# Annual Research Review: An expanded account of information-processing mechanisms in risk for child and adolescent anxiety and depression

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# Annual Research Review: An expanded account of information-processing mechanisms in risk for child and adolescent anxiety and depression

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**Background:** Anxiety and depression occurring during childhood and adolescence are common and costly. While early-emerging anxiety and depression can arise through a complex interplay of 'distal' factors such as genetic and environmental influences, temperamental characteristics and brain circuitry, the more proximal mechanisms that transfer risks on symptoms are poorly delineated. Information-processing biases, which differentiate youth with and without anxiety and/or depression, could act as proximal mechanisms that mediate more distal risks on symptoms. This article reviews the literature on information-processing biases, their associations with anxiety and depression symptoms in youth and with other distal risk factors, to provide direction for further research. **Methods:** Based on strategic searches of the literature, we consider how youth with and without anxiety and/or depression vary in how they deploy attention to social-affective stimuli, discriminate between threat and safety cues, retain memories of negative events and appraise ambiguous information. We discuss how these information-processing biases are similarly or differentially expressed on anxiety and depression and whether these biases are linked to genetic and environmental factors, temperamental characteristics and patterns of brain circuitry functioning implicated in anxiety and depression. **Findings:** Biases in attention and appraisal characterise both youth anxiety and depression but with some differences in how these are expressed for each symptom type. Difficulties in threat-safety cue discrimination characterise anxiety and are understudied in depression, while biases in the retrieval of negative and overgeneral memories have been observed in depression but are understudied in anxiety. Information-processing biases have been studied in relation to some distal factors but not systematically, so relationships remain inconclusive. **Conclusions:** Biases in attention, threat-safety cue discrimination, memory and appraisal may characterise anxiety and/or depression risk. We discuss future research directions that can more systematically test whether these biases act as proximal mechanisms that mediate other distal risk factors. **Keywords:** Anxiety; depression; risk factors.

## Introduction

Anxiety and depressive disorders are common in childhood and adolescence either occurring alone but often together (Merikangas, Nakamura, & Kessler, 2009). Anxiety disorders include several conditions that vary by the content of the anxiety symptoms and the degree to which symptoms are elicited by specific cues (as in specific phobia), specific sets of circumstances around particular themes (as in social phobia and agoraphobia), or are pervasive across general events and activities in the present or future (as in generalised anxiety disorder). Nonetheless, all anxiety conditions are characterised by overwhelming, persistent fears and worries. Depressive disorders include conditions where there are recurrent episodes of mood disturbance with effects on various physical and cognitive functions. While mood disturbances can present as low mood, loss of pleasure or irritability such as in major (unipolar) depression, these can also involve elevations in mood such as in bipolar depression. However, given reported differences in the clinical presentation of major and bipolar depression in adults (Forty et al., 2008) and controversy over whether these conditions share a similar aetiology and pathophysiology (Smith & Craddock, 2011), and instead, copious evidence suggesting comorbidity and similar features between major depression and anxiety (Clark & Watson, 1991), we focus only on major depression and anxiety disorders in our review of risk mechanisms.

Anxiety and depression that emerge in childhood and adolescence are debilitating, negatively impacting social and educational functioning, adult work functioning, life satisfaction and mental well-being (Essau, Lewinsohn, Olaya, & Seeley, 2014; Jaycox et al., 2009). Because of their recurrent nature and their effects on health and morbidity, anxiety and depression in youth incur major financial costs (Bodden, Dirksen, & Bogels, 2008; Mathews, Hall, Vos, Patton, & Degenhardt, 2011). Yet, current treatments for these early-emerging conditions are suboptimal (Ginsburg et al., 2014; Kennard et al., 2006), and accessing evidence-based treatments is also problematic (Merikangas et al., 2009). Delineating the risk mechanisms and their observable, measurable expression for child and adolescent anxiety and

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depression is crucial to identify at-risk youth, facilitate prevention or identify possible subtypes within these conditions. It can also permit an examination of whether current treatments target risk mechanisms and/or whether new complementary interventions are needed. Considering the similarities and differences between anxiety and depression in risk mechanisms can further inform the development of transdiagnostic interventions for shared features and symptom-specific interventions for unique aspects.

This article discusses risk mechanisms for child and adolescent anxiety and depression at the level of information processing. Information-processing factors have been discussed extensively in adult anxiety and depression, but it is important to consider their role in youth separately for three reasons. First, as many anxiety and depressive symptoms onset during development (Merikangas et al., 2009), information-processing factors studied in adult conditions could reflect consequences rather than precursors of symptoms. Second, the nature of information-processing factors and their association with symptoms could change with age based on maturational or experiential processes. This means that information-processing factors associated with adult conditions may differ in magnitude and direction to when they first appear during development, which is vital for detecting at-risk individuals. Third, as childhood and adolescence may reflect periods of protracted brain development and associated plasticity (Cohen Kadosh, Linden, & Lau, 2013), delivering interventions including altering maladaptive information-processes factors in childhood and adolescence could yield stronger effects and be more cost-effective in the long-term than interventions applied in adulthood.

On this basis, information-processing factors have been the subject of many reviews on anxiety and/or depression in childhood or adolescence (e.g. Dudeney, Sharpe, & Hunt, 2015; Haller, Cohen Kadosh, Scerif, & Lau, 2015; Pine & Fox, 2015; Platt, Waters, Schulte-Koerne, Engelmann, & Salemink, 2016; Shechner et al., 2012). However, our review expands these reviews in three ways. First, we focus on both conditions rather than one and explicitly consider which information-processing factors are common to both conditions, common to both but differentially expressed, unique to only one condition or understudied in one or both conditions. Second, whereas previous reviews have reviewed anxiety/depression-associated differences in attention, memory and interpretation stages of information processing separately from differences in fear conditioning, we consider an expanded conceptualisation that incorporates all of these forms of information processing (Figure 1A). Specifically, we conceptualise the evidence from fear conditioning studies of elevated responding to safety cues as reflective of biased information processing. Finally, we review these information-processing factors in relation to broader aetiological factors (Figure 1B). Longstanding models consider information-processing factors to maintain symptoms (e.g. Beck & Clark, 1997) but with some findings also suggesting that they are involved in symptom onset (Platt *et al.*, 2016). We consider information-processing factors as possibly 'mediating' the effects of 'distal' risk factors on symptom expression. As ample data point to factors such as genetic and environmental influences, temperament risks and perturbed neural functioning in many developmental disorders, including anxiety and depression in youth, it has been argued that these influences could give rise to cognitive disturbances that then influence behaviours or symptoms (Morton & Frith, 1995). It may be that factors such as genetics, environmental influences, temperament and perturbed brain function are more 'distal' and predispositional in their influence on symptom expression and are mediated through more proximal, precursory information-processing factors (Figure 1B). Of note, establishing whether variables mediate genetic risks has been discussed extensively through the concept of endophenotypes (markers that reflect genetic risks that are shared with particular psychiatric outcomes). However, we consider information-processing factors as mediating broader, nongenetic influences too.

As our review of information-processing factors for youth anxiety and depression culminates in the consideration of their linkages with more distal risk factors, we briefly summarise next what these distal risk factors are. Then, we consider each information-processing factor in Figure 1A, reviewing the nature of their relationship to youth anxiety and/or depression, and whether they characterise youth with candidate distal risk factors, potentially highlighting a mediational role of information-processing factors between distal risks and symptom expression (Figure 1B). In the final section, we discuss research directions for verifying whether information-processing factors mediate distal risk factors and highlight briefly implications for treatment.

