

**The Stress–Reward–Mentalizing Model of Depression:
An Integrative Developmental Cascade Approach to Child and Adolescent Depressive
Disorder Based on the Research Domain Criteria Approach**

Patrick Luyten

KU Leuven (University of Leuven) and UCL (University College London)

Peter Fonagy

UCL

Author Note

Patrick Luyten, Faculty of Psychology and Educational Sciences, KU Leuven, Leuven, Belgium; Research Department of Clinical, Educational and Health Psychology, UCL, London, UK; Peter Fonagy, Research Department of Clinical, Educational and Health Psychology, UCL, London, UK.

Correspondence concerning this article should be addressed to Patrick Luyten, Faculty of Psychology and Educational Sciences, KU Leuven, Tiensestraat 102 - box 3722, 3000 Leuven, Belgium.

E-mail: patrick.luyten@ppw.kuleuven.be

Manuscript submitted to: *Clinical Psychology Review*

Abstract

The Research Domain Criteria (RDoC) propose a much-needed change in approach to the study of vulnerability factors implicated in mental disorders, shifting away from a categorical, disease-oriented model to a dimensional approach that focuses on underlying systems implicated in psychopathology. In this paper we illustrate this approach with a focus on the emergence of depression in childhood and adolescence. Based on evolutionary biological and developmental psychopathology considerations, we present an integrative developmental cascade model of depression that essentially suggests that depression emerges out of a three-pronged series of interacting impairments in the domains of stress regulation, reward, and mentalizing. We discuss the relation of these impairments to the five domains proposed by RDoC. We also focus on how this model may explain in large part the marked comorbidity of depression with other psychiatric disorders, as well as with functional somatic and somatic disorders. Limitations of this theoretical approach are discussed, as well as implications for the development, evaluation, and dissemination of interventions aimed at preventing or treating depression.

The U.S. National Institute of Mental Health Research Domain Criteria (RDoC) propose a much-needed change in approach to the study of mediating factors implicated in mental disorders, shifting away from a categorical, disease-oriented model to a dimensional approach. The RDoC approach essentially proposes a matrix of domains and levels of analyses that relate to different types of psychopathologies and behavioral problems, with the aim of furthering our insights into the nature of psychopathology and its treatment across discrete consensus-based diagnoses (Cuthbert & Insel, 2013).

This paper presents a novel comprehensive approach based on RDoC methodology to the emergence of depression in childhood and adolescence, with the aim of setting an agenda for future basic and intervention research in this area. We first review findings concerning the nature and prevalence of depression in childhood and adolescence from a developmental and evolutionary biology perspective. Next, we review the evidence for the involvement of three core biobehavioral systems or domains of functioning in depression (i.e., stress, reward, and mentalizing or social cognition), and situate these within a comprehensive developmental cascade model of child and adolescent depression. Most theories of depression tend to focus on and prioritize one of these domains, although some more integrative approaches have recently been published (Auerbach, Admon, & Pizzagalli, 2014; Davey, Yücel, & Allen, 2008; Dillon et al., 2014; Pizzagalli, 2014). This paper builds on these previous efforts and extends them to provide an integrated, developmental account of these three areas in relation to the RDoC approach, illustrating the heuristic power of the RDoC.

Basically, we argue that the emergence of depression in childhood and adolescence results from a series of three-pronged interactions among impairments in the domains of stress regulation, reward (and the incentive value of attachment and agency/autonomy in particular), and the emerging capacity for mentalizing or social cognition, leading to a vicious cycle characterized by impaired stress regulation and reward sensitivity (Figure 1). These

interacting impairments interfere with normative developmental tasks that rely on capacities associated with these domains, increasing the risk for depression and associated conditions, particularly during developmental transitions (e.g., from childhood to adolescence, and from adolescence to early adulthood). In adolescence and early adulthood, in particular, the establishment of new and more complex relationships and a sense of agency and autonomy rely heavily on the stress regulation, reward, and mentalizing systems, which may explain the increased prevalence of depression during these developmental transitions (Figure 2). Both biological and environmental factors and their interactions are likely to be involved in the negative development cascade, which may originate in any of these three domains.

As the focus in RDoC is on neural circuitry (Insel et al., 2010), with levels of analysis progressing “upward” to behavior and “downward” to genetic and molecular levels, we take a similar approach here, focusing on the domains of neural circuits/physiology, behavior, and genes. Limitations of the approach are discussed, as are implications for intervention.

Child and Adolescent Depression:

The Need for a Developmental and Evolutionary Biology Perspective

Depression is one of the leading causes of disability, morbidity, and mortality (Collins et al., 2011), and is a major risk factor for suicide in adults and adolescents (Nock et al., 2013; Wilkinson, Kelvin, Roberts, Dubicka, & Goodyer, 2011). A meta-analysis by Costello, Erklani, and Angold (2006) estimated that 2.8% of children under the age of 13 and 5.6% of 13–18-year-olds suffer from depressive disorders. Studies focusing solely on major depressive disorder as defined in subsequent editions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM; American Psychiatric Association, 2013) have found a prevalence of approximately 2% in children and 4–8% in adolescents. Lifetime estimates of prevalence range between 15% and 20% (Birmaher, Ryan, Williamson, Brent, & Kaufman, 1996). For dysthymic disorder, epidemiological studies suggest prevalences between 0.6%

and 1.7% for children, and between 1.6% and 8.0% for adolescents (Birmaher et al., 2007; Birmaher et al., 1996; Hazell & Mirzaie, 2013). Until adolescence, depressive disorders are equally prevalent in boys and girls, but from age 14 the female:male ratio changes to approximately 2:1, and this ratio persists throughout adulthood (see Angold, Erkanli, Silberg, Eaves, & Costello, 2002; Birmaher et al., 2007). Hence, it is crucially important for any theoretical approach to depression to provide an explanation for the emergence of these gender differences in adolescence, an issue to which we return later.

From a developmental psychopathology perspective, it is equally important to note that while the symptomatic expression of depression in children and adolescents resembles in many respects that in adults, there are also some important differences. First, children and adolescents typically show more anxiety and anger, fewer vegetative symptoms, and less verbalization of hopelessness than adults (American Psychiatric Association, 2013). Second, there is a high correlation between depression and other internalizing and externalizing symptoms and disorders in childhood and adolescence (Lee & Stone, 2012). From a developmental psychopathology perspective, these findings question whether a neat distinction can be made between depression and other disorders and behavioral problems, particularly in childhood and adolescence (Blatt & Luyten, 2009)—a speculation that is congruent with the RDoC approach. Indeed, the dimensional approach, focusing on neural circuits that cut across descriptive diagnoses as proposed by the RDoC, is likely to lead to “fuzzy” boundaries between different “disorders” and thus, equally, between factors implicated in vulnerability for depression and other disorders.

The Stress–Reward–Mentalizing Model of Depression

Introduction

Extant theories have linked depression to impairments in stress, reward sensitivity, and mentalizing. While there is a respectable body of research in relation to each of these

domains, research in these areas has developed relatively independently, although notable efforts to integrate them have recently appeared (Auerbach et al., 2014; Davey et al., 2008; Dillon et al., 2014; Pizzagalli, 2014).

In this paper we propose an integrative, developmental cascade model of depression, building on previous efforts in this domain, and relating this approach to the RDoC domains. Specifically, we argue that three basic biobehavioral systems have evolved in response to the continuing need to adapt to ever-changing circumstances and the growing complexity of human interpersonal relationships in particular: (a) a system that deals with distress following threat (the stress/threat system); (b) a system that produces rewarding features associated with positive environmental features, including the formation of interpersonal relationships involved in infant–mother, mother–infant, pair-bonding, and other attachment relationships, and experiences of agency and autonomy (the reward system); and (c) a mentalizing or social cognition system, which subserves the capacity to understand oneself and others in terms of intentional mental states such as feelings, desires, wishes, attitudes, and values, and delivers the necessary computational power human beings need to navigate their complex interpersonal world and to acquire a sense of agency and autonomy.

While these systems are adaptive from an evolutionary perspective, both internal and contextual threats may disrupt their highly interrelated and coordinated functions, and such disruptions may reflect what we have come to see as different forms of depression. From an evolutionary perspective, a condition such as depression thus is not in itself maladaptive. The genetic predisposition to depression may have been maintained in the human genome because depression is a mechanism that attempts to minimize or terminate distress associated with separation and loss (Davey et al., 2008; Gilbert, 2006; Panksepp & Watt, 2011).

Furthermore, the proposed model argues that excessive and/or age-inappropriate stress, most probably in combination with increased stress sensitivity, typically sets in motion

a developmental cascade leading to increasing impairments in reward sensitivity (and the incentive value of attachment and agency/autonomy in particular) and in the capacity for mentalizing or social cognition (Figure 1); these impairments then interfere with normative developmental tasks. The establishment of mature and differentiated relationships and the development of a sense of agency and autonomy, notable features of adolescence and young adulthood, seem particularly relevant in the context of the emergence of depression. These developmental tasks have been shown to be the most central sources of stress associated with the emergence of depression in these developmental stages, putting emerging mentalizing capacities under considerable pressure, while at the same time being potentially key sources of reward. The challenging nature of these developmental tasks is further compounded by a major structural and functional reorganization of the neural circuits involved in mentalizing, stress, and reward during adolescence. Together, these factors lead to a considerable increase in the risk for depression and associated conditions in adolescence (Figure 2).

We will discuss research findings concerning each of these systems in depression and outline their relation to the proposed RDoC domains of functioning.

Stress (RDoC Negative Valence and Arousal/Regulatory Systems)

Neural circuitry and physiology.

Stress-regulating systems are currently discussed in the RDoC under the negative valence and arousal/regulatory systems. Their relevance for understanding vulnerability for depression from a developmental perspective has been amply demonstrated in both adults (Heim & Binder, 2012) and in children and adolescents (Auerbach et al., 2014; Hankin, 2012; Pizzagalli, 2014). It is believed that depression is best seen as a developmental, stress-related disorder, with elevated and/or age-appropriate levels of stress, most likely in combination with increased stress sensitivity, leading to increased vulnerability to depression and other stress-related disorders.

