Empathy as a "Risky Strength": A Multilevel Examination of Empathy and Risk for Internalizing Disorders

Erin B. Tone and **Erin C. Tully**
Georgia State University

Abstract

Learning to respond to others' distress with well-regulated empathy is an important developmental task linked to positive health outcomes and moral achievements. However, this important interpersonal skill set may also, paradoxically, confer risk for depression and anxiety when present at extreme levels and in combination with certain individual characteristics or within particular contexts. The purpose of this review is to describe an empirically-grounded theoretical rationale for the hypothesis that empathic tendencies can be "risky strengths". We propose a model in which typical development of affective and cognitive empathy can be influenced by complex interplay among intraindividual and interindividual moderators that increase risk for empathic personal distress and excessive interpersonal guilt. These intermediate states, in turn, precipitate internalizing problems that map onto empirically-derived fear/arousal and anhedonia/misery subfactors of internalizing disorders. The intraindividual moderators include a genetically-influenced propensity toward physiological hyperarousal, which is proposed to interact with genetic propensity to empathic sensitivity to contribute to neurobiological processes that underlie personal distress responses others' pain or unhappiness. This empathic personal distress then increases risk for internalizing problems, particularly fear/arousal symptoms. Similarly, interactions between genetic propensities toward negative thinking processes and empathic sensitivity are hypothesized to contribute to excess interpersonal guilt in response to others' distress. In turn, this interpersonal guilt increases risk for internalizing problems, especially anhedonia/misery symptoms. Interindividual moderators, such as maladaptive parenting or chronic exposure to parents' negative affect, further interact with these genetic liabilities to amplify risk for personal distress and interpersonal guilt, as well as for consequent internalizing problems. Age-related increases in the heritability of depression, anxiety, and empathy-related constructs are consistent with developmental shifts toward greater influence of intraindividual moderators throughout childhood and adolescence, with interindividual moderators exerting their greatest influence during early childhood. Efforts to modulate neurobiological and behavioral expressions of genetic dysregulation liabilities and to promote adaptive empathic skills must thus begin early in development.

Correspondence concerning this article should be addressed to Erin B. Tone, Department of Psychology, Georgia State University, P.O. Box 5010, Atlanta, GA 30302-5010. etone@gsu.edu, Phone: 404-413-6291; Fax: 404-413-6207.
Erin B. Tone, Department of Psychology, Georgia State University; Erin C. Tully, Department of Psychology, Georgia State University.

Proposed Model of Risky Empathy Development

A primary aim of this review is to integrate several empirical literatures that each may hold clues regarding why, how, and when in the course of the lifespan genetically-mediated neurobiological processes support deviations from normative and healthy pathways for empathy development. In particular, this review examines research that converges to support the existence of a deviant path in which moderating variables alter the normative course of empathy development so that it leads progressively to pathological empathy and internalizing problems. Although these literatures are sizable and growing, they vary in the degree to which they contextualize findings developmentally; studies in many relevant domains, for example, focus largely on adults, attending minimally to whether or how well their results are relevant to individuals in other developmental periods. They also vary in their consideration of contextual factors (e.g., chaotic home environments or parent mental health). As a means of addressing these limitations, we approach our core aim within the framework of the developmental psychopathology perspective (Cicchetti & Cohen, 1995).

In adopting this perspective, we make a number of implicit assumptions about how internalizing conditions develop and persist or recede across the lifespan. For example, we assume that dynamic transactions over time among multiple factors determine the life course of a disorder. Thus, for each individual, varied genetic and environmental risk factors can combine in idiosyncratic ways to facilitate the emergence of internalizing problems, including anxiety (Ollendick & Hirshfeld-Becker, 2002; McGrath et al., 2012) and depression (Cicchetti & Toth, 2009). Such equifinality is not, however, a given; indeed in different contexts, the same genetic or environmental characteristics may interact in ways that result in multifinality, serving variously as precipitants of internalizing pathology or as protective buffers against the same kinds of problem (see Caspi et al., 2003 for an example).

In addition, we assume that one cannot understand atypical behavior, such as that which manifests as a function of internalizing pathology, without also studying typical behavior and embedding each type of behavior in its developmental context. The line between atypical and typical is a moving target over the lifespan; behaviors considered normal at one developmental point (e.g., emotional contagion crying during infancy) become atypical at other developmental stages (e.g., excessive crying in response to others' distress during adolescence). In the context of the present review, we thus must keep in mind the temporal, interpersonal, and affective contexts that may render an empathic stance a disadvantage rather than a strength.

Using these tenets of developmental psychopathology as a foundation, we examine ways in which factors that manifest at multiple levels (i.e., genetic, neurobiological, environmental) may interact across development to create trajectories toward maladaptive empathy and clinically-significant internalizing problems. We open by setting forth a definition of empathy that, consistent with current theoretical models (e.g., Decety, 2007; Shamay-Tsoory, 2011; Shamay-Tsoory, Aharon-Peretz, & Perry 2009), distinguishes affective and cognitive components of the construct. In addition, in line with Klimecki and Singer (2013), we differentiate affective and cognitive empathy from the reactions that serve as their precursors (e.g., mimicry, emotional contagion) and the complex emotional and cognitive

states (e.g., compassion, personal distress, interpersonal guilt) that constitute their immediate sequelae. We then briefly summarize the growing literature regarding links among empathy, personal distress, and interpersonal guilt, and internalizing problems across the lifespan. We highlight ways in which developmental changes in both empathic capacity and its genetic and neurobiological underpinnings, may unfold in particular contexts that increase risk for personal distress and interpersonal guilt, as well as for internalizing pathology.

We propose, more specifically, as illustrated in Figure 1, that several interindividual and intraindividual factors modulate the ways in which empathic development and its correlates unfold at both neural and behavioral levels. More precisely, we suggest that when a genetically-influenced proclivity to empathic sensitivity is expressed in the context of a) intraindividual moderating influences such as genetically-influenced predispositions to physiological hyperarousal and negative thinking, and/or b) interpersonal moderators such as maladaptive parenting or chronic exposure to parents' negative affect, individuals experience heightened risk for intermediate states—personal distress and interpersonal guilt —that may, in turn, precipitate internalizing symptoms. We suggest that, in light of age-related increases in the heritability of both empathy-related constructs (Knafo & Uzefovsky, 2013) and internalizing problems (Tully, Iacono, & McGue, 2010), as well as evidence that the early home environment can help shape empathic skills (e.g., Robinson, Zahn-Waxler, & Emde, 1994; Tong et al., 2012; Zahn-Waxler & Radke-Yarrow, 1990), efforts to facilitate the development of healthy empathic responses, and thus to minimize risk for internalizing problems, may be most effective when implemented as early as possible during childhood.

The Development of Empathy

Developing the capacity to respond empathically to distress expressed by parents, siblings, peers, and others is important for healthy trajectories of social, emotional, and moral development. In this section, we review environmental, neurobiological, and genetic influences on the development of empathy. We begin by defining empathy.

Defining Empathy

The construct of "empathy" has received ample research attention since the early 1900's, with recent literature searches yielding roughly 5700 (PubMed, searched 4/16/14) to 7000 (PsycINFO, searched 4/16/14) works that have included the term as a key word and thousands more that mention empathy in their abstracts. Reviews of this literature are complicated by the myriad ways in which empathy is defined across studies. Derived from the Greek word empatheia, which translates roughly to "passion" (Merriam-Webster, 2013), the word "empathy" has acquired a number of related, but distinct and often subtly nuanced, connotations in the research literature (e.g., Batson, 2009; Decety, 2011; Preston & de Waal, 2002). Developmental psychologists define empathy as an affective state that a) is elicited by observing or imagining another's affective state, b) is similar to the other's emotional state, and c) is caused by the other's emotional state. Further, they distinguish empathy from a variety of related processes (e.g., self-regulation and executive control) that influence social behaviors, as well as from moral and motivational outcomes of empathy, such as compassion and prosocial behavior (e.g., de Vignemont & Singer, 2006; Eisenberg, 2010;

Batson, 2010). Although individuals can respond empathically to both negative and positive emotions, this review will focus on empathic responses to others' negative affective states.

Researchers also consistently distinguish affective empathy, which can be observed as early as the neonatal period, from cognitive empathic processes that emerge later in development. Affective empathy, often termed empathic concern, is a response to witnessing another's emotions that involves both basic emotion understanding skills (e.g., emotion recognition) and emotional reactivity processes (e.g., emotion contagion). In its typical or adaptive form, affective empathy leads to compassionate responses to other's emotional states (Davis, Luce, & Kraus, 1994; Shamay-Tsoory, Aharon-Peretz, & Perry, 2009).

Cognitive empathy refers to more advanced cognitive perspective-taking systems (Shamay-Tsoory et al., 2009) that underlie the ability to understand and consider others' viewpoints when solving interpersonal problems (Davis, 1983). It involves the related, but not identical, constructs of theory of mind [i.e., the ability to distinguish one's own emotional state from others' emotional states (Blair, 2005)] and empathic accuracy [i.e., the ability to infer others' feelings from their behaviors (Ickes et al., 1990)]. The presence of this cognitive aspect of empathy is generally associated with positive social behaviors, such as cooperation, provision of social support, and volunteering (Carlo, Allen, & Buhman, 1999; Cliffordson, 2002; Eisenberg et al., 1995; Ferguson & Austin, 2010; Gleason, Jensen-Campbell, & Ickes, 2009; Johnson, Cheek, & Smither, 1983; Schreiter, Pijnenborg, & aan het Rot, 2013; Verhofstadt et al., 2008).

While clearly related, these two interpersonal response tendencies appear to function independently, such that the ability to practice cognitive perspective-taking does not necessarily predict one's proclivity to experience affective empathy, or vice versa. Behavioral research has broadly supported this distinction from early childhood onward, with ample evidence of at least partial dissociation between the two during preschool (e.g., Belacchi & Farina, 2012; Strayer, 1980), elementary school (e.g., Feshbach & Roe, 1968, Zajdel, Bloom, Fireman, & Larsen, 2013), adolescence (e.g., Jones, Happe, Gilbert, Burnett, & Viding, 2010), and adulthood (e.g., Cox et al., 2012). Indeed, depending on the interpersonal and intrapersonal contexts in which it emerges, an empathic response may draw on either or both components (Schnell, Bluschke, Konradt, Walter, 2011; Shamay-Tsoory, Torner, Goldsher, Berger, & Aharon-Peretz, 2004). The strength and the quality of each component's contributions are further likely to vary as a function of numerous factors, including the individual's developmental status and idiosyncratic functional neural dynamics (Cox et al., 2012). Thus, affective and cognitive empathy are related but distinct constructs that are usually associated with positive social, emotional, and moral outcomes. Under some circumstances, however, as detailed in forthcoming sections, both can also develop in ways that increase risk for maladaptive outcomes.

Developmental Pathways for Empathy

Most individuals acquire cognitive and affective empathy in a relatively predictable progression (see Hoffman, 2000); however, there is considerable variability within the normative developmental range in both infancy and childhood (Bryant, 1982; Knafo et al., 2008). Evidence suggests that humans enter life with a tendency to respond preferentially to

emotion signals, and even newborns imitate others' emotional cues (Diego & Jones, 2007). During the first year of life, typically-developing infants demonstrate the capacity to exhibit distress when confronted with others' signals of negative affect (Dondi, Simion, & Caltran, 1999; Geangu, Hauf, Bhardwaj, & Bentz, 2011) and to orient attention toward distressed others (Hay, Nash, & Pederson, 1981). As they transition into their second year, infants show marked changes in their patterns of empathic responding, presumably because they become better able to differentiate themselves from others and thus more capable of directing their concern externally (Hoffman, 1985; Hoffman, 2000; Eisenberg, Fabes & Spinrad, 2006). In addition, the ability to reason about others' goals and intentions improves steadily during the first few years of life, which likely facilitates a more sophisticated understanding of why others might show signs of distress (Sodian, 2011). Findings from at least one study suggest that individuals show relatively stable levels of empathy after age 3 years (Knafo, Zahn-Waxler, Van Hulle, Robinson, & Rhee, 2008).

During the preschool and school years, as a function of their growing cognitive and behavioral competence, children become increasingly capable of generating and implementing complex and differentiated prosocial behaviors based on empathic feelings and thoughts (Eisenberg & Miller, 1987). For example, verbal language skill serves as a potent predictor of later concern for others in preschoolers (Rhee et al., 2013); notably, these variables appear to be reciprocally and dynamically related, with empathic responding in early toddlerhood also predicting later language skill (Hutman, Rozga, DeLaurentis, Sigman, & Dapretto, 2012). Nonverbal language development also appears to facilitate empathic responding; as children's understanding of emotions and their causes increases with age, for example, their ability to generate empathic responses to others' nonverbal affective displays expands (Catherine & Schonert-Reichl, 2011).

Over the course of middle childhood, typically-developing children show a growing proclivity to manage their feelings with cognitive strategies (Altshuler & Ruble, 1989; Band & Weisz, 1988; Losoya, Eisenberg, & Fabes, 1998; Rice, Levine, & Pizarro, 2007). Research has identified links between maturing emotion regulation capacities and the emergence of more sophisticated empathic skills. For example, as children's cognitive perspective-taking skills improve, their ability to regulate both negative and positive emotions also improves (Bengtsson & Arvidsson, 2010). Although researchers have focused primarily on the idea that empathy may support effective emotion regulation (Schipper & Petermann, 2013), the two constructs likely interact dynamically across the course of development, such that effective emotion regulation also reinforces an individual's capacity for empathy (Ungerer et al., 1990). For instance, whereas emotionally-dysregulated individuals are likely to focus attention reflexively on themselves (Wood et al., 1990), those who can competently modulate their own emotional reactions may be more likely to direct attentional resources toward others when an external focus is appropriate (e.g., Eisenberg, 2010; Eisenberg et al., 1996).

Patterns of empathic responding appear to remain stable during and after the transition to adolescence (e.g., Davis & Franzoi, 1991), although some skills, such as the capacity to take others' perspectives and to empathize with individuals who are not present, apparently increase in this developmental period (Eisenberg et al., 2005; Hoffman, 2000). Findings are

mixed regarding the developmental course of empathy in adulthood. These inconsistencies appear to reflect differences across studies in (a) the facets of empathy that were measured —cognitive empathy has been found to decline more with age than does affective empathy (Sze, Gyurak, Goodkind, & Levenson, 2012); (b) longitudinal study duration—decreases in empathy have been observed over several decades (e.g., Eisenberg & Miller, 1987; Helson, Jones, & Kwan, 2002) but not necessarily over shorter durations (Grühn et al., 2008); (c) the cohort in which empathy was measured—college students since 2000 endorsed lower cognitive and affective empathy than did students enrolled in college in the 1980's and 1990's (Konrath, O'Brien, & Hsing, 2011); and (d) the period of adulthood studied—one study found higher levels of cognitive and affective empathy in middle-aged adults than in either young or old adults (O'Brien, Konrath, Grühn, & Hagen, 2013).

Taken together, findings from studies targeting age groups from infancy through adulthood suggest that empathic emotions, thoughts, and behaviors emerge and evolve in most individuals according to fairly predictable developmental patterns. Notably, some research indicates variability associated with individual differences such as sex and/or gender identity (Adams, Schvaneveldt, & Jenson, 1979; Karniol, Gabay, Ochion, & Harari, 1998; Mestre, Samper, Frias, & Tur, 2009; Van der Graaff et al., 2014). For example, by early adolescence, girls endorse more sensitivity than do boys to others' perspectives, and this perceived sensitivity predicts both better relationships with peers and more vulnerability to experiencing distress in the face of others' discomfort (Smith & Rose, 2011). Research has also has yielded evidence that empathic concern and perspective taking follow different developmental trajectories over the course of adolescence in girls and boys (Van der Graaff et al, 2014).