## A brief summary of distal risk factors for anxiety and depression in childhood and adolescence

### *Genetic factors*

Reasonably consistent twin data show moderate *genetic* effects in anxiety and depression in youth. The magnitude of genetic effects on symptoms may increase with age (Waszczuk, Zavos, Gregory, & Eley, 2014); 'new' sources of genetic influence may emerge at particular time points across adolescence (Waszczuk, Zavos, Gregory, & Eley, 2016); and finally, there may be shared genetic variance between anxiety and depression in youth (Waszczuk et al., 2014). Studies uncovering which genes are involved have revealed

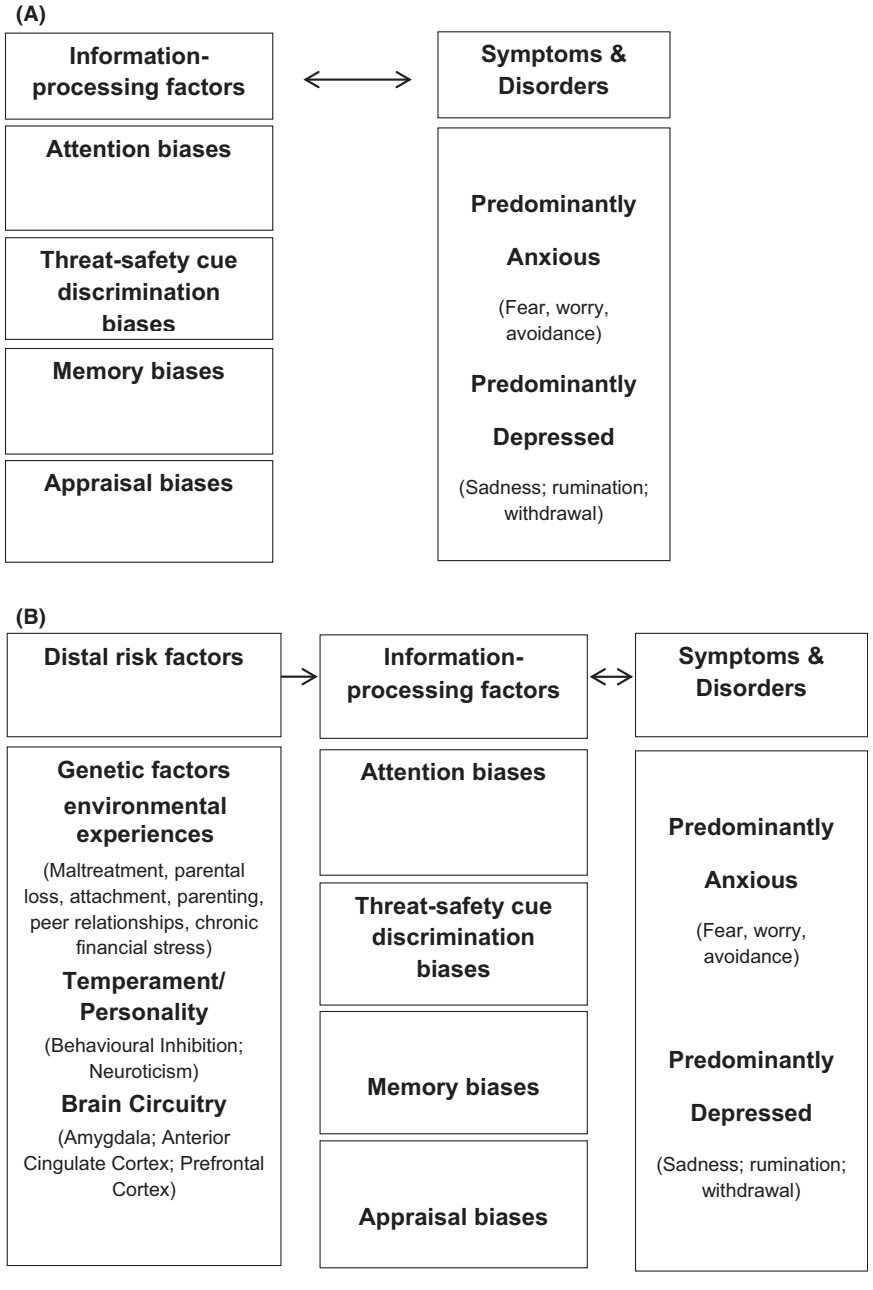


**Figure 1** (A) Information-processing biases in attention, threat-safety discrimination learning, memory and appraisal biases characterise anxious and/or depressed youth, with suggestions that these biases may maintain symptoms. (B) These biases in information processing could mediate or mark risks associated with more distal and predispositional factors

inconsistent findings with many candidate–gene association studies being unable to replicate initially promising associations between specific gene polymorphisms and behaviours, and more hypothesis-free genome-wide association studies failing to find associations that meet genome-wide level significance (Lester et al., 2016; Trzaskowski et al., 2013). Despite these uncertain results, there have nonetheless been efforts to investigate how genetic vulnerability is expressed through more intermediate mechanisms to influence symptoms. To establish whether information-processing factors mediate genetic risk (consistent with Figure 1B), family (including offspring of affected parent) studies, twin studies and candidate–gene studies have been used. Specifically, these data can assess whether the factor co-occurs with the condition within families, is heritable and has shared genetic variance with anxiety or depression, or is linked to the same candidate–gene region as that previously linked to anxiety/depression. These findings are summarised for each information-processing factor separately in subsequent sections.

### *Environmental factors*

Twin data also point to the importance of *nonshared environmental* contributions (experiences unique to the individual) to anxiety and depression in youth. These likely emerge across age but unlike genetic

factors appear different for anxiety and depression outcomes, potentially explaining their distinct rather than common features (Waszczuk et al., 2016). Other genetically informative designs also point to the *shared environment* that is, aspects of the environment that family members share with one another and which, independently from genetic inheritance, also contribute to family resemblance for anxiety and depression (Eley et al., 2015; Harold et al., 2011; Tully, Iacono, & McGue, 2008). Shared environmental influences may become less important with age on symptoms (Waszczuk et al., 2016).

While these data are informative in supporting environmental influences that are distinct from genetics on symptoms, they do not specify which social or experiential factors are involved. However, there is extant literature listing a plethora of social experiences associated with early-emerging anxiety and depression. These include *dysfunctional family dynamics* (e.g. abuse and neglect), nondysfunctional but *traumatic or stressful life events* (e.g. death or separation from parents), and variations in a range of interpersonal experiences such as *attachment*, *parent–child relationships*, *family relationships*, *negative peer relationships*, chronic *lifestyle* or *financial stressors* (Booth-Laforce et al., 2012; Goodyer, Kolvin, & Gatzanis, 1985; Jinyao et al., 2012; Lindert et al., 2014; McLaughlin, Costello, Leblanc, Sampson, & Kessler, 2012; Melhem, Porta, Shamseddeen, Walker Payne, & Brent, 2011; Platt, Cohen Kadosh, & Lau, 2013; Yap, Pilkington, Ryan, & Jorm, 2014; Zeanah et al., 2009). As with genetic influences, risks associated with environmental influences may be expressed on symptomatic outcomes by shaping patterns of information processing (Figure 1B); studies linking social/experiential factors to information-processing factors are discussed in subsequent sections.

### *Temperament traits*

Temperaments are early-emerging, stable patterns of behaviour that characterise an individual across contexts and which may predispose to certain symptomatic outcomes. One temperament style studied extensively in relation to anxiety and depression is behavioural inhibition (BI). BI refers to the tendency to respond fearfully to, or withdraw from novel or unfamiliar objects, people and situations. It has been captured through parent report and behavioural observations (across various laboratory-based challenges) and by various neurophysiological markers (Fox, Henderson, Marshall, Nichols, & Ghera, 2005). There is robust evidence from longitudinal studies suggesting that BI predicts anxiety disorder onset, particularly social anxiety (Gladstone, Parker, Mitchell, Wilhelm, & Malhi, 2005; Schwartz, Snidman, & Kagan, 1999), and may also be linked with depression (although this may be mediated through social anxiety; Gladstone & Parker, 2006). To the extent that BI increase risks on emotional symptoms, family studies of BI suggest that it reflects familial, genetic risks for anxiety or depression (Rosenbaum et al., 1993) such that offspring of depressed and anxious parents (particularly panic disorder) are more likely to have high BI than offspring of psychiatrically healthy parents, and that infants with high versus low BI have greater familial loadings of anxiety. However, several 'environmental' factors can moderate BI and whether it predicts anxiety outcomes. For example, infants high in BI and who are either insecurely attached (Shamir-Essakow, Ungerer, & Rapee, 2005) or experience permissive parenting (Williams et al., 2009) have higher anxiety. BI is, therefore, likely to mediate the complex interplay between genetic and early-life environment factors on anxious and possibly depressive symptoms. In the following sections, we consider whether the risks associated with BI are expressed on symptoms through information-processing factors, consistent with predictions in Figure 1B.

