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Imaging Phenotypes of Major Depressive Disorder: Genetic Correlates

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Abstract

Imaging techniques are a potentially powerful method of identifying phenotypes that are associated with, or are indicative of a vulnerability to developing major depressive disorder (MDD). Here we identify seven promising MDD-associated traits identified by magnetic resonance imaging (MRI) or positron emission tomography (PET). We evaluate whether these traits are state-independent, heritable endophenotypes, or state-dependent phenotypes that may be useful markers of treatment efficacy. In MDD, increased activity of the amygdala in response to negative stimuli appears to be a mood-congruent phenomenon, and is likely moderated by the serotonin transporter gene (SLC6A4) promoter polymorphism (5-HTTLPR). Hippocampal volume loss is characteristic of elderly or chronically-ill samples and may be impacted by the val66met brain-derived neurotrophic factor (BDNF) gene variant and the 5-HTTLPR SLC6A4 polymorphism. White matter pathology is salient in elderly MDD cohorts but is associated with cerebrovascular disease, and is unlikely to be a useful marker of a latent MDD diathesis. Increased blood flow or metabolism of the subgenual anterior cingulate cortex (sgACC), together with gray matter volume loss in this region, is a well-replicated finding in MDD. An attenuation of the usual pattern of fronto-limbic connectivity, particularly a decreased temporal correlation in amygdala-anterior cingulate cortex (ACC) activity, is another MDD-associated trait. Concerning neuroreceptor PET imaging, decreased 5-HT_{1A} binding potential in the raphe, medial temporal lobe, and medial prefrontal cortex (mPFC) has been strongly associated with MDD, and may be impacted by a functional single nucleotide polymorphism in the promoter region of the 5-HT_{1A} gene (HTR1A: -1019C/G; rs6295). Potentially indicative of inter-study variation in MDD etiology or mood state, both increased and decreased binding potential of the serotonin transporter has been reported. Challenges facing the field include the problem of phenotypic and etiological heterogeneity, technological limitations, the confounding effects of medication, and non-disease related inter-individual variation in brain morphology and function. Further advances are likely as epigenetic, copy-number variant, gene-gene interaction, and genome-wide association (GWA) approaches are brought to bear on imaging data.

Introduction

The last decade has been characterized by intensive efforts to elucidate the genetic basis of psychiatric conditions such as major depressive disorder (MDD); a quest that has met with modest success due to the complexity of disease phenotypes. The putative additive effect of multiple loci of small effect size, the contribution of unknown or unquantifiable environmental factors, and the phenotypically and genetically heterogeneous nature of MDD has frustrated

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the efforts of researchers. While the use of DSM-IV criteria has enhanced the reliability of psychiatric research, the current diagnostic system has drawbacks for psychiatric genetic investigations because it is not based on the underlying neurobiology of psychiatric disorders.

These difficulties have encouraged alternative methodological approaches such as the use of endophenotypes; a term first introduced by (Gottesman and Shields, 1973) who referred to internal phenotypes discoverable by biochemical assays. An endophenotype is a heritable, intermediate phenotype that is associated with the disease of interest, but presumably has a simpler genetic basis, making it more amenable to genetic analysis (Gottesman and Gould, 2003).

Currently, some of the best tools in our armory for identifying endophenotypes are neuroimaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET). In the section of the paper to follow, entitled, “Imaging Major Depressive Disorder”, we discuss what in our subjective opinion, are some of the more promising imaging phenotypes associated with MDD and review what is known about their genetic basis. In addition, we evaluate whether these neurophysiological changes qualify as endophenotypes. The next section of the paper entitled, “Theoretical Challenges” addresses some of the more salient challenges facing the field. Finally, we end the paper by discussing potential future directions of the imaging genetics enterprise (“Future Directions” pp. 34).

Imaging Major Depressive Disorder

MRI

(1) The Amygdala: An Emotional Processing Bias—Patients with MDD have repeatedly demonstrated increased amygdala reactivity to negative stimuli as evinced by functional MRI (fMRI) (table 1). (Siegle et al., 2002) found that amygdalar responses to negative words were no longer visible after 10 seconds in healthy controls but persisted in depressed patients for a mean of 25 seconds. Similarly, depressed individuals reportedly remember negative words better than positive words (Watkins et al., 1992), a finding that correlates with increased BOLD activity of the right amygdala (Hamilton and Gotlib, 2008). Increased activity of the amygdala is also seen in conjunction with the expectation of a negative stimulus. MDD patients who were receiving treatment with antidepressant medication (AD), and were cued to anticipate the arrival of disgusting pictures, displayed greater BOLD activation in a broad region which encompassed the dorsal amygdala and the sublenticular nucleus compared with healthy subjects (Abler et al., 2007). In contrast, a group of MDD subjects, receiving AD were found not to differ from healthy control subjects when presented with sad or fearful faces (Lawrence et al., 2004).

The amygdala-associated emotional processing bias appears to hold for stimuli presented below the threshold of conscious awareness. (Sheline et al., 2001) reported that MDD patients displayed a greater BOLD response in the left but not right amygdala in response to masked fearful faces. Furthermore, this exaggerated response was no longer present after 8 weeks of treatment with sertraline. More recently, (Dannlowski et al., 2007a) reported that a greater amygdala response to masked sad or angry faces, was found to coincide with an unconscious, negative judgment bias in a group of AD-treated MDD patients.

An insertion/deletion promoter polymorphism (5-HTTLPR) of the serotonin transporter gene (SLC6A4) has been shown to impact transcriptional activity, anxiety-related traits (Lesch et al., 1996) (Savitz and Ramesar, 2004), and resilience to adversity (Caspi et al., 2003) (Stein et al., 2008). Substantial evidence that altered transcriptional activity of the serotonin transporter also impacts intermediate brain phenotypes, including an MDD-associated negative processing bias, can be found in the literature.

In healthy volunteers, the short (*s*) allele of the 5-HTTLPR polymorphism has been associated with increased amygdala activation in response to negatively valenced faces or decreased amygdala activation in response to neutral stimuli (Hariri et al., 2002) (Canli et al., 2005b) (Hariri et al., 2005) (Heinz et al., 2005) (Canli et al., 2008). Similar results have been reported using different paradigms such as emotionally-valenced pictures (Heinz et al., 2007) (Smolka et al., 2007), and public speaking (Furmark et al., 2004). The impact of SLC6A4 genotype on amygdala function also appears to hold in stressed rhesus monkeys (Kalin et al., 2008), phobia-prone individuals (Bertolino et al., 2005), and patients with MDD (Dannlowski et al., 2007b) (Dannlowski et al., 2008). Furthermore, the *s* allele has been associated with elevated baseline amygdala activity (Rao et al., 2007) and reduced amygdala volume in healthy subjects (Pezawas et al., 2005) (Pezawas et al., 2008); although see (Canli et al., 2005b) who argue that increased amygdala activation in response to negative stimuli is an artifact of decreased response to neutral stimuli in *s* allele carriers.

One possibility is that these SLC6A4-amygdala associations are mediated by an attentional bias. (Beevers et al., 2007) explored this hypothesis using a dot-probe task to measure reaction time to masked and unmasked words designed to elicit anxiety or dysphoria. Patients with various different mood disorders who carried the *s* allele showed a greater bias towards anxious stimuli than *l/l* homozygotes. This result was replicated by (Osinsky et al., 2008) who found that healthy *s* allele carriers selectively shifted their attention towards pictures of spiders compared with their counterparts homozygous for the *l* allele. In a similar vein, the *s* allele has been associated with a stronger startle response to bursts of noise in healthy individuals (Brocke et al., 2006).

The SLC6A4 gene promoter variant has also been shown to modulate neurophysiological response to aversive stimuli in regions of the brain that are directly or indirectly connected to the amygdala, namely the orbital prefrontal cortex (OFC), basal nucleus of the stria terminalis (BNST) (Kalin et al., 2008), and the fusiform gyrus (Surguladze et al., 2008).

On the other hand, (Domschke et al., 2006), in a sample of patients with panic disorder, found that *s* allele carriers showed greater amygdala response to happy faces compared with neutral cues. Similarly, a fluorodeoxyglucose (FDG) PET study reported that during tryptophan depletion, MDD carriers of the *s* allele showed reduced glucose metabolism of the left amygdala compared with *l/l* homozygotes (Neumeister et al., 2006b). (Lee and Ham, 2008a) found that the 5-HTTLPR *l* allele was associated with greater BOLD response to angry versus neutral faces in healthy individuals. (Lau et al., 2009) reported that healthy adolescent carriers of the *s* allele exhibited stronger amygdala responses to fearful faces but anxious or depressed patients homozygous for the *l* allele had greater right, but not left amygdalar activity when exposed to fearful faces.

The serotonin 1A receptor which is coded for by the HTR1A gene, plays a critical role in serotonergic signaling and has been strongly implicated in MDD (Savitz et al., 2009). (Dannlowski et al., 2007b) reported that the G allele of a functional single-nucleotide polymorphism (SNP rs6295) was associated with greater amygdala reactivity in response to emotionally-valenced faces in a MDD sample. Similarly, after correcting for the effects of SLC6A4 genotype, (Fakra et al., 2009) found that the G allele of rs6295 was associated with strength of amygdala activation in response to threat-related stimuli and level of trait anxiety in healthy individuals.

The tryptophan hydroxylase-2 (TPH2) gene is another strong candidate for impacting amygdala function. Tryptophan hydroxylase-2 catalyses the rate-limiting step in the synthesis of neuronal serotonin. We are aware of 5 studies that have reported significant effects of the TPH2 rs4570625 SNP on amygdala function in the context of emotional processing (Brown

et al., 2005) (Canli et al., 2005a) (Canli et al., 2008) (Furmark et al., 2008) (Lee and Ham, 2008a). These studies have largely been carried out with healthy volunteers. (Brown et al., 2005) reported that the T allele of rs4570625 was associated with greater amygdala response to angry or fearful faces while (Canli et al., 2005a) found that the effect of the rs4570625 variant on amygdala function extended to both positively and negatively valenced stimuli. In a later study, (Canli et al., 2008) reported an additive effect of the TPH2 and SLC6A4 genes on amygdala reactivity that was most robust for sad or fearful faces: carriers of the T and s alleles displayed a 0.24% greater BOLD response in the amygdala than subjects who did not possess either a T or an s allele. These data derive further support from a positron emission tomography (PET) study. (Furmark et al., 2008) showed that the TPH2 G allele predicted a placebo-induced improvement in social anxiety that was associated with a reduction in amygdala activity. In contrast, (Lee and Ham, 2008a) reported that individuals homozygous for the G allele of rs4570625 showed higher levels of amygdala activity in response to sad (but not angry) faces than their counterparts who did not carry the G allele.

Polymorphisms of the brain-derived neurotrophic factor (BDNF) (Montag et al., 2008), catechol-o-methyltransferase (COMT) (Smolka et al., 2005) (Smolka et al., 2007) (Domschke et al., 2008), and monoamine oxidase A (MAO-A) (Lee and Ham, 2008b) genes have also been associated with degree of amygdala reactivity in healthy controls and different patient groups. Further, a 4-marker haplotype of the regulator of G-protein signaling 2 (RGS2) gene was found to correlate with both self-reported levels of introversion and amygdala reactivity to emotionally-valenced faces (Smoller et al., 2008).

The negative processing bias seen in MDD may be reversed by antidepressant (AD) treatment. (Sheline et al., 2001) showed that the elevated BOLD response seen in the left amygdala of depressed patients in response to masked fearful faces was reduced by sertraline. This finding has received support from more recent studies (Fu et al., 2004) (Chen et al., 2007b). Moreover, the ADs, citalopram (Harmer et al., 2006), reboxetine (Norbury et al., 2007), and escitalopram (Arce et al., 2008) have been reported to attenuate neural response of the amygdala to negatively valenced faces in healthy individuals. (Fu et al., 2008) showed that the increased BOLD activity in the right amygdala-hippocampus region observed in their sample of patients with MDD was normalized following cognitive-behavior therapy (CBT). Nevertheless, 2 previous PET studies making use of interpersonal therapy and CBT, respectively, were unable to detect any changes in the glucose metabolic rate of the amygdala (Brody et al., 2001) (Goldapple et al., 2004).