It is unclear, however, how to interpret such findings, given evidence that adult males and females show largely comparable patterns of neural response to empathy-eliciting cues, despite sex differences in self-reported empathic experience (Groen, Wijers, Tucha, & Althaus, 2013; Michalska, Kinzler, & Decety, 2013; but see Schulte-Rüther et al, 2008 for evidence of sex differences). One possibility is that observed sex differences in endorsements of empathy may more heavily reflect gendered social norms regarding the expression of empathic feelings than they reflect sex-linked differences in the experience of such feelings per se. Alternatively, similar patterns of neural activity between males and females during the presentation of empathy-relevant stimuli may correspond with different cognitive, emotional, and behavioral experiences. Clearly, regardless of the underpinnings of observed sex differences in response to stimuli that can provoke empathic responses, associations between empathy and sex are complex and may vary depending on how empathy is measured (Michalska, Kinzler, & Decety, 2013).

Genetic Proclivity toward Empathy

Behavior genetic studies support the heritability of affective and cognitive empathy (Knafo & Uzefovsky, 2013), with evidence of moderately strong genetic influences even in the second and third years of life (Knafo et al, 2008). Such findings are consistent with a significant role for genetically-influenced neurobiological processes in the emergence of individual differences in empathy early in development. The ways in which genetic effects

manifest appear to vary over time; Knafo et al. (2008) found that whereas genetic influences accounted for change in empathy in the second year of life, they accounted for continuity of empathy during the third year. This pattern suggests that at different points during development, genetic factors mediate both early empathic development and stability of more trait-like empathy. Notably, behavior genetic findings also suggest that genetic influences serve as the primary mediator of the association between positive affect and cognitive empathy (Volbrecht et al., 2007), although environmental factors also play key roles in the development of each (Knafo et al., 2009). Environmental influences also appear to mediate associations between empathy measured broadly and prosocial behavior (Knafo et al., 2008).

Research suggests several probable candidate genes that influence the development of empathy-related constructs. Much of the molecular genetics work to date in this area has focused on single nucleotide polymorphisms (SNPs) within the oxytocin receptor (OXTR) gene, particularly the RS53576 SNP, demonstrating that varied allele distributions for polymorphisms in this gene predict different social/emotional outcomes. Across studies, for example, individuals with two copies of the G allele at varied loci exhibit higher levels of dispositional empathy, interpersonal trust, sensitivity to children, prosocial temperament, and desire for social approval than do those with AG or AA allele configurations (Bakermans-Kranenburg & van Ijzendoorn, 2008; Costa et al., 2009; Krueger et al., 2012; Rodrigues et al., 2009; Tost et al., 2010). Although the OXTR gene appears to have links to both affective and cognitive components of empathy, some evidence suggests the OXTR gene locus differs for the two (Wu, Li, & Su, 2012).

The OXTR gene may affect behavioral and experiential outcomes, including those associated with adaptive states, such as compassion, and maladaptive states, such as personal distress and interpersonal guilt, in several ways. Animal and nasal oxytocin administration studies suggest that genetically-mediated variations in the release of oxytocin, as well as in the density, location, and function of oxytocin receptors, underlie individual differences in positive social behaviors, such as trust, calm social interaction, and generosity (Ishak, Kahloon, & Fakhry, 2011; Kosfeld et al., 2005). Although most studies find evidence that introducing exogenous oxytocin increases these positive behaviors, at least two studies have shown that it can decrease such behaviors in subgroups of adults with disrupted attachment histories (Bartz, Zaki, Ochsner, et al., 2010, Bartz, Simeon, et al., 2011), which is consistent with a moderating role for relevant contextual factors.

Other genes, such as the arginine vasopressin 1a receptor (AVPR1a) gene (Ebstein et al., 2009; Meyer-Lindenberg et al., 2009; Yirmiya et al., 2006) are receiving growing attention from researchers as likely mediators of empathy-relevant social behavior. Vasopressin, a neuropeptide hormone that, like oxytocin, has been implicated in emotional bonding and related interpersonal experiences (Bales, 2014), may be particularly important for social cognition and behavior in males (Atzil et al., 2012; Uzefovsky, Israel, Knafo, & Ebstein, 2012). Although vasopressin appears to play a role in the development of disorders, such as autism, that are marked by empathic deficits (Ebstein, Knafo, Mankuta, Chew, & Lai, 2012), limited research has specifically linked this hormone to empathic behavior. Research on parent-child and pair-bonding constitutes one notable exception (Atzil et al., 2012; Gray &

Campbell, 2009) and provides a foundation for future work exploring associations between vasopressin and empathy more broadly.

The promoter region of the 5-HTTLPR gene (Fox, Zougkou, Ridgewell, & Garner, 2011; Bakermans-Kranenburg & van Ijzendoorn, 2008) may also play a role in the development of empathy. Research points to both direct and indirect effects of this gene on empathy-relevant behavior, which underscores the complexity of genetic influences on downstream outcomes. Bakermans-Kranenburg and van Ijzendoorn (2008), for example, found direct associations between 5-HTTLPR allele variations and maternal sensitivity, with high sensitivity associated with the heterozygous short/long (SL) and homozygous (LL) variants, rather than with the homozygous short (SS) variant, which is associated with the least efficient serotonin functioning. Thus, this gene, like other relevant genetic influences, is likely to function in multiple ways that vary across environmental contexts to contribute to socioemotional outcomes.

Researchers have made notable strides in characterizing genetic influences on empathy and its development. It is likely, however, that genes associated with a broad range of additional neurochemicals, such as cortisol, estrogen, opiates, and monoamines, converge to shape the way in which empathic capacities emerge and change across development and very little is known about how different empathy-related genes interact to influence social behavior. Beyond identifying individual candidate genes, it will be important for future studies to begin to delineate how these genes interact across varied genetic and environmental contexts to influence an individual's trajectory of empathy-relevant neurobiological, physiological, and behavioral development.

Neurobiology of Empathy

Although research has shown that variations in oxytocin and other genes relate to empathy and empathy-relevant behavior, these genes exert their influence primarily by modulating the development and function of brain regions and systems that implement empathic experiences and responses. These systems have been carefully studied and described in the literature and a number of similar, but subtly distinct, models have been articulated (e.g., Decety, 2007; Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2005). For the purposes of this review, we use Decety and colleagues' developmentally-informed neural model of empathy as a framework (Decety, 2007; Decety, 2010; Decety, 2011; Decety & Jackson, 2004). In addition to its attention to development, this model has the advantage of encompassing bottom-up processes that emerge early and map loosely onto affective empathy, top-down processes that emerge slightly later in development and correspond broadly to cognitive empathy, and an array of integrated processes that contribute interactively to the generation and modulation of empathic responses and behaviors. Notably, the nature of the interactions among these processes appears to vary as a function of age-related changes in their mediating neural structures (Decety & Michalska, 2010). Indeed, considerable evidence lends support to the premise that neural structures critical to both affective and cognitive empathy follow varying developmental trajectories, as Decety and colleagues (Decety, 2011; Decety & Michalska, 2010) have pointed out in overviews of the relevant literature.

Basic, largely involuntary capacities to detect and respond to others' affective cues (fundamental aspects of affective empathy) appear to be implemented, at least in part, by subcortical structures that include the amygdala, hypothalamus, and hippocampus. These brain regions begin to mature early; indeed, some interpersonal responses that they support, such as affective sharing, appear to emerge within the first few weeks after birth (e.g., Dondi, Simion, & Caltran, 1999; Field, Woodson, Greenberg, & Cohen, 1987). Cortical regions that engage during affective empathy, particularly the anterior insula, which is implicated in varied relevant functions that include sharing others' experiences of physical and emotional pain (Lamm, Decety, & Singer, 2011; Lamm & Singer, 2010), also appear to show marked developmental changes very early in life (Kalani et al., 2009). However, researchers have demonstrated that the insula also reliably undergoes thinning, or gray matter reduction, during middle childhood, which suggests that its developmental course may be more protracted than are those of subcortical areas (Muftuler et al., 2011).

Despite this research that implicates several brain regions in empathy-related processes, questions remain regarding the specific mechanisms by which these regions support the development and experience of affective empathy. Nevertheless, findings from numerous studies suggest key roles for several neurochemicals, particularly oxytocin and vasopressin, that have been linked to a range of social behaviors from the neonatal period onward (e.g., Bartz, Zaki, Bolger, & Ochsner, 2011; Clark et al., 2013) and that modulate functioning in salient regions such as the amygdala and hippocampus (Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011; Owen et al., 2013; Zink & Meyer-Lindenberg 2012). Oxytocin, in particular, appears to exert subcortical effects primarily by modulating neural activity in the amygdala, midbrain regions, and dorsal striatum. Not only does it attenuate activation in these areas, which are engaged during the experience of affective states that include fear or distress (Phelps, 2009; Mobbs et al., 2009; Schiller et al., 2008), but it also weakens functional coupling of the amygdala to brainstem regions implicated in autonomic and behavioral manifestations of fear (Baumgartner et al., 2008; Kirsch et al., 2005), which may underlie the calming and bonding effects of oxytocin.

Notably, the small pool of existing data is mixed regarding whether and how these neurochemicals, particularly oxytocin, modulate empathy-related activity in relevant cortical regions such as the anterior insula (Riem et al., 2011; Singer et al., 2008). Whereas at least two studies yielded findings suggesting that intranasally-administered oxytocin and vasopressin enhance amygdala-insula connectivity in adults during the presentation of infants' emotional cues (Riem et al., 2011) or during a social interaction task (Rilling et al., 2012), other research has failed to generate evidence of such modulatory activity (Riem et al., 2012).

In contrast to those structures that show involvement in bottom-up processes associated with affective empathy, structures such as the medial and dorsolateral regions of the prefrontal cortex, which mediate top-down regulatory processes linked to cognitive empathy, mature slowly (Zelazo, Carlson, & Kesek, 2008), with synaptic developmental trajectories that extend into young adulthood (e.g., Gogtay et al., 2004; Shaw et al., 2008). Notably, however, findings summarized in a recent review suggest that prefrontal regions are functionally active in newborns and that subsequent maturation of this structural domain

revolves around changes in connectivity with other parts of the brain (Grossman, 2013). Thus, the neural elements necessary to experience not only the affective, but also the cognitive, aspects of empathy are present and engaged from birth; however, these elements interact and shape each other change in a slowly unfolding process that extends into adulthood.

Some evidence suggests that dopamine, rather than oxytocin, serves as the primary neuromodulator for prefrontal regions involved in top-down cognitive components of empathy (Lackner, Bowman, & Sabbagh, 2010; Lackner et al., 2012; Xia, Wu, & Su, 2012). Effects of oxytocin on the circuitry involved in cognitive empathy, where present, appear to be indirect (Shamay-Tsoory, 2011). More precisely, data—primarily from preclinical studies —indicate that the oxytocin and dopamine systems may interact to influence a range of social cognitive and interpersonal outcomes (Young & Wang, 2004; see Baskerville & Douglas, 2010 for a review).

Complicating the neurodevelopmental picture for empathy and its component processes is evidence that the social environment shapes the expression of relevant neurobiological processes and genetic liabilities (Knafo & Uzefovsky, 2013). Exposure, for example, to responsive, supportive, and sensitive parenting appears to strengthen young children's proclivity to take others' perspectives (Farrant, Devine, Maybery, & Fletcher, 2012) and adolescents' capacity for both empathic concern and perspective taking (Miklikowska, Duriez, & Soenens, 2011). Such associations, however, appear to vary in strength across youths with different neurobiological and genetic profiles; for instance, Cornell and Frick (2004) found that parenting consistency was more weakly associated with child empathy in behaviorally inhibited youths than it was in children with behaviorally disinhibited temperaments.

Further, the effects of the social environment on maturing brain structures and circuitry wax and wane, with some developmental periods constituting key windows for the acquisition or expression of particular socioemotional functions (Nelson & Guyer, 2011). For example, evidence from one study suggests that whereas subcortical regions, such as the hippocampus, may be especially vulnerable in the preschool years to such environmental insults as physical abuse, the prefrontal cortices may be more profoundly affected by maltreatment during adolescence (Andersen et al., 2008). Further, findings from studies of several mammalian species indicate that experiences across development shape the functioning of the oxytocin system (Bales & Perkeybile, 2012), which raises the possibility that similar critical periods may exist for this and other neuropeptide systems as well. Thus, the temporal pattern of an individual's life experiences may shape, in an idiosyncratic fashion, the developmental courses of structures and neurochemical pathways that subserve affective and cognitive aspects of empathy, respectively.

Individual differences beyond age, such as pubertal status and sex, may also influence the boundaries of sensitive periods for varied neural regions and systems (Herting et al., 2012; Ladouceur, 2012; Wang et al., 2012). Several research groups, for example, have found evidence of sex differences in the microstructure of neural white matter distributed throughout the adolescent brain (e.g., Herting et al., 2012; Wang et al., 2012), with the bulk

of findings suggestive of faster white matter development in girls than in boys. Functional neural differences between males and females during empathy-related tasks have also been observed in at least one study of adults; Schulte-Rüther and colleagues (2008), for instance, found evidence of distinctive patterns of neural activation in men and women during assessment of their own and others' emotional states. Other studies, however, have yielded limited evidence that neural activation to empathy-related cues differs according to sex (Groen, Wijers, Tucha, & Althaus, 2013; Michalska, Kinzler, & Decety, 2013), which suggests the need for further research to sort out this pattern of inconsistent findings.

Herting and colleagues (2012) also identified structural differences associated with pubertal status instead of sex in some empathy-relevant regions, including the insula. Further, in a study focused only on girls, Klapwijk and colleagues (2013) linked adolescent increases in pubertal hormones, particularly estradiol, to enhanced functional neural connectivity within circuits activated during thoughts about others' mental states. Taken together, these findings suggest a role for pubertal hormonal changes in the emergence of at least some neural correlates of empathic experience.

Thus, if we are to understand how empathy functions—and malfunctions—across development, it will be important that we build on emerging knowledge about the ways in which genetically-mediated neurochemical processes—including, but not limited to, release of hormones such as estrogen and testosterone, which are linked to sex and puberty—participate in relevant processes both directly and via interactions with such neuropeptides as oxytocin and dopamine and relevant aspects of the social environment (e.g., Bos, Terburg, & van Honk, 2010; Gabor, Phan, Clipperton-Allen, Kavaliers, & Choleris, 2012). Identifying additional candidate genes and further elucidating the genetic variants that influence the functioning of such neurochemicals and their receptors will also help us learn how empathy can veer from serving as a strength to functioning as a liability.

From Empathy to Internalizing Conditions

Although empathy typically constitutes a protective factor for mental health, maladaptive alterations in the typical trajectories of empathy development may result in qualitatively and quantitatively atypical emotional and cognitive experiences in response to empathy-eliciting cues and consequential risky outcomes. Empathic reactions to others' distress that a) are excessively aversive, b) involve excessive cognitive perspective-taking, and/or c) result in self-focused comforting responses or self-focused rumination about one's role in the observed distress may facilitate the emergence of internalizing problems. In this section, we describe two empirically-supported internalizing subfactors and review the literature regarding ways in which two related, yet distinct, empathy response patterns—personal distress and excessive interpersonal guilt—may contribute to risk for internalizing symptoms within both subfactor domains.