Neuroticism (or negative affect) is another early-emerging personality/temperament trait studied in relation to youth anxiety and depression. Characterised as being emotionally unstable, overly reactive, and showing high levels of negative affect, for example, worry and nervousness, adolescents high in neuroticism are at increased risk of developing anxiety and depression across time (Aldinger et al., 2014). As with BI, neuroticism may also reflect genetic risks for anxiety and depression (Luciano et al., 2012), and in the following sections, we consider whether neuroticism (and the risks that it reflects) also influences symptoms through information-processing factors, consistent with predictions in Figure 1B.

### *Brain circuitry abnormalities*

Differences in *functional* brain activity during the presentation of emotional stimuli have been reported between youth with and without anxiety and/or depression. Differences in terms of activity within a single region have emerged but also in the co-activation or functional connectivity between regions during specific tasks where brain activity is time locked to differential events that may probe distinct psychological processes and during resting state when there is no specific task instruction. Abnormalities relating to anxiety in youth have been found in the amygdala and within an extended medial prefrontal cortex (mPFC) network across emotion-generation tasks. These tasks typically present negative face emotions or negative situations such as peer evaluation/feedback (Beesdo et al., 2009; Blair et al., 2011; Ferri, Bress, Eaton, & Proudfit, 2014; Guyer et al., 2008; Lau, Belli, Gregory, Napolitano, & Eley, 2012; McClure et al., 2007; Spielberg et al., 2015; Thomas et al., 2001). A fairly reliable finding

regardless of the complexity of stimuli or task instructions is that anxious youth show increased amygdala activation than nonanxious youth to emotional (usually negative emotion) stimuli (Beesdo et al., 2009; Lau et al., 2012) with some studies showing that the degree of activation also correlates continuously with anxiety symptoms (Ferri et al., 2014; McClure et al., 2007; Thomas et al., 2001). During these simple emotion-generation tasks, differences between anxious and nonanxious youth in the anterior cingulate cortex (ACC; Spielberg et al., 2015) and other medial areas of the PFC such as ventromedial PFC (vmPFC) and dorsal medial PFC (dmPFC; McClure et al., 2007) and the orbitofrontal cortex (OFC; Beesdo et al., 2009) have also been reported as well as the ventrolateral PFC (vlPFC; Guyer et al., 2008). When considering neural differences associated with the processing of positive stimuli, anxiety-altered striatal activity has frequently been reported (Benson, Guyer, Nelson, Pine, & Ernst, 2015; Galvan & Peris, 2014; Guyer et al., 2012; Jarcho et al., 2015; Spielberg et al., 2015). Anxiety-associated differences have also been reported in the co-activation between these regions in response to task-based negative emotion provocation (Guyer et al., 2008; McClure et al., 2007; Spielberg et al., 2015) and during resting state. For instance, resting-state differences in the intrinsic functional connectivity between the amygdala and regions of the PFC including vmPFC, dmPFC and dorsolateral prefrontal cortex (dlPFC) have been reported, as well as with the insula and posterior cingulate cortex (Hamm et al., 2014; Roy et al., 2013).

Functional neuroimaging studies of youth with depression have used similar emotion-generation tasks to those in youth anxiety research finding perturbations in the amygdala and its connections with other regions within medial prefrontal cortical networks (Kerestes, Davey, Stephanou, Whittle, & Harrison, 2014). Responses to positive stimuli have uncovered anomalies in striatal activity (localised in the caudate) during reward anticipation and outcome of mostly monetary reward but social rewards, for example, peer acceptance too, with some alterations in the OFC during risky reward-related decisions. Finally, fMRI studies have examined neural differences during so-called cold cognitive tasks (Kerestes et al., 2014) which typically tap processes collectively described as involving (nonemotional) executive control, for example, working memory, selective or sustained attention, attention set-shifting and cognitive flexibility, and response inhibition. These tasks differentially activate other frontocingulate regions including dlPFC and vlPFC and ACC in depressed versus nondepressed youth, although the direction of group differences has been inconsistent across studies (Kerestes et al., 2014). Adopting a meta-analytic quantitative approach on a subset of these neuroimaging studies, Miller, Hamilton, Sacchet, and Gotlib (2015) studied regional brain functioning to the emotional content of stimuli (negative or positive) and to specific processes (those involved in emotion processing or executive function) – finding abnormalities in the thalamus and parahippocampal gyrus during affective processing; in the posterior insula during positive-valence tasks; in dlPFC and superior temporal cortex during negative valence tasks; and finally in the cuneus, dorsal cingulate cortex and dorsal anterior insula during executive control tasks. The connectivity between some of these regions, notably, within medial PFC areas including the pregenual ACC and subgenual ACC, and dorsomedial and ventromedial divisions of the PFC has also been found to be greater during resting state in depressed youth (Kerestes et al., 2014).

These patterns of neural disruptions during emotionally provocative but also nonemotional executive control tasks have been found to reflect distal genetic and environmental influences risks on anxiety and depression in youth (Christensen, Van Ameringen, & Hall, 2015; Gee et al., 2013; Goff et al., 2013; Lau et al., 2009, 2010; Maheu et al., 2010; Monk, Klein, et al., 2008; Tottenham et al., 2011), and their influence may be further expressed by modulating patterns of information processing (Figure 1B). Functional MRI studies that have employed tasks that specifically assess neural effects on information-processing factors are discussed in subsequent sections.

## A review of information-processing factors involved in child and adolescent anxiety and depression and their role as candidate mediators of distal risk factors

### *Biases in selective attention*

*Adult findings.* Anxiety and depression have been associated with attention biases for emotional stimuli (Cisler & Koster, 2010; Everaert, Koster, & Derakshan, 2012), manifesting as a disproportionate allocation of attention towards (a) threat-related stimuli in anxiety (angry faces and threat words) and (b) negative and/or pleasant stimuli in depression (sad and happy faces, negative and positive words). However, theoretical models and empirical evidence differ regarding the underlying mechanisms that mediate the bias and the extent to which automatic (involuntary) and controlled (voluntary) processes are implicated (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van, 2007; Beck & Clark, 1997; Eysenck, Derakshan, Santos, & Calvo, 2007; Gotlib & Joormann, 2010; Mogg & Bradley, 1998; Williams, Watts, MacLeod, & Matthews, 1997).

*Measuring attention biases in youth.* Studies measuring attention biases in youth often use the emotional Stroop task or the visual-probe task. These tasks infer attention biases for threat, negative

or positive stimuli from differences in response times to a secondary task under conditions where an emotional stimulus is overtly or covertly presented relative to conditions where a neutral stimulus is present. The degree to which an emotional stimulus interferes with this secondary task (in the Stroop task, this is colour labelling a word, while in the visual-probe task, it is responding to the location/type of a probe) suggests a preferential attention focus on the emotional stimulus. These studies have more recently been supplemented with eye tracking to provide more continuous assessments of attention allocation.

*Attention biases and youth anxiety.* A meta-analysis of 38 studies showed a significantly greater bias towards threat-related stimuli compared with neutral stimuli ($d$ = .54) in anxious youth that was greater than the bias shown by control children ($d$ = .15). Yet, group differences between anxious and nonanxious youth in how much attention was 'captured' by threat stimuli was modest ($d$ = .21; Dudeney et al., 2015). Age strongly moderated these effects, with a threat bias common to younger children and becoming more specific to anxious children with age.

