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Exposure to early adversity: Points of cross-species translation that can lead to improved understanding of depression

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Abstract

The relationship between developmental exposure to adversity and affective disorders is reviewed. Adversity discussed herein includes physical and sexual abuse, neglect, or loss of a caregiver in humans. While these stressors can occur at any point during development, the unique temporal relationship to specific depressive symptoms was the focus of discussion. Further influences of stress exposure during sensitive periods can vary by gender and duration of abuse as well. Data from animal studies are presented to provide greater translational and causal understanding of how sensitive periods, different types of psychosocial stressors, and sex interact to produce depressive-like behaviors. Findings from maternal separation, isolation rearing, chronic variable stress, and peer–peer rearing paradigms clarify interpretation about how various depressive behaviors are influenced by age of exposure. Depressive behaviors are broken down into the following categories: mood and affect, anhedonia, energy, working memory, sleep–wake, appetite changes, suicide, and general malaise. Cross-species evidence from humans, nonhuman primates, rats, and mice within each of these categories is discussed. In conclusion, sensitive periods for affective-related behaviors (anxiety, mood, and controllability) occur earlier in life, while other aspects of depression are associated with adversity later during adolescence.

Approximately 33% of the population is exposed to adversity during the course of development in the form of physical/sexual abuse, neglect, loss of a parent or caregiver, or a natural disaster. Bullying is another form of adversity to which approximately 25% of children under the age of 11 years are exposed. Depression occurs in nearly 67% of the early life maltreatment population (Andersen & Teicher, 2008; Andersen et al., 2008; Widom, DuMont, & Czaja, 2007), compared to a lifetime prevalence rate in the general population of approximately 20% (Kessler et al., 1994). Depression emerges earlier than normal in children with a maltreatment history (Teicher, Samson, Polcari, & Andersen, 2009; Widom et al., 2007). The Treatment of SSRI-Resistant Depression in Adolescents Study has shown that cases of depression that present with a severe baseline of emotional dysregulation, a sense of hopelessness, elevated anxiety, and high levels of stress due to family conflict are less likely to achieve remission (Brent, 2009). The majority of individuals with a history of maltreatment or childhood anxiety disorder fall into this group.

The causal relationship between a history of maltreatment and subsequent depression is difficult to prove in human studies. Prospective studies (e.g., Widom et al., 2007) suggest that individuals with a developmental exposure to adversity have a higher risk of depression. Similarly, co-twin studies where women were exposed to varying degrees of childhood sexual abuse also show increased vulnerability to depression (Kendler et al., 2000; Nelson et al., 2002). Greater understanding of the relationship between maltreatment and depressive outcomes is likely to have an impact on improved treatment approaches, especially given the limited positive outcome from current pharmacological approaches.

This review paper will examine what is known about the relationship between depression and childhood exposure to maltreatment from a translational viewpoint. Various paradigms of early life stress are presented to address the maturational timing issue, followed by a breakdown of findings reported in the literature of specific symptoms of depression. This review does not include any extensive discussion of the role of the hypothalamic–pituitary–adrenal axis (HPA) that certainly influences depression; the reader is referred to (Eiland & Romeo, 2013) for such a discussion. Finally, ways to improve existing preventative interventions in the treatment of depression in this population are discussed.

Basic Definition and Across-Species Comparisons

The potential for any translational study to have an impact lies in its ability to facilitate valid, reliable, and direct comparisons across species. Behavioral, biochemical, or anatomical changes can provide points of shared reference. This framework is one through which cross-species comparisons are made in this paper with the goal of identifying translational

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points of commonality. Relationships among development, adversity, and depression will be examined with a particular focus on assessment across human, nonhuman primate, and rodents.

Utility of animal models

Animal model often refers to the use of animals to demonstrate a behavioral or biochemical phenotype that is found in humans. Given that animals will never sufficiently model the human condition and its complexities (Andersen & Thompson, 2011), the more appropriate terminology that should be used is *endophenotype* (e.g., Castellanos & Tannock, 2002). Endophenotypes are elemental components of a given disorder or condition that allows direct comparisons to be made across species if they have the same effect.

From a slightly different perspective, the Research Domain Criteria Project framework provides "constructs" and "domains" that are more amenable to translation. A construct is the basic unit of analysis, which includes motivation, cognition, and social behavior; the NIMH lists five domain systems: negative or positive valence, cognition, social processing, and arousal/regulatory (www.nimh.nih.gov). The next step taken in this categorization accounts for the level of analysis. Recognizing that analyses occur from behavior to genes and span from circuits to physiology, all the information necessary to produce a complete picture can occur neither within clinical studies nor in animal studies. The interdependence among different species is needed to fully understand the domains.

Another point about the use of animals needs to be addressed: evolutionary adaptation. Behaviors evolve over a very long time (tens of thousands of years) to increase the survival of the species but not necessarily the individual; other behaviors are passed across generations (Maestripieri, 2005). As environmental demands can shift relatively quickly, the species may be slow to adapt or display adaptive behaviors that do not seem to make sense in the current environment, but may allow the animal to survive a hostile world (Teicher, 2002); this model is known as adaptive calibration (McEwen, 2000). For example, corticosteroids may mediate the maturation of adult defensive systems, such that low levels of stress (e.g., novelty) will down-regulate reactivity to external stressors whereas high levels increase reactivity (Macri, Zoratto, & Laviola, 2011). Equally worth considering is at what point behavior is "abnormal" (reviewed in (Haller & Kruk, 2006). As development proceeds, adolescence is characterized by typical, yet more extreme, changes in behavior (e.g., risk taking and moodiness) and adolescence is also the period for the emergence of psychopathology (Cicchetti & Rogosch, 2002). Epigenetics provides a mechanism to pass environmental impact across the generations (Champagne, 2013).

A final consideration is how manipulations in animals parallel findings in humans and what that difference can tell us. While we aim to explain the human condition, animals may not experience the same psychosocial pressures or at least we do not know enough to model them. In other words, data from both sides can increase the understanding of the other.