The Structure of Internalizing Disorders

For most individuals, empathy is linked throughout the lifespan with positive interpersonal and intrapsychic outcomes, including better relationships with friends and partners (Chow, Ruhl, & Buhrmester, 2013; Cramer & Jowett, 2010), increased social engagement (Bailey,

Henry, & Von Hippel, 2008), and resilience (Shiner & Masten, 2012). One can clearly demonstrate too little empathy; a sizable body of research documents associations between an impaired empathic capacity and psychopathological conditions as varied as conduct disorder and autism spectrum disorders (Bons et al., 2013; Decety & Michalska, 2010; Miller & Eisenberg, 1988). Less research has described potential psychopathological correlates of excessive empathy; however, as Zahn-Waxler and colleagues (1991) have suggested in a model focused explicitly on girls, extreme empathy or a combination of heightened sensitivity to others' distress and inadequate skills for coping with that distress may increase vulnerability to internalizing conditions marked by negative affect.

The research we review here suggests that risk for internalizing disorders may increase when empathy's typical, healthy developmental trajectory is altered in ways that lead to maladaptive consequences. We find the model that Zahn-Waxler and her collaborators have proposed, in which highly empathic girls may be at particular risk for internalizing conditions due in part to gendered patterns of socialization (Zahn-Waxler et al., 1991), to be compelling. However, we contend that although base rates of excessive empathy may be lower in males than in females by early adolescence (Olweus & Endresen, 1998), those males who fall at the extreme end of the empathy continuum may also be at heightened risk for internalizing conditions, as a function of moderating variables that manifest in less sex-specific ways. As a consequence, we do not postulate distinct empathy-related pathways to internalizing disorders for males and females. Instead, we propose that the intersection of a strong propensity for empathy with any of a range of intraindividual and interindividual moderators will increase risk regardless of an individual's sex.

One key to unraveling the sources of atypical, maladaptive developmental trajectories in boys and girls alike may derive from the hierarchical structure of internalizing disorders and the genetically-influenced regulation liabilities that give rise to this structure. Although the internalizing disorders are often referenced as if they constitute one undifferentiated group, multivariate studies of the latent structure of internalizing disorders have consistently yielded evidence of two highly correlated, but distinct, subfactors: a) a fear/arousal subfactor that underlies agoraphobia, social phobia, specific phobia, and panic disorder, and b) an anhedonia/misery subfactor that explains the covariance of MDD, dysthymic disorder, and GAD (e.g., Kendler, Prescott, Myers, & Neale, 2003; Krueger & Markon, 2006). Comorbidity is highest among disorders that load onto a single subfactor (Kessler et al., 2005); however, disorders that load onto the two internalizing subfactors also tend to co-occur. The fear/arousal and anhedonia/misery subfactors are thought to derive from genetically-influenced biological liabilities that are expressed as spectra of related cognitive processes and behavioral tendencies (Tully & Iacono, 2014).

The substantial role of genes in the etiology of internalizing disorders is supported by evidence from twin and adoption studies (e.g., Ehringer, Rhee, Young, Corley, & Hewitt, 2006; Garcia, Tully, Tarantino, South, Iacono, McGue, 2013; Tully, Iacono, McGue, 2010), and research findings consistently support separate, though positively correlated, genetic loadings on these two subfactors (Kendler, Prescott et al., 2003). Tully and Iacono (2014) proposed an empirically-derived model to explain the hierarchical factor structure of internalizing disorders. In this model, the anhedonia/misery and fear/arousal subfactors

derive from distinct, but related, genetically-influenced dysregulation liabilities. These liabilities, in turn, are expressed as discrete, yet overlapping, spectra of behavioral tendencies, cognitive processes, affective experiences, and neurobiological systems (Tully & Iacono, 2014). Tully and Iacono (2014) hypothesized that a genetic liability for negative thought processes (e.g., habitual negative attributions and expectations, biased attention and memory, worry, rumination) would contribute to anhedonia/misery symptoms, and a genetic liability to physiological arousal (e.g., heightened psychophysiological responses to aversive stimuli, behavioral inhibition) would provoke fear/arousal pathology.

In the following sections, we describe how these two liabilities may interact with genetic propensities for high empathic sensitivity to amplify vulnerability for internalizing problems. Confirmation of such interactions and their effects would help explain how empathic tendencies, which usually function as strengths (e.g., a high need for affiliation and/or a communal orientation) may, paradoxically, serve as risk factors for internalizing conditions.

Personal Distress and Interpersonal Guilt

Our model proposes that developmental trajectories from empathic tendencies to fear/arousal and misery/distress internalizing problems encompass two intermediate conditions: interpersonally-oriented personal distress and guilt, respectively. Personal distress, as defined in the empathy literature, is a maladaptive affective response to negative emotions in others. Unlike compassionate empathic concern, a response oriented toward another person who is in physical or emotional pain, personal distress is a self-focused response accompanied by physiological hyperarousal and behavioral withdrawal (Eisenberg, 1989; Zahn-Waxler & Van Hulle, 2012). Interpersonal guilt, in contrast, is a maladaptive form of cognitive empathy that is driven by excessive and irrational altruistic concerns, such as unreasonable beliefs that one is responsible for alleviating the suffering of others and intense worries about harming others (O'Connor et al., 2007; O'Connor et al., 2002; Oakley, Knafo, & McGrath, 2012; Zahn-Waxler et al., 2012).

In adults, both personal distress and interpersonal guilt show associations with a range of maladaptive outcomes—some overlapping and others distinct. Research findings link tendencies toward personal distress reactions with a variety of internalizing problems, including anxiety, guilt, and depression in both adults and youths (e.g., O'Connor, Berry, Weiss, & Gilbert, 2002; O'Connor, Berry, Lewis, & Stiver, 2012; Schreiter et al., 2013; Thoma et al., 2011; Zahn-Waxler & Van Hulle, 2012). Personal distress also shows significant associations with neuroticism (Mooradian, Davis, & Matzler, 2011), burnout (Carmel & Glick, 1996; Klimecki & Singer, 2012), and pathological or irrational altruistic behavior (Oakley, Knafo, & McGrath, 2012). Fewer studies have focused explicitly on interpersonal guilt; however, the construct has been linked in adult samples to loneliness and alienation (Bruno, Lutwak, & Agin, 2009), as well as to depression and anxiety symptoms (O'Connor, Berry, & Weiss, 1999).

Putative associations between interpersonal guilt and maladaptive outcomes have yet to be directly examined in youths. Zahn-Waxler and colleagues (e.g., Zahn-Waxler, Kochanska, Krupnick, & McKnew, 2009; Zahn-Waxler & Van Hulle, 2012), however, have proposed

that guilt that can arise when failed efforts to care for a chronically depressed parent lead to inaccurate assumptions of responsibility for the parent's unhappiness, and that such guilt can, in turn, contribute to the onset of depression. Such guilt and its negative sequelae may be further magnified if parents actively induce guilt in their children, a parenting strategy observed more commonly in depressed than non-depressed parents (Donatelli et al., 2007; Rakow et al., 2009).

Mechanisms underlying the transitions from empathy to personal distress and interpersonal guilt, and subsequently to internalizing disorders, have only begun to be described in the literature; indeed, at this point, few studies explicitly examine factors that may skew the normative developmental trajectory for empathy in these maladaptive directions. Indirect evidence, however, converges to suggest that personal distress and, potentially, interpersonal guilt, reflect, at least in part, dysregulation of the neural systems that subserve typical affective and cognitive empathy development.

Maladaptive Moderators of Empathy Development

The processes underlying atypical empathy trajectories are moderated by intraindividual and interindividual factors. We propose that genetically-influenced biological predispositions to regulation difficulties serve as key intraindividual moderators, and that environmental exposures to inadequate parenting and negatively-valenced home environments serve as crucial intraindividual moderators. These moderators of typical empathy development give rise, via effects on neurobiological development, to personal distress and interpersonal guilt, which in turn amplify risk for fear/arousal internalizing symptoms and anhedonia/misery symptoms, respectively.

Data from varied literatures suggest that a complex set of environmental, genetic and neurobiological factors interact to facilitate progression along the path from healthy empathic sensitivity to personal distress and/or interpersonal guilt to internalizing conditions. As illustrated in Figure 1, both intraindividual and interindividual factors are likely to play important roles. At the intraindividual level, genetic liabilities can be expressed in ways that heighten risk for developing a neurobiological profile marked by proclivity to physiological hyperarousal and/or negative thinking. We propose that neurobiological processes underlying personal distress in response to others' pain or suffering arise as a function of interactions between genetically-mediated tendencies toward both empathic sensitivity and physiological hyperarousal. Further, we suggest that interpersonal guilt and its neurobiological substrates emerge as a consequence of comparable interactions between genetic propensities toward empathic sensitivity and negative thinking.

Such genetic and neurobiological liabilities are particularly likely to be expressed in the context of interindividual moderators such as poor parenting and overexposure to others' negative affect. When environmental moderators support the expression of genetically-mediated neurobiological vulnerability, the typical developmental trajectories for affective and cognitive empathy can alter, leaving the affected individual prone to maladaptive states such as personal distress and interpersonal guilt, which in turn elevate risk for fear/arousal and anhedonia/misery internalizing conditions.

Intraindividual Moderators: Genetically-Influenced Dysregulation Liabilities

Liability to Physiological Hyperarousal—A genetically-influenced proclivity to experience physiological over-arousal in response to stressors and/or disadvantageous physiological arousal in response to mild stressors has been proposed to increase risk for internalizing disorders that load on the fear/arousal subfactor (Tully & Iacono, 2014). These disorders are characterized by exaggerated physiological responses (e.g., accelerated heart rate, sweating, shortness of breath) to affectively arousing stimuli, heightened attention and startle response to threats, and behavioral inhibition (Cuthbert et al., 2003; Hofmann, Moscovitch, & Kim, 2006; Larson, Nitschke, & Davidson, 2007; Martin-Soelch, Stocklin, Dammann, Opwis, & Seifritz, 2006). Some physiological arousal in response to others' negative emotions is normative and adaptive, particularly during early development (e.g., Feldman, 2007) and in the context of parents' distress (Tully, Donohue, & Garcia, 2014; Zahn-Waxler et al., 2012). It is also common later in life (Buchanan et al., 2012; Out, Pieper, Bakermans-Kranenburg, & Ijzendoorn, 2010). However, the propensity to experience prolonged, intense, and poorly regulated arousal in response to stressors that include mildly distressing interpersonal encounters may interfere with children's social and emotional development by evoking an enduring tendency to focus cognitive resources inward on self-soothing efforts during emotional interpersonal interactions. We hypothesize that among children with a proclivity to be empathically sensitive and thus intensely aware of others' emotions, those who also show a proclivity to experience physiological hyperarousal in distressing interpersonal situations will be particularly prone to personal distress empathic reactions.

Although research that focuses explicitly on associations between physiological hyperarousal and personal distress is limited, some evidence lends support to our hypothesis. At least one study, for example, has linked physiological dysregulation in the face of others' emotional cues, particularly those that signal or trigger negative emotions, to the development of personal distress (Sze, Gyurak, Goodkind, & Levenson, 2012). Such vulnerability to dysregulation manifests across multiple biological systems in ways that appear to shift across development (see, for example, Romeo, 2013). Research has long implicated the sympathetic nervous system and the hypothalamic pituitary axis (HPA) in the generation of short- and longer-term reactions to stressful cues across the lifespan (Muscatell & Eisenberger, 2012); some evidence suggests that neuropeptides such as oxytocin participate in modulating this reactivity, both directly and indirectly via effects on function in neural regions, such as the amygdala, that have been implicated in emotional processing and responding (Bartz & Hollander, 2006; Neumann, 2002; Rodrigues et al., 2009).

Few investigations into the heritability of physiological arousal constructs have been conducted. Some research on adults, however, is consistent with the presence of modest genetic influences on conditioned eyeblink responses (Merrill, Steinmetz, Viken, & Rose, 1999) and absolute, but not emotion modulated, startle reflexes (Anokhin, Golosheykin, & Heath, 2007; Carlson, Katsanis, Iacono, & McGue, 1997). Furthermore, although the specific genes associated with these liabilities are at present unknown, a few candidates, including the promoter region of the 5-HTTLPR gene (Armbruster et al., 2009; Brocke et

al., 2006; Lonsdorf, Weike, Nikamo, Schalling, Hamm, & Ohman, 2009) and the tryptophan hydroxylase 2 gene (Armbruster et al., 2010), show promise for elucidating a complicated interplay in which many genes each contribute small effects.

Much of the relevant research to date has focused on associations between 5-HTTLPR allele variants and aspects of physiological hyperarousal. In a recent meta-analysis, Miller and colleagues (2013) found that, across studies, individuals homozygous for the short 5-HTTLPR allele (SS) show elevated HPA-axis reactivity, defined as elevated cortisol secretion, to a broad range of stressors. The observed association, while significant, was small, and the authors suggest that taking gene-gene and gene-environment interactions into account might have yielded stronger results. Researchers have also found links between the homozygous SS allele variant and other measures of hyperarousal. Lonsdorf and colleagues (2009), for example, found that adults with short 5-HTTLPR allele variations show stronger startle potentiation in fear conditioning paradigms than do peers with other allele configurations.

Notably, although we focus in this paper on physiological hyperarousal as a key intrapersonal moderator of empathic development, anomalous physiological patterns of response to empathy-eliciting cues vary considerably across (and potentially within) individuals who are vulnerable to depression and anxiety. More specifically, whereas many adults with internalizing conditions show hyperresponsivity to empathy-eliciting stimuli, others exhibit atypically muted reactions (Barrett et al., 2012; Laurent & Ablow, 2013). It thus appears that relationships among physiological reactivity, empathy, personal distress, and internalizing symptoms may be complex and nonlinear and that they may vary depending on how, and when in the life course, both reactivity and behavior are measured.

Genetic Liability to Negative Thinking Processes—A genetic predisposition for various interrelated negative thought processes that have empirical links to depression and anxiety has been proposed to contribute to risk for internalizing disorders in the anhedonia/ misery subfactor (Tully & Iacono, 2014). These thought processes include attentional biases to threatening and sad stimuli, excessive contemplation of negative information, difficulty shifting attention away from negative information, and trouble suppressing pessimistic cognitions (e.g., Everaert, Koster, & Derakshan, 2012; Gotlib & Joormann, 2010; Mathews & MacLeod, 2005). Individuals with high doses of this liability are thought to be prone to poor regulation of these cognitive processes, which can manifest, for example, as excessive worry or rumination. When empathically sensitive children also exhibit this cognitive dysregulation liability, we hypothesize that the interaction between liabilities for empathic sensitivity and cognitive dysregulation yields heightened risk for a tendency to respond to other's misfortunes with empathic guilt.

Few studies have investigated the heritability of the many cognitive constructs associated with a liability to negative thinking processes, particularly in samples of youth, but the existing studies support moderately strong genetic influences on attributional style, a cognitive pattern characterized by internal, global, and stable attributions for negative events, in adolescents (35%; Lau, Rijsdijk, & Eley, 2006). Moderately strong genetic influences on anxiety sensitivity, which refers to beliefs about the harmful consequences of

anxiety, have also been documented in children (Eley, Gregory, Clark, & Ehlers, 2007) and adolescents (Zavos, Gregory, & Eley, 2012).

