Imaging Genetics of Depression

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Introduction

Major depressive disorder (MDD) is typified by aberrations in cognitive, emotional, and behavioral functioning, including the hallmark characteristics of depressed mood and loss of interest or pleasure (anhedonia). MDD is a particularly burdensome disorder. In 2004, depression was identified as the third largest contributor to global disease burden, and it is predicted to be the leading contributor by 2030 (World Health Organization 2008). Three hundred and fifty million people worldwide are estimated to suffer from depression (World Health Organization 2012), and an estimated 20% of the US population will experience a clinical episode of depression during their lifetimes (Kessler and Wang 2009). Depression is also highly recurrent, with 75% of depressed individuals having more than a single episode of depression and often relapsing within two years of recovery (Boland and Keller 2009).

MDD has been posited to have a genetic component, with heritability estimated to be between 31% and 42% (Sullivan, Neale, and Kendler 2000). Given this high heritability, there has been considerable interest in candidate genes related to neural phenotypes of depression. It is important to recognize, however, that the genetic underpinnings of depression are complex; genes do not uniquely encode for the diagnosis of MDD or for depression-related symptoms. Not surprisingly, therefore, scientific investigation has been slowed by inconsistent and small effect sizes (Meyer-Lindenberg and Weinberger 2006).

Imaging genetics is a rapidly developing field in which investigators use neuroimaging to elucidate variations in brain structure and function as they relate to genotype (Hariri and Weinberger 2003). Recently, investigators have applied this

approach to the study of MDD (for reviews of the imaging genetics of depression, see Savitz and Drevets 2009; Scharinger, Rabl, Sitte, and Pezawas 2010; Northoff 2013). Indeed, despite the complexity of the genetic basis of mood disorders, findings from imaging genetics studies have been important in supporting the formulation that candidate genes influence emotional processing at the neural systems level (Scharinger et al. 2010), and that these gene-related variations contribute to the hallmark characteristics of MDD.

In this chapter, we present an overview of neuroimaging genetics research in the context of MDD. We begin by reviewing well-documented associations between candidate genes and susceptibility to depression, the course of MDD, cognitive and emotional aspects of this disorder, and the treatment response of depressed individuals. Specifically, we describe findings from investigations of three of the most widely studied genetic polymorphisms related to the psychobiology of depression: in the serotoin transporter (*5-HTT*) coding gene (SLC6A4), catechol-O-methyltransferase gene (*COMT*), and brain-derived neurotrophic factor gene (*BDNF*). We then review recent research documenting the utility for neuroimaging in depression of moving beyond a single-gene research approach, including gene-gene, gene-environment, and polygenic methodologies. Finally, we offer what we believe are important directions for future research in the field of imaging genetics in depression.

5-HTT

Due in part to the effectiveness of selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression, genetic variation in the serotonin transporter (*5-HTT*) coding gene (*SLC6A4*) has become a focal theme for neuroscientists interested in the genetic

substrates of major depression. Indeed, the single most studied variant involves a variable repeat sequence in the promoter region (*5-HTTLPR*) of *SLC6A4*; whereas the long (*l*) allele in this region is associated with increased concentrations of 5-HTT messenger RNA and increased serotonin (5-HT) uptake, the lower-expressing short (*s*) allele is linked with decreased 5-HT reuptake (Lesch et al. 1996). A single nucleotide polymorphism (SNP; A to G [denoted l_G] substitution) that occurs within the *l* allele (rs25531; Hu et al. 2005; Wendland, Martin, Kruse, Lesch, and Murphy 2006) also renders a phenotype that similar to the *s* variant in transcriptive efficacy.

A decade ago, researchers became enthusiastic about the role of *5-HTTLPR* in the pathophysiology of major depression. This excitement came in part from studies documenting that *s*-allele carriers have a greater likelihood than do homozygous *l*-allele carriers of developing MDD in the context of environmental adversity (Caspi et al. å2003), and from findings linking the *s* allele with a tendency to exhibit temperamental traits associated with increased risk for MDD, such as anxiety and neuroticism (Lesch et al. 1996; Munafò, Clark, Roberts, and Johnstone å2006). In addition, a reduction of available 5-HT levels, either induced through tryptophan depletion or occurring naturally through genetic polymorphisms of *5-HTTLPR*, has been found to be associated with cognitive difficulties similar to those found in depressed adults, including reduced specificity of autobiographical memory (Alhaj et al. 2012) and enhanced encoding of and attention to negatively valenced emotional material (Murphy, Smith, Cowen, Robbins, and Sahakian 2002; Beevers, Wells, Ellis, and Fischer 2008; Roiser et al. 2009; Wang et al. 2009).

5-HTTLPR and Brain Function

Similar to the literature documenting the cognitive effects of *5-HTTLPR*, imaging genetics studies of this polymorphism have found that non-disordered individuals who carry at least one copy of the lower expressing *s* allele demonstrate patterns of brain activation that have been reported to be characteristic of depressed individuals. For example, in one of the earliest studies to examine associations between *5-HTTLPR* and neural activation, Hariri et al. (2002) found that individuals who carry the *s* allele exhibited greater amygdala activation while they were viewing fearful stimuli than did individuals homozygous for the *l* allele. This pattern of increased amygdala responsivity to negative stimuli in *5-HTTLPR s*-allele carriers has been replicated by a number of investigators (e.g., Heinz et al. 2004; Hariri et al. 2005; Pezawas et al. 2005) and suggests that activity in this region, which has been found both to be hyperactive in major depression (Sheline et al. 2001; Siegle, Steinhauer, Thase, Stenger, and Carter 2002) and to be central to the generation and experience of negatively valenced affective states, is uniquely sensitive to genetically based alterations in serotonergic neurotransmission.

Building on this work, convergent evidence from neuroimaging studies indicates that *5-HTTLPR s*-allele carriers have volumetric anomalies in the amygdala and aberrations in functional connectivity between the amygdala and distinct subregions of the frontal cortex (e.g., anterior cingulate cortex [ACC], ventromedial prefrontal cortex [vmPFC]; Heinz et al. 2004; Pezawas et al. 2005)—areas that have been implicated in the control of negative emotional states through influencing, in part, activation in the amygdala (Ochsner et al. 2004; Urry et al. 2006; Wager, Davidson, Hughes, Lindquist, and Ochsner 2008). For example, Pezawas et al. (2005) found significantly lower volume of the perigenual ACC and the amygdala in *s*-allele carriers than in *l*-allele homozygotes.

S-allele carriers in this study also showed a reduction in the strength of negative functional connectivity between the amygdala and the ACC—particularly in the subgenual region—during the perceptual processing of fearful and threatening facial expressions (see also Hariri and Holmes 2006). Consistent with the view that these reductions are related to reduced cortical regulation of the amygdala, levels of functional connectivity in this investigation were found to predict 30% of the variance in level of harm avoidance, a personality trait that is related to vulnerability to anxiety and depression. Other studies document that *s*-allele carriers also show increased positive functional connectivity between the amygdala and the vmPFC (Heinz et al. 2004; Pezawas et al. 2005), which has been posited to reflect a compensatory effort for the impaired control function of the subgenual ACC (Hariri and Holmes 2006). Again, this anomalous functional connectivity is consistent with the neural hallmarks of major depression (Drevets et al. 1997; Mayber et al. 1999; Drevets et al. 2002) and supports the formulation that *5-HTTLPR* -associated increases in the susceptibility for MDD occur through a primed, hyper-responsive limbic system (Pezawas et al. 2005).

Importantly, several neuroimaging studies have now been conducted examining the influence of *5-HTTLPR* on amygdala function in MDD. These investigations generally find that, relative to their *l/l* counterparts, depressed individuals who carry at least one copy of the *s* allele exhibit increased amygdala activation, both at rest (Brockmann et al. 2011) and in response to negatively valenced stimuli (Dannlowski et al. 2007a; Dannlowski, Ohrmann, Bauer, Kugel, et al. 2007b; Costafreda et al. 2013). While the specific clinical implications of this association are unclear, Dannlowski et al. (2007a) found that *s*-allele-related increases in amygdala reactivity to masked emotional

faces were related to chronicity of depression, as indexed by number of hospitalizations. Further delineating relations among prognosis, treatment, and *5-HTTLPR*-related variation in amygdala function in depressed individuals is an important direction for future research.