The positive impact of AD treatment on amygdala reactivity raises the question of whether the MDD-associated emotional processing bias is only seen in the acute stage of depression or is a permanent trait. This is an important issue because a true endophenotype should be mood-independent (Gottesman and Gould, 2003).

A number of studies suggest that amygdala activation is a mood-congruent, temporally-limited phenomenon. Transient sadness concomitant with amygdala activation has been induced by sad facial expressions (Schneider et al., 1997) (Posse et al., 2003) (Habel et al., 2005), movie clips (Aalto et al., 2002) (Wang et al., 2006), and recall of negative life events (George et al., 1995). In fact, it is known that direct electrical stimulation of the amygdala in humans may temporarily elicit positive and especially, negative emotions (Gloor et al., 1982) (Lanteaume et al., 2007).

On the other hand, at least 2 studies have suggested that increased amygdala reactivity is salient early in life in humans and monkeys with an anxious temperament. (Fox et al., 2008) showed that rhesus monkeys with an anxious disposition showed increased glucose metabolism (measured with PET FDG) of the amygdala and a downstream circuit, including the BNST and PAG. This echoes the result of a longitudinal study in humans demonstrating that infants

classified as “inhibited” displayed a greater BOLD response in the amygdala when viewing novel faces as adults than their counterparts who were classified as “uninhibited” infants (Schwartz et al., 2003).

Consistent with these data, (Neumeister et al., 2006a) reported increased blood flow to the amygdala, as measured by $O^{15}H_2O$ PET in unmedicated, *remitted* MDD patients. Further, we have recently found that currently remitted MDD patients show a *reduced* hemodynamic response to masked *happy* faces compared with healthy controls (Ferguson et al., 2008). The issue of facial masking may be relevant to the endophenotypic criterion of heritability.

A number of studies have provided evidence that greater amygdala activation to negatively-valenced faces is characteristic of MDD even when these stimuli are masked, and no conscious processing of the faces is possible (Sheline et al., 2001) (Dannlowski et al., 2007a). Certainly, this does not prove that MDD-associated hyper-reactivity to socio-emotional stimuli is heritable, but the automatic, limbic system-mediated nature of the phenomena does raise the possibility that genetic factors at play.

To the best of our knowledge, only one study has examined facial processing biases in a high-risk sample. (Monk et al., 2008) reported that the pediatric offspring of parents with MDD showed a greater amygdala response to passively-viewed fearful faces than their healthy counterparts with no family history of affective illness. Nevertheless, more than half of the high-risk group had been diagnosed with an anxiety disorder, limiting the conclusions that can be drawn from the study.

Other studies shed partial light on the issue of state versus trait. Trait anxiety as measured by the State-Trait Anxiety Inventory (STAI) was found to correlate ($r=0.74$) significantly with basolateral amygdala activity in response to masked fearful faces in healthy volunteers (Etkin et al., 2004). Analogous findings have since been reported (Stein et al., 2007) (Dickie and Armony, 2008). In a similar vein, healthy individuals have demonstrated long-term (1–2 years) stability of right amygdala BOLD responses to angry faces (Manuck et al., 2007). (van der Veen et al., 2007) reported that healthy individuals with a family history of MDD showed a lowering of mood together with greater amygdala activation in response to fearful faces after tryptophan depletion. A latent emotional processing bias in high-risk individuals may thus be precipitated by some kind of “insult”, whether pharmacological or environmental.

In sum, greater amygdala reactivity in response to negatively valenced cues appears to be at least partly mood-state independent. Extant data suggest that the *s* allele of the SLC6A4 5-HTTLPR variant contributes to this “risk” phenotype. Nevertheless, not all studies are consistent (Domschke et al., 2006) (Lee and Ham, 2008a) (Lau et al., 2009).

Despite the apparent early onset of exaggerated amygdala reactivity, the status of the emotional-processing bias phenotype as an endophenotype for MDD remains unclear given the attenuating effects of AD medication and the dearth of family studies.

(2) Hippocampal Volume Loss in MDD—Hippocampal volume reduction is a common finding in patients with MDD (Sheline et al., 1996) (Sheline et al., 1999) (Mervaala et al., 2000) (MacQueen et al., 2003) (Janssen et al., 2004) (Lloyd et al., 2004) (O’Brien et al., 2004) (Hickie et al., 2005) (Neumeister et al., 2005) (Frodl et al., 2006) (Janssen et al., 2007) (Macmaster et al., 2007) (Ballmaier et al., 2007) (table 2). These data are supported by recent longitudinal studies. MDD patients with smaller hippocampal volumes are reportedly less likely to remit after a 1 year follow-up (Frodl et al., 2004a). A 3-year follow-up by the same group showed a greater decrease in hippocampal volumes over time in the MDD group (Frodl et al., 2008b). Similarly, (Kronmuller et al., 2008) reported that male patients who relapsed

within a 2 year follow-up period displayed smaller hippocampal volumes than healthy controls. Congruent with these data, a 36% increase in hippocampal neuronal density together with a 20% reduction in neuronal size, indicative of neuropil loss, has been detected at post-mortem (Stockmeier et al., 2004).

(Pezawas et al., 2004) showed that the *met* allele of a common functional SNP (val66met) in the brain-derived neurotrophic factor (BDNF) gene was associated with smaller hippocampal volumes in a healthy sample, and similar effect has since been noted in both healthy subjects and individuals with schizophrenia or bipolar disorder (BD) (Szeszko et al., 2005) (Bueller et al., 2006) (Ho et al., 2006) (Takahashi et al., 2008) (Chepenik et al., 2009). According to a recent study, the association between the *met* allele and reduced hippocampal volume may be more salient in healthy people exposed to early life stress (Gatt et al., 2009) and healthy subjects with higher levels neuroticism as measured by the NEO-Five Factor Personality Inventory, and trait depression as measured by the Depression Anxiety Stress Scale (DASS-42) (Joffe et al., 2008). To our knowledge, only one study has examined the effect of the val66met SNP on hippocampal volume in MDD: (Frodl et al., 2007) found smaller hippocampal volumes in both controls and acutely ill, medicated MDD patients carrying the *met* allele.

The SLC6A4 gene has also been postulated to modulate the association between MDD and hippocampal volume. (Frodl et al., 2004b) (Frodl et al., 2008a) found that *l* allele MDD homozygotes had smaller hippocampal volumes than *s* allele carriers with MDD. (Taylor et al., 2005a) noted that in patients with late onset depression (> 50 years), *l* allele homozygotes displayed smaller right hippocampal volumes, but in MDD patients with early illness-onset (< 50 years), the *s* allele homozygotes had smaller hippocampal volumes. Further, the *s* allele has been reported to be associated with lower hippocampal concentrations of N-acetylaspartate (NAA), a neuronal and axonal marker of damage to the brain (Gallinat et al., 2005).

Other genes reported to impact hippocampal volume in MDD or healthy subjects include COMT (Cerasa et al., 2008), vascular endothelial growth factor (VEGF) (Blumberg et al., 2008) and the glucocorticoid receptor (NR3C1) (Zobel et al., 2008).

Although hippocampal volume decrements are widely reported in MDD the data are contradictory. For negative results see (Axelson et al., 1993) (Pantel et al., 1997) (Ashtari et al., 1999) (Vakili et al., 2000) (von Gunten et al., 2000) (Rusch et al., 2001) (Hastings et al., 2004) (Inagaki et al., 2004) (Rydmark et al., 2006). One hypothesis is that hippocampal atrophy is more pronounced in elderly, middle-aged or chronically ill populations. A hypothalamic-pituitary-adrenal (HPA) axis-driven excitotoxic process is one heuristic model of hippocampal volume loss and associated MDD that is consistent with the impact of age and length of illness. Since, at least in rodents, the hippocampus is believed to exert inhibitory control over the amygdala and HPA axis (Jacobson and Sapolsky, 1991) (Barden, 2004), hippocampal tissue loss may activate a positive feedback loop which further potentiates the release of cortisol and hippocampal excitotoxicity.

On the other hand, hippocampal volume reduction has been reported in children (MacMaster and Kusumakar, 2004) (MacMaster et al., 2008) and young adults with MDD (Lange and Irle, 2004) (Vythilingam et al., 2002). Nevertheless, the sample studied by (Vythilingam et al., 2002) had a history of significant childhood abuse. It is also questionable whether findings from the pediatric literature can be extrapolated to adult samples.

If neurophysiological changes to the hippocampus are indeed stress-related, then this limits the utility of this imaging trait as an endophenotype. Clearly, HPA-induced hippocampal atrophy may be a latent predisposition which manifests itself only under particular environmental conditions. As such, it will not readily identify people at risk for future depressive episodes precipitated by situational adversity. Nevertheless, interrogation of the

genetic correlates of hippocampal volume reduction in acutely ill patients remains valuable. For example, the association between hippocampal volume and the BDNF val66met polymorphism is intuitively compelling based on animal data showing decreased expression of BDNF in the hippocampus after exposure to corticosteroids or stressors (Gronli et al., 2006) (Jacobsen and Mork, 2006) (Tsankova et al., 2006) (Xu et al., 2006).

(3). Increased Incidence of Deep White Matter Hyperintensities—White Matter Hyperintensities (WMH), seen on T2-weighted MRI scans are probably indicative of leukoaraiosis: a decrease in the density of white matter due to demyelination, atrophy of the neuropil, or ischemia-associated microangiopathy (Ovbiagele and Saver, 2006). The increased incidence of MDD seen in elderly individuals led to the concept of “vascular depression”, a condition associated with multiple subcortical infarcts of an ischemic origin (Alexopoulos et al., 1997) (Krishnan et al., 1997). At least 20 studies have reported a robust relationship between the presence of WM lesions and depression in elderly samples (table 3). For recent publications see (Godin et al., 2007) (Janssen et al., 2007) (Sheline et al., 2008) (Sneed et al., 2008). Younger adult or middle aged MDD samples do not usually provide evidence of WM disease (Dupont et al., 1995a) (Iosifescu et al., 2006), although see (Sassi et al., 2003).

Consistent with some of the data, post-mortem analyses have reported altered expression of genes impacting myelin or oligodendrocyte function in MDD (Aston et al., 2005) (Sequeira et al., 2006). Variants of this gene class such as oligodendrocyte lineage transcription factor 2 (*OLIG2*), Neuregulin 1 (*NRG1*), and v-erb-a erythroblastic leukemia viral oncogene homolog 4 (*ERBB4*) have been directly associated with affective illness (Carter, 2007) (Sokolov, 2007).

The specificity of WMH to age-associated vascular depression (Sneed et al., 2008) reinforces the notion that MDD is a heterogeneous disorder. Although the data suggest that T-2 weighted WMH are related to late-onset MDD, reports suggestive of microstructural WM changes as evinced by diffusion tensor imaging (DTI) in young adults with MDD have been published in the literature (Li et al., 2007) (Ma et al., 2007). The age-associated relationship between WMH and MDD may preclude the use of this trait to identify young individuals at risk of developing MDD. Nevertheless, an understanding of the mechanisms by which microvascular lesions lead to depression may help elucidate important pathophysiological pathways and facilitate the development of new treatments.

(4). Structural and Functional Alterations of the Subgenual Anterior Cingulate Cortex (sgACC)—The term sgACC was originally used to refer to Brodmann areas (BA) 24b and, to a lesser extent, 24a anteriorly, and BA25 posteriorly (Ongur et al., 2003). This region was initially shown by (Drevets et al., 1997b) to display an MDD-associated reduction in blood flow and glucose metabolism, with a corresponding reduction in GM volume of the left sgACC. Later, we refined our anatomical characterization of the region, separating the sgACC into cytoarchitectonically distinct anterior and posterior components, which correspond approximately to BA 24 and 25, respectively (Ongur et al., 2003).