Molecular genetics research also supports the role of genes that modulate varied aspects of neural function in these cognitive processes. For instance, variations in the serotonin transporter gene have been linked to biased attention for emotional stimuli, with most studies indicating that carriers of genotype variants associated with less efficient serotonin function, specifically the short allele variant (SS), as well as the more recently identified G variant of the long allele (SL_G, L_GL_G), show attentional vigilance toward threat cues (see Pergamin-Hight et al., 2012 for a meta-analytic review). Notably, however, the few studies that focus on children have yielded a less consistent pattern of findings. Gibb and colleagues (2009), for example, found that attentional biases to *avoid* sad cues were amplified in 8 to 12 year old offspring of depressed mothers, particularly if their 5-HTTLPR genotype included at least one copy of the lower expressing S or L_G alleles. Such findings, along with the possibility that children in general show a normative bias toward threat cues (e.g., Kindt & van den Hout, 2001; Pine, 2007) suggest that potential developmental changes in patterns of gene expression warrant investigation.

Additional research implicates low-efficiency variants of the 5-HTTLPR gene in the tendency to overcontemplate negative information or to exhibit cognitive reactivity to experienced sadness (Antypa & Van der Does, 2010; Clasen, Wells, Knopik, McGeary, Beevers, 2011). Context, however, appears critically important to the emergence of these associations. The links that Clasen and colleagues (2011) found between the SS genotype variant and heightened rumination, for instance, were particularly strong in the context of adverse life events. Similarly, Antypa and Van der Does (2010) found that the association between reactivity to sad mood and the SS allele type only emerged in adults who reported having experienced maltreatment during childhood.

Other genes that modulate neural function, including those for brain derived neurotrophic factor (BDNF) (Beevers, Wells, & McGeary, 2009; Clasen et al., 2011), the D2 dopamine receptor (DRD2) (Whitmer & Gotlib, 2012), and CREB1 and KCNJ6 (Lazary et al., 2011) have been identified as potential contributors to the development of ruminative tendencies in adults. Patterns of association, however, vary across some studies focused on the same genes. One study, for instance, found that adults who carry a heterozygous variant of the Val66Met polymorphism of the brain derived neurotrophic factor (BDNF) gene show stronger ruminative tendencies than do those who carry other variants (Beevers, Wells, & McGeary, 2009). Another study from the same research group, however, found that rumination in the context of life stress was more likely in those who carried a homozygous Met polymorphism, particularly if they also carried the SS 5-HTTLPR allele variant (Clasen et al., 2011). Attention to context at genetic, environmental, and developmental levels will clearly be necessary to elucidate the circumstances under which particular allele variants contribute to tendencies toward negative thinking.

The expression and influence of these negative thought process liabilities change over development. Limited cognitive capacity during early childhood restricts the emergence of stable cognitive dysregulation processes; during this period negative thought process

liabilities may be expressed as behavioral avoidance, shyness, and poor attention regulation. Improved cognitive abilities during late childhood and adolescence promote the development of more stable and pathological cognitive styles, and by early adolescence, dysfunctional cognitive proclivities, such as rumination and negatively biased attention and interpretation schemas, are associated with internalizing problems (Abela & Sarin, 2002; Schwartz, Kaslow, Seeley & Lewinsohn, 2000).

Interindividual Moderators: Environmental Exposure

The extent to which a) early empathy develops atypically, b) genetic liabilities result in neurobiological and physiological regulation difficulties, and c) regulation difficulties lead to personal distress and interpersonal guilt depends on exposure to negative emotions in others, to inadequate parenting practices, and to other environmental variables that exert their greatest influence early in development.

Long-term exposure to a parent's negative affect, particularly when that parent is severely affected by mood difficulties, has a broad range of negative consequences for many, but not all, youths (e.g., Goodman et al., 2011; Katz, Hammen, & Brennan, 2013). Researchers increasingly recognize that the likelihood of negative outcomes for children of depressed parents depends on a complex matrix of interacting factors, both genetic and environmental (e.g., Kerr et al., 2013; Harold et al., 2011). Consistent with this idea, we suggest that children with strong proclivities toward empathic sensitivity who also carry genetic liabilities for physiological hyperarousal and/or negative thinking are at particularly amplified risk for maladaptive empathy development when they live for protracted periods in the context of parent depression.

Researchers have long been interested in the association between maternal depression and child empathy; Zahn-Waxler and colleagues, in particular, have articulated sophisticated models of the ways in which these variables dynamically interact, particularly for girls (Radke-Yarrow et al., 1994; Zahn-Waxler et al., 1990). Despite this enduring interest, few studies to date have examined the idea that exposure to parent negative emotion, such as that observed in the context of depression, interacts with child genetic liabilities to predict the developmental course for empathy and related characteristics. One investigation found that the homozygous GG variant of the OXTR gene was associated with both low salivary oxytocin and maternal depression, which in turn predicted child internalizing disorders (Apter-Levy, Feldman, Vakart, Ebstein, & Feldman, 2013). Further, rates of offspring psychopathology were markedly lower among mothers who carried the GA or AA allele variants. Clarifying how this and other relevant genes, particularly varied 5-HTLLPR and AVPR1 polymorphisms contribute in both independent and interactive ways to modulate the parent affect/child empathy association, as well as the function of neural structures that support relevant processes, is a critically important line of research that is poised to burgeon in coming years.

It will also be of value to explore the role of parenting behavior in the association between parent affect and child empathy outcomes. A small body of evidence supports a link between effective parenting—which studies have defined to include such practices as

fostering secure attachment, providing support, and encouraging emotional expression—and healthy empathic development (e.g., Kestenbaum, Farber, & Sroufe, 1989; Soenens, Duriez, Vansteenkiste, & Goossens, 2007; Taylor, Eisenberg, Spinrad, Eggum, & Sulik, 2013). Some evidence suggests that this association may not always be direct; Yoo and colleagues (2013), for example found that parent-child connectedness mediated relationships between parenting behavior and empathy in an adolescent sample. Regardless of the path, however, positive parenting practices appear to contribute to adaptive empathy in offspring.

It follows logically, then, that maladaptive parenting behaviors that commonly occur in the context of negative parent affect, such as failure to facilitate emotion regulation, insensitivity to children's emotional cues, excessive control, and lack of warmth, may skew children's empathic development toward problematic outcomes (Kanat-Maymon & Assor, 2010; Hastings et al., 2000; McGrath & Zook, 2011; Valiente & Eisenberg, 2006; van der Mark, van Ijzendoorn, & Bakermans-Kranenburg, 2002). We propose that the effects of inadequate parenting on the developmental trajectory for empathy will be particularly potent in youths who carry a genetically mediated neurobiological liability for empathic sensitivity, especially those who also carry liabilities for physiological hyperarousal and/or negative thinking.

Evidence of such gene by environment interactions have been detected in recent research focused on the development of empathy and prosocial behavior. Knafo and colleagues (2011), for instance, in a large longitudinal twin study, examined the possibility that preschoolers who carry different polymorphisms of the dopamine DRD4-III gene, which has been found in other contexts to influence child responsiveness to both positive and negative parenting behaviors, would exhibit differential sensitivity to parenting influences. No significant direct associations between parenting and prosocial behavior were observed. However, a significant gene x parenting interaction emerged, such that maternal positivity, negativity, and unexplained punishment correlated significantly with children's prosocial behavior only among children who carried the DRD4-7 allele. In this subgroup of youths, maternal positivity related meaningfully and positively to mother-rated prosocial behavior, and maternal tendency to use unexplained punishment related positively to self-initiated prosocial behavior in the experimental context.

In another twin study, Shikishima and colleagues (2011) obtained evidence of a different, but related, gene by parenting interaction. In this study of adolescent and adult twins, the association between parental warmth and child empathy was driven largely by genetic factors, with no significant effects detected for shared environmental factors for the sample as a whole. However, tests of a gene by environment interaction model yielded significant findings, indicating that shared family factors linked to parental warmth were significantly associated with indices of empathy in offspring whose parents demonstrated very high or very low levels of warmth.

Comparable findings emerged from at least one study focused on interactions between parenting and physiological, rather than genetic, characteristics as predictors of empathic behavior. Diamond, Fagundes, and Butterworth (2012) found, in a sample of mother-adolescent dyads, that attachment style interacted with vagal tone, which provides an index

of emotion regulation capacities, to predict adolescents' empathic responsiveness to their mothers in the context of emotional interactions. Empathic responsiveness was lowest among youths with high levels of attachment insecurity and low levels of vagal tone.

Although research has revealed evidence of interactions between parenting and broad profiles such as temperament, that are associated with distinct patterns of psychophysiological functioning, as predictors of externalizing (e.g., Bradley & Corwyn, 2008) and internalizing (e.g., Kiff, Lengua, & Bush, 2011) disorders, such findings are weaker with regard to child empathic behavior and experiences, such as personal distress or interpersonal guilt. Spinrad and Stifter (2006), for example, in a study of child temperament and maternal responsivity as predictors of child empathic behavior, found main effects of both constructs, but minimal evidence of interactions between them as predictors of personal distress or empathic behavior. Viewed in the context of recent research that highlights ways in which more specific biological features, such as gene polymorphisms, interact with parenting to predict empathy-relevant outcomes, these findings suggest that it may be more fruitful to focus research into biological/environmental interactions on more narrowly defined factors.

Fostering Healthy Empathic Development

Given decreases across development in the relative influence of the environment (as compared to genes, which show an increasing influence) on empathic development, we propose that the intraindividual and interindividual moderators outlined above likely exert their greatest influence during early childhood. Efforts to provide environmental contexts that modulate neurobiological and behavioral expressions of the genetic dysregulation liabilities so as to promote the emergence of adaptive empathic skills must therefore begin early in development.

Taken together, the evidence we have reviewed from the genetic, neurobiological, and behavioral literatures suggests that genetically-mediated liabilities for physiological hyperarousal, and negative thinking, which manifest as alterations in neural functioning, interact with environmental influences such as exposure to parent negative affect and maladaptive parenting to disrupt normal patterns of empathic development in ways that heighten risk for internalizing symptoms in a subset of individuals with strong proclivities for empathic sensitivity. This complex and dynamic interplay among numerous variables provides multiple targets for intervention and preventive efforts aimed at minimizing such risk. Further, behavioral genetic findings regarding the temporal trajectories along which genes and the environment exert their effects suggest that implementation of such efforts should begin early in life if they are to have maximal impact.

A small, but growing, literature reflects widespread interest in developing interventions that bolster healthy empathic development; notably, however, many target school-aged children, adolescents, and adults (e.g., Castillo, Fernández-Berrocal, & Balluerka, 2013; Decety & Moriguchi, 2007;   ahin, 2012; Schonert-Reichl, Smith, Zaidman-Zait, & Hertzman, 2012), who typically show benefits, but have already passed the ages at which effects of such interventions may be strongest. At least one program aimed at optimizing the development

of prosocial behavior in preschoolers via parent training in emotion socialization skills shows promise for promoting the sequelae of healthy empathy (Tuning in to Kids; Havighurst, Wilson, Harley, Prior, & Kehoe, 2010; Wilson, Havighurst, & Harley, 2012).

The "Tuning in to Kids" intervention focuses on improving parents' emotion coaching skills to enhance their children's emotion regulation capacities, and has been shown to yield significant increases in children's parent-reported empathic behavior (Havighurst et al., 2010), among other positive outcomes. In the context of our model of maladaptive empathy development, this approach targets the interindividual moderator of inadequate parenting, but does not explicitly take into account the intraindividual moderators that we enumerate in this manuscript. It will be useful to clarify in future research whether children who display genetic and physiological profiles linked to heightened risk for personal distress, interpersonal guilt, and internalizing symptoms respond distinctively to these interventions and to tailor the interventions to the strengths and weaknesses of each child and family.

It may also be helpful to improve parents' knowledge about the contexts and experiences that distress their children, as well as about the strategies and approaches that best comfort them when they are distressed (Vinik, Almas, & Grusec, 2011). Given that parent negative affect and maladaptive parenting behavior appear to play important roles in moderating the developmental trajectory for empathy, interventions focused on relieving parent depression and/or chronic stress may provide indirect benefits for offspring, particularly those genetically liable for empathic sensitivity and hyperarousal and/or negative thinking. Evidence suggests that a range of treatment approaches to parent depression, which include psychoeducation, promotion of healthy family interactions, and training in effective parenting skills, have a positive impact on broadly defined child functioning (Boyd & Gillham, 2009); specific effects on empathic development warrant research attention. It may also be useful to implement treatments designed to prevent psychological problems in the offspring of depressed parents, which have been shown both to decrease children's internalizing symptoms (Compas et al., 2011) and to increase their prosocial behavior (Solantaus, Paavonen, Toikka, & Punamäki, 2010).

Interventions aimed more broadly at decreasing cognitive and emotional dysregulation difficulties in very young children may also be useful for promoting healthy empathic development. Eisenberg, Spinrad, and Eggum (2010) describe a variety of approaches that show utility for improving self-regulation in preschool- and school-aged children and that might also help promote healthy empathy. These programs variously focus on strengthening inhibitory control and emotion identification (Riggs et al., 2006), general socio-emotional skills (Bierman et al., 2008), and providing direct instruction in emotion understanding and regulation strategies (Izard et al., 2008). More recently, Razza, Bergen-Cico, and Raymond (2013) found that a mindfulness-based yoga intervention improved behavioral self-regulation in a sample of 3 to 5 year old children. Whether the benefits of such child-focused interventions extend to include improved emotion regulation is unclear, but future research might examine the degree to which behavioral effects generalize to other aspects of regulatory function and the mechanisms (e.g., modification of brain function; Rueda, Rothbart, Saccomanno, & Posner, 2007) by which such changes occur.

Given the role that proclivity toward negative thinking can play in interactions leading to personal distress/interpersonal guilt and internalizing disorders, it may also be useful to address cognitive biases in interventions aimed at supporting healthy empathic development. Considerable research attention has focused in recent years on attentional or interpretational retraining, which involves helping individuals learn to shift attention away from threat cues or to decrease biases to evaluate ambiguous cues as negative, as an intervention for internalizing conditions, particularly anxiety disorders. Although findings are not entirely consistent (Emmelkamp, 2012), evidence from several randomized controlled trials converges to suggest that this approach may hold utility for at least subsets of anxious youths and adults (Hakamata et al., 2010). Various types of bias modification retraining have led to decreases in anxiety symptoms for both adolescents (Britton et al., 2013; Fu, Du, Au, & Lau, 2013) and school-aged children (Waters, Pittaway, Mogg, Bradley, & Pine, 2013). However, it is unclear whether bias modification programs as currently conceptualized constitute an appropriate or effective intervention for preschoolers.

Fewer data are available regarding the potential efficacy of intervention approaches that target intraindividual, rather than interindividual moderators of empathy's developmental trajectory. The results of several clinical trials, however, suggest that intranasally-administered oxytocin may help improve social cognition and emotion regulation both in individuals with internalizing conditions such as social anxiety and in those with disorders such as autism, that are characterized by empathic deficits (Guastella, Howard, Dadds, Mitchell, & Carson, 2009; Yamasue et al., 2012). Further research is needed, however, that explores the short- and long-term consequences of oxytocin administration in individuals across the lifespan, as well as optimal dosing and administration routes, before such interventions can be safely considered as tools for widespread implementation, particularly in vulnerable populations such as infants and children (Harris & Carter, 2013).

