COGNITION AND EMOTION, 2013
Vol. 27, No. 2, 193–216, http://dx.doi.org/10.1080/02699931.2012.712950

Routledge
Taylor & Francis Group

INVITED REVIEW

Toward an integration of cognitive and genetic models of risk for depression

Brandon E. Gibb[1], Christopher G. Beevers[2], and John E. McGeary[3,4]

[1]Psychology Department, Binghamton University (SUNY), Binghamton, NY, USA
[2]Department of Psychology, University of Texas, Austin, TX, USA
[3]Providence Veterans Affairs Medical Center, Rhode Island Hospital, Providence, RI, USA
[4]Department of Psychiatry and Human Behavior, Brown University, Providence, RI, USA

Downloaded by [State University NY Binghamton] at 10:13 26 February 2013

There is growing interest in integrating cognitive and genetic models of depression risk. We review two ways in which these models can be meaningfully integrated. First, information-processing biases may represent intermediate phenotypes for specific genetic influences. These genetic influences may represent main effects on specific cognitive processes or may moderate the impact of environmental influences on information-processing biases. Second, cognitive and genetic influences may combine to increase reactivity to environmental stressors, increasing risk for depression in a gene × cognition × environment model of risk. There is now growing support for both of these ways of integrating cognitive and genetic models of depression risk. Specifically, there is support for genetic influences on information-processing biases, particularly the link between 5-HTTLPR and attentional biases, from both genetic association and gene × environment (G × E) studies. There is also initial support for gene × cognition × environment models of risk in which specific genetic influences contribute to increased reactivity to environmental influences. We review this research and discuss important areas of future research, particularly the need for larger samples that allow for a broader examination of genetic and epigenetic influences as well as the combined influence of variability across a number of genes.

Keywords: Depression; Information processing; Psychiatric genetics; G × E.

Correspondence should be addressed to: Brandon E. Gibb, Department of Psychology, Binghamton University (SUNY), Binghamton, NY 13902-6000, USA. E-mail: bgibb@binghamton.edu

This project was supported by National Institute of Child Health and Human Development grant HD057066 awarded to BEG, and National Institute of Mental Health grant MH076897awarded to CGB.

© 2013 Taylor & Francis

Downloaded by [State University NY Binghamton] at 10:13 26 February 2013

INTRODUCTION OF COGNITIVE AND GENETIC MODELS OF DEPRESSION RISK

According to cognitive models of depression (e.g., Beck, 1967, 1987; Clark, Beck, & Alford, 1999; Williams, Watts, MacLeod, & Mathews, 1997), individuals' characteristic ways of attending to, interpreting, and remembering stimuli in their environment may contribute to the development and maintenance of the disorder. These information-processing biases are hypothesised to be disorder specific such that depression and depression-risk is characterised by biases specifically for stimuli conveying themes of sadness or loss, whereas anxiety, for example, is characterised by information-processing biases specifically to threat-relevant stimuli (Clark et al., 1999; Mathews & MacLeod, 2005; Williams et al., 1997). In cognitive models of depression, information-processing biases are conceptualised within a vulnerability–stress framework. That is, although all individuals are at increased risk for depression following negative life events, this risk is thought to be moderated by one's information-processing such that risk is greater among individuals exhibiting more biased information processing. There is considerable support for cognitive models of depression, including the vulnerability–stress hypothesis, in predicting symptoms and diagnoses of depression in children, adolescents, and adults (see Abela & Hankin, 2008; Clark et al., 1999; Gotlib & Joormann, 2010; Haeffel et al., 2008, for reviews).

There is also clear evidence for genetic influences on depression risk. Specifically, heritability estimates suggest that approximately 37% of the variance in risk for depression is due to genetic influences (Sullivan, Neale, & Kendler, 2000). Given this, researchers have become increasingly interested in identifying specific genetic influences on depression risk. Building from the monoamine hypothesis of depression (Schildkraut & Kety, 1967), researchers initially focused on genes known to regulate neurotransmission of monoamines, particularly serotonin. These studies yielded some support for links between specific genes and depression, including genes coding for serotonin and dopamine transmission, though the magnitude of these relations is generally small (see López-León et al., 2000, for a meta-analytic review). More recent studies, therefore, have taken two approaches to address these relatively weak findings. First, paralleling research testing cognitive vulnerability–stress models of depression, researchers have examined the role of specific genetic influences that may increase reactivity to environmental stressors within a gene × environment (G × E) model of risk. Although there have been some mixed findings, there is growing evidence that genes influencing serotonergic and hypothalamic–pituitary–adrenal (HPA) axis functioning moderate the impact of environmental stress on depression risk (see Karg, Burmeister, Shedden, & Sen, 2011; Nugent, Tyrka, Carpenter, & Price, 2011, for reviews). Second, recent association studies have taken a broader, more atheoretical approach, focusing on genome-wide scans (genome-wide association studies; GWAS) of hundreds of thousands of polymorphisms at a time. Although the GWAS approach has yielded some positive findings, there has been little replication across samples (Lewis et al., 2010; Muglia et al., 2010; Shi et al., 2010; Shyn et al., 2010). Most recently, therefore, researchers have begun exploring endophenotypes/intermediate phenotypes (Gottesman & Gould, 2003), which are more basic processes that may be more directly under the influence of specific genes that may increase depression risk. It is this line of research that has led to the emerging interest in integrating cognitive and genetic models of depression risk.

INTEGRATING COGNITIVE AND GENETIC MODELS

Information-processing biases as an intermediate phenotype

As noted above, depressed individuals are often plagued by an inability to process emotional information in an unbiased manner. They are

Downloaded by [State University NY Binghamton] at 10:13 26 February 2013

confronted by ruminative dysphoric thoughts that they find difficult to disengage from (Ellenbogen, Schwartzman, Stewart, & Walker, 2002, 2006; Koster, De Raedt, Goeleven, Franck, & Crombez, 2005), often experience depression-relevant intrusive thoughts even when intentionally trying to avoid such thoughts (Beevers, Wenzlaff, Hayes, & Scott, 1999; Wenzlaff, Rude, Taylor, Stultz, & Sweatt, 2001; Wenzlaff, Wegner, & Roper, 1988), and selectively attend to dysphoric stimuli (Gotlib, Krasnoperova, Yue, & Joormann, 2004; Kellough, Beevers, Ellis, & Wells, 2008).

These mood congruent cognitive biases appear to have good biological validity, as experimental depletion of central serotonin predicts facilitated processing of sad stimuli on a Go/No-go task (Murphy, Smith, Cowen, Robbins, & Sahakian, 2002) and decreased cognitive flexibility (Clarke, Dalley, Crofts, Robbins, & Roberts, 2004). There is also preliminary evidence for the heritability of similar biases, such as ruminative thought (Kendler, Gardner, & Prescott, 1999) and negative attributional styles (Lau, Rijskijk, & Ely, 2006), in familial association studies. Further, twin studies have suggested that cognitive processes that likely support biased information processing—such as inhibiting dominant responses, updating working memory representations, and shifting between tasks—are highly heritable (Friedman et al., 2008).

Hasler, Drevets, Manji and Charney (2004) concluded that "attentional and mnemonic biases toward processing of mood-congruent information including sad, unpleasant and negative words, emotional facial expressions, and memories are reliable and relatively specific neuropsychological findings in MDD [major depressive disorder]" (p. 1767). Further, they concluded that biased processing of mood-congruent information is a key component of MDD, has good biological validity, can be assessed reliably, and has high clinical relevance. As a result, they concluded that biased processing of mood congruent stimuli is a highly plausible and important putative intermediate phenotype for MDD. As discussed below, a significant challenge now facing researchers is to determine which genes are most likely to influence this intermediate phenotype of biased information processing.

Gene × cognition × environment model of risk

Although most of the focus on integrating cognitive and genetic models of depression has been on the role of information-processing biases as intermediate phenotypes, we have recently highlighted a second way in which these models may be meaningfully integrated (Gibb, Benas, Grassia, & McGeary, 2009; Gibb, Urhlass, Grassia, Benas, & McGeary, 2009). Specifically, both cognitive and genetic models of depression risk focus on factors that affect individual differences in reactivity to environmental stress (Abramson, Metalsky, & Alloy, 1989; Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Clark et al., 1999; Rutter, Moffitt, & Caspi, 2006). The theories are framed in terms of vulnerability–stress or stress–diathesis models of risk in which characteristics of the individual (information-processing biases or genetic profile) may heighten reactivity to environmental stress. As noted above, there is considerable support for cognitive theories' vulnerability–stress hypothesis in children, adolescents, and adults (see Abela & Hankin, 2008; Haeffel et al., 2008; Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008, for reviews) and there is growing support for G × E models of depression risk (see Karg et al., 2011; Nugent et al., 2011, for reviews). Based on this, we have proposed that individuals exhibiting biased information processing who also carry specific genetic profiles associated with heightened stress reactivity would be particularly likely to develop depression following exposure to environmental stressors (a gene × cognition × environment, G × C × E, model of risk).

CHOICE OF GENES

A key consideration of either method of integrating cognitive and genetic models of depression

Downloaded by [State University NY Binghamton] at 10:13 26 February 2013

risk is the choice of which of the approximately 25,000 genes (encompassing approximately 3 billion DNA base pairs; Pertea & Salzberg, 2010) in the human genome upon which to focus. As noted above, there are two typical approaches taken in genetic association studies: a theory-driven focus on a relatively small number of polymorphisms using a candidate gene approach or a theory-free examination of hundreds of thousands of single-nucleotide polymorphisms (SNPs) using a genome-wide association approach. There is a tension in the field between these two approaches related to the sample size required for an adequately powered analysis of the (intermediate) phenotype examined. For example, one would expect that phenotypes closer to the mechanism of action of the gene (such as neuroimaging as compared to the more distantly impacted behavioural or diagnostic phenotypes) would show larger effects of genetic variation. However, the cost and difficulty of more intensive phenotyping efforts often precludes the acquisition of the large-scale samples that would be required for GWAS-level investigation. If one accepts the premise that there is substantial heterogeneity in the diagnosis of depression, then it is perhaps unsurprising that GWAS studies of depression would yield disappointing findings. An oft argued point in psychiatric genetics is that diagnostic criteria can be very reliably assessed, without necessarily describing a homogeneous condition from a genetics standpoint. Use of a heterogeneous phenotype might therefore dilute the ability of GWAS to detect a consistent signal. An intermediate phenotype or endophenotype such as information-processing bias may be a more homogenous outcome that would be more amenable to determining genetic influences. However, the relative difficulty in obtaining these data has the consequence of limiting sample size below that typically required for GWAS-scale analysis. Another related point is the idea that some endophenotypes may not be specific to DSM-described diagnoses (e.g., attention bias to salient cues may underlie multiple forms of psychopathology including depression, anxiety, and substance misuse). This further complicates GWAS studies based upon diagnoses because diagnostically defined cases and controls may not segregate with the underlying biology that contributes to the psychopathology (cf. the Research Domain Criteria Project developed by the National Institute of Mental Health). In addition, the specific targets of domains of attentional bias may be influenced by specific forms of environmental exposure (e.g., to sad vs. angry facial expressions from a parent while growing up). Failure to account for this environmental variability would necessarily cloud GWAS attempts to study genetic underpinnings of this neurocognitive construct. Because of this, therefore, research examining information-processing biases has focused on candidate polymorphisms in specific genes. The key question, then, is which of the 25,000 genes should offer the greatest promise in this research. Many strategies may be useful to narrow the list of potential genes to examine in these types of studies. Traditional strategies would include the use of animal models, pharmacology, and neurobiological knowledge related to candidate gene selection (e.g., determining which genes are highly expressed in brain regions thought to underlie the phenomenon).