Since our initial report, reduced sgACC volume has been independently reported [reviewed in (Drevets et al., 2008)] (table 4). (Botteron et al., 2002) observed reduced left sgACC volumes in an early-onset sample of largely unmedicated MDD cases, while (Hastings et al., 2004) detected a similar effect in males but not females. A sex-specific effect was also reported by (Boes et al., 2008) who found volume reductions of the broader left perigenual ACC in boys but not girls with subclinical depression.

The posterior sgACC (infralimbic cortex or BA 25) was found to be reduced in volume in MDD cases with psychotic features, but not in a psychiatric control group with schizophrenia

(Coryell et al., 2005). Furthermore, the MDD group showed an increase in posterior sgACC GM volume after 2 years of naturalistic treatment. Consistent with this finding, chronic lithium treatment, which exerts neurotrophic effects in animal models, has been associated with a recovery of GM volume of the sgACC in treatment responders (Moore, 2008). (Yucel et al., 2008) also reported a decrease in volume of the infralimbic cortex in a MDD sample treated for an average of one month with AD prior to scanning. There was no significant difference in sgACC (BA 24) volume between the MDD and its healthy comparison group. However, when the MDD group was stratified by AD exposure, it was found that the AD-exposed MDD patients had smaller sgACC volumes than both healthy subjects and their drug-naïve counterparts with MDD (Yucel et al., 2008).

The imaging data are supported by a histopathological analysis of BA 24, which suggested that the volume reduction seen on MRI was associated with a reduction in neuropil (Ongur et al., 1998).

Imaging studies that assessed sgACC activity in designs that controlled for partial volume effects, are indicative of increased resting glucose metabolism or BOLD activity in the sgACC and infralimbic cortex of depressed patients (Inagaki et al., 2007) (Kumano et al., 2007) (Mah et al., 2007) (table 5). In addition, (Greicius et al., 2007) conducted a resting-state connectivity analysis of persons with MDD and interpret their data to suggest that the altered pattern of resting state connectivity in MDD is driven primarily by elevated activity of the sgACC. In line with these data, sgACC metabolism and cerebral blood flow (CBF) are higher in the depressed, unmedicated phase versus the remitted phase within MDD subjects (Mayberg et al., 1999) (Drevets et al., 2002) (Neumeister et al., 2004) (Hasler et al., 2008). Elevated sgACC BOLD activity has also been observed in MDD patients performing the stop-signal test (Yang et al., 2009) and an emotional interference task (Fales et al., 2008).

The impact of increased neural activity on brain structure is not fully understood. One possibility is stress-induced dendritic remodeling, observed as increases or decreases in GM volume on MRI scans. Glucocorticoid hormones, which are thought to be over-secreted in MDD and other stress-related conditions, regulate glutamate release through the inhibition of glutamate transporter expression, the upregulation of N-methyl-D-aspartate (NMDA) glutamate receptor subunit expression, and the activation of voltage-gated sodium channels, thereby modulating intracellular calcium influx (McEwen and Magarinos, 2001) (Lee et al., 2002). Since glucose metabolism is primarily reflective of the level of glutamatergic transmission in the brain (Patel et al., 2004) (Shulman et al., 2004), increased glucose metabolism may explain the decreased sgACC GM volume reported in MDD.

We are aware of 2 studies that investigated the effects of the 5-HTTLPR variant on perigenual ACC volume in healthy subjects. (Canli et al., 2005b) found that the *s* allele was associated with reduced left middle frontal gyrus (BA 9: -27; 31; 46) and pregenual ACC (-10; 35; 17) volume; while (Pezawas et al., 2005) reported an *s*-allele associated volume reduction of the subgenual (-3; 33; -2) and pregenual (reported as “supragenual” 0; 30; 4 and 0; 35; 13) ACC. Short allele carriers also show reduced structural covariation between the amygdala and perigenual ACC, suggestive of attenuated functional coupling between these two regions (Pezawas et al., 2005). The association between reduced volume of BA 9 and the short 5-HTTLPR allele (Canli et al., 2005b) is interesting because glial cell loss and a reduction in neuronal size at post-mortem has also been reported in this region in MDD (Rajkowska et al., 1999).

Consistent with observations that experimentally-induced sadness increases blood-flow to the sgACC (George et al., 1995) (Mayberg et al., 1999), the severity of depressive symptomatology in MDD and BD subjects was shown by (Osuch et al., 2000) to be correlated with glucose

metabolism of this region. Moreover, various treatment paradigms including antidepressant treatment (Mayberg et al., 2000) (Holthoff et al., 2004), electroconvulsive therapy (ECT) (Nobler et al., 2001), and deep brain stimulation of the sgACC (Mayberg et al., 2005) result in decreased activity of the sgACC. On the other hand, (Drevets et al., 1997b) found that altered sgACC glucose metabolism persisted during antidepressant drug treatment and was present in both the manic and depressed phases of BD.

State-trait issues have received less attention in the structural imaging literature, and most studies have imaged currently depressed patients. One recent study showed that response to lithium treatment was associated with a recovery of GM volume of the sgACC of individuals with BD (Moore, 2008), and another found initial and progressive loss of GM volume in BD subjects, most of whom were not receiving lithium (Koo et al., 2008).

Studies of individuals who are at high familial risk for developing mood disorders are unfortunately rare. (Boes et al., 2008) found that the left perigenual ACC volume was smaller in boys with sub-clinical depression, and that the negative correlation between left sgACC volume and depression symptoms was strongest in boys with a family history of depression. Similarly reduced sgACC volumes have been reported in the unaffected relatives of patients with bipolar disorder (McDonald et al., 2004). In a recent fMRI study, (Mannie et al., 2008) found that children of parents with MDD showed an absence of activation in the pregenual ACC in response to emotionally valenced stimuli (emotional Stroop) compared with their control group. How these data related to the structural MRI findings are unclear.

(5). Disrupted Fronto-Limbic Connectivity—A heuristic model of MDD is a loss of top-down, PFC control over limbic regions such as the amygdala, leading to the emotional, behavioral, cognitive and endocrine changes characteristic of the disorder (Savitz and Drevets, 2009). Partly consistent with this model, reduced fronto-limbic connectivity (measured by the degree of temporal correlation in activity across different brain regions) has been consistently reported in the fMRI literature (table 6). What is less clear, however, is the specific region of the PFC that is functionally-decoupled from the amygdala.

(Anand et al., 2005a) reported a decreased correlation between activity in the broader ACC and the amygdala in both the resting state and during exposure to neutral, negative and positively valenced pictures in their MDD sample. After 6 weeks of treatment with sertraline, the same MDD sample displayed an increase in ACC-limbic connectivity in the resting state and during exposure to neutral and positive, but not negative pictures (Anand et al., 2005b). Similarly, (Chen et al., 2008) found that the reduced functional coupling of the medial and ventral PFC with the amygdala observed in their MDD sample during exposure to sad faces, was ameliorated by 8 weeks of treatment with fluoxetine.

(Siegle et al., 2007) reported that MDD subjects demonstrated greater activation of the amygdala in response to affectively-valenced words, and reduced activity of the left DLPFC during a working memory task than healthy control subjects. Further, the temporal association between DLPFC and amygdala activity was reduced in the MDD sample compared with the healthy control sample. These data are consistent with the results of a previous study reporting an inverse correlation between amygdala and DLPFC activation in response to the presentation of negatively valenced words (Siegle et al., 2002). Most recently, a functional correlation between activity in the amygdala and three PFC regions, the DLPFC, the dACC, and the ventrolateral PFC (vIPFC), was shown to be reduced in individuals with MDD (Dannlowski et al., 2009).

The vIPFC was also implicated by (Johnstone et al., 2007) who reported an inverse relationship between left vIPFC and amygdala activation in healthy controls but the opposite effect in MDD

cases. (Johnstone et al., 2007) attribute this vPFC-amygdala disconnect to dysfunction of the ventromedial PFC (vmPFC) which serves as an inhibitory link between the lateral PFC and the amygdala. (Matthews et al., 2008) reported *increased* functional connectivity between the broader amygdala region and the sgACC but decreased functional connectivity between the extended amygdala and the supragenual ACC in response to the presentation of emotional faces.

Anxiety may be an important confounding factor. (Kienast et al., 2008) reported a negative correlation between trait anxiety in healthy males and the degree of functional connectivity between the sgACC (BA24) and the amygdala in response to negatively-valenced visual stimuli. In addition, degree of habituation to emotional go-no-go stimuli has been reported to be negatively correlated with functional connectivity of the ventral PFC and the amygdala in healthy controls with higher levels of self-reported anxiety (Hare et al., 2008).

The genetic basis of this abnormal PFC-limbic functional coupling is in the early stage of investigation. (Pezawas et al., 2005) found that the *s* allele of the 5-HTTLPR polymorphism was associated with reduced functional coupling between the supragenual ACC, but increased functional coupling between the vmPFC and the amygdala in healthy controls exposed to threatening faces. Additionally, the degree of functional coupling between the perigenual ACC and the amygdala predicted approximately 30% of the variance in scores on the harm avoidance subscale of the Temperament and Personality Questionnaire (Pezawas et al., 2005). The greater vmACC-amygdala coupling observed in *s* 5-HTTLPR allele carriers replicated the finding of (Heinz et al., 2005) who observed a similar effect in healthy volunteers shown aversive pictures.

(Dannlowski et al., 2009) reported that the inverse functional correlation between dACC and amygdala activity observed in their healthy control sample, was attenuated in carriers of the high activity monoamine oxidase A (MAOA) promoter polymorphism alleles (3.5R or 4R). Further, MDD cases with the high activity MAOA variants showed the weakest amygdala-dACC coupling and the most severe course of illness. (Buckholtz et al., 2008) had earlier reported increased vmPFC-amygdala coupling in healthy male carriers of the low activity MAOA VNTR alleles, an effect which predicted higher harm avoidance personality scores in this sample.

In sum, the extant data suggest that a functional decoupling exists within the neural circuits connecting PFC and amygdala areas that are involved in the cognitive control of emotions in MDD. The anatomical correlates of these neural circuits are not entirely clear but may include both dorsomedial, ventromedial and dorsolateral aspects of the PFC. Conversely there is some evidence for enhanced functional connectivity between the amygdala and the vmPFC in MDD. Given reports of an AD-induced strengthening in PFC-limbic coupling (Anand et al., 2005b) (Chen et al., 2008), the utility of this trait as a biomarker for the efficacy of AD-treatment is deserving of greater exploration.

PET Neuroreceptor Studies

(1). 5-HT_{1A} Receptor-Signaling Abnormalities in MDD—The 5-HT_{1A} (serotonin 1A) receptor is a G-protein-coupled receptor concentrated in regions which receive serotonergic input from the raphe nuclei such as the frontal cortex, amygdala, hippocampus, and hypothalamus (Lesch and Gutknecht, 2004) (Sharp et al., 2007). The 5-HT_{1A} receptor serves as the predominant release- and synthesis-controlling autoreceptor for the serotonergic neurons in the raphe nuclei, reducing the serotonergic transmission to its projection areas (Kreiss and Lucki, 1994). In these frontal and limbic projection regions, the 5-HT_{1A} receptor is distributed post-synaptically (Sharp et al., 2007). The 5-HT_{1A} receptor modulates neuronal migration, neurite outgrowth and synapse during development as well as serotonergic activity in the mature brain (Whitaker-Azmitia et al., 1996).

