

# An Overview of Psychological and Neurobiological Mechanisms by which Early Negative Experiences Increase Risk of Mood Disorders

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## Abstract

**Objective:** Early life experiences are associated with severe and long-lasting effects on behavioural and emotional functioning, which in turn are thought to increase the risk for unipolar depression and other disorders of affect regulation. The neurobiological and psychological mechanisms through which adverse early life experiences confer risk are poorly understood. **Method:** Alterations in brain structure and function in limbic and prefrontal cortical regions have been linked to early negative experiences and to mood disorders. **Results:** There are a number of psychological domains that may be dysfunctional in people with mood disorders, and which, if the dysfunction occurs prior to onset of mood symptoms, may signify a risk factor for depression. Cognitive dysfunction has been examined in patients with mood disorders, with some suggestion that changes in cognitive function may antedate the onset of mood symptoms, and may be exacerbated in those who experienced early negative trauma. Social cognition, including emotion comprehension, theory of mind and empathy, represent under-studied domains of psychological function that may be negatively influenced by early adverse experience. Temperament and personality factors may also leave people vulnerable to mood instability. **Conclusion:** This review summarizes the evidence for dysfunction in each of these domains for people with mood disorders.

**Key words:** mood disorder, stress, early adverse experience, temperament, personality, cognition, depression

## Résumé

**Objectifs:** Les expériences de la petite enfance ont des effets graves et durables sur le comportement et les émotions, ce qui accroît le risque de dépression unipolaire et de troubles de régulation de l'affect. Les études sur les mécanismes neurobiologiques et psychologiques qui accompagnent les expériences négatives de la petite enfance et peuvent donner lieu à un risque sont peu nombreuses. **Méthodologie:** Les expériences négatives de la petite enfance et les troubles de l'humeur sont liées à des modifications de la structure et du fonctionnement des régions corticales, limbiques et préfrontales du cerveau. **Résultats:** Un certain nombre de domaines psychologiques peuvent être dysfonctionnels chez les sujets qui présentent des troubles de l'humeur; si ce dysfonctionnement apparaît avant les symptômes des troubles de l'humeur, il peut entraîner un risque de dépression. L'étude du dysfonctionnement cognitif chez les sujets présentant des troubles de l'humeur permet de croire que la modification de la fonction cognitive peut précéder l'apparition des troubles de l'humeur, et qu'elle peut être exacerbée chez les sujets traumatisés dans la petite enfance. La reconnaissance sociale, la compréhension émotionnelle, la théorie de l'esprit et l'empathie sont des aspects du fonctionnement psychologique peu étudiés qui peuvent être affectés par les expériences négatives de la petite enfance. Le tempérament et la personnalité peuvent également prédisposer les sujets aux troubles de l'humeur. **Conclusion:** Cette étude résume le dysfonctionnement constaté dans chacun de ces domaines chez les sujets souffrant de troubles de l'humeur.

**Mots clés:** trouble de l'humeur, stress, expérience négative, enfance, tempérament, personnalité, cognition, dépression

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There is growing interest in early intervention for psychiatric illness, and this research focus on people in the early stages of illness has been extended to those who are at risk for developing psychiatric symptoms. Risk factors are not limited to those that are heritable, as individuals' neural systems, patterns of cognition, behaviour and emotional regulation develop out of a complex interaction of genetic factors and environmental experiences. This paper is intended to provide an overview of the neurobiological and psychological factors through which risk for depression and other disorders of affect regulation may be conferred.

Dysregulation of neurobiological systems can result from psychosocial stressors (e.g., Cicchetti & Blender, 2004; De Bellis, 2005; Heim & Nemeroff, 2002; Fishbein et al., 2009). Traumatic early life experiences, such as maltreatment, abuse and neglect affect neuroendocrine, psychophysiological and cognitive activities, which in turn increase vulnerability to psychopathology, including mood disorders, substance abuse and personality pathology (Fumagalli, Molteni, Racagni, & Riva, 2007; Sousa, Cerqueira, & Almeida, 2008).