Only two studies have examined the impact of *5-HTTLPR* genotype on prefrontal cortical function in individuals with major depression. In the first, Friedel et al. (2009) found that, whereas an increase in the number of lower-expressing *s* alleles was associated with an increase in vmPFC activation during the processing of negatively valenced images in non-depressed individuals, this effect was absent in participants with MDD. Further, while healthy controls in this study exhibited a greater positive correlation between activity in the vmPFC and amygdala with an increasing number of *s* alleles, MDDs demonstrated the opposite pattern. Thus, greater vmPFC activation, seen in healthy carriers of *5-HTT* low-expression alleles but not in their depressed counterparts, may reflect a protective mechanism that breaks down in MDD. In the second study, Brockmann et al. (2011) found that depressed *s*-allele carriers exhibited high resting-state activity in the vmPFC. Thus, the precise influence of *5-HTTLPR* on prefrontal function in individuals with MDD is inconclusive. It is important to note, however, that whereas Brockmann et al. (2011) sampled from participants who were treated with a variety of mood-stabilizing medications, depressed individuals in Friedel et al.'s (2009) investigation were untreated. It is possible, therefore, that associations between *5-HTTLPR* and prefrontal function in MDD vary as a function of medication. This possibility is consistent with findings reported by Neumeister et al. (2006) indicating that, whereas perturbation of the serotonin system using tryptophan depletion influenced

resting-state activity in the amygdala, hippocampus, and the subgenual ACC of *l*-allele carriers, this association was not evident in carriers of the risk (*s* or l_G) alleles.

Taken together, although the literature on the relation between *5-HTTLPR* and prefrontal function is equivocal, investigators have found more consistently that allelic variations in *5-HTTLPR* contribute to increased amygdala response in MDD. Further, given data demonstrating that depressed *s*-allele carriers show a greater bias toward anxious stimuli than do their *l/l* counterparts (Beevers, Gibb, McGeary, and Miller 2007), it is possible that the associations between *5-HTTLPR* and amygdala hyper-reactivity are secondary to genetic influences on attention. Thus, whether *5-HTTLPR*-related alterations in amygdala activity occur directly, or are influenced indirectly, through *5-HTTLPR*-related alterations in cognition, remains to be determined. Moreover, we have reviewed evidence that clinical aspects of MDD (e.g., medication) may affect associations between *5-HTTLPR* genotype and brain function (e.g., Neumeister et al. 2006). Thus, the potential role of clinical factors in mediating *5-HTTLPR*-related neural effects in MDD warrants further investigation. And finally, as we discuss in further detail later in this chapter, although several studies have found a significant interaction among *5-HTTLPR*, stress, and depression (e.g., Caspi et al. 2003; Karg, Burmeister, Shedden, and Sen 2011), no investigations have examined the relation among these factors in the context of brain function in MDD. It is important, therefore, that future studies consider these issues in increasing our understanding of the genetic mechanisms of neural dysfunction in major depression.

5-HTTLPR and Brain Structure

In addition to identifying associations between *5-HTTLPR* and brain *function* in MDD, researchers have begun to address whether *5-HTTLPR* polymorphisms might be associated with depression-related anomalies in brain *structure*. Given accumulating evidence of reduced hippocampal structure in the pathophysiology of MDD (Koolschijn, van Haren, Lensvelt-Mulders, Hulshoff Pol, and Kahn 2009), genetic neuroimaging studies of MDD have focused largely on the gray and white matter volume of this region. The results of studies in this area are mixed. While two early reports documented smaller hippocampal volumes among depressed individuals who were homozygous for the *l* allele compared to *s*-allele carriers (Frodl et al. 2004; Frodl et al. 2008), a third study found smaller hippocampal volumes among depressed individuals who were homozygous for the *s* allele (Eker et al. 2011), and a fourth investigation did not find any effects of *5-HTTLPR* polymorphism on hippocampal structure (Hickie et al. 2007). Although the reasons for these inconsistencies are not clear, they may be related to specific illness characteristics. For example, Taylor et al. (2005) found that depressed individuals who were homozygous for the *s* allele had smaller hippocampi than did *l*-allele carriers when the onset of depression occurred early in life. This pattern was reversed, however, in individuals who reported a later onset of depression (i.e., larger hippocampi were found in *s/s* homozygotes), suggesting that the effects of *5-HTTLPR* on hippocampal volume are dependent on the timing of MDD.

Few investigations have documented associations between *5-HTTLPR* and gray matter structure in other areas of the brain in depressed individuals. Hickie et al. (2007) found that *s*-allele carriers with late-life depression had smaller caudate volumes than did depressed *l/l* homozygotes, a pattern that was not present in never-depressed controls. In

a second study, Frodl et al. (2008) found that whereas healthy controls carrying the *s* or l_G allele had less gray matter in the dorsolateral prefrontal cortex (dlPFC), left ACC, left amygdala, and right hippocampus than did *l/l* homozygotes, this association was not found in depressed participants. Instead, individuals with MDD showed reductions in gray matter of these regions overall compared to never-depressed control participants, suggesting that morphological anomalies in the depressed individuals were more sensitive to the presence of disorder than to genetic polymorphisms.

Taken together, the literature examining associations between *5-HTTLPR* and brain structure in depression has been largely inconclusive, suggesting that other factors related to disease course (e.g., early life stress, medication, chronicity of depression) exert a stronger influence on brain structure than does *5-HTTLPR* genotype. It is also possible, however, that these factors interact with genotype to influence morphology. For example, Frodl et al. (2010) found that depressed individuals who carried the *s* allele and had a history of emotional neglect had smaller hippocampal volumes than did depressed patients who only had one risk factor (environmental or genetic). Further, childhood stress in this study resulted in larger prefrontal volumes in depressed subjects who carried the *l* allele, suggesting preventive effects of this polymorphism. These findings are important in indicating that stress represents a mechanism by which illness risk and outcome might be genetically mediated and, together, provide neurobiological support for an interaction among early life stress, *5-HTTLPR* polymorphism, and the likelihood of developing depression (e.g., Caspi et al. 2003; Karg, Burmeister, Shedden, and Sen 2011). Again, however, studies are needed that explicitly assess interactions among stress, genetics, and neural function and structure.

COMT

The COMT enzyme is involved in monoamine (including dopamine [DA]) catabolism. Consequently, COMT has been posited to play a role in the neurobiological and clinical manifestations of psychiatric disorders that involve anomalies in DA systems, such as MDD (Craddock, Owen, and O'Donovan 2006). Located on chromosome 22q11, a common G-to-A polymorphism of the *COMT* gene results in a valine (Val) to methionine (Met) substitution. Met-allele homozygotes have been found to have three to four times lower COMT enzyme activity than do Va homozygotes and, therefore, less breakdown of monoamines, including DA and norepinephrine; heterozygotes exhibit activity that is intermediate (Weinshilboum, Otterness, and Szumlanski 1999). Given the consequences of catecholamine catabolism (e.g., the role of DA in cognition and affect regulation; Lelli-Chiesa et al. 2010), investigators have studied the relation between the Val/Met substitution and psychiatric phenotypes (Bilder, Volavka, Lachman, and Grace 2004). We review findings from this literature in the following sections.

COMT and Brain Function

While researchers have not yet examined the impact of COMT on brain function in MDD specifically, a number of studies assessing non-disordered individuals suggest that the study of the Val/Met *COMT* substitution in MDD is an important research direction. Indeed, investigators have found associations between COMT and neural function in many of the same brain regions that are involved in depression, including the amygdala, ACC, orbitofrontal cortex (OFC), and hippocampus, although findings have not been entirely consistent (Scharinger et al. 2010). For example, studies have linked the *COMT* Met allele with both increased (Smolka et al. 2005; Smolka et al. 2007) and decreased

(Kempton et al. 2009) responsivity of the amygdala. Further, Drabant et al. (2006) found no associations between the Val/Met *COMT* polymorphism and amygdala activity.

Similar inconsistencies have been observed in the frontal cortices (Scharinger et al. 2010). *COMT* Met-allele carriers have shown decreased activity in the ACC relative to Val-allele homozygotes (Smolka et al. 2007; Williams et al. 2010); the reverse has also been found (Pomarol-Clotet et al. 2010). Moreover, Val-carrier status has been associated with both increased (Bishop, Cohen, Fossella, Casey, and Farah 2006; Pomarol-Clotet et al. 2010) and decreased OFC activity (Dreher, Kohn, Kolachana, Weinberger, and Berman 2009). Findings related to function of the hippocampus have been more consistent, with a majority of studies finding that Val homozygosity is related to decreased hippocampal activity (Smolka et al. 2005; Drabant et al. 2006; Smolka et al. 2007; Krach et al. 2010).

In attempting to understand the reasons for these inconsistencies, researchers have suggested that gender dimorphism may explain the ambiguous relations between *COMT* and brain function (Harrison and Tunbridge 2007; Scharinger et al. 2010). For example, the Val/Met polymorphism has been found to be related to obsessive-compulsive disorder in men but not in women, and to anxiety-related phenotypes in women but not in men (for review, see Harrison and Tunbridge 2007). Another factor that might lead to deviations in the association between *COMT* genotype and brain function involves gene-gene interactions. For example, Smolka et al. (2007) found that the combined effects of *COMT* and *5-HTTLPR* polymorphisms accounted for approximately 40% of BOLD signal variance in amygdala, hippocampus, and related limbic cortical regions and, further, that these effects were greater than the effects for either genotype individually.