Age-related differences in development in general

The brain continues to mature into the third decade of life. In general, synapses are formed and then competitively pruned back to optimize function for the demands of the environment (Brenhouse & Andersen, 2011). This process occurs differentially across brain regions. More fundamental brain regions undergo this process earlier, whereas the more complex brain regions, such as the cortex, prune later in adolescence and young adulthood. Different neurotransmitters play different roles during maturation, with GABA and glutamate acting as principal players (discussed below). We have previously reviewed this subject in typically developing species (Brenhouse & Andersen, 2011).

Sensitive periods of vulnerability

Sensitive periods are points in maturation when environmental input has a maximal impact on development. Sensitive periods differ from critical periods. Critical periods are well described in sensory systems (Hubel & Wiesel, 1970, 1998; Hubel, Wiesel, & LeVay, 1977), where all or none stimulation is needed for proper development. As a classic example, visual input programs the development of the ocular dominance columns such as those studied in kittens (Hubel et al., 1977; Kuppermann & Kasamatsu, 1984). Sensitive periods occur after critical periods close and fine-tune the system to match the needs of the environment (e.g., neuronal imprinting). This process can be further broken down into an experience-dependent process, which is a more individualized process, or an experience-expectant process, where the brain is primed to certain aspects of environmental information (Greenough, Black, & Wallace, 1987). Inappropriate stimulation (too much, too little, or none at all) can shift the development of a phenotype that differs from typicality.

Exposure to adverse environments during sensitive periods of development will produce neuroanatomical and behavioral consequences that may be predictable if we understood all of the factors (Andersen & Teicher, 2008; Cicchetti & Toth, 1995). Studies on the relationship among abuse, depression, and maturation support the hypothesis that clinical outcome depends on timing of the abusive episode. If an abusive episode occurs before 12 years of age, depression is a likely outcome; if the episode occurs after 12 years of age, posttraumatic stress disorder is more likely (Kaplow & Widom, 2007; Schoedl et al., 2010). A more recent study examined smaller sensitive periods to identify the strongest relationships between child abuse and depression (Dunn, McLaughlin, Slopen, Rosand, & Smoller, 2013). Data from the National Longitudinal Study of Adolescent Health demonstrate a significant relationship between physical abuse that occurred between 3 and 5 years of age and depression; suicidal ideation

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was higher in individuals sexually abused during preschool compared with adolescence. The data on risk for depression is consistent with a first wave of depressive risk that we observed in individuals with an early abuse history (Andersen et al., 2008; Andersen & Teicher, 2008). Cortisol dysregulation is also stronger when physical or sexual abuse with depression or internalizing symptoms occurs earlier than when neglect or abuse plus depression occur together during adolescence (Cicchetti, Rogosch, Gunnar, & Toth, 2010).

Neuroanatomical studies show that abuse that occurs prior to puberty has more selective effects on the hippocampus, whereas abuse after puberty appears more selective for the prefrontal cortex in humans (Andersen & Teicher, 2008). Studies on sensitive periods in typically developing children suggest that the optimal window for environmental impact on hippocampal development is before 8 years of age (Rao et al., 2010). In bonnet monkeys that were peer raised, significant reductions in the corpus callosum and hippocampus were observed during late adolescence (Jackowski et al., 2011); these findings are consistent with those observed in humans (Andersen et al., 2008; Teicher et al., 2004). Animal research shows that different windows of early stress exposure produce unique behavioral (Freund, Thompson, Denormandie, Vacarro, & Andersen, 2013; Lehmann, Pryce, Bettschen, & Feldon, 1999) and neuroanatomical effects (Leussis & Andersen, 2008; Leussis, Freund, Brenhouse, Thompson, & Andersen, 2012). These paradigms will be discussed in more detail below under the animal model section.

The nature of the abuse

The type of abuse (e.g., sexual, physical, or neglect) or nature of the early trauma can influence the brain region affected as well as the behavioral outcome (Tomoda et al., 2009, 2011; van Veen et al., 2013). The nature of depressive symptoms differs (described in more detail below), although exposure to different types of stressors may provide some basis for their etiological underpinnings. Depression can present as either more anxious or anhedonic in children or adolescents (Mitchell, McCauley, Burke, & Moss, 1988). Adolescents with an anxious depression report more guilt, agitation, hypersomnia, and weight changes (gain or loss; Mitchell et al., 1988). Depression with conduct disorder also appears to be another subtype (Mitchell et al., 1988). A recent study examined specific outcomes in 2,615 individuals enrolled in the Netherlands Study for Depression and Anxiety (van Veen et al., 2013). The authors found that emotional neglect had the greatest impact, affecting arousal and anhedonia dimensions. Physical and sexual abuse, as well as psychological abuse, was associated with a more anxious arousal; the former two were also associated with greater generalized arousal. Earlier studies show that physical abuse is associated with higher lifetime rates of major depression in women, but not men (MacMillan et al., 2001). Higher rates of psychopathology, including drug use, were higher in women following childhood sexual abuse than in men (MacMillan et al., 2001).

Nature of depressive symptoms

Depression is multifaceted, resulting from genetics, different environmental variables (including the timing of exposure to environmental factors), or both. A more extensive review of risk factors for depression can be found in Beardslee, Gladstone, and O'Connor (2012). Different treatment modalities support this notion, and depressive symptoms can include the following categories:

1. mood changes: sad, anxious, or "empty"; hopelessness, guilt, worthlessness, or helplessness; irritability; restlessness
2. anhedonia: a loss of interest in activities or things once pleasurable, including sex
3. changes in energy and feeling fatigued
4. working-memory problems and difficulty concentrating or making decisions
5. sleep–wake changes: insomnia, early-morning wakefulness, or excessive sleeping
6. changes in appetite
7. thoughts of suicide or suicide attempts
8. malaise: aches or pains, headaches, cramps, or digestive problems

Sex differences in depression

Sex differences in depression emerge during adolescence (Cyranowski, Frank, Young, & Shear, 2000) and are maintained into adulthood. Depressive symptoms are often experienced differently between men and women. Men are more likely to report symptoms 2, 3, and 5 (above), whereas women usually endorse 1, 3, and 6 (Cochran, 2000; Pollack, 1998). The initiating events that can underlie depressive symptoms may also be sexually dimorphic. Depression in female teens is more strongly associated with maternal depressive behavior, whereas males are more strongly affected by changes in supportive early care (Duggal, Carlson, Sroufe, & Egeland, 2001).