With regard to attentional biases, although animal models do exist, few studies have used these paradigms (e.g., Passetti, Chudasama, & Robbins, 2002). Further, to our knowledge, none have been conducted with genetically informative animal models in a fashion that would identify potential candidate genes (e.g., differential attention bias in conditional knock-out mice to identify genetic underpinnings of the phenotype). Use of such behavioural paradigms may provide new avenues of investigation for the human condition when coupled with technologies that provide a means for identifying which genes impact the phenotype (e.g., knockout and other transgenic manipulations, RNA interference, etc.).

The literature on medications that alter attention bias is similarly sparse (though growing). This strategy for candidate gene identification leverages knowledge of pharmacology to identify biological systems that underlie a phenotype and, by extension, the genes involved in that biological system. An example of this approach was the use of olanzapine to validate the

Downloaded by [State University NY Binghamton] at 10:13 26 February 2013

importance of the dopamine system (in particular D4 receptors coded by the *DRD4* gene) in the phenotype of craving for alcohol (Hutchison et al., 2003). Care must be taken in this approach to assure that the specific phenotype of interest is not being altered through some non-specific mechanism. For example, attention broadly defined is likely to be impacted by a variety of pharmacological agents—e.g., the sedating effects of the antihistamine diphenhydramine alter attention broadly (Kay, 2000), but may not have specific effects on biased attention for emotional stimuli. Studies that have looked for pharmacological impacts on depression-relevant attentional bias find compelling evidence that selective serotonin reuptake inhibitors (SSRIs) impact biased attention in both depressed individuals and healthy controls (Harmer, Goodwin, & Cowen, 2009) suggesting that variation in the serotonin (*SLC6A4*) and noradrenalin (*SLC6A2*) transporter genes may be important genetic influences.

Currently, one of the most promising strategies for targeting genetic systems that may underlie information-processing biases is leveraging knowledge of the neuroanatomical correlates of these biases. Information-processing biases are driven by a combination of bottom-up (amygdala) and top-down (prefrontal cortex; PFC) processes (see Bishop, 2008; De Raedt & Koster, 2010; Frewen, Dozois, Joanisse, & Neufeld, 2008, for reviews). Therefore, genes influencing activity of the amygdala, prefrontal cortex, and functional connectivity between these two regions provide good targets for association studies. Another potentially important target is the group of genes known to affect HPA axis activity, as the HPA axis also affects information-processing biases (De Raedt & Koster, 2010). These may be particularly appealing genes to examine in studies testing G × E (and G × C × E) models of risk.

Thus far, the strongest candidate gene to emerge with respect to these considerations is a functional polymorphism (5-HTTLPR) in the serotonin transporter gene (*SLC6A4*). There are two common variants in 5-HTTLPR, a short allele (S) and a long allele (L), with the S allele exhibiting less transcriptional efficiency than the L allele (Lesch et al., 1996). More recently, studies have suggested a triallelic variation (S, L_G, L_A; e.g., Hu et al., 2005), with the L_G allele exhibiting functional equivalence with the S allele. There is increasing evidence that carriers of these lower expressing alleles (S or L_G) exhibit stronger amygdala reactivity to emotional stimuli (see Munafò, Brown, & Hariri, 2008, for a review) and decreased functional connectivity between the amygdala and subregions of the prefrontal cortex (Pacheco et al., 2009; Pezawas et al., 2005). There is also evidence that 5-HTTLPR genotype may moderate age-related increases in functional connectivity between prefrontal and other brain areas between childhood and adolescence, with S homozygotes showing fewer age-related increases in connectivity than L homozygotes (Wiggins et al., 2012). Finally, studies have found that 5-HTTLPR genotype predicts cortisol reactivity to laboratory-based stressors, with the majority of research showing that carriers of the lower expressing 5-HTTLPR alleles exhibit stronger and more sustained cortisol response to these stressors (Gotlib, Joormann, Minor, & Hallmayer, 2008; Mueller, Brocke, Fries, Lesch, & Kirschbaum, 2010; Way & Taylor, 2010; but see also Bouma & Riese, 2010), though there is evidence that this effect may be moderated by prior stress exposure (Alexander et al., 2009; Mueller et al., 2011) or polymorphisms in other candidate genes (Armbruster et al., 2009; Dougherty, Klein, Congdon, Canli, & Hayden, 2010). Given these findings, the majority of research examining genetic influences on information-processing biases thus far has focused on 5-HTTLPR genotype.

This said, research in imaging genomics has also suggested the potential importance of other candidate genes. For instance, the catechol-O-methyltransferase (COMT) enzyme breaks down dopamine and is primarily responsible for clearing out dopamine in the prefrontal cortex, as it has little impact on striatal dopamine (Frank, Doll, Oas-Terpstra, & Moreno, 2009). The Val variant

Downloaded by [State University NY Binghamton] at 10:13 26 February 2013

of the *COMT* (rs4680) genotype catabolises dopamine at up to four times the rate of the *COMT* Met variant (Egan et al., 2001). Thus, *COMT* Met allele homozygotes generally perform better than *COMT* Val allele carriers on tasks that require prefrontal function (Egan et al., 2001; Camara et al., 2010). The dopamine receptor D4 (DRD4) is also highly distributed in the prefrontal cortex and minimally expressed in the striatum (Oak, Oldenhof, & Van Tol, 2000). The short (S) version (2–6 repeats) of the *DRD4* gene is believed to be a more efficient variant in terms of RNA transcription compared to the long (L) repeat (7 or more repeats; Schoots & Van Tol, 2003), though we should note that coding schemes for this polymorphism have been inconsistent and more work is required to characterise this highly variable gene (see McGeary, 2009, for a review). That said, *DRD4* genotype has been associated with enhanced anterior cingulate cortex function (a dopamine rich brain region) and better executive attention (Fan, Fossella, Sommer, Wu, & Posner, 2003). The executive attention network is involved in the control of cognition and emotion (Bush, Luu, & Posner, 2000), which suggests that the *DRD4* is a good candidate for studying cognitive vulnerability to depression. Finally, given that the development of information-processing biases reflects neural plasticity to some extent, neurotrophic factors such as brain-derived neurotrophic factor (BDNF) may be relevant. BDNF is a protein involved in neuronal and synaptic development (Egan et al., 2003). The *BDNF* gene contains a non-synonymous single nucleotide polymorphism resulting in the amino acid substitution (valine to methionine) at codon 66 (Val66Met, rs6265). Importantly, variation in the *BDNF* gene has been linked to depression, related endophenotypes, and antidepressant medication response (Yu & Chen, 2011). However, since BDNF has been shown to modulate serotonergic neurons (Martinowich & Lu, 2008), it is unclear if the neurotrophic factors represent a unique aetiological pathway or are a critical component of the already identified serotonergic pathway.

SUPPORT FOR THE ROLE OF INFORMATION-PROCESSING BIASES AS AN INTERMEDIATE PHENOTYPE

Genetic association studies of information-processing biases

A number of studies have examined whether genetic polymorphisms are directly associated with different aspects of cognitive vulnerability to depression (Elliott, Zahn, Deakin, & Anderson, 2011). By far, the majority of prior work has examined genetic associations with biased attention for emotional stimuli; therefore, we will review that literature in more depth. Fewer genetic association studies have examined other cognitive processes such as rumination and recall of emotional information. We review all published findings to date in these areas; however, we will not review genetic association studies that have examined other aspects of neuropsychological functioning (e.g., executive functions). Although other neuropsychological functions likely contribute to biases in attention, interpretation, and recall, an exhaustive review of all prior neuropsychological research and depression is beyond the scope of this article. We instead focus on studies that measure biased processing of emotional information as the primary outcome of interest.

Genetic association studies of attentional biases. Many studies have now associated genetic variants with biased attention for emotional information. Notably, several studies have linked the 5-HTTLPR insertion/deletion polymorphism (Lesch et al., 1996) with biased attention for emotion stimuli. The first study to do so (Beevers, Gibb, McGeary, & Miller, 2007) presented negative emotional stimuli at two different stimulus durations (14 ms and 750 ms) to a small sample of psychiatric inpatients genotyped for 5-HTTLPR. Carriers of the 5-HTTLPR S allele demonstrated biased attention toward anxiety-related words (e.g., scared, attack) at both stimulus durations relative to those homozygous for the L allele.

Downloaded by [State University NY Binghamton] at 10:13 26 February 2013

More recently, partly in an effort to rule out third variable explanations such as differential severity of psychopathology across allele groups, researchers have examined genetic associations with attentional bias in healthy populations. For instance, across two studies that presented stimuli for longer durations (1,500 ms), 5-HTTLPR S allele homozygotes had greater difficulty disengaging attention from happy, fearful, and sad faces than 5-HTTLPR L allele homozygotes. Further, difficulty disengaging attention from emotional stimuli increased as the number of short alleles increased (Beevers, Wells, Ellis, & McGeary, 2009). When stimuli are presented briefly (e.g., 500 ms), individuals homozygous for the 5-HTTLPR L allele exhibit attentional avoidance of negative images and preferential attention toward positive images (Fox, Ridgewell, & Ashwin, 2009) and a bias away from negative (anxiety, dysphoric, and self-esteem) word stimuli (Kwang, Wells, McGeary, Swann, & Beevers, 2010). Finally, within an adolescent sample, the number of S alleles was positively associated with attentional bias for angry faces and inversely associated with attentional bias for happy faces (Pérez-Edgar et al., 2010). Taken together, these studies suggest that among healthy individuals, carriers of the 5-HTTLPR S allele display an attentional bias towards negative stimuli and have difficulty disengaging attention from emotional stimuli in general, whereas those homozygous for the 5-HTTLPR L allele display biased attention away from negative stimuli and do not experience difficulty with disengagement of attention from emotional stimuli.

We should note, however, that this work provides an incomplete picture of biased attention, as none of these studies examined the effortful regulation of emotional information (Beevers, 2005; Carver, Johnson, & Joormann, 2008). Rather, most prior work has examined relatively automatic attentional biases observed early in the stream of information processing. Recently, two studies have examined associations between the 5-HTTLPR and a more effortful form of information processing. Among healthy control participants, eye movements were recorded to obtain a relatively continuous index of attention allocation (cf. Hermans, Vansteenwegen, & Eelen, 1999; Isaacowitz, 2006) while participants viewed a 2×2 matrix of positive and negative images (International Affective Picture Set, IAPS; Lang, Bradley, & Cuthbert, 2005) for 30 seconds (Beevers, Ellis, Wells, & McGeary, 2010). Notably, individuals homozygous for the 5-HTTLPR S allele selectively attended to positive images over time to a greater extent than threatening, neutral or dysphoric images. This bias was not evident in the first five seconds, but instead emerged in the later stages of processing (i.e., seconds 5–20). A second study, this time using emotional facial expressions rather than emotional images, found a very similar pattern of results. Carriers of the 5-HTTLPR S allele were more likely to direct attention towards happy faces compared to sad faces over the course of the 30-second trial (Beevers, Marti et al., 2011). In contrast, those homozygous for the 5-HTTLPR L allele viewed the stimuli in an unbiased manner. In sum, carriers of the 5-HTTLPR S allele display a bias towards emotional information during the earliest stages of information processing (e.g., $<1{,}500$ ms). However, after this initial period of information processing, 5-HTTLPR S allele carriers may then begin to strategically shift attention towards positive stimuli in an effort to regulate heightened reactivity to negative stimuli. In contrast, individuals homozygous for the 5-HTTLPR L allele appear to show an early bias towards positive information and away from negative information and then subsequently regulate emotional information in a more unbiased manner.