Consistent with the developmental approach taken in this paper, understanding the developmental origins of the capacity for stress regulation is therefore imperative. Rather than taking a narrow focus on the hypothalamic–pituitary–adrenal (HPA) axis system and the sympathetic nervous system as core structures of the stress system, here we take a systems approach to the neural structures involved in detecting, integrating, and responding to what is threatening and stressful to the individual. Research has delineated a distributed set of neural structures involving the amygdala and hippocampus, and areas in the prefrontal cortex (PFC), most notably the anterior cingulate cortex, orbitofrontal cortex, and medial PFC (MPFC), as key in this network (McEwen, 2007; Pervanidou & Chrousos, 2012). Together, these structures serve *allostasis*, the capacity to continuously adapt to ever-changing circumstances (McEwen, 2007). *Allostatic load* ensues when attempts to establish allostasis fail. Research findings indicate the existence of a series of closely interrelated physiological systems responsible for establishing and maintaining allostasis, serving the fight/flight/freeze response faced with acute stress, and a broader set of regulatory responses associated with the stress response more generally (Gunnar & Quevedo, 2007; McEwen, 2007; Pervanidou & Chrousos, 2012). These include the HPA axis and the autonomic nervous system, as well as the metabolic system, gut, kidneys, and immune system, each with their relatively distinct biomediators (e.g., cortisol, sympathetic and parasympathetic transmitters, metabolic hormones, and cytokines, respectively). This demonstrates the close intertwining of the stress system with several other bodily systems, which interact in complex ways (McEwen, 2007). This assumption has important implications for the emergence of comorbidity, particularly from a developmental perspective, an issue to which we will return.

Together with the marked heterogeneity in the etiology of depression (discussed in more detail later), the complexity of the stress response may in part explain some of the inconsistent findings regarding the neurobiology of stress dysregulation in depression. For

instance, congruent with findings in adults (Heim, Newport, Mletzko, Miller, & Hemeroff, 2008), a meta-analysis of studies of HPA axis response to the dexamethasone suppression test in depressed youth (17 studies, totaling 926 participants) and of studies of basal HPA axis functioning (17 studies, totaling 1332 participants), reported HPA axis hyperactivity in combination with greater sensitivity to psychological stressors in children and adolescents with depression, compared with normal controls (Lopez-Duran, Kovacs, & George, 2009). However, not all studies have confirmed these findings. There is indeed some evidence in adults, children, and adolescents to suggest that while acute stress may initially lead to hyperactivity of the HPA axis, chronic stress may over time lead to a switch to hypoactivity because of the wear and tear on physiological systems (Miller, Chen, & Zhou, 2007); again, this points to the need for a developmental perspective to untangle the major pathways to depression. For instance, HPA axis hypoactivity may delineate atypical depression and may also explain high comorbidity with other stress-related syndromes, as they may share similar developmental pathways (see below).

Strong evidence for programming of the stress system in early life has emerged from animal research and is increasingly being confirmed by studies in humans, with evidence suggesting that sensitive or critical periods for these programming effects last until adolescence and likely into early adulthood (Heim & Binder, 2012; Lupien, McEwen, Gunnar, & Heim, 2009). As a consequence, researchers are increasingly adopting a developmental approach to the study of the stress response across the lifespan (Lupien et al., 2009). Although most research in this area has focused on the prenatal and perinatal periods, evidence is amassing that core structures of the stress system, such as the amygdala and hippocampus, undergo major structural changes and functional reorganization in adolescence. This is also the case for the PFC, which is subject to cortical thinning during adolescence, due in part to synaptic pruning and programmed cell death (Mutlu et al., 2013; Shaw et al., 2008).

Thus, the developing stress and mentalizing system (discussed later) are particularly sensitive to social and biological stress during this period, with immediate and often lasting effects on these and associated systems such as the immune, metabolic, and cardiovascular systems (Lupien et al., 2009; Pervanidou & Chrousos, 2012). These findings are consistent with the structural and functional abnormalities that have been found in the hippocampus in depressed individuals—particularly those with early adversity—both in adults (Gobinath, Mahmoud, & Galea, 2014) and in children and adolescents (Serafini et al., 2014). Furthermore, adolescence is marked by a considerable increase in HPA axis reactivity to stress (Casey, Getz, & Galvan, 2008), particularly in response to social rejection (Masten et al., 2009; Sebastian, Viding, Williams, & Blakemore, 2010; Sebastian et al., 2011).

The RDoC proposes that the stress and arousal/regulatory systems are different domains. Yet, the RDoC links the latter system to homeostatic regulation, which is also a core task of the stress system (McEwen, 2006). Furthermore, stress and disturbances of circadian rhythm have mutually reinforcing effects (as sleep deprivation is a powerful stressor that itself contributes to allostatic load; McEwen, 2006); thus, further research is needed to investigate whether the arousal and regulatory systems are really different systems. The fact that depression is the disorder that is perhaps most closely associated with sleep problems and problems related to disturbances of the circadian rhythm, at least in adults (Tsuno, Besset, & Ritchie, 2005), might be an important bias in this context, and in other disorders the dissociation between both domains might be clearer.

Genetic level.

The heritability of depression in adulthood is well established, with estimates of around 30–40% in adults (Sullivan, Neale, & Kendler, 2000). For pediatric depression, behavioral genetic studies suggest that heritability may be considerably lower in early childhood (Rice, 2010), but by early adolescence similar estimates are typically obtained to

those in adults, although estimates have varied widely between studies (Middeldorp et al., 2010). There is increasing evidence for the role of gene–environment correlations and interactions in depression, with much research focusing on candidate genes involved in the stress system, such as the serotonin transporter gene-linked polymorphic region (*5-HTTLPR*; Caspi, Hariri, Holmes, Uher, & Moffitt, 2010). While this research has included adolescent depression studies (Owens et al., 2012; Walsh et al., 2012), the body of evidence it has produced continues to be controversial given the many methodological limitations of existing research (Dick et al., 2015). There is a paucity of research on gene–environment transactions in pediatric depression (Auerbach et al., 2014), and association studies of candidate genes related to the stress system in children and adolescents have not led to conclusive results (Middeldorp et al., 2010; Rice, 2010). Yet, the fact that genetic polymorphisms related to the stress-regulating system may be involved in depression is in line with findings from animal research, although it is highly likely that other social susceptibility genes that have not yet been adequately studied may also have a role (Dick et al., 2015). A relatively new promising field is that of epigenetics, which refers to the often-enduring effects of environmental factors on gene expression. Epigenetic modifications of cytosine–guanine dinucleotide sites in DNA as a result of early adversity have been prospectively demonstrated in a community sample of 109 15-year-olds (Essex et al., 2013). Much more research in this area is needed.

Despite the limitations of current research on gene–environment transactions, it is clear that current research is moving away from pure diathesis–stress models of depression to broader differential susceptibility models, that is, the idea that individuals show marked differences in terms of sensitivity to the environment, for better or for worse (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2011).

The Developmental Origins of Health and Disease (DOHaD) paradigm (Gluckman et al., 2009) argues in this context that developmental plasticity is a major feature of organisms

that enables them to adapt to ever-changing circumstances, thus assisting the survival of the species. Research findings are converging to suggest that, particularly during critical time windows, physical and psychological stressors may reset or “reprogram” a wide array of developmental trajectories involving brain areas involved in stress regulation and related biological systems such as the immune system, pain-regulating systems, the metabolic system, and the reproductive system (McEwen, 2007). Epigenetic mechanisms such as DNA methylation may play a key role in this (Champagne & Curley, 2009).

As there is mounting evidence that the environment may have an important influence on phenotypic variation, particularly under poor environmental conditions (to which individuals with a history of trauma and neglect have often been exposed), this also leads us to consider the role of the broader environment in depression. Indeed, most types of adversity do not occur in isolation but are part of so-called risky families and environments (Repetti, Taylor, & Seeman, 2002) or “pathogenic relational environments” (Cicchetti & Toth, 2005, p. 414). The role of the environment in depression is still poorly understood, despite major findings demonstrating that such a link exists. Ethnic and sexual minority status, for instance, is an important but relatively neglected area in research on childhood and adolescent depression (Marshall et al., 2011; Smith & Silva, 2011).

Behavioral level.

Consistent with the neurobiological research reviewed earlier, the link between stress and depression is well established at the behavioral level, and individuals with increased stress sensitivity seem to be particularly at risk for depression.

Early adversity has been shown to play a key role in the emergence of depression and suicide in childhood and adolescence (O'Brien & Sher, 2013) because of its potential negative effects on the programming of the stress response, particularly in already vulnerable individuals (Auerbach et al., 2014; McCrory, De Brito, & Viding, 2012). Population

attributable fractions (i.e., the proportion of psychiatric disorders and suicide that could be explained by early adversity) range from 20% (Afifi et al., 2008) to 80% (Dube et al., 2001), and are typically highest in childhood and adolescence.

Congruent with the broad programming effects of early adversity and the interrelationship between stress and other neurobiological systems, it seems that multifinality is the rule rather than the exception, with studies typically finding a dose–response relationship between early adversity and the number of psychiatric disorders, functional somatic disorders, somatic diseases, and general indices of maladaptive intrapersonal and interpersonal functioning (Anda et al., 2006; Roseboom, Painter, van Abeelen, Veenendaal, & de Rooij, 2011). Importantly, the relationship between stress and depression onset has been found to remain stable across the lifespan, even when controlling for the onset of previous episodes, consistent with the notion of programming effects (McLaughlin et al., 2010).

In addition to early adversity, later-life stress may also be important. Both *major and minor life stressors* and *chronic stress*, particularly in interaction with personality features that confer vulnerability to depression (e.g., neuroticism and self-critical perfectionism) and genetic risk, have been causally related to the onset of depression. This has been most clearly demonstrated in adults, but an emerging literature shows similar findings in children and adolescents (Kendler & Gardner, 2014; Kendler, Kuhn, & Prescott, 2004; Luyten, Blatt, Van Houdenhove, & Corveleyn, 2006). Stressful life events seem to be associated with depression because of the increased stress sensitivity that is associated with vulnerability for depression.

However, the stress-generation (Hammen, 2005), active vulnerability (Shahar, 2006), or dynamic interactionism (Luyten et al., 2006) view proposes that individuals who are vulnerable to depression also tend to generate, in part, their own stressful environment. There is good evidence to support this assumption from experimental studies and large clinical, epidemiological, and twin studies (Hammen, 2005; Kendler et al., 2004). Maladaptive

behaviors and unhealthy lifestyles also contribute (McEwen, 2007). Evidence for stress-generation effects has also been reported in pediatric depression (Auerbach et al., 2014; Blatt, 2004). Congruent with the notion that the stress system undergoes major structural and functional changes in adolescence, studies suggest that stress may play an even greater role in explaining the onset of depression in childhood and adolescence than in adulthood, with interpersonal stressors in particular predicting the onset of depression in childhood and adolescence (Auerbach et al., 2014). This may be primarily explained by the finding that relationships with peers become more important at this stage, although issues of agency, autonomy, and achievement are also increasingly important (Figure 2). The recognition by others that interpersonal experiences may bring (or, indeed, fail to bring) could explain the increase in depression in adolescence (Auerbach et al., 2014). It should also be borne in mind that, as the onset of puberty is advanced by early social stress (Belsky, Houts, & Fearon, 2010) and the timing of puberty determines the maturation of neural circuitry (Paus, 2013), early adversity can increase the window of vulnerability of adolescence by bringing forward puberty and enhancing the salience of relational and emotional stressors.