Summary and Conclusions

In this review, we proposed a model in which characteristics typically associated with resilience and mental health, such as empathic tendencies, serve, under some conditions, as "risky strengths" that magnify vulnerability for psychological disorders. According to our model, complex interactions among an array of moderating variables can increase risk for empathic personal distress and excessive interpersonal guilt in youths who show enhanced proclivities for empathic sensitivity. Personal distress and interpersonal guilt, in turn, contribute to heightened risk for fear/arousal symptoms and anhedonia/misery symptoms, respectively.

We identify a number of putative moderators, including such intraindividual characteristics as genetically-influenced propensities toward physiological hyperarousal and negative thinking processes, and interindividual characteristics, such as maladaptive parenting or chronic exposure to parents' negative affect. This list is not exhaustive; others have, for example, proposed gendered socialization patterns (e.g., pressure on girls to tend to others' needs over their own) as a likely moderating variable (Zahn-Waxler et al., 1991). However, it provides a starting point for conceptualizing the varied influences that might skew the developmental trajectory of empathy in problematic ways for children of both sexes.

Further research is needed that explores, in an integrative fashion, the ways in which these varied intraindividual and interindividual moderators interact dynamically with empathic tendencies across development to yield pathological outcomes. Most relevant studies to date have focused on individual moderators in isolation, and a shift toward simultaneous analyses of variables at multiple levels (e.g., genetic, neurobiological, and behavioral) and their impacts on empathic development would advance the field notably. In addition, longitudinal studies that examine how different moderating variables' influences wax and wane across the lifespan could provide more nuanced pictures of both ways in which empathic function develops and points at which maladaptive paths might be interrupted. By adopting a multilevel, developmentally-aware perspective, researchers can leverage a much broader array of tools and capitalize on knowledge acquired across a wide range of disciplines in the service of both clarifying how strengths such as empathic sensitivity can become points of vulnerability and helping ensure that such strengths remain assets for most youths.

Acknowledgments

References

Abela JRZ, Sarin S. Cognitive vulnerability to hopelessness depression: A chain is only as strong as its weakest link. Cognitive Therapy and Research. 2002; 26(6):811–829.

Adams GR, Schvaneveldt JD, Jenson GO. Sex, age and perceived competency as correlates of empathic ability in adolescence. Adolescence. 1979; 14(56):811–818.

Altshuler JL, Ruble DN. Developmental changes in children's awareness of strategies for coping with uncontrollable stress. Child Development. 1989; 60(6):1337–1349. [PubMed: 2612245]

Andersen SL, Tomada A, Vincow ES, Valente E, Polcari A, Teicher MH. Preliminary evidence for the sensitive periods in the effect of childhood sexual abuse on regional brain development. The Journal Of Neuropsychiatry And Clinical Neurosciences. 2008; 20(3):292–301. [PubMed: 18806232]

Anokhin AP, Golosheykin S, Heath AC. Genetic and environmental influences on emotion-modulated startle reflex: A twin study. Psychophysiology. 2007; 44(1):106–112. [PubMed: 17241146]

Antypa NN, Van der Does AW. Serotonin transporter gene, childhood emotional abuse and cognitive vulnerability to depression. Genes, Brain & Behavior. 2010; 9(6):615–620.

Apter-Levy Y, Feldman M, Vakart A, Ebstein RP, Feldman R. Impact of maternal depression across the first 6 years of life on the child's mental health, social engagement, and empathy: The moderating role of oxytocin. The American Journal Of Psychiatry. 2013; 170(10):1161–1168. [PubMed: 23846912]

Armbruster D, Moser DA, Strobel A, Hensch T, Kirschbaum C, Lesch KP, et al. Serotonin transporter gene variation and stressful life events impact processing of fear and anxiety. International Journal of Neuropsychopharmacology. 2009; 12(3):393–401. [PubMed: 18925984]

Armbruster D, Mueller A, Strobel A, Kirschbaum C, Lesch KP, Brocke B. Influence of functional tryptophan hydroxylase 2 gene variation and sex on the startle response in children, young adults, and older adults. Biological Psychology. 2010; 83(3):214–221. [PubMed: 20064585]

Atzil S, Hendler T, Zagoory-Sharon O, Winetraub Y, Feldman R. Synchrony and specificity in the maternal and the paternal brain: Relations to oxytocin and vasopressin. Journal Of The American Academy Of Child & Adolescent Psychiatry. 2012; 51(8):798–811. [PubMed: 22840551]

Bailey PE, Henry JD, Von Hippel W. Empathy and social functioning in late adulthood. Aging & Mental Health. 2008; 12(4):499–503. [PubMed: 18791898]

Bakermans-Kranenburg MJ, van Ijzendoorn MH. Oxytocin receptor (OXTR) and serotonin transporter (5-HTT) genes associated with observed parenting. Social Cognitive and Affective Neuroscience. 2008; 3(2):128–134. [PubMed: 19015103]

Bales, KL. Comparative and developmental perspectives on oxytocin and vasopressin. In: Mikulincer, M.; Shaver, PR., editors. Mechanisms of social connection: From brain to group. Washington, DC US: American Psychological Association; 2014. p. 15-31.

Bales KL, Perkeybile AM. Developmental experiences and the oxytocin receptor system. Hormones And Behavior. 2012; 61(3):313–319. [PubMed: 22245313]

Band EB, Weisz JR. How to feel better when it feels bad: Children's perspectives on coping with everyday stress. Developmental Psychology. 1988; 24(2):247–253.

Barrett J, Wonch KE, Gonzalez A, Ali N, Steiner M, Hall GB, Fleming AS. Maternal affect and quality of parenting experiences are related to amygdala response to infant faces. Social Neuroscience. 2012; 7(3):252–268. [PubMed: 21943083]

Bartz JA, Hollander E. The neuroscience of affiliation: Forging links between basic and clinical research on neuropeptides and social behavior. Hormones And Behavior. 2006; 50(4):518–528. [PubMed: 16884725]

Bartz J, Simeon D, Hamilton H, Kim S, Crystal S, Braun A, Vicens V, Hollander E. Oxytocin can hinder trust and cooperation in borderline personality disorder. Social Cognitive Affective Neuroscience. 2011; 6(5):556–563. [PubMed: 21115541]

Bartz JA, Zaki J, Bolger N, Ochsner KN. Social effects of oxytocin in humans: Context and person matter. Trends In Cognitive Sciences. 2011; 15(7):301–309. [PubMed: 21696997]

Bartz JA, Zaki J, Ochsner KN, Bolger N, Kolevzon A, Ludwig N, Lydon JE. Effects of oxytocin on recollections of maternal care and closeness. PNAS Proceedings Of The National Academy Of Sciences Of The United States Of America. 2010; 107(50):21371–21375.

Baskerville T, Douglas A. Dopamine and oxytocin interactions underlying behaviors: potential contributions to behavioral disorders. CNS Neuroscience & Therapeutics. 2010; 16(3):e92–e123. [PubMed: 20557568]

Batson, C. These things called empathy: Eight related but distinct phenomena. In: Decety, J.; Ickes, W., editors. The social neuroscience of empathy. Cambridge, MA US: MIT Press; 2009. p. 3-15.

Batson, C. Empathy-induced altruistic motivation. In: Mikulincer, M.; Shaver, PR., editors. Prosocial motives, emotions, and behavior: The better angels of our nature. Washington, DC US: American Psychological Association; 2010. p. 15-34.

Baumgartner T, Heinrichs M, Vonlanthen A, Fischbacher U, Fehr E. Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. Neuron. 2008; 58(4):639–650. [PubMed: 18498743]

Beevers CG, Wells TT, McGeary JE. The BDNF Val66Met polymorphism is associated with rumination in healthy adults. Emotion. 2009; 9(4):579–584. [PubMed: 19653783]

Belacchi C, Farina E. Feeling and Thinking of Others: Affective and Cognitive Empathy and Emotion Comprehension in Prosocial/Hostile Preschoolers. Aggressive Behavior. 2012; 38(2):150–165. [PubMed: 25363639]

Bengtsson H, Arvidsson Å. The Impact of Developing Social Perspective-taking Skills on Emotionality in Middle and Late Childhood. Social Development. 2011; 20(2):353–375.

Bierman KL, Domitrovich CE, Nix RL, Gest SD, Welsh JA, Greenberg MT, Gill S. Promoting academic and social-emotional school readiness: The Head Start REDI program. Child Development. 2008; 79(6):1802–1817. [PubMed: 19037951]

Blair RJR. Responding to the emotions of others: Dissociating forms of empathy through the study of typical and psychiatric populations. Consciousness and Cognition: An International Journal. 2005; 14(4):698–718.

Bons D, van den Broek E, Scheepers F, Herpers P, Rommelse N, Buitelaaar JK. Motor, emotional, and cognitive empathy in children and adolescents with autism spectrum disorder and conduct disorder. Journal Of Abnormal Child Psychology. 2013; 41(3):425–443. [PubMed: 23096764]

Bos PA, Terburg D, van Honk J. Testosterone decreases trust in socially naive humans. Proceedings of the National Academy of Sciences of the United States of America. 2010; 107(22):9991–9995. [PubMed: 20498056]

Boyd RC, Gillham JE. Review of interventions for parental depression from toddlerhood to adolescence. Current Psychiatry Reviews. 2009; 5(4):226–235. [PubMed: 20824114]

Bradley RH, Corwyn RF. Infant temperament, parenting, and externalizing behavior in first grade: A test of the differential susceptibility hypothesis. Journal Of Child Psychology And Psychiatry. 2008; 49(2):124–131. [PubMed: 18211274]

Britton JC, Bar-Haim Y, Clementi MA, Sankin LS, Chen G, Shechner T, Pine DS. Training-associated changes and stability of attention bias in youth: Implications for Attention Bias Modification Treatment for pediatric anxiety. Developmental Cognitive Neuroscience. 2013; 4:452–464.

Brocke B, Armbruster D, Müller J, Hensch T, Jacob CP, Lesch KP, et al. Serotonin transporter gene variation impacts innate fear processing: Acoustic startle response and emotional startle. Molecular Psychiatry. 2006; 11(12):1106–1112. [PubMed: 17033630]

Bruno S, Lutwak N, Agin MA. Conceptualizations of guilt and the corresponding relationships to emotional ambivalence, self-disclosure, loneliness and alienation. Personality And Individual Differences. 2009; 47(5):487–491.

Bryant BK. An index of empathy for children and adolescents. Child Development. 1982; 53(2):413–425.

Buchanan TW, Bagley SL, Stansfield R, Preston SD. The empathic, physiological resonance of stress. Social Neuroscience. 2012; 7(2):191–201. [PubMed: 21777106]

Carlo G, Allen JB, Buhman DC. Facilitating and disinhibiting prosocial behaviors: The nonlinear interaction of trait perspective taking and trait personal distress on volunteering. Basic and Applied Social Psychology. 1999; 21(3):189–197.

Carlson SR, Katsanis J, Iacono WG, McGue M. Emotional modulation of the startle reflex in twins: Preliminary findings. Biological Psychology. 1997; 46(3):235–246. [PubMed: 9360775]

Carmel S, Glick SM. Compassionate-empathic physicians: Personality traits and social-organizational factors that enhance or inhibit this behavior pattern. Social Science and Medicine. 1996; 43(8):1253–1262. [PubMed: 8903130]

Carr, L.; Iacoboni, M.; Dubeau, M.; Mazziotta, JC.; Lenzi, G. Neural Mechanisms of Empathy in Humans: A Relay from Neural Systems for Imitation to Limbic Areas. In: Cacioppo, JT.; Berntson, GG., editors. Social neuroscience: Key readings. New York, NY US: Psychology Press; 2005. p. 143-152.

Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, Poulton R. Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. Science. 2003 Jul 18.301:386–389. [PubMed: 12869766]

Castillo R, Salguero JM, Fernández-Berrocal P, Balluerka N. Effects of an emotional intelligence intervention on aggression and empathy among adolescents. Journal Of Adolescence. 2013; 36(5):883–892. [PubMed: 24011104]

Catherine NA, Schonert-Reichl KA. Children's perceptions and comforting strategies to infant crying: Relations to age, sex, and empathy-related responding. British Journal Of Developmental Psychology. 2011; 29(3):524–551. [PubMed: 21848745]

Chow C, Ruhl H, Buhrmester D. The mediating role of interpersonal competence between adolescents' empathy and friendship quality: A dyadic approach. Journal Of Adolescence. 2013; 36(1):191–200. [PubMed: 23176745]

Cicchetti, D.; Cohen, DJ. Perspectives on developmental psychopathology. In: Cicchetti, D.; Cohen, DJ., editors. Developmental Psychopathology: Vol. 1. Theory and methods. New York: Wiley; 1995. p. 3-20.

Cicchetti, D.; Toth, SL. A developmental psychopathology perspective on adolescent depression. In: Nolen-Hoeksema, S.; Hilt, LM., editors. Handbook of depression in adolescents. New York, NY US: Routledge/Taylor & Francis Group; 2009. p. 3-32.

Clark CL, St John N, Pasca AM, Hyde SA, Hornbeak K, Abramova M, Penn AA. Neonatal CSF oxytocin levels are associated with parent report of infant soothability and sociability. Psychoneuroendocrinology. 2013; 38(7):1208–1212. [PubMed: 23507187]

Clasen PC, Wells TT, Knopik VS, McGeary JE, Beevers CG. 5-HTTLPR and BDNF Val66Met polymorphisms moderate effects of stress on rumination. Genes, Brain & Behavior. 2011; 10(7):740–746.

Cliffordson C. The hierarchical structure of empathy: Dimensional organization and relations to social functioning. Scandinavian Journal of Psychology. 2002; 43(1):49–59. [PubMed: 11885760]

Compas BE, Forehand R, Thigpen JC, Keller G, Hardcastle EJ, Cole DA, et al. Family group cognitive–behavioral preventive intervention for families of depressed parents: 18- and 24-month outcomes. Journal of Consulting and Clinical Psychology. 2011; 79(4):488–499. [PubMed: 21707137]

Cornell AH, Frick PJ. The moderating effects of parenting styles in the association between behavioral inhibition and parent-reported guilt and empathy in preschool children. Journal Of Clinical Child And Adolescent Psychology. 2007; 36(3):305–318. [PubMed: 17658976]

Costa B, Pini S, Gabelloni P, Abelli M, Lari L, Cardini A, Martini C. Oxytocin receptor polymorphisms and adult attachment style in patients with depression. Psychoneuroendocrinology. 2009; 34(10):1506–1514. [PubMed: 19515497]

Cox CL, Uddin LQ, Di Martino A, Castellanos F, Milham MP, Kelly C. The balance between feeling and knowing: Affective and cognitive empathy are reflected in the brain's intrinsic functional dynamics. Social Cognitive And Affective Neuroscience. 2012; 7(6):727–737. [PubMed: 21896497]

Cramer D, Jowett S. Perceived empathy, accurate empathy and relationship satisfaction in heterosexual couples. Journal Of Social And Personal Relationships. 2010; 27(3):327–349.

Cuthbert BN, Lang PJ, Strauss C, Drobes D, Patrick CJ, Bradley MM. The psychophysiology of anxiety disorder: Fear memory imagery. Psychophysiology. 2003; 40(3):407–422. [PubMed: 12946114]

Davis MH. Measuring individual differences in empathy: Evidence for a multidimensional approach. Journal of Personality and Social Psychology. 1983; 44(1):113–126.

Davis MH, Franzoi SL. Stability and change in adolescent self-consciousness and empathy. Journal Of Research In Personality. 1991; 25(1):70–87.