Part of these changes may also be related to different sensitive periods in brain development (for a review, see Brenhouse & Andersen, 2011). In general, males show greater overproduction and pruning in most brain regions compared to females (Giedd, Castellanos, Rajapakse, Vaituzis, & Rapoport, 1997). The process of overproduction and elimination may render males more vulnerable to environmental impacts (Andersen & Teicher, 2009). Greater decreases in hippocampus and corpus callosum size are observed in males with a history of maltreatment than in females (DeBellis & Keshavan, 2003; Teicher et al., 2004). Diurnal changes in cortisol levels also are higher in boys than in girls with a history of maltreatment (Doom, Cicchetti, Rogosch, & Dackis, 2013).

Animal studies, however, have either not examined females in regard to stress and depression (Kaufman, Plotsky, Nemeroff, & Charney, 2000; Marais, van Rensburg, van Zyl, Stein, & Daniels, 2008) or failed to find sex differences

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(discussed below). In genetic models bred to be more sensitive to depressive-like behavior, males, but not females, show greater immobility during adolescence (Mehta, Wang, & Redei, 2013). Females are more resistant to stressful events at the level of controllability that is related to escape behavior (Dalla, Edgecomb, Whetstone, & Shors, 2007; Leussis & Andersen, 2008; Leussis et al., 2012). Consistent with the human literature, sex differences only became evident when we examined different aspects of depressive-like behavior in rats. Specifically, females showed slightly higher baseline levels of helplessness that are not what one would expect based on human studies. Two possibilities exist. One hypothesis is that human males underreport their depressive symptoms. However, findings from large, community-based samples suggest that such underreporting is not the case (Wolk & Weissman, 1995) and that the reported 2:1 female to male sex difference in prevalence rate is found in the United States (Marcus et al., 2005) and around the globe (Wolk & Weissman, 1995). A second possibility is that the nature of what is measured in animals does not accurately reflect the human condition. In other words, the standard measures of depressive-like behavior in animals, the forced swim test (Detke, Rickels, & Lucki, 1995), or the active avoidance paradigm (Olton, Johnson, & Howard, 1974), miss an important aspect of depression found in females.

While depressive-like behavior in females may be elusive in animal studies, estrogen and stress are known to interact and influence affective behaviors (Dalla, Pitychoutis, Kokras, & Papadopoulou-Daifoti, 2011). In both animals and humans, low levels of estrogen are associated with greater depressive symptoms (Hajszan et al., 2010; Young & Korszun, 2010). Low or falling levels of estrogen typically occur during premenstrual dysphoria disorder and menopause, which are both associated with depressive symptoms. As estrogen modulates corticotropin releasing factor (CRF), a stress hormone, and serotonin (Bangasser & Valentino, 2012), stress-induced changes in estrogen are likely to modulate depressive behaviors. Developmentally, exposure to social stress during the juvenile period delays the onset of puberty in female nonhuman primates (Wilson et al., 2013). As a result, estrogen levels do not rise during the normal developmental stage. Because estrogen increases dendritic spine density (Woolley, Gould, Frankfurt, & McEwen, 1990) that is instrumental for the overproduction of synapses during adolescence, changes in estrogen in response to stress can cause lifelong susceptibility to depressive behaviors that emerge during adolescence.

Animal Models of Early Adversity: Sensitive Periods and Socially Relevant Stress

A number of animal models have been developed to facilitate understanding changes in brain development. Generally, these paradigms are based on the social stage of the animal. Early developmental manipulations involve maternal care, whereas child to adolescent stage manipulations typically involve separation from peers. The latter manipulations can be escalated further by social defeat paradigms. By adulthood, exposure to stressful manipulations will temporarily perturb a system, but do not seem to permanently alter the course of its development. For example, both early life and adult stress exposure decrease dendritic spines that last into adulthood, but adult stress decreases the spines only temporarily and they regenerate within a 3-week time point. In contrast, growing up in a complex environment increases spine density (Volkmar & Greenough, 1972).

Maternal separation paradigms

Maternal care has a significant effect on subsequent development. Our initial interest in the neurobiological consequences of childhood maltreatment emerged from preclinical studies on the effects of early experience (e.g., Brunelli, Shindledecker, & Hofer, 1989; Denenberg, Garbanati, Sherman, Yutzey, & Kaplan, 1978; Harlow & Harlow, 1965; Levine, Johnson, & Gonzalez, 1985). For rodent species, which are typically born relatively immature like humans, reliance on the dam for care is necessary for survival. Initially proposed as the "maternal mediation hypothesis" (Smotherman, Wiener, Mendoza, & Levine, 1977), the dam will adjust her care to match the environment in a way that maximizes survival. These experimental paradigms include manipulating environmental factors such as nest building material, foraging for food, and making resource availability unpredictable (primates; Rosenblum & Paully, 1984). Once these basic needs are met, the dam then focuses her time on the direct care of the offspring, including licking and grooming. If circumstances are favorable, she will often assume the more effective nursing posture of arched-back nursing (Anisman, Zaharia, Meaney, & Merali, 1998; Liu et al., 1997). Pups that are raised by dams that demonstrate high licking and grooming behavior are more resilient to stress: cortisol and ACTH levels are reduced at baseline and in response to stress challenge later in life (Liu et al., 1997).

Paradigms that reduce arched-back nursing involve disruption of maternal care by separating the pups from the dam for various lengths of time. The original model by Levine (1967) used a 24-hr separation period, while the most common duration is 3–4 hr a day between Postnatal (P) Days 2–4 (P2–P14) or P2–P20 (Leussis et al., 2012; Mourlon et al., 2010; Plotsky & Meaney, 1993; Reus et al., 2011). Variations exist within the maternal separation (MS) literature as well. We will use the designations of MS(24h) for separation for 24 hr, MS(3) for 3 hr a day between P2 and P14, or MS(4) for 4 hr a day between P2 and P20. Exceptions to the ages and/or times of separation for the different studies will be noted. In general, the MS(3) and MS(4) paradigms do not appear to differ significantly because they both include separation periods during the first week of life. The other factor that can differ among MS paradigms is whether the litter is separated as a unit from the dam or individual pups are separated from the dam and each other. While this distinction is not always clear, our unpublished observations suggest that the latter will have greater effects on the offspring.

