not emerge until adulthood (Isgor et al., 2004; Tsoory et al., 2008) and the effects of threat on hippocampal function appear to be larger when exposure occurs in childhood as compared to adulthood (Chen et al., 2006). Early threat exposure also appears to influence hippocampus-dependent aspects of fear conditioning. For example, in multiple studies, early exposure to repeated foot shock stress predicts attenuated extinction of fear-related freezing behavior during exposure to a contextual CS in adulthood, but no differences in the response to initial conditioning (Ishikawa et al., 2012; Matsumoto et al., 2008). Similarly, impaired extinction recall of context-dependent fear extinction following early threat results from disruptions in signaling in the vmPFC-hippocampus circuit, including poor synaptic transmission between these regions (Toledo-Rodriguez and Sandi, 2007). Multiple studies have found that the effects of early threat experiences on hippocampal development are mediated by excess levels of CRH and activation of CRH receptors in the hippocampus (Brunson et al., 2001; Ivy et al., 2010). These effects have sometimes been found to vary by sex. For example, exposure to predator odor followed by placement on an elevated platform in pre-adolescence is associated with impaired contextual learning in females during adolescence, as evidenced by reduced freezing to a contextual CS. In contrast, males exhibit enhanced fear conditioning to a cued CS in adolescence and reduced extinction to the cued CS in adulthood following this exposure (Toledo-Rodriguez and Sandi, 2007).

Early exposure to threatening stimuli also leads to long-term changes in the structure and function of the amygdala. In paradigms involving uncontrollable shock delivered to pups, early threat exposure is associated with persistent anxiety and depression-like behaviors, absence of paired-pulse inhibition in the amygdala—reflecting deficits in inhibitory pathways regulating amygdala activity, and widespread changes in gene expression in the amygdala, particularly in genes that regulate serotonin and GABA (Sarro et al., 2014; Sevelinges et al., 2011). In addition, chronic threat exposure leads to increased expression of CRH mRNA in the amygdala, potentially lowering the threshold for the expression of fear (Hatalski et al., 1998). Pre-adolescent chronic restraint stress is associated with atypical dendritic morphology, including increased spines, in the amygdala (Eiland et al., 2012). Similar effects on the amygdala have been observed in rodents exposed to the maternal minimal bedding paradigm. These include persistent elevations in c-Fos expression in the amygdala that increase with development (Cohen et al., 2013) and elevated amygdala activity to a forced swim test in adolescence that mediates depression-like responses to the stressor (Raineki et al., 2012).

Taken together, the rodent literature suggests that early exposure to uncontrollable threat results in long-term changes in hippocampal and amygdala structure and function as well as deficits in inhibitory control of these regions by the mPFC. Specifically, early threat predicts, (a) reduced dendritic length and arborization in the hippocampus in adulthood, (b) dampened long-term potentiation in the hippocampus, (c) poor performance on hippocampus-dependent learning and memory tasks, (d) increased dendritic length in the amygdala; (e) elevations in basal amygdala activity as well as amygdala response to novelty and stress, (f) increased anxiety and depression-like behaviors mediated by amygdala over-activity; and (g) deficits in the functional coupling of the mPFC with the hippocampus and amygdala, as evidenced by reduced synaptic transmission between these regions and poor recall of extinction learning.

3.2. Consistency with human studies

The learning mechanisms and neural circuitry underlying fear conditioning and extinction are highly conserved across species. As in the animal model, amygdala activation is associated with fear acquisition and expression during conditioning (LaBar et al., 1998; Phelps et al., 2004). Likewise, the vmPFC is activated during extinction recall (Milad et al., 2007; Phelps et al., 2004), and increased vmPFC activity during such recall is associated with dampened amygdala activity (Milad et al., 2007, 2009; Milad and Quirk, 2012). The vmPFC is thus essential for retention of extinction learning and plays a central role in modulating the amygdala. Because acquiring neuroimaging data requires participants to be in a highly salient and novel context, the role of the hippocampus in contextual fear conditioning has been difficult to study in humans.