Genetic association studies of other information-processing biases. Although the majority of work in this area has focused on attentional biases, there is also some evidence for genetic influences on rumination, the tendency to perseverate on problems and negative feelings, which represents an important cognitive vulnerability for depression (Nolen-Hoeksema, 2000). Ruminative thinking predicts the onset of depression, prolongs episodes

Downloaded by [State University NY Binghamton] at 10:13 26 February 2013

of negative mood, and hinders cognitive and behavioural efforts to improve mood (see Nolen-Hoeksema et al., 2008, for a review). Variation in a gene regulating brain-derived neurotropic factor (BDNF) has been linked to the tendency to ruminate, though results have been somewhat mixed. For example, one study found that the presence of the *BDNF* Met allele was associated with *lower* levels of rumination, compared to Val/Val homozygotes, in adolescent girls; however, no relation was observed between *BDNF* and rumination in their mothers until the authors focused specifically on mothers with adult-onset depression, among whom the *BDNF* Met allele was associated with *higher* levels of rumination (Hilt, Sander, Nolen-Hoeksema, & Simen, 2007). In a separate study of adults with no history of major depression, Met allele carriers exhibited *higher* levels of rumination than Val/Val homozygotes (Beevers, Wells, & McGeary, 2009). In contrast, results from a large community sample showed that carriers of the Met allele exhibited *lower* levels of rumination than Val/Val homozygotes (Juhasz et al., 2011). Finally, one study found no evidence for the link between *BDNF* genotype and brooding rumination in women or their children (Gibb, Grassia, Stone, & Uhrlass, 2012). Therefore, although there is some evidence that the Val66Met polymorphism gene may contribute to differences in rumination, the direction of this relation has differed across studies and future research is needed to determine factors (environmental, demographic, or epistatic) that may moderate the relation between *BDNF* genotype and rumination (see further discussion below).

Relatively few studies have linked genetic variants to memory biases for emotional information. One interesting study found that a deletion variant in *ADRA2B*, a gene that encodes for the α2b-adrenergic receptor, was associated with enhanced memory for emotional stimuli in a large sample of healthy adults and in survivors of the Rwandan civil war (De Quervain et al., 2007). The α2b-adrenergic receptor influences amygdala function (Cousijn et al., 2010), which in turn may modulate hippocampal activity and enhance memory consolidation for emotionally salient information (Maheu, Joober, Beaulieu, & Lupien, 2004). Prior work had found that pharmacologic manipulation of the α2b-adrenergic receptor influences recall of emotional information in humans (O'Carroll, Drysdale, Cahill, Shajahan, & Ebmeier, 1999), so this result appears quite promising. Variation in the catechol-O-methyltransferase (*COMT*) Val158Met polymorphism has also been associated with enhanced recall of emotional memory, with Val homozygotes showing better recognition of negative emotional expressions than Met homozygotes (Weiss et al., 2007). In contrast, two studies have found no 5-HTTLPR genotype main effect for verbal emotional memory (Roiser, Müller, Clark, & Sahakian, 2007; Strange, Kroes, Roiser, Tan, & Dolan, 2008), though other work has found significant 5-HTTLPR × life stress effects for recall of emotional information (Lemogne et al., 2009; see below for further discussion).

Finally, 5-HTTLPR genotype has been linked to various other forms of cognitive vulnerability to depression in individual studies, though firm conclusions await replication in independent samples. For example, children carrying the 5-HTTLPR S allele, compared to those homozygous for the L allele, exhibit more negative attributional styles (Sheikh et al., 2008) and more negative self-referent memory biases (Hayden et al., 2008). In addition, undergraduates carrying the 5-HTTLPR S allele exhibited more dysfunctional attitudes than those homozygous for the L allele, but only for one of the two subscales of the Dysfunctional Attitudes Scale (Weissman & Beck, 1978)—dysfunctional attitudes regarding performance evaluation but not approval by others (Whisman, Johnson, & Smolen, 2011). In this study, dysfunctional attitudes were not related to variation in two other genes, the dopamine D2 receptor gene (*DRD2*, rs18000497) or *COMT* (rs4680).

Gene × environment studies of information-processing biases

The majority of studies examining genetic influences on information-processing biases has

Downloaded by [State University NY Binghamton] at 10:13 26 February 2013

focused on the main effects of candidate polymorphisms. However, building from research examining environmental contributors to the development of cognitive vulnerability to depression (see Abela & Hankin, 2008, for a review), we and others have proposed that candidate polymorphisms should be most strongly linked to the presence of information-processing biases in the context of environmental stress. Said another way, specific candidate polymorphisms may help to identify which subgroups of individuals are most likely to develop information-processing biases in the presence of specific environmental stressors.

Gene × environment studies of attentional biases. Focusing first on attentional biases, there is growing evidence that 5-HTTLPR genotype moderates the link between exposure to specific environmental stressors and the presence of experience-specific biases in attention. Building from research suggesting that children with a history of physical abuse exhibit attentional biases specifically for angry faces but not other facial displays of emotion (see Pollak, 2003, for a review), researchers have proposed that the attentional biases observed among abused children result from conditioning to the angry expressions of the abuser (cf. Lee, Lim, Lee, Kim, & Choi, 2009; Pischek-Simpson, Boschen, Neumann, & Waters, 2009), which then generalised to facial displays of anger from other individuals. To the extent that this is true, consistent exposure to any specific emotional expression from a parent would result in the development of attentional biases specific to that emotion type. Framed within a G × E model of risk for the development of attentional biases, this link should be stronger among individuals whose genetic profile may make them more responsive or sensitive to emotionally salient environmental cues. For example, as reviewed above, carriers of the 5-HTTLPR S allele appear to exhibit difficulty disengaging attention from emotional stimuli generally, rather than any specific emotion type (Beevers, Wells, Ellis et al., 2009), which is consistent with fMRI data showing that S allele carriers exhibit heightened amygdala reactivity to a variety of emotional facial expressions (Dannlowski et al., 2007; Munafò et al., 2008). Supporting this G × E model of risk, children of mothers with a history of major depression exhibited attentional biases specifically for sad (but not angry or happy) faces, but only if they carried at least one copy of the 5-HTTLPR S or L_G allele (Gibb, Benas et al., 2009). Among children homozygous for the L_A allele, there was no significant relation between maternal depression history and children's attentional biases. Complementing these findings, children of mothers who displayed high levels of criticism (expressed emotion-criticism) exhibited attentional biases specifically for angry (but not happy or sad) faces, but again only if they carried the 5-HTTLPR S allele (Gibb et al., 2011). Finally, women's 5-HTTLPR genotype moderated the link between reports of childhood physical abuse and attentional biases for angry faces (Johnson, Gibb, & McGeary, 2010). Specifically, among women carrying the 5-HTTLPR S allele, a reported history of childhood physical abuse was associated with attentional biases for angry (but not happy or sad) faces; among women homozygous for the L allele, the relation between physical abuse history and attentional biases was not significant. Though based on cross-sectional data, these studies provide preliminary support for the hypothesis that candidate polymorphisms associated with increased reactivity to environmental stress, when combined with the occurrence of environmental stress, may contribute to the development of attentional biases. They also provide preliminary support for potential specificity between the types of environmental stress experienced (e.g., maternal depression vs. maternal criticism) and the types of attentional bias exhibited (e.g., attentional biases for sad vs. angry faces).

Gene × environment studies of other information-processing biases. There is also preliminary evidence that 5-HTTLPR genotype moderates the link between environmental events and

Downloaded by [State University NY Binghamton] at 10:13 26 February 2013

individuals' sensitivity in detecting facial displays of emotion. Specifically, using a task in which facial displays of emotion are gradually morphed between neutral and full expressions of emotion, adults with higher, compared to lower, levels of childhood emotional abuse correctly identified angry faces at lower levels of signal strength (lower morph level), but only if they carried at least one copy of the 5-HTTLPR S or L_G allele (Antypa, Cerit, Kruijt, Verhoeven, & Van der Does, 2011). These differences were limited to participants' sensitivity in detecting angry facial expressions (level of signal strength/morph required for correct identification); there were no differences in participants' accuracy in labelling the emotions. Paralleling the findings for attentional biases presented above, this G × E effect appeared to be experience-specific in that it was only observed for angry faces and not for happy or sad faces. In contrast, studies examining the role of 5-HTTLPR genotype in moderating the link between parental depression and individuals' ability to recognise facial displays of emotion have yielded more mixed results. For example, in one study, 5-HTTLPR genotype did not moderate the link between family history of depression and young adults' sensitivity or accuracy in recognising facial displays of emotion (Mannie, Brostow, Harmer, & Cowen, 2007). However, in another study, adolescents exposed to maternal depression who carried two copies of the 5-HTTLPR S allele were less, rather than more, accurate in labelling emotional faces (particularly angry faces) than adolescents with only one or no copies of the S allele (Jacobs et al., 2011). With these two studies, however, it should be noted that maternal/parental depression was defined as a history of depression during the parents' lifetime and it is not clear whether the adolescent/young adults were actually exposed to parental depression during their lifetimes. To the extent that children develop information-processing biases through associative learning mechanisms as suggested above, one would only expect these biases to be present in individuals exposed to parental depression during their lifetimes. Future research is needed, therefore, to clarify whether the mixed results for parental depression are due to timing differences across studies or to some other factor(s).

As noted in the previous section, there is some evidence for a relation between *BDNF* genotype and rumination, though the results are decidedly mixed, suggesting the presence of moderating factors. Addressing this, studies have examined whether environmental influences moderate the impact of *BDNF* genotype on levels of rumination and findings from studies testing G × E models are much more consistent. People who ruminate tend to believe that ruminative thinking helps them understand and solve problems (Papageorgiou & Wells, 2001, 2003). Thus, adverse events may provide the fodder for rumination and increases in adverse events are likely to increase rumination. Consistent with a G × E model of rumination, one small study found that carriers of the 5-HTTLPR short allele reported higher levels of rumination than L allele homozygotes but only when they experienced recent life stress (Canli et al., 2006). Similarly, individuals homozygous for the 5-HTTLPR S allele who also experienced higher levels of emotional abuse in childhood reported higher levels of rumination in adulthood than individuals carrying at least one copy of the L allele (Antypa & Van der Does, 2010). Further expanding this research, a study that simultaneously examined *BDNF*, 5-HTTLPR, and life stress found significant 5-HTTLPR × life stress and *BDNF* × life stress interactions. Individuals carrying two copies of the 5-HTTLPR S allele or two copies of the *BDNF* Met allele ruminate more under conditions of life stress, compared to the other genotypes (Clasen, Wells, Knopik, McGeary, & Beevers, 2011). Moreover, the accumulation of risk alleles (i.e., aggregate number of 5-HTTLPR S and *BDNF* Met alleles) across genes was associated with significantly greater rumination in the context of life stress. These results suggest that both 5-HTTLPR and *BDNF* Val66Met moderate the relation between life stress and rumination.