A key question is at what stage of information processing do anxiety-differences emerge? Using eye-tracking, many studies report biases at early stages (Dodd et al., 2015; Shechner et al., 2013, 2015). Whether this bias is sustained varies across studies: Shechner et al. (2013) found no significant between-group differences during later stages of processing in one study, but in another reported sustained avoidance in anxious adolescents only (Shechner et al., 2015), a pattern that also characterised much younger anxious children (Dodd et al., 2015). Still others report sustained attention vigilance towards threat stimuli after anxiety induction (Seefeldt, Kramer, Tuschen-Caffier, & Heinrichs, 2014). Such findings appear consistent with studies employing behavioural measures, which have found patterns of threat vigilance and threat avoidance across stimulus exposure durations ranging from 500 to 1,250 ms (Salum et al., 2013; Waters, Bradley, & Mogg, 2014). Collectively behavioural and eye-tracking studies show that anxious youth do show biases in attention for threat stimuli relative to nonanxious peers. These biases are likely to involve involuntary and voluntary processes, emerging as attention biases towards threat and away from threat stimuli, compared with nonanxious youth for whom attention biases for threat appear to decline with development.

*Attention biases and youth depression.* Early studies comparing depressed and nondepressed youth primarily with the emotional Stroop task suggested no group differences in attention biases for negative stimuli (Dalgleish et al., 1997, 2003; Neshat-Doost, Moradi, Taghavi, Yule, & Dalgleish, 2000). However, more recent studies using the visual-probe task have found attention biases towards negative stimuli in clinical and community samples of depressed versus nondepressed youth. Biases have been observed across stimulus durations of between 500 and 1,250 ms and thus may reflect biases in voluntary attention allocation (Hankin, Gibb, Abela, & Flory, 2010; Osinsky, Losch, Hennig, Alexander, & MacLeod, 2012; Salum et al., 2013). Also consistent with these data are studies using inhibitory control tasks, where participants revert between trials where behavioural responses to emotional stimuli need to be inhibited, and ones where they do not. Therefore, it becomes crucial to pay attention to the changing response rule. These studies generally find attention biases towards negative stimuli in depressed relative to nondepressed youth (Kyte, Goodyer, & Sahakian, 2005; Ladouceur et al., 2006; Maalouf et al., 2012). Supplementing behavioural data with eye-tracking, one study using a passive-viewing task (with relatively long duration time of 20 s) found that depressed versus nondepressed children spent less time attending to sad faces and more time on positive faces, differences not observed at shorter stimulus durations (Harrison & Gibb, 2015). Together, the data suggest that in depression, there may be biases in the voluntary allocation of attention towards and away from negative stimuli.

*Attention biases and genetic/environmental risks.* Studies measuring attention biases in offspring of parents with anxiety disorders have shown attention biases towards threat stimuli compared with offspring of nonanxious parents (Mogg, Wilson, Hayward, Cunning, & Bradley, 2012; Waters, Forrest, Peters, Bradley, & Mogg, 2015), suggesting that attention biases in at-risk children may be familial. Candidate–gene association studies show that individuals with the low transmission efficacy allele variant of the 5-HTTLPR serotonin transporter gene (Pergamin-Hight, Bakermans-Kranenburg, van Ijzendoorn, & Bar-Haim, 2012), a candidate–gene polymorphism linked to both anxiety and depression, also show biased attention for threat. In terms of environmental factors, several studies have examined the relationship between threat attention bias and early-life adversity. However, while some have reported threat vigilance in maltreated samples (Pollak & Tolley-Schell, 2003; Shackman, Shackman, & Pollak, 2007), others have reported threat avoidance (Kelly et al., 2015; Pine et al., 2005). Studies have also examined the interaction of genetic and environmental factors on youth threat attention bias, with one finding that children who were carriers of the *5-HTTLPR* short allele and who also had a critical mother exhibited attentional avoidance (rather than vigilance) of angry faces (Gibb et al., 2011). Still, other studies have found that attention

avoidance of negative faces by anxious compared with nonanxious children was not due to genetic or shared environment influences but instead to large nonshared environmental contributions (Brown et al., 2013).

Two studies employing the visual-probe task with exposure durations of 500 ms and longer demonstrated that youth at-risk for depression by virtue of maternal depression exhibited an attention bias towards sad faces (Joormann, Talbot, & Gotlib, 2007; Kujawa et al., 2011). Some studies have examined how these familial risk effects on attention biases could be further moderated by genetic factors. In one study, increased maternal symptoms of depression predicted a greater attention bias away from threat but only in youths carrying the short (S or LG) alleles versus those homozygous for the long (LA) allele of the 5-HTTLPR genotype (Gibb, Benas, Grassia, & McGeary, 2009), but in another, it was only children of depressed mothers with reactive genotypes across the corticotropin-releasing hormone type 1 receptor (but not the 5-HTTLPR) who exhibited less sustained attention to sad faces and more sustained attention to happy faces (Owens et al., 2016). Finally, some studies examined the interaction of other risk variables relevant for depression. First, one study noted interactions between maternal depression and suppression, a maladaptive form of emotion regulation on youth attention bias away from/towards negative stimuli. For youth with mothers reporting high levels of depression, low suppression was associated with an attention bias towards negative stimuli, while high suppression was associated with an attention bias away from negative stimuli (Connell, Patton, Klostermann, & Hughes-Scalise, 2013). A second study found that offspring of mothers with either depression or anxiety displayed an attention bias towards negative stimuli if their mothers also lacked an attention bias towards positive stimuli (Waters et al., 2015).

*Attention biases and temperament risks.* A handful of studies assessed whether high BI is linked to attention biases. These studies have reported attention bias towards threat in those with high but not low BI (Perez-Edgar et al., 2010) and that attention bias towards threat moderated the relationship between BI during toddlerhood and social withdrawal in adolescence (Perez-Edgar et al., 2010, 2011), a key symptom of several anxiety and depressive conditions. Finally, a third study found a correlation between bias for negative words and neuroticism, but only in children with low effortful control (a trait marker of poor ability to control attention; Lonigan & Vasey, 2009).

*Attention biases and neural risks.* Threat attention biases may involve neural disruptions within circuits implicated in youth anxiety. Anxious youth manifest greater activation in the right vlPFC and the right amygdala to masked angry faces with a modestly weaker negative correlation between these structures compared with nonanxious youth (Monk et al., 2006; Monk, Telzer, et al., 2008) suggesting that biases during involuntary stages of attention allocation may be modulated by neural factors. There is also suggestion that initial heightened engagement of threat in bilateral parahippocampal/hippocampal clusters among anxious participants takes longer to attenuate when attention is directed away from threat than nonanxious adolescents (Price et al., 2014), suggestive of neural-based difficulties in voluntary attention disengagement. Consistent with this, studies examining brain activity when emotional distractors need to be ignored to carry out another task have reported significant between-group differences in the ACC (Swartz et al., 2014), in the left mPFC and right vlPFC (Strawn et al., 2012) and in connectivity between regions. Neuroimaging studies of youth depression have not investigated the neural substrates of biased attention.

### *Impaired threat-safety cue discrimination*

*Adult findings.* Associative learning theory has been used to explain how early emerging but persistent fears characteristic of anxiety may arise through fear conditioning: the process by which a neutral stimulus becomes a conditioned threat stimulus (CS+) through being paired with an aversive fear-provoking stimulus (often referred to as the unconditioned stimulus, UCS). Such fear associations are more effectively formed with repeated pairings of the neutral stimulus (or situation) with the aversive event (or outcome) but can also occur through one-trial learning (Ohman, Eriksson, & Olofsson, 1975). Conditioned fear does not have to occur through direct exposure, but can emerge when the contingency between the neutral stimulus and the aversive UCS is observed in or informed by other individuals (Rachman, 1977). However, as exposure to fear associations under these circumstances does not install fear in everyone, contemporary learning theories focus on how anxious individuals differ across processes of fear learning.

A meta-analysis of 44 studies containing 963 anxious individuals and 1,222 healthy participants (Duits et al., 2015) showed that while anxious individuals did not show differences in acquired fear to a CS+ (compared with nonanxious adults), they showed: (a) greater fear to a safety cue (or CS−) that had never been paired with an aversive UCS and (b) difficulties extinguishing fear, that is, when the CS+ no longer predicted the occurrence of the UCS, their fear to the CS+ persisted rather than attenuated across trials. In other studies, anxious adults also show greater fear to the wider context in which conditioning occurred (Grillon, 2002). These findings

relating to elevated fear to safe cues, a poorer capacity to extinguish fear to the conditioned threat cue, and a tendency to experience fear to context cues have been interpreted as difficulties discriminating threat from safety information (Craske, Kircanski, et al., 2008; Lissek, 2012). Because these learning differences are associated with fear responses, most of this literature has focused on linkages with anxiety rather than depression.