The PET data are largely suggestive of reduced 5-HT_{1A} receptor binding potential (BP) in MDD [reviewed in (Savitz et al., 2009)]. BP usually refers to the product of receptor number and affinity. In an [¹¹C]WAY-100635 PET study, (Drevets et al., 1999) (Drevets et al., 2000) found that depressed bipolar disorder and MDD patients with a familial form of illness exhibited reduced BP in the medial temporal cortex and hippocampus (25–33%), as well as the midbrain raphe (42%) compared with healthy controls. We recently replicated this result, detecting a mean 5-HT_{1A} receptor BP reduction of 26% in the medial temporal cortex and 43% in the raphe nucleus in non-medicated recurrent depressives (Drevets et al., 2007). This finding is supported by other groups (table 7). (Sargent et al., 2000) reported a wide-spread reduction (frontal, temporal and limbic cortices) in 5-HT_{1A} receptor binding in both medicated and unmedicated individuals with MDD. (Hirvonen et al., 2008) reported 9–25% reductions in receptor binding across large regions of the brain (but not the raphe) in drug-naïve individuals with MDD, and (Bhagwagar et al., 2004) replicated this finding in remitted, as well as currently depressed patients. Reduced BP in the dorsal raphe nucleus of elderly depressed subjects (Meltzer et al., 2004), and the sgACC, pgACC, lateral orbital, and mesiotemporal cortices of post-partum MDD cases (Moses-Kolko et al., 2008), has also been reported.

The animal literature is generally consistent with the decreased 5-HT_{1A} receptor BP. Subordinate monkeys who showed behavioral signs of depression after exposure to social defeat, had reduced 5-HT_{1A} receptor binding in the raphe nuclei, amygdala, hippocampus, and anterior cingulate cortex (Shively et al., 2006). Furthermore, parentally-deprived monkeys display reduced hippocampal 5-HT_{1A} receptor binding and mRNA expression relative to their normally-reared siblings although in males 5-HT_{1A} receptor binding was actually *increased* in the dentate gyrus and CA3 (Law et al., 2008). The decrease in 5-HT_{1A} receptor binding is consistent with studies reporting reduced postsynaptic 5-HT_{1A} receptor density and mRNA expression in the hippocampus and other brain regions in rats and tree shrews exposed to repeated or chronic stress (Mendelson and McEwen, 1991) (Chalmers et al., 1993) (McKittrick et al., 1995) (Meijer et al., 1997) (Flugge et al., 1998) (Lopez et al., 1998).

Post-mortem studies provide further evidence for reduced 5-HT_{1A} receptor binding or numbers in the ventrolateral prefrontal cortex and the temporal polar cortex (Bowen et al., 1989); caudal aspects of the dorsal raphe nucleus (Arango et al., 2001) (Boldrini et al., 2007); DLPFC (Lopez-Figueroa et al., 2004), and hippocampus (Lopez et al., 1998). In contrast, in the rostral portion of the dorsal raphe nucleus the 5-HT_{1A} receptor density was elevated in depressed suicide victims, demonstrating that a rostral-caudal difference exists within the dorsal raphe nucleus (i.e., abnormally increased rostrally, but decreased caudally in depression) may exist below the spatial resolution of PET (Stockmeier et al., 1998) (Boldrini et al., 2007). Clearly, the data are not altogether consistent, and the contradictory or negative results reported in other PET studies of MDD subjects (Parsey et al., 2006a) or *post mortem* studies of depressed suicides (Arranz et al., 1994) (Arango et al., 1995) (Lowther et al., 1997) suggest that substantial heterogeneity exists within the pathophysiology underlying MDD and other psychiatric disorders that predispose to suicide.

A single nucleotide polymorphism SNP (HTR1A: –1019C/G; rs6295) has been reported to regulate gene expression of the 5-HT_{1A} receptor (Lemondé et al., 2003). The G allele is believed to disrupt an inhibitory transcription factor-binding site, thereby up-regulating autoreceptor expression in presynaptic raphe neurons, decreasing the firing rate of these cells, and reducing serotonergic neurotransmission in projection areas (Lemondé et al., 2003).

(Lemondé et al., 2003) reported a two-fold increase in the frequency of the rs6295 G/G genotype in patients with MDD, and a four-fold increase in the frequency of the G/G genotype in suicide attempters. These data have been independently replicated in another MDD sample (Parsey et al., 2006a), as well as elderly patients who became depressed after suffering hip-

fractures (Lenze et al., 2008), and hepatitis C patients with interferon-induced depression (Kraus et al., 2007). A recent paper reported an over-representation of the G allele and G/G genotype in an MDD sample, and a subsequent linkage analysis conditional on possession of at least one G allele generated a significant signal on chromosome 10, suggesting a possible epistatic interaction with a gene in this region (Neff et al., 2008). As in all psychiatric genetic studies, negative results are also common (Zill P, 2001) (Huang et al., 2004) (David et al., 2005) (Hettema et al., 2007).

MDD may be associated with abnormal sensitivity of 5-HT_{1A} autoreceptors in sub-nuclei of the raphe, together with a reduction in post-synaptic 5-HT_{1A} receptor sensitivity in limbic regions. The genetic expression of 5-HT_{1A} receptor mRNA is tonically inhibited by glucocorticoid receptor stimulation, and thus the phenomenon may be secondary to a disturbance in hypothalamic-pituitary-adrenal (HPA) axis function. If this is indeed the case, then changes to 5-HT_{1A} receptor BP may not identify at-risk individuals unless HPA disturbances are prodromal. Not enough research has been completed in order to properly address this issue.

(2). Changes in Serotonin Transporter Binding in MDD—The serotonin transporter (5-HTT) contributes to the regulation of serotonergic neurotransmission through the reuptake of serotonin in the synaptic cleft. An inverse relationship exists between 5-HTT BP and extracellular serotonin levels.

A study making use of [11C](+)McN5652, which measures 5-HTT BP in the thalamus and midbrain, reported a 23% *increase* in thalamic (but not midbrain) 5-HTT BP in medication-free MDD subjects compared with controls (Ichimiya et al., 2002). Similarly, a small sample (N=4) of MDD subjects yielded evidence of larger distribution volume (DV) ratios in the left prefrontal cortex (24%) and the right anterior cingulate cortex (18%) compared with controls (Reivich et al., 2004). On the other hand, (Parsey et al., 2006b) reported *decreased* 5-HTT BP in the amygdala and midbrain but no change in other regions of the brain using [11C](+)McN5652. The same group later reported that lower 5-HTT BP in the midbrain, amygdala and ACC predicted the absence of remission at one year (Miller et al., 2008). Nevertheless, this ligand has been reported to show non-specific binding, biasing results (Buck et al., 2000). More recent studies have been carried out with the [11C] DASB ligand which has a greater ratio of specific to non-specific binding, and therefore allows for the measurement of BP in cortical as well as subcortical brain regions (Meyer, 2007).

In one such study, (Reimold et al., 2008) reported *reduced* 5-HTT BP in the thalamus (but not other regions such as the amygdala and midbrain) of people with MDD, and a negative correlation between 5-HTT availability in the thalamus and amygdala, and depression and anxiety scores. In contrast, although no overall intergroup difference in 5-HTT BP was detected by (Meyer et al., 2004), scores on the Dysfunctional Attitude Scale (DAS) were found to be positively correlated with an *increase* in BP in the anterior cingulate, putamen and thalamus. This finding is consistent with the data of (Cannon et al., 2007) who showed that relative to healthy subjects, depressed, unmedicated MDD patients had *increased* BP in the thalamus (24%), periaqueductal gray matter (PAG) (22%), insula (15%), and striatum (12%). Furthermore, the depression-associated personality trait, neuroticism, is reportedly associated with higher thalamic BP (Takano et al., 2007), and clinically depressed patients with Parkinson's disease (PD) show increased 5-HTT BP in the PFC compared with HC (Boileau et al., 2008).

An increase in 5-HTT BP might be indicative of greater serotonin reuptake capacity in response to elevated serotonin secretion during stress or depression (Cannon et al., 2007). Conversely, lower 5-HTT BP might reflect a downregulation of 5-HTT in response to lower intrasynaptic

levels of serotonin, a loss of raphe serotonergic projections to corticolimbic regions, or a decrease in SLC6A4 gene expression (Frokjaer et al., 2009). Although the 5-HTTLPR polymorphism is known to affect mRNA transcription *in vitro* (Lesch et al., 1996) (Hu et al., 2006), the impact of the polymorphism on *in vivo* 5-HTT binding is less clear. While some studies have reported that the *l* allele is associated with higher 5-HTT BP in the putamen (Praschak-Rieder et al., 2007), others have found no relationship between 5-HTTLPR genotype and 5-HTT BP as measured by the radioligand [11C](+)-McN5652 (Parsey et al., 2006c). Further, (Willeit et al., 2008) found no 5-HTTLPR-V_{max} or B_{max} association in platelet cells.

The PET imaging data may be confounded by a number of factors. For instance, the magnitude of 5-HTT BP may be seasonal in nature. (Praschak-Rieder et al., 2008) observed higher BP in diverse brain regions in the fall and winter months compared with spring and summer. Further, 5-HTT BP correlated negatively with daily hours of sunshine, suggesting a potential pathophysiological mechanism for seasonal affective disorder (SAD). (Willeit et al., 2008) reported increased platelet 5-HTT function in the guise of increased uptake velocity (V_{max}) in depressed patients with SAD but no group differences in substrate affinity (K_m) or binding capacity (B_{max}) were detected. It is unclear, however, if the V_{max} changes seen in the platelets from the (Willeit et al., 2008) sample extend to the CNS of patients with MDD.

As in the case of other imaging phenotypes associated with MDD, the impact of clinical state at the time of scanning has not been resolved. In the only study of unmedicated remitted patients with MDD of which we are aware, (Bhagwagar et al., 2007) failed to discern significant abnormalities in 5-HTT binding in a number of anatomical regions such as the amygdala, anterior cingulate, hippocampus, and thalamus. Further, in the studies of (Cannon et al., 2007) and (Reimold et al., 2008), DASB binding was significantly correlated with severity of depression and anxiety.

The preclinical literature largely supports the hypothesis that 5-HTT binding is stress-sensitive. Reduced 5-HTT mRNA expression has been noted in the CA1, CA2 and CA3 regions of the hippocampus (but not the raphe or dentate gyrus) of subordinate and dominant, and therefore stressed rodents (McKittrick et al., 2000). Nevertheless, these stressed rats also showed apical dendritic atrophy of the CA3 pyramidal neurons, raising the possibility that the decrease in 5-HTT binding was secondary to a reduction in dendritic arborization. Acute immobilization stress has been reported to decrease 5-HTT mRNA levels in the dorsomedial hypothalamus (Hoffman et al., 1998) and raphe pontis (Vollmayr et al., 2000), but not other raphe nuclei. In monkeys, stress sensitive females showed decreased 5-HTT mRNA levels in the caudal region of the dorsal raphe but again this result may reflect a corresponding loss of raphe neurons in the stress-sensitive animals (Bethea et al., 2005).

In contrast, rats exposed to stressors or threats show *increased* serotonin turnover in the mPFC, striatum, amygdala and lateral hypothalamus (Inoue et al., 1994), and rats selectively bred for high-anxiety phenotypes, which show depression-like behaviors in the forced swim test, have increased hippocampal 5-HTT levels (Keck et al., 2005). A similarly complex pattern is evident in olfactory-bulbectomized rats (a putative rodent model of depression), which show elevated 5-HTT density, serotonin concentrations (Grecksch et al., 1997) (Zhou et al., 1998), and serotonin turnover in the frontal and cingulate cortices, thalamus, medial forebrain bundle and hippocampus, but reduced serotonin synthesis rates in the dorsal and median raphe nuclei (Watanabe et al., 2003). Although the pattern of 5-HTT binding abnormalities in these rodent models of stress and depression resemble those found in depressed humans (Cannon et al., 2007), if acute illness or stress is indeed impacting 5-HTT transporter numbers or binding in MDD, then this may restrict the utility of the phenotype as a marker of vulnerability to MDD.

(Frokjaer et al., 2009) found that healthy individuals who were at high-risk of developing MDD by virtue of having a co-twin with the disorder, displayed reduced 5-HTT BP in the DLPFC and to a lesser extent, the anterior cingulate cortex. Nevertheless, given the nature of this study, it is unclear if the reduction in 5-HTT BP is indicative of a genetic vulnerability to MDD or whether it reflects an adaptive compensation for impaired serotonergic function.