Thus, the influence of *COMT* on brain activation may vary as a function of *5-HTTLPR* status. We discuss the involvement of gene-gene interactions, and the relation of these factors in MDD, in greater detail later in this chapter.

COMT and Brain Structure

Similar to studies of brain function, a large body of literature has examined the influence of the Val/Met *COMT* polymorphism on brain structure in non-disordered adults (Scharinger et al. 2010). Findings from this research document that Met-allele carriers are characterized by decreases in OFC volume (Cerasa et al. 2008), increases in amygdala volume (Taylor et al. 2007b; Cerasa et al. 2008; Ehrlich et al. 2010) and increases in hippocampal volume (Taylor et al. 2007b; Cerasa et al. 2008; Honea et al. 2009; Ehrlich et al. 2010), although some investigators have failed to replicate these findings (Ohnishi et al. 2005; Zinkstok et al. 2006). Several studies have also been conducted attempting to relate structural brain differences in depression to the Val/Met substitution (Pan et al. 2009; Seok et al. 2013). Given known cortico-subcortical network abnormalities related to this disorder (Mayberg 2003; Kempton et al. 2011) that include white matter disturbances of frontal-limbic networks (Sexton, Mackay, and Ebmeier 2009; Liao et al. 2013), Seok et al. (2013) examined the relation between frontal-to-limbic structural connectivity and the Val/Met *COMT* substitution in MDD. These investigators found that depressed Val homozygotes had lower fractional anisotropy (FA; an index of white matter integrity) of this network, specifically in the middle temporal gyrus, right middle frontal gyrus, and right cingulum bundle, than did depressed individuals carrying one or no copies of this allele. Thus, the *COMT* Val/Met polymorphism may exacerbate depression-related brain abnormalities.

In a second study, Pan et al. (2009) examined interactions of the *COMT* Val/Met polymorphism, polymorphisms of a gene coding for methylenetetrahydrofolate reductase (MTHFR; an enzyme that aids the conversion of homocysteine to methionine that has been implicated in MDD; Folstein et al. 2007), and volume of the basal ganglia, an important target in understanding depression given its strong connections with both the limbic system and the prefrontal cortex (Steffens, Tupler, Ranga, and Krishnan 1998). Pan et al. (2009) found an interaction of diagnosis and gene such that bilateral putamen volume in depressed *MTHFR* C/C participants decreased as the number of *COMT* Val alleles increased, and left putamen volumes decreased in the *COMT* Met/Met depressed participants as the number of *MTHFR* T alleles increased. These findings suggest that *COMT* Val/Met and *MTHFR C*/T interact to affect putamen volumes in depression, with neither gene individually controlling putamen volume.

Although research explicitly examining the effects of *COMT* on brain structure in depression is limited, associations between *COMT* and neural structure have been found in brain regions related to depression (e.g., Pan et al. 2009; Seok et al. 2013). Clearly, future research is necessary to replicate and extend these studies, and to continue to explicate the role of *COMT* on depression-related brain structure and function. Moreover, given promising results assessing the interaction of *COMT* and *MTHFR* on brain volume (Pan et al. 2009), future research is likely to benefit from assessing additional gene-gene relations to brain structure.

BDNF

Neurotrophins are a family of proteins that are centrally involved in the regulation of neural development, maintenance, function, survival, and plasticity in the vertebrate

nervous system (for a review, see Huang and Reichardt 2001). The neurotrophin hypothesis of depression (Duman and Monteggia 2006; Groves 2007) posits that reduced levels of neurotrophins contribute to the pathogenesis of MDD through neuronal atrophy and cell loss in integral brain areas associated with this disorder. Further, this hypothesis posits that the restoration of neurotrophins is integral to the effectiveness of antidepressant medications.

Brain-derived neurotrophic factor (BDNF), coded by the *BDNF* gene, represents one type of neurotrophin that is likely to be involved in the neural underpinnings of depression. A common single nucleotide polymorphism (SNP; rs6265) leads to a non-conservative valine (Val) to methionine (Met) amino acid alteration in the *BDNF* coding exon at position 66 (Val66Met). In rodents, the Met allele has been related to altered intracellular trafficking and activity-dependent release of the BDNF protein (Egan, Kojima, Callicott, & Goldberg, 2003; Chen et al. 2004). In humans, association studies have documented relations between the Val and the Met variants and anxiety (Sen et al. 2003; Jiang, Xu, Hoberman, Tian, and Marko et al. 2005; Lang et al. 2005). Sen et al. (2003) found that *BDNF* Val66Met was related to neuroticism, a strong marker of depression vulnerability (Duggan, Sham, Lee, Minne, and Murray 1995).

These findings, as well as a possible role of *BDNF* in the pathophysiology of MDD, have stimulated research examining the relation of this gene to brain function and structure in depression (Castrén 2005; Berton et al. 2006; Krishnan et al. 2007). This literature is reviewed in the following section.

BDNF and Brain Function

A growing body of literature has examined the impact of BDNF on brain function in healthy humans (e.g., Egan et al. 2003; Hariri et al. 2003; Montag, Reuter, Newport, Elger, and Weber 2008; for review, see Hong, Liou, and Tsai 2011). In the earliest imaging genetics studies of *BDNF*, Met-allele carriers, compared with Val-allele homozygotes, exhibited increased bilateral caudal hippocampal activity (as assessed by functional magnetic resonance imaging [fMRI]) during an N-back working memory task (Egan et al. 2003). In another seminal neuroimaging genetics study examining the role of *BDNF* on hippocampal activity during a declarative memory task, Hariri et al. (2003) found that while all participants activated the posterior hippocampal formation bilaterally during both encoding and retrieval, hippocampal activations occurring during the encoding and retrieval epochs were stronger in individuals who were homozygous for the Val-allele than for Met-allele carriers. Importantly, Met-allele carriers in this study also had a high number of recognition errors; in fact, 25% of the variance in recognition memory performance was explained by the interaction of *BDNF* genotype and hippocampal activity during encoding. Thus, consistent with the known function of *BDNF* in hippocampal plasticity, *BDNF* modulation of hippocampal activity appears to be important for information encoding (Poo 2001; Tyler, Alonso, Bramham, and Posso-Miller 2002) and, therefore, could underlie impairments in memory that have been documented in depressed individuals (Burt, Zembar, and Niederehe 1995).

The effects of the *BDNF* Val66Met polymorphism on emotional processing have also been studied using fMRI in non-disordered individuals. In an investigation of unselected adults, Montag et al. (2008) had participants complete an affective auditory startle reflex task in which startle probes were administered binaurally as participants

viewed pleasant, unpleasant, and neutral images. The *BDNF* Met polymorphism (relative to Val-allele homozygosity) was associated with greater activation in the right amygdala during the processing of positive and negative stimuli. Interestingly, in a subsequent study, Gasic et al. (2009) found that Val-allele homozygotes exhibited greater amygdala activation than did Val/Met heterozygotes. This discrepancy in the findings of these two studies may be due to gender differences in the studies; whereas 45% of the participants in Gasic et al.'s (2009) study were female, 100% of the subjects Montag et al.'s (2008) study were female. Indeed, a recent meta-analysis of 14 studies suggests that the *BDNF* Val66Met polymorphism has a differential impact on males and females (Verhagen et al. 2010).

Only one study to date has examined the effects of the *BDNF* Val66Met polymorphism on functional activation in a sample of depressed individuals. Lau et al. (2010) extended previous findings of *BDNF*-related effects on hippocampus and amygdala activation during emotional processing in healthy adults, by examining Val66Met-mediated neural activation to emotional faces in depressed and anxious adolescents. These investigators found an interaction of diagnosis and genotype: whereas in the depressed and anxious adolescents, Met-carriers showed greater neural response than did Val-homozygotes in bilateral amygdala and bilateral anterior hippocampus during processing of emotional faces, this genotype-activity relation was not observed in the control group. Thus, *BDNF* genotype may account for variations in brain function subserving emotional processing in MDD. Clearly, however, more studies are needed to support his hypothesis.

BDNF and Brain Structure

The relation of *BDNF* to brain structure, in particular the hippocampus, has received considerable research attention, with a majority of studies in healthy populations documenting an association between the Met allele and decreased hippocampal volume (for a review, see Scharinger et al. 2010). Examining the effect of this genotype in MDD, Frodl et al. (2007) found that the Met allele was associated with reduced hippocampal volumes in both depressed and nondepressed participants. More recently, however, Gonul et al. (2011) found that, while there was a main effect of diagnosis on hippocampal volume within Val-allele homozygotes, with the left hippocampus smaller in depressed than in non-depressed Val/Val individuals, no depression-associated effect was found for individuals who carried a Met allele. In another study, Kanellopoulos et al. (2011) found increased right hippocampal volumes in elderly depressed Val-allele homozygotes compared to their non-depressed counterparts; again, there was no difference between depressed and healthy Met-allele carriers. We should note, however, that several other studies have failed to find significant effects of Val66Met on hippocampal size in depression (Jessen et al. 2009; Benjamin et al. 2010; Cole et al. 2011).