Thus far, we have focused on the role of distal or proximal negative events in moderating the magnitude of genetic influences on

Downloaded by [State University NY Binghamton] at 10:13 26 February 2013

information-processing biases. However, an important component of cognitive models of depression (e.g., Clark et al., 1999) is that information-processing biases are hypothesised to remain latent until primed by negative life events or negative mood. Given this, a complementary line of work is now examining whether experimentally manipulating mood state can amplify the genetic association with cognitive biases for emotional information. Depression often follows the onset of life stress (Kessler, 1997), so how an individual processes emotional information in the context of a negative mood may be particularly important for revealing a cognitive vulnerability to depression (Scher, Ingram, & Segal, 2005). Consistent with this approach, the interaction between 5-HTTLPR and *BDNF* Val66Met polymorphisms significantly predicted change in dysfunctional thinking from before to after a sad mood induction (Wells, Beevers, & McGeary, 2010). Specifically, carriers of two copies of the lower expressing 5-HTTLPR alleles (S or L_G) who were also homozygous for the *BDNF* Val allele endorsed higher levels of dysfunctional attitudes after a dysphoric mood induction. In contrast, the presence of a Met allele was associated with attenuated dysfunctional thinking among S/L_G 5-HTTLPR homozygotes. Further, across two studies, the dopamine D4 receptor (*DRD4*) genotype has been linked to attentional biases after a dysphoric mood induction (Wells, Beevers, & McGeary, 2011). Specifically, Study 1 demonstrated that long (i.e., seven or greater tandem repeats) DRD4 allele-carriers versus short *DRD4* homozygotes had increased attention for sad facial stimuli, but only after a sad mood induction. Study 2 demonstrated an association between the *DRD4* long allele and attention for negative stimuli (sad and fear expressions) following a sad mood provocation. Finally, 5-HTTLPR S allele carriers experience greater difficulty disengaging attention from negative stimuli after a dysphoric mood induction compared to L allele homozygotes (Beevers, Wells, Ellis, & McGeary, 2011). These studies are the first to demonstrate that genetic variation may influence information processing in the context of a dysphoric mood state, a theoretically important facet of depression vulnerability.

Summary of studies examining information-processing biases as an intermediate phenotype

In summary, studies have provided initial support for the role of information-processing biases as an intermediate phenotype for specific genetic influences, particularly the link between 5-HTTLPR genotype and attentional biases (see Permagin-Hight, Bakermans-Kranenburg, van IJzendoorn, & Bar-Haim, 2012, for a recent meta-analytic review). Evidence from association studies suggests that the presence of one or two lower expressing 5-HTTLPR alleles (S or L_G) contributes to preferential attention for emotional stimuli broadly, particularly difficulty disengaging attention. There is also support for G × E models of risk for attentional biases. Specifically, individuals carrying one or two lower expressing 5-HTTLPR alleles appear to be particularly sensitive to environmental influences on attentional biases. Importantly, within this research, there is evidence for specificity between the type of environmental influence experienced and the form of attentional bias exhibited (experience-specific information-processing biases). Thus, exposure to maternal depression is associated with attentional biases specifically for sad faces while exposure to childhood abuse or maternal criticism is associated with attentional biases specifically for angry faces, and each of these links is stronger among individuals carrying one or two copies of the 5-HTTLPR S or L_G allele than among those homozygous for the L_A allele. Finally, there is evidence that variation in specific genes (e.g., 5-HTTLPR, *BDNF*, and *DRD4*) may moderate the extent to which information-processing biases are activated or primed when individuals experience mild dysphoric moods. These studies provide important clues not only regarding how genetic and environmental influences may combine to influence the development of information-processing biases, but also how these biases may get activated in the context of negative moods.

Downloaded by [State University NY Binghamton] at 10:13 26 February 2013

SUPPORT FOR THE GENE × COGNITION × ENVIRONMENT MODELS OF RISK

As noted above, a second way in which cognitive and genetic models of depression may be integrated is in a gene × cognition × environment (G × C × E) model of risk. That is, information-processing biases and genetic influence may combine to increase risk for depression following environmental stress. Providing early support for this type of integration, findings from a twin study suggest that the link between cognitive risk (negative attributional styles) and depression may be moderated by both genetic and environmental factors (Eley et al., 2008; Lau et al., 2006). More recently, we have examined specific combinations of genetic, cognitive, and environmental influences hypothesised to increase risk for depression in children. In the first, we focused on cognitive and genetic influences hypothesised to moderate the link between mother and child depressive symptoms over time (Gibb, Benas et al., 2009). In this study, mothers' fluctuations in depressive symptoms during the multi-wave follow-up was treated as a stressor in children's lives, based on previous research supporting this type of cognitive vulnerability–stress model of risk in children (Abela, Skitch, Adams, & Hankin, 2006; see also Hammen, 2002). Building from Beck's (1987; Clark et al., 1999) vulnerability–event congruency hypothesis—that depression is most likely when there is a match between the type of cognitive vulnerability exhibited and the type of stress experienced—we hypothesised that a mother's increases in depressive symptoms would be a particularly salient stressor for children exhibiting attentional biases for sad faces. In terms of genetic influence, we focused on children's 5-HTTLPR genotype. Supporting the proposed G × C × E, we found that the strongest link between mother and child depressive symptoms over time was observed among children exhibiting attentional biases for sad faces who also carried at least one copy of the 5-HTTLPR S or L_G allele. Supporting the vulnerability–event congruency hypothesis, we found no support for the G × C × E model of risk when focusing on children's attentional biases for angry or happy faces, suggesting that the effects were specific to children exhibiting attentional biases for sad faces who were then exposed to higher levels of depression in their mothers.

Seeking to extend these initial findings, we tested a new G × C × E model of risk, focusing on a different combination of cognitive and environmental influences (Gibb, Uhrlass et al., 2009). Specifically, in this second study, we focused on children's reactions to maternal criticism (expressed emotion-criticism), which has been linked to children's depression risk in previous research (e.g., Asarnow, Goldstein, Tompson, & Guthrie, 1993; Asarnow, Tompson, Woo, & Cantwell, 2001; Silk et al., 2009). In terms of cognitive vulnerability, we focused on the hopelessness theory of depression (Abramson et al., 1989). Cognitive vulnerability in the hopelessness theory is defined as the tendency to attribute the occurrence of negative events to stable, global causes and to infer negative consequences and negative self-characteristics from these events. Although these three inferential styles appear to load onto a single higher-order factor in adults, they are relatively distinct in children (see Abela & Hankin, 2008; Haeffel et al., 2008). Building again from Beck's vulnerability–event congruency hypothesis, we predicted that children's depressive reactions to maternal criticism would be more strongly predicted by children's inferences regarding self-characteristics than inferences for causes or consequences because criticism directly targets one's view of oneself. Consistent with our G × C × E model of risk, we predicted that these depressive reactions would be particularly strong among children carrying one or two copies of the lower expressing 5-HTTLPR alleles (S or L_G). This is exactly what we found. Specifically, we found no evidence for a G × E interaction among children exhibiting relatively positive inferential styles for their self-characteristics. However, among children with relatively negative inferential styles for their self-characteristics, we found a strong relation between levels of

Downloaded by [State University NY Binghamton] at 10:13 26 February 2013

maternal criticism and children's depressive symptoms, a relation that increased in a stepwise fashion based on the number of lower expressing 5-HTTLPR alleles the child carried. We also found support for vulnerability–event congruency hypothesis in that the cognitive vulnerability–stress interaction was significant among carriers of the 5-HTTLPR S or L_G allele only when there was a match between the type of cognitive vulnerability (inferential style for self-characteristics) and the type of environmental stressor (maternal criticism); there was no support for the G × C × E model of risk for other forms of cognitive vulnerability (inferential for causes or consequences) or stress (fluctuations in maternal depressive symptoms).

Most recently, Osinsky, Lösch, Hennig, Alexander, and MacLeod (2012) reported that young adults' 5-HTTLPR genotype and attentional biases interact to predict emotional reactivity across students' first semester at university. In this study, participants' genotype, attentional biases and symptoms of depression and anxiety were assessed during their first week at the university and their symptoms were reassessed 12 weeks later, at the end of the semester. Although levels of environmental stress was not directly assessed in this study, all participants were exposed to the common stress of transitioning to college. Consistent with G × C × E model of risk, therefore, the impact of attentional bias (amount of bias toward negative words in a dot-probe task) on prospective changes in depressive symptoms across the semester was significant among students homozygous for the 5-HTTLPR S allele, but not among carriers of the L allele. In contrast, changes in anxiety were predicted by the main effect of attentional bias, with no evidence of moderation by 5-HTTLPR genotype.

Summary of studies testing gene × cognition × environment models of risk

These results provide encouraging initial support for G × C × E models of depression risk. Specifically, three studies across two separate laboratories have found support for distinct G × C × E models focused on different cognitive vulnerabilities and environmental influences in children and young adults carrying the lower expressing 5-HTTLPR alleles. Clearly this line of research is still in its infancy, but the results of these two studies are consistent with the hypothesis that 5-HTTLPR genotype modulates reactivity to salient environmental stressors generally, whereas specific types of information-processing biases affect the likelihood that a specific type of environmental stressor will result in depression.

CONCLUSIONS AND FUTURE DIRECTIONS

In summary, there is now growing support for two specific ways of integrating cognitive and genetic models of depression risk. First, there is support for genetic influences on information-processing biases, particularly the link between 5-HTTLPR and attentional biases, from both genetic association and G × E studies. There is also initial support for G × C × E models of risk in which specific genetic influences contribute to increased reactivity to environmental influences (cf. Belsky et al., 2009; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011), which then act in concert with specific combinations of cognitive and environmental risk factors to increase risk for depression. We believe that these two ways of integrating cognitive and genetic models of depression offer complementary rather than alternative approaches. That is, information-processing biases are thought to develop during childhood and then stabilise into relatively trait-like vulnerability factors during adolescence. The current review suggests that the development of these biases may be influenced by the combination of genetic and environmental influences. Once developed, however, the risk conferred by these biases may be triggered not only by environmental stressors as currently conceptualised within cognitive models, but also by one's underlying genetically influenced level of stress reactivity.

Downloaded by [State University NY Binghamton] at 10:13 26 February 2013

Despite the promise of existing studies, this line of research is still in its infancy and there are a number of important areas for future research. First, sample sizes for studies in this area have been relatively small (with studies typically including ~30–150 participants). This said, results have been fairly consistent across samples and laboratories, particularly for those investigating 5-HTTLPR, suggesting that the findings are not due simply to Type I errors or publication bias (cf. Permagin-Hight et al., 2012). However, research with larger samples is needed to provide more reliable estimates of genetic and environmental influences on information-processing biases and depression risk. This will be particularly important as research moves from a focus on single candidate polymorphisms to a broader examination of genetic influences. The investigation of genetic influences on cognitive processes related to depression holds great promise but has substantial challenges. Among these challenges are the complications inherent to all phenotypes with complex genetic underpinnings: namely that the multitude of genetic variants spanning multiple genes that contribute (singly and interactively) to these phenotypes is difficult to model without extremely large samples. Couple this requirement for large samples with the increased cost of assessing putative intermediate phenotypes compared with clinical diagnosis and the cost of such an approach can quickly become prohibitive. Substantial work is also required to better define the genetic architecture of cognitive phenotypes as they relate to the clinical disorder and also one another. Twin studies and other quantitative genetic approaches will be required to disentangle these questions, to determine whether they meet the requirements of an endophenotype (Gottesman & Gould, 2003), and to assess how genetic influences may vary developmentally. Moreover, it has long been known in animal genetics that manipulation of a single gene can have vastly different effects phenotypically depending upon the genetic background. Therefore it should come as no surprise that examination of a single genetic variant in outbred human samples would yield inconsistent results across studies. New developments in statistical genetics that approach this problem using cumulative genetic scores, pathway-based, and systems-based analyses to account for the complex genetic influences may assist in advancing the field. It is notable that even facing the challenges described above, a remarkably consistent literature is emerging (as described in this review). Given the difficulty in obtaining a consistent signal across mixed genetic backgrounds, this may suggest a relatively robust effect for the variants supported by these findings.