Psychological risk factors can be conceptualized in various dimensions of human brain functioning. Personality and related features of temperament and traits can be examined for whether extremes of certain personality or temperamental traits confer risk. Cognitive function, occasionally referred to as 'cold' cognition, and including domains such as early information processing, attentional capacity, various aspects of memory and executive function, has been examined for whether dysfunction arising as a consequence of toxic stress may represent a risk factor for vulnerability to mood dysregulation. Subtle dysfunction in elements of social cognition, including affect recognition, empathy and theory of mind, may also increase risk for psychiatric illness.

Below, we briefly review selected evidence suggesting that each of these domains may represent fruitful dimensions of study for those attempting to understand the pathways through which early adverse experiences confer risk for psychopathology. A natural extension of these studies would be investigations examining the degree to which these represent modifiable risk factors, for which intervention following adverse life experiences might delay or even prevent the onset of illness. That literature, however, is in a nascent stage.

## Neurobiological Risk Factors

### *Gene by Environment Interactions*

Both genetic and environmental factors mediate the degree to which early adverse experiences confer risk for psychopathology. Polymorphisms in genes coding for the serotonin transporter (SERT), the corticotrophin-releasing hormone (CRH) receptor, the FK506 binding protein 5 (FKBP5), the serotonin transporter-linked promoter region (5HTTLPR) and brain-derived neurotrophic factor (BDNF) are thought to regulate vulnerability to depression following childhood stress (Heim, Shugart, Craighead, & Nemeroff, 2010). Some, although not all, studies have found that the short (s) form of the 5HTTLPR is linked to increased vulnerability to early-life-stress-related depression, whereas the long (l) allele seems to present a protective factor (Caspi et al., 2003; Cervilla et al., 2007; Risch et al., 2009). A variant of the long allele (Lg) has also been linked to increased vulnerability to depression. Social support moderates the risk for depression in children with the s/s genotype who experienced early negative trauma (Kaufman et al., 2004). Wilhelm and colleagues reported that the 5HTTLPR genotype predicts age-of-illness onset in individuals with unipolar depression who experienced multiple early negative events (Wilhelm et al., 2006).

Polymorphisms of CRH-R1 influence whether early negative experiences are linked to depression (Bradley et al., 2008; Polanczyk et al., 2009) and this same polymorphism moderates the effects of early negative experiences on HPA-axis reactivity (Tyrka et al., 2009). A polymorphism of the glucocorticoid receptor co-chaperone, FKBP5, moderates the risk of developing childhood-trauma-related post-traumatic stress disorder (PTSD) (Binder et al., 2008).

Gene-gene interactions may also influence risk of depression following early negative experiences. For instance, the Val66Met polymorphism of the BDNF gene may interact with the 5HTTLPR genotype to increase the risk of depression in those who experienced early life trauma (Kaufman et al., 2006). Those with the BDNF gene Val66Met polymorphism, the s/s 5HTTLPR genotype and early negative experiences show the highest depression scores. An interaction between CRH-R1 and 5HTTLPR polymorphisms may also moderate depression risk following early negative experiences (Ressler et al., 2010).

### *Hypothalamic Pituitary Adrenal (HPA) Axis*

Early negative experiences are associated with disturbances of the HPA axis in people with major depression (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008). Women with unipolar depression following early negative experiences show HPA axis profiles that are distinct from those of depressed women without early negative experiences

(Heim et al., 2008; Heim, Plotsky, & Nemeroff, 2004). Increased cerebro-spinal fluid CRH concentrations have been detected in people who experienced multiple early negative experiences, particularly physical abuse (Hart, Gunnar, & Chicchetti, 1996). Depressed patients who completed suicide had reduced CRH binding sites in frontal regions, consistent with the idea that CRH is also hyper-secreted in depression (Merali et al., 2004).

Increased neuroendocrine and autonomic responses to stress and depression-like behaviours are observed in rats exposed to maternal separation within the first two weeks of life, and this dysregulation in the stress systems persist throughout life (Huot, Thirivikraman, Meaney, & Plotsky, 2001). Early negative experiences in the form of repeated maternal separation result in increases in CRH mRNA expressions in the hypothalamus, the locus coeruleus and the amygdala in rats (Plotsky et al., 2005). Maternal separation also results in reduced neurogenesis in the rat hippocampus (Mirescu, Peters, & Gould, 2004). Furthermore, early maternal deprivation is linked to low levels of 5-HT<sub>1B</sub> receptor expression (Gutman & Nemeroff, 2002), decreased expression of GABA A receptors (Caldji, Francis, Sharma, Plotsky, & Meaney, 2000) and impaired dopamine transporter (DAT) expression (Meaney, Brake, & Gratton, 2002).