In attempting to understand the reasons for these discrepancies, researchers have implicated the complexity of the hippocampus, positing that *BDNF*-related neurotrophic effects may differentially affect specific hippocampal subfields (e.g., dentate gyrus, *Cornu Ammonis* areas), or regions (e.g., head, body, tail). Therefore, future studies in which scanning is conducted at resolutions sufficient to examine specific hippocampal subfields or regions may help to clarify the observed inconsistencies (Molendijk et al. 2012a).

Investigators have also examined the amygdala in the context of *BDNF* polymorphisms. In non-depressed individuals, Montag, Weber, Fliessbach, Elger, and Reuter (2009) found the Met allele to be associated with decreased amygdala size. Most other studies, however, have failed to observe this association (Pezawas et al., 2004; Nemoto et al. 2006; Matsuo et al. 2009; Schofield, Williams, Paul, and Gatt 2009), including a study of depressed individuals (Frodl et al. 2007).

Other studies of the association of *BDNF* with brain structure have focused on white matter of the uncinate fasciculus, a primary white matter tract connecting limbic (hippocampus and amygdala) with prefrontal regions that is posited to subserve emotional-cognitive processing, declarative memory, and self-awareness (Levine et al. 1998; Taylor, MacFall, Gerig, and Krishnan 2007a; Mabbott, Rovet, Noseworthy, Lou Smith, and Rockel 2009). Importantly, one study found reduced FA of the uncinate fasciculus in depressed participants who carried a Met allele compared to both healthy Met-allele carriers and depressed individuals who were homozygous for the Val allele (Carballedo et al. 2012). Thus, *BDNF* polymorphisms may affect neural circuits not only through structure of anatomic subregions, but also by influencing the structural connections among these regions.

Summary: *5-HTT*, *COMT*, and *BDNF*

Considered collectively, this literature suggests possible roles for *5-HTT*, *COMT*, and *BDNF* in influencing the anomalous structure and function of limbic and prefrontal brain regions associated with depression. As we discussed earlier, given the inconsistency of findings relating these genes to brain structure and function in both healthy and depressed individuals, it is clear that further research is required to explicate more precisely the

specific roles of these genes in affecting neural characteristics and their relation to MDD. The equivocal results reviewed previously may be due to heterogeneity in the samples studied in these investigations with respect to gender composition, ethnicity, age, type of treatment, methods of diagnosis, and experimental approaches. Studies also differ in analytic procedures and the specific genetic polymorphisms assessed. For example, the Val66Met polymorphism that is targeted by neuroimaging genetics researchers is only one variant of the *BDNF* gene. While future research should systematically address these potential confounding factors, a number of other variables that are related to gene-brain associations must also be considered. We discuss these factors in the following section.

Beyond Single Genes

Given the inconsistencies noted earlier in studies of neuroimaging and single-gene polymorphisms in depression, investigators have developed increasingly complex and sophisticated methods to elucidate gene-brain relations in major depression. This research extends prior work by assessing gene-gene and gene-environment interactions, as well as the association between neural measures and multiple genetic risk factors for depression, or *polygenic burden*. In the following section, we review findings from studies addressing interactions among *5-HTT*, *BDNF*, and *COMT*, in addition to interactions of *BDNF* and *5-HTT* with environmental stress. Finally, we discuss recent polygenic approaches to the neuroimaging genetics of depression.

Gene-Gene Interactions

Given the associations between single candidate genes (*5-HTT*, *COMT*, and *BDNF*) and the structure and function of prefrontal and limbic brain regions involved in the generation and regulation of emotion, investigators have begun to examine how these

genes interact to affect neural structure and function (Hariri, Drabant, and Weinberger 2006). Several studies have documented interactions of the *COMT* Val/Met substitution and *5-HTTLPR s* allele in predicting brain function. Given the research that we reviewed earlier showing associations among single-gene polymorphisms, anxiety phenotypes, and amygdala-related processing of negative stimuli (Hariri et al. 2002; Heinz et al. 2004; Smolka et al. 2005), as well as anxiety-related phenotypes, Smolka et al. (2007) assessed the roles of *COMT* and *5-HTTLPR* on brain activation during the processing of valenced stimuli. They found that a higher total number of *COMT* or *5-HTT* risk variants (Met and *s* or l_G, respectively) were related to increased neural activation in the amygdala, hippocampus, and limbic cortex and, further, that the combined effect of these *COMT* and *5-HTTLPR* variants during the processing of aversive material was greater than either genotype individually. Moreover, risk variants of *COMT* and *5-HTTLPR* explained 40% of the variance in brain function of limbic regions. Importantly, this estimate is considerably larger than the variance explained by these genes individually, and larger than their relation to personality traits documented in previous research (e.g., Lesch et al. [1996] found risk variants of *5-HTTLPR* to explain 4% of the variance in anxiety scores).

Investigators have begun to examine the interaction of *5-HTTLPR* and *BDNF* on brain structure and function. Importantly, 5-HT signaling has been found to mediate both neurotrophin-related synaptic plasticity (Castrén 2005; McEwen and Olié 2005; Martinowich and Lu 2007) and the modulation of *BDNF* expression (Nestler et al. 2002). Further, *BDNF* plays a role in the plasticity and function of serotonergic neurons and serotonergic-related emotional processing (Nestler et al. 2002; Murphy et al. 2003; de Foubert et al. 2004; Ren-Patterson et al. 2005; Martinowich and Lu 2007; Tan et al.

2007). Pezawas et al. (2008) assessed the relation between *BDNF* and *5-HTTLPR* in the context of brain volume, with a particular focus on structures that have been found to be associated with depression (e.g., the amygdala). These researchers found that the *BDNF* Met allele appears to protect against structural anomalies associated with the *5-HTTLPR s* allele, such as decreased amygdala and ACC volume (Lesch et al. 1996; Caspi et al. 2003), and against reduced structural connectivity between these regions (Raz et al. 1997; Woodruff et al. 1997; Raz et al. 2004; Raz et al. 2005). These findings suggest that a critical link between serotonergic and neurotrophic systems that can be elucidated through the use of a neuroimaging genetics approach. Although no studies have yet been conducted examining gene-gene interactions predicting neural function or structure in MDD, it is clear that future conceptions of MDD will benefit from the study of these interactions as they relate to neural anomalies in depression.

Gene-Environment Interaction

Adverse life events have long been posited to relate to the development of depression (see Monroe, Slavich, and Georgiades 2009, for a review). In addition, the increased likelihood of developing depression in response to a stressful life event appears to be driven, at least in part, by genetic factors (Kendler et al. 1995; Kessler 1997; Kendler, Gardner, and Prescott 2002). Using a neuroimaging genetics approach to understanding this unique gene-environment interaction at the neurobiological level is important for identifying neural risk factors for depression, which could yield more effective treatments that target relevant neural mechanisms associated with the negative effects of stress in MDD (Gordon 2007; Kemp, Gordon, Rush, and Williams 2008).

Using functional neuroimaging, Canli et al. (2006) found that early life stress (ELS) interacts with the effect of *5-HTTLPR* genotype on resting activity in the amygdala and hippocampus, both of which have been associated with stress and depression; more specifically, activation was positively correlated with ELS in the *s*-allele carriers and negatively correlated with ELS in the *l*-allele homozygotes. Thus, Canli et al.'s (2006) study may elucidate the mechanisms underlying the relations among *5-HTTLPR* genotype, stress, and depression, and lays the foundation for future research examining processes involved in reduced resilience and the development of depression.

Given the neurotrophin hypothesis of depression, as well as data implicating ELS as a vulnerability marker for MDD (Gatt et al. 2008), Gatt et al. (2009) examined the interaction of *BDNF* and ELS in predicting anomalies in brain structure in regions that have been implicated in depression (e.g., hippocampus). Gatt et al. found that *BDNF* Met carriers who had experienced ELS had smaller hippocampus and amygdala volumes than did participants in the other gene-environment groups. Similarly, Gerritsen et al. (2011) found reduced volume in subgenual ACC in *BDNF* Met allele carriers who had experienced ELS, relative to individuals with Met-allele carriers without ELS and Val/Val homozygotes with ELS, a finding not obtained in the hippocampus, amygdala, or orbitofrontal prefrontal cortex. In contrast to these findings, however, in examining hippocampal structure, Molendijk et al. (2012b) did not find an interaction of genotype and childhood abuse. As we noted earlier, however, this negative finding may change with more sophisticated neuroimaging analysis techniques focusing on specific neuroanatomic subregions.

To date, investigators have generally examined separately the relations of genetic polymorphisms, stress, personality traits, and brain function and structure with depression. Moving forward, it will be important to conduct integrative studies of how stress and genes are related to neural aspects of MDD in order to gain a better understanding of the complex mechanisms that underlie this disorder.