Theoretical Challenges

(a). Phenotypic Heterogeneity

A great deal of genetic and phenotypic variation is encompassed within current nosological categories, and it is thus likely that the exact pattern of MDD-associated neuropathology will vary across subgroups of affectively ill patients. The relatively embryonic state of the field has unfortunately meant that these issues have thus far been largely neglected.

For example, there is some evidence that patients who are recurrently ill and those subjects who have experienced one life-time episode of depression may differ from each other genetically or clinically (Zubenko et al., 2002) (Smith et al., 2005) (Mondimore et al., 2007). Other important sources of heterogeneity include age-of-onset (Alpert et al., 1999) (Hammen et al., 2008), chronicity of course (Mondimore et al., 2007) (Eaton et al., 2008), family history of MDD or BD illness (Mannie et al., 2007) (Verhagen et al., 2008), and the effect of exposure to childhood trauma (Brodsky et al., 2008) (Danese et al., 2008).

Clearly the use of endophenotypes is designed to overcome these very difficulties. Nevertheless, the failure to carefully parse clinically heterogeneous samples into more refined subgroups attenuates the statistical power needed to identify intermediate phenotypes. In this sense, until genuine breakthroughs are achieved, the endophenotypic strategy remains beholden to less biological, clinical methodologies.

(b). Defining Remission

An endophenotype is by definition a trait which is present in both ill and remitted individuals. Not all individuals remit spontaneously, however. Many remissions are treatment-induced and it is unclear if AD or other interventions mask intermediate traits which would otherwise be present if the illness followed its natural course. Our opinion (based on anecdotal observations) is that MDD patients who are capable of spontaneous remission, and remain well for years at a time, are clinically different from their counterparts who are chronically ill. Thus caution should be exercised when evaluating potential endophenotypes using the state versus trait criterion.

(c). Non-Disease Related Inter-Individual Variation in Brain Morphology and Function

The ability to distinguish disease-associated functional or anatomical changes from natural, non-clinically related inter-individual variation presents a formidable challenge. For example, (Paus et al., 1996; Fornito et al., 2006) have described how the shape and therefore the volume of the anterior cingulate gyrus, a region of the brain that has been implicated in affective illness, varies significantly among healthy individuals. Specifically, 30–60% of individuals possess a paracingulate sulcus, which runs dorsal and parallel to the cingulate sulcus, and may or may not have functional significance (Fornito et al., 2006).

Reductions in hippocampal volume have been associated with MDD (Sheline, 1996) (Neumeister et al., 2005), and in healthy individuals are often viewed as a precursor to a senescence-associated cognitive decline. Nevertheless, (Lupien et al., 2007) found that there was just as much variability in the hippocampal volumes of healthy young adults as older individuals. A quarter of their subjects in the 18–24-year age group had hippocampal volumes

as small as the average hippocampal size in their 60–75-year-old sample, and the mean difference in hippocampal volumes between the upper and lower quartiles of the young age group (12–16%) was greater than volumetric reductions typically reported in depressed samples (Lupien et al., 2007).

Distinguishing between adaptive and non-adaptive compensatory responses to brain insults may also become a pernicious source of bias. For example, Alzheimer's disease (AD) researchers have grappled with the problem of whether the phosphorylation of tau proteins which make up the neurofibrillary tangles seen at post-mortem, is a protective, compensatory response to oxidative stress, or is the primary causal process underpinning the disease (Lee et al., 2005).

A hint of this difficulty already exists in the MDD literature. While a potentially stress-induced, excitotoxicity-driven process has been reported to produce dendritic atrophy in the basolateral amygdala (BLA) (Vyas et al., 2002) of rodents, other studies demonstrate *hypertrophy* in response to immobilization stress (Radley and Morrison, 2005) (Vyas et al., 2006) which persists for at least 21 days (Vyas et al., 2004). This pattern may be recapitulated in MRI-analyses of MDD patients with studies indicative of both volumetric reductions (Sheline et al., 1998) (Tang et al., 2007) and increases (Lange and Irle, 2004) in amygdala volume.

(d). The Specificity of Phenotypes or Endophenotypes

Understanding the genetic basis of certain imaging phenomena such as volumetric changes, increased BOLD response of the amygdala and white matter hyperintensities will be invaluable, but will not necessarily elucidate the susceptibility variants that make MDD unique from other forms of psychiatric illness.

For example, in addition to MDD, hippocampal GM loss has been reported in schizophrenia (Steen et al., 2006), bipolar disorder (Moorhead et al., 2007), post-traumatic stress disorder (PTSD) (Karl et al., 2006); borderline personality disorder (Tebartz van Elst et al., 2003), antisocial personality disorder (Laakso et al., 2001), obsessive compulsive disorder (Kwon et al., 2003), autism (Aylward et al., 1999) and old age (Convit et al., 1995). White matter hyperintensities are characteristic of multiple sclerosis, and have been noted in MDD (Taylor et al., 2005b) (Godin et al., 2007), schizophrenic (Sachdev and Brodaty, 1999), BD (McDonald et al., 1999), substance abuse (Lyoo et al., 2004), autistic (Wong, 2007), and elderly (Kertesz et al., 1988) samples.

The counter argument to this potential problem of non-specificity is that we are guilty of the reification of DSM-IV psychiatric categories. The *raison d'être* of endophenotyping is the avoidance of DSM categorization. If supposedly distinct categories of psychiatric illnesses share genetic risk factors then this may be indicative of the failure of current diagnostic systems rather than the inferiority of the relevant endophenotype. Nevertheless, the presence of the same biological trait across such clinically diverse samples raises questions about the explanatory power of any disease model derived from the imaging endophenotype.

(e). The Effects of Medication

Given the difficulty of recruiting unmedicated patients for research, perhaps the most important confounding variable is medical treatment. While, recent studies have detailed the neurotrophic effects of lithium and mood stabilizers on hippocampal and other neural tissue, there has been some suggestion that antidepressants, long considered *not* to impact neuronal or gray matter volumes, may also exert a neurotrophic effect in particular regions of the brain (Stewart and Reid, 2000) (Rocher et al., 2004) (Duman and Monteggia, 2006). These data are supported by an fMRI study which showed that depressed patients suffer from reduced functional coupling

of the amygdala with diverse brain regions including the hippocampus, caudate, putamen, and ACC; an effect reversed by treatment with fluoxetine (Chen et al., 2007b). Similarly, with respect to amygdala hypermetabolism, a decrease in left amygdala activity to normal has been observed after antidepressant treatment (Drevets et al., 2002). Interestingly, a decrement in amygdala activity in response to aversive stimuli also been observed in healthy individuals treated with citalopram (Harmer et al., 2006) and reboxetine (Norbury et al., 2007).

(f). Methodological Variability

Data acquisition, data analysis, and in the case of some functional imaging studies, the choice of experimental paradigm may make inter-study comparison difficult. A detailed discussion of methodological issues is beyond the scope of this review. One brief example concerns the primary philosophical orientations to imaging data analysis; voxel-wise analysis which compares the differences between two or more subject groups at each individual voxel in the brain (Ashburner and Friston, 2000), and MRI-based region-of-interest analysis, which relies on extant empirical or theoretical data to identify candidate regions that may show inter-group differences.

Voxelwise analyses are highly sensitive to Type II errors because spatial normalization algorithms cannot precisely overlay small structures like the amygdala and subgenual ACC across subjects, exaggerating the statistical variance. On the other hand, the ROI approach is time and resource intensive especially when subject groups are large. The strength of the method is critically dependent on the quality of the tracing, as well as the reproducibility of the anatomical landmarks chosen to delineate the structure.

(g). Technological Limitations and Reification of Imagable Units

The limited spatial and temporal resolution of current neuroimaging technologies are important bottlenecks to progress in the field. Current structural imaging platforms do not have the necessary spatial resolution to accurately detail volumetric changes in diminutive anatomical structures such as the amygdala and periaqueductal gray. The impact of this limitation can be felt in the functional imaging literature where perfusion or metabolic measurements are subject to the problem of partial volume effects. That is, inadequate spatial resolution of the region-of-interest causes adjacent white matter (WM) and neural tissue with lower metabolic rates to be included in the analysis, leading to an underestimation of metabolic activity.

While technology will no doubt improve over the coming years, finite limits to PET resolution exist because of Compton scattering (leading to non-collinearity of emitted photon pairs), and positron range (the distance that the positron travels before annihilating with an electron and emitting a photon pair). Regarding PET measures of glucose metabolism, it is the neuropil (where the greatest degree of ion pumping across cell membranes occurs) that has the greatest metabolic demand. Thus elevated glucose metabolism as measured by PET FDG, does not necessarily reflect local activity but increased activity of distal neurons projecting to the region in question (Herscovitch, 2003). The obverse is also true. Loss of neuronal projections from damage in one region may decrease glucose metabolism in its projection field. Similarly, draining vein effects place fundamental limits on the accuracy of spatial localization that can be obtained with blood oxygenation level dependent (BOLD) changes measured by fMRI.

There is a danger that these limitations may lead to the implicit reification of neuroanatomical function; that is, the notion that gross anatomical structures should be uniformly affected by mood disorders simply because they are imagable units. For example, the amygdala is a heterogeneous structure made up of at least 14 different nuclei (Bachevalier and Loveland, 2006), some of which may be homologous to the ventral striatum and olfactory cortex (Swanson and Petrovich, 1998).

(h). Targeted Hypotheses or Genome Wide Association (GWA)?

Genetic association studies are plagued by false positive results because the large number of genes expressed in the brain translates into a low *a priori* probability of a true association. In response, journal editors are demanding increasingly stringent corrections for multiple testing, a trend that reaches its zenith in GWA studies which typically have a significance threshold of at least 5×10^{-7} . GWA studies have proven highly successful at detecting disease-predisposing variations in complex disorders such as prostate cancer and diabetes mellitus (reviewed in (Seng and Seng, 2008)), although the chorus of excitement has been more muted in the case of psychiatric disorders (Wellcome-Trust-Case-Control-Consortium, 2007) (Kirov et al., 2008) (Sklar et al., 2008) (Shifman et al., 2008a).

A wave of GWA studies of imaging phenotypes is likely to follow on the heels of DSM-IV-based GWA analyses. The suitability of this “brute-force” approach to analyzing imaging phenotypes remains, however, unclear. Certainly, GWA analyses hold out great promise for uncovering disease causing polymorphisms, but imaging samples are by nature small, especially in the case of functional studies. The problem becomes all too clear in the context of GWA studies of diseases like type II diabetes where sample sizes of over 1000 are the norm, and a meta-analysis of approximately 14,000 cases and 18,000 controls produced promising results (Zeggini et al., 2008). (Manolio et al., 2008) point out that in order to obtain 80% power to identify a risk allele with a frequency of 10% and an odds ratio of 1.5, 1,590 cases and 1,590 controls are needed to breach the statistical threshold of 5×10^{-7} .

Whether the imaging data are “clean” enough to compensate for the loss of statistical power inherent to small samples is currently unknown. On the positive side, as noted by David Goldman (Goldman, 2008, personal communication), many of the highly significant results obtained in GWA studies conducted to date [reviewed in (Manolio et al., 2008)] have been obtained with intermediate phenotypes as well as traditional clinical diagnoses. Nevertheless, the substantial inter-individual variability in the volumes of anatomical subregions of the brain should inject a note of caution into the discussion.

We recently reported an association between a SNP in the galactose mutarotase (*GALM*) gene and serotonin transporter binding potential (measured with [^{11}C] DASB) which survived a genome-wide correction for multiple testing (Liu et al., 2008), thus suggesting that GWA studies are in principle feasible even in very small samples. Nevertheless, the veracity of this result awaits replication.

GWA approaches raise other problematic issues such as whether structural scans obtained on different MRI scanners or functional data obtained with similar experimental paradigms can be pooled together. Certainly, this would be considered methodologically unsound in a traditional imaging study. These difficulties can be partially ameliorated by classical genetic association approaches although the strength of any finding likely depends on the depth of convergent evidence implicating the gene in a disease or relevant physiological process.

(i). Is the Genetic Architecture of an Imaging Phenotype or Endophenotype Really Simple?