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The effectiveness of MS to produce changes in depression, fear, and anxiety depends on the timing of the paradigm as well as the species of animal. MS paradigms that include the first week but not the second week of life seem to produce differential effects. For example MS between P2 and P13 produces stronger fear responses to innate predator odors than in animals exposed to MS between P11 and P13 (Litvin et al., 2010). Similarly, exposure to saline injections at P9–P14 produces greater helplessness than injections at P2–P9 (Freund et al., 2013). The effects of MS can vary by strain of mice (Kundakovic, Lim, Gudsnuk, & Champagne, 2013) or rat (Sterley, Howells, & Russell, 2011). For example, the spontaneously hypertensive rat is resistant to anxiogenic effects of MS, but demonstrates hyperactivity that has also been reported in abuse cases (Sterley et al., 2011). More examples will be given within different sections below.

Whether all of the effects on the offspring are "mediated" by dam as originally proposed is certainly debatable. A maternal "modulation" hypothesis has been put forth that states mom can play gatekeeper in her pup's exposure to novelty and stressors (Tang, Reeb-Sutherland, Romeo, & McEwen, 2013). This modulation is consistent with the findings of Macri, Mason, and Wurbel (2004), who describe dissociation among HPA responses, early life experiences, and fear responses.

Changes in rearing conditions

A number of paradigms can change rearing conditions, including changes in bedding (Coccurello et al., 2014), communal nursing paradigm in rats nesting (Macri, Laviola, Leussis, & Andersen, 2009) or in mice (Branchi & Alleva, 2006), or reducing nest bedding (Raineki, Cortes, Belnoue, & Sullivan, 2012). Collectively, these paradigms are designed to disrupt maternal behavior, or in the case of mice, elevate maternal behavior.

Social isolation paradigms

While removing a pup from the dam when very young is considered stressful, removal of pups from the dam when they are entering adolescence may not be as effective. Like humans, separation from peers is highly stressful. A number of social isolation paradigms are found in the literature, with the most common one being the isolation rearing paradigm. Pups are weaned from the dam and isolation housed typically from 28 to 55 days (Sahakian & Robbins, 1977; Warren & Ivinskis, 1973). During young adulthood, these subjects demonstrate a number of changes in behavior and HPA axis activity.

Other paradigms, including social defeat and chronic variable stress

The social defeat paradigm involves exposure of a subordinate rat to a dominant rat, whose dominance is established by previous bouts or age. A recent study subjected juvenile male and female rats to a dominant male adult for 10 min/day for 10 days (Weathington, Arnold, & Cooke, 2012).

The chronic variable stress paradigm includes twice-daily exposures to a number of different stressors, including crowding, social isolation, restraint, shaker stress, swimming, change in temperature, and air quality (Jankord et al., 2011). While a number of these stressors can be used individually to produce chronic stress, the variability in their presentation typically produces different results (e.g., decreased HPA reactivity versus no change or elevation; Cruz, Marin, Leao, & Planeta, 2012). This paradigm, like the MS paradigm, has variations in duration of exposure and the number of stressors used that are likely to make cross-study comparisons difficult.

Peer–peer rearing

Initially used in the classic study of Harlow and Harlow (1965), this model has been primarily used in studies of nonhuman primates (Bowden & McKinney, 1972; Suomi, Harlow, & Domek, 1970). These studies have been instrumental in illustrating the importance of age, rearing conditions, and rehousing during the stressor (Gilmer & McKinney, 2003).

Important Variables That Influence the Observed Results

Sex of the subject

A number of studies show that the effects of early exposure to adversity are sex dependent. Specific examples within each sensitive period of early adversity exposure are described within the next section.

Duration of the stressor

Clinical work shows that the duration of the stressor is often associated with worse outcomes (Beitchman et al., 1992). However, disentangling the age of onset of the stressor from its duration is almost impossible, except in adult systems. Exposure to adversity early in development has a great impact not only on the foundational maturation of a number of systems, including basic behavioral processes, but also on the underlying neural structures. Alterations in behavior affecting basic self-regulatory processes that occur during the first few years of life are likely to lead to other issues later in life (Cicchetti & Rogosch, 2002). Similarly, exposure to early adversity is less evident during the building-up phase of hippocampal development, but without basic synaptic structure present before pruning, some minimal amount of foundation is lost and becomes evident during adolescence when excess synapses are pruned away (Andersen & Teicher, 2004).

Timing of assessment postadversity

Does the clock start at the age of initiation or the age of termination? Increasing cross-talk among disciplines (e.g., developmental psychologists, clinical outreach workers, and

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prevention scientists) will facilitate early identification of psychopathology, if it is going to manifest, earlier. Depression often appears as children enter adolescence. In our studies (Andersen, Tordera, Lasheras, Del Rio, & Ramirez, 2008; Teicher et al., 2009) and others (Widom et al., 2007), depression and substance-use disorder are among the most likely outcomes (Kaplow & Widom, 2007). The delay in the diagnosis for depression in our sample was ~9.2 years, unless the abuse occurred during adolescence. Childhood maltreatment accelerates the onset of depression relative to the typical age of onset in nonmaltreated individuals. Earlier studies that examined the expression of depressive symptoms within 8 weeks of an abusive episode demonstrated that adolescent maltreatment is associated with the appearance of greater depressive symptoms (reviewed by Feiring, Taska, & Lewis, 1999). However, this conclusion is likely incorrect given the extensive work in animals and humans reviewed in this paper that suggests interactive effects between maltreatment and maturation. In other words, children with a maltreatment history are strongly at risk for the development of depression too.

