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Imaging genetics of mood disorders

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Abstract

Mood disorders are highly heritable and have been linked to brain regions of emotion processing. Over the past few years, an enormous amount of imaging genetics studies has demonstrated the impact of risk genes on brain regions and systems of emotion processing *in vivo* in healthy subjects as well as in mood disorder patients. While sufficient evidence already exists for several monaminergic genes as well as for a few nonmonoaminergic genes, such as brain-derived neurotrophic factor (*BDNF*) in healthy subjects, many others only have been investigated in single studies so far. Apart from these studies, the present review also covers imaging genetics studies applying more complex genetic disease models of mood disorders, such as epistasis and gene–environment interactions, and their impact on brain systems of emotion processing. This review attempts to provide a comprehensive overview of the rapidly growing field of imaging genetics studies in mood disorder research.

Keywords

Imaging genetics; Mood disorders; Major depressive disorder; Emotion; Amygdala; Anterior cingulate cortex; Ventromedial prefrontal cortex; Orbitofrontal cortex; Hippocampus; Functional connectivity; Genetics; Phenotype–genotype

Introduction

Depression is among the four leading causes of disease burden throughout the world and is associated with medical morbidity and mortality across the lifespan (Wong and Licinio, 2001). Since depression is highly heritable (Wong and Licinio, 2001), there has been intense interest in candidate genes related to this behavioral phenotype. As the genetic architecture of depression is complex and genes are not directly encoding for psychiatric diagnoses or psychiatric symptoms, scientific progress was hindered by weak or contradictory results (Meyer-Lindenberg and Weinberger, 2006). The emergence of imaging genetics (Hariri and Weinberger, 2003) as a strategy for mapping neural phenotypes as a function of genotype

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Appendix A. Supplementary data

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has fostered new enthusiasm in depression research, because this approach allows for assessing the neural impact of candidate genes *in vivo* and thus provides for a new level of evidence. Although imaging genetics was initially proposed as a research tool (Hariri and Weinberger, 2003), it has by now evolved into a new field of research, which is reflected in a dramatic increase of publications over the past few years. Efforts thus undertaken address several questions, such as neural effects of single genes, gene–gene (epistasis) and gene–environment interactions as well as the impact of chromosomal aberration disorders and small deletion syndromes on systems neurobiology.

Despite the genetic complexity of mood disorders, imaging genetics studies corroborate the assumption that effects of risk genes are converging at brain systems of emotion processing (Canli et al., 2009) comprising regions involved in the identification of stimulus-related emotional significance as well as the initiation and regulation of affective states, emotional response, and subsequent behavior (Phillips et al., 2003a,b). Furthermore, they inherently point toward the exploitation of those quantitative imaging traits (QTs) that are thought to more directly index biology than behavioral phenotypes of depression, and hence will likely be helpful in shaping mood disorder diagnostics (Meyer-Lindenberg and Weinberger, 2006).

The growing evidence of gene effects on brain systems of emotion processing is accompanied by a more thorough understanding of the anatomical interconnections between regions of emotion processing (Price and Drevets, 2009), highlighting the crucial role of the orbital and medial prefrontal cortex (OMPFC) for mood disorders. The OMPFC comprises two major networks (Price and Drevets, 2009): (1) the orbital network, which is more sensory-related and acts as a system for integrating multi-modal stimuli as well as a system for assessing the value of those stimuli, is therefore connected to olfactory, gustatory, visual, and somatic sensory cortical areas; (2) the medial prefrontal network, which is a more output-related system that can modulate visceral function in relation to emotion as well as several other factors, is connected to important structures in the context of mood disorders, such as the amygdala, cingulate cortex and hippocampus.

Given the emerging genetic and anatomical knowledge of mood disorders, this review attempts to provide a comprehensive summary of available imaging genetics studies including reports on single genes (see Tables 1 and 2, and Fig. 1) as well as gene–gene and gene–environment interactions with regard to key structures being involved in emotion processing within the OMPFC networks. Only studies available in PubMed have been considered and following inclusion criteria have been applied: (1) studies have been conducted in adult samples of healthy subjects or mood disorder patients, (2) genes have been linked to MDD by at least one association study, and (3) only functional and structural MRI imaging genetics studies have been eligible for inclusion. Age and imaging methods restrictions have been chosen, because those topics are extensively elaborated within this special issue elsewhere (Durston, 2010; Willeit and Praschak-Rieder, 2010).