A second avenue for future research relates to the fact that, although most existing research has conceptualised the presence of specific genotypes within candidate polymorphisms as reflecting "risk", there is increasing evidence that these genotypes may more accurately be conceptualised as conferring increased "plasticity" or "reactivity" to environmental influences (cf. Belsky et al., 2009; Ellis et al., 2011). According to these models of differential susceptibility, the same factors that increase risk for maladaptive outcomes in the context of negative environmental influences may also increase the chances of positive outcomes in the context of positive environmental influences. There is preliminary support for this differential susceptibility model from a number of studies examining various outcomes (see B. J. Ellis et al., 2011, for a review). Of particular relevance to the current review, there is evidence that 5-HTTLPR genotype moderates the impact of a computer-based intervention designed to reduce attentional biases (Fox, Zoughou, Ridgewell, & Garner, 2011) as well as cognitive-behavioural treatment for anxious youth (Eley et al., 2011). In both cases, individuals with the lower expressing 5-HTTLPR genotypes (S or L_G) exhibited the greatest benefit from these interventions. Additional research is needed to more fully understand the mechanisms by which 5-HTTLPR and other polymorphisms may be associated with both better and worse outcomes depending on the type of environmental influence experienced.

A third area for future research is that in depression, as in other psychiatric disorders, there is a so called "missing heritability" problem such that the individual polymorphisms account for a

Downloaded by [State University NY Binghamton] at 10:13 26 February 2013

low proportion of the phenotypic variance. For example, a meta-analysis of genetic association studies in depression suggested that single candidate polymorphisms only account for 0.001–0.03% of the variance in depression risk (López-León et al., 2008). Although these links were significant, they do not come close to explaining the nearly 40% of depression risk estimated to be due to genetic factors (Sullivan et al., 2000). As noted in our introduction, this has prompted the search for intermediate phenotypes or endophenotypes(Gottesman & Gould, 2003) because the effects of specific genetic influences should be stronger for characteristics or traits more proximally influenced by the action of specific genes. However, studies examining genetic main effects or G × E models or risk for information-processing biases typically only explain 5–10% of the variance in these biases. Similarly, the G × C × E findings reviewed above accounted for approximately 10% of variance in depression risk (Gibb, Benas et al., 2009; Gibb, Uhrlass et al., 2009). Therefore, although these approaches help to explain a greater proportion of the variance than typical candidate gene association studies of depression risk and are quite large by typical behavioural genetics standards, there is clear room for further improvement.

There are several potential explanations for this disconnect between heritability estimates and the variance explained by candidate genes. First, there are a number of sources of variation (e.g., copy number variants, rare variants, fragment length polymorphisms, and chromosomal translocations) that are not typically assessed (even in GWA studies) and may help to explain some of the missing variance. The rapidly declining cost of next generation sequencing (NGS) may provide an empirical test to this hypothesis, though it will likely still require supplementation with traditional sequencing techniques for regions that are not amenable to NGS due to read length limitations(e.g., the exon 3 VNTR of the *DRD4* gene). New statistical approaches will also be required to jointly model all such variation. For example, the low allele frequency of rare variants revealed by NGS make traditionally powered comparisons impossible and require relatively unsophisticated rare variant count methods for analyses.

Second, researchers increasingly recognise that genetic influences are probably best conceptualised as a cumulative level of risk contributed by variation across a number of genes. One way this has been addressed is to test for epistatic influences (G × G interactions predicting an outcome of interest). A limitation of this approach, however, is that G × G interactions are not readily modelled using measured genes because the low minor allele frequencies of studied variants significantly reduces power for finding these effects. Another strategy is to use an aggregate genetic risk approach, according to which even if single common variants have very small effects individually, they may collectively account for a more substantial amount of the variation in risk. By accounting for multiple variants in a single score, the variability in "background" genetic risk factor "noise" can be diminished to allow a clearer signal (i.e., associations of a single candidate polymorphism may be obscured when there are multiple other variants contributing to a phenotype, but modelling them concurrently should allow a stronger and more reliable estimate of genetic influence). From a pure psychometric/scale construction perspective, the more indicators of (genetic influences on) a given construct (e.g., heightened stress reactivity) you have, the greater your signal to noise ratio will be. Although not yet applied to the study of information-processing biases, there is growing support for this type of approach in other areas of psychology, including imaging genetics (e.g., Belsky & Beaver, 2011; Derringer et al., 2010; International Schizophrenia Consortium, 2009; Nikolova, Ferrell, Manuck, & Hariri, 2011).

We believe that this approach holds significant promise for better understanding genetic influences on depression risk. To effectively do this, however, we will need to broaden our focus on candidate genes and polymorphisms beyond "the usual suspects" by referring again to the emerging literature in imaging genetics as well as research examining pharmacological influences on information-processing biases. First, research in

Downloaded by [State University NY Binghamton] at 10:13 26 February 2013

imaging genetics can help to identify promising candidate genes based on their influence on neural reactivity in regions underlying information-processing biases as well as reactivity to environmental stress. For example, neuropeptide Y (NPY) is a neuropeptide transmitter found in particularly high concentrations in the amygdala, nucleus accumbens and basal ganglia (Adrian et al., 1983). NPY appears to have effects on numerous phenotypes including feeding behaviours, anxiety, depression, alcohol consumption and circadian rhythms (Brother & Wahlestedt, 2010). Of particular importance in the current context, variation in the *NPY* gene is associated with amygdala reactivity as well as reactivity to stress (Mickey et al., 2011; Witt et al., 2011; Zhou et al., 2008) suggesting its potential relevance for studies examining genetic main effects as well as G × E and G × C × E models of risk. Another potentially promising candidate gene is *HOMER1*, which influences glutamate transmission and has been associated with activity in prefrontal cortex during cognitive tasks (Rietschel et al., 2010). There is also growing interest in the oxytocin receptor gene (*OXTR*) given the role of oxytocin in social cognition and behaviour (see Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011, for a review). Variation in *OXTR* is associated with amygdala volume and reactivity, and affects stress reactivity (Furman, Chen, & Gotlib, 2011; Rodrigues, Saslow, Garcia, John, & Keltner, 2009; Tost et al., 2010). Further, intranasal oxytocin administration improves recognition of, and memory for, facial expressions of emotion (Guastella, Mitchell, & Mathews, 2008; Marsh, Yu, Pine, & Blair, 2010). When seeking to examine reactivity to environmental stressors (within a G × E or G × C × E model of risk), researchers should also focus on polymorphisms in genes known to affect HPA axis reactivity such as *FKBP5* and the glucocorticoid (*GR*) and mineralocorticoid (*MR*) receptor genes (see DeRijk, 2009; Velders et al., 2011). Finally, with regard to identifying candidate genes based on their impact on neural reactivity in brain regions thought to underlie information processing biases, we should highlight the Allen's Brain atlas (www.brain-map.org), which allows one to identify likely candidate genes by their level of expression within specific neuroanatomical locations. Second, drawing from pharmacological studies, there are a number of agents with differential pharmacology that also appear to have effects on biased attention including: (i) mirtazapine with effects on multiple serotonergic and adrenergic receptors as well as *SLC6A2*; (ii) aprepitant with Neurokinin 1 (*NK1*) receptor effects implicates the importance of the tachykinin receptor 1 (*TACR1*) gene; (iii) rimonabant, the CB1 anatagonist, suggests that the cannabinoid receptor type 1 (*CNR1*) gene may be a worthwhile genetic candidate; (iv) agomelatine is known to affects attention bias and highlights the potential roles of the melatonin receptor 1A (*MTNR1A*), metallothionein 3 (*MT3*) and serotonin receptor 2C (*5HTR2C*) genes; and (v) erythropoietin's impact on both attention bias and neurotrophic effects may highlight new genes. To truly capture the varied genetic influences that likely underlie information-processing biases, researchers will need to draw from both domains of research—imaging genetics and pharmacology studies.

Finally, with regard to addressing the missing heritability problem, research is needed to examine epigenetic influences. Theorists and researchers recognise the important distinction between one's genotype and potential modification of one's DNA (epigenetics) that may impact the expression of genes. Since epigenetic modification, such as DNA methylation, can impact gene expression, this modification can trump the importance of genetic variation on a phenotype insofar as any variation in the genetic sequence becomes irrelevant if the gene is not transcribed. Indeed recent findings related to DNA methylation of the serotonin transporter gene, *SLC6A4*, suggest the need to characterise both genetic and epigenetic differences to understand how this gene impacts reactivity to environmental stress (e.g., Beach, Brody, Todorov, Gunter, & Philibert, 2011; Koenen et al., 2011; van IJzendoorn, Caspers, Bakermans-Kranenburg, Beach, & Philibert, 2010). Importantly, epigenetic modifications are

Downloaded by [State University NY Binghamton] at 10:13 26 February 2013

not limited to DNA methylation. Indeed, recent evidence of histone modification related to exon 6 of the *BDNF* gene as it relates to depression through both stress reactivity and antidepressant response (see Calabrese et al., 2009, for a review) highlights the importance of considering the multiple genetic and epigenetic influences on gene expression. Failure to consider these manifold influences conjointly may result in a highly inconsistent literature. The inability to access the tissue of interest (e.g., brain) in humans for studies of epigenetic and gene expression will continue to be a hindrance to the field until such a time that evidence supports the use of peripheral markers (e.g., from blood or saliva samples) or new techniques are developed to assess gene expression through neuroimaging (Massoud, Singh, & Gambhir, 2008).

In summary, although research into the integration of cognitive and genetic models of depression risk is still in its infancy, there is a growing amount of research supporting two specific ways in which these models can be meaningfully integrated—information-processing biases as an intermediate phenotype and gene × cognition × environment models of risk. This is an exciting time for researchers seeking to understand how multiple levels of influence may combine to increase risk for depression. Future research is needed not only to replicate existing findings, but also to seek to more fully account for genetic influences on depression risk.

Manuscript received 19 September 2011
Revised manuscript received 7 July 2012
Manuscript accepted 11 July 2012
First published online 24 August 2012

REFERENCES

Abela, J. R. Z., & Hankin, B. L. (2008). Cognitive vulnerability to depression in children and adolescents: A developmental psychopathology perspective. In J. R. Z. Abela & B. L. Hankin (Eds.), *Handbook of depression in children and adolescents* (pp. 35–78). New York, NY: Guilford Press.

Abela, J. R. Z., Skitch, S. A., Adams, P., & Hankin, B. L. (2006). The timing of parent and child depression: A hopelessness theory perspective. *Journal of Clinical Child and Adolescent Psychology*, *35*, 253–263.

Abramson, L. Y., Metalsky, G. I., & Alloy, L. B. (1989). Hopelessness depression: A theory-based subtype of depression. *Psychological Review*, *96*, 358–372.

Adrian, T. E., Allen, J. M., Bloom, S. R., Ghatei, M. A., Rossor, M. N., Roberts, G. W., et al. (1983). Neuropeptide Y distribution in brain. *Nature*, *306*, 584–586.

Alexander, N., Kuepper, Y., Schmitz, A., Osinsky, R., Kozyra, E., & Henning, J. (2009). Gene–environment interactions predict cortisol responses after acute stress: Implications for the etiology of depression. *Psychoneuroendocrinology*, *34*, 1294–1303.

Antypa, N., Cerit, H., Druijt, A. W., Verhoeven, F. E. A., & Van der Does, A. J. W. (2011). Relations among 5-HTT genotype, life events and gender in the recognition of facial emotions. *Neuroscience*, *172*, 303–313.

Antypa, N., & Van der Does, A. J. W. (2010). Serotonin transporter gene, childhood emotional abuse and cognitive vulnerability to depression. *Genes Brain and Behavior*, *9*, 615–620.