There is some evidence that gender differences in the prevalence of depression that emerge around this time in development may be associated with the greater valuing, at least within Western societies, of agency, autonomy, and self-definition in men, while women tend to place greater emphasis on relatedness and attachment (for a review, see Blatt, 2008). Social stress in adolescence may affect women more because of their greater social orientation (Eiland & Romeo, 2013); consequently, they are more prone to internalizing disorders such as so-called somatic depression (i.e., depression characterized by anxious and somatic concerns) and other stress-related disorders involving preoccupation with issues of relatedness (such as pain and exhaustion syndromes; Kendler & Gardner, 2014). Further research, particularly in adolescents, is needed to further substantiate these assumptions.

Reward (RDoC Positive Valence Systems)**Neural circuitry and physiology.**

Early and later-life adversity seem to lead to a downward spiral marked by the presence of distress and negative affect and the absence of positive affect, which brings us to the RDoC domains of positive valence and, specifically, reward. Just as for dysfunctions in stress regulation, evidence is growing for the role of altered reward sensitivity in depression. Impairments in reward and incentive motivation in particular have been implicated in depression—particularly in typical features such as anhedonia—in both adults and adolescents (Auerbach et al., 2014; Forbes & Dahl, 2012).

From the perspective of both evolutionary (Gilbert, 2006) and social (Beck, 2009; Blatt, 2008) science, there are two key areas of reward that seem particularly relevant for depression, particularly as they overlap with areas of stress associated with depression: social/attachment relationships and agency/autonomy (see Figure 2).

The RDoC has included problems with reward in the positive valence systems domain, while affiliation and attachment are categorized in the systems for the social processes domain. Evidence suggests, however, that there is a substantial overlap between the behavioral and neurobiological systems involved in reward and attachment (Insel & Young, 2001; Panksepp & Watt, 2011; Rutherford, Williams, Moy, Mayes, & Johns, 2011; Swain, Lorberbaum, Kose, & Strathearn, 2007). Indeed, attachment cues (such as infant faces, infant cries, proximity of and interaction with attachment figures) are associated with the activation of neural circuits that are typically considered to be central to the reward system (such as the ventral tegmental area and nucleus accumbens). Individual differences in attachment styles and history, in turn, are associated with differential activation of brain regions that are part of the reward circuit (for reviews, see Fonagy & Luyten, 2016; Leckman et al., 2005; Vrticka & Vuilleumier, 2012). Social cognition or mentalizing seems to involve related, but different,

capacities and behavioral and neurobiological systems (Luyten & Fonagy, 2015). We therefore also prefer the notion of *social cognition* or *mentalizing systems* for this domain, rather than systems for social processes.

Less is known about the relationship between agency/autonomy and the reward system, although behavioral research has abundantly demonstrated the rewarding nature of experiences of agency, autonomy, and autonomous motivation more generally (Ryan, Deci, & Vansteenkiste, 2016). This clearly reflects a gap in the literature, and future efforts should concentrate on the relationship between the reward system and the development of feelings of agency, autonomy, and achievement (Murayama, Matsumoto, Izuma, & Matsumoto, 2010).

The reward system itself is relatively well described, and consists of mesolimbic and mesocortical pathways. Mesolimbic pathways originate from the ventral tegmental area and project mainly to ventral striatal regions and the nucleus accumbens in particular, as well as the hippocampus and amygdala. The mesocortical pathways involve projections to the PFC and anterior cingulate cortex (Pizzagalli, 2014; Russo & Nestler, 2013; Spear, 2000). Recent research has mainly focused on dopamine and oxytocin as key biological mediators involved in this system. Opioid and cannabinoid systems seem to be equally relevant, particularly as they have been related to the pain associated with social loss and rejection, which is increased in adolescence, particularly in females (Hsu et al., 2015; Panksepp & Watt, 2011; Spear, 2000). From a developmental perspective, it is important to realize that the attachment system plays a key role in the development and regulation of the stress system through activation of the reward system, as suggested by studies in animals (including higher primates) and a growing body of research in humans (Hostinar, Sullivan, & Gunnar, 2014; Strathearn, 2011; Swain et al., 2014). Studies in normatively developing children have shown that secure attachment experiences typically buffer the effects of stress in early development, resulting in so-called adaptive hypoactivity of the HPA axis in early development (Gunnar & Quevedo,

2007). By contrast, insecure attachment experiences typically lead to increased vulnerability for stress, as expressed in dysfunctions of the HPA axis as well as the reward system (Auerbach et al., 2014; Pizzagalli, 2014; Strathearn, 2011).

Further emphasizing the links between attachment and the reward system, neuropeptides such as oxytocin and vasopressin have been shown to be key modulators in this context. Particularly for securely attached individuals, and in relation to in-group members, oxytocin has been shown to increase affiliative behavior when faced with distress; this optimizes the opportunities for effective co-regulation of stress with others, and reduces behavioral and neuroendocrinological responses to stress (Neumann, 2008). Generally, mothers with higher serum levels of oxytocin tend to make more affectionate contact with their infants, are more likely to follow the infant's gaze with an affectionate touch, and generally present themselves to their infant with increased social salience (Apter-Levi, Zagoory-Sharon, & Feldman, 2014; Kim, Fonagy, Koos, Dorsett, & Strathearn, 2014). Oxytocin has also been associated with direct anxiolytic and anti-stress effects in community samples via downregulation of the HPA system (Feldman, Vengrober, & Ebstein, 2014). Furthermore, oxytocin has been shown to enhance mentalizing and trust in others, again increasing opportunities for effective downregulation of distress and exploration (Bartz, Zaki, Bolger, & Ochsner, 2011; Neumann, 2008), and leading to so-called broaden-and-build cycles associated with secure attachment and effective stress regulation (Fredrickson, 2001; Mikulincer & Shaver, 2007). However, these effects seem to be limited to enhancing existing positive affiliations (with in-group members); in fact, studies have reported that oxytocin administration leads to increased distrust, more bias in attributing intentions, and decreases in cooperative behavior in relation to out-group members, even in normatively developing individuals (Bartz et al., 2011). Furthermore, in individuals with an insecure attachment history, decreased basal oxytocin levels, negative effects of oxytocin administration on social

behavior, and an increased cortisol response to stress have been reported (Bartz et al., 2011). Oxytocin therefore seems to increase the salience of attachment issues.

From a developmental perspective, the reorganization of the reward system—at the same time as the stress and mentalizing systems undergo major reorganization—in combination with the major changes in sociocultural expectations that occur in adolescence, seems to play an important role in explaining the emergence of depression in adolescence (Auerbach et al., 2014; Davey et al., 2008; Forbes & Dahl, 2012; Luciana, 2013; Spear, 2000) (Figure 2). Adolescence is marked by major changes with regard to both relatedness and agency/autonomy because of entry into the complex world of peer and romantic relationships (expressed in increased rejection sensitivity) as well as increasing demands for achievement (reflected in increased sensitivity to failure). Yet, both animal and human research suggests that adolescence is characterized by the lowest levels of dopamine in striatal regions and the highest levels of dopamine in prefrontal regions, possibly leading to a so-called mini-reward deficiency syndrome (Spear, 2007). This may also lead to compensatory behaviors such as risk-taking and drug abuse, explaining the high comorbidity between depression and externalizing psychopathology in adolescence (Davey et al., 2008; Spear, 2000).

These findings may also explain why disappointment and/or frustration of needs for relationships, belongingness, and achievement/status (which are often intertwined, particularly in adolescence) may lead to a downward spiral marked by suppression of the reward system, increased levels of stress, and impairments in mentalizing, as we will discuss in more detail later. The normative decrease in the incentive value of rewards in adolescence has been speculated to be evolutionarily adaptive, as it is likely to increase novelty- and sensation-seeking behavior, assisting adolescents to accomplish important developmental tasks such as gaining independence, developing feelings of agency and autonomy, and establishing more complex relationships (including romantic relationships) with others. Low

levels of tonic dopamine and high levels of phasic dopamine in response to rewards might drive this effect (Davey et al., 2008; Luciana, 2013). Yet, high normative levels of negative affect and impairments in reward sensitivity might also result from excessive downregulation of the PFC through high levels of dopamine in the PFC, which have been observed as a result of increased stress in adolescents (Pizzagalli, 2014; Spear, 2000). High levels of mesocortical dopamine not only inhibit mentalizing (see also below) but, because of increased representational capacities, the incentive value of rewards may further decrease because important rewards in adolescence (e.g., love, status) are increasingly seen and experienced as abstract and temporally distant (Davey et al., 2008).

Particularly for adolescents with a history of insecure attachment experiences and associated impairment in the reward and stress system, a vicious cycle may be set in motion, resulting in increased levels of depression and associated compensatory strategies such as risky (sexual) behaviors and drug abuse (Andersen & Teicher, 2009). More longitudinal research is needed in this context, particularly in at-risk adolescents.

Genetic level.

Whereas earlier studies of the genetics of depression concentrated mainly on the stress system, as reviewed earlier, there has been an increasing focus on the role of genes associated with key neuromodulators of the reward system, such as dopamine (Auerbach et al., 2014) and oxytocin (McQuaid, McInnis, Abizaid, & Anisman, 2014). This focus has increased as a result of evidence for epigenetic modification of these neuromodulators through environmental factors and parental (Feldman et al., 2014) and the growing evidence for relationships between neuromodulators of the stress system (such as serotonin) and the reward system (Spear, 2000). For instance, early insecure attachment experiences have been related to polymorphisms in the oxytocin receptor gene in adult patients with unipolar depression (Costa et al., 2009), in line with studies reporting dysregulated peripheral oxytocin

release in women with depression (Cyranski et al., 2008; McQuaid et al., 2014) and decreased activation of the reward system (Gotlib et al., 2010). A study in a community sample of 441 youths reported that the *rs53576* oxytocin receptor gene polymorphism moderated the association between maternal depression in early childhood and depressive symptoms at age 15 (Thompson, Hammen, Starr, & Najman, 2014). Further research along these lines is needed, as studies in this area may shed more light on an important pathway involved in the intergenerational transmission of vulnerability for depression. Importantly, behavioral genetic studies support the conclusion that while genetic influences on individual differences in the capacity to form attachment relationships are negligible during early childhood (Bokhorst et al., 2003), one study found that in adolescence they predict 38% of security and 35% of insecurity (Fearon, Shmueli-Goetz, Viding, Fonagy, & Plomin, 2014). The continuity of attachment from infancy to adulthood may also be moderated by the presence of the OXTR G/G phenotype (Raby, Cicchetti, Carlson, Egeland, & Collins, 2013).

Behavioral level.

Studies have amply demonstrated a relationship between impairments related to the rewarding features of both agency and attachment, vulnerability for depression, poor prognosis, and negative treatment response in children and adolescents (Luyten & Blatt, 2013). Problems with agency/autonomy, in particular, as expressed in, for instance, high levels of self-criticism, have been related to increased vulnerability for depression, a more negative course of treatment, and poor response to treatment across a number of therapeutic modalities (Blatt, Zuroff, Hawley, & Auerbach, 2010; Shahar, 2015).