### **Structural Brain Changes**

Early life experiences influence brain morphology, and these changes, in an immature brain, are thought to be interactive processes between genetic programming, cell function and environmental factors (Andersen, 2003). The earliest, and likely the most important, phases of brain maturation occur during fetal development and early childhood (Toga, Thowipson, & Sowell, 2006).

In animal models, changes in brain morphology have been observed in offspring of mothers exposed to prenatal stress. Lemaire et al. (Lemaire, Koehl, LeMoal, & Abrous, 2000) reported alterations of the cytoarchitecture of the rat hippocampus as a consequence of prenatal stress, and significant enlargement of the lateral nucleus of the amygdala has been noted in offspring of rats that were stressed during pregnancy (Salm et al., 2004). In non-human primates, daily acute prenatal stress has been associated with alterations in size of the corpus callosum (Coe, Lulbach, & Schneider, 2002), with reduction in hippocampal volume and with the inhibition of neurogenesis in the dentate gyrus (Coe et al., 2003).

Limbic structures, such as the hippocampus, are prominent targets for early life stress in humans (Buss et al., 2007). The hippocampus is critically involved in cognitive functioning; it also has a role in regulating the HPA axis. Early negative experiences are linked to decreased hippocampal volume (Stein, Koverola, Hanna, Torchia, & McClarty,

1997; Vythilingam et al., 2002) and decreased hippocampal activation during memory performance (Carrion, Haas, Garrett, Song, & Reiss, 2010). Changes in regional brain volumes have also been reported in association with pre-term birth and low birth weight (Beauchamp et al., 2008; Buss et al., 2007) as well as prenatal maternal anxiety during specific prenatal periods (Buss, Davis, Muftuler, Head, & Sandman, 2010). Pregnancy anxiety at 19 weeks gestation is linked to grey matter volume reductions in a number of cortical regions, including prefrontal, premotor, medial and lateral temporal cortices, as well as postcentral, middle occipital and fusiform gyri (Buss, Davis, Muftuler, Head, & Sandman, 2010). These regions are associated with executive cognitive functions, such as reasoning and planning, attention, working memory, certain aspects of language (e.g. Connolly, Goodale, Menon, & Munoz, 2002), with storage and recall of facts and events (e.g. Squire et al., 2010) as well as with social and emotional processing (Olson, Plotzker, & Ezzyat, 2007).

## **Psychological Risk Factors**

### **Traits, Temperament and Personality**

The relations between mood disorders and personality traits and temperament are complicated clinically, conceptually (for an extensive review see Krueger, 2005) and possibly neurobiologically (for a review see Goodman, New, Triebwasser, Collins, & Siever, 2010b).

A common trait in people with mood disorders is the tendency to engage in ruminative thought. This trait involves a focus on negative thoughts and events (McBride & Bagby, 2006; Moulds, Kandris, & Williams, 2007; Nolen-Hoeksema, 1991; Thomsen, 2006), and is associated with an increased risk of developing depression (Broderick & Korteland, 2004; Just & Alloy, 1997; Nolen-Hoeksema, Parker, & Larson, 1994) as well as increased length and severity of depressive episodes (Kuyken, Watkins, Holden, & Cook, 2006b). Rumination may also exert a negative effect on cognitive performance by reducing working memory and executive capacity. This results in poor performance on higher-level cognitive tasks (Sutherland & Bryant, 2007; Watkins & Teasdale, 2001; Watkins, Teasdale, & Williams, 2000) and may therefore represent a risk factor for impaired cognitive functioning in mood disorders (see below).

Rates of heritability for personality traits, such as those specified in the five-factor model, are high, with heritability estimates ranging from 33 to 65% (e.g., Jang, Livesley, Vernon, & Jackson, 1996; Loehlin, McCrae, Costa, & John, 1998). High neuroticism may confer risk for mood disorders (Kendler, Gatz, Gardner, & Pedersen, 2006). In pediatric bipolar disorder, personality traits such as behavioural disinhibition and severe emotion dysregulation are

linked to residual symptoms of mania and depression and are therefore thought to be indicators of a bipolar diathesis (West, Schenkel, & Pavuluri, 2008).