Davis MH, Luce C, Kraus SJ. The heritability of characteristics associated with dispositional empathy. Journal of Personality. 1994; 62(3):369–391. [PubMed: 7965564]

de Vignemont F, Singer T. The empathic brain: How, when and why? Trends In Cognitive Sciences. 2006; 10(10):435–441. [PubMed: 16949331]

Decety, J. A social cognitive neuroscience model of human empathy. In: Harmon-Jones, E.; Winkielman, P., editors. Social neuroscience: Integrating biological and psychological explanations of social behavior. New York, NY US: Guilford Press; 2007. p. 246-270.

Decety J. The neurodevelopment of empathy in humans. Developmental Neuroscience. 2010; 32(4): 257–267. [PubMed: 20805682]

Decety J. Dissecting the neural mechanisms mediating empathy. Emotion Review. 2011; 3(1):92–108.

Decety J, Jackson PL. The Functional Architecture of Human Empathy. Behavioral and Cognitive Neuroscience Reviews. 2004; 3(2):406–412.

Decety J, Michalska KJ. Neurodevelopmental changes in the circuits underlying empathy and sympathy from childhood to adulthood. Developmental Science. 2010; 13:886–899. [PubMed: 20977559]

Decety J, Moriguchi Y. The empathic brain and its dysfunction in psychiatric populations: Implications for intervention across different clinical conditions. Biopsychosocial Medicine. 2007; 1

Diamond LM, Fagundes CP, Butterworth MR. Attachment style, vagal tone, and empathy during mother–adolescent interactions. Journal of Research on Adolescence. 2012; 22(1):165–184.

Diego, MA.; Jones, NA. Neonatal antecedents for empathy. In: Farrow, T.; Woodruff, P., editors. Empathy in mental illness. New York, NY US: Cambridge University Press; 2007. p. 145-167.

Donatelli JA, Bybee JA, Buka SL. What do mothers make adolescents feel guilty about? Incidents, reactions, and relation to depression. Journal of Child and Family Studies. 2007; 16:859–875.

Dondi M, Simion F, Caltran G. Can newborns discriminate between their own cry and the cry of another newborn infant? Developmental Psychology. 1999; 35(2):418–426. [PubMed: 10082012]

Ebstein, RP.; Israel, S.; Lerer, E.; Uzefovsky, F.; Shalev, I.; Gritsenko, I., et al. Arginine vasopressin and oxytocin modulate human social behavior. In: Vilarroya, O.; Altran, S.; Navarro, A.; Ochsner,

K.; Tobeña, A., editors. Values, empathy, and fairness across social barriers. Vol. 1167. New York, NY US: New York Academy of Sciences; 2009. p. 87-102.

Ebstein RP, Knafo A, Mankuta D, Chew S, Lai P. The contributions of oxytocin and vasopressin pathway genes to human behavior. Hormones And Behavior. 2012; 61(3):359–379. [PubMed: 22245314]

Ehringer MA, Rhee S, Young S, Corley R, Hewitt JK. Genetic and Environmental Contributions to Common Psychopathologies of Childhood and Adolescence: A Study of Twins and Their Siblings. Journal Of Abnormal Child Psychology: An Official Publication Of The International Society For Research In Child And Adolescent Psychopathology. 2006; 34(1):1–17.

Eisenberg, N. Empathy and sympathy. In: Damon, W., editor. Child development today and tomorrow. San Francisco, CA US: Jossey-Bass; 1989. p. 137-154.

Eisenberg, N. Empathy-related responding: Links with self-regulation, moral judgment, and moral behavior. In: Mikulincer, M.; Shaver, PR., editors. Prosocial motives, emotions, and behavior: The better angels of our nature. Washington, DC US: American Psychological Association; 2010. p. 129-148.

Eisenberg N, Carlo G, Murphy B, Van Court P. Prosocial development in late adolescence: A longitudinal study. Child Development. 1995; 66(4):1179–1197. [PubMed: 7671655]

Eisenberg N, Cumberland A, Guthrie IK, Murphy BC, Shepard SA. Age Changes in Prosocial Responding and Moral Reasoning in Adolescence and Early Adulthood. Journal Of Research On Adolescence. 2005; 15(3):235–260. [PubMed: 20592955]

Eisenberg N, Fabes RA, Murphy B, Karbon M, Smith M, Maszk P. The relations of children's dispositional empathy-related responding to their emotionality, regulation, and social functioning. Developmental Psychology. 1996; 32(2):195–209.

Eisenberg, N.; Fabes, RA.; Spinrad, TL. Prosocial Development. In: Eisenberg, N.; Damon, W.; Lerner, RM., editors. Handbook of child psychology: Vol. 3, Social, emotional, and personality development (6th ed.). Hoboken, NJ US: John Wiley & Sons Inc; 2006. p. 646-718.

Eisenberg N, Miller PA. The relation of empathy to prosocial and related behaviors. Psychological Bulletin. 1987; 101:91–119. [PubMed: 3562705]

Eisenberg N, Spinrad TL, Eggum ND. Emotion-related self-regulation and its relation to children's maladjustment. Annual Review of Clinical Psychology. 2010; 6:495–525.

Eley TC, Gregory AM, Clark DM, Ehlers A. Feeling anxious: A twin study of panic/somatic ratings, anxiety sensitivity and heartbeat perception in children. Journal Of Child Psychology And Psychiatry. 2007; 48(12):1184–1191. [PubMed: 18093023]

Emmelkamp PMG. Attention bias modification: the Emperor's new suit? BMC Medicine. 2012; 10(63)

Empathy. Merriam-Webster.com. 2013. Retrieved October 4, 2013, from http://www.merriam-webster.com/dictionary/empathy

Everaert J, Koster EHW, Derakshan N. The combined cognitive bias hypothesis in depression. Clinical Psychology Review. 2012; 32(5):413–424. [PubMed: 22681914]

Farrant BM, Devine TJ, Maybery MT, Fletcher J. Empathy, perspective taking and prosocial behaviour: The importance of parenting practices. Infant And Child Development. 2012; 21(2):175–188.

Feldman R. Parent–Infant Synchrony: Biological Foundations and Developmental Outcomes. Current Directions In Psychological Science (Wiley-Blackwell). 2007; 16(6):340–345.

Ferguson FJ, Austin EJ. Associations of trait and ability emotional intelligence with performance on Theory of Mind tasks in an adult sample. Personality and Individual Differences. 2010; 49(5):414–418.

Feshbach ND, Roe K. Empathy in six- and seven-year-olds. Child Development. 1968; 39(1):133. [PubMed: 5645790]

Field TM, Woodson R, Greenberg R, Cohen D. Discrimination and imitation of facial expressions by neonates. Annual Progress In Child Psychiatry & Child Development. 1983:119–125.

Fox E, Zougkou K, Ridgewell A, Garner K. The serotonin transporter gene alters sensitivity to attention bias modification: Evidence for a plasticity gene. Biological Psychiatry. 2011; 70(11):1049–1054. [PubMed: 21840502]

Fu X, Du Y, Au S, Lau JF. Reducing negative interpretations in adolescents with anxiety disorders: A preliminary study investigating the effects of a single session of cognitive bias modification training. Developmental Cognitive Neuroscience. 2013:429–37.

Gabor CS, Phan A, Clipperton-Allen AE, Kavaliers M, Choleris E. Interplay of oxytocin, vasopressin, and sex hormones in the regulation of social recognition. Behavioral Neuroscience. 2012; 126(1): 97–109. [PubMed: 22141469]

Garcia SE, Tully EC, Tarantino N, South S, Iacono WG, McGue M. Changes in genetic and environmental influences on trait anxiety from middle adolescence to early adulthood. Journal Of Affective Disorders. 2013; 151(1):46–53. [PubMed: 23768528]

Geangu E, Hauf P, Bhardwaj R, Bentz W. Infant pupil diameter changes in response to others' positive and negative emotions. Plos ONE. 2011; 6(11)

Gibb BE, Benas JS, Grassia M, McGeary J. Children's attentional biases and 5-HTTLPR genotype: Potential mechanisms linking mother and child depression. Journal Of Clinical Child And Adolescent Psychology. 2009; 38(3):415–426. [PubMed: 19437301]

Gleason KA, Jensen-Campbell LA, Ickes W. The role of empathic accuracy in adolescents' peer relations and adjustment. Personality and Social Psychology Bulletin. 2009; 35(8):997–1011. [PubMed: 19498068]

Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, Nugent TF III, Herman DH, Clasen LS, Toga AW, et al. Dynamic mapping of human cortical development during childhood through early adulthood. Proceedings of the National Academy of Sciences of the United States of America. 2004; 101:8174–8179. [PubMed: 15148381]

Goodman SH, Rouse MH, Connell AM, Broth M, Hall CM, Heyward D. Maternal depression and child psychopathology: A meta-analytic review. Clinical Child And Family Psychology Review. 2011; 14(1):1–27. [PubMed: 21052833]

Gotlib IH, Joormann J. Cognition and depression: Current status and future directions. Annual Review of Clinical Psychology. 2010; 6:285–312.

Gray, PB.; Campbell, BC. Human male testosterone, pair-bonding, and fatherhood. In: Ellison, PT.; Gray, PB., editors. Endocrinology of social relationships. Cambridge, MA US: Harvard University Press; 2009. p. 270-293.

Groen YY, Wijers AA, Tucha OO, Althaus MM. Are there sex differences in ERPs related to processing empathy-evoking pictures? Neuropsychologia. 2013; 51(1):142–155. [PubMed: 23174404]

Grossmann T. Mapping prefrontal cortex functions in human infancy. Infancy. 2013; 18(3):303–324.

Grühn D, Rebucal K, Diehl M, Lumley M, Labouvie-Vief G. Empathy across the adult lifespan: Longitudinal and experience-sampling findings. Emotion. 2008; 8(6):753–765. [PubMed: 19102586]

Guastella AJ, Howard AL, Dadds MR, Mitchell P, Carson DS. A randomized controlled trial of intranasal oxytocin as an adjunct to exposure therapy for social anxiety disorder. Psychoneuroendocrinology. 2009; 34(6):917–923. [PubMed: 19246160]

Hakamata Y, Lissek S, Bar-Haim Y, Britton JC, Fox NA, Leibenluft E, Pine DS. Attention Bias Modification Treatment: A meta-analysis toward the establishment of novel treatment for anxiety. Biological Psychiatry. 2010; 68(11):982–990. [PubMed: 20887977]

Harold GT, Rice FF, Hay DF, Boivin JJ, van den Bree MM, Thapar AA. Familial transmission of depression and antisocial behavior symptoms: Disentangling the contribution of inherited and environmental factors and testing the mediating role of parenting. Psychological Medicine: A Journal Of Research In Psychiatry And The Allied Sciences. 2011; 41(6):1175–1185.

Harris JC, Carter C. Therapeutic interventions with oxytocin: Current status and concerns. Journal Of The American Academy Of Child & Adolescent Psychiatry. 2013; 52(10):998–1000. [PubMed: 24074464]

Hastings PD, Zahn-Waxler C, Robinson J, Usher B, Bridges D. The development of concern for others in children with behavior problems. Developmental Psychology. 2000; 36(5):531–546. [PubMed: 10976595]

Havighurst, SS.; Harley, A. Tuning in to Kids: Emotionally intelligent parenting program manual. Melbourne, Australia: University of Melbourne; 2007.

Havighurst SS, Wilson KR, Harley AE, Prior MR, Kehoe C. Tuning in to kids: Improving emotion socialization practices in parents of preschool children-findings from a community trial. Journal Of Child Psychology And Psychiatry. 2010; 51(12):1342–1350. [PubMed: 20735794]

Hay DF, Nash A, Pedersen J. Responses of six-month-olds to the distress of their peers. Child Development. 1981; 52(3):1071–1075. [PubMed: 7285646]

Helson R, Jones C, Kwan VSY. Personality change over 40 years of adulthood: Hierarchical linear modeling analyses of two longitudinal samples. Journal of Personality and Social Psychology. 2002; 83:752–766. [PubMed: 12219867]

Herting MM, Maxwell EC, Irvine C, Nagel BJ. The impact of sex, puberty, and hormones on white matter microstructure in adolescents. Cerebral Cortex. 2012; 22(9):1979–1992. [PubMed: 22002939]

Hoffman, ML. Interaction of affect and cognition in empathy. In: Izard, CE.; Kagan, J.; Zajonc, RB., editors. Emotions, cognition, and behavior. New York, NY US: Cambridge University Press; 1985. p. 103-131.

Hoffman, ML. Empathy and moral development: Implications for caring and justice. New York, NY US: Cambridge University Press; 2000.

Hofmann SG, Moscovitch DA, Kim H. Autonomic correlates of social anxiety and embarrassment in shy and non-shy individuals. International Journal Of Psychophysiology. 2006; 61(2):134–142. [PubMed: 16288811]

Hutman T, Rozga A, DeLaurentis A, Sigman M, Dapretto M. Infants' pre-empathic behaviors are associated with language skills. Infant Behavior & Development. 2012; 35(3):561–569. [PubMed: 22728336]

Ishak WW, Kahloon M, Fakhry H. Oxytocin role in enhancing well-being: a literature review. Journal of Affective Disorders. 2011; 130(1–2):1–9. [PubMed: 20584551]

Ickes W, Stinson L, Bissonnette V, Garcia S. Naturalistic social cognition: Empathic accuracy in mixed-sex dyads. Journal of Personality and Social Psychology. 1990; 59(4):730–742.

Johnson JA, Cheek JM, Smither R. The structure of empathy. Journal of Personality and Social Psychology. 1983; 45(6):1299–1312.

Jones AP, Happé FGE, Gilbert F, Burnett S, Viding E. Feeling, caring, knowing: Different types of empathy deficit in boys with psychopathic tendencies and autism spectrum disorder. Journal of Child Psychology and Psychiatry. 2010; 51(11):1188–1197. [PubMed: 20633070]

Kalani MY, Kalani MA, Gwinn R, Keogh B, Tse VC. Embryological development of the human insula and its implications for the spread and resection of insular gliomas. Neurosurgical Focus. 2009; 27(2):E2. [PubMed: 19645558]

Kanat-Maymon M, Assor A. Perceived maternal control and responsiveness to distress as predictors of young adults' empathic responses. Personality And Social Psychology Bulletin. 2010; 36(1):33–46. [PubMed: 19820178]

Karniol R, Gabay R, Ochion Y, Harari Y. Is gender or gender-role orientation a better predictor of empathy in adolescence? Sex Roles. 1998; 39:45–59.

Katz SJ, Hammen CL, Brennan PA. Maternal depression and the intergenerational transmission of relational impairment. Journal Of Family Psychology. 2013; 27(1):86–95. [PubMed: 23421836]

Kendler KS, Prescott CA, Myers J, Neale MC. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. Archives Of General Psychiatry. 2003; 60(9):929–937. [PubMed: 12963675]

Kerr DR, Leve LD, Harold GT, Natsuaki MN, Neiderhiser JM, Shaw DS, Reiss D. Influences of biological and adoptive mothers' depression and antisocial behavior on adoptees' early behavior trajectories. Journal Of Abnormal Child Psychology. 2013; 41(5):723–734. [PubMed: 23408036]

Kessler RC, Chiu W, Demler O, Walters EE. Prevalence, Severity, and Comorbidity of 12-Month DSM-IV Disorders in the National Comorbidity Survey Replication. Archives Of General Psychiatry. 2005; 62(6):617–627. [PubMed: 15939839]

Kestenbaum R, Farber EA, Sroufe L. Individual differences in empathy among preschoolers: Relation to attachment history. New Directions For Child Development. 1989:4451–64.