With regard to the rewarding nature of affiliation, insecure attachment has similarly been related to vulnerability for depression in children, adolescents, and adults (Grunebaum et al., 2010; Lee & Hankin, 2009) and has been shown to negatively influence the course of depression from adolescence to adulthood (Agerup, Lydersen, Wallander, & Sund, 2015).

Insecure attachment has also been related to the intergenerational transmission of vulnerability for depression in both animal and human studies (Luyten, Blatt, & Fonagy, 2013; Moutsiana et al., 2014; Moutsiana et al., 2015; Murray et al., 2011).

Studies have also provided evidence for a relationship between disruptions in the attachment/reward systems and adversity. Insecure attachment has been shown to mediate the relationship between early adversity and later vulnerability for depression through impaired affect regulation, stress responsivity, and impairments in social problem-solving skills, in a number of longitudinal studies (Bifulco et al., 2006; Styron & Janoff-Bulman, 1997).

There is no evidence for a specific association between particular attachment categories and vulnerability for depression. Both individuals who predominantly use attachment *hyperactivating strategies* (strategies that reflect desperate attempts to find security, rooted in the belief that others are not there to provide security and support, typical of individuals with anxious-preoccupied attachment styles) and those who predominantly use attachment *deactivating strategies* (i.e., strategies involving denying attachment needs and asserting one's own autonomy and independence in an attempt to downregulate stress, based on the conviction that others cannot provide support and comfort, correlating with anxious-avoidant and dismissive attachment styles) are at increased risk for depression. However, parental avoidant/dismissive attachment might be associated with greater vulnerability for a hostile/aggressive subtype of depression (MacGregor et al., 2014). Furthermore, there is some evidence that individuals with disorganized attachment, that is, individuals who interchangeably use attachment hyperactivating and deactivating strategies, are at increased risk for a subtype of depression that is typically associated with borderline personality disorder, marked by greater severity of depression, feelings of emptiness, anger, shame, and identity diffusion (Lecompte, Moss, Cyr, & Pascuzzo, 2014; Luyten & Fonagy, 2014).

From an evolutionary perspective, it has been speculated that insecure attachment strategies reflect different strategies to deal with (perceived) unavailability, unresponsivity, or intrusiveness of attachment figures (Ein-Dor, Mikulincer, Doron, & Shaver, 2010). These strategies have been shown to overlap theoretically and empirically with personality traits or cognitive-affective schemas that are rooted in disruptive attachment experiences, notably interpersonal dependency and self-criticism (Blatt & Luyten, 2009). Different insecure attachment strategies have been related to different psychosocial and biological profiles in youth and in adults, which may shed important light on the vexing question of the heterogeneity of depression. Indeed, studies in community samples suggest that attachment deactivating strategies and associated personality styles such as self-criticism are related to downregulation of the reward and threat detection system very early in information processing. Attachment hyperactivating strategies and related personality styles such as interpersonal dependency have been related to upregulation of the stress and threat detection systems and a failure to downregulate threat, leading to increasing hypervigilance (Luyten & Fonagy, 2015; Vrticka & Vuilleumier, 2012).

Mentalizing (RDoC Social Cognition and Cognitive Systems)

Neural circuitry and physiology.

Somewhat surprisingly, despite the centrality of interpersonal problems and distortions in cognitive-affective schemas of self and others in many theories of depression, research has only relatively recently begun to focus on the neural circuitry underlying mentalizing in depression in both adults and youth (Billeke, Boardman, & Doraiswamy, 2013; Luyten et al., 2013). Although the neural circuits involved in mentalizing are distinct from those involved in attention and general (cognitive) reasoning and other cognitive systems such as planning, memory, and executive functioning (Adolphs, 2015; Van Overwalle, 2011), mentalizing is partly dependent on these capacities and, in turn, fosters

them. Hence, we will discuss the RDoC social processes and cognitive systems domains together in this section.

The human capacity for social cognition or mentalizing represents a major leap in evolution that conferred substantial survival value, as it enabled new and complex forms of collaboration and learning far beyond conditioning and imitative learning (Humphrey, 1988). This capacity accounts to a large extent for other major differences between humans and animals, which lack this ability. These include (a) the capacity for self-awareness and self-consciousness; (b) the human striving to transcend physical reality; and (c) the human capacity for complex forms of collaboration and relatedness (see Davey et al., 2008). However, these capacities also appear to confer increased risk for the development of depression (Luyten, Fonagy, Lemma, & Target, 2012). First, the emergence of self-awareness and self-consciousness as a path to emulation brought with it social emotions, such as embarrassment, regret, shame, and guilt, that are commonly implicated in depression. Second, the species-specific striving to achieve something in life brings with it not only visions of an ideal state, but also the awareness of being unable to achieve one's goals and desires, leading to feelings of distress, emotional pain and, ultimately, helplessness and/or hopelessness. Finally, humans' strong emphasis on relatedness—the basis for social learning and the transgenerational transmission of culture and knowledge—brought with it a need to feel validated and recognized by others; this translates to social experience of oneself as worthy of being loved, cared for, respected, and admired—but also creates a risk for feelings of depression when these needs are chronically frustrated or thwarted (Luyten et al., 2012).

These three aspects of social cognition linked with depression are at the forefront of adolescent development (Crone & Dahl, 2012), which might explain the increase in prevalence of depression in this age period. The social-cognitive changes of adolescence (such as increasing importance of self-awareness, emotion regulation, conformity, reputation

management, and monitoring information about other individuals) are supported by social-cognitive brain networks as well as by cognitive control, implying more powerful working memory and inhibition of action, as have been shown in various functional magnetic resonance imaging studies. Studies of normatively developing youth suggest that the mature capacity for perspective-taking develops in late adolescence, and the medial PFC and temporoparietal junction—key areas recruited during mentalizing—change radically in their relative weighting over the course of adolescence (Blakemore & Mills, 2014).

Consistent with this line of argument, impairments in the neural circuits implicated in mentalizing have been consistently reported in adult depression. These include the MPFC, amygdala, hippocampus, and ventromedial parts of the basal ganglia (Cusi, Nazarov, Holshausen, MacQueen, & McKinnon, 2012; Drevets, Price, & Furey, 2008).

Impairments in mentalizing circuits in different domains of social cognition have also been reported in adolescent depression (Kerestes, Davey, Stephanou, Whittle, & Harrison, 2014). Despite some differences from findings in adults, which might be related to developmental changes specifically associated with adolescence as well as severity of depression (see below), these findings are largely in line with models of depression in adults. Together, they suggest that depression may be related to a failure to reappraise and regulate negative affect, reflecting a failure of controlled mentalizing more generally, which gives rise to more automatic, biased, and affect-driven mentalizing (i.e., based on nonreflective assumptions about the self and others).

Studies suggest in this respect that young people who predominantly use attachment hyperactivating strategies might most closely match the above pattern of affect-driven mentalizing as a result of hypervigilance for social rejection and exclusion. Attachment deactivating strategies, by contrast, have been related to downregulation of reward circuitry, but relative hyperactivation in the MPFC and ventral anterior cingulate cortex, areas that are

involved in controlled mentalizing, social rejection, and emotion suppression; this suggests a pattern of cognitive overcontrol and overregulation (Luyten & Fonagy, 2015; Vrticka & Vuilleumier, 2012).

Like those involved in the stress and reward systems, the neural circuits involved in mentalizing undergo major functional and structural reorganization as a result of synaptogenesis in early adolescence, followed by synaptic pruning into early adulthood; this probably increases the efficiency of these brain networks (Blakemore & Mills, 2014). Hence, at a time when adolescents are faced with major developmental tasks involving a redefinition of autonomy and relatedness, necessitating considerable mentalizing skills, their capacity for mentalizing is greatly challenged because of an imbalance between neural circuits subserving mentalizing and a functionally more mature limbic region. The emergence of sexuality and new forms of aggression, together with increased peer pressure, challenges mentalizing skills even further. This may explain the typical picture of greater self-consciousness (and thus greater rejection sensitivity) and growing realization of the social costs of failure in adolescence. These are areas of stress that have been particularly linked to the onset of depression in adolescence, as discussed earlier (Davey et al., 2008; see Figure 2). The inability to make sense of these changes may lead either to excessive mentalizing (*hypermentalizing*) and/or the avoidance of mentalizing (*hypomentalizing*) as a defensive strategy to avoid thinking about the painful nature of these experiences. Both hypermentalizing and hypomentalizing may be implicated in the reward deficiency syndrome that seems to be typical of adolescence, leading to increased risk for depression.

As the neural circuits involved in executive functioning follow a similar pathway in adolescence to those of mentalizing (Hare et al., 2008), the observed comorbidity between youth depression and externalizing problems seems to involve, perhaps to various degrees, (a) increasing distress and negative affect (the stress system); (b) impairments in incentive

motivation (the reward system), leading to compensatory strategies (e.g., drug abuse, sexual promiscuity, risk-taking); (c) impairments in mentalizing (the mentalizing system), leading to compensatory efforts to deal with a perceived loss of status and/or rejection (e.g., violent behavior to increase status, made possible by a denial or justification of the subjective suffering of others); and (d) loss of cognitive control mechanisms (the cognitive system).

Genetic level.

Research on the molecular genetics of social cognition in pediatric depression is still in its infancy. Most contemporary approaches have focused on systems that influence social cognition, such as the oxytocinergic, dopaminergic, and serotonergic systems, or on specific domains of social cognition, such as empathy or Theory of Mind (Gordon, Martin, Feldman, & Leckman, 2011; Skuse & Gallagher, 2011). For instance, polymorphisms in *5-HTTLPR* have been related to biases in facial interpretation; more generally, several polymorphisms implicated in the stress and reward domains have been related to openness to environmental influences. These findings have led to a shift from diathesis–stress models to social susceptibility models. There is also some evidence for gene–culture coevolution in relation to these genes, although research in this area remains controversial (Laland, Odling-Smee, & Myles, 2010). Current ongoing genome-wide association studies and studies using neuroeconomic paradigms promise to shed further light on this area.

It also seems likely that genetic factors implicated in cognitive systems may influence the development of mentalizing as well as the reward system (Blakemore & Mills, 2014). These influences may become particularly dominant in adolescence, as demonstrated, for instance, by a study reporting a considerable genetic component in the capacity for linguistic coherence when reflecting about past attachment experiences (Fearon et al., 2014).

Behavioral genetic studies have generally found little heritability specific to social cognition that was not accounted for by genetic influence over verbal ability (Hughes et al.,

2005). Evidence suggests that learning about mental states is strongly influenced by social context (Mayer & Träuble, 2012; Pyers & Senghas, 2009).

Behavioral level.