Armbruster, D., Mueller, A., Moser, D. A., Lesch, K. P., Brock, B., & Kirschbaum, C. (2009). Interaction effect of D4 dopamine receptor gene and serotonin transporter promoter polymorphism on the cortisol stress response. *Behavioral Neuroscience*, *123*, 1288–1295.

Asarnow, J. R., Goldstein, M. J., Tompson, M., & Guthrie, D. (1993). One-year outcomes of depressive disorders in child psychiatric in-patients: Evaluation of the prognostic power of a brief measure of expressed emotion. *Journal of Child Psychology and Psychiatry*, *34*, 129–137.

Asarnow, J. R., Tompson, M., Woo, S., & Cantwell, D. P. (2001). Is expressed emotion a specific risk factor for depression or a nonspecific correlate of psychopathology? *Journal of Abnormal Child Psychology*, *29*, 573–583.

Beach, S. R., Brody, G. H., Todorov, A. A., Gunter, T. D., & Philibert, R. A. (2011). Methylation at 5HTT mediates the impact of child sex abuse on women's antisocial behavior: An examination of the Iowa adoptee sample. *Psychosomatic Medicine*, *73*, 83–87.

Downloaded by [State University NY Binghamton] at 10:13 26 February 2013

Beck, A. T. (1967). *Depression: Clinical, experimental, and theoretical aspects*. New York, NY: Harper & Row.

Beck, A. T. (1987). Cognitive models of depression. *Journal of Cognitive Psychotherapy*, *1*, 5–37.

Beevers, C. G. (2005). Cognitive vulnerability to depression: A dual process model. *Clinical Psychology Review*, *25*, 975–1002.

Beevers, C. G., Ellis, A. J., Wells, T. T., & McGeary, J. E. (2010). Serotonin transporter gene promoter region polymorphism and selective processing of emotional images. *Biological Psychology*, *83*, 260–265.

Beevers, C. G., Gibb, B. E., McGeary, J. E., & Miller, I. W. (2007). Serotonin transporter genetic variation and biased attention for emotional word stimuli among psychiatric inpatients. *Journal of Abnormal Psychology*, *116*, 208–212.

Beevers, C. G., Marti, C. N., Lee, H.-J., Stote, D. L., Ferrell, R. E., Hariri, A. R., et al. (2011). Associations between serotonin transporter gene promoter region (5-HTTLPR) polymorphism and gaze bias for emotional information. *Journal of Abnormal Psychology*, *120*, 187–197.

Beevers, C. G., Wells, T., Ellis, A. J., & McGeary, J. E. (2009). Association of the serotonin transporter gene promoter region (5-HTTLPR) polymorphism with biased attention for emotional stimuli. *Journal of Abnormal Psychology*, *118*, 670–681.

Beevers, C. G., Wells, T. T., Ellis, A. J., & McGeary, J. E. (2011). *Attentional bias for emotional information following a dysphoric mood induction: Associations with the 5-HTTLPR*. Manuscript in preparation.

Beevers, C. G., Wells, T. T., & McGeary, J. E. (2009). The *BDNF* Val66Met polymorphism is associated with rumination in healthy adults. *Emotion*, *9*, 579–584.

Beevers, C. G., Wenzlaff, R. M., Hayes, A. M., & Scott, W. D. (1999). Depression and the ironic effects of thought suppression: Therapeutic strategies for improving mental control. *Clinical Psychology: Science and Practice*, *6*, 133–148.

Belsky, J., & Beaver, K. M. (2011). Cumulative-genetic plasticity, parenting and adolescent self-regulation. *Journal of Child Psychology and Psychiatry*, *52*, 619–626.

Belsky, J., Jonassaint, C., Pluess, M., Stanton, M., Brummett, B., & Williams, R. (2009). Vulnerability genes or plasticity genes? *Molecular Psychiatry*, *14*, 746–754.

Bishop, S. J. (2008). Neural mechanisms underlying selective attention to threat. *Annals of the New York Academy of Sciences*, *1129*, 141–152.

Bouma, E., & Riese, H. (2010). No replication of genotype effect of 5-HTTLPR on cortisol response to social stress in larger adolescent sample. *Biological Psychiatry*, *68*, E33–E34.

Brother, S. P., & Wahlestedt, C. (2010). Therapeutic potential of neuropeptide Y (NPY) receptor ligands. *EMBO Molecular Medicine*, *2*, 429–439.

Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Science*, *4*, 215–222.

Calabrese, F., Molteni, R., Racagni, G., & Riva, M. A. (2009). Neuronal plasticity: A link between stress and mood disorders. *Psychoneuroendocrinology*, *34*, S208–216.

Camara, E., Krämer, U. M., Cunillera, T., Marco-Pallarés, J., Cucurell, D., Nager, W., et al. (2010). The effects of *COMT* (Val108/158Met) and *DRD4* (SNP-521) dopamine genotypes on brain activations related to valence and magnitude of rewards. *Cerebral Cortex*, *20*, 1985–1996.

Canli, T., Qiu, M., Omura, K., Congdon, E., Haas, B. W., Amin, Z., et al. (2006). Neural correlates of epigenesis. *Proceedings of the National Academy of Sciences*, *103*, 16033–16038.

Carver, C. S., Johnson, S. L., & Joormann, J. (2008). Serotonergic function, two-mode models of self-regulation, and vulnerability to depression: What depression has in common with impulsive aggression. *Psychological Bulletin*, *134*, 912–943.

Caspi, A., Hariri, A. R., Holmes, A., Uher, R., & Moffitt, T. E. (2010). Genetic sensitivity to the environment: The case of the serotonin transporter gene and its implications for studying complex diseases or traits. *American Journal of Psychiatry*, *167*, 509–527.

Clark, D. A., Beck, A. T., & Alford, B. A. (1999). *Scientific foundations of cognitive theory and therapy of depression*. New York, NY: Wiley.

Clarke, H. F., Dalley, J. W., Crofts, H. S., Robbins, T. W., & Roberts, A. C. (2004). Cognitive inflexibility after prefrontal serotonin depletion. *Science*, *304*, 878–880.

Clasen, P. C., Wells, T. T., Knopik, V. S., McGeary, J. E., & Beevers, C. G. (2011). 5-HTTLPR and *BDNF* Val66Met polymorphisms moderate effects of stress on rumination. *Genes, Brain & Behavior*, *10*, 740–746.

Downloaded by [State University NY Binghamton] at 10:13 26 February 2013

Cousijn, H., Rijpkema, M., Qin, S., van Marle, H. J. F., Franke, B., Hermans, E. J., et al. (2010). Acute stress modulates genotype effects on amygdala processing in humans. *Proceedings of the National Academy of Sciences*, *107*, 9867–9872.

Dannlowski, U., Ohrmann, P., Bauer, J., Kugel, H., Baune, B. T., Hohoff, C., et al. (2007). Serotonergic genes modulate amygdala activity in major depression. *Genes, Brain and Behavior*, *6*, 672–676.

De Quervain, D. J.-F., Kolassa, I.-T., Ertl, V., Onyut, P. L., Neuner, F., Elbert, T., et al. (2007). A deletion variant of the alpha2b-adrenoceptor is related to emotional memory in Europeans and Africans. *Nature Neuroscience*, *10*, 1137–1139.

De Raedt, R., & Koster, E. H. W. (2010). Understanding vulnerability to depression from a cognitive neuroscience perspective: A reappraisal of attentional factors and a new conceptual framework. *Cognitive, Affective, and Behavioral Neuroscience*, *10*, 50–70.

DeRijk, R. H. (2009). Single nucleotide polymorphisms related to HPA axis reactivity. *Neuroimmunododulation*, *16*, 340–352.

Derringer, J., Krueger, R. F., Dick, D. M., Saccone, S., Grucza, R. A., Agrawal, A., et al. (2010). Predicting sensation seeking from dopamine genes: A candidate-system approach. *Psychological Science*, *21*, 1282–1290.

Dougherty, L. R., Klein, D. N., Congdon, E., Canli, T., & Hayden, E. P. (2010). Interaction between 5-HTTLPR and *BDNF* Val66Met polymorphisms on HPA axis reactivity in preschoolers. *Biological Psychiatry*, *83*, 93–100.

Egan, M. F., Goldberg, T. E., Kolachana, B. S., Callicott, J. H., Mazzanti, C. M., Straub, R. E., et al. (2001). Effect of *COMT* Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proceedings of the National Academy of Sciences*, *98*, 6917–6922.

Egan, M. F., Kojima, M., Callicott, J. H., Goldberg, T. E., Kolachana, B. S., Bertolino, A., et al. (2003). The *BDNF* val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell*, *112*, 257–269.

Eley, T. C., Gregory, A. M., Lau, J. Y. F., McGuffin, P., Napolitano, M., Rijsdijk, F. V., et al. (2008). In the face of uncertainty: A twin study of ambiguous information, anxiety and depression in children. *Journal of Abnormal Child Psychology*, *36*, 55–65.

Eley, T. C., Hudson, J. L., Creswell, C., Tropeano, M., Lester, K. J., Cooper, P., et al. (2011). Therapygenetics: The 5HTTLPR and response to psychological therapy. *Molecular Psychiatry*, *17*, 236–237.

Ellenbogen, M. A., Schwartzman, A. E., Stewart, J., & Walker, C.-D. (2002). Stress and selective attention: The interplay of mood, cortisol levels, and emotional information processing. *Psychophysiology*, *39*, 723–732.

Ellenbogen, M. A., Schwartzman, A. E., Stewart, J., & Walker, C.-D. (2006). Automatic and effortful emotional information processing regulates different aspects of the stress response. *Psychoneuroendocrinology*, *31*, 373–387.

Elliott, R., Zahn, R., Deakin, J. F. W., & Anderson, I. M. (2011). Affective cognition and its disruption in mood disorders. *Neuropsychopharmacology*, *36*, 153–182.

Ellis, B. J., Boyce, W. T., Belsky, J., Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2011). Differential susceptibility to the environment: An evolutionary-neurodevelopment theory. *Development and Psychopathology*, *23*, 7–28.

Fan, J., Fossella, J., Sommer, T., Wu, Y., & Posner, M. I. (2003). Mapping the genetic variation of executive attention onto brain activity. *Proceedings of the National Academy of Sciences*, *100*, 7406–7411.

Fox, E., Ridgewell, A., & Ashwin, C. (2009). Looking on the bright side: Biased attention and the human serotonin transporter gene. *Proceedings of the Royal Society, B: Biological Sciences*, *276*, 1747–1751.

Fox, E., Zoughou, K., Ridgewell, A., & Garner, K. (2011). The serotonin transporter gene alters sensitivity to attentional bias modification: Evidence for a plasticity gene. *Biological Psychiatry*, *70*, 1049–1054.

Frank, M. J., Doll, B. B., Oas-Terpstra, J., & Moreno, F. (2009). Prefrontal and striatal dopaminergic genes predict individual differences in exploration and exploitation. *Nature Neuroscience*, *12*, 1062–1068.

Frewen, P. A., Dozois, D. J. A., Joanisse, M. F., & Neufeld, R. W. J. (2008). Selective attention to threat versus reward: Meta-analysis and neural-network modeling of the dot-probe task. *Clinical Psychology Review*, *28*, 307–337.

Friedman, N., Miyake, A., Young, S., Defries, J., Corley, R., & Hewitt, J. (2008). Individual differences in executive functions are almost entirely genetic in origin. *Journal of Experimental Psychology: General*, *137*, 201–225.

Furman, D. J., Chen, M. C., & Gotlib, I. H. (2011). Variant in oxytocin receptor gene is associated with

Downloaded by [State University NY Binghamton] at 10:13 26 February 2013

amygdala volume. *Psychoneuroendocrinology*, *36*, 891–897.