Polygenic Burden

Although MDD has been documented to be a highly heritable disorder (Sullivan et al. 2000), and investigations of the effects of individual candidate genes have yielded promising results, so far investigators have found only weak relations between depression-related phenotypes and single genes (Meyer-Lindenberg and Weinberger 2006). This discrepancy has led to the formulation that a large set of allelic variants may have small effects individually, but may explain considerable variation collectively in cognitive, behavioral, and neural aspects of depression.

Building on this work, Holmes et al. (2012) examined the relation between neural structure and function and polygenic risk for depression. These investigators identified young adults via genome-wide association analysis who had polygenic risk for MDD (n = 438) and assessed gray matter volume in relation to this risk. Holmes et al. (2012) found that decreased mPFC thickness was related to greater polygenic risk for MDD, heightened negative affect, poorer social cognition, and lower performance on a facial emotion recognition task. While these are promising preliminary findings, it will be important in future research to examine larger and more diverse samples and denser SNP arrays, the effects of environmental influences (e.g., ELS), and neuroanatomic subregions (Whalen et al. 2001; Etkin et al. 2004). Elucidating the relations of gene-gene and gene-

environment interactions with depressive pathology is likely to provide insight about the complex neurogenetic mechanisms underlying MDD, as evidenced by the interactions among *5-HTT*, *COMT*, *BDNF*, and ELS in predicting activation in neural structures and characteristics that have been implicated in depression.

Summary and Future Directions

Imaging genetics has begun to be widely applied. Investigators have now used single-gene, gene-gene, gene-environment, and polygenic approaches to examine whether and how genetic variation influences brain structure and function in the general population (Hariri and Weinberger 2003; Hariri et al. 2006) and, more recently, in depressed individuals (Savitz and Drevets 2009; Scharinger et al. 2010; Northoff 2013). Although at present it is not possible to elucidate the precise role of genetics in affecting neural structure and function in depression, particularly with respect to single-gene effects (e.g., 5-HTTLPR, COMT, BDNF), there is growing evidence suggesting that polygenic risk, in combination with environmental factors (e.g., ELS), may play a role in the development of depressive pathophysiology. Nevertheless, documented throughout this review are indications that replication is critical and that improved experimental controls are necessary before we can be confident about the role of genetics in explicating the biological and, in particular, the neural bases of MDD.

In order to delineate genetic influences on the development and course of depression, future research will benefit from the use of longitudinal designs that permit the assessment of the genetic impact on the trajectory of depressive disorder. Moreover, although there are many possible genetic mechanisms identified in studies of non-disordered individuals that may be implicated in MDD, it is important that a

neuroimaging genetics approach be extended to study individuals diagnosed with this disorder. Perhaps most important to increase our confidence in the reliability and validity of the findings obtained thus far, replications and larger sample sizes are required. This issue, of course, raises questions regarding feasibility, which may be at least partially addressed by large-scale endeavors to create databases of neural and genetic data for depression and other psychiatric disorders similar to the Alzheimer's Disease Neuroimaging Initiative (http://adni.loni.ucla.edu). Finally, it is important that investigators consider the impact of cohort characteristics (e.g., gender, medication, age) in the imaging genetics of depression; these variables may differentially affect the expression and influence of genetic mechanisms involved in the development of depression and in the effectiveness of treatments for MDD. It is clear that considerably more research is required before we can draw strong conclusions about the ultimate value of imaging genetics of depression. Nevertheless, we believe that despite the difficulties inherent in this work, imaging genetics holds the potential to significantly increase our understanding of depression and to improve our efforts aimed at the prevention, assessment, and treatment of this debilitating disorder.

References

Alhaj HA, Selman M, Jervis V, Rodgers J, Barton S, McAllister-Williams, RH. (2012). Effect of low-dose acute tryptophan depletion on the specificity of autobiographical memory in healthy subjects with a family history of depression. *Psychopharmacology*. *222*(2): 285–292.

Beevers CG, Gibb BE, McGeary JE, Miller IW. (2007). Serotonin transporter genetic variation and biased attention for emotional word stimuli among psychiatric inpatients. *J Abnorm Psychology*. *116*(1): 208–212.

Beevers CG, Wells TT, Ellis AJ, Fischer K. (2008). Identification of emotionally ambiguous interpersonal stimuli among dysphoric and nondysphoric individuals. *Cognitive Ther Res*. *33*(3): 283–290.

Benjamin S, McQuoid DR, Potter GG, Payne ME, MacFall JR, Steffens DC, Taylor WD. (2010). The brain-derived neurotrophic factor val66met polymorphism, hippocampal volume, and cognitive function in geriatric depression. *Am J Geriat Psychiatry*. *18*(4): 323–331.

Berton O, McClung CA, DiLeone RJ, Krishnan V, Renthal W, Russo SJ, et al. (2006). Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. *Science, New Series*. *311*(5762): 864–868.

Bilder RM, Volavka J, Lachman HM, Grace AA. (2004). The catechol-o-methyltransferase polymorphism: relations to the tonic–phasic dopamine hypothesis and neuropsychiatric phenotypes. *Neuropsychopharmacology*. 29(11): 1943–1961.

Bishop SJ, Cohen JD, Fossella J, Casey BJ, Farah MJ. (2006). COMT genotype influences prefrontal response to emotional distraction. *Cogn Affect Behav Neurosci*. 6(1): 62–70.

Boland RJ, Keller MB. (2009) Course and outcome of depression. In Gotlib IH and Hammen CL, eds., *Handbook of depression*, 2nd ed. (pp. 23–43). New York: Guilford Press.

Brockmann H, Zobel A, Schuhmacher A, Daamen M, Joe A, Biermann K, et al. (2011). *J Psychiat Res*. 45(4): 442–451.

Burt DB, Zembar MJ. Niederehe G. (1995). Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. *Psychol Bull*. 117(2): 285.

Canli T, Qiu M, Omura K, Congdon E, Haas BW, Amin Z, et al. (2006). Neural correlates of epigenesis. *Proc Natl Acad Sci U S A*. 103(43): 16033–16038.

Carballedo A, Amico F, Ugwu I, Fagan AJ, Fahey C, Morris D, et al. (2012). Reduced fractional anisotropy in the uncinate fasciculus in patients with major depression carrying the met-allele of the Val66Met brain-derived neurotrophic factor genotype. *Am J Med Genet B.* 159B(5): 537–548.

Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science Signaling*. 301(5631): 386–389.

Castrén E. (2005). Is mood chemistry? *Nat Rev Neurosci*. 6(3): 241–246.

Cerasa A, Gioia MC, Labate A, Liguori M, Lanza P, Quattrone A. (2008). Impact of catechol-O-methyltransferase Val108/158 Met genotype on hippocampal and prefrontal gray matter volume. *Neuroreport*. 19(4): 405–408.

Chen ZY, Patel PD, Sant G, Meng CX, Teng KK, Hempstead BL, Lee FS. (2004). Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. *J Neurosci*. 24(18): 4401–4411. doi:10.1523/JNEUROSCI.0348-04.2004.

Cole J, Weinberger DR, Mattay VS, Cheng X, Toga AW, Thompson PM, et al. (2011). No effect of 5HTTLPR or BDNF Val66Met polymorphism on hippocampal morphology in major depression. *Genes Brain Behav*. 10(7): 756–764.

Costafreda SG, McCann P, Saker P, Cole JH, Cohen-Woods S, Farmer AE, et al. (2013).. *J Affect Disord*. 1–8.

Craddock N, Owen MJ, O'Donovan MC. (2006). The catechol-O-methyl transferase (COMT) gene as a candidate for psychiatric phenotypes: evidence and lessons. *Mol Psychiatry*. 11(5): 446–458.

Dannlowski U, Ohrmann P, Bauer J, Deckert J, Hohoff C, Kugel H, et al. (2007a). 5-HTTLPR biases amygdala activity in response to masked facial expressions in major depression. *Neuropsychopharmacology*, 33(2): 418–424. doi: 10.1038/sj.npp.1301411.

Dannlowski U, Ohrmann P, Bauer J, Kugel H, Baune BT, Hohoff C, et al. (2007b). Serotonergic genes modulate amygdala activity in major depression. *Genes Brain Behav*. 6(7): 672–676.

de Foubert G, Carney SL, Robinson CS, Destexhe EJ, Tomlinson R, Hicks CA, et al. (2004). Fluoxetine-induced change in rat brain expression of brain-derived

neurotrophic factor varies depending on length of treatment. *Neuroscience*. 128(3): 597–604.

Drabant EM, Hariri AR, Meyer-Lindenberg A, Munoz KE, Mattay VS, Kolachana BS, et al. (2006). Catechol O-methyltransferase val158met genotype and neural mechanisms related to affective arousal and regulation. *Arch Gen Psychiatry*. 63(12): 1396.