Kiff CJ, Lengua LJ, Bush NR. Temperament variation in sensitivity to parenting: Predicting changes in depression and anxiety. Journal Of Abnormal Child Psychology: An Official Publication Of

The International Society For Research In Child And Adolescent Psychopathology. 2011; 39(8): 1199–1212.

Kindt M, Van Den Hout M. Selective attention and anxiety: A perspective on developmental issues and the causal status. Journal Of Psychopathology And Behavioral Assessment. 2001; 23(3): 193–202.

Kirsch P, Esslinger C, Chen Q, Mier D, Lis S, Siddhanti S, et al. Oxytocin modulates neural circuitry for social cognition and fear in humans. The Journal Of Neuroscience: The Official Journal Of The Society For Neuroscience. 2005; 25(49):11489–11493. [PubMed: 16339042]

Klapwijk ET, Goddings A, Heyes S, Bird G, Viner RM, Blakemore S. Increased functional connectivity with puberty in the mentalising network involved in social emotion processing. Hormones And Behavior. 2013; 64(2):314–322. [PubMed: 23998674]

Klimecki, O.; Singer, T. Empathic distress fatigue rather than compassion fatigue? Integrating findings from empathy research in psychology and social neuroscience. In: Oakley, B.; Knafo, A.; Madhavan, G.; Wilson, D., editors. Pathological altruism. New York, NY US: Oxford University Press; 2012. p. 368-383.

Klimecki, O.; Singer, T. Empathy from the perspective of social neuroscience. In: Armony, J.; Vuilleumier, P., editors. The Cambridge handbook of human affective neuroscience. New York, NY US: Cambridge University Press; 2013. p. 533-549.

Knafo A, Israel S, Ebstein RP. Heritability of children's prosocial behavior and differential susceptibility to parenting by variation in the dopamine receptor D4 gene. Development And Psychopathology. 2011; 23(1):53–67. [PubMed: 21262039]

Knafo, A.; Uzefovsky, F. Variation in empathy: The interplay of genetic and environmental factors. In: Legerstee, M.; Haley, DW.; Bornstein, MH., editors. The infant mind: Origins of the social brain. New York, NY US: Guilford Press; 2013. p. 97-120.

Knafo, A.; Zahn-Waxler, C.; Davidov, M.; Hulle, CV.; Robinson, JL.; Rhee, SH. Empathy in early childhood: Genetic, environmental, and affective contributions. In: Vilarroya, O.; Altran, S.; Navarro, A.; Ochsner, K.; Tobeña, A., editors. Values, empathy, and fairness across social barriers. New York, NY US: New York Academy of Sciences; 2009. p. 103-114.

Knafo A, Zahn-Waxler C, Van Hulle C, Robinson JL, Rhee SH. The developmental origins of a disposition toward empathy: Genetic and environmental contributions. Emotion. 2008; 8(6):737–752. [PubMed: 19102585]

Konrath SH, O'Brien EH, Hsing C. Changes in dispositional empathy in American college students over time: A meta-analysis. Personality And Social Psychology Review. 2011; 15(2):180–198. [PubMed: 20688954]

Kosfeld M, Heinrichs M, Zak PJ, Fischbacher U, Fehr E. Oxytocin increases trust in humans. Nature. 2005; 435(7042):673–676. [PubMed: 15931222]

Krueger F, Parasuraman R, Iyengar V, Thornburg M, Weel J, Lin M, et al. Oxytocin receptor genetic variation promotes human trust behavior. Frontiers in Human Neuroscience. 2012; 6

Krueger RF, Markon KE. Understanding Psychopathology: Melding Behavior Genetics, Personality, and Quantitative Psychology to Develop an Empirically Based Model. Current Directions In Psychological Science. 2006; 15(3):113–117. [PubMed: 18392116]

Lackner CL, Bowman LC, Sabbagh MA. Dopaminergic functioning and preschoolers' theory of mind. Neuropsychologia. 2010; 48(6):1767–1774. [PubMed: 20206642]

Lackner C, Sabbagh MA, Hallinan E, Liu X, Holden JA. Dopamine receptor D4 gene variation predicts preschoolers' developing theory of mind. Developmental Science. 2012; 15(2):272–280. [PubMed: 22356182]

Ladouceur CD. Neural systems supporting cognitive-affective interactions in adolescence: The role of puberty and implications for affective disorders. Frontiers In Integrative Neuroscience. 2012:6. [PubMed: 22375106]

Lamm C, Decety J, Singer T. Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. Neuroimage. 2011; 54(3):2492–2502. [PubMed: 20946964]

Lamm C, Singer T. The role of anterior insular cortex in social emotions. Brain Structure & Function. 2010; 214(5–6):579–591. [PubMed: 20428887]

Larson CL, Nitschke JB, Davidson RJ. Common and distinct patterns of affective response in dimensions of anxiety and depression. Emotion. 2007; 7(1):182–191. [PubMed: 17352573]

Lau JF, Rijsdijk F, Eley TC. I think, therefore I am: A twin study of attributional style in adolescents. Journal Of Child Psychology And Psychiatry. 2006; 47(7):696–703. [PubMed: 16790004]

Laurent HK, Ablow JC. A face a mother could love: Depression-related maternal neural responses to infant emotion faces. Social Neuroscience. 2013; 8(3):228–239. [PubMed: 23330663]

Lazary J, Juhasz G, Anderson IM, Jacob CP, Nguyen T, Lesch K, Bagdy G. Epistatic interaction of CREB1 and KCNJ6 on rumination and negative emotionality. European Neuropsychopharmacology. 2011; 21(1):63–70. [PubMed: 20943350]

Lonsdorf TB, Weike AI, Nikamo P, Schalling M, Hamm AO, Ohman A. Genetic gating of human fear learning and extinction. Psychological Science. 2009; 20:198–206. [PubMed: 19175757]

Losoya S, Eisenberg N, Fabes RA. Developmental issues in the study of coping. International Journal Of Behavioral Development. 1998; 22(2):287–313.

Martin-Soelch C, Stöcklin M, Dammann G, Opwis K, Seifritz E. Anxiety trait modulates psychophysiological reactions, but not habituation processes related to affective auditory stimuli. International Journal Of Psychophysiology. 2006; 61(2):87–97. [PubMed: 16135389]

Mathews A, MacLeod C. Cognitive Vulnerability To Emotional Disorders. Annual Review of Clinical Psychology. 2005; 1(1):167–195.

McGrath LM, Weill S, Robinson EB, MacRae R, Smoller JW. Bringing a developmental perspective to anxiety genetics. Development And Psychopathology. 2012; 24(4):1179–1193. [PubMed: 23062290]

McGrath MP, Zook JM. Maternal control of girls versus boys: Relations to empathy and persuasive style with peers. Journal Of Child And Family Studies. 2011; 20(1):57–65.

Merrill KA, Steinmetz JE, Viken RJ, Rose RJ. Genetic influences on human conditionability: A twin study of the conditioned eyeblink response. Behavior Genetics. 1999; 29(2):95–102. [PubMed: 10405458]

Mestre M, Samper P, Frías M, Tur A. Are women more empathetic than men? A longitudinal study in adolescence. The Spanish Journal Of Psychology. 2009; 12(1):76–83. [PubMed: 19476221]

Meyer-Lindenberg A, Domes G, Kirsch P, Heinrichs M. Oxytocin and vasopressin in the human brain: Social neuropeptides for translational medicine. Nature Reviews Neuroscience. 2011; 12(9):524–538.

Meyer-Lindenberg A, Kolachana B, Gold B, Olsh A, Nicodemus KK, Mattay V, et al. Genetic variants in AVPR1A linked to autism predict amygdala activation and personality traits in healthy humans. Molecular Psychiatry. 2009; 14(10):968–975. [PubMed: 18490926]

Michalska KJ, Kinzler KD, Decety J. Age-related sex differences in explicit measures of empathy do not predict brain responses across childhood and adolescence. Developmental Cognitive Neuroscience. 2013; 3(1):22–32. [PubMed: 23245217]

Miklikowska M, Duriez B, Soenens B. Family roots of empathy-related characteristics: The role of perceived maternal and paternal need support in adolescence. Developmental Psychology. 2011; 47(5):1342–1352. [PubMed: 21767014]

Miller PA, Eisenberg N. The relation of empathy to aggressive and externalizing/antisocial behavior. Psychological Bulletin. 1988; 103(3):324–344. [PubMed: 3289071]

Miller RR, Wankerl MM, Stalder TT, Kirschbaum CC, Alexander NN. The serotonin transporter gene-linked polymorphic region (5-HTTLPR) and cortisol stress reactivity: A meta-analysis. Molecular Psychiatry. 2013; 18(9):1018–1024. [PubMed: 22945032]

Mobbs D, Marchant JL, Hassabis D, Seymour B, Tan G, Gray M, Frith CD. From threat to fear: The neural organization of defensive fear systems in humans. The Journal Of Neuroscience. 2009; 29(39):12236–12243. [PubMed: 19793982]

Mooradian TA, Davis M, Matzler K. Dispositional empathy and the hierarchical structure of personality. The American Journal of Psychology. 2011; 124(1):99–109. [PubMed: 21506454]

Muftuler L, Davis E, Buss C, Head K, Hasso AN, Sandman CA. Cortical and subcortical changes in typically developing preadolescent children. Brain Research. 2011; 1399:15–24. [PubMed: 21640983]

Muscatell KA, Eisenberger NI. A social neuroscience perspective on stress and health. Social And Personality Psychology Compass. 2012; 6(12):890–904. [PubMed: 23227112]

Nelson EE, Guyer AE. The development of the ventral prefrontal cortex and social flexibility. Developmental Cognitive Neuroscience. 2011; 1(3):233–245. [PubMed: 21804907]

Neumann ID. Involvement of the brain oxytocin system in stress coping: Interactions with the hypothalamo-pituitary-adrenal axis. Progress in Brain Research. 2002; 139:147–162. [PubMed: 12436933]

Oakley, B.; Knafo, A.; McGrath, M. Pathological altruism—An introduction. In: Oakley, B.; Knafo, A.; Madhavan, G.; Wilson, DS., editors. Pathological altruism. New York, NY US: Oxford University Press; 2012. p. 3-9.

O'Brien E, Konrath SH, Grühn D, Hagen A. Empathic concern and perspective taking: Linear and quadratic effects of age across the adult life span. The Journals Of Gerontology: Series B: Psychological Sciences And Social Sciences. 2013; 68B(2):168–175.

O'Connor, LE.; Berry, JW.; Lewis, T.; Mulherin, K.; Crisostomo, PS. Empathy and depression: The moral system on overdrive. In: Farrow, T.; Woodruff, P., editors. Empathy in mental illness. New York, NY US: Cambridge University Press; 2007. p. 49-75.

O'Connor, LE.; Berry, JW.; Lewis, TB.; Stiver, DJ. Empathy-based pathogenic guilt, pathological altruism, and psychopathology. In: Oakley, B.; Knafo, A.; Madhavan, G.; Wilson, D., editors. Pathological altruism. New York, NY US: Oxford University Press; 2012. p. 10-30.

O'Connor LE, Berry JW, Weiss J. Interpersonal guilt, shame, and psychological problems. Journal Of Social And Clinical Psychology. 1999; 18(2):181–203.

O'Connor LE, Berry JW, Weiss J, Gilbert P. Guilt, fear, submission, and empathy in depression. Journal of Affective Disorders. 2002; 71(1–3):19–27. [PubMed: 12167497]

Ollendick TH, Hirshfeld-Becker DR. The developmental psychopathology of social anxiety disorder. Biological Psychiatry. 2002; 51(1):44–58. [PubMed: 11801230]

Olweus D, Endresen IM. The Importance of Sex-of-Stimulus Object: Age Trends and Sex Differences in Empathic Responsiveness. Social Development. 1998; 7(3):370–388.

Out D, Pieper S, Bakermans-Kranenburg MJ, van IJzendoorn MH. Physiological reactivity to infant crying: A behavioral genetic study. Genes Brain and Behavior. 2010; 9:868–876.

Owen SF, Tuncdemir SN, Bader PL, Tirko NN, Fishell G, Tsien RW. Oxytocin enhances hippocampal spike transmission by modulating fast-spiking interneurons. Nature. 2013; 500(7463):458–462. [PubMed: 23913275]

Pergamin-Hight L, Bakermans-Kranenburg MJ, van IJzendoorn MH, Bar-Haim Y. Variations in the promoter region of the serotonin transporter gene and biased attention for emotional information: A meta-analysis. Biological Psychiatry. 2012; 71(4):373–379. [PubMed: 22138391]

Phelps, EA. The human amygdala and the control of fear. In: Whalen, PJ.; Phelps, EA., editors. The human amygdala. New York, NY US: Guilford Press; 2009. p. 204-219.

Pine DS. Research review: A neuroscience framework for pediatric anxiety disorders. Journal Of Child Psychology And Psychiatry. 2007; 48(7):631–648. [PubMed: 17593144]

Preston SD, de Waal FM. Empathy: Its ultimate and proximate bases. Behavioral And Brain Sciences. 2002; 25(1):1–20. [PubMed: 12625087]

Radke-Yarrow M, Zahn-Waxler C, Richardson DT, Susman A. Caring behavior in children of clinically depressed and well mothers. Child Development. 1994; 65(5):1405–1414. [PubMed: 7982358]

Rakow A, Forehand R, McKee L, Coffelt N, Champion J, Fear J, Compas B. The relation of parental guilt induction to child internalizing problems when a caregiver has a history of depression. Journal Of Child And Family Studies. 2009; 18(4):367–377. [PubMed: 20090863]

Razza RA, Bergen-Cico D, Raymond K. Enhancing preschoolers' self-regulation via mindful yoga. Journal Of Child And Family Studies. 2013

Rhee S, Boeldt DL, Friedman NP, Corley RP, Hewitt JK, Young SE, Zahn-Waxler C. The role of language in concern and disregard for others in the first years of life. Developmental Psychology. 2013; 49(2):197–214. [PubMed: 22545842]

Rice JA, Levine LJ, Pizarro DA. 'Just stop thinking about it': Effects of emotional disengagement on children's memory for educational material. Emotion. 2007; 7(4):812–823. [PubMed: 18039051]

Riem ME, Bakermans-Kranenburg MJ, Pieper S, Tops M, Boksem MS, Vermeiren RM, Rombouts SB. Oxytocin modulates amygdala, insula, and inferior frontal gyrus responses to infant crying: A randomized controlled trial. Biological Psychiatry. 2011; 70(3):291–297. [PubMed: 21470595]

Riem ME, van IJzendoorn MH, Tops M, Boksem MS, Rombouts SB, Bakermans-Kranenburg MJ. No laughing matter: Intranasal oxytocin administration changes functional brain connectivity during exposure to infant laughter. Neuropsychopharmacology. 2012; 37(5):1257–1266. [PubMed: 22189289]

Riggs NR, Greenberg MT, Kusché CA, Pentz M. The Mediational Role of Neurocognition in the Behavioral Outcomes of a Social-Emotional Prevention Program in Elementary School Students: Effects of the PATHS Curriculum. Prevention Science. 2006; 7(1):91–102. [PubMed: 16572300]

Rilling JK, DeMarco AC, Hackett PD, Thompson R, Ditzen B, Patel R, Pagnoni G. Effects of intranasal oxytocin and vasopressin on cooperative behavior and associated brain activity in men. Psychoneuroendocrinology. 2012; 37(4):447–461. [PubMed: 21840129]

Robinson JL, Zahn-Waxler C, Emde RN. Patterns of development in early empathic behavior: Environmental and child constitutional influences. Social Development. 1994; 3(2):125–145.