Key regions of mood disorders

Amygdala—The amygdala is a complex neural hub critically involved in both normal behavior and mental illness (LeDoux, 2007). Its almond-shaped body encompasses several nuclei receiving inputs from cortical and subcortical regions, such as the hippocampus,

sensory thalamus, sensory and association cortices, sensory brainstem, olfactory regions as well as medial prefrontal cortex. Two nuclei – the central and the basal nucleus – act as effector organs and project to a variety of brain regions, such as the ventral striatum involved in controlling actions (running to safety) and brainstem areas critical for controlling emotions (freezing) (LeDoux, 2007). In addition, other regions such as prefrontal cortical as well as association cortices are important projection targets. On a behavioral level, the amygdala has been predominantly associated with fear conditioning and reaction, but evidence for other behavioral correlates, such as an important role in reward processing and the generation of emotional states associated with aggressive, maternal, sexual and ingestive behaviors, exists as well (Costafreda et al., 2008; LeDoux, 2007; Sergerie et al., 2008). Although most concepts evolved from animal experiments, human imaging studies support their validity in humans (Stein et al., 2007).

Due to its prominent role in emotion processing, the amygdala has also been implicated in pathological states such as major depressive disorder (MDD) (Phillips et al., 2003b) along with anxiety disorders (Domschke and Dannlowski, 2010). Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies predominantly report increased amygdala activation in patients with acute MDD (Savitz and Drevets, 2009). With regard to volumetric alterations of the amygdala in MDD, studies are contradictory; it would be thus premature to draw final conclusions (Drevets et al., 2008a; Hamilton et al., 2008).

As MDD is frequently treated with drugs selectively inhibiting serotonin (5-HT) uptake (SSRIs), genetic variation of the serotonin transporter (5-HTT) and its coding gene (*SLC6A4*) has become a focal theme for the neuroscientific community. Since a variable number of tandem repeats (VNTR) polymorphism in the promoter region (5-HTTLPR) of *SLC6A4* has been related to neuroticism (Lesch et al., 1996) and is thought to be a risk factor of MDD (Schinka et al., 2004; Sen et al., 2004), a whole area of study of 5-HTTLPR in the context of emotion processing and MDD (Canli et al., 2009) has emerged. Further enthusiasm regarding 5-HTTLPR stems from a study of MDD patients (Caspi et al., 2003). This study was able to demonstrate that the lower-expressing S allele, which is thought to be the risk allele for MDD, becomes disease-relevant in the context of environmental adversity in a manner similar to animal studies (Barr et al., 2004). However, those initially enthusiastic findings linking 5-HTTLPR to neuroticism as well as underlining the importance of environmental interactions have been questioned by recent meta-analyses (Flint and Munafo, 2008; Munafo et al., 2009a,b; Risch et al., 2009). Such contradictory study results highlight the difficulties in unraveling genetically complex disorders that have been attributed to clinical, neurobiological and genetic heterogeneity as well as the problems regarding the sample size necessary to detect such effects (Flint and Munafo, 2008). Specifically, variable penetrance, epistasis, imprinting, epigenetics, pleiotropy (Murphy and Lesch, 2008) as well as further functional genetic variability in *SLC6A4*, such as a single nucleotide polymorphism (A–G substitution, rs25531) within the L allele (Hu et al., 2006) and a VNTR in the second intron (Hranilovic et al., 2004), are probable other contributors toward this inconsistency.