Dreher J-C, Kohn P, Kolachana B, Weinberger DR, Berman KF. (2009). Variation in dopamine genes influences responsivity of the human reward system. *Proc Natl Acad Sci*. 106(2): 617–622.

Drevets WC, Price JL, Bardgett ME, Reich T, Todd RD, Raichle ME. (2002). Glucose metabolism in the amygdala in depression: relationship to diagnostic subtype and plasma cortisol levels. *Pharmacol Biochem Behav*. 71(3): 431–447.

Drevets WC, Price JL, Simpson JR, Todd RD, Reich T, Vannier M, Raichle ME. (1997). Subgenual prefrontal cortex abnormalities in mood disorders. *Nature*. 386(6627): 824–827.

Duggan C, Sham P, Lee A, Minne C, Murray R. (1995). Neuroticism: a vulnerability marker for depression evidence from a family study. *J Affect Disord*. 35(3): 139–143.

Duman RS, Monteggia LM. (2006). A neurotrophic model for stress-related mood disorders. *Biol Psychiatry*. 59(12): 1116–1127. doi:10.1016/j.biopsych.2006.02.013

Egan MF, Kojima M, Callicott JH, Goldberg TE. (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell*. 112(2): 257–269.

Ehrlich S, Morrow EM, Roffman JL, Wallace SR, Naylor M, Bockholt HJ, et al. (2010). The COMT Val108/158Met polymorphism and medial temporal lobe volumetry in patients with schizophrenia and healthy adults. *NeuroImage*, *53*(3), 992–1000.

Eker MC, Kitis O, Okur H, Eker OD, Ozan E, Isikli S, et al. (2011). Smaller hippocampus volume is associated with short variant of 5-HTTLPR polymorphism in medication-free major depressive disorder patients. *Neuropsychobiology*. 63(1): 22–28.

Etkin A, Klemenhagen KC, Dudman JT, Rogan MT, Hen R, Kandel ER, Hirsch J. (2004). Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces. *Neuron*. 44(6): 1043–1055.

Folstein M, Liu T, Peter I, Buel J, Arsenault L, Scott T, Qiu W. (2007). The homocysteine hypothesis of depression. *Am J Psychiatry*. 164(6): 861–867.

Friedel E, Schlagenhauf F, Sterzer P, Park SQ, Bermpohl F, Ströhle A, et al. (2009). 5-HTT genotype effect on prefrontal–amygdala coupling differs between major depression and controls. *Psychopharmacology*. 205(2): 261–271.

Frodl T, Reinhold E, Koutsouleris N, Donohoe G, Bondy B, Reiser M, et al. (2010). Childhood stress, serotonin transporter gene and brain structures in major depression. *Neuropsychopharmacology*. 35(6): 1383–1390.

Frodl T, Schüle C, Schmitt G, Born C, Baghai T, Zill P, et al. (2007). Association of the brain-derived neurotrophic factor Val66Met polymorphism with reduced hippocampal volumes in major depression. *Arch Gen Psychiatry*. 64(4): 410–416.

Frodl T, Zill P, Baghai T, Schüle C, Rupprecht R, Zetzsche T, et al. (2008). Reduced hippocampal volumes associated with the long variant of the tri-and diallelic serotonin transporter polymorphism in major depression. *Am J Med Genet B*. 147(7): 1003–1007.

Gasic GP, Smoller JW, Perlis RH, Sun M, Lee S, Kim BW, et al. (2009). BDNF, relative preference, and reward circuitry responses to emotional communication. *Am J Med Genet B*. 150(6): 762–781.

Gatt JM, Kuan SA, Dobson-Stone C, Paul RH, Joffe RT, Kemp AH, et al. (2008). Association between BDNF Val66Met polymorphism and trait depression is mediated via resting EEG alpha band activity. *Biol Psychol*. 79(2): 275–284.

Gatt JM, Nemeroff CB, Dobson-Stone C, Paul RH, Bryant RA, Schofield PR, et al. (2009). Interactions between BDNF Val66Met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety. *Mol Psychiatry* 14(7): 681–695.

Gerritsen L, Tendolkar I, Franke B, Vasquez AA, Kooijman S, Buitelaar J, et al. (2011). BDNF Val66Met genotype modulates the effect ofchildhood adversity on subgenual anterior cingulatecortex volume in healthy subjects. *Mol Psychiatry*. 17(6): 597–603.

Gonul AS, Kitis O, Eker MC, Eker OD, Ozan E, Coburn K. (2011) Association of the brain-derived neurotrophic factor Val66Met polymorphism with hippocampus volumes in drug-free depressed patients. *World J Biol Psychiatry*. 12: 110–118.

Gordon E. (2007). Integrating genomics and neuromarkers for the era of brain-related personalized medicine. *Pers Med*. 4(2): 201–215.

Groves JO. (2007). Is it time to reassess the BDNF hypothesis of depression? *Mol Psychiatry*. 12(12): 1079–1088.

Hariri AR, Mattay VS, Tessitore A, Kolachana B, Fera F, Goldman D, Egan MF, Weinberger DR. (2002). Serotonin transporter genetic variation and the response of the human amygdala. *Science*. 297(5580): 400–403. doi: 10.1126/science.1071829.

Hariri AR, Weinberger DR. (2003). Imaging genomics. *Br Med Bull*. 65(1): 259–270.

Hariri AR, Holmes A. (2006). Genetics of emotional regulation: the role of the serotonin transporter in neural function. *Trends Cogn Sci*. *10*(4): 182–191.

Hariri AR, Drabant EM, Weinberger DR. (2006). Imaging genetics: perspectives from studies of genetically driven variation in serotonin function and corticolimbic affective processing. *Biol Psychiatry*. 59(10): 888–897.

Hariri AR, Drabant EM, Munoz KE, Kolachana BS, Mattay VS, Egan MF, Weinberger DR. (2005). A susceptibility gene for affective disorders and the response of the human amygdala. *Arch Gen Psychiatry*. *62*(2), 146–152.

Hariri AR, Goldberg TE, Mattay VS, Kolachana BS, Callicott JH, Egan MF, Weinberger DR. (2003). Brain-derived neurotrophic factor val66met polymorphism affects

human memory-related hippocampal activity and predicts memory performance. *J Neurosci*. 23(17): 6690–6694.

Harrison PJ, Tunbridge EM. (2007). Catechol-O-methyltransferase (COMT): a gene contributing to sex differences in brain function, and to sexual dimorphism in the predisposition to psychiatric disorders. *Neuropsychopharmacology*. 33(13): 3037–3045.

Heinz A, Braus DF, Smolka MN, Wrase J, Puls I, Hermann D, et al. (2004). Amygdala-prefrontal coupling depends on a genetic variation of the serotonin transporter. *Nat Neurosci*. 8(1): 20–21.

Hickie IB, Naismith SL, Ward PB, Scott EM, Mitchell PB, Schofield PR, et al. (2007). Serotonin transporter gene status predicts caudate nucleus but not amygdala or hippocampal volumes in older persons with major depression. *J Affect Disord*. 98(1–2): 137–142.

Holmes AJ, Lee PH, Hollinshead MO, Bakst L, Roffman JL, Smoller JW, Buckner RL. (2012). Individual differences in amygdala-medial prefrontal anatomy link negative affect, impaired social functioning, and polygenic depression risk. *J Neurosci*. 32(50): 18087–18100.

Honea R, Verchinski BA, Pezawas L, Kolachana BS, Callicott JH, Mattay VS, et al. (2009). Impact of interacting functional variants in COMT on regional gray matter volume in human brain. *NeuroImage*: 45(1): 44–51.

Hong C-J, Liou Y-J, Tsai S-J. (2011). Effects of BDNF polymorphisms on brain function and behavior in health and disease. *Brain Res Bull*. 86(5–6): 287–297.

Hu X, Oroszi G, Chun J, Smith TL, Goldman D, Schuckit MA. (2005). An Expanded Evaluation of the Relationship of Four Alleles to the Level of Response to Alcohol and the Alcoholism Risk. *Alcohol Clin Exper Res*. 29(1): 8–16.

Huang EJ, Reichardt LF. (2001). Neurotrophins: roles in neuronal development and function 1. *Ann Rev Neurosci*. 24(1): 677–736.

Jessen F, Schuhmacher A, von Widdern O, Guttenthaler V, Hofels S, Suliman H, et al. (2009). No association of the Val66Met polymorphism of the brain-derived neurotrophic factor with hippocampal volume in major depression. *Psychiat Genet*. 19(2): 99–101.

Jiang X, Xu K, Hoberman J, Tian F, Marko AJ, Waheed JF, Harris CR, et al. (2005). Neuropsychopharmacology—Abstract of article: BDNF variation and mood disorders: a novel functional promoter polymorphism and Val66Met are associated with anxiety but have opposing effects. *Neuropsychopharmacology*. 30(7): 1353–1361.