Gibb, B. E., Benas, J. S., Grassia, M., & McGeary, J. (2009). Children's attentional biases and 5-HTTLPR genotype: Potential mechanisms linking mother and child depression. *Journal of Clinical Child and Adolescent Psychology*, *38*, 415–426.

Gibb, B. E., Grassia, M., Stone, L. B., & Uhrlass, D. J. (2012). Brooding rumination and risk for depression in children of depressed mothers. *Journal of Abnormal Child Psychology*, *40*, 317–312.

Gibb, B. E., Johnson, A. L., Benas, J. S., Uhrlass, D. J., Knopik, V. S., & McGeary, J. E. (2011). Children's 5-HTTLPR genotype moderates the link between maternal criticism and attentional biases specifically for facial displays of anger. *Cognition and Emotion*, *25*, 1104–1120.

Gibb, B. E., Urhlass, D. J., Grassia, M., Benas, J. S., & McGeary, J. (2009). Children's inferential styles, 5-HTTLPR genotype, and maternal expressed emotion-criticism: An integrated model for the intergenerational transmission of depression. *Journal of Abnormal Psychology*, *118*, 734–745.

Gotlib, I. H., & Joormann, J. (2010). Cognition and depression: Current status and future directions. *Annual Review of Clinical Psychology*, *6*, 285–312.

Gotlib, I. H., Joormann, J., Minor, K. L., & Hallmayer, J. (2008). HPA axis reactivity: A mechanism underlying the associations among 5-HTTLPR, stress, and depression. *Biological Psychiatry*, *63*, 847–851.

Gotlib, I. H., Krasnoperova, E., Yue, D. N., & Joormann, J. (2004). Attentional biases for negative interpersonal stimuli in clinical depression. *Journal of Abnormal Psychology*, *113*, 127–135.

Gottesman, I. I., & Gould, T. D. (2003). The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry*, *160*, 636–645.

Guastella, A. J., Mitchell, P. B., & Mathews, F. (2008). Oxytocin enhances the encoding of positive social memories in humans. *Biological Psychiatry*, *64*, 256–258.

Haeffel, G. J., Gibb, B. E., Metalsky, G. I., Alloy, L. B., Abramson, L. Y., Hankin, B. L., et al. (2008). Measuring cognitive vulnerability to depression: Development and validation of the Cognitive Style Questionnaire. *Clinical Psychology Review*, *28*, 824–836.

Hammen, C. (2002). Context of stress in families of children with depressed parents. In S. H. Goodman & I. H. Gotlib (Eds.), *Children of depressed parents: Mechanisms of risk and implications for treatment* (pp. 175–199). Washington, DC: American Psychological Association.

Harmer, C. J., Goodwin, G. M., & Cowen, P. J. (2009). Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant action. *British Journal of Psychiatry*, *195*, 102–108.

Hasler, G., Drevets, W. C., Manji, H. K., & Charney, D. S. (2004). Discovering endophenotypes for major depression. *Neuropsychopharmacology*, *29*, 1765–1781.

Hayden, E. P., Dougherty, L. R., Maloney, B., Olino, T. M., Sheikh, H., Durbin, C. E., et al. (2008). Early emerging cognitive vulnerability to depression and the serotonin transporter promoter region polymorphism. *Journal of Affective Disorders*, *107*, 227–230.

Hermans, D., Vansteenwegen, D., & Eelen, P. (1999). Eye movement registration as a continuous index of attention deployment: Data from a group of spider anxious students. *Cognition and Emotion*, *13*, 419–434.

Hilt, L. M., Sander, L. C., Nolen-Hoeksema, S., & Simen, A. A. (2007). The *BDNF* Val66Met polymorphism predicts rumination and depression differently in young adolescent girls and their mothers. *Neuroscience Letters*, *429*, 12–16.

Hu, X., Oroszi, G., Chun, J., Smith, T. L., Goldman, D., & Schuckit, M. A. (2005). An expanded evaluation of the relationship of four alleles to the level of response to alcohol and the alcoholism risk. *Alcoholism: Clinical and Experimental Research*, *29*, 8–16.

Hutchison, K. E., Wooden, A., Swift, R. M., Smolen, A., McGeary, J., Adler, L., et al. (2003). Olanzapine reduces craving for alcohol: A DRD4 VNTR polymorphism by pharmacotherapy interaction. *Neuropsychopharmacology*, *28*, 1882–1888.

International Schizophrenia Consortium. (2009). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*, *460*, 748–752.

Isaacowitz, D. M. (2006). Motivated gaze: The view from the gazer. *Current Directions in Psychological Science*, *15*, 68–72.

Jacobs, R. H., Pine, D. S., Schoeny, M., Henry, D. B., Gollan, J. K., Moy, G., et al. (2011). Maternal depressive history, teen 5-HTTLPR genotype, and the processing of emotional faces: Exploring

Downloaded by [State University NY Binghamton] at 10:13 26 February 2013

mechanisms of risk. *Behaviour Research and Therapy*, *49*, 80–84.

Johnson, A. L., Gibb, B. E., & McGeary, J. (2010). Reports of childhood physical abuse, 5-HTTLPR genotype, and women's attentional biases for angry faces. *Cognitive Therapy and Research*, *34*, 380–387.

Juhasz, G., Dunham, J. S., McKie, S., Thomas, E., Downey, D., Chase, D., et al. (2011). The *CREB1–BDNF–NTRK2* pathway in depression: Multiple gene–cognition–environment interactions. *Biological Psychiatry*, *69*, 762–771.

Karg, K., Burmeister, M., Shedden, K., & Sen, S. (2011). The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: Evidence of genetic moderation. *Archives of General Psychiatry*, *68*, 444–454.

Kay, G. G. (2000). The effects of antihistamines on cognition and performance. *Journal of Allergy and Clinical Immunology*, *105*, S622–S627.

Kellough, J., Beevers, C. G., Ellis, A., & Wells, T. (2008). Time course of selective attention in clinically depressed young adults: An eye tracking study. *Behaviour Research and Therapy*, *46*, 1238–1243.

Kendler, K. S., Gardner, C. O., & Prescott, C. A. (1999). Clinical characteristics of major depression that predict risk of depression in relatives. *Archives of General Psychiatry*, *56*, 322–327.

Kessler, R. C. (1997). The effects of stressful life events on depression. *Annual Review of Psychology*, *48*, 191–214.

Koenen, K. C., Uddin, M., Chang, S. C., Aiello, A. E., Wildman, D. E., Goldmann, E., et al. (2011). SLC6A4 methylation modifies the effect of the number of traumatic events on risk for posttraumatic stress disorder. *Depression and Anxiety*, *28*, 639–647.

Koster, E. H. W., De Raedt, R., Goeleven, E., Franck, E., & Crombez, G. (2005). Mood-congruent attentional bias in dysphoria: Maintained attention to and impaired disengagement from negative information. *Emotion*, *5*, 446–455.

Kwang, T., Wells, T. T., McGeary, J. E., Swann, W. B., Jr., & Beevers, C. G. (2010). Association of the serotonin transporter promoter region polymorphism with biased attention for negative word stimuli. *Depression and Anxiety*, *27*, 746–751.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (2005). *International Affective Picture System (IAPS): Affective ratings of pictures and instruction manual* (Technical report A-6). Gainesville, FL: University of Florida.

Lau, J. Y. F., Rijsdijk, F., & Eley, T. C. (2006). I think, therefore I am: A twin study of attributional style in adolescents. *Journal of Child Psychology and Psychiatry*, *47*, 696–703.

Lee, T.-H., Lim, S.-L., Lee, K., Kim, H.-T., & Choi, J.-S. (2009). Conditioning-induced attentional bias for face stimuli measured with the emotional Stroop task. *Emotion*, *9*, 134–139.

Lemogne, C., Bergouignan, L., Boni, C., Gorwood, P., Pélissolo, A., & Fossati, P. (2009). Genetics and personality affect visual perspective in autobiographical memory. *Conscious and Cognition*, *18*, 823–830.

Lesch, K. P., Bengel, D., Heils, A., Sabol, S. Z., Greenberg, B. D., Petri, S., et al. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*, *274*, 1527–1531.

Lewis, C. M., Ng, M. Y., Butler, A. W., Cohen-Woods, S., Uher, R., Pirlo, K., et al. (2010). Genome-wide association study of major recurrent depression in the UK population. *American Journal of Psychiatry*, *167*, 949–957.

López-León, S., Janssens, A. C. J. W., González-Zuloeta Ladd, A. M., Del-Favero, J., Claes, S. J., Oostra, B. A., & van Duijn, C. M. (2008). Meta-analyses of genetic studies on major depressive disorder. *Molecular Psychiatry*, *13*, 772–785.

Maheu, F. S., Joober, R., Beaulieu, S., & Lupien, S. J. (2004). Differential effects of adrenergic and corticosteroid hormonal systems on human short- and long-term declarative memory for emotionally arousing material. *Behavioral Neuroscience*, *118*, 420–428.

Mannie, Z. N., Bristow, G. C., Harmer, C. J., & Cowen, P. J. (2007). Impaired emotional categorization in young people at increased familial risk of depression. *Neuropsychologia*, *45*, 2975–2980.

Marsh, A. A., Yu, H. H., Pine, D. S., & Blair, R. J. R. (2010). Oxytocin improves specific recognition of positive facial expressions. *Psychopharmacology*, *209*, 225–232.

Martinowich, K., & Lu, B. (2008). Interaction between BDNF and serotonin: Role in mood disorders. *Neuropsychopharmacology*, *33*, 73–83.

Massoud, T. F., Singh, A., & Gambhir, S. S. (2008). Noninvasive molecular neuroimaging using reporter genes: Part I, principles revisited. *American Journal of Neuroradiology*, *29*, 229–234.

Downloaded by [State University NY Binghamton] at 10:13 26 February 2013

Mathews, A., & MacLeod, C. (2005). Cognitive vulnerability to emotional disorders. *Annual Review of Clinical Psychology*, *1*, 167–195.

McGeary, J. (2009). The *DRD4* exon 3 VNTR polymorphism and addiction-related phenotypes: A review. *Pharmacology Biochemistry and Behavior*, *93*, 222–229.

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

Mickey, B. J., Zhou, Z., Heitzeg, M. M., Heinz, E., Hodgkinson, C. A., Hsu, D. T., et al. (2011). Emotion processing, major depression, and functional genetic variation in neuropeptide Y. *Archives of General Psychiatry*, *68*, 158–166.

Mueller, A., Armbruster, D., Moser, D. A., Canli, T., Lesch, K.-P., Brock, B., et al. (2011). Interaction of serotonin transporter-linked polymorphic region and stressful life events predicts cortisol stress response. *Neuropsychopharmacology*, *36*, 1332–1339.

Mueller, A., Brocke, B., Fries, E., Lesch, K.-P., & Kirschbaum, C. (2010). The role of the serotonin transporter polymorphism for the endocrine stress response in newborns. *Psychoneuroendocrinology*, *35*, 289–296.

Muglia, P., Tozzi, F., Galwey, N. W., Franks, C., Upmanyu, R., Kong, X. Q., et al. (2010). Genome-wide association study of recurrent major depressive disorder in two European case-control cohorts. *Molecular Psychiatry*, *15*, 589–601.

Munafò, M. R., Brown, S. M., & Hariri, A. R. (2008). Serotonin transporter (5-HTTLPR) genotype and amygdala activation: A meta-analysis. *Biological Psychiatry*, *63*, 852–857.

Murphy, F. C., Smith, K. A., Cowen, P. J., Robbins, T. W., & Sahakian, B. J. (2002). The effects of tryptophan depletion on cognitive and affective processing in healthy volunteers. *Psychopharmacology*, *163*, 42–53.