Despite these divergent findings in genetic studies attempting to link *SLC6A4* function to clinical phenotypes, imaging genetics studies investigating the impact of 5-HTTLPR on

amygdala reactivity in normal subjects exhibit a more homogeneous picture (Brown and Hariri, 2006; Munafo et al., 2008). With the exception of one study (Surguladze et al., 2008), numerous studies suggest that S allele carriers of European ancestry show exaggerated amygdala activation in the presence of fearful or negatively valenced stimuli as compared with subjects with L/L genotype (Bertolino et al., 2005; Brown and Hariri, 2006; Canli et al., 2005b; Dannlowski et al., 2010; Dannlowski et al., 2008; Friedel et al., 2009; Hariri et al., 2005, 2002; Heinz et al., 2005; Perlis et al., 2008; Pezawas et al., 2005; Smolka et al., 2007; Williams et al., 2009), a finding that does not necessarily apply to other ethnicities (Lee and Ham, 2008b). It is noteworthy that this difference might also exist during resting state (Canli et al., 2006; Rao et al., 2007), and hence baseline periods may have an impact on those results (Canli et al., 2005b; Heinz et al., 2007). Those findings are in accordance with animal studies showing high levels of 5-HT that are accompanied by blood-level oxygen-dependent (BOLD) signal increases (Preece et al., 2009), which is assumed to apply to adult S allele carriers. Only a few studies so far have investigated the effects of 5-HTTLPR on brain development in humans, although 5-HT is one of the best-studied brain developmental factors available today (Gaspar et al., 2003). Three voxel-based morphometry (VBM) studies in large samples of healthy subjects indicate that S allele carrier status implies a smaller relative amygdala volume (Frodl et al., 2008a; Pezawas et al., 2005; Pezawas et al., 2008), whereas two studies investigating smaller samples either reported the opposite (Scherk et al., 2009) or did not detect any genetic impact on amygdala volume (Canli et al., 2005b). With regard to studies of 5-HTTLPR effects on amygdala function or development in acute MDD, results are sparse, and further replications are needed. Authors have reported S-allele-associated increases in amygdala activation (Dannlowski et al., 2008, 2007; Friedel et al., 2009) as well as, counterintuitively, increases of amygdala volume in a small-scale study of bipolar patients (Scherk et al., 2009).

Overwhelming evidence provided by imaging genetics studies today argues in favor of a specific role of *SLC6A4* in amygdala regulation and development in healthy subjects. Thus it is not surprising that other genes involved in clearing 5-HT from the synaptic cleft have been identified as significant contributors. One example is the X-chromosome linked monoamine oxidase A gene (*MAOA*). *MAOA* is expressed in the outer mitochondrial membrane of monoaminergic neurons and is a key enzyme in the degradation of 5-HT. A functional VNTR polymorphism in the promoter region of the *MAOA* gene has been found to impact gene expression by genetic variability of its highly active MAOA-H and less active MAOA-L allele (Sabol et al., 1998). Similar to 5-HTTLPR, this polymorphism is also believed to interact with environmental factors in order to contribute to the formation of complex behaviors, such as antisocial behavior, which is less likely to occur in maltreated children with MAOA-H allele status (Caspi et al., 2002). *MAOA* has frequently been related to aggressive and impulsive behavior; however, studies have also singled out an association with MDD (Schulze et al., 2000; Yu et al., 2005). Regarding amygdala regulation, one study recorded increased amygdala reactivity and decreased amygdala volume in healthy Caucasian MAOA-L carriers (Meyer-Lindenberg et al., 2006), a finding that was replicated in an Asian sample (Lee and Ham, 2008a). Similarly, it has been suggested that the *MAOB* gene is related to amygdala volume (Good et al., 2003). This assumption has been made in connection with X-monosomal Turner syndrome patients exhibiting functional (Skuse et al.,

2005) and volumetric (Cutter et al., 2006; Good et al., 2003; Kesler et al., 2004) amygdala alterations, which can also be found in Turner patients with partial X-chromosome deletions only lacking the genetic locus Xp11.3 containing *MAOB* (Good et al., 2003). Complementary findings indicating X-chromosomal effects on amygdala volume exist for Klinefelter syndrome (Patwardhan et al., 2002; Shen et al., 2004).