Rodrigues SM, Saslow LR, Garcia N, John OP, Keltner D. Oxytocin receptor genetic variation relates to empathy and stress reactivity in humans. PNAS Proceedings of the National Academy of Sciences of the United States of America. 2009; 106(50):21437–21441.

Romeo RD. The teenage brain: The stress response and the adolescent brain. Current Directions In Psychological Science. 2013; 22(2):140–145. [PubMed: 25541572]

Rueda, MR.; Rothbart, MK.; Saccomanno, L.; Posner, MI. Modifying brain networks underlying self-regulation. In: Romer, D.; Walker, EF., editors. Adolescent psychopathology and the developing brain: Integrating brain and prevention science. New York, NY US: Oxford University Press; 2007. p. 401-419.

ahin M. An investigation into the efficiency of empathy training program on preventing bullying in primary schools. Children And Youth Services Review. 2012; 34(7):1325–1330.

Schiller D, Levy I, Niv Y, LeDoux JE, Phelps EA. From fear to safety and back: Reversal of fear in the human brain. The Journal Of Neuroscience. 2008; 28(45):11517–11525. [PubMed: 18987188]

Schipper M, Petermann F. Relating empathy and emotion regulation: Do deficits in empathy trigger emotion dysregulation? Social Neuroscience. 2013; 8(1):101–107. [PubMed: 23327297]

Schnell K, Bluschke S, Konradt B, Walter H. Functional relations of empathy and mentalizing: An fMRI study on the neural basis of cognitive empathy. Neuroimage. 2011; 54(2):1743–1754. [PubMed: 20728556]

Schonert-Reichl KA, Smith V, Zaidman-Zait A, Hertzman C. Promoting children's prosocial behaviors in school: Impact of the 'Roots of Empathy' program on the social and emotional competence of school-aged children. School Mental Health. 2012; 4(1):1–21.

Schreiter S, Pijnenborg GHM, aan het Rot M. Empathy in adults with clinical or subclinical depressive symptoms. Journal of Affective Disorders. 2013

Schulte-Rüther M, Markowitsch HJ, Shah N, Fink GR, Piefke M. Gender differences in brain networks supporting empathy. Neuroimage. 2008; 42(1):393–403. [PubMed: 18514546]

Schwartz JAJ, Kaslow NJ, Seeley J, Lewinsohn P. Psychological, cognitive, and interpersonal correlates of attributional change in adolescents. Journal of Clinical Child Psychology. 2000; 29(2):188–198. [PubMed: 10802828]

Shamay-Tsoory SG. The neural bases for empathy. The Neuroscientist. 2011; 17(1):18–24. [PubMed: 21071616]

Shamay-Tsoory SG, Aharon-Peretz J, Perry D. Two systems for empathy: A double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions. Brain: A Journal of Neurology. 2009; 132(3):617–627. [PubMed: 18971202]

Shamay-Tsoory SG, Tomer RR, Goldsher DD, Berger BD, Aharon-Peretz JJ. Impairment in Cognitive and Affective Empathy in Patients with Brain Lesions: Anatomical and Cognitive Correlates. Journal Of Clinical And Experimental Neuropsychology. 2004; 26(8):1113–1127. [PubMed: 15590464]

Shaw P, Kabani NJ, Lerch JP, Eckstrand K, Lenroot R, Gogtay N, Wise SP. Neurodevelopmental trajectories of the human cerebral cortex. The Journal Of Neuroscience. 2008; 28(14):3586–3594. [PubMed: 18385317]

Shikishima C, Hiraishi K, Yamagata S, Ando J. Factors affecting the formation of empathy: A gene-environment interaction model. The Japanese Journal Of Social Psychology. 2011; 26(3):188–201.

Shiner RL, Masten AS. Childhood personality as a harbinger of competence and resilience in adulthood. Development And Psychopathology. 2012; 24(2):507–528. [PubMed: 22559127]

Singer T, Snozzi R, Bird G, Petrovic P, Silani G, Heinrichs M, Dolan RJ. Effects of oxytocin and prosocial behavior on brain responses to direct and vicariously experienced pain. Emotion. 2008; 8(6):781–791. [PubMed: 19102589]

Smith RL, Rose AJ. The "cost of caring" in youths' friendships: Considering associations among social perspective taking, co-rumination, and empathetic distress. Developmental Psychology. 2011; 47(6):1792–1803. [PubMed: 21895362]

Sodian B. Theory of mind in infancy. Child Development Perspectives. 2011; 5(1):39–43.

Soenens B, Duriez B, Vansteenkiste M, Goossens L. The Intergenerational Transmission of Empathy-Related Responding in Adolescence: The Role of Maternal Support. Personality And Social Psychology Bulletin. 2007; 33(3):299–311. [PubMed: 17312313]

Solantaus T, Paavonen EJ, Toikka S, Punamäki RL. Preventive interventions in families with parental depression: Children's psychosocial symptoms and prosocial behaviour. European Child & Adolescent Psychiatry. 2010; 19(12):883–892. [PubMed: 20890622]

Spinrad TL, Stifter CA. Toddlers' Empathy-Related Responding to Distress: Predictions From Negative Emotionality and Maternal Behavior in Infancy. Infancy. 2006; 10(2):97–121.

Strayer J. A naturalistic study of empathic behaviors and their relation to affective states and perspective-taking skills in preschool children. Child Development. 1980; 51(3):815–822.

Sze JA, Gyurak A, Goodkind MS, Levenson RW. Greater emotional empathy and prosocial behavior in late life. Emotion. 2012; 12(5):1129–1140. [PubMed: 21859198]

Taylor ZE, Eisenberg N, Spinrad TL, Eggum ND, Sulik MJ. The relations of ego-resiliency and emotion socialization to the development of empathy and prosocial behavior across early childhood. Emotion. 2013; 13(5):822–831. [PubMed: 24098930]

Thoma P, Zalewski I, von Reventlow H, Norra C, Juckel G, Daum I. Cognitive and affective empathy in depression linked to executive control. Psychiatry Research. 2011; 189(3):373–378. [PubMed: 21868105]

Tong L, Shinohara R, Sugisawa Y, Tanaka E, Yato Y, Yamakawa N. Japan Children's Study G. Early development of empathy in toddlers: Effects of daily parent–child interaction and home-rearing environment. Journal Of Applied Social Psychology. 2012; 42(10):2457–2478.

Tost H, Kolachana B, Hakimi S, Lemaitre H, Verchinski BA, Mattay VS, Meyer–Lindenberg A. A common allele in the oxytocin receptor gene (OXTR) impacts prosocial temperament and human hypothalamic-limbic structure and function. PNAS Proceedings Of The National Academy Of Sciences Of The United States Of America. 2010; 107(31):13936–13941.

Tully EC, Donohue MR, Garcia SE. Children's empathy responses and their understanding of mother's emotions. Cognition & Emotion. 2014; 28:1–12. [PubMed: 24303928]

Tully, EC.; Iacono, WG. An integrative common genetic liabilities model for the comorbidity of substance use disorders with externalizing and internalizing disorders. In: Sher, K., editor. The Oxford Handbook of Substance Use Disorders. New York: Oxford University Press; 2014.

Tully EC, Iacono WG, McGue M. Changes in genetic and environmental influences on the development of nicotine dependence and major depressive disorder from middle adolescence to early adulthood. Development And Psychopathology. 2010; 22(4):831–848. [PubMed: 20883585]

Ungerer JA, Dolby R, Waters B, Barnett B, Kelk N, Lewin V. The early development of empathy: Self-regulation and individual differences in the first year. Motivation And Emotion. 1990; 14(2):93–106.

Uzefovsky F, Shalev I, Israel S, Knafo A, Ebstein RP. Vasopressin selectively impairs emotion recognition in men. Psychoneuroendocrinology. 2012; 37(4):576–580. [PubMed: 21856082]

Valiente, C.; Eisenberg, N. Parenting and Children's Adjustment: The Role of Children's Emotion Regulation. In: Snyder, DK.; Simpson, J.; Hughes, JN., editors. Emotion regulation in couples and families: Pathways to dysfunction and health. Washington, DC: American Psychological Association; 2006. p. 123-142.

Van der Graaff J, Branje S, De Wied M, Hawk S, Van Lier P, Meeus W. Perspective Taking and Empathic Concern in Adolescence: Gender Differences in Developmental Changes. Developmental Psychology. 2014; 50(3):881–888. [PubMed: 24040846]

van der Mark IL, van IJzendoorn MH, Bakermans-Kranenburg MJ. Development of empathy in girls during the second year of life: Associations with parenting, attachment, and temperament. Social Development. 2002; 11(4):451–468.

Verhofstadt LL, Buysse A, Ickes W, Davis M, Devoldre I. Support provision in marriage: The role of emotional similarity and empathic accuracy. Emotion. 2008; 8(6):792–802. [PubMed: 19102590]

Vinik J, Almas A, Grusec J. Mothers' knowledge of what distresses and what comforts their children predicts children's coping, empathy, and prosocial behavior. Parenting: Science and Practice. 2011; 11(1):56–71.

Volbrecht MM, Lemery-Chalfant K, Aksan N, Zahn-Waxler C, Goldsmith HH. Examining the familial link between positive affect and empathy development in the second year. Journal of Genetic Psychology. 2007; 168(2):105–129. [PubMed: 17936968]

Wang Y, Adamson C, Yuan W, Altaye M, Rajagopal A, Byars AW, Holland SK. Sex differences in white matter development during adolescence: A DTI study. Brain Research. 2012:14781–15.

Waters AM, Pittaway M, Mogg K, Bradley BP, Pine DS. Attention training towards positive stimuli in clinically anxious children. Developmental Cognitive Neuroscience. 2013:477–84.

Whitmer AJ, Gotlib IH. Depressive rumination and the C957T polymorphism of the DRD2 gene. Cognitive, Affective & Behavioral Neuroscience. 2012; 12(4):741–747.

Wilson KR, Havighurst SS, Harley AE. Tuning in to Kids: An effectiveness trial of a parenting program targeting emotion socialization of preschoolers. Journal Of Family Psychology. 2012; 26(1):56–65. [PubMed: 22182335]

Wood JV, Saltzberg JA, Goldsamt LA. Does affect induce self-focused attention? Journal Of Personality And Social Psychology. 1990; 58(5):899–908. [PubMed: 2348375]

Wu N, Li Z, Su Y. The association between oxytocin receptor gene polymorphism (OXTR) and trait empathy. Journal of Affective Disorders. 2012; 138(3):468–472. [PubMed: 22357335]

Xia H, Wu N, Su Y. Investigating the genetic basis of theory of mind (ToM): The role of Catechol-O-Methyltransferase (COMT) gene polymorphisms. Plos ONE. 2012; 7(11)

Yamasue H, Yee JR, Hurlemann R, Rilling JK, Chen FS, Meyer-Lindenberg A, Tost H. Integrative approaches utilizing oxytocin to enhance prosocial behavior: From animal and human social behavior to autistic social dysfunction. The Journal Of Neuroscience. 2012; 32(41):14109–14117. [PubMed: 23055480]

Yirmiya N, Rosenberg C, Levi S, Salomon S, Shulman C, Nemanov L, et al. Association between the arginine vasopressin 1a receptor (AVPR1a) gene and autism in a family-based study: Mediation by socialization skills. Molecular Psychiatry. 2006; 11(5):488–494. [PubMed: 16520824]

Yoo H, Feng X, Day RD. Adolescents' empathy and prosocial behavior in the family context: A longitudinal study. Journal Of Youth And Adolescence. 2013; 42(12):1858–1872. [PubMed: 23283695]

Young LJ, Wang Z. The neurobiology of pair bonding. Nature Neuroscience. 2004; 7(10):1048–1054.

Zahn-Waxler, C.; Cole, PM.; Barrett, KC. Guilt and empathy: Sex differences and implications for the development of depression. In: Garber, J.; Dodge, KA., editors. The Development of Emotion Regulation and Dysregulation. Cambridge: Cambridge University Press; 1991. p. 243-272.

Zahn-Waxler C, Kochanska G, Krupnick J, McKnew D. Patterns of guilt in children of depressed and well mothers. Developmental Psychology. 1990; 26(1):51–59.

Zahn-Waxler C, Radke-Yarrow M. The origins of empathic concern. Motivation And Emotion. 1990; 14(2):107–130.

Zahn-Waxler, C.; Van Hulle, C. Empathy, guilt, and depression: When caring for others becomes costly to children. In: Oakley, B.; Knafo, A.; Madhavan, G.; Wilson, D., editors. Pathological altruism. New York, NY US: Oxford University Press; 2012. p. 321-344.

Zajdel RT, Bloom J, Fireman G, Larsen JT. Children's understanding and experience of mixed emotions: The roles of age, gender, and empathy. The Journal Of Genetic Psychology: Research And Theory On Human Development. 2013; 174(5):582–603.

Zavos HMS, Gregory AM, Eley TC. Longitudinal genetic analysis of anxiety sensitivity. Developmental Psychology. 2012; 48(1):204–212. [PubMed: 21842987]

Zelazo, P.; Carlson, SM.; Kesek, A. The development of executive function in childhood. In: Nelson, CA.; Luciana, M., editors. Handbook of developmental cognitive neuroscience. 2. Cambridge, MA US: MIT Press; 2008. p. 553-574.

Zink CF, Meyer-Lindenberg A. Human neuroimaging of oxytocin and vasopressin in social cognition. Hormones And Behavior. 2012; 61(3):400–409. [PubMed: 22326707]
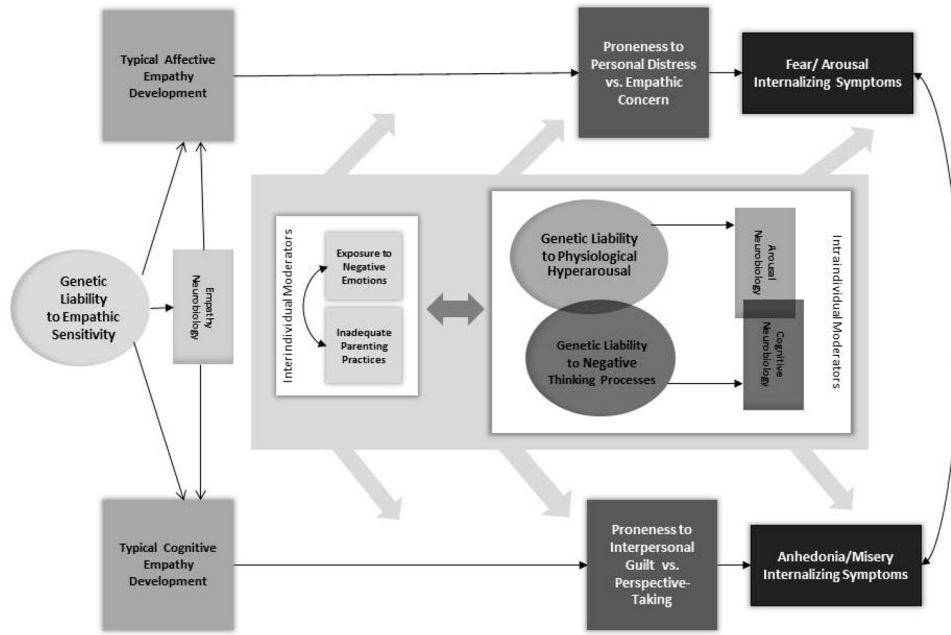
Figure 1.
Model of Risky Empathy Development.