While earlier theories of depression focused on distortions in the *content* of beliefs and assumptions about the self and others, more recent mindfulness-based cognitive and mentalization-based approaches focus on distortions in the *process* of mentalizing or metacognition as such (Luyten et al., 2013; Watkins & Teasdale, 2004). Mood-congruent mentalizing impairments in depression in adults and youths have been identified in a wide variety of areas, ranging from facial emotion recognition and Theory of Mind to more complex social understanding (Billeke et al., 2013; Bistricky, Ingram, & Atchley, 2011; Kerestes et al., 2014; Weightman, Air, & Baune, 2014). These impairments have also been related to relapse in major depression and have been shown to persist in euthymic patients, even when controlling for basic cognitive dysfunctions associated with depressed mood, although studies have not always yielded consistent findings. Both the severity and duration of depressive episodes have been shown to increase impairments in mentalizing in adults with depression (Bistricky et al., 2011; Weightman et al., 2014), suggestive of a negative cycle marked by increasing mentalizing impairments. Similarly, a recent review of 37 studies of clinical and subclinical depression in adults found depression to be associated with high empathic distress, suggesting poor self–other differentiation and high sensitivity to the mental states of others (Schreiter, Pijnenborg, & Aan Het Rot, 2013).

Individual differences in the use of secondary attachment strategies again might explain some conflicting findings of studies in this area (Manstead, Dosmukhambetova, Shearn, & Clifton, 2013). For instance, there is evidence to suggest that depressed young people who predominantly use attachment hyperactivating strategies might be highly attuned

to the mental states of others, whereas those who predominantly use attachment deactivating strategies might show severe deficits in this capacity (Luyten et al., 2012).

An RDoC Approach to Comorbidity in Depression

Findings reviewed in this paper suggest that the high comorbidity of depression with other disorders may naturally follow from the fact that depression in young people (as well as in adults) involves impairments in three major basic biobehavioral systems. These views are in line with the developmental psychopathology principles of *equifinality* and *multifinality* (Cicchetti & Rogosch, 1996). These principles hold that different etiological factors (e.g., childhood trauma and current stress) are implicated in developmental pathways toward depression (equifinality), while the same etiological factors that are implicated in depression may also play a role in the etiology of other conditions (multifinality). Because of its focus on basic biobehavioral systems or domains implicated in depression and related disorders, the RDoC framework provides an exciting avenue for further research in this respect, as the dismantling of heterogeneity in depression is a major and daunting task facing the field.

More research on developmental pathways in the emergence of depression is therefore needed, and should also include a clear focus on functional somatic disorders (i.e., chronic pain and fatigue) and somatic disorders such as type 2 diabetes and cardiovascular disease, which are often associated with depression and anxiety. Indeed, these disorders may have a common etiology rooted in adversity with effects mediated by neurobiological dysfunctions and unhealthy behaviors (Pervanidou & Chrousos, 2012).

Conclusions and Directions for Future Research

This paper presents an integrative, evolutionary-based developmental framework for child and adolescent depression rooted in the RDoC approach. It fundamentally argues that depression in children and adolescents results from interacting impairments in stress systems, leading to problems with reward, particularly in the areas of attachment and

agency/autonomy, and to problems with mentalizing. Particularly in adolescence and young adulthood, this negative cascade of effects may lead to a reward deficiency syndrome at a time of increased stress and decreased mentalizing capacities, leading to a state commonly referred to as subclinical or clinical depression, which further interferes with negotiating normative developmental tasks and challenges. The challenges presented by changes in relationships and demands for agency, autonomy, and achievement in adolescence might also explain the emergence in adolescence of gender differences in depression and symptomatic expression of mood problems. Because of women's somewhat greater emphasis on relationships, and consequent greater rejection sensitivity, women may be at higher risk for depression and other internalizing disorders (e.g., anxiety, eating disorders). Men's relatively greater emphasis on agency and achievement may put them at greater risk for externalizing disorders as a defensive attempt to ward off feelings of depression. Deficiencies in reward sensitivity, particularly sensitivity to the rewarding nature of attachment relationships, may also explain impairments in exploratory behavior (Pizzagalli, 2014) and broaden-and-build cycles in pediatric depression, further maintaining and exacerbating symptoms and complaints.

These formulations have major implications for the development and evaluation of intervention strategies (Auerbach et al., 2014). In particular, we suggest that there is a need for a reevaluation of current intervention strategies for depression and the extent to which these strategies are able to address—or fail to address—each of the domains involved in depression in youth. From the perspective of the RDoC-inspired approach proposed in this paper, evidence-based psychotherapy based on DSM diagnoses has always had a built-in inefficiency because diagnostic categories such as depression are heterogeneous, involving a number of disease mechanisms. The future is therefore likely to see the development of a new set of prevention and intervention strategies that explicitly target each of the domains of

functioning involved in child and adolescent depression. Similarly, evaluation studies should focus on the effects of these treatments at different levels of analysis, ranging from the behavioral to the molecular, in these different domains of functioning.

The conceptualization of child and adolescent depression advanced here supports rather than replaces the DSM/ICD classification of depression, yet offers a fresh subtyping of the current diagnostic entities. Implicit in the approach outlined here is a departure from research strategies that focus on a single diagnosis, such as depression, in isolation. Instead, the neurobiological basis of RDoC constructs must be examined using models of a dimensional structure of psychopathology and classes of patients whose psychopathological signs and behavioral trajectories are common to different clinical phenotypes. The investigation of these trajectories will require analytic techniques capable of managing this complexity. Additionally, as most studies in this domain have been conducted in Western samples, with a majority of participants of European descent, there is a particular need for cross-cultural studies.

Nonetheless, a multidimensional approach, however descriptive, will remain essentially unhelpful if it cannot be applied to the prediction of such things as the course of illness and treatment outcome. We have therefore taken a developmental perspective, characterizing specific domains within depression and examining the emergence of clinical phenotypes over time. More longitudinal data need to be made available to enhance the identification of such clinical phenotypes with precision and validity. As we have tried to show in this paper, a focus on the RDoC domains of functioning seems to be a good starting point from which to achieve this goal.

References

- Adolphs, R. (2015). The unsolved problems of neuroscience. *Trends in Cognitive Sciences*, *19*, 173-175. doi: 10.1016/j.tics.2015.01.007
- Afifi, T. O., Enns, M. W., Cox, B. J., Asmundson, G. J. G., Stein, M. B., & Sareen, J. (2008). Population attributable fractions of psychiatric disorders and suicide ideation and attempts associated with adverse childhood experiences. *American Journal of Public Health*, *98*, 946-952. doi: 10.2105/ajph.2007.120253
- Agerup, T., Lydersen, S., Wallander, J., & Sund, A. M. (2015). Associations between parental attachment and course of depression between adolescence and young adulthood. *Child Psychiatry and Human Development*, *46*, 632-642. doi: 10.1007/s10578-014-0506-y
- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Press.
- Anda, R., Felitti, V., Bremner, J., Walker, J., Whitfield, C., Perry, B., . . . Giles, W. (2006). The enduring effects of abuse and related adverse experiences in childhood. *European Archives of Psychiatry and Clinical Neuroscience*, *256*, 174-186.
- Andersen, S. L., & Teicher, M. H. (2009). Desperately driven and no brakes: Developmental stress exposure and subsequent risk for substance abuse. *Neuroscience & Biobehavioral Reviews*, *33*, 516-524. doi: 10.1016/j.neubiorev.2008.09.009
- Angold, A., Erkanli, A., Silberg, J., Eaves, L., & Costello, E. J. (2002). Depression scale scores in 8–17-year-olds: Effects of age and gender. *Journal of Child Psychology and Psychiatry*, *43*, 1052-1063.
- Apter-Levi, Y., Zagoory-Sharon, O., & Feldman, R. (2014). Oxytocin and vasopressin support distinct configurations of social synchrony. *Brain Research*, *1580*, 124-132. doi: 10.1016/j.brainres.2013.10.052

- Auerbach, R. P., Admon, R., & Pizzagalli, D. A. (2014). Adolescent depression: Stress and reward dysfunction. *Harvard Review of Psychiatry, 22*, 139-148. doi: 10.1097/hrp.0000000000000034
- Bartz, J. A., Zaki, J., Bolger, N., & Ochsner, K. N. (2011). Social effects of oxytocin in humans: Context and person matter. *Trends in Cognitive Sciences, 15*, 301-309. doi: 10.1016/j.tics.2011.05.002
- Beck, A. T. (2009). Cognitive aspects of personality disorders and their relation to syndromal disorders: A psychoevolutionary approach. In C. R. Cloninger (Ed.), *Personality and psychopathology* (pp. 411-429). Washington, DC: American Psychiatric Press.
- Belsky, J., Houts, R. M., & Fearon, R. M. (2010). Infant attachment security and the timing of puberty: Testing an evolutionary hypothesis. *Psychological Science, 21*, 1195-1201. doi: 10.1177/0956797610379867
- Bifulco, A., Kwon, J., Jacobs, C., Moran, P., Bunn, A., & Beer, N. (2006). Adult attachment style as mediator between childhood neglect/abuse and adult depression and anxiety. *Social Psychiatry and Psychiatric Epidemiology, 41*, 796-805.
- Billeke, P., Boardman, S., & Doraiswamy, P. M. (2013). Social cognition in major depressive disorder: A new paradigm? *Translational Neuroscience, 4*, 437-447.
- Birmaher, B., Brent, D., AACAP Work Group on Quality Issues, Bernet, W., Bukstein, O., Walter, H., . . . Medicus, J. (2007). Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 46*, 1503-1526. doi: 10.1097/chi.0b013e318145ae1c
- Birmaher, B., Ryan, N. D., Williamson, D. E., Brent, D. A., & Kaufman, J. (1996). Childhood and adolescent depression: A review of the past 10 years. Part II. *Journal of the American Academy of Child and Adolescent Psychiatry, 35*, 1575-1583. doi:

10.1097/00004583-199612000-00008

- Bistricky, S. L., Ingram, R. E., & Atchley, R. A. (2011). Facial affect processing and depression susceptibility: Cognitive biases and cognitive neuroscience. *Psychological Bulletin*, *137*, 998-1028. doi: 10.1037/a0025348
- Blakemore, S. J., & Mills, K. L. (2014). Is adolescence a sensitive period for sociocultural processing? *Annual Review of Psychology*, *65*, 187-207. doi: 10.1146/annurev-psych-010213-115202
- Blatt, S. J. (2004). *Experiences of depression: Theoretical, clinical, and research perspectives*. Washington, DC: American Psychological Association.
- Blatt, S. J. (2008). *Polarities of experience: Relatedness and self definition in personality development, psychopathology, and the therapeutic process*. Washington, DC: American Psychological Association.
- Blatt, S. J., & Luyten, P. (2009). A structural-developmental psychodynamic approach to psychopathology: Two polarities of experience across the life span. *Development and Psychopathology*, *21*, 793-814. doi: 10.1017/S0954579409000431
- Blatt, S. J., Zuroff, D. C., Hawley, L. L., & Auerbach, J. S. (2010). Predictors of sustained therapeutic change. *Psychotherapy Research*, *20*, 37-54.
- Bokhorst, C. L., Bakermans-Kranenburg, M. J., Fearon, R. M., van, I. M. H., Fonagy, P., & Schuengel, C. (2003). The importance of shared environment in mother–infant attachment security: A behavioral genetic study. *Child Development*, *74*, 1769-1782. doi: 10.1046/j.1467-8624.2003.00637.x
- Casey, B. J., Getz, S., & Galvan, A. (2008). The adolescent brain. *Developmental Review*, *28*, 62-77. doi: 10.1016/j.dr.2007.08.003
- Caspi, A., Hariri, A. R., Holmes, A., Uher, R., & Moffitt, T. E. (2010). Genetic sensitivity to the environment: The case of the serotonin transporter gene and its implications for