An exaggerated BOLD response of the amygdala to negatively valenced faces or disease-association reductions in brain volume, are likely complex traits underpinned by multiple genetic and environmental factors. Elucidating the genetic basis of these traits may thus be deceptively difficult. Perhaps the one exception to this rule is PET-based neuroreceptor mapping which allows for quantification of the binding potential of individual receptor types in the brain. Nevertheless, the financial and logistical challenges inherent to scanning large numbers of subjects reduces statistical power, and essentially limits researchers to the testing of common, high frequency alleles.

(j). The Heritability of Endophenotypes

Ideally, the imaging phenotype found to be associated with MDD should be heritable (Gottesman and Gould, 2003) but testing this hypothesis is difficult because it requires large numbers of related individuals to undergo scanning. Besides logistical challenges, the effects of age, gender, and medication may bias intra, as well as inter-familial analyses.

(k). Evaluation of the Evidence

While our knowledge of the genetic basis of brain function remains *in statu nascendi*, imaging genetics faces a problem of evidence evaluation. While some relatively clear-cut instances of replication are likely to occur (the 5-HTTLPR polymorphisms is probably one such example), in many cases the data will likely be contradictory, and numerous (Popperian) *ad hoc* hypotheses will be forwarded to explain away positive or negative gene-phenotype associations. Examples of *ad hoc* hypotheses that can be used to justify results include gene-gene interactions, gene-environment interactions, genetic heterogeneity, type II errors due to lack of statistical power, and false positive results due to low *a priori* probability of a true effect.

The problem can be ameliorated to some extent by collecting convergent bioinformatic, biochemical, neuropathological, or animal-based data supportive of the proposed gene-imaging phenotype association. Nevertheless, unless pending GWA studies produce a rash of replicable findings, progress is likely to be slow, and this is underscored by the current inability of researchers to agree on a definitive list of true MDD-associated genetic variants.

Future Directions

(a). Gene-Gene Interactions

Assuming the veracity of the common disease-common variant (CDCV) hypothesis, analyzing the additive effects of common polymorphisms on imaging phenotypes, and by extension, genetic risk for MDD, is an important project. Evidence for gene-gene interactions are beginning to emerge in the literature. The SLC6A4 gene has been reported to interact with BDNF to impact amygdala and anterior cingulate cortex volume (Pezawas et al., 2008); tryptophan hydroxylase 2 (TPH2) (Canli et al., 2008), and catechol-o-methyltransferase (COMT) (Smolka et al., 2007), to modulate amygdala response to negatively valenced stimuli.

(b). Epigenetics

Epigenetic inheritance refers to a regulated pattern of gene expression which is transmitted intact from one or other parent to their offspring. The process is mediated by the methylation and histone acetylation of cytosine residues and chromatin, respectively, leading to the activation or silencing of particular genes. The phenomenon is epi-genetic because it results in phenotypic traits that are inherited independently of the informational content of DNA.

Evidence is accumulating that these epigenetic mechanisms allow for a dynamic response to the environment. Rodent studies, for instance, have demonstrated that stress sensitivity in rat pups is modulated by parental grooming behavior which exerts its effect through a histone modification-driven regulation of glucocorticoid receptor gene expression (Meaney and Szyf, 2005). If these biological mechanisms generalize to humans then exposure to adversity may modify gene expression in pathways that impact neuroplasticity. (Philibert et al., 2008) for instance, recently reported that CpG methylation of a motif surrounding exon 1 of the 5-HTT gene was increased (trended towards statistical significance) in individuals with a life time history of MDD. In a similar vein, the GABA_A receptor gene has been reported to be hypermethylated in suicide victims (Poulter et al., 2008). Since human lymphoblast cell lines reportedly maintain their transcriptional signature (Philibert et al., 2007), searching for

methylation pattern-imaging phenotype associations in SLC6A4 and other genes may prove feasible and informative.

(c). Modeling the Impact of Medication

Evaluating medication-induced changes in neurophysiological function may allow researchers to “work backwards” in order to identify MDD-associated imaging abnormalities in much the same way that the efficacy of tricyclic AD and selective serotonin reuptake inhibitors implicated the serotonergic system in MDD. As noted above, a decrease in left amygdala activity to normal has been observed in MDD patients following AD treatment (Drevets et al., 2002) and a similar decrement in amygdala activity in response to aversive stimuli has been observed in healthy individuals treated with citalopram (Harmer et al., 2006) and reboxetine (Norbury et al., 2007). Medication-induced recovery from depression has also been associated with a recovery of dorsolateral prefrontal cortex BOLD signal (Fales et al., 2008) or glucose metabolism (Kennedy et al., 2001). Thus, imaging phenotypes which are state sensitive, and therefore by definition, poor endophenotypes, may nevertheless be useful, objective markers of treatment efficacy.

(d). Perturbing the System

Clearly ethical considerations prevent researchers from deliberately placing subjects under enough stress to precipitate any latent vulnerability to MDD. Nevertheless, certain approaches to perturbing neurophysiological function are open to researchers. Chief among these, are administration of drugs which temporarily deplete serotonin or catecholamines. For example, in a recent catecholamine depletion study (Hasler et al., 2008) showed that under depletion, metabolism (as measured by fluorodeoxyglucose (FDG) PET) increased in remitted MDD subjects, but decreased in healthy controls in diverse areas of the brain. These regions included the ventromedial frontal polar cortex, right thalamus, left ventral striatum (ventral putamen), infralimbic cortex, left superior temporal gyrus, left inferior parietal lobe, and left precentral gyrus.

Serotonin depletion may also uncover a genetic vulnerability to depression: Six out of 20 healthy males with a family-history of affective illness but 0 out of 19 male controls without a family-history of MDD displayed a lowering of mood in response to tryptophan depletion (Benkelfat et al., 1994). Similarly, (van der Veen et al., 2007) reported that healthy individuals with a family history of MDD showed a lowering of mood together with greater amygdala activation in response to fearful faces after tryptophan depletion.

(e). Beyond SNPs?

Copy number variants (CNV) refer to microstructural chromosomal changes: deletions, duplications, inversions; variable number tandem repeats (VNTRs), and microsatellites. Approximately 18,000 CNV have been identified to date (<http://projects.tcag.ca/variation/>).

De novo CN mutations have been shown to be strongly associated with sporadic cases of schizophrenia (Xu et al., 2008); autism (Marshall et al., 2008) (Weiss et al., 2008), and perhaps bipolar disorder (Lachman et al., 2007). Further, a recent GWA study of the anxiety-related personality trait, Neuroticism, found that SNPs in regions of the genome known to have CNV, yielded a disproportionate number of low p-values (Shifman et al., 2008b). If changes in CNV are associated with subtypes of MDD, then the identification of correlated imaging phenotypes, perhaps through array hybridization techniques, may help to clarify the pathophysiological mechanisms underpinning mood disorders.

(f). Beyond Psychology?

The importance of testing for gene-environment interactions as an adjunct to traditional psychiatric genetic association studies is now well established in the literature. To date, the emphasis has been placed on psychological phenomena such as early childhood abuse (Caspi et al., 2003) (Kaufman et al., 2006) (Ducci et al., 2007) (Reif et al., 2007) (Savitz et al., 2007) (Perroud et al., 2008) (Savitz et al., 2008) (Stein et al., 2008) but other, perhaps less subjective phenomena may prove equally valuable to examine. Examples include low birth-weight/fetal growth (Raikkonen et al., 2008) (Schmidt et al., 2008), paternal or maternal age at conception (Reichenberg et al., 2006) (Laursen et al., 2007), viral infections (Dickerson et al., 2006) (Fatemi et al., 2008), pre or postnatal exposure to drugs like nicotine, marijuana, and alcohol (Williams and Ross, 2007) (Becker et al., 2008) (Caldwell et al., 2008), as well as other potential environmental toxins such as lead (de Souza Lisboa et al., 2005) (Stewart et al., 2006) (Cecil et al., 2008), methylmercury (Onishchenko et al., 2008), and polychlorinated biphenyls (PCBs) (Fitzgerald et al., 2008).

(g). Beyond Neurons?

Intriguing evidence of a systemic dysregulation of immune function in MDD is beginning to surface in the literature. The leitmotif running through many of these studies is that of a cytokine-induced proinflammatory state associated with physical or psychological stress which impacts monoaminergic neurotransmission and HPA axis function (Schiepers et al., 2005). Cytokines such as interleukin-1, interleukin-6, C-reactive protein, and the pro-inflammatory enzyme, myeloperoxidase (MPO), have been found to be elevated in the blood and cerebrospinal fluid (CSF) of patients with MDD (Lanquillon et al., 2000) (Ford and Erlinger, 2004) (Vaccarino et al., 2008); a phenomenon that may be ameliorated with AD treatment (Myint et al., 2005) (Malemud and Miller, 2008). Consistent with these data, variants of genes such as tumour necrosis factor alpha (TNF- α), interleukin 1 (Fertuzinhos et al., 2004), and T-BET (TBX21) and proteasome beta4 subunit (PSMB4), which are involved in T-cell function (Wong et al., 2008), have been reported to be overrepresented in MDD populations.

Theoretically, therefore, molecular signatures of inflammation may be useful intermediate phenotypes or treatment markers for MDD. PET ligands such as [C^{11}](R) PK11195 which quantify peripheral benzodiazepine receptors (Fujita et al., 2008), a marker of inflammation, are currently under development.

Conclusion

We have discussed 7 (MRI and PET) imaging phenotypes which appear to be strongly associated with MDD. Strictly speaking, an endophenotype is a heritable trait present in periods of illness and remission that should be found in biological relatives of affected individuals at a greater frequency than the general population (Gottesman and Gould, 2003). The extant literature is not mature enough to allow us to evaluate whether the neurophysiological markers discussed above qualify as *endophenotypes*. More family-based studies are needed. Nevertheless, what seems clear is that useful imaging *phenotypes* (correlates of MDD) have been identified. These (presumably) simpler traits have led to early progress in identifying the pathophysiological and genetic basis of MDD.

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Table 1

Endophenotype 1. Amygdala Reactivity in Subjects with MDD.

Study	Sample	Medication Status	fMRI Task	Finding
(Sheline et al., 2001)	11 MDD 11 HC	No meds for 4+ weeks	Masked N, H and F faces	↑ left but not right amygdala activation to all faces, especially fearful faces. Effect was no longer present after AD treatment.
(Siegle et al., 2002)	7 MDD 10 HC	No tricyclic AD. Most other AD permitted.	Positive, negative and neutral words.	Sustained amygdala activation in response to negative words.
(Davidson et al., 2003)	12 MDD 5 HC	No meds	Positive, negative and neutral pictures.	↑ bilateral amygdala activation in response to negative pictures.
(Fu et al., 2004)	19 MDD 19 HC	No meds for 4+ weeks	Low, medium and high intensity sad faces	↑ left amygdala response to sad faces which was no longer visible after AD treatment.
(Lawrence et al., 2004)	9 MDD 11 HC	Various AD	S, H, N and F faces	NS
(Abler et al., 2007)	12 MDD 12 HC	Various AD	Pleasant, disgusting, and neutral pictures	↑ bilateral amygdala when anticipating negative pictures
(Hamilton and Gotlib, 2008)	14 MDD 12 HC	9 on AD (mostly SNRI)	Negative, neutral and positive pictures	↑ right amygdala when encoding negative pictures

Note: Studies stratifying subjects by genotype are not included in this table. A=angry; AD=Antidepressant medication; F=Fearful; H=Happy, HC=Healthy Control; MDD=Major Depressive Disorder; N=Neutral, NS=Not significant; S=Sad; SNRI=Serotonin-Noradrenaline Reuptake Inhibitor

Table 2

Endophenotype 2. Hippocampal Volume Reduction.