*Measuring impairments in threat-safety cue discrimination in youth.* Threat-safety cue discrimination experiments can comprise three phases: fear acquisition (where the CS+ and UCS are first co-presented); fear generalisation (where fear responses to the CS− and perceptually/conceptually similar stimuli to the CS− are presented); and fear extinction (where the CS+ no longer predicts the UCS). However, studying fear learning in youth has been hindered by the challenge of both (a) having to produce conditioned fear that is sufficiently high that it does not habituate before the end of the initial fear acquisition phase (so that individual differences to generalisation stimuli (GS) and during extinction can be assessed), and (b) ensuring that the UCS is ethically acceptable. Thus, most youth studies have used aversive noises (e.g. screams) as UCSs, which while unpleasant may differ in threat value to UCSs more conventionally used in adults such as shock. Conditioning to the context has been defined as the experimental setup (the room, the equipment) in which the conditioning experiment took place, the actual background screen in which the cues were presented, the intertrial interval, or the level of predictability with which the CS+ and UCS occur together (on the basis that more unpredictable occurrences generate increased contextual fear).

*Impaired threat-safety cue discrimination and youth anxiety.* Studies of youth anxiety report greater conditioned fear responses to the CS+ in anxious children and adolescents relative to nonanxious peers, although there are some inconsistencies across measures (skin conductance responses (SCR); verbal fear ratings; Britton et al., 2013; Craske, Waters, Craske, Bergman, & Treanor, 2008; Lau et al., 2008; Waters, Henry, & Neumann, 2009). Responses to the CS− during acquisition are also higher in anxious compared with nonanxious youth (Britton et al., 2013; Craske, Waters, et al., 2008; Haddad, Bilderbeck, James, & Lau, 2015; Waters et al., 2009). One study did not find group differences (Pliszka, Hatch, Borcherding, & Rogeness, 1993) though this investigated anxiety in attention-deficit hyperactivity disorder children, and another study found that group differences emerged in the absence of fear discrimination to the CS+ versus CS− in anxious children only (Liberman, Lipp, Spence, & March, 2006). These data largely replicate adult findings of elevated fear to the safety cue (CS−) in anxious individuals, but unlike adult data suggest that elevated fear may occur to the threat cue (CS+) as well depending on the measure utilised.

Studies investigating extinction in anxious youth yield mixed findings. Two studies reported higher fear to the CS+ in anxious compared with nonanxious children (Craske, Waters, et al., 2008; Waters et al., 2009) with another study of adolescents not finding this effect, though this could be explained by greater attrition among anxious participants (Lau et al., 2008). While there is evidence that during extinction, both anxious and nonanxious children and adolescents are more afraid of the CS+ than the CS− (Lau et al., 2008), there is also evidence that only anxious youth display differential fear to the CS+ versus the CS− (Liberman et al., 2006; Pliszka et al., 1993). Although more studies are needed to clarify these findings, the adult findings of greater fear to the CS+ during extinction among anxious individuals have nonetheless been reported in youth. Cohen Kadosh et al. (2015) investigated elevated fear to contextual cues by measuring differences in threat learning in unpredictable and predictable conditions in high and low anxious adolescents (aged 13–18). High anxious adolescents failed to discriminate between the CS+ and CS− and generalised their fear from the CS+ to the contexts in which they appeared. Using different methodology, affective picture viewing, another study found that young 4- to 8-year-old anxious children showed elevated SCRs throughout a baseline phase and to angry and neutral faces during picture viewing, suggestive also of elevated contextual fear (Waters, Neumann, Henry, Craske, & Ornitz, 2008).

Together these findings support the notion that anxiety during childhood and adolescence is associated with poor ability to discriminate threat and safety cues/contexts. Interestingly, longitudinal studies of youth have found elevated responding to safety stimuli but not threat stimuli (suggestive of threat-safety discrimination impairments) prospectively predicted anxiety disorder onset over a 4-year follow-up (Craske et al., 2012).

*Impaired threat-safety cue discrimination and youth depression.* As with adult data, fewer studies have explored fear conditioning and threat-safety cue discrimination differences in youth with depression. In the same longitudinal study investigating threat-safety cue discrimination as a predictor of anxiety disorders (Craske et al., 2012), depression onset was also investigated but with no support for a significant predictive association. These data alone, therefore, suggest that threat-safety cue discrimination is specific to anxiety. However, in a cross-sectional study of fear conditioning and extinction in community adolescents and adults (Den et al., 2015), high levels of depression (but not anxiety) predicted stronger conditioning and weaker extinction. Thus,

the degree to which depression is linked to threat-safety cue discrimination awaits further clarification.

*Threat-safety cue discrimination impairments and genetic/environmental risks.* Various studies show that children at-risk for anxiety due to familial history of anxiety show larger SCRs to the CS+ and the CS− relative to low-risk comparisons during conditioning, extinction and extinction retest phases of fear learning (Craske, Kircanski, et al., 2008; Craske, Waters, et al., 2008; Waters, Peters, Forrest, & Zimmer-Gembeck, 2014) as well as elevated contextual fear indexed by elevated SCRs throughout baseline and fear-potentiation protocols relative to low-risk youth (Grillon, Dierker, & Merikangas, 1998; Grillon et al., 2005). In one study assessing distal environmental risks on fear conditioning, maltreated children failed to exhibit differential SCRs to the CS+ versus CS− during conditioning (McLaughlin et al., 2016), and in another study, elevated fear to safe cues/contexts predicted anxiety after controlling for age and trauma exposure in children of low-income families, a chronic, early-life stressor (Jovanovic et al., 2014).

*Threat-safety cue discrimination impairments and temperament risks.* Elevated responding to safety cues has been observed in adolescents at-risk for emotional disorders due to neuroticism (Craske et al., 2009). BI in toddlerhood also positively predicted anxiety at 9 years but only among children with elevated context fear at age 7, indexed by startle responses during the intertrial interval when no explicit threat or safe cues were present (Barker et al., 2015). Thus, temperament risks may be associated with threat-safety discrimination impairments or interact with these impairments on anxiety symptoms.

*Threat-safety cue discrimination impairments and neural risks.* Several studies have assessed the neural modulation of fear conditioning and generalisation to safety cues. In the first, healthy adults, anxious adults, healthy adolescents and anxious adolescents were compared on fear to a previously conditioned but now extinguished threat stimulus (CS+), a safety stimulus never paired with the UCS (CS−) and GS, which were intermediate morphs of the CS+ and CS− during extinction recall (Britton et al., 2013). While there were some age-*independent* anxiety group differences (i.e. characterised both anxious adolescents and adults) during the evaluation of fear across all stimuli (CS+, CS− and GS) in the subgenual ACC, anxiety-by-age-group differences emerged in the vmPFC. Anxious adults showed general hypoactivation of this region to stimuli, while anxious youth showed an inverted u-shaped pattern of activity with greater activation to the CS+ and CS−, and the least activity for the GSs. The vmPFC may play a role in sensitivity to fear to threat and safety cues (and their indiscrimination), but this varies across anxiety group, and crucially, development. In a secondary analysis of these same data, Gold et al. (2016) investigated the effects of anxiety group and development on amygdala-PFC connectivity. As with the first study, intriguing differences emerged between anxious adults and anxious adolescents. When individuals were asked to either rate fear to one of the threat, safety or generalised stimuli or to remember if the face was one that had been associated with the UCS (i.e. the scream), anxious adults showed positive coupling between the amygdala and vmPFC, while anxious adolescents showed a negative connectivity. Both these sets of findings (Britton et al., 2013; Gold et al., 2016) suggest that neural correlates of fear generalisation and extinction in anxiety may change with age.