Nikolova, Y. S., Ferrell, R. E., Manuck, S. B., & Hariri, A. R. (2011). Multilocus genetic profile for dopamine signaling predicts ventral striatum reactivity. *Neuropsychopharmacology*, *36*, 1940–1947.

Nolen-Hoeksema, S. (2000). The role of rumination in depressive disorders and mixed anxiety/depressive symptoms. *Journal of Abnormal Psychology*, *109*, 504–511.

Nolen-Hoeksema, S., Wisco, B. E., & Lyubomirsky, S. (2008). Rethinking rumination. *Perspectives on Psychological Science*, *3*, 400–424.

Nugent, N. R., Tyrka, A. R., Carpenter, L. L., & Price, L. H. (2011). Gene–environment interactions: Early life stress and risk for depression and anxiety disorders. *Psychopharmacology*, *214*, 175–196.

Oak, J. N., Oldenhof, J., & Van Tol, H. H. M. (2000). The dopamine D-4 receptor: One decade of research. *European Journal of Pharmacology*, *405*, 303–327.

O'Carroll, R. E., Drysdale, E., Cahill, L., Shajahan, P., & Ebmeier, K. P. (1999). Stimulation of the noradrenergic system enhances and blockade reduces memory for emotional material in man. *Psychological Medicine*, *29*, 1083–1088.

Osinsky, R., Lösch, A., Hennig, J., Alexander, N., & MacLeod, C. (2012). Attentional bias to negative information and 5-HTTLPR genotype interactively predict students' emotional reactivity to first university semester. *Emotion*, *12*, 460–469.

Pacheco, J., Beevers, C. G., Benavides, C., McGeary, J., Stice, E., & Schnyer, D. M. (2009). Frontal-limbic white matter pathway associations with the serotonin transporter gene promoter region (5-HTTLPR) polymorphism. *Journal of Neuroscience*, *29*, 6229–6233.

Papageorgiou, C., & Wells, A. (2001). Positive beliefs about depressive rumination: Development and preliminary validation of a self-report scale. *Behavior Therapy*, *32*, 13–26.

Papageorgiou, C., & Wells, A. (2003). An empirical test of a clinical metacognitive model of rumination and depression. *Cognitive Therapy & Research*, *27*, 261–273.

Passetti, F., Chudasama, Y., & Robbins, T. W. (2002). The frontal cortex of the rat and visual attentional performance: Dissociable functions of distinct medial prefrontal subregions. *Cerebral Cortex*, *12*, 1254–1268.

Pérez-Edgar, K., Bar-Haim, Y., McDermott, J. M., Gorodetsky, E., Hodgkinson, C. A., Goldman, D., et al. (2010). Variations in the serotonin-transporter gene are associated with attention bias patterns to positive and negative emotion faces. *Biological Psychology*, *83*, 269–271.

Permagin-Hight, L., Bakermans-Kranenburg, M. J., van IJzendoorn, M. H., & Bar-Haim, Y. (2012). Variations in the promoter region of the serotonin transporter gene and biased attention for emotional

Downloaded by [State University NY Binghamton] at 10:13 26 February 2013

information: A meta-analysis. *Biological Psychiatry*, *71*, 373–379.

Pertea, M., & Salzberg, S. L. (2010). Between a chicken and a grape: Estimating the number of human genes. *Genome Biology*, *11*, 206.

Pezawas, L., Meyer-Lindenberg, A., Draband, E. M., Verchinski, B. A., Munoz, K. E., Kolachana, B. S., et al. (2005). 5-HTTLPR polymorphism impacts human cingulate–amygdala interactions: A genetic susceptibility mechanism for depression. *Nature Neuroscience*, *8*, 828–834.

Pischek-Simpson, L. K., Boschen, M. J., Neumann, D. L., & Waters, A. M. (2009). The development of an attentional bias for angry faces following Pavlovian fear conditioning. *Behaviour Research and Therapy*, *47*, 322–330.

Pollak, S. D. (2003). Experience-dependent affective learning and risk for psychopathology in children. In J. A. King, C. F. Ferris, & I. I. Lederhendler (Eds.), *Roots of mental illness in children* (pp. 102–111). New York, NY: Annals of the New York Academy of Sciences.

Rietschel, M., Mattheisen, M., Frank, J., Treutlein, J., Degenhardt, F., Breuer, R., et al. (2010). Genome-wide association-, replication-, and neuroimaging study implicates *HOMR1* in the etiology of major depression. *Biological Psychiatry*, *68*, 578–585.

Rodrigues, S. M., Saslow, L. R., Garcia, N., John, O. P., & Keltner, D. (2009). Oxytocin receptor genetic variation relates to empathy and stress reactivity in humans. *Proceedings of the National Academy of Sciences*, *106*, 21437–21441.

Roiser, J. P., Müller, U., Clark, L., & Sahakian, B. J. (2007). The effects of acute tryptophan depletion and serotonin transporter polymorphism on emotional processing in memory and attention. *International Journal of Neuropsychopharmacology*, *10*, 449–461.

Rutter, M., Moffitt, T. E., & Caspi, A. (2006). Gene–environment interplay and psychopathology: Multiple varieties but real effects. *Journal of Child Psychology and Psychiatry*, *47*, 226–261.

Scher, C. D., Ingram, R. E., & Segal, Z. V. (2005). Cognitive reactivity and vulnerability: Empirical evaluation of construct activation and cognitive diatheses in unipolar depression. *Clinical Psychology Review*, *25*(4), 487–510.

Schildkraut, J. J., & Kety, S. S. (1967). Biogenic amines and emotion. *Science*, *156*, 21–37.

Schoots, O., & Van Tol, H. H. (2003). The human dopamine D4 receptor repeat sequences modulate expression. *Journal of Pharmacogenomics*, *3*, 343–348.

Sheikh, H. I., Hayden, E. P., Singh, S. M., Dougherty, L. R., Olino, T. M., Durbin, C. E., et al. (2008). An examination of the association between the 5-HTT promoter region polymorphism and depressogenic attributional styles in childhood. *Personality and Individual Differences*, *45*, 425–428.

Shi, J., Potash, J. B., Knowles, J. A., Weissman, M. M., Coryell, W., Scheftner, W. A., et al. (2010). Genome-wide association study of recurrent early onset major depressive disorder. *Molecular Psychiatry*, *16*, 193–201.

Shyn, S. I., Shi, J., Kraft, J. B., Potash, J. B., Knowles, J. A., Weissman, M. M., et al. (2011). Novel loci for major depression identified by genome-wide association study of sequenced treatment alternatives to relieve depression and meta-analysis of three studies. *Molecular Psychiatry*, *16*, 202–215.

Silk, J. S., Ziegler, M. L., Whalen, D. J., Dahl, R. E., Ryan, N. D., Dietz, L. J., et al. (2009). Expressed emotion in mothers of currently depressed, remitted, high-risk, and low-risk youth: Links to child depression status and longitudinal course. *Journal of Clinical Child and Adolescent Psychopathology*, *38*, 36–47.

Strange, B. A., Kroes, M. C. W., Roiser, J. P., Tan, G. C. Y., & Dolan, R. J. (2008). Emotion-induced retrograde amnesia is determined by a 5-HTT genetic polymorphism. *Journal of Neuroscience*, *28*, 7036–7039.

Sullivan, P. F., Neale, M. C., & Kendler, K. S. (2000). Genetic epidemiology of major depression: Review and meta-analysis. *American Journal of Psychiatry*, *157*, 1552–1562.

Tost, H., Kolachana, B., Hakimi, S., Lemaitre, H., Verchinski, B. A., Mattay, V. S., et al. (2010). A common allele in the oxytocin receptor gene (*OXTR*) impacts prosocial temperament and human hypothalamic-limbic structure and function. *Proceedings of the National Academy of Sciences*, *107*, 13936–13941.

van IJzendoorn, M. H., Caspers, K., Bakermans-Kranenburg, M. J., Beach, S. R. H., & Philibert, R. (2010). Methylation matters: Interaction between methylation density and serotonin transporter genotype predicts unresolved loss or trauma. *Biological Psychiatry*, *68*, 405–407.

Velders, F. P., Kuningas, M., Kumari, M., Dekker, M. J., Uitterlinden, A. G., Kirschbaum, C., et al.

(2011). Genetics of cortisol secretion and depressive symptoms: A candidate gene and genome wide association approach. *Psychoneuoendocrinology*, *36*, 153–161.

Way, B. M., & Taylor, S. E. (2010). The serotonin transporter polymorphism is associated with cortisol response to psychosocial stress. *Biological Psychiatry*, *67*, 487–492.

Weiss, E. M., Stadelmann, E., Kohler, C. G., Brensinger, C. M., Nolan, K. A., Oberacher, H., Parson, W., Pitterl, F., Niederstätter, H., Kemmler, G., Hinterhuber, H., & Marksteiner, J. (2007). Differential effect of catechol-O-methyltransferase Val158Met genotype on emotional recognition abilities in healthy men and women. *Journal of the International Neuropsychological Society*, *13*, 881–887.

Weissman, A., & Beck, A. T. (1978). *The Dysfunctional Attitude Scale: A validation study*. Paper presented at the Association for Advancement of Behavior Therapy, Chicago, IL.

Wells, T. T., Beevers, C. G., & McGeary, J. E. (2010). Serotonin transporter and *BDNF* genetic variants interact to predict cognitive reactivity in healthy adults. *Journal of Affective Disorders*, *126*, 223–229.

Wells, T. T., Beevers, C. G., & McGeary, J. E. (2011). DRD4 variation is associated with attention for contextually relevant stimuli. *International Journal of Neuropsychopharmacology*.

Wenzlaff, R. M., Rude, S. S., Taylor, C. J., Stultz, C. H., & Sweatt, R. A. (2001). Beneath the veil of thought suppression: Attentional bias and depression risk. *Cognition and Emotion*, *15*, 435–452.

Wenzlaff, R. M., Wegner, D. M., & Roper, D. W. (1988). Depression and mental control: The resurgence of unwanted negative thoughts. *Journal of Personality and Social Psychology*, *55*, 882–892.

Whisman, M. A., Johnson, D. P., & Smolen, A. (2011). Dysfunctional attitudes and the serotonin transporter promoter polymorphism. *Behavior Therapy*, *42*, 300–305.

Wiggins, J. L., Bedoyan, J. K., Peltier, S. J., Ashinoff, S., Carrasco, M., Weng, S.-J., et al. (2012). The development of serotonin transporter (5-HTTLPR) genotype on the development of resting-state functional connectivity in children and adolescents: A preliminary report. *NeuroImage*, *59*, 2760–2770.

Williams, J. M. G., Watts, F. N., MacLeod, C., & Mathews, A. (1997). *Cognitive psychology and emotional disorders* (2nd ed). New York, NY: Wiley.

Witt, S. H., Buchmann, A. F., Blomeyer, D., Nieratschker, V., Treutlein, J., Esser, G., et al. (2011). An interaction between neuropeptide Y gene polymorphism and early adversity modulates endocrine stress responses. *Psychoneuroendocrinology*, *36*, 1010–1020.

Yu, H., & Chen, Z. Y. (2011). The role of *BDNF* in depression on the basis of its location in the neural circuitry. *Acta Pharmacologica Sinica*, *32*, 3–11.

Zhou, Z., Zhu, G., Hariri, A. R., Enoch, M.-A., Scott, D., Sinha, R., et al. (2008). Genetic variation in human NPY expression affects stress response and emotion. *Nature*, *452*, 997–1001.

Downloaded by [State University NY Binghamton] at 10:13 26 February 2013