Study	Sample	Age	Method	Medication Status	Findings
(Axelson et al., 1993)	19 MDD 30 HC	46.7±7.4 56.6±19.1	1.5T 5mm ROI	NR	NS
(Sheline et al., 1996)	10 MDD 10 HC	68.5±10.4 68.0±9.5	1.5T 1.25mm ROI	8 AD	↓ BL hippocampus
(Pantel et al., 1997)	19 MDD 13 HC	72.4±8.8 68.2±5.3	1.5T 1.25mm	NR	NS
(Ashtari et al., 1999)	40 MDD 40 HC	74.3±6.0 71.4±0.3	1T 3.1mm ROI	NR	NS
(Sheline et al., 1999)	24 MDD 24 HC	52.8±18.4 52.8±17.8	1.5T 1.25mm ROI	16 on AD	↓ BL hippocampus
(Mervaala et al., 2000)	34 MDD (6 BD) 17 HC	42.2±12.2 42.1±14.6	1.5T 8mm ROI	AD	↓ L hippocampus. Trend for R hippocampus.
(Steffens et al., 2000)	66 MDD 18 HC	71.74±8.42 67.11±5.04	1.5T 3mm	NR	↓ BL hippocampus
(von Gunten et al., 2000)	14 MDD (with memory complaints) 14 HC	57.6 58.1	1.5T 5mm	7 AD, 2 BZ	NS
(Rusch et al., 2001)	25 MDD 15 HC	33.2±9.5 37.4±14.4	1.5T 1.2mm VOI	Free of medication for 4+ weeks.	NS
(Frodil et al., 2002)	30 FE MDD 30 HC	40.3±12.6 40.6±12.5	1.5T 3mm ROI	AD	↓ L hippocampus in male MDD
(MacQueen et al., 2003)	20 FE MDD. 17 multi-episode MDD. 20 HC 17HC	28.4±11.8 35.9±11.1 28.4±11.5 36.2±11.9	1.5T 1.2mm ROI	FE MDD group medication naïve. AD in multi-episode group.	↓ hippocampus in multi-episode patients.
(Frodil et al., 2004a)	30 MDD 30 HC	48.4±13.4 45.7±12.9	1.5T 1.5mm ROI	AD + lithium	↓ R hippocampal volume in non-remitted group at base-line and follow-up.
(Hastings et al., 2004)	18 MDD 18 HC	38.9±11.4 34.8±13.6	1.5T 1.5mm ROI	NR	NS
(Lange and Irle, 2004)	17 female MDD 17 female HC	34±10 34±6	1.5T 1.3mm ROI	AD	↓ hippocampus

Study	Sample	Age	Method	Medication Status	Findings
(Lloyd et al., 2004)	51 MDD (23 early onset; 28 late-onset) 39 HC	72.7±6.7 75.1±5.8 73.1±6.7	1T 1mm	AD	BL hippocampal atrophy in late-onset MDD compared with early-onset MDD + HC
(MacMaster and Kusumakar, 2004)	17 MDD 17 HC	16.67±1.83 16.23±1.61	1.5T 1.5mm ROI	14 treatment naïve, 3 AD or methylphenidate	↓ BL (especially L) of hippocampus
(O'Brien et al., 2004)	61 MDD 40 HC	73.9±6.7 73.3±6.7	1T 1mm ROI	51 AD, 7 lithium	↓ hippocampus
(Hickie et al., 2005)	66 (14 BD) MDD 20 HC	53.5±13.5 55.8±10.8	1.5T 1.5mm ROI	NR	↓ hippocampus
(Neumeister et al., 2005)	31 MDD 57 HC	40.1±10.1 38.0±10.9	3T 0.6mm	Unmedicated	↓ hippocampus
(Frodl et al., 2006)	34 MDD 34 HC	45.5±11.9 43.6±13.2	1.5– 3mm ROI	AD, 4 AP	↓ BL hippocampus
(Rydmann et al., 2006)	29 female MDD 28 HC	47.7±4.9 47.6±4.2	1.5T VBM	AD	NS
(Frodl et al., 2007)	60 MDD 60 HC	44.2±11.8 41.6±12.3	1.5T 1mm ROI	AD	↓ hippocampus.
(Janssen et al., 2007)	13 early onset MDD 15 late-onset MDD 22 HC	70.38±8.3 72.67±6.7 71.05±7.5	1.5T	4 lithium	↓ hippocampus in early-onset group only.
(Macmaster et al., 2007)	32 MDD 35 HC	14.08±2.08 14.51±2.72	1.5T 1.5mm ROI	naïve	↓ L+R hippocampus
(Frodl et al., 2008b)	38 MDD 35 HC	46.1±11.3 43.6±11.3	1.5T 1.5mm VBM	AD	Decrease in hippocampal volume over 3 year follow-up.
(Kronmüller et al., 2008)	57 MDD 30 HC	43.54±12.82	1.5T ROI	NR	Male patients who relapsed over 2 years had ↓ hippocampi

Note: AD=antidepressant; BL=bilateral; BZ=benzodiazepine; FE=first episode; HC=healthy controls; NR=not reported; NS=not significant; ROI=Region of Interest; VBM=Voxel-Based Morphometry

Table 3
Endophenotype 3. White Matter Hyperintensities in MDD.

Study	Sample	Age	Medication Status	Findings
(Coffey et al., 1989)	51 MDD	71.3	Variety of medication for medical illness.	PVH in 100% of sample. WMH in 86% of sample.
(Zubenko et al., 1990)	67 MDD 44 HC	73.2±6.5 68.0±6.2	NR	↑ incidence of infarcts + leukoencephalopathy in MDD
(Guze and Szuba, 1992)	119 MDD (44 young +75 old) 60 HC (30 young + 30 old).	33.4 66.2 34.1 68.7	NR	Old MDD group had more WMH than young MDD and old HC.
(Dupont et al., 1995b)	33 MDD 32 HC	38.9±10.2 39.2±8.9	13 AD, 18 no meds	NS
(Hickie et al., 1995)	39 MDD	64.4	AD, lithium, ECT	Late onset group (>50) showed more WM changes than earlier onset group.
(Lewine et al., 1995)	27 MDD 150 HC	40±11 33±9	NR	↑ deep WMH
(Greenwald et al., 1996)	48 MDD 39 HC	74.6±6.1 72.6±6.4	NR	NS
(O'Brien et al., 1996)	60 MDD 39 HC	71.2±7.9 71.4±11.0	NR	↑ deep WMH in BG and frontal lobes. Patients with late-onset MDD had more WMH than early-onset MDD.
(Salloway et al., 1996)	30 MDD	Early onset: 73.3±7.8 Late onset: 77.5±4.4	NR	↑ deep WMH + PVH in late onset group.
(Greenwald et al., 1998)	35 MDD 31 HC	74.7±6.4 72.9±4.7	NR	↑ L deep frontal and L putaminal WMH
(Lenze et al., 1999)	24 MDD 24 HC	52.7±18.4	AD	No significant differences in total number of lesions
(Kumar et al., 2000)	51 MDD 30 HC	74.3±6.56 69.43±6.09	AD, BZ	↑ in lesion volume
(MacFall et al., 2001)	88 MDD 47 HC	72.6±7.9 72.2±6.3	NR	Trend towards ↑ deep WMH
(Murata et al., 2001)	20 early onset MDD 27 late onset MDD	62.7±6.7 60.3±6.9	AD, BZ	More severe WMH in late onset group.
(Tupler et al., 2002)	115 MDD (69 late- onset, 46 early onset) 37 HC	66.7±10.9 65.9±9.4	NR	More severe WMH rating in deep frontal regions in late-onset cases.
(Sassi et al., 2003)	17 MDD 38 HC	42.8±9.2 36.8±9.7	No medication for 2+ weeks	MDD patients with longer illness duration had ↑ WMH.
(Janssen et al., 2004)	28 MDD 41 HC	64.04±10.9 62.37±11.38	22 AD, 4 lithium, 1 BZ	NS
(Lloyd et al., 2004)	51 MDD (23 early onset; 28 late-onset) 39 HC	72.7±6.7 75.1±5.8 73.1±6.7	AD	NS
(Taylor et al., 2005b)	253 MDD 146 HC	70.48±6.23 69.85±7.54	NR	↑ WM lesion volumes
(Chen et al., 2006)	164 MDD 126 HC	68.93±7.04 69.83±6.25	Yes – not specified	↑ WM lesions at baseline + at 2-year + 4-year follow-up
(Hannestad et al., 2006)	182 MDD 62 HC	70.2±5.8 70.0±7.7	NR	↑ WML.
(Iosifescu et al., 2006)	84 MDD 35 HC	40.7±10.2 39.3±9.8	No meds	NS

Study	Sample	Age	Medication Status	Findings
(Janssen et al., 2007)	13 early-onset MDD 15 late-onset MDD 22 HC	70.38±8.3 72.67±6.7 71.05±7.5	4 lithium	↑ large WMH in late-onset (>60) MDD
(Sheline et al., 2008)	83 MDD 32 HC	68.7±7.6 69.7±6.0	No meds	Widespread ↑ in WMH

Note: BZ=benzodiazepine; ECT=electroconvulsive therapy; FA=fractional anisotropy; MDD=major depressive disorder; HC=healthy control; NR=not reported; NS=not significant; PVH=periventricular hyperintensities; WMH=white matter hyperintensities

Table 4

Endophenotype 4. Volumetric Abnormalities of the sgACC in MDD.

Study	Sample	Age	Method	Clinical Status at Testing	Medication Status	Findings
(Drevets et al., 1997a)	10 MDD 21 HC	39±7.3 34±8.2	1mm ROI	Depressed	Unmedicated 4+ weeks	Decreased volume of L sgACC in MDD group
(Botteron et al., 2002)	30 MDD 8HC	20.2±1.6	1mm ROI	Depressed	Less than 10% of MDD sample on medication.	Decreased volume of L sgACC in MDD
(Kegeles et al., 2003)	19 (14 MDD, 5 BD) 10 HC	36±11 39±19	1.5mm ROI	Depressed	BZ discontinued 24 hours before study in 12 cases. 7 subjects on BZ. Patients free of other medication for 2+ weeks.	NS
(Hastings et al., 2004)	18 MDD 18 HC	38.9±11.4 34.8±13.6	1.5mm ROI	Depressed	Unmedicated	Volume reduction in L sgACC in males only
(Coryell et al., 2005)	10 MDD 10 SCZ 10 HC	22±4.9 22±6.0	1mm ROI	Depressed	NR	Volume reductions in L posterior sgACC but not anterior sgACC in MDD with psychotic features
(Boes et al., 2008)	31 HC - no family history 28 HC - + family history	12.0±2.72 12.1±2.13	1.5mm ROI	Mixed	NR	In boys (but not girls) with subclinical depression smaller L perigenual (sgACC + pgACC) volumes.
(Chen et al., 2007a)	17 MDD	44.1±8.36	3mm VBM	Depressed	Scanned before and after treatment with fluoxetine. Patients unmedicated 4+ weeks before study.	Greater GM volume of pgACC (0, 41, 2) and sgACC (0, -31, -2) associated with faster improvement to fluoxetine
(Tang et al., 2007)	14 MDD 13 HC	29.5±6.84 29.5±6.86	1.6mm ROI	Depressed	Naive	Decreased volume of sgACC in MDD at x=2; y=30; z= -2
(Yucel et al., 2008)	65 MDD 93 HC	28.8±10.3 28.4±10.7	1.2mm ROI	Depressed	Short-term treatment with various AD	Decreased volume of BA25 in MDD Only MDD patients with medication exposure had smaller BA24 volume.

Note: AD=antidepressant medication; BZ=benzodiazepenes; HC=healthy control; MDD=major depressive disorder; NR=not reported; NS=not significant; pgACC=perigenual anterior cingulate cortex; sgACC=subgenual anterior cingulate cortex; ROI=region of interest; VBM=voxel-based morphometry.

Table 5

Endophenotype 4. Neurophysiological Abnormalities of the sgACC.