Finally, a third study also reported Age × Anxiety interactions, but rather than comparing how anxious adolescents varied to anxious adults, this study investigated how age trajectories of neural substrates of threat-safe discrimination varied between healthy and anxious participants. Although Haddad et al. (2015) reported some contradictory findings by reporting decreased activation in mPFC, bilateral amygdala and right hippocampus to the CS+ (vs. a neutral stimulus) in anxious compared with control participants, there were different age patterns in anxious versus nonanxious individuals. Anxious participants tended to show more negative associations with age in the bilateral anterior insula, right dlPFC and left amygdala to the CS− (vs. a neutral stimulus) than control participants where associations with age tended to be positive. The authors interpreted these findings to reflect relatively delayed maturation of regions involved in inhibiting fear to a safe stimulus in anxious adolescents, potentially reflective of poorer ability to discriminate safe from threat stimuli.

### Memory differences

*Adult findings.* Some literature has linked anxiety with memory biases, the tendency to selectively remember anxiety-congruent threatening stimuli, but these data remain contradictory (Mitte, 2008) with meta-analyses showing no significant impact of anxiety on implicit memory and recognition of threat-related information. In contrast, memory biases have been robustly implicated in adult depression. Adults with depression (and healthy individuals under negative mood induction) *recall and recognise more negative words* and fewer positive words than controls – findings that also appear when memories are measured using implicit tasks (though only when words are encoded conceptually; see Gotlib & Joormann, 2010 for a review). Another memory phenomenon, overgeneral memory (OGM), the tendency to describe general categories of

similar events when given a cue word rather than specific autobiographical memories (memories of one's own experiences; e.g. I always enjoy a good party instead of I enjoyed Jane's party on Friday) has also been studied extensively in adults with depression (but not anxiety). Specifically, adults with depression struggle to provide specific memories on tasks probing OGM compared with nondepressed adults, differences that are large, and not easily explained by education, IQ or more general episodic memory difficulties (Williams et al., 2007). OGM could represent a strategy of managing emotional distress following an aversive event by truncating memory searches to avoid recalling unwanted memories.

*Measuring memory biases in youth.* Explicit memory tasks ask participants either to freely recall or recognise words that have been processed in self-referential ways while implicit memory tasks prompt participants to complete word fragments or make lexical decisions about words they had previously encoded. OGM has been measured by asking participants to give a specific memory to a cue word that can be positive (hopeful), negative (ashamed) or neutral (grass). Generated memories are then coded for specificity.

*Memory biases and youth anxiety.* Studies of anxious youth report memory biases for threat information, but as with adults, there are discrepant findings (Daleiden, 1998; Dalgleish et al., 2003; Moradi, Taghavi, Neshat-Doost, Yule, & Dalgleish, 2000; Zupan, Hammen, & Jaenicke, 1987). Field and Field (2013) found that anxiety did not predict negative memory biases. However, when using a self-referent memory task, Vassilopoulous (2012) found that high compared with low socially anxious children recalled fewer positive self-referent words and more negative self-referent words even after controlling for depression. No studies have investigated OGM in anxious youth.

*Memory biases and youth depression.* The tendency to recall/recognise negative material and/or the reduced ability to remember positive information are mixed in youth with depression. Some studies have reported between-group differences (Hammen & Zupan, 1984; Neshat-Doost, Taghavi, Moradi, Yule, & Dalgleish, 1998; Zupan et al., 1987) or significant associations with symptoms (Bishop, Dalgleish, & Yule, 2004; Gencoz, Voelz, Gencoz, Pettit, & Joiner, 2001; Goldstein, Hayden, & Klein, 2015) but many do not find differences (Dalgleish et al., 2003; Timbremont, Braet, Bosmans, & Van Vlierberghe, 2008). The association between explicit memory biases in depression may be more consistent in adolescents than in children – age trends that could relate to methodological considerations such as whether self-referent encoding tasks in younger children pose difficulties in discerning meaning/relevance. Alternatively, they could suggest that neurocognitive and/or experiential maturation may be required before memory biases emerge as a stable characteristic of depression.

Many studies have investigated OGM in youth depression. Except one study that investigated depression in a mixed-disorder inpatient group (de Decker, Hermans, Raes, & Eelen, 2003), studies have mostly revealed less specific autobiographical memories in adolescents but also children with depression (compared with nondepressed peers; Kuyken, Howell, & Dalgleish, 2006; Park, Goodyer, & Teasdale, 2002; Rawal & Rice, 2012; Vrielynck, Deplus, & Phillippot, 2007). What studies have differed on is whether individuals with other psychiatric diagnoses also show similar patterns of OGM, raising questions over whether these are distinct features of depression. Several studies (Kleim & Ehlers, 2008; Rawal & Rice, 2012; Sumner et al., 2011) have found that fewer specific memories predict subsequent episodes of depression longitudinally (after controlling for baseline depressive symptoms) especially in girls (Hamlat et al., 2015) and in those with previous depressive episodes (Kleim & Ehlers, 2008). However, not all studies have been promising (Crane et al., 2016).

*Memory biases and genetic/environmental risks.* Memory biases do characterise youth of depressed mothers, particularly when their cognitive schema are primed (Taylor & Ingram, 1999). In terms of specific genes, one study found that the observed effect of memory biases in at-risk offspring only characterised daughters of depressed mothers who had a particular genotype within the catechol-O-methyltransferase gene (chromosome 22q11.2) which has been linked to depression (Asarnow, Thompson, Joormann, & Gotlib, 2014). Thus, mood-congruent memory biases could reflect inherited risks for depression with no studies yet examining genetic links to anxiety.

Studies of the origins of OGM have focused on environmental risk factors, possibly because OGM has been conceptualised as a way of regulating emotional responses against traumatic events. Indeed, many studies have investigated the link between early-life childhood exposure to trauma and OGM finding mostly positive linkages (Crane et al., 2014; Valentino, Toth, & Cicchetti, 2009). In addition, many studies (though not all, e.g. Crane et al., 2014) find that memory specificity interacts with stressors including emotional maltreatment to predict depression (Hamlat et al., 2015; Sumner et al., 2011). These suggest that while OGM could mediate distal early-life environmental adversity on depression, acute stress may then precipitate the effects of OGM on symptoms.

*Memory biases and temperament risks.* One study assessed the effects of temperament and trait anxiety on memory for pain. Although trait-anxious children showed a greater likelihood of recalling more pain than they initially reported, emotionality (which has some similarities to neuroticism) had no significant effect on memory performance (Rocha, Marche, & von Baeyer, 2009). As studies are few in number and the data are inconsistent, it is not yet clear whether temperaments associated with anxiety and depression are linked to mood-congruent memory biases.

*Memory biases and neural risks.* One study has measured amygdala responses during the encoding phase of emotional faces, before a postscan recognition test (Roberson-Nay et al., 2006). Adolescents with depression showed poorer recognition performance compared with healthy and anxious participants as well as greater amygdala responses to faces that were subsequently remembered versus those that were forgotten. Though not directly addressing memory biases for negative versus positive material, these data suggest that heightened amygdala responses during encoding of emotional faces may influence memory biases for particular emotional stimuli. As child and adolescent anxiety and depression are linked to hyperactive amygdala responses, these neural risks may be expressed via memory processes.

### Biases in stimulus appraisals

*Adult findings.* Biased appraisal processes have been associated with both anxiety and depression in adults (Beck & Clark, 1997). Anxious and depressed adults show a tendency to *interpret* ambiguous information negatively and/or in threatening ways and are more likely to *attribute* negative events to internal causes and positive events to external causes. Although there may be differences in the expression of these biases, notably that anxiety is linked to threat interpretations and depression with negative interpretations, methodologically, definitively determining whether one explanation is threatening versus generally negative is challenging – and most studies collapse across these distinctions. As it has been difficult to measure these more subtle differences in expression of appraisal biases, findings for youth anxiety and depression are reviewed together.