Despite the consistency with which fear learning mechanisms have been specified across animal and human models, there is a surprising lack of human research on how exposure to early experiences of threat influences fear conditioning across development. Although numerous studies have examined fear conditioning processes in adults with post-traumatic stress disorder (Orr et al., 2000; Peri et al., 2000), research on early threat exposure and fear learning in youths or adults is absent in the current literature. One of the challenges is developing paradigms that can be used ethically in children and adolescents, given that effective adult fear conditioning paradigms utilize shock as the US (Pine et al., 2001). A recently-developed task pairing emotional faces with a human scream as the US holds promise in this regard (Lau et al., 2011), but has yet to be applied to the study of early threat exposure. We review existing human studies examining associations between early threat and structure and function of the hippocampus, amygdala, and vmPFC, although we note that direct comparisons between animal and humans studies should be made with caution given the lack of studies examining early threat and fear learning in humans.

Based on the animal literature, we predict that early threat exposure leads to parallel changes in the structure and function of the hippocampus, amygdala, and vmPFC observed in animals. We review evidence for these predictions from studies of children exposed to threatening environments, including physical and sexual abuse, domestic violence, and other types of interpersonal violence. These environments share the characteristic of being significant threats to survival and therefore activate the neural circuitry underlying fear learning. Importantly, as noted above, because of the high co-occurrence of threat and deprivation exposure and because few studies have examined both dimensions within the same sample of children, the specificity of these effects remains to be confirmed in future studies.

Although early threat exposure has consistently been associated with reduced hippocampal volume in adults (Andersen and Teicher, 2008; Hart and Rubia, 2012; Teicher et al., 2012), studies of children have generally not found a relationship between threat exposure and hippocampal volume (De Bellis et al., 2001; Woon

and Hedges, 2008). This pattern has led some to suggest that the effects of early threat on hippocampal development are not evident until adulthood (Tottenham and Sheridan, 2009), consistent with evidence from animal studies (Isgor et al., 2004), although the exact mechanisms explaining this developmental pattern remain to be identified. Atypical hippocampal function associated with early threat has been observed, however. For example, children with maltreatment-related PTSD symptoms exhibit less hippocampal activation during retrieval in a verbal declarative memory task than non-maltreated children (Carrion et al., 2010).

Differences in the volume of the amygdala as a function of threat exposure have generally not been found in children (De Bellis et al., 2001). However, atypical processing of emotional information – particularly facial emotion – has been observed consistently. Children exposed to threat exhibit amplified neural response to angry faces in ERP studies (Pollak et al., 1997, 2001), and heightened amygdala activation to angry faces (McCrory et al., 2011) even when faces are presented pre-attentively (McCrory et al., 2013). These alterations in neural processing of facial emotion are consistent with behavioral findings suggesting that children with early threat exposure identify facial displays of anger more quickly and with less sensory information than non-exposed children (Pollak and Sinha, 2002), suggesting attention biases that facilitate the identification of anger.

Consistent with animal literature demonstrating differences in the development of the vmPFC following early threat, multiple recent studies observe that threat exposure in childhood is associated with reduced volume and/or thickness of the vmPFC (De Brito et al., 2013; Edmiston et al., 2010; Hanson et al., 2010; Kelly et al., 2013), consistent with our prediction that low recruitment of vmPFC will lead to accelerated pruning in this region. In addition, a recent study documents reduced resting-state amygdala-vmPFC connectivity in adolescent females exposed to child abuse (Herringa et al., 2013).