So far we have discussed genes impacting amygdala function and structure that are critically involved in the elimination of 5-HT, such as *SLC6A4* and *MAOA*. In contrast, the tryptophan hydroxylase 2 gene (*TPH2*) is critical for the synthesis of 5-HT, and several functional variants with an impact on *TPH2* expression have been identified (Haghighi et al., 2008). The T allele of G(−703)T TPH2 (rs4570625) has been associated with increased amygdala reactivity in two studies of healthy subjects (Brown et al., 2005; Canli et al., 2005a), whereas the opposite was ascertained in an Asian sample, once more suggesting the significance of ethnic background (Lee and Ham, 2008b).

The importance of the serotonergic system in the context of amygdala activation is further highlighted by imaging genetics studies, suggesting an important role of 5-HT receptor genes, such as the 5-HT_{1A} auto-receptor gene (*HTR1A*) crucially involved in the regulation of 5-HT signaling (Lemonde et al., 2003). G allele carriers of C(−1019)G *HTR1A* (rs6295), a functional SNP in the promoter region of HTR1A, have been associated with diminished transcriptional repression, leading to increased 5-HT_{1A} density and decreased amygdala reactivity in healthy subjects as compared with the C/C genotype (Fakra et al., 2009), a finding that has not been replicated in a Korean sample (Lee and Ham, 2008b). Similarly, a PET study reported an inverse correlation between 5-HT_{1A} auto-receptor binding in the dorsal raphe nuclei and amygdala reactivity (Fisher et al., 2006). With regard to MDD, increased amygdala activation has been identified in G allele carriers (Dannlowski et al., 2007). Some evidence exists for other genes regulating postsynaptic 5-HT receptor expression, such as *HTR2A* and *HTR3A*. A promoter polymorphism (rs6311) within the 5-HT_{2A} receptor gene (*HTR2A*) has been linked to aggressive behavior (Giegling et al., 2006) as well as to increased amygdala activity in healthy subjects (Lee and Ham, 2008b). Furthermore, C(178)T HTR3A of the 5-HT_{3A} receptor gene (*HTR3A*) has been related to harm avoidance and altered amygdala reactivity in healthy subjects (Iidaka et al., 2005).

In addition to 5-HT, dopamine (DA) has been implicated in depression since anhedonia is a prominent clinical symptom of depression, and euphoria can be induced by dopaminergic drugs. Due to a lack of cortical DA transporters, the monoamine-degrading enzyme catechol-*O*-methyltransferase (COMT) is specifically important for DA catabolism and has been linked to a variety of psychiatric disorders including MDD (Craddock et al., 2006). The Met allele of Val158Met COMT (rs4680) has been associated with significantly lower enzymatic activity than the Val allele (Chen et al., 2004) putatively affecting tonic and phasic dopamine level relations (Bilder et al., 2004). Although several other variants have been shown to profoundly affect COMT expression (Nackley et al., 2006), with respect to imaging genetics studies Val158Met COMT has been shown to be more informative than haplotype analysis likely due to a reduction of complexity (Puls et al., 2009). With regard to Val158Met COMT effects on amygdala volume and function in healthy subjects, results suggest Met-allele-associated volume increase (Cerasa et al., 2008b; Ehrlich et al., 2010;

Taylor et al., 2007) and amygdala hyperreactivity (Smolka et al., 2007; Smolka et al., 2005; Williams et al., 2010), while a minority of studies reported contrary (Kempton et al., 2009) or even lacking effects (Drabant et al., 2006), which might in part be explained by sexual dimorphism (Harrison and Tunbridge, 2008).

It is noteworthy that 5-HT might impact *BDNF* expression via induction of the cyclic adenosine monophosphate response element-binding protein gene (*CREB1*), which by itself has been related to altered amygdala activation in a single study (Perlis et al., 2008). This relationship between monoamines and neurotrophins has resulted in the controversially discussed (Groves, 2007) neuroplasticity hypothesis of depression (Castren, 2005), which pushed BDNF into the spotlight of mood disorder research (Berton et al., 2006; Krishnan et al., 2007). Cultured neurons transfected