*Measuring appraisal styles in youth.* Biases in interpretations have commonly been assessed using hypothetical ambiguous scenarios, that is, those where a threatening/negative or a benign/positive explanation are possible. These are presented verbally or visually, and participants select/endorse between different interpretations. One strength of these methods is that they describe realistic exchanges and events, but a weakness is that they are susceptible to overt response biases. Another method uses homophones and homographs, words with the same sound but different meanings (e.g. pain/pane) and words that have several meanings (e.g. mug), where one meaning is always threatening and at least one is benign. Asking participants to generate sentences with these words offers ways of implicitly assessing biases. However, the limited number of homophones/homographs with salient threat and nonthreat meanings restricts their usefulness. Another method that again implicitly assesses interpretative biases presents participants with faces exhibiting ambiguous expressions (e.g. angry or fearful faces not displaying emotions at full intensity) to investigate whether there are different thresholds for interpreting nonverbal cues as threatening or negative. While some studies have assessed fear ratings towards different face emotions, others measure misclassification. Attributional style is usually measured with verbal hypothetical scenarios that resemble positive and negative everyday events. Participants are presented with competing internal and external attributions, which they can differentially endorse.

*Appraisal biases and youth anxiety and depression.* Anxious and depressed youth both endorse threatening/negative interpretations more and benign/positive ones less often than healthy comparisons (Haller, Raeder, Scerif, Cohen Kadosh, & Lau, 2016; Orchard, Pass, & Reynolds, 2016). Using the homophone/homograph tasks, anxious and depressed youth more often select threatening/negative meanings of words than healthy comparisons (Eley et al., 2008; Hadwin, Frost, French, & Richards, 1997; Taghavi, Moradi, Neshat-Doost, Yule, & Dalgleish, 2000). With ambiguous faces, anxiety-associated effects have been found in the miscategorisation (but not fear ratings) of various negative faces (Lau et al., 2012; Waters et al., 2008). However, few studies have adopted this approach with depressed youth. Anxiety- and depression-linked biases have been found in the appraisal of locus of control with respect to negative versus positive events, such that anxious and depressed individuals tend to attribute negative events to internal causes (e.g. failing an exam because I'm not clever) and positive events to external causes (e.g. passing an exam because the teacher set easy questions; Haller et al., 2016; Lau et al., 2012; Lau, Rijsdijk, & Eley, 2006). While biases in interpretations and attributions appear to robustly relate with anxiety and depression, there has been suggestion that some of these associations with symptoms are more frequently found or are stronger in adolescents than children (Waite, Codd, & Creswell, 2015), or

change in their nature with development (Lau et al., 2012).

*Appraisal biases and genetic/environmental risks.* Some studies have found that offspring of parents with anxiety disorders or parents of anxious children do not differ to children/parents of nonanxious children on indices of threat interpretation bias (Gifford, Reynolds, Bell, & Wilson, 2008; Waters et al., 2008). However, others have found such differences between groups in addition to significant correlations between mothers' and children's threat interpretations cross-sectionally (Creswell, Schniering, & Rapee, 2005) and across time (Creswell, Shildrick, & Field, 2011). Still other studies have found that offspring of parents with panic disorder showed larger threat interpretations after priming with panic stimuli than offspring of parents with animal phobia and healthy controls (Schneider, Unnewehr, Florin, & Margraf, 2002), suggesting tentatively that the content of appraisal biases in at-risk offspring closely match those of their parents.

High-risk offspring of depressed mothers form significantly more negative interpretations than offspring of mothers with no psychiatric history across a number of tasks (Dearing & Gotlib, 2009) – as well as negative attributions (Jaenicke et al., 1987). Twin studies of attributional biases have also shown genetic influences on these two types of negative cognition, and moreover, these genetic effects are shared with those for depressive symptoms (Lau, Rijsdijk, & Eley, 2006; Lau et al., 2012). Thus, genetic risks for depression (and anxiety, given there is shared genetic variance) may be reflected in negative attributions.

In relation to environmental factors, one study of older adolescents (Wells, Vanderlind, Selby, & Beevers, 2014) found that participants who had compared to those who had not experienced child abuse systematically interpreted ambiguous sentences negatively and were more likely to experience depressive symptoms. Studies of abused children have also shown hostile attributions, but this may mediate externalising rather than internalising problems (e.g. Dodge, Pettit, Bates, & Valente, 1995).

*Appraisal biases and temperament risks.* To our knowledge, no studies have linked temperament or personality risk factors for anxiety and depression with appraisal biases.

*Appraisal biases and neural risks.* One study (Peris & Galván, 2013) presented anxious and nonanxious youth with faces that were paired with anxiety-provoking vignettes or neutral vignettes. The anxious group showed significantly greater activation in the mPFC to faces paired with anxiety-provoking vignettes relative to the control group and to faces paired with neutral vignettes. Moreover, greater activation in mPFC significantly correlated with ratings of the anxiety-provoking vignettes in the anxious group. Data from this preliminary study suggest that brain circuitry implicated in anxious (and depressed) children and adolescents may contribute to the tendency to resolve ambiguous cues and situations negatively or in threatening ways.

## Summary and future directions

### *Associations between information-processing biases and anxiety and depression outcomes in youth*

This review first considered the empirical basis for biases in (a) attention deployment to threatening/negative stimuli, (b) discriminating between conditioned threat stimuli and safety cues, (c) the retrieval of negative versus positive information and general versus specific information, and (d) the appraisal of ambiguous or emotional information as characterising youth with anxiety and/or depression (Figure 1A). Our review showed some similarities but also differences between biases implicated in youth anxiety versus depression (Table 1). Reasonably robust data showed that both anxiety and depression were characterised by attention biases; however, there were differences in the expression of this

**Table 1** Assessment of whether biases in attention, threat-safety discrimination learning, memory and appraisal characterise youth with anxiety and/or depression (upper section), and whether these biases mark risk effects of more distal influences (genetics, environment, temperament, neural; lower section)

| | | | | | |
|---|---|---|---|---|---|
| Symptom expression | Anxiety | ✓✓ (Threat) | ✓ | ✓ | ✓✓ |
| | Depression | ✓✓ (Negative) | ? | ✓✓ | ✓✓ |
| Information-processing variables | | Attention biases | Threat-safety cue discrimination biases | Memory biases | Appraisal biases |
| Distal risks | Genetics | ✓ | ? | ✓ | ✓ |
| | Environment | ✓ | ? | ? | ? |
| | Temperament | ✓ | ✓ | ? | ? |
| | Neural | ✓ | ✓ | ? | ✓ |

✓✓ denotes solid evidence for an association; ✓ denotes weak evidence for an association; and ? denotes a lack of studies investigating the association or where the association is ambiguous with respect to linking to a particular distal risk factor.

bias across symptom type. In individual studies that included both anxious and depressed youth, a threat-specific bias emerged in anxious youth and a negative/sad-specific bias emerged in depressed youth (Hankin et al., 2010). Across studies, there was a suggestion of biases in involuntary and voluntary attention towards and away from threat in anxiety, while depression studies were more supportive of biases towards negative stimuli and away from positive material during later voluntary stages of processing. The ability to discriminate between conditioned threat and safety stimuli was studied mostly in relation to anxiety with mixed evidence over the association with depression. Depression was consistently linked to memory retrieval biases of negative material and of overgeneral memories. The few studies of anxiety-related memory biases suggest that they manifest on self-referent encoding tasks rather than on recall tasks of little personal relevance. Finally, interpretation and attribution biases were generally consistent in characterising both anxiety and depression.