Study	Sample	Age	Method	Clinical Status	Medication Status	Findings	Brodman Area /Stereotaxic Coordinates
(Drevets et al., 1997b)	10 MDD 21 HC	39±7.3 34±8.2	¹⁸ FDG-PET	Depressed	Cohort not treated for 4 weeks prior to scans	Decreased metabolism of L sgACC in MDD group.	sgACC BA 24 -2; 32; -2
(Wu et al., 1999)	12 MDD responders 24 MDD non-responders 26 HC	28.8±9.2 30.8±9.9 29.4±9.5	¹⁸ FDG-PET	Depressed	No medication for 2+ weeks	Responders to sleep deprivation had higher metabolic rates in sgACC at baseline.	sgACC BA 24; 25 3; 25; -4 5; 48; -4
(Mayberg et al., 2000)	17 MDD	49±9	¹⁸ FDG-PET	Depressed	Scanned before and after fluoxetine treatment	Improvement associated with decreased activity of sgACC. No sgACC changes in non- responders to fluoxetine.	sgACC BA 25 4; 2; -4 BA 24 2; 26; -8
(Drevets et al., 2002)	20 MDD 14 HC	36±10 34±9.1	¹⁸ FDG-PET	Depressed	Scanned off medication ≥3 weeks before and again after sertraline	Depressed group had lower baseline metabolism in sgACC; activity decreased further with treatment	sgACC BA 24 3; 31; -10
(Kegeles et al., 2003)	19 (14 MDD, 5 BD) 10 HC	36±11 39±19	¹⁸ FDG-PET	Depressed	BZ discontinued 24 hours before study in 12 cases. 7 subjects on BZ. Patients free of other medication for 2+ weeks.	Reduced metabolism in depressed subjects vs. controls under placebo baseline condition	sgACC BA 24/32 4; 34; -12
(Pizzagalli et al., 2004)	38 MDD (20 melancholic) 18 non- melancholic 18 HC	33.1±8.8 36.5±12.9 38.1±13.6	¹⁸ FDG-PET	Depressed	Free of medication 2+ months	Decreased metabolism of sgACC in melancholic patients only	sgACC BA25 -3; 9; -6
(Gotlib et al., 2005)	18 MDD 18 HC	35.2 30.8	3T fMRI	Depressed	9 on AD	Greater BOLD response to sad faces in L sgACC (BA 25) in MDD.	BA 25 – coordinates not given
(Kumano et al., 2006)	19 cancer patients followed longitudinally	58.4±15.7 (group developing depression) 57.9±16.4 (group without depression)	¹⁸ FDG-PET	Depressed + euthymic	Anti-cancer medication	Patients who became more depressed over time showed prodromal hypermetabolism of sgACC	sgACC BA 25 -4; 9; -12 2; 11; -7
(Nahas et al., 2007)	17 MDD No controls	46.8±6.3	1.5T fMRI	Depressed	Yes – not specified	VNS decreased activity of the R sgACC	sgACC BA 25 0; 8; -16
(Greicius et al., 2007)	28 MDD 20 HC	38.5 35.4	3T fMRI Default mode network study	Depressed	Stabilized on medication for 2+ weeks prior to scan	Increased activity of the sgACC drives altered pattern of default mode network activity in MDD	BA 25 -10; 5; -10
(Fales et al., 2008)	27 MDD 24 HC	33.4±8 36.4±9	3T fMRI ROI Emotional interference task - houses and faces.	Depressed	Unmedicated for 4+ weeks	Elevated activity of sgACC in MDD	BA 24; 10; 35; -2 0; 13; 29 0; 13; 34
(Keedwell et al., 2008)	12 MDD No HC	49	Sad, neutral and happy faces	Depressed	Various AD started within 2 weeks of scan	At baseline, depression severity positively correlated with activity in right sgACC in response to sad faces.	BA 25 4; 15; -7

Study	Sample	Age	Method	Clinical Status	Medication Status	Findings	Brodman Area /Stereotaxic Coordinates
(Yang et al., 2009)	13 MDD 13 HC	16.0±1.5 15.8±1.5	3T fMRI Stop-signal task	Depressed	Unmedicated	Decreased response of sgACC associated with recovery at 12 weeks. Elevated activity of sgACC during task	BA 24, 25, 32 −12; 35; −5

Note: We have included studies implicating both BA24 and BA25 in this table. We consider BA24 to be sgACC and BA25 to be infralimbic cortex. Nevertheless, different nomenclatures have been used across research groups.

Abbreviations: ¹⁸F-FDG-PET=[¹⁸F]-fluorodeoxyglucose positron emission tomography; BZ=benzodiazepine; HC=healthy control; MDD=major depressive disorder; sgACC=subgenual anterior cingulate cortex; ROI=region of interest; VNS=vagal nerve stimulation.

Table 6

Endophenotype 5. Impaired Fronto-Limbic Connectivity in MDD.

Study	Sample	Medication Status	fMRI Task	Finding
(Siegle et al., 2002)	7 MDD 10 HC	No tricyclic AD	Positive, negative and neutral words	↓ connectivity between DLPFC and amygdala in response to negative words
(Anand et al., 2005b)	12 MDD 11 HC	Unmedicated	Positive, negative and neutral pictures	After 6 weeks treatment with sertraline, ↑ in ACC-limbic connectivity in the resting state and during exposure to neutral and positive but not negative pictures
(Anand et al., 2005a)	15 MDD 15 HC	Unmedicated	Positive, negative and neutral pictures	↓ connectivity between broader ACC and amygdala in both the resting state as well as during exposure to all pictures
(Johnstone et al., 2007)	21 MDD 18 HC	Unmedicated	Positive, negative and neutral pictures	Inverse relationship between left vIPFC and amygdala activation in HC but opposite effect in MDD. Conversely, greater connectivity between vmACC and amygdala in MDD.
(Siegle et al., 2007)	27 MDD 25 HC	Unmedicated 2+ weeks	Positive, negative and neutral words	↓ DLPFC and amygdala connectivity in response to negative words
(Chen et al., 2008)	19 MDD 19 HC	Unmedicated 4+ weeks	Recognition of sad faces	↓ connectivity between inferior and middle PFC and the amygdala during exposure to sad faces. Connectivity between right PFC, ACC and amygdala normalized by 8 weeks of treatment with fluoxetine.
(Matthews et al., 2008)	15 MDD 16 HC	Unmedicated 3+ months	Recognition of neutral, angry, happy and sad faces	↑ connectivity between amygdala and sgACC but ↓ functional connectivity between amygdala and supragenual ACC
(Dannlowski et al., 2009)	34 MDD 31 HC	Various AD	Neutral, angry, happy and sad faces	↓ amygdala-dACC/DLPFC connectivity in MDD, especially in high-activity MAO-A allele carriers

Note: dACC=dorsal anterior cingulate cortex; DLPFC=dorsolateral prefrontal cortex; HC=healthy control; MDD=major depressive disorder; MAO-A=monoamine oxidase; vIPFC=ventrolateral prefrontal cortex.

Table 7
Endophenotype 6. Altered 5-HT_{1A} Receptor Binding Potential in MDD.

Study	Sample	Age	% Difference M/F Ratio	% AD Drug Naive	Radioligand	Presynaptic	Postsynaptic
(Drevets et al., 1999)	12 MDD 8 HC	35.8±9.7 35.3±13.5	8	0	[carbonyl- ¹¹ C]WAY-100635	↓ raphe (27%)	↓ MTC (42%)
(Sargent et al., 2000)	15 unmedicated MDD 20 medicated MDD 18 HC	37.7±1.7 43.1±14.8 36.4±8.3	-6	47	[carbonyl- ¹¹ C]WAY-100635	↓ raphe (±20%)	↓MTC, OFC, dACC, VLPFC, DLPFC and insula in both MDD groups.
(Bhagwagar et al., 2004)	14 MDD 18 HC	48±14.9 43.2±13	0	0	[carbonyl- ¹¹ C]WAY-100635	NS	↓ broad areas of cortex (17%), including ACC, hippocampus, amygdala, frontomedial cortex
(Meltzer et al., 2004)	17 MDD 17 HC	71.4±5.9 70±6.7	58	47	[carbonyl- ¹¹ C]WAY-100635	↓ raphe (±38%)	NS
(Parsey et al., 2006a)	13 remitters 9 nonremitters 43 HC	39.9±10.4 42.9±14.9 38.2±15.0	46	36	[carbonyl- ¹¹ C]WAY-100635	NS	↑ non-remitters: ACC, hippocampus, DLPFC, VLPFC and other cortical regions
(Drevets et al., 2007)	16 MDD 8 HC	32±10 32±12	13	NR	[carbonyl- ¹¹ C]WAY-100635	↓ raphe (43%)	↓ MTC (26%)
(Hirvonen et al., 2008)	21 MDD 15 HC	40.1±9 32.6±7.7	-12	100	[carbonyl- ¹¹ C]WAY-100635	NS (↓)	↓ (9-25%) in diverse regions including amygdala, hippocampus, ACC, and mPFC
(Mickey et al., 2008)	14 MDD 17 HC	38±11 34±12	17	71	[carbonyl- ¹¹ C]WAY-100635	NS	NS
(Moses-Kolko et al., 2008)	9 PPD 7 HC	26.9±7.9 33.0±3.9	-100	78	[carbonyl- ¹¹ C]WAY-100635	NS (↓) (10%)	↓ (20-28%) sgACC, pgACC, MTC, OFC

Note: ACC=anterior cingulate cortex; DLPFC=dorsolateral prefrontal cortex; F=female; HC=healthy control; M=male; MDD=major depressive disorder; mPFC=medial prefrontal cortex; MTC=mesiotemporal cortex, NA=not applicable; NR=not reported; NS=not significant; OFC=orbital frontal cortex; pgACC=pregenual ACC; PPD=postpartum depression; sgACC=subgenual ACC; VLPFC=ventrolateral prefrontal cortex.

Endophenotype 7. Altered Serotonin-Transporter Binding Potential in MDD.

Table 8

Study	Sample	Age	Medication Status	Radioligand	Finding
(Ichimiya et al., 2002)	7 MDD 21 HC	44.1±13.5 42.3±14.5	Unmedicated 6+ weeks	[¹¹ C](+)-McN5652	↑ BP in thalamus (23%) but not the midbrain
(Meyer et al., 2004)	20 MDD 20 HC	35±11 35±11	Unmedicated 3+ months	[¹¹ C]DASB	NS
(Reivich et al., 2004)	4 MDD 4 HC	22–56 23–59	Unmedicated 5 elimination ½ lives of drug	[¹¹ C](+)-McN5652	↑ BP left frontal cortex, right cingulate cortex
(Parsey et al., 2006b)	25 MDD 43 HC	38.0±13.4 38.8±15.9	Unmedicated 2+ weeks	[¹¹ C](+)-McN5652	↓ BP in amygdala (20%) and midbrain (20%) in AD-native MDD sample
(Bhagwagar et al., 2007)	24 remitted MDD 24 HC	38.9±11.9 35.7±9.8	Unmedicated 23+ months	[¹¹ C]DASB	NS
(Cannon et al., 2007)	18 MDD 34 HC	35±8.9 33±8.4	Unmedicated 3+ weeks	[¹¹ C]DASB	↑ BP in thalamus (27%), insula (15%), anteroventral striatum (12%), pgACC (16%), PAG (22%)
(Miller et al., 2008)	7 MDD 12 MDD nonremitter 41 HC	38.9±11.4 41.7±15.1 39.0±16.1	Unmedicated 2+ weeks	[¹¹ C](+)-McN5652	↓ BP in non-remitters in midbrain, amygdala and ACC
(Reimold et al., 2008)	10 MDD 19 HC	48.3±9.7 44.2±10.1	Unmedicated 5 elimination ½ lives of drug	[¹¹ C]DASB	↓ BP in thalamus, midbrain and amygdala
(Frokjaer et al., 2009)	9 HR (6F) 11 LR (7F)	32.2±4.2 32.4±5.0	naive	[¹¹ C]DASB	↓ BP in DLPFC (35%) and trend towards significance in ACC (15%) in HR

Note: ACC=anterior cingulate; BP=binding potential; HC=healthy control; HR=high risk; MDD=major depressive disorder; NS=not significant; PAG=periaqueductal gray.