- studying complex diseases and traits. *American Journal of Psychiatry*, *167*, 509-527.
doi: 10.1176/appi.ajp.2010.09101452
- Champagne, F. A., & Curley, J. P. (2009). Epigenetic mechanisms mediating the long-term effects of maternal care on development. *Neuroscience & Biobehavioral Reviews*, *33*, 593-600. doi: 10.1016/j.neubiorev.2007.10.009
- Cicchetti, D., & Rogosch, F. A. (1996). Equifinality and multifinality in developmental psychopathology. *Development and Psychopathology*, *8*, 597-600.
- Cicchetti, D., & Toth, S. L. (2005). Child maltreatment. *Annual Review of Clinical Psychology*, *1*, 409-438. doi: 10.1146/annurev.clinpsy.1.102803.144029
- Collins, P. Y., Patel, V., Joestl, S. S., March, D., Insel, T. R., Daar, A. S., . . . Stein, D. J. (2011). Grand challenges in global mental health. *Nature*, *475*, 27-30. doi: 10.1038/475027a
- Costa, B., Pini, S., Gabelloni, P., Abelli, M., Lari, L., Cardini, A., . . . Martini, C. (2009). Oxytocin receptor polymorphisms and adult attachment style in patients with depression. *Psychoneuroendocrinology*, *34*, 1506-1514. doi: 10.1016/j.psyneuen.2009.05.006
- Costello, E. J., Erkanli, A., & Angold, A. (2006). Is there an epidemic of child or adolescent depression? *Journal of Child Psychology and Psychiatry*, *47*, 1263-1271. doi: 10.1111/j.1469-7610.2006.01682.x
- Crone, E. A., & Dahl, R. E. (2012). Understanding adolescence as a period of social-affective engagement and goal flexibility. *Nature Reviews. Neuroscience*, *13*, 636-650. doi: 10.1038/nrn3313
- Cusi, A. M., Nazarov, A., Holshausen, K., MacQueen, G. M., & McKinnon, M. C. (2012). Systematic review of the neural basis of social cognition in patients with mood disorders. *Journal of Psychiatry and Neuroscience*, *37*, 154-169. doi:

10.1503/jpn.100179

Cuthbert, B. N., & Insel, T. R. (2013). Toward the future of psychiatric diagnosis: The seven pillars of RDoC. *BMC Medicine*, *11*, 126. doi: 10.1186/1741-7015-11-126

Cyranowski, J. M., Hofkens, T. L., Frank, E., Seltman, H., Cai, H. M., & Amico, J. A. (2008). Evidence of dysregulated peripheral oxytocin release among depressed women. *Psychosomatic Medicine*, *70*, 967-975. doi: 10.1097/PSY.0b013e318188ade4

Davey, C. G., Yücel, M., & Allen, N. B. (2008). The emergence of depression in adolescence: Development of the prefrontal cortex and the representation of reward. *Neuroscience & Biobehavioral Reviews*, *32*, 1-19. doi: 10.1016/j.neubiorev.2007.04.016

Dick, D. M., Agrawal, A., Keller, M. C., Adkins, A., Aliev, F., Monroe, S., . . . Sher, K. J. (2015). Candidate gene-environment interaction research: Reflections and recommendations. *Perspectives on Psychological Science*, *10*, 37-59. doi: 10.1177/1745691614556682

Dillon, D. G., Rosso, I. M., Pechtel, P., Killgore, W. D. S., Rauch, S. L., & Pizzagalli, D. A. (2014). Peril and pleasure: An RDoC-inspired examination of threat responses and reward processing in anxiety and depression. *Depression and Anxiety*, *31*, 233-249. doi: 10.1002/da.22202

Drevets, W. C., Price, J. L., & Furey, M. L. (2008). Brain structural and functional abnormalities in mood disorders: Implications for neurocircuitry models of depression. *Brain Structure and Function*, *213*, 93-118. doi: 10.1007/s00429-008-0189-x

Dube, S. R., Anda, R. F., Felitti, V. J., Chapman, D. P., Williamson, D. F., & Giles, W. H. (2001). Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span: Findings from the Adverse Childhood Experiences Study.

JAMA, 286, 3089-3096. doi: 10.1001/jama.286.24.3089

Eiland, L., & Romeo, R. D. (2013). Stress and the developing adolescent brain.

Neuroscience, 249, 162-171. doi: 10.1016/j.neuroscience.2012.10.048

Ein-Dor, T., Mikulincer, M., Doron, G., & Shaver, P. R. (2010). The attachment paradox:

How can so many of us (the insecure ones) have no adaptive advantages?

Perspectives on Psychological Science, 5, 123-141. doi: 10.1177/1745691610362349

Ellis, B. J., Boyce, W. T., Belsky, J., Bakermans-Kranenburg, M. J., & van Ijzendoorn, M. H.

(2011). Differential susceptibility to the environment: An evolutionary–

neurodevelopmental theory. *Development and Psychopathology*, 23, 7-28. doi:

doi:10.1017/S0954579410000611

Essex, M. J., Boyce, W. T., Hertzman, C., Lam, L. L., Armstrong, J. M., Neumann, S. M., &

Kobor, M. S. (2013). Epigenetic vestiges of early developmental adversity: Childhood stress exposure and DNA methylation in adolescence. *Child Development*, 84, 58-75.

doi: 10.1111/j.1467-8624.2011.01641.x

Fearon, P., Shmueli-Goetz, Y., Viding, E., Fonagy, P., & Plomin, R. (2014). Genetic and

environmental influences on adolescent attachment. *Journal of Child Psychology and*

Psychiatry, 55, 1033-1041. doi: 10.1111/jcpp.12171

Feldman, R., Vengrober, A., & Ebstein, R. P. (2014). Affiliation buffers stress: Cumulative

genetic risk in oxytocin-vasopressin genes combines with early caregiving to predict

PTSD in war-exposed young children. *Translational Psychiatry*, 4, e370. doi:

10.1038/tp.2014.6

Fonagy, P., & Luyten, P. (2016). A multilevel perspective on the development of borderline personality disorder. In D. Cicchetti (Ed.), *Developmental Psychopathology* (3rd ed.,

Vol. 3: Maladaptation and psychopathology, pp. 726-792). New York, NY: Wiley.

Forbes, E. E., & Dahl, R. E. (2012). Research Review: Altered reward function in adolescent

- depression: What, when and how? *Journal of Child Psychology and Psychiatry*, *53*, 3-15. doi: 10.1111/j.1469-7610.2011.02477.x
- Fredrickson, B. L. (2001). The role of positive emotions in positive psychology. The broaden-and-build theory of positive emotions. *American Psychologist*, *56*, 218-226.
- Gilbert, P. (2006). Evolution and depression: Issues and implications. *Psychological Medicine*, *36*, 287-297. doi: 10.1017/s0033291705006112
- Gluckman, P. D., Hanson, M. A., Bateson, P., Beedle, A. S., Law, C. M., Bhutta, Z. A., . . . West-Eberhard, M. J. (2009). Towards a new developmental synthesis: Adaptive developmental plasticity and human disease. *Lancet*, *373*, 1654-1657. doi: 10.1016/S0140-6736(09)60234-8
- Gobinath, A. R., Mahmoud, R., & Galea, L. A. (2014). Influence of sex and stress exposure across the lifespan on endophenotypes of depression: Focus on behavior, glucocorticoids, and hippocampus. *Frontiers in Neuroscience*, *8*, 420. doi: 10.3389/fnins.2014.00420
- Gordon, I., Martin, C., Feldman, R., & Leckman, J. F. (2011). Oxytocin and social motivation. *Developmental Cognitive Neuroscience*, *1*, 471-493. doi: 10.1016/j.dcn.2011.07.007
- Gotlib, I. H., Hamilton, J. P., Cooney, R. E., Singh, M. K., Henry, M. L., & Joormann, J. (2010). Neural processing of reward and loss in girls at risk for major depression. *Archives of General Psychiatry*, *67*, 380-387. doi: 10.1001/archgenpsychiatry.2010.13
- Grunebaum, M. F., Galfalvy, H. C., Mortenson, L. Y., Burke, A. K., Oquendo, M. A., & Mann, J. J. (2010). Attachment and social adjustment: Relationships to suicide attempt and major depressive episode in a prospective study. *Journal of Affective Disorders*, *123*, 123-130. doi: 10.1016/j.jad.2009.09.010
- Gunnar, M., & Quevedo, K. (2007). The neurobiology of stress and development. *Annual*

- Review of Psychology*, 58, 145-173. doi: 10.1146/annurev.psych.58.110405.085605
- Hammen, C. (2005). Stress and depression. *Annual Review of Clinical Psychology*, 1, 293-319. doi: 10.1146/annurev.clinpsy.1.102803.143938
- Hankin, B. L. (2012). Future directions in vulnerability to depression among youth: Integrating risk factors and processes across multiple levels of analysis. *Journal of Clinical Child and Adolescent Psychology*, 41, 695-718. doi: 10.1080/15374416.2012.711708
- Hare, T. A., Tottenham, N., Galvan, A., Voss, H. U., Glover, G. H., & Casey, B. J. (2008). Biological substrates of emotional reactivity and regulation in adolescence during an emotional go-nogo task. *Biological Psychiatry*, 63, 927-934. doi: 10.1016/j.biopsych.2008.03.015
- Hazell, P., & Mirzaie, M. (2013). Tricyclic drugs for depression in children and adolescents. *Cochrane Database of Systematic Reviews*, CD002317. doi: 10.1002/14651858.CD002317.pub2
- Heim, C., & Binder, E. B. (2012). Current research trends in early life stress and depression: Review of human studies on sensitive periods, gene–environment interactions, and epigenetics. *Experimental Neurology*, 233, 102-111. doi: 10.1016/j.expneurol.2011.10.032
- Heim, C., Newport, D. J., Mletzko, T., Miller, A. H., & Hemeroff, C. B. (2008). The link between childhood trauma and depression: Insights from HPA axis studies in humans. *Psychoneuroendocrinology*, 33, 693-710. doi: 10.1016/j.psyneuen.2008.03.008
- Hostinar, C. E., Sullivan, R. M., & Gunnar, M. R. (2014). Psychobiological mechanisms underlying the social buffering of the hypothalamic–pituitary–adrenocortical axis: A review of animal models and human studies across development. *Psychological Bulletin*, 140, 256-282. doi: 10.1037/a0032671

Hsu, D. T., Sanford, B. J., Meyers, K. K., Love, T. M., Hazlett, K. E., Walker, S. J., . . .