These data suggest that the brain must reach some maturational stage that permits the expression of the underlying pathology. A number of possibilities may explain this delay. First, the physical change in synapses must reach a certain level of loss in order for the deficit to be observed. Parkinson disease, for example, requires >90% loss of dopamine neurons before the patient experiences symptoms. Second, maturational processes need to occur to unmask the deficit. These processes may involve either the failure to overproduce synapses or the pruning of excess synapses, such as what we have observed in MS(4) subjects as they enter adulthood (e.g., (Andersen & Teicher, 2004); or age-related changes in connectivity between brain regions. A number of anxiety-driven responses that are associated with depression involve reciprocal connections between the amygdala and the prefrontal cortex (Cressman et al., 2010; Cunningham, Bhattacharyya, & Benes, 2002). In rats, amygdalar–cortical projections increase in age up until P60 (late adolescence; Cunningham et al., 2002). While they appear to stabilize with age, projections from the prefrontal cortex to the basolateral amygdala prune into adulthood (Cressman et al., 2010). Connections between the prefrontal cortex and the accumbens may have similar developmental effects on the appearance of anhedonia (Brenhouse, Sonntag, & Andersen, 2008).

Increases in EEG coherence are evident in limbic regions of individuals with a history of maltreatment, including both child and adult trauma in humans (Nelson et al., 2009). Consistent with a number of the depressive features listed below, resting-state functional connectivity in areas related to episodic memory and retrieval is impaired (van der Werff et al., 2013b). In contrast, areas related to declarative memory and stronger emotional processing show stronger resting-state connectivity between the dorsal anterior cingulate and regions containing the lingual and orbital fusiform gyri in individuals who experienced maltreatment but were resilient (van der Werff et al., 2013a).

Only recently has clinical research revealed that cortisol levels or its regulation by ACTH in response to CRF challenge transition with either further maturation or time since the last episode of abuse. Children exposed to early adversity demonstrate elevated levels of cortisol initially during or immediately following the abusive episode (Bevans, Cerbone, & Overstreet, 2008; Carrion & Wong, 2012; DeBellis et al., 2005). Later, these elevations give way to blunted responses by adulthood or even shortly after the abuse ends (reviewed in Struber, Struber, & Roth, 2013). This transition makes sense, given that elevated cortisol will facilitate fight or flight. Over time, the allostatic load becomes too great for the system to bear and, eventually, cortisol regulation is blunted.

Alternatively, some behaviors may require full maturation to occur before manifesting. Animals that underwent MS for 3 hr during postnatal development showed significantly more time spent in the open arm of an elevated plus maze when assessed at P37, but less time when assessed at P54 (Feng et al., 2013).

Part of the delay in the appearance of behavioral changes is the result of delayed maturation. For example, a loss in gray matter volume in the hippocampus has been well documented in adults with a history of childhood maltreatment (Bremner et al., 1997; DeBellis et al., 1999) and in animals that were exposed to early life stress (Andersen & Teicher, 2008; Huot, Plotsky, Lenox, & McNamara, 2002). When children were examined for volume changes in the hippocampus, none were observed (DeBellis et al., 1999). Longitudinal studies now show that the loss of hippocampal volume is progressive (Tupler & DeBellis, 2006). These delayed effects are not unique to humans. Rhesus monkeys that were peer raised did not show changes in the hippocampus or corpus callosum when assessed at 24–30 months (~6–8 years human), although enlargements in the cerebellar vermis and cortical regions were found (Spinelli et al., 2009). Hippocampal and corpus callosum decreases were documented in peer-reared bonnet monkeys that were assessed at an older age (Jackowski et al., 2011). Similarly, no difference in hippocampal synaptophysin (a measure of synapses) was evident until after the onset of puberty in rats exposed to MS(4) (Andersen & Teicher, 2004). These data imply that maltreatment interacts with maturation for the full effect to manifest.

Clinical and Clinically Relevant Findings

Depression cross-species

Mood changes: Sad, anxious, or "empty"; hopelessness, guilt, worthlessness, or helplessness; irritability; restlessness. Depression often emerges during young adolescence following exposure to early life adversity (Teicher et al., 2009; Widom et al., 2007), with few depressive symptoms observed in childhood. Feelings of worthlessness and guilt have been reported in females with a maltreatment history (Schuck & Widom, 2001). Receiving welfare as a child and living with alcoholic parents increase the strength of the relationship between abuse and worthlessness. Victims of

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bullying report greater internalizing behaviors (miserable, fearful, worried, solitary, apathetic, and not liked), whereas the bullies rate higher externalizing scores (lies, irritability, steals, fights, not liked, disobedient, and destructive) based on the Rutter scale (Kumpulainen et al., 1998).

Anxiety and fear. Nonhuman primates that were reared by peers and not their mother demonstrated increased fear-potentiated startle as juveniles (Nelson et al., 2009). The effects of maternal separation early in life, for as little as one or two 6-day separations, persist in primates' approach to novelty in adulthood (Hinde, Spencer-Booth, & Bruce, 1966).

Changes in fear and anxiety are evident in the animal models, but inconsistently (discussed in Stevenson, Meredith, Spicer, Mason, & Marsden, 2009). One of the plausible explanations for these inconsistencies points to the amount of learning the assessment task requires. MS subjects in general show some degree of impaired learning of fear-related tasks (Aisa et al., 2008). Regardless, a number of studies show decreased time in the open arm of the elevated plus maze, which is an index of anxiety-like behavior. MS(3) decreases open arm time in adulthood (Lee et al., 2001) in both males and females, although the effects are greater in males (Wigger & Neumann, 1999). Communal nursing in both rats (Macri et al., 2009) and mice (Branchi & Alleva, 2006) also increase anxiety-like behavior. Our study in rats demonstrated reduced maternal care the first few days of life, which may be sufficient to produce lasting changes in affect (Macri et al., 2009). These findings are consistent with other paradigms that manipulate maternal cues (Moriceau, Wilson, Levine, & Sullivan, 2006).

Isolation rearing increased anxiety-like behavior in the elevated plus maze that was not reversed upon resocialization (Wright, Upton, & Marsden, 1991). Similarly, isolation rearing increased fear reactivity and social anxiety in early adulthood in male rats (Lukkes, Vuong, Scholl, Oliver, & Forster, 2009; Lukkes, Watt, Lowry, & Forster, 2009). Isolation rearing enhances anxiety-like behavior in females (Da Silva, Ferreira, Carobrez Ade, & Morato, 1996). Anxiety-like behavior also depended on species and testing conditions; isolation rearing increased anxiety more in Fawn Hooded rats than in Wistar rats under low light conditions, but Wistars were less anxious when the lights were brighter (Hall, Huang, Fong, Pert, & Linnoila, 1998). In a different test of anxiety, defensive marble burying was reduced in both males and females that were isolated during adolescence (Arakawa, 2007).