4. Recommendations for future research

The exposures that give rise to experiences of deprivation and threat co-occur at high rates in children and adolescents (Green et al., 2010; McLaughlin et al., 2012). This co-occurrence has generated many of the methodological and conceptual challenges in identifying dimensions of experience that influence specific aspects of neural development. We do not advocate that future research attempt to identify children who experience only one specific form of adversity, as that would surely result in conclusions that are not generalizable to most children exposed to adverse developmental environments. Instead, we propose the following concrete recommendations for future research. First, future studies examining neural development in children exposed to adverse early environments should measure the underlying dimensions of experience described here in addition to the traditional categories of exposure (e.g., physical and sexual abuse, neglect, poverty) to determine whether deprivation and threat are indeed associated with the predicted patterns of neural development proposed here. Dimensional measures of trauma exposure frequency and severity are widely available (Bernstein et al., 2003), and measures of environmental enrichment have been developed for young children (Caldwell and Bradley, 1984). Developing more extensive measures of social and cognitive inputs and environmental complexity that can be used over a wider range of development would facilitate this endeavor.

Relatedly, a second central challenge in characterizing the impact of deprivation on neural development involves determining the specific types of social and cognitive inputs that are required for the brain to develop normally. Characterizing the inputs necessary to facilitate sensory development is relatively straightforward, but this is far more challenging in the domain of more complex cognitive and social skills (e.g., executive functioning) and the cortical regions that support these types of functions, perhaps with the exception of language development (Kuhl, 2004). Determining the specific environmental inputs that are necessary to scaffold the development of these skills is critical to understand how deprivation in exposure to these types of experiences shapes brain development.

Third, experimental manipulation of specific aspects of experience would allow our predictions about deprivation and neural development to be tested in a more rigorous way. For example, a variety of experimental improvements in environmental context for children who are institutionalized would shed light on the veracity of our model. Ideally, all children could be removed from institutions and placed into family care; however, in societies where that is currently impossible, providing enhanced complexity of care could be advantageous. Potential environmental manipulations include increasing enriching cognitive experiences (e.g., greater access to complex toys and games, greater exposure to complex language, and more opportunities for adult instruction), reducing caregiver-to-child ratios, and staff schedules that ensure consistent caregiving of particular children by the same adults over time to facilitate the formation of more selective attachments as well as the provision of greater opportunities for cognitive enrichment. Such an approach was used by the St. Petersburg-USA Orphanage Research Team, which attempted to improve the institutional environment by reducing caregiver-to-child ratios and providing more consistent and responsive caregiving (The St. Petersburg-USA Orphanage Research Team, 2008). Although this intervention resulted in improvements in general cognitive ability, the effects on neural development are unknown. Collection of neuropsychological and neuroimaging data following this type of experimental design is an important next step in identifying causal pathways through which the absence of species-typical cognitive and social experience shapes neurodevelopment.

Fourth, despite consistencies in the neural circuitry underlying fear learning in animals and humans, there is a surprising lack of human research on how early threat influences fear learning across development. As noted above, only recently have developmentally appropriate and effective fear learning paradigms been developed for children and adolescents (Glenn et al., 2012; Lau et al., 2011). Examining the effects of early threat exposure on fear acquisition, expression, extinction, and generalization as well as the underlying neural circuitry supporting these learning processes represents a critical area for future research.

Fifth, the issue of developmental timing of exposure and outcome measurement is of central importance to studying the impact of environmental experience on neural development (Hensch, 2005). Although sensitive periods in sensory and language development have been clearly identified, progress in identifying similar periods when the brain is particularly likely to be influenced by more complex cognitive and social environmental inputs has proved challenging due to measurement issues with regard to exposure timing as well as the more complicated neural circuitry that underlies higher-order cognition. We have learned the most about sensitive periods in social and cognitive development from studies of institutionalization, where precise information about the timing and duration of exposure is often available (McLaughlin et al., 2011; Nelson et al., 2007). Consistent with the above recommendations about the importance of experimental manipulation, random assignment to improved environments for children exposed to high deprivation or threat may hold the most promise for identifying how the impact of these environments varies according to timing and duration of exposure. An additional possibility rarely used in the human literature involves examining the differential impact of exposures occurring in childhood versus

adulthood, which has frequently been used in animal models (Chen et al., 2006). Such an approach will determine whether early exposure to deprivation and threat influences the brain in ways that are either qualitatively or quantitatively different than adult exposure.