Zubieta, J. K. (2015). It still hurts: Altered endogenous opioid activity in the brain during social rejection and acceptance in major depressive disorder. *Molecular Psychiatry*, *20*, 193-200. doi: 10.1038/mp.2014.185

Hughes, C., Jaffee, S. R., Happe, F., Taylor, A., Caspi, A., & Moffitt, T. E. (2005). Origins of individual differences in theory of mind: From nature to nurture? *Child Development*, *76*, 356-370. doi: 10.1111/j.1467-8624.2005.00850.x

Humphrey, N. K. (1988). The social function of intellect. In R. W. Byrne & A. Whiten (Eds.), *Machiavellian intelligence: Social expertise and the evolution of intellect in monkeys, apes, and humans* (pp. 13-26). New York: Oxford University Press.

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., . . . Wang, P. (2010). Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. *American Journal of Psychiatry*, *167*, 748-751. doi: 10.1176/appi.ajp.2010.09091379

Insel, T. R., & Young, L. J. (2001). The neurobiology of attachment. *Nature Reviews. Neuroscience* *2*, 129-136. doi: 10.1038/35053579

Kendler, K. S., & Gardner, C. O. (2014). Sex differences in the pathways to major depression: A study of opposite-sex twin pairs. *American Journal of Psychiatry*, *171*, 426-435. doi: 10.1176/appi.ajp.2013.13101375

Kendler, K. S., Kuhn, J., & Prescott, C. A. (2004). The interrelationship of neuroticism, sex, and stressful life events in the prediction of episodes of major depression. *American Journal of Psychiatry*, *161*, 631-636. doi: 10.1176/appi.ajp.161.4.631

Kerestes, R., Davey, C. G., Stephanou, K., Whittle, S., & Harrison, B. J. (2014). Functional brain imaging studies of youth depression: A systematic review. *NeuroImage: Clinical*, *4*, 209-231. doi: 10.1016/j.nicl.2013.11.009

- Kim, S., Fonagy, P., Koos, O., Dorsett, K., & Strathearn, L. (2014). Maternal oxytocin response predicts mother-to-infant gaze. *Brain Research, 1580*, 133-142. doi: 10.1016/j.brainres.2013.10.050
- Laland, K. N., Odling-Smee, J., & Myles, S. (2010). How culture shaped the human genome: Bringing genetics and the human sciences together. *Nature Reviews. Genetics, 11*, 137-148. doi: 10.1038/nrg2734
- Leckman, J. F., Carter, C. S., Hennessy, M. B., Hrdy, S. B., Keverne, E. B., Klann-Delius, C., . . . von Holst, D. (2005). Biobehavioral processes in attachment and bonding. In C. S. Carter, L. Ahnert, K. E. Grossman, S. B. Hrdy, M. E. Lamb, S. W. Porges & N. Sachser (Eds.), *Attachment and bonding: A new synthesis* (pp. 1011-1021). Boston, MA: MIT Press.
- Lecompte, V., Moss, E., Cyr, C., & Pascuzzo, K. (2014). Preschool attachment, self-esteem and the development of preadolescent anxiety and depressive symptoms. *Attachment and Human Development, 16*, 242-260. doi: 10.1080/14616734.2013.873816
- Lee, A., & Hankin, B. L. (2009). Insecure attachment, dysfunctional attitudes, and low self-esteem predicting prospective symptoms of depression and anxiety during adolescence. *Journal of Clinical Child and Adolescent Psychology, 38*, 219-231. doi: 10.1080/15374410802698396
- Lee, E. J., & Stone, S. I. (2012). Co-occurring internalizing and externalizing behavioral problems: The mediating effect of negative self-concept. *Journal of Youth and Adolescence, 41*, 717-731. doi: 10.1007/s10964-011-9700-4
- Lopez-Duran, N. L., Kovacs, M., & George, C. J. (2009). Hypothalamic–pituitary–adrenal axis dysregulation in depressed children and adolescents: A meta-analysis. *Psychoneuroendocrinology, 34*, 1272-1283. doi: 10.1016/j.psyneuen.2009.03.016
- Luciana, M. (2013). Adolescent brain development in normality and psychopathology.

- Development and Psychopathology*, 25, 1325-1345. doi:
10.1017/s0954579413000643
- Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews. Neuroscience*, 10, 434-445. doi: 10.1038/nrn2639
- Luyten, P., & Blatt, S. J. (2013). Interpersonal relatedness and self-definition in normal and disrupted personality development: Retrospect and prospect. *American Psychologist*, 68, 172-183. doi: 10.1037/a0032243
- Luyten, P., Blatt, S. J., & Fonagy, P. (2013). Impairments in self structures in depression and suicide in psychodynamic and cognitive behavioral approaches: Implications for clinical practice and research. *International Journal of Cognitive Therapy*, 6, 265-279. doi: 10.1521/ijct.2013.6.3.265
- Luyten, P., Blatt, S. J., Van Houdenhove, B., & Corveleyn, J. (2006). Depression research and treatment: Are we skating to where the puck is going to be? *Clinical Psychology Review*, 26, 985-999. doi: 10.1016/j.cpr.2005.12.003
- Luyten, P., & Fonagy, P. (2014). Psychodynamic treatment for borderline personality disorder and mood disorders: A mentalizing perspective. In L. Choi-Kain & J. Gunderson (Eds.), *Borderline personality disorder and mood disorders: Controversies and consensus* (pp. 223–251). New York, NY: Springer.
- Luyten, P., & Fonagy, P. (2015). The neurobiology of mentalizing. *Personality Disorders: Theory, Research and Treatment*, 6, 366-379.
- Luyten, P., Fonagy, P., Lemma, A., & Target, M. (2012). Depression. In A. Bateman & P. Fonagy (Eds.), *Handbook of mentalizing in mental health practice* (pp. 385-417). Washington, DC: American Psychiatric Association.
- MacGregor, E. K., Grunebaum, M. F., Galfalvy, H. C., Melhem, N., Burke, A. K., Brent, D.

- A., . . . Mann, J. J. (2014). Depressed parents' attachment: Effects on offspring suicidal behavior in a longitudinal family study. *Journal of Clinical Psychiatry, 75*, 879-885. doi: 10.4088/JCP.13m08794
- Manstead, A. S. R., Dosmukhambetova, D., Shearn, J., & Clifton, A. (2013). The influence of dysphoria and depression on mental state decoding. *Journal of Social and Clinical Psychology, 32*, 116-133.
- Marshal, M. P., Dietz, L. J., Friedman, M. S., Stall, R., Smith, H. A., McGinley, J., . . . Brent, D. A. (2011). Suicidality and depression disparities between sexual minority and heterosexual youth: A meta-analytic review. *Journal of Adolescent Health, 49*, 115-123. doi: 10.1016/j.jadohealth.2011.02.005
- Masten, C. L., Eisenberger, N. I., Borofsky, L. A., Pfeifer, J. H., McNealy, K., Mazziotta, J. C., & Dapretto, M. (2009). Neural correlates of social exclusion during adolescence: Understanding the distress of peer rejection. *Social Cognitive and Affective Neuroscience, 4*, 143-157. doi: 10.1093/scan/nsp007
- Mayer, A., & Träuble, B. E. (2012). Synchrony in the onset of mental state understanding across cultures? A study among children in Samoa. *International Journal of Behavioral Development, 37*, 21-28. doi: 10.1177/0165025412454030
- McCrory, E., De Brito, S. A., & Viding, E. (2012). The link between child abuse and psychopathology: A review of neurobiological and genetic research. *Journal of the Royal Society of Medicine, 105*, 151-156. doi: 10.1258/jrsm.2011.110222
- McEwen, B. S. (2006). Sleep deprivation as a neurobiologic and physiologic stressor: Allostasis and allostatic load. *Metabolism, 55 (10 Suppl 2)*, S20-23. doi: 10.1016/j.metabol.2006.07.008
- McEwen, B. S. (2007). Physiology and neurobiology of stress and adaptation: Central role of the brain. *Physiological Reviews, 87*, 873-904. doi: 10.1152/physrev.00041.2006

- McLaughlin, K. A., Green, J. G., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., & Kessler, R. C. (2010). Childhood adversities and adult psychiatric disorders in the National Comorbidity Survey Replication II: Associations with persistence of DSM-IV disorders. *Archives of General Psychiatry, 67*, 124-132. doi: 10.1001/archgenpsychiatry.2009.187
- McQuaid, R. J., McInnis, O. A., Abizaid, A., & Anisman, H. (2014). Making room for oxytocin in understanding depression. *Neuroscience & Biobehavioral Reviews, 45*, 305-322. doi: 10.1016/j.neubiorev.2014.07.005
- Middeldorp, C. M., Slof-Op 't Landt, M. C. T., Medland, S. E., van Beijsterveldt, C. E. M., Bartels, M., Willemsen, G., . . . Boomsma, D. I. (2010). Anxiety and depression in children and adults: Influence of serotonergic and neurotrophic genes? *Genes, Brain and Behavior, 9*, 808-816. doi: 10.1111/j.1601-183X.2010.00619.x
- Mikulincer, M., & Shaver, P. R. (2007). *Attachment in adulthood: Structure, dynamics, and change*. New York, NY: Guilford Press.
- Miller, G. E., Chen, E., & Zhou, E. S. (2007). If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychological Bulletin, 133*, 25-45. doi: 10.1037/0033-2909.133.1.25
- Moutsiana, C., Fearon, P., Murray, L., Cooper, P., Goodyer, I., Johnstone, T., & Halligan, S. (2014). Making an effort to feel positive: Insecure attachment in infancy predicts the neural underpinnings of emotion regulation in adulthood. *Journal of Child Psychology and Psychiatry, 55*, 999-1008. doi: 10.1111/jcpp.12198
- Moutsiana, C., Johnstone, T., Murray, L., Fearon, P., Cooper, P. J., Pliatsikas, C., . . . Halligan, S. L. (2015). Insecure attachment during infancy predicts greater amygdala volumes in early adulthood. *Journal of Child Psychology and Psychiatry, 56*, 540-548. doi: 10.1111/jcpp.12317