Kanellopoulos D, Gunning FM, Morimoto SS, Hoptman MJ, Murphy CF, Kelly RE, Jr, et al. (2011). Hippocampal volumes and the BDNF Val66Met polymorphism in geriatric major depression. *Am J Geriat Psychiatry*. 19(1): 13–22.

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. *Arch Gen Psychiatry*. 68(5): 444–454.

Kemp AH, Gordon E, Rush AJ, Williams LM. (2008). Improving the prediction of treatment response in depression: integration of clinical, cognitive,

psychophysiological, neuroimaging, and genetic measures. *CNS Spectr*. 13(12): 1066–1086.

Kempton MJ, Salvador Z, Munafò MR, Geddes JR, Simmons A, Frangou S, Williams SC. (2011). Structural neuroimaging studies in major depressive disorder: meta-analysis and comparison with bipolar disorder. *Arch Gen Psychiatry*. 68(7): 675–690.

Kempton MJ, Haldane M, Jogia J, Powell J, Collier D, Williams SC, Frangou S. (2009). The effects of gender and COMT Val158Met polymorphism on fearful facial affect recognition: a fMRI study. *Int J Neuropsychopharm*. 12(3): 371–381.

Kendler KS, Gardner CO, Prescott CA. (2002). Toward a comprehensive developmental model for major depression in women. *Am J Psychiatry*. 159(7): 1133–1145.

Kendler KS, Kessler RC, Walters EE, MacLean C, Neale MC, Heath AC, Eaves LJ. (1995). Stressful life events, genetic liability, and onset of an episode of major depression in women. *Am J Psychiatry*. 152(6): 833–842.

Kessler RC. (1997). The effects of stressful life events on depression. *Ann Rev Psychol*. 48(1): 191–214.

Kessler, R. C., & Wang, P. S. (2009) The epidemiology of depression. In Gotlib IH and Hammen CL, eds., *Handbook of depression*, 2nd ed. (pp. 5–22). New York: Guilford Press.

Koolschijn PCMP, van Haren NEM, Lensvelt-Mulders GJLM, Hulshoff Pol HE, Kahn RS. (2009). Brain volume abnormalities in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. *Human Brain Mapping*. 30(11): 3719–3735.

Krach S, Jansen A, Krug A, Markov V, Thimm M, Sheldrick AJ, et al. (2010). COMT genotype and its role on hippocampal–prefrontal regions in declarative memory. *NeuroImage*. 53(3): 978–984.

Krishnan V, Han M-H, Graham DL, Berton O, Renthal W, Russo SJ, et al. (2007). Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. *Cell*. 131(2): 391–404.

Lang UE, Hellweg R, Kalus P, Bajbouj M, Lenzen KP, Sander T, et al. (2005). Association of a functional BDNF polymorphism and anxiety-related personality traits. *Psychopharmacology*. 180(1): 95–99.

Lau JYF, Goldman D, Buzas B, Hodgkinson C, Leibenluft E, Nelson E, et al. (2010). BDNF gene polymorphism (Val66Met) predicts amygdala and anterior hippocampus responses to emotional faces in anxious and depressed adolescents. *NeuroImage*. 53(3): 952–961.

Lelli-Chiesa G, Kempton MJ, Jogia J, Tatarelli R, Girardi P, Powell J, et al. (2010). The impact of the Val158Met catechol- O-methyltransferase genotype on neural correlates of sad facial affect processing in patients with bipolar disorder and their relatives. *Psychol Med*. 41(04): 779–788.

Lesch K-P, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, et al. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*. 274(5292): 1527–1531.

Levine B, Black SE, Cabeza R, Sinden M, McIntosh AR, Toth JP, et al. (1998). Episodic memory and the self in a case of isolated retrograde amnesia. *Brain*. 121(10): 1951–1973.

Liao Y, Huang X, Wu Q, Yang C, Kuang W, Du M, et al. (2013). Is depression a disconnection syndrome? Meta-analysis of diffusion tensor imaging studies in patients with MDD. *J Psychiat Neurosci*. 38(1): 49–56. doi: 10.1503/jpn.110180.

Mabbott DJ, Rovet J, Noseworthy MD, Lou Smith M, Rockel C. (2009). The relations between white matter and declarative memory in older children and adolescents. *Brain Res*. 1294(C): 80–90.

Martinowich K, Lu B. (2007). Interaction between BDNF and serotonin: role in mood disorders. *Neuropsychopharmacology*. 33(1): 73–83. doi: 10.1038/sj.npp.1301571

Matsuo K, Walss-Bass C, Nery FG, Nicoletti MA, Hatch JP, Frey BN, et al. (2009). Neuronal correlates of brain-derived neurotrophic factor Val66Met polymorphism and morphometric abnormalities in bipolar disorder. 34(8): 1904–1913.

Mayberg HS. (2003). Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. *Br Med Bull*. 65(1): 193–207.

Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, et al. (1999). Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am J Psychiatry*. 156(5): 675–682.

McEwen BS, Olié JP. (2005). Neurobiology of mood, anxiety, and emotions as revealed by studies of a unique antidepressant: tianeptine. *Mol Psychiatry*. 10(6): 525–537.

Meyer-Lindenberg A, Weinberger DR. (2006). Intermediate phenotypes and genetic mechanisms of psychiatric disorders. *Nat Rev Neurosci*. 7(10): 818–827.

Molendijk ML, Bus BAA, Spinhoven P, Kaimatzoglou A, Voshaar RCO, Penninx BWJH, et al. (2012a). A systematic review and meta-analysis on the association

between BDNF val66met and hippocampal volume-A genuine effect or a winners curse? *Am J Med Genet B*. 159B(6): 731–740.

Molendijk ML, van Tol M-J, Penninx BWJH, van der Wee NJA, Aleman A, Veltman DJ, et al. (2012b). Met affects hippocampal volume and emotion-related hippocampal memory activity. *Transl Psychiatry* 2(1): e74–78.

Montag C, Reuter M, Newport B, Elger C, Weber B. (2008). The BDNF Val66Met polymorphism affects amygdala activity in response to emotional stimuli: evidence from a genetic imaging study. *NeuroImage*. 42(4): 1554–1559.

Montag C, Weber B, Fliessbach K, Elger C, Reuter M. (2009). The BDNF Val66Met polymorphism impacts parahippocampal and amygdala volume in healthy humans: incremental support for a genetic risk factor for depression. *Psychol Med*. 39(11): 1831–1839.

Munafò MR, Clark TG, Roberts KH, Johnstone EC. (2006). Neuroticism mediates the association of the serotonin transporter gene with lifetime major depression. *Neuropsychobiology*. *53*(1): 1–8.

Murphy DL, Uhl GR, Holmes A, Ren Patterson R, Hall FS, Sora I, et al. (2003). Experimental gene interaction studies with SERT mutant mice as models for human polygenic and epistatic traits and disorders. *Genes Brain Behav*. 2(6): 350–364.

Murphy FC, Smith KA, Cowen PJ, Robbins TW, Sahakian BJ. (2002). The effects of tryptophan depletion on cognitive and affective processing in healthy volunteers. *Psychopharmacology*. 163(1): 42–53.

Nemoto K, Ohnishi T, Mori T, Moriguchi Y, Hashimoto R, Asada T, Kunugi H. (2006). The Val66Met polymorphism of the brain-derived neurotrophic factor gene affects age-related brain morphology. *Neurosci Lett*. *397*(1–2): 25–29.

Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. (2002). Neurobiology of depression. *Neuron*. 34(1): 13–25.

Neumeister A, Hu XZ, Luckenbaugh DA, Schwarz M, Nugent AC, Bonne O, et al. (2006). Differential effects of 5-HTTLPR genotypes on the behavioral and neural responses to tryptophan depletion in patients with major depression and controls. *Arch Gen Psychiatry*. 63(9): 978–986.

Northoff G. (2013). Gene, brains, and environment: genetic neuroimaging of depression. *Curr Opin Neurobiol*. 23(1): 133–142.

Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, Gabrieli JDE, Gross JJ. (2004). For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. *NeuroImage*. 23(2): 483–499.

Ohnishi T, Hashimoto R, Mori T, Nemoto K, Moriguchi Y, Iida H, et al. (2005). The association between the Val158Met polymorphism of the catechol-O-methyl transferase gene and morphological abnormalities of the brain in chronic schizophrenia. *Brain*. 129(2): 399–410.

Pan C-C, McQuoid DR, Taylor WD, Payne ME, Ashley-Koch A, Steffens DC. (2009). Association analysis of the COMT/MTHFR genes and geriatric depression: an MRI study of the putamen. (Smith GS and Alexopoulos GS, eds.) *Int J Geriat Psychiatry*. 24(8): 847–855.

Pezawas L, Verchinski BA, Mattay VS, Callicott JH, Kolachana BS, Straub RE, et al. (2004). The brain-derived neurotrophic factor Val66Met polymorphism and variation in human cortical morphology. *J Neurosci*. 24(45): 10099–10102.

Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, Kolachana BS, et al. (2005). 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. *Nat Neurosci*. 8(6): 828–834.

Pezawas L, Meyer-Lindenberg A, Goldman AL, Verchinski BA, Chen G, Kolachana BS, et al. (2008). Evidence of biologic epistasis between BDNF and SLC6A4 and implications for depression. *Mol Psychiatry*. 13(7): 709–716.

Pomarol-Clotet E, Fatjó-Vilas M, McKenna PJ, Monté GC, Sarró S, Ortiz-Gil J, et al. (2010). COMT Val158Met polymorphism in relation to activation and de-activation in the prefrontal cortex: a study in patients with schizophrenia and healthy subjects. *NeuroImage*. 53(3): 899–907.

Poo M-M. (2001). Neurotrophins as synaptic modulators. *Nat Rev Neurosci*. 2(1): 24–32.

Raz N, Lindenberger U, Rodrigue KM, Kennedy KM, Head D, Williamson A, Dahle C, Gerstorf D, Acker JD. (2005). Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cerebral Cortex*. 15(11): 1676–1689.

Raz N, Gunning FM, Head D, Dupuis JH, McQuain J, Briggs SD, et al. (1997). Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter. *Cerebral Cortex*. 7(3): 268–282.

Raz N, Gunning-Dixon F, Head D, Rodrigue KM, Williamson A, Acker JD. (2004). Aging, sexual dimorphism, and hemispheric asymmetry of the cerebral cortex: replicability of regional differences in volume. *Neurobiol Aging*. 25(3): 377–396.

Ren-Patterson RF, Cochran LW, Holmes A, Sherrill S, Huang S-J, Tolliver T, et al. (2005). Loss of brain-derived neurotrophic factor gene allele exacerbates brain monoamine deficiencies and increases stress abnormalities of serotonin transporter knockout mice. *J Neurosci Res*. 79(6): 756–771.

Roiser JP, Levy J, Fromm SJ, Nugent AC, Talagala SL, Hasler G, et al. (2009). The effects of tryptophan depletion on neural responses to emotional words in remitted depression. *Biol Psychiatry*. 66(5): 441–450.

Savitz JB, Drevets WC. (2009). Imaging phenotypes of major depressive disorder: genetic correlates. *Neuroscience*. 164(1): 300–330.

Scharinger C, Rabl U, Sitte HH, Pezawas L. (2010). Imaging genetics of mood disorders. *NeuroImage*. 53(3): 810–821.

Schofield PR, Williams LM, Paul RH, Gatt JM. (2009). Disturbances in selective information processing associated with the BDNF Val66Met polymorphism: evidence from cognition, the P300 and fronto-hippocampal systems. *Biol Psychology*. 80(2): 176–188.

Sen S, Nesse RM, Stoltenberg SF, Li S, Gleiberman L, Chakravarti A, et al. (2003). A BDNF coding variant is associated with the NEO personality inventory domain neuroticism, a risk factor for depression. *Neuropsychopharmacology*. 28: 397–401.

Seok JH, Choi S, Lim HK, Lee S-H, Kim I, Ham BJ. (2013). Effect of the COMT val158met polymorphism on white matter connectivity in patients with major depressive disorder. *Neurosci Lett*. 545: 35–39.

Sexton CE, Mackay CE, Ebmeier KP. (2009). A systematic review of diffusion tensor imaging studies in affective disorders. *Biol Psychiatry*. 66(9): 814–823.

Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, Mintun MA. (2001). Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biol Psychiatry*. 50(9): 651–658.

Siegle GJ, Steinhauer SR, Thase ME, Stenger VA, Carter CS. (2002). Can't shake that feeling: event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. *Biol Psychiatry*. 51(9): 693–707.

Smolka MN, Schumann G, Wrase J, Gruesser SM, Flor H, Mann K, Braus DF, Goldman D, Buechel C, Heinz A. (2005). Catechol-O-methyltransferase Val158Met genotype affects processing of emotional stimuli in the amygdala and prefrontal cortex. *J Neurosci*. 25(4): 836–842.

Smolka MN, Bühler M, Schumann G, Klein S, Hu X-Z, Moayer M, et al. (2007). Gene–gene effects on central processing of aversive stimuli. *Mol Psychiatry*. 12(3): 307–317.

Steffens DC, Tupler LA, Ranga K, Krishnan R. (1998). Magnetic resonance imaging signal hypointensity and iron content of putamen nuclei in elderly depressed patients. *Psychiat Res Neuroim*. 83(2): 95–103.

Sullivan PF, Neale MC, Kendler KS. (2000). Genetic epidemiology of major depression: review and meta-analysis. *Am J Psychiatry*. 157(10): 1552–1562.

Tan H-Y, Chen Q, Sust S, Buckholtz JW, Meyers JD, Egan MF, et al. (2007). Epistasis between catechol-O-methyltransferase and type II metabotropic glutamate receptor 3 genes on working memory brain function. *Proc Natl Acad Sci.* 104(30): 12536–12541.

Taylor WD, MacFall JR, Gerig G, Krishnan RR. (2007a). Structural integrity of the uncinate fasciculus in geriatric depression: Relationship with age of onset. *Neuropsychiat Dis Treat*. 3(5): 669–674.

Taylor WD, Steffens DC, Payne ME, MacFall JR, Marchuk DA, Svenson IK, Krishnan KRR. (2005). Influence of serotonin transporter promoter region polymorphisms on hippocampal volumes in late-life depression. *Arch Gen Psychiatry*. 62(5): 537–544.

Taylor WD, Züchner S, Payne ME, Messer DF, Doty TJ, MacFall JR, et al. (2007b). The COMT Val158Met polymorphism and temporal lobe morphometry in healthy adults. *Psychiat Res Neuroim*. 155(2): 173–177.

Tyler WJ, Alonso M, Bramham CR, Posso-Miller LD. (2002). From acquisition to consolidation: on the role of brain-derived neurotrophic factor signaling in hippocampal-dependent learning. *Learning & Memory*. 9(5): 224–237.

Urry HL, van Reekum CM, Johnstone T, Kalin NH, Thurow ME, Schaefer HS, et al. (2006). Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. *J Neurosci*. 26(16): 4415–4425.

Wager TD, Davidson ML, Hughes BL, Lindquist MA, Ochsner KN. (2008). Prefrontal-subcortical pathways mediating successful emotion regulation. *Neuron*. 59(6): 1037–1050.

Wang L, Mullette-Gillman OA, Gadde KM, Kuhn CM, McCarthy G, Huettel SA. (2009). The effect of acute tryptophan depletion on emotional distraction and subsequent memory. *Social Cogn Affect Neurosci*. 4(4): 357–368.

Weinshilboum RM, Otterness DM, Szumlanski CL. (1999). Methylation pharmacogenetics: catechol O-methyltransferase, thiopurine methyltransferase, and histamine N-methyltransferase. *Ann Rev Pharmacol Toxicol*. 39(1): 19–52.

Wendland JR, Martin BJ, Kruse MR, Lesch KP, Murphy DL. (2006). Simultaneous genotyping of four functional loci of human SLC6A4, with a reappraisal of 5-HTTLPR and rs25531. *Mol Psychiatry*. 11(3): 224–226.

Whalen PJ, Shin LM, McInerney SC, Fischer H, Wright CI, Rauch SL. (2001). A functional MRI study of human amygdala responses to facial expressions of fear versus anger. *Emotion*. 1(1): 70–83.

Williams LM, Gatt JM, Grieve SM, Dobson-Stone C, Paul RH, Gordon E, Schofield PR. (2010). COMT Val108/158Met polymorphism effects on emotional brain function and negativity bias. *NeuroImage*. 53(3): 918–925.

Wong M-L, Licinio J. (2001). Research and treatment approaches to depression. *Nat Rev Neurosci*. 2(5): 343–351.

Woodruff PWR, Wright IC, Shurique N, Russouw H, Rushe T, Howard RJ, et al. (1997). Structural brain abnormalities in male schizophrenics reflect fronto-temporal dissociation. *Psychol Med*. 27(6): 1257–1266.

World Health Organization. (2008). *The global burden of disease: 2004 update*. Geneva: WHO.

World Health Organization. (2012). *Depression fact sheet no. 369*. www.who.int/mediacentre/factsheets/fs369/en/.

Frodl T, Meisenzahl EM, Zill P, Baghai T, Rujescu D, Leinsinger G, Bottlendder R, et al. (2004). Reduced hippocampal volumes associated with the long variant of theserotonin transporter polymorphism in major depression. *Arch Gen Psychiatry*. 61(2): 177–183.

Zinkstok J, Schmitz N, van Amelsvoort T, de Win M, van den Brink W, Baas F, Linszen D. (2006). The COMT val158met polymorphism and brain morphometry in healthy young adults. *Neurosci Lett*. 405(1–2): 34–39.