Chronic variable stress during adolescence did not affect anxiety-like behavior (plus maze) in either males or females during adolescence (Taylor, Taylor, & Koenig, 2013). However, this same paradigm *reduced* freezing in females, but had no effect in males (Taylor et al., 2013).

Depressive-like behavior. Nonhuman primates that were isolated during development show depressive-like behaviors (Laudenslager, Held, Boccia, Reite, & Cohen, 1990; Suomi, Delizio, & Harlow, 1976). Depressive-like behaviors include postural changes and locomotor retardation (others are specifically discussed below). These behaviors are reversible if the monkeys are rehoused with their peers (Suomi et al., 1976).

The forced swim test (FST) has been used to test antidepressant efficacy, and by proxy, depressive-like behavior (Detke et al., 1995). Increased depressive-like symptoms occur in the MS model (Matthews, Wilkinson, & Robbins, 1996). MS(3) with the whole litter separated as a unit increased the time spent immobile in adulthood in Wistar (Aisa et al., 2008), Fischer (Ruedi-Bettschen et al., 2006), and Sprague-Dawley rats (Marais, van Rensburg, van Zyl, Stein, & Daniels, 2008); Flinders Sensitive Line (FSL) of rats also show greater depressive-like behavior that depends on the quality of maternal care (Friedman, Berman, & Overstreet, 2006). If FSL rats were cross-fostered to the more nurturing Flinders Resistant strain, the depressive effects were less than if raised by FSL dams. Similarly, increased maternal care following brief handling made males more resistant to immobility later in life (Papaioannou, Gerozissis, Prokopiou, Bolaris, & Stylianopoulou, 2002).

The ability of the medial prefrontal cortex to exert behavioral control over a stressor plays a critical role in protecting the brain from depression (Maier & Watkins, 2005; Robbins, 2005). Loss of such control results in hopelessness, which is strongly associated with depression and posttraumatic stress disorder (Maier & Watkins, 2005). MS(4) increases depressive-like symptoms in the triadic model of learned helplessness (Freund et al., 2013; Leussis et al., 2012). Specifically, males show a greater loss of controllability over their perceived ability to escape their situation (e.g., footshock); in contrast, females show greater deficits in their motivation to escape footshock upon first exposure (Leussis et al., 2012). Sensitive periods that are sex sensitive exist before weaning and are expressed during adolescence. We found that males showed more helplessness in response to saline injections at P9–P14, than at P2–P9; conversely, females showed increased resiliency when given a daily saline injection between P2 and P9, but only a modest effect at P9–P14 (Freund et al., 2013). The effects of MS on the FST were minimal in Long–Evans rats (Mourlon et al., 2010).

When rats were housed in isolation between 30 and 35 days of age and then tested 2 days later in adolescence, the male rats demonstrated learned helplessness and the females spent more time in the closed arm of the elevated plus maze (Leussis & Andersen, 2008). Isolation rearing for longer periods (weaning to late adolescence) in rats increased immobility in the FST, although these subjects also received saline injections during preweanling stages (Kuramochi & Nakamura, 2009). The same results were observed in noninjected social isolates (Brenes, Padilla, & Fornaguera, 2009), although no enduring effect on immobility has been reported (Hong et al., 2012). These effects were lower in animals raised in an enriched environment. In contrast, no effect on swimming behavior was observed in Wistar or Fawn-Hooded rats that were isolated and tested in adulthood (Hall et al., 1998). Isolation-reared rats also show reduced exploration of novelty (File, 1978).

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The use of social defeat paradigms to examine depressive-like behavior is a relatively young field. Female adolescent rats exposed to 7 days of consecutive social defeat demonstrated transient depressive behaviors in the FST (Ver Hoeve, Kelly, Luz, Ghanshani, & Bhatnagar, 2013). In contrast, exposure to a dominant male for 10 min/day for 10 days during the juvenile period produced lasting depressive-like effects in females, but not males, in adulthood (Weathington et al., 2012). Similar to the transient effects on FST behavior if social defeat occurred during adolescence, exposure to chronic variable stress during early or late adolescence failed to affect immobility in the FST; this stressor increased immobility in adult-exposed subjects only (Jankord et al., 2011).

Anhedonia: A loss of interest in activities or things once pleasurable, including sex. Only a few studies have examined anhedonia in adolescents or adults with a history of childhood maltreatment. One such study reported elevated anhedonia based on the Mood and Anxiety Symptoms Questionnaire in individuals when the abuse occurred before 14 years of age (Weathington et al., 2012).

Anhedonia in animals is measured with a variety of paradigms, including decreased consumption of sucrose solutions, decreased sexual activity, and a rightward shift in intracranial self-stimulation currents (ICSS) where more current is needed to activate reward systems (Kornetsky & Esposito, 1979). MS(3) decreased responding to novel environments (Matthews, Wilkinsin, et al., 1996). MS(3) rats also show reduced sucrose drinking compared with controls, and this reduction did not differ across males and females in both a positive and negative contrast challenge, where subjects were exposed to a low/high percentage of sucrose followed by a higher/lower one, respectively (Matthews, Hall, Wilkinson, & Robbins, 1996). Similarly, MS(3) Wistar rats also worked less for a sucrose reward in adulthood (Leventopoulos, Russig, Feldon, Pryce, & Opacka-Juffry, 2009). In a slight modification of the MS(3) paradigm, mice separated from the dam and placed on clean bedding between P1 and P14 reduced saccharin drinking in adulthood (Coccurello et al., 2014).

Sucrose drinking was increased in a positive contrast design in rats that were raised in social isolation from weaning until young adulthood (Hall, Humby, Wilkinson, & Robbins, 1997). In a separate study, these effects were not observed in males, but in female adult rats that were isolated (Hong et al., 2012). These effects may also depend on the strain of rat used. The Wistar Kyoto rat has been used in previous studies of depression (Overstreet, 2012). When this strain is exposed to social isolation between 27 and 49 days, females have reduced sucrose consumption compared to controls both immediately after the stressor in late adolescence or in adulthood; males did not show any change (Bourke & Neigh, 2011). Taken together, these data suggest that social stress manipulations on sucrose drinking depend on the age of manipulation as well as the strain of rat.