- Murayama, K., Matsumoto, M., Izuma, K., & Matsumoto, K. (2010). Neural basis of the undermining effect of monetary reward on intrinsic motivation. *Proceedings of the National Academy of Sciences of the United States of America*, *107*, 20911-20916. doi: 10.1073/pnas.1013305107
- Murray, L., Arteche, A., Fearon, P., Halligan, S., Goodyer, I., & Cooper, P. (2011). Maternal postnatal depression and the development of depression in offspring up to 16 years of age. *Journal of the American Academy of Child and Adolescent Psychiatry*, *50*, 460-470. doi: 10.1016/j.jaac.2011.02.001
- Mutlu, A. K., Schneider, M., Debbane, M., Badoud, D., Eliez, S., & Schaer, M. (2013). Sex differences in thickness, and folding developments throughout the cortex. *NeuroImage*, *82*, 200-207. doi: 10.1016/j.neuroimage.2013.05.076
- Neumann, I. D. (2008). Brain oxytocin: A key regulator of emotional and social behaviours in both females and males. *Journal of Neuroendocrinology*, *20*, 858-865. doi: 10.1111/j.1365-2826.2008.01726.x
- Nock, M. K., Green, J. G., Hwang, I., McLaughlin, K. A., Sampson, N. A., Zaslavsky, A. M., & Kessler, R. C. (2013). Prevalence, correlates, and treatment of lifetime suicidal behavior among adolescents: Results from the National Comorbidity Survey Replication Adolescent Supplement. *JAMA Psychiatry*, *70*, 300-310. doi: 10.1001/2013.jamapsychiatry.55
- O'Brien, B. S., & Sher, L. (2013). Child sexual abuse and the pathophysiology of suicide in adolescents and adults. *International Journal of Adolescent Medicine and Health*, *25*, 201-205. doi: 10.1515/ijamh-2013-0053
- Owens, M., Goodyer, I. M., Wilkinson, P., Bhardwaj, A., Abbott, R., Croudace, T., . . . Sahakian, B. J. (2012). 5-HTTLPR and early childhood adversities moderate cognitive and emotional processing in adolescence. *PLoS One*, *7*, e48482. doi:

10.1371/journal.pone.0048482

Panksepp, J., & Watt, D. (2011). Why does depression hurt? Ancestral primary-process separation-distress (PANIC/GRIEF) and diminished brain reward (SEEKING) processes in the genesis of depressive affect. *Psychiatry*, *74*, 5-13. doi:

10.1521/psyc.2011.74.1.5

Paus, T. (2013). How environment and genes shape the adolescent brain. *Hormones and Behavior*, *64*, 195-202. doi: 10.1016/j.yhbeh.2013.04.004

Pervanidou, P., & Chrousos, G. P. (2012). Metabolic consequences of stress during childhood and adolescence. *Metabolism*, *61*, 611-619. doi: 10.1016/j.metabol.2011.10.005

Pizzagalli, D. A. (2014). Depression, stress, and anhedonia: Toward a synthesis and integrated model. *Annual Review of Clinical Psychology*, *10*, 393-423. doi:

10.1146/annurev-clinpsy-050212-185606

Pyers, J. E., & Senghas, A. (2009). Language promotes false-belief understanding: Evidence from learners of a new sign language. *Psychological Science*, *20*, 805-812. doi:

10.1111/j.1467-9280.2009.02377.x

Raby, K. L., Cicchetti, D., Carlson, E. A., Egeland, B., & Collins, W. A. (2013). Genetic contributions to continuity and change in attachment security: A prospective, longitudinal investigation from infancy to young adulthood. *Journal of Child Psychology and Psychiatry*, *54*, 1223-1230. doi: 10.1111/jcpp.12093

Repetti, R. L., Taylor, S. E., & Seeman, T. E. (2002). Risky families: Family social environments and the mental and physical health of offspring. *Psychological Bulletin*, *128*, 330-366.

Rice, F. (2010). Genetics of childhood and adolescent depression: Insights into etiological heterogeneity and challenges for future genomic research. *Genome Medicine*, *2*, 68.

doi: 10.1186/gm189

- Roseboom, T. J., Painter, R. C., van Abeelen, A. F., Veenendaal, M. V., & de Rooij, S. R. (2011). Hungry in the womb: What are the consequences? Lessons from the Dutch famine. *Maturitas*, *70*, 141-145. doi: 10.1016/j.maturitas.2011.06.017
- Russo, S. J., & Nestler, E. J. (2013). The brain reward circuitry in mood disorders. *Nature Reviews. Neuroscience*, *14*, 609-625. doi: 10.1038/nrn3381
- Rutherford, H. J., Williams, S. K., Moy, S., Mayes, L. C., & Johns, J. M. (2011). Disruption of maternal parenting circuitry by addictive process: Rewiring of reward and stress systems. *Frontiers in Psychiatry*, *2*, 37. doi: 10.3389/fpsy.2011.00037
- Ryan, R. M., Deci, E. L., & Vansteenkiste, M. (2016). Autonomy and autonomy disturbances in self-development and psychopathology: Research on motivation, attachment, and clinical process. In D. Cicchetti (Ed.), *Developmental Psychopathology* (3rd ed., Vol. 1: Theory and method). New York, NY: Wiley.
- Schreiter, S., Pijnenborg, G. H., & Aan Het Rot, M. (2013). Empathy in adults with clinical or subclinical depressive symptoms. *Journal of Affective Disorders*, *150*, 1-16. doi: 10.1016/j.jad.2013.03.009
- Sebastian, C., Viding, E., Williams, K. D., & Blakemore, S. J. (2010). Social brain development and the affective consequences of ostracism in adolescence. *Brain and Cognition*, *72*, 134-145. doi: 10.1016/j.bandc.2009.06.008
- Sebastian, C. L., Tan, G. C., Roiser, J. P., Viding, E., Dumontheil, I., & Blakemore, S. J. (2011). Developmental influences on the neural bases of responses to social rejection: Implications of social neuroscience for education. *NeuroImage*, *57*, 686-694. doi: 10.1016/j.neuroimage.2010.09.063
- Serafini, G., Pompili, M., Borgwardt, S., Houenou, J., Geoffroy, P. A., Jardri, R., . . . Amore, M. (2014). Brain changes in early-onset bipolar and unipolar depressive disorders: A systematic review in children and adolescents. *European Child and Adolescent*

Psychiatry, 23, 1023-1041. doi: 10.1007/s00787-014-0614-z

Shahar, G. (2006). Clinical action: Introduction to the special section on the action perspective in clinical psychology. *Journal of Clinical Psychology*, 62, 1053-1064.

doi: 10.1002/jclp.20290

Shahar, G. (2015). *Erosion: The psychopathology of self-criticism*. Oxford, UK: Oxford University Press.

Shaw, P., Kabani, N. J., Lerch, J. P., Eckstrand, K., Lenroot, R., Gogtay, N., . . . Wise, S. P. (2008). Neurodevelopmental trajectories of the human cerebral cortex. *Journal of Neuroscience*, 28, 3586-3594. doi: 10.1523/jneurosci.5309-07.2008

Skuse, D. H., & Gallagher, L. (2011). Genetic influences on social cognition. *Pediatric Research*, 69, 85R-91R. doi: 10.1203/pdr.0b013e318212f562

Smith, T. B., & Silva, L. (2011). Ethnic identity and personal well-being of people of color: A meta-analysis. *Journal of Counseling Psychology*, 58, 42-60. doi: 10.1037/a0021528

Spear, L. (2007). The developing brain and adolescent-typical behavior patterns: An evolutionary approach. In D. Romer & E. F. Walker (Eds.), *Adolescent psychopathology and the adolescent brain* (pp. 9-30). New York, NY: Oxford University Press.

Spear, L. P. (2000). The adolescent brain and age-related behavioral manifestations. *Neuroscience & Biobehavioral Reviews*, 24, 417-463. doi: 10.1016/S0149-7634(00)00014-2

Strathearn, L. (2011). Maternal neglect: Oxytocin, dopamine and the neurobiology of attachment. *Journal of Neuroendocrinology*, 23, 1054-1065. doi: 10.1111/j.1365-2826.2011.02228.x

Styron, T., & Janoff-Bulman, R. (1997). Childhood attachment and abuse: Long-term effects

- on adult attachment, depression, and conflict resolution. *Child Abuse & Neglect*, *21*, 1015-1023.
- Sullivan, P. F., Neale, M. C., & Kendler, K. S. (2000). Genetic epidemiology of major depression: Review and meta-analysis. *American Journal of Psychiatry*, *157*, 1552-1562. doi: doi:10.1176/appi.ajp.157.10.1552
- Swain, J. E., Kim, P., Spicer, J., Ho, S. S., Dayton, C. J., Elmadih, A., & Abel, K. M. (2014). Approaching the biology of human parental attachment: Brain imaging, oxytocin and coordinated assessments of mothers and fathers. *Brain Research*, *1580*, 78-101. doi: 10.1016/j.brainres.2014.03.007
- Swain, J. E., Lorberbaum, J. P., Kose, S., & Strathearn, L. (2007). Brain basis of early parent–infant interactions: Psychology, physiology, and in vivo functional neuroimaging studies. *Journal of Child Psychology and Psychiatry*, *48*, 262-287. doi: 10.1111/j.1469-7610.2007.01731.x
- Thompson, S. M., Hammen, C., Starr, L. R., & Najman, J. M. (2014). Oxytocin receptor gene polymorphism (rs53576) moderates the intergenerational transmission of depression. *Psychoneuroendocrinology*, *43*, 11-19. doi: 10.1016/j.psyneuen.2014.01.012
- Tsuno, N., Besset, A., & Ritchie, K. (2005). Sleep and depression. *Journal of Clinical Psychiatry*, *66*, 1254-1269.
- Van Overwalle, F. (2011). A dissociation between social mentalizing and general reasoning. *NeuroImage*, *54*, 1589-1599. doi: 10.1016/j.neuroimage.2010.09.043
- Vrticka, P., & Vuilleumier, P. (2012). Neuroscience of human social interactions and adult attachment style. *Frontiers in Human Neuroscience*, *6*, 212. doi: 10.3389/fnhum.2012.00212
- Walsh, N. D., Dalglish, T., Dunn, V. J., Abbott, R., St Clair, M. C., Owens, M., . . . Goodyer, I. M. (2012). 5-HTTLPR-environment interplay and its effects on neural

reactivity in adolescents. *NeuroImage*, 63, 1670-1680. doi:

10.1016/j.neuroimage.2012.07.067

Watkins, E., & Teasdale, J. D. (2004). Adaptive and maladaptive self-focus in depression.

Journal of Affective Disorders, 82, 1-8. doi: 10.1016/j.jad.2003.10.006

Weightman, M. J., Air, T. M., & Baune, B. T. (2014). A review of the role of social cognition

in major depressive disorder. *Frontiers in Psychiatry*, 5, 179. doi:

10.3389/fpsyt.2014.00179

Wilkinson, P., Kelvin, R., Roberts, C., Dubicka, B., & Goodyer, I. (2011). Clinical and

psychosocial predictors of suicide attempts and nonsuicidal self-injury in the

Adolescent Depression Antidepressants and Psychotherapy Trial (ADAPT). *American*

Journal of Psychiatry, 168, 495-501. doi: 10.1176/appi.ajp.2010.10050718