Sixth, longitudinal studies are needed to determine whether disruptions in typical patterns of neural development following deprivation and threat are, indeed, mechanisms linking these experiences to the onset of psychopathology. Given evidence for greater fear expression during conditioning paradigms, deficits in extinction learning, and disruptions in the neural circuitry underlying fear learning and extinction among both children and adults with anxiety disorders (Britton et al., 2013; Craske et al., 2008; Lau et al., 2008; Liberman et al., 2006), these pathways are likely involved in the association between threat exposure and anxiety pathology. The neural changes we argue to be a result of deprivation exposure – including age-specific reductions in cortical thickness, poor performance on complex cognitive tasks, and inefficient neural recruitment during such tasks – have also been linked to externalizing disorders in numerous studies (Anderson et al., 1999; Durston et al., 2003; Shaw et al., 2006). Moreover, age-specific cortical thinning in association cortex has been shown to link severe early-life deprivation to ADHD (McLaughlin et al., 2014). However, additional studies are needed to confirm these predictions.

Seventh, most adverse developmental environments are likely to include some degree of exposure to both deprivation and threat dimensions (Fig. 1). As such, it is important to consider how neural consequences related to deprivation interact with those related to threat in shaping neural development. For example, the pattern of cortical thinning in lateral PFC and related deficits in inhibition that has been associated with exposure to deprivation (Farah et al., 2006; McLaughlin et al., 2014; Mueller et al., 2010; Noble et al., 2007) might interact with the heightened amygdala and emotional reactivity to emotional stimuli associated with exposure to threat (McCrory et al., 2013; McCrory et al., 2011) to produce deficits not only in automatic aspects of emotion regulation, such as fear extinction, but also in effortful emotion regulation processes, such as cognitive reappraisal. Effortful emotion regulation involves a more complex network including connectivity of the lateral PFC and superior temporal cortex, which alters the semantic representative of emotional stimuli and, in turn, inhibits the amygdala (Buhle et al., 2014). The most pronounced deficits in these processes would likely result from exposure to both deprivation and threat dimensions, although this remains to be determined empirically. Understanding how these dimensions interact to influence neural development will be necessary to understand the wide range of negative developmental outcomes stemming from complex adverse experiences.

Finally, we have focused on two dimensions of experience that are particularly likely to impact neural development, but there are undoubtedly others. For example, the degree of environmental predictability has been argued to be central aspect of environmental experience that shapes the development and evolution of human life history strategies (Ellis et al., 2009), and unpredictability or chaos in childhood predicts psychological adjustment and early-onset sexual behavior (Belsky et al., 2012; Evans et al., 2005). Another dimension that is like to have relevance for early neural development is loss of an attachment figure. This is differentiated from the frequently studied exposure of institutional rearing, which involves complete absence of a preferential attachment figure in early life. Loss of such a figure has been consistently linked to a life-course persistent risk for major depression, which could be explained by changes in development of the ventral striatum and reward processing (Wacker et al., 2009). These highlight just two additional dimensions of early life experience that are likely to have meaningful effects on brain development. Future studies should identify of other key dimensions of experience and characterize their impact on the developing brain.

5. Conclusion

We propose a novel conceptual framework for understanding the impact of childhood adversity on neural development and argue that the field must move beyond the prevailing approach of examining the impact of complex and co-occurring exposures on brain development to distilling those complex experiences into their core underlying dimensions. Two important dimensions that appear to have distinct effects on neural development are deprivation and threat. Existing evidence from human studies provides preliminary support for our predictions about how these types of experiences influence neural development, although additional work is needed to ultimately determine the utility of our conceptual framework. We believe that such an approach will improve our understanding of how atypical experience influences the developing brain and, ultimately, confers risk for psychopathology.

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