These traits have also emerged in studies testing for associations between specific polymorphisms in the brain derived neurotrophic gene (BDNF Val66Met substitution). Associations between personality dimensions and the Val66Met genotype have been reported by some (Itoh, Hashimoto, Kumakiri, Shimizu, & Iyo, 2004; Sen et al., 2003) although not all (Lang et al., 2005; Tochigi et al., 2006; Willis-Owen et al., 2005) investigators. Over 25 studies have examined the association between a polymorphism in the serotonin transporter protein gene (5-HTTLPR) and anxiety- and depression-related personality traits, but have struggled to reconcile conflicting results of meta-analyses.

Impulsivity and emotional lability are also linked to the development of mood disorders and an increased risk for suicide (Beauchaine, Klein, Crowell, Derbidge, & Gatzke-Kopp, 2009). Individuals with these traits were more likely to have experienced childhood abuse and neglect (Beauchaine et al., 2009). Stable anxiety-related personality traits, notably neuroticism, are strongly associated with a genetic risk for depression. Vulnerability genes, however, may often be detected only in the presence of environmental stressors (Harro & Kiive, 2011).

Early negative experiences are additionally associated with psychological difficulties in the short- and long-term, and reactions to early negative experiences involve the disruption of normal psychological development, painful emotions and cognitive distortions (Conte & Schuerman, 1987). Children with early negative experiences have chronic self-perceptions of helplessness and hopelessness, impaired trust, self-blame, and low self-esteem, as well as feelings of guilt and other dysfunctional and inaccurate attributions (Jehu, 1988; Lipovsky, Finch, & Belter, 1989). Alterations in social functioning due to early negative experiences (Briere, 1992), including feeling less socially competent, more socially withdrawn, and more aggressive (Friedrich, Urquiza, & Beilke, 1986) likely add to the risk of both depression and maladaptive personality styles (Briere, 1992). In fact, the probability of receiving a diagnosis of unipolar depression is increased four-fold in those with early negative experiences (Lanktree, Briere, & Zaidi, 1991).

Various investigators have suggested that personality disorders (PDs) such as borderline, avoidant and dependent PD are associated with elevated rates of mood disorders, likely reflecting the increased risk for development of mood disorders in people with problematic personality traits (Gunderson et al., 2004; Kendler et al., 2006). Estimates of co-morbid borderline PD hover around 30 percent in patients assessed during euthymic phases of illness (Kay,

Altsheler, Ventura, & Mintz, 1999; Vieta, Colum, Martinez-Aran, Benabarre, & Gasto, 1999) and 60 percent in patients assessed during active phases (Bieling et al., 2003; Peselow, Sanfilippo, & Fiere, 1995). Some have suggested that borderline PD may be conceptualized as part of the bipolar spectrum of illness (Paris, Gunderson, & Weinberg, 2007).

The presence of clinically significant personality features in adolescents and young adults have been described as a prodromal phase of illness in individuals with early-onset mood disorders (e.g., First et al., 2002; Zanarini, Frankenburg, & Vujanovic, 2004). Other illnesses, such as substance abuse, Attention Deficit-Hyperactivity Disorder (ADHD) and anxiety disorders co-occur in individuals with early-onset mood disorders (Harro & Kiive, 2011). Heavy consumption of alcohol or substance abuse during adolescence is associated with an increased likelihood of experiencing a mood or anxiety disorder (Saraceno, Munafo, Heron, Craddock, & van den Bree, 2009). Comorbid substance abuse disorders in people with BD are associated with male gender, impulsive-aggressive traits, number of suicide attempts and comorbid conduct and Cluster B PDs (Grunebaum et al., 2006).

### **Cognition**

As noted above, changes in neurobiological systems as a consequence of early adverse experience are relatively well described; some studies have also examined the possible behavioural (cognitive-executive and emotional-regulatory) manifestations of early negative experiences. Early adversity alters cognitive development, including cognitive-executive and emotion-regulatory functions (Fishbein et al., 2009). Prefrontal functions, in concert with activity in limbic structures (e.g. amygdala, hippocampus, hypothalamus), integrate motivational, goal-directed behaviours, sensitivity to consequences, perception of social cues and inhibition. Therefore, the development of the prefrontal – limbic circuitry, which underlies cognitive function and emotion regulation, may be particularly sensitive to early negative adversity (Bremne & Vermetten, 2001; Critchley et al., 2000; Koenen et al., 2001). Beers and De Bellis (2002) have found that children with PTSD due to early negative experience perform poorly on tasks assessing frontal lobe function, i.e. Wisconsin Card Sort Test and a word association task, and on those assessing abstract reasoning and executive functioning. These children were also more susceptible to distraction, and more impulsive, as indicated by more errors on tasks of sustained attention. These findings are consistent with neuroimaging studies showing changes in prefrontal cortex activity in patients with post-traumatic stress disorder (De Bellis, Keshavan, Spencer, & Hall, 2000; De Bellis & Thomas, 2003).

Carrey and colleagues have observed that children with early negative experiences but no PTSD have low skin conductance responses to emotional and cognitive stimuli, suggesting a reduced physiological responsiveness to environmental input (Carrey, Butter, Persinger, & Bialik, 1995). Meta-analyses have confirmed that there are persistent neuropsychological deficits in remitted patients with mood disorders relative to healthy controls (Robinson et al., 2006; Torres, Bolidreau, & Yatham, 2007; Arts, Jabben, Krabendam, & van Os, 2008; Bora, Yucel, & Pantelis, 2009a). Patients with mood disorders have moderate to large impairments on tests of attention, processing speed, explicit memory, and several aspects of executive function. In addition to impairment in higher order cognition, early life stressors are also linked to deficits in verbal comprehension (e.g., Katz, 1992), poor academic achievement (Kendall-Tackett, 1997; Kendall-Tackett & Eckenrode, 1996; Niederhofer & Reiter, 2004) and decrements in general intelligence (Navalta, Polcari, Webster, Boghossian, & Teicher, 2006; Saigh, Yasik, Oberfield, Halamandaris, & Bremner, 2006). In the aggregate, these results suggest that cognitive dysfunction may antedate onset of psychiatric syndromes for some patients with early adverse experiences, and this dysfunction is persistent over the course of illness.

### **Autobiographical Memory**

Autobiographical memory (AM) contributes to a sense of self-awareness and self-identity across time (Conway, 2003; Tulving, 2001; Tulving, 2002), and its disruption in mood disorders may contribute to the core alterations in a sense of self that has been observed in these disorders. AM serves a variety of functions including establishing our sense of self (Conway, 2003), provides us with “meaning making” (MacLean, 2005) and facilitates our ability to form new social bonds (Walker, Skowronski, Gibbons, Vogl, & Ritchie, 2009). Numerous studies have reported elevated levels of over-general autobiographical memory among depressed patients and also among those previously exposed to traumatic events (King, MacDougall, Ferris, Levine, MacQueen, & McKinnon, 2010).

Autobiographical memory deficits are reported for children experiencing early negative trauma. Goodman et al. (Goodman, Quas, & Ogle, 2010a) have observed that children who experienced maltreatment either show especially robust memories for emotionally distressing material or impaired memory, particularly in those individuals who defensively avoid recall of it. Aglan and colleagues report that women with early negative experiences show over-generalized memory regardless of whether they also had a history of depression (Aglan, Williams, Pickles, & Hill, 2010). However, over-generalized memory is increased in women who report early negative experiences and depression, particularly in relation to positive cues, and highest scores are

seen in those with adult rather than juvenile-onset depression. Earlier age-of-onset of childhood trauma is associated with greater over-generalized memory as indexed by fewer specific and more categoric memories (Crane & Duggan, 2009). Raymaekers et al. (Raymaekers, Smeets, Peters, & Merckelbach, 2010) reported that healthy controls are better at retrieving specific autobiographical memories relative to individuals with depression who tend to recover early negative memories. Valentino and colleagues evaluated autobiographical memory for positive and negative non-traumatic events in abused, neglected, and control children, and show that the memories of abused children are more general and contain more negative self-representations than those of control children (Valentino, Toth, & Cicchetti, 2009).

Unipolar depression is associated with over-generalized recall on tests of AM in children and adolescents (Kuyken, Howell, & Dalgleish, 2006a; Park, Goodyear, & Teasdale, 2002), and Drummond et al. (Drummond, Dritschel, Astell, O’Carroll, & Dalgleish, 2006) has reported that children aged 7-8 with dysphoric mood recall fewer positive memories than controls without dysphoric mood. By contrast, children aged 10-11 with a similar level of dysphoric mood show poor autobiographical recall in response to both negative and positive cues. In a related study, (Vrielynck, Delpus, Philippot, 2007) have found that children aged 9-13 with a history of unipolar depression retrieve fewer specific autobiographical memories than children with other behavioural and anxiety disorders whose performance falls between that of the depressed sample and healthy controls.

Adolescent inpatients with various psychiatric disorders have shown less specific recall than healthy adolescents. Higher measures of hopelessness and depression correlate with *more* specific recall in clinical groups, a finding attributed to patients’ tendency to recall the same traumatic memory repeatedly despite the use of different cue words (Goodman et al., 2010a; Swales, Williams, & Wood, 2001). Park and colleagues compared AM performance in healthy controls, currently depressed, and euthymic adolescents, and reported that depressed adolescents have less specific *negative* memories than controls, while euthymic adolescents over-generalize recall of *positive* events (Park et al., 2002). This finding of over-generalized recall in depressed adolescents persists in samples without trauma history (Kuyken et al., 2006a).

Given the presence of verbal recollective memory deficits in children with mood disorders and those at risk for the development of mood disorders due to early negative trauma (see above), it will be important for future studies to examine the extent to which autobiographical memory is altered in these samples.

## Social Cognition

Social cognition involves the ability to understand and respond to the thoughts and feelings of others, and is believed critical for successful social interactions (Adolphs, 2001; Brothers, 1990). Social reasoning abilities such as emotion comprehension, Theory of Mind (ToM), and empathy undergo an extended development from early childhood to adolescence (Blakemore, 2008; Frith & Frith, 2003; Hoffman, 1991). Adolescence, a period of time characterized by marked changes in social relationships with peers and family (Adams & Berzonsky, 2003; Choudhury, Blakemore, & Charman, 2006), is also associated with increased vulnerability to depression and affect dysregulation (e.g., Fleming & Offord, 1990; Lewinsohn, Rohde, Seeley, & Fischer, 1993; Merikangas et al., 2007), particularly so for youth who have had early traumatic experiences. It is possible that any alterations in social cognitive processes during this period of development may contribute to the onset of mood disorders. Alternatively, the development of psychiatric morbidity during adolescence could alter or delay the development of social reasoning abilities. A better understanding of social cognition in mood disorders as well as factors that may influence social cognitive functioning could improve early intervention efforts aimed at reducing the peak morbidity and mortality observed in youth who have experienced early adverse experiences.

### Facial Emotion Processing

A nascent literature suggests that adolescents with early negative experience show impaired performance on tests of facial emotion processing. Children exposed to neglect have shown deficits when asked to distinguish between emotional expressions (Pollak, Cicchetti, Hornung, & Reed, 2000), yet those exposed to childhood abuse show an enhanced ability to distinguish emotional expressions (Pollak & Sinha, 2002). These discrepancies are likely due to the fact that during neglect the child's ability to correctly identify an adult's expression (and therefore intentions) diminishes because of the experienced inconsistency between facial expressions and behaviours (Fishbein et al., 2009).

Adolescents with mood disorders also demonstrate facial expression recognition deficits (Guyer et al., 2007; McClure, Pope, Hoberman, Pine, & Leibenluft, 2003; McClure et al., 2005; Rich et al., 2008; Schenkel, Pavuluri, Herbener, Harral, & Sweeney, 2007). For example, global emotion recognition deficits have been reported in heterogeneous samples of euthymic and symptomatic patients (Guyer et al., 2007), as well as in hypomanic/mixed bipolar youth (Rich et al., 2008). Relative to healthy controls and medicated euthymic patients, unmedicated pediatric patients in mixed and manic states have shown deficits in differentiating between subtle variations of happy or sad facial expressions (Schenkel et al., 2007). Moreover, acutely ill and euthymic adolescents misjudge emotionally intense happy

and sad faces as relatively moderate in intensity (Schenkel et al., 2007). Finally, euthymic youth with mood disorders demonstrate difficulties labeling disgusted and happy faces (Rich et al., 2008). Impaired ability to recognize facial expressions in bipolar youth has been shown to be significantly associated with altered social reciprocity skills (Rich et al., 2008).

Neuroimaging studies conducted in adolescents with mood disorders similarly show enhanced activations in subcortical limbic regions and hypoactivation in prefrontal regions in response to emotional faces (reviewed in McClure-Tone, 2009; Dickstein & Leibenluft, 2006). These findings have also been noted in euthymic youth (e.g., Pavuluri, O'Connor, Harral, & Sweeney, 2007; Rich et al., 2008) and a heterogeneous sample of patients in a variety of mood states (Rich et al., 2006).

Adults with established mood disorders also experience difficulty identifying and labeling facial emotions, including sadness (Lembke & Ketter, 2002; Lennox, Jacob, Calder, Lupson, & Bullmore, 2004), disgust (Lembke & Ketter, 2002), and fear (Getz, Shear, & Strakowski, 2003; Lembke & Ketter, 2002; McClure et al., 2005; Yurgelun-Todd et al., 2000). Studies examining patients in a depressed illness phase suggest a mood congruent bias, where depressed patients experience difficulty labeling happy faces (Almeida, Versace, Hassel, Kupfer, & Phillips, 2010), and a tendency to misinterpret neutral facial stimuli as sad (George et al., 1998; Gur et al., 1992) and happy faces as angry (McClure et al., 2003). Patients with more severe depressive symptoms also show a reduction in sensitivity to happy facial expressions (Gray et al., 2006). In summary, deficits in facial recognition appear to be present early in the course of mood disorders. They may arise as a consequence of early adverse experiences, persist and even be exacerbated in people with established mood disorders.

### Theory of Mind and Empathy

Theory of mind (ToM) refers to the ability to infer the mental states of other individuals, including their beliefs, desires, and intentions in order to explain or predict human behaviour (Premack & Woodruff, 1978). Recent theoretical models propose that ToM draws on both cognitive (e.g., understanding another's perspective) and affective (e.g., emotional response to feeling states of others) processing resources (Leslie, Friedman, & German, 2004; McKinnon & Moscovitch, 2007).

Empathy, broadly, refers to the ability to infer and share feelings or emotional states of others, in reference to oneself (Decety & Moriguchi, 2007), and plays a central role in successful interpersonal engagement and higher social functioning (Baron-Cohen & Wheelwright, 2004). The construct of empathy involves both cognitive (e.g., inferring

another's mental state) and affective (e.g., affective response to the feeling state of another) components.

Inoue and colleagues have reported ToM deficits in a combined sample of remitted patients with unipolar and bipolar disorder on tasks that place high demands on working memory and executive functioning (i.e., second-order false-belief questions) (Inoue, Tonooka, Yamada, & Kanba, 2004). No such impairments, however, have been observed for tasks involving lower-level ToM reasoning (i.e., first-order false-belief stimuli). Similarly, recent reports have demonstrated that euthymic patients are impaired on ToM tests that involve high levels of cognitive processing demands (Bora et al., 2005; Lahera et al., 2008; Olley et al., 2005), but perform comparably to matched controls on ToM tasks of fewer cognitive demands (Shamay-Tsoory, Shur, Harari, & Levkovitz, 2009). These results suggest that even euthymic patients remain vulnerable to poor performance on those ToM tasks drawing heavily on cognitive processing resources (e.g., working memory, executive functioning) known to be impacted in mood disorders (e.g., Bora, Yucel, & Pantelis, 2009b).

We have found that patients experiencing sub-syndromal symptoms of illness performed more poorly than healthy controls on both first-order and second-order ToM false-belief questions (McKinnon, Cusi, & MacQueen, 2010), however, these deficits are most pronounced for cognitively demanding second-order stimuli. In line with the hypothesis that the extent of ToM impairment varies with cognitive processing demands, Wolf and colleagues reported that increasingly poor performance on ToM tasks is associated with impairments on tests of executive functioning and non-verbal reasoning among patients in various mood states (Wolf, Brüne, & Assion, 2010). ToM deficits remained significant after controlling for level of intellectual functioning and performance on tests of executive functioning, confirming that some elements of ToM performance (e.g., emotion comprehension) are independent of cognitive processing demands.

Deficits in empathic responding have been reported in schizophrenia (Montag, Heinz, Kunz, & Gallinat, 2007; Shamay-Tsoory et al., 2007) and autism spectrum disorders (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001; Rogers, Dziobek, Hassenstab, Wolf, & Convit, 2007). Very few studies have assessed empathic responding in patients with mood disorders, and early evidence indicates reduced empathic capacity in people with mood disorders (Cusi, MacQueen, Spreng, & McKinnon, 2011; Cusi, MacQueen, & McKinnon, 2010; Shamay-Tsoory, Harari, Szepeswol, & Levkovitz, 2009). People with bipolar disorder have decreased cognitive empathy ('Perspective Taking') and elevated levels of affective personal discomfort in response to others' distress as assessed by Davis' (1983) Interpersonal

Reactivity Index (Cusi et al., 2010; Davis, 1983; Shamay-Tsoory et al., 2009),

The literature on early negative experiences and its impact on the development of ToM and empathy remain sparse. It is known, however, that maltreatment is related to delays in the development of ToM (Cicchetti, Rogosch, Maughan, Toth, & Bruce, 2003), and that children reared in foster care perform poorly on tasks of emotion understanding and ToM-capabilities, even when accounting for age, intelligence and executive function (Pears & Fisher, 2005).

### Affective Decision Making

Affective decision-making focuses on the effect of reward and punishment on action selection. The Iowa Gambling Task (IGT) (Bechara, Damasio, Damasio, & Anderson, 1994) and the Cambridge Gamble Test (CGT) (Rogers et al., 1999) are commonly used paradigms which involve simulated "gambling" where optimal performance is based on participants' ability to weigh short-term gains against potential long-term losses and to hold in mind differing contingencies. Children who have experienced early negative trauma select risk options faster than healthy controls, yet healthy controls respond more quickly as the chance of winning increases. When choosing between high- and low-risk options, maltreated children with depressive disorders frequently select safer over the more risky choices (Guyer et al., 2006).

Depressed patients also show impaired risk adjustment on these tasks (Murphy et al., 2001; Roiser et al., 2009; Rubinsztein, Michael, Underwood, Tempest, & Sahakian, 2006; Taylor Tavares et al., 2007). Clark et al. (Clark, Iversen, & Goodwin, 2001) and Yechiam et al. (Yechiam, Hayden, Bodkins, O'Donnell, & Hetrick, 2008) have reported that manic patients underperform compared to healthy controls on gambling tasks. Investigating responses to reward processing in relation to mood disorders and early negative experiences may be relevant for developing treatment plans for maltreated children, particularly those with depression.

## Conclusions

Neuropsychiatric illnesses, such as mood disorders, anxiety disorders and addictive disorders do not emerge at random in adults. Rather, early adverse experiences, in concert with heritable factors, alter the brain and the behavior (cognition, emotional regulation, social interaction styles) of children from a young age. These alterations likely result in vicious cycles, whereby vulnerable neural networks and maladaptive behavioral styles result in consequences (poor academic performance, unstable relationships, early engagement in high risk behaviors) that further contribute to risk of psychopathology. Over the last decade or two, work has outlined multiple neurobiological and psychological

consequences of early adverse experiences. Significant effort is now required to delineate the types of interventions that can minimize the consequences of early adverse experiences and to understand the ways in which such interventions act to alter long-term neural and behavioral patterns.

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## New appointment to Editorial Board

Dr. Amanda Newton is a clinician scientist in the Department of Pediatrics, Faculty of Medicine and Dentistry at the University of Alberta. Dr. Newton obtained her BScN (1999) and PhD (2004) from McMaster University with advanced clinical training in CBT and psychoanalytic psychotherapy with the Clinical Behavioural Sciences Program (Department of Psychiatry and Behavioural Neurosciences). She completed a post-doctoral fellowship in knowledge translation science at the University of Alberta before joining the Department of Pediatrics in 2007. Dr. Newton holds a Career Development Award from the Canadian Child Health Clinician Scientist Program and is a Canadian Institutes of Health Research (CIHR) New Investigator. Her research focuses on improving child and youth emergency mental health care.