Measures of ICSS for anhedonia suggest that the MS effect is modest. Rats that underwent MS(3) between P1 and P14 failed to show an anhedonic-like shift in ICSS currents under baseline conditions (Der-Avakian & Markou, 2010; Matthews & Robbins, 2003), but required greater current following 7 days of repeated social defeat (Der-Avakian & Markou, 2010). These data suggest that MS produces a subthreshold effect that requires additional stress for an underlying effect to emerge. In another study, MS(3) rats tested in adulthood demonstrated reduced ICSS response rates in females only with no change between MS(3) males and controls (Michaels, Easterling, & Holtzman, 2007). A subset of isolation-reared rats show equivocal changes to ICSS thresholds that are modulated by D2 receptors (Sundstrom, Hall, Stellar, & Waugh, 2002).

In general, appetitive behavior decreases following early life MS, whereas social isolations increase appetitive behavior (Harmer & Phillips, 1998). However, this relationship may also depend on when the behavior is measured. Rhesus monkeys that were peer raised, which produces stressful-like effects, demonstrated an increase in sweet drinking as juveniles (Nelson et al., 2009); maternally deprived rhesus monkeys had reduced sweet drinking in adulthood (Paul, English, & Halaris, 2000).

Changes in energy and feeling fatigued. A history of childhood sexual abuse is predictive of levels of fatigue (Taylor & Jason, 2002). Abuse that occurred during childhood has a stronger association with levels of fatigue than when abuse occurred during adolescence. Childhood maltreatment, independent of type, increases risk for chronic fatigue syndrome three- to eightfold (Heim et al., 2006). These relationships are all further associated with elevated levels of depression and anxiety, and stronger if criteria for posttraumatic stress syndrome are met (Heim et al., 2009).

Working-memory problems and difficulty concentrating or making decisions. The ability to maintain negative instead of positive affective information when processing emotional material is associated with an increased risk of depression. In multiple studies of individuals with depression and a history of maltreatment, this negativity bias is a common finding (Goodman, Quas, & Ogle, 2010). Young women (mean age = 20 years) with a history of childhood maltreatment have difficulty maintaining positively valenced information relative to nonmaltreated controls (Cromheeke, Herpoel, & Mueller, 2013). In addition, longer duration of abuse is positively associated with memory impairment (Navalta, Polcairi, Webster, Boghossian, & Teicher, 2006). These results held in an adult population-based study, where greater memory impairment was associated with greater adverse childhood experiences (ACEs; Brown et al., 2007).

Working-memory impairment has been observed in both MS(3) and MS(4) subjects tested prepubertally or during adolescence, respectively (Brenhouse & Andersen, 2011; Frankola et al., 2010). MS rats showed more errors and greater latency on the win-shift paradigm during adolescence, but the effect was no longer apparent in adulthood (Brenhouse & Andersen, 2011). The effects on memory were also

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specific for males, because MS(3) females did not show impairment when tested prepubertally (Frankola et al., 2010). Isolation rearing impairs working and spatial memory in adult gerbils (Winterfeld, Teuchert-Noodt, & Dawirs, 1998) and in rats (Quan, Tian, Xu, Zhang, & Wang, 2010).

Relative to hooded rats raised in an enriched environment, rats raised in isolation after weaning have more errors in a radial arm maze (Juraska, Henderson, & Muller, 1984). No sex differences were evident. Similar findings were found in Wistar rats (Gorisch & Schwarting, 2006).

Sleep–wake changes: Insomnia, early-morning wakefulness, or excessive sleeping. Sleep difficulties are a common occurrence in children and adolescents with depression, such that insomnia is more prevalent than hypersomnia (Morielli, Ladan, Ducharme, & Brouillette, 1996). Posttraumatic stress disorder includes reexperiencing and nightmares as a factor in diagnosis. In adults with a history of child maltreatment, three fourths report significant sleep disturbances (Krakow et al., 2002). However, the relationship between the type of abuse and sleep disturbance may be surprising. Consistent with the notion of a maturational delay in symptoms following abuse, sleep disturbances have been reported to emerge years after the abuse (Trickett, Noll, Reiffman, & Putnam, 2001). In cases where the abuse was deemed "less serious," the sleep disturbances were greater (Noll, Trickett, Susman, & Putnam, 2006). Such children may have been older, exposed to little violence, a shorter duration of abuse, or not closely related to the perpetrator. Other reports on sleep difficulties suggest that the type of abuse or perpetrator does not significantly matter (Rimsza, Berg, & Locke, 1988). A likely explanation is that children with "less serious abuse" may not have received sufficient treatment, possibly because they may have seemed asymptomatic (known as sleeper effects; Briere, 1992).

Early research has shown that basic sleep–wake behavior is modulated by maternal behavior and milk delivery (Hofer, 1975). MS(3) rats demonstrate greater REM sleep (~35% more than controls) and more time sleeping than controls (Kinkead, Montandon, Bairam, Lajeunesse, & Horner, 2009). These findings have been replicated (Mrdalj et al., 2013). No effect on sleep architecture was observed in Wistar rats that were exposed to *prenatal* stress (Dugovic, Maccari, Weibel, Turek, & Van Reeth, 1999). Social isolation later in life (P50–P60) had little effect on sleep architecture in rats, although living within an enriched environment improves sleep quality (Kiyono, Seo, & Shibagaki, 1981).

Changes in appetite. Clinical and preclinical studies show a relationship between the postnatal environment and the risk of developing obesity (Felitti, 1991; Vamosi, Heitmann, & Kyvik, 2010). The risk is higher in girls. Exposure to chronic stress may lead to "comfort" eating, where children and adolescents are likely to overeat. Elevations in cortisol can elevate insulin secretion, ultimately leading to its dysregulation; together, these factors further enhance appetite and/or weight gain (Pervanidou & Chrousos, 2011). Binge eating has been associated with greater weight gain in victims of childhood sexual abuse (Gustafson & Sarwer, 2004).

Changes in growth and eating behavior are programmed early in life (Kuhn, Pauk, & Schanberg, 1990; Plotsky & Meaney, 1993). Maternal behavior affects growth hormone, corticosterone, and other hormones involved in development in rats (Kuhn, Butler, & Schanberg, 1978) and in nonhuman primates (Kaufman et al., 2007). For example, leptin, a hormone involved in regulating energy intake and use (including thermogenesis), peaks at ~P10 in rats before declining (Blumberg, Deaver, & Kirby, 1999; Delahaye et al., 2008). Leptin can modify the effects of MS by reducing responsivity to external ACTH (Salzmann et al., 2004). Given that MS pups show reduced rates of growth before puberty (Freund et al., 2013), early life changes in leptin make MS subjects less vulnerable to gaining weight in adulthood when fed a high-fat diet (Paternain et al., 2012). However, male MS subjects fed a regular chow diet showed increased weight gain in adulthood and females did not (Matthews, Wilkinson, et al., 1996); this weight gain following a chow diet or one deficient in omega 3s, in which insulin resistance biomarkers are decreased (Bernardi et al., 2013; Delaunay et al., 1997; Lambillotte, Gilon, & Henquin, 1997; Solas et al., 2010).

Rats exposed to MS(3), and then subjected to social isolation, gained more weight than either manipulation alone (Ryu, Yoo, Kang, Lee, & Jahng, 2009). In contrast, rats exposed to a chronic variable stress paradigm during early or late adolescence or adulthood lost weight in general, as well as fat weight specifically (Jankord et al., 2011; Taylor et al., 2013); others have reported no weight loss (Cruz et al., 2012).

Thoughts of suicide, suicide attempts. Early ACEs significantly increase the risk of attempted suicide by two to five times, raising the rates from the general population prevalence of 1.1% to as high as 35% if seven or more ACEs are present (Dube et al., 2001). A recent longitudinal study in New Zealand that followed 900 individuals less than 30 years of age demonstrated a significant relationship between childhood sexual abuse and both suicidal ideation and attempts (Fergusson, McLeod, & Horwood, 2013). Of note, elevated suicidality is also evident in individuals with a history of physical abuse (Fuller-Thomson, Baker, & Brennenstuhl, 2012). Other studies have found similar results in teenagers (Klomek et al., 2013). The study of suicide, attempts, and ideation in animals at this stage is impossible.

Malaise: Aches or pains, headaches, cramps, or digestive problems. Digestion problems, including nausea, stomachaches, and vomiting, have been associated with early abuse in boys and girls (Kugler, Bloom, Kaercher, Truax, & Storch, 2012). Digestive issues have been documented in animals that experienced MS and are reviewed elsewhere (Barreau, Ferrier, Fioramonti, & Bueno, 2007).

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Treatment Implications

Exposure to adversity early in life is associated with increased susceptibility to other disorders in adulthood besides mental illness, including cancer, diabetes mellitus, and obesity (Burdge, Lillycrop, & Jackson, 2009; Felitti et al., 1998). A greater understanding about how important variables an many different levels of analysis contribute to the negative consequences of adversity exposure can be used to design interventions (Cicchetti & Gunnar, 2008). Such variables include the duration of the stressor, the immediacy or lack thereof of consequences, and the transitions that occur during the course of the resultant shifts in brain development. Discussion of these variables from a translational perspective may shed light on the gaps in our knowledge. As we (Andersen, 2005; Stanis & Andersen, in press) and others (Fishbein, 2000; Studts & van Zyl, 2013) have discussed elsewhere, interventions need to be developmentally appropriate for the subject, specific to the modality affected, and well timed to maximize their effects (Wachs, Georgieff, Cusick, & McEwen, 2013).

Maternal behavior has a significant influence on the outcome of fear, anxiety, and depressive behaviors. A recent clinical study found that reducing the child's exposure to a depressed mother (presumably a condition that reduces her caregiving) by placing the child in daycare was associated with a significant reduction in internalizing behaviors (Herba et al., 2013). Programs that aim to increase support to a mother who is experiencing domestic abuse, which is likely to reduce her ability to care for her child and expose the child to a traumatizing event, may further provide an effective intervention to break the chain of abuse (Taft et al., 2011). The beneficial effects of brief separations during development have been documented where brief handling for 15 min daily in rats reduces stress responsiveness (Plotsky et al., 2005) and improves spatial working memory and novel object recognition in female rats (Plescia et al., 2013). Even improved environments during pregnancy may have positive benefits. Environmental enrichment during pregnancy and lactation had long-lasting effects on reactivity to acute and chronic stress in offspring that were not highly dependent on early postpartum maternal behavior (Welberg, Thrivikraman, & Plotsky, 2006). A number of intervention approaches for older children with a history of maltreatment are being developed (reviewed by Toth & Cicchetti, 2013).

Interventions would benefit greatly from improved reporting of abusive experiences. A single episode of abuse is associated with more favorable outcomes than repeated exposures (Copeland, Keeler, Angold, & Costello, 2007). Unfortunately, females are more likely to experience higher rates of revictimization of abuse, which may explain higher rates of depression in females (Koenen & Widom, 2009). Secondary to increased revictimization, a window of opportunity exists for intervention even though the individual is not symptomatic (Teicher et al., 2009). As depression is accelerated into early adolescence following maltreatment (Gladstone et al., 2004), symptoms do not emerge until this period. In our clinical sample, we found that an average of 9.2 years lapsed between the initial abusive event and depression onset (Teicher et al., 2009).

This review highlighted the historical and current understanding of the effects of social stress manipulations on behaviors related to depression. While much research has been conducted in this area, a greater understanding of the specific aspects of depression is still warranted. A number of factors need to be considered when identifying the individual's degree of risk to develop depression (e.g., genetics, gender, age of abuse, and duration of abuse), as well as what symptoms to predict. Early life stress seems to more strongly influence anxiety, mood, and anhedonia, whereas later life stress appears to have greater effects on externalizing behaviors, which were not discussed in this review. Early interventions (Wachs et al., 2013) that consider the implications of any or all of these factors are likely to impact depression reduction.

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