While these data appear to suggest a strong case for the role of information-processing biases in anxiety and depression in youth, some caveats need to be recognised. We have already alluded to an uneven distribution of research efforts in establishing associations between some domains of information processing with specific symptom types. For example, threat-safety cue conditioning was not studied much in depression, whereas memory biases were not studied much in anxiety. Before conclusions on differences in the information-processing profiles of anxiety and depression in children and adolescents are reached, these gaps need to be addressed. A strong research design would be one where anxiety and depression are both assessed and analysis would assess the unique/common effects associated with each. Even where particular patient groups are selected, the co-occurrence of the other condition should be taken into account to gain a clearer picture over these unique versus common biases. A second caveat is that most studies examining information-processing biases in children and adolescents use cross-sectional designs limiting conclusions over whether these variables are actually precursory to symptoms. Longitudinal or experimental designs need to be conducted to examine temporal precedence or causality to inform whether these factors mediate risks. While longitudinal designs involve data collection at two distinct time points to enable prospective associations to be computed, in experimental designs, causal relationships are supported by changes in symptoms following manipulation/induction of bias. A final caveat is that many of these studies rarely consider the moderating role of age or development on associations. It was intriguing that for many of the biases (attention, memory, appraisal), the association with symptoms changed, usually growing stronger (or more consistently established) with age. This could be due to methodological reasons, whereby the same tasks or measures were not appropriate to particular age groups. Alternatively, it may be that some biases are only triggered by experience, or once a particular level of neurocognitive maturity is achieved. Regardless, from the point of view of establishing biases in relation to anxiety or depression, it may be important to take a wide age range and explicitly control for age differences, or to only examine associations in narrow age ranges, rather than to allow potential age differences to affect the real magnitude of bias.

### *Associations between information-processing biases and distal factors in youth*

This review then considered the evidence on whether these information-processing biases are associated with 'distal' risk factors, specifically genetic, environmental, temperament and neural factors, linked to anxiety and depression outcomes in youth (Figure 1B). While there was support that one or more 'distal' risk factor is linked to each information-processing factor (Table 1), the review highlights the large-scale systematic research that is needed to provide a more comprehensive account.

Questions about whether information-processing variables mediate *genetic* risks for anxiety and depression in youth were generally inconclusive. There was preliminary support from studies linking candidate genes associated with symptoms to attention bias and memory bias measures, but as the findings of many candidate–gene studies have been difficult to replicate, these initial findings need to be treated with caution until further data from larger samples are acquired and analysed. This is particularly true as some of the findings linking gene variants and information-processing biases involved complex interactions with third variables (e.g. having a critical parent), it is unclear whether these are valid or false-positive findings. Comparatively more studies assessing the familial origins of information-processing biases have assessed at-risk youth, defined as those with a family history (usually in parents) of anxiety or depression. However, while such studies are informative about the presence of information-processing biases in at-risk youth, they are ambiguous with respect to whether this risk reflects inherited risks or occur through shared environmental variables such as parenting. In this respect, twin studies do enable specific genetic explanations to be tested while controlling for shared environmental influences, but such studies have mostly been conducted for appraisal biases only. Thus, the degree to which these information-processing variables are heritable and mediate genetic risks for anxiety and depression in youth remains unclear.

A handful of studies assessed 'environmental' factors involved in information-processing biases – and

again because of a paucity of work in this area, conclusions are unclear. For attention biases, one twin study suggested large nonshared environmental effects – and other studies conducted in maltreated samples also suggested an effect of early-life adversity on the later emergence of biases. Similarly, child maltreatment has also been associated with difficulties in threat-safety discrimination, OGM and appraisal biases – data that seem to imply an environmental origin. However, the presence of gene–environment correlations, that is, genetic effects on many aspects of environmental exposure including early-life adversity means that we cannot be sure that these are pure environmental effects.

The most convincing findings linking temperament variables and biases are those investigating attention biases in BI. A few studies have investigated temperament and threat-safety cue discrimination, but these preliminary results require replication. Finally, studies examining BI, neuroticism and biases in memory and appraisal are needed to assess whether temperament risk might be expressed through biases at these other stages of information processing. A growing number of fMRI studies have assessed the neural correlates of biased information processing in anxious/depressed youth. While this area of research is in its infancy, data so far suggest that brain circuitry dysfunctions could be expressed to alter the way that individuals attend to emotional information, learn about emotional situations, encode emotional events, and categorise or appraise emotional situations. However, a limitation of these data is that the tasks used during brain data acquisition are not always equivalent to those used to establish associations at the observed behavioural level. Thus, it is unclear whether neural activation during these tasks really tap these information-processing biases.

We have already highlighted some caveats in the reported relationships between specific distal factors and symptoms, but a wider issue is that to assess whether the information-processing variables reviewed here are mediational in nature, that is, acting as the bridge between other putatively distal risk factors and symptoms, statistical mediation analysis ideally in the context of longitudinal designs needs to be conducted. Mediation analyses assess the extent to which direct paths between a distal factor and symptom outcomes can be explained by a statistically significant 'indirect' path, which involves an association between the distal factor and a third variable (the mediator) and an association between this third variable and symptom outcome. Addressing questions of mediation will involve acquiring data of a particular distal factor (e.g. candidate–gene information, a measure of early-life adversity, a measure of BI or even a measure of neural activity during emotion-generation), a particular information-processing variable and symptom outcomes. Longitudinal designs would enable temporal precedence to be established in the mediation of risks. Such data are not yet available and will be easier to obtain for some mediation pathways than others. For example, these analyses will be more difficult with neural data given the costs of running fMRI studies preventing large sample sizes needed for mediation. For other risk factors, such as genetics, mediational analyses may be challenging as the direct association between genetic risk variants and symptoms is only tentatively supported.

## Conclusions

Establishing whether information-processing factors mediate distal risks as illustrated in Figure 1B is only the beginning of a more comprehensive account of risk mechanisms of anxiety and depression in youth. Eventually, one may begin to further differentiate distal risk factors into those that are very distal in the timing of their effects (e.g. early-life adversity) and those that are much more proximal on symptom expression (e.g. acute life events, neural factors) – differences that could have implications in whether and how their effects are mediated via information processing. Information-processing factors reviewed here could also collectively reflect more basic deficiencies in executive functions, a set of cognitive processes important for the control of behaviour but this is not well-established in youth. Finally, it is not yet clear how the constellation of distal risks leads to differences in the expression of biases that characterise anxiety versus depression. There has been some suggestion that common features between anxiety and depression could arise from shared genetics while differences in environmental experience (threat vs. loss) lead to their distinction. Whether shared genes for anxiety and depression result in similar information-processing biases while different environmental experiences shape differences in the expression of biases is not yet known. Addressing these gaps provides a roadmap for future research to more systematically assess intermediate risk mechanisms for anxiety and depression in youth.

It is also worth discussing how identifying information-processing variables and their expanded role in mediating risks can potentially drive treatment innovations. Some information-processing factors are already targeted in cognitive-behavioural therapy for youth anxiety and depression: exposure-based therapy is used to encourage fear extinction in anxiety, while cognitive restructuring can target maladaptive appraisals in both anxiety and depression. Behavioural experiments can then reinforce these principles in real life. However, other information-processing variables may be targeted less directly or in less

standardised ways in current treatments. In response to this, recent years have seen the development of new experimental interventions for targeting attention and interpretation biases but also for encouraging more specific memories and learning to differentiate threat from safety stimuli. The fact that both the well-established and newer experimental interventions have varied in how effective they have been at changing information-processing biases and symptoms highlights how greater knowledge about the role of information-processing biases in mediating the influence of distal risks on anxiety and depression in youth can help guide the continued development of improved interventions for the prevention and treatment of anxiety and depression in children and adolescence.

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## Key points

- While early-emerging anxiety and depression can arise through a complex interplay of distal factors such as genetic and environmental influences, temperament characteristics and brain circuitry, the more immediate or proximal precursory mechanisms that confer risks on symptoms are poorly delineated.
- Reasonably robust data showed that both anxiety and depression are characterised by attention biases; while anxiety was characterised by biases in involuntary and voluntary attention towards and away from threat, depression studies supported biases towards negative stimuli and away from positive material during later voluntary stages of processing.
- The ability to discriminate between conditioned threat and safety stimuli was studied mostly in relation to anxiety with mixed evidence over the association with depression.
- Depression was consistently linked to memory retrieval biases of negative material and of overgeneral memories.
- Interpretation and attribution biases were generally consistent in characterising both anxiety and depression.
- While there was support that one or more 'distal' risk factor (genetic, environmental, temperamental, and neural) is linked to each information-processing factor, our review highlights the large-scale systematic research that is needed to provide more concrete evidence that cognitive and learning variables mediate the effects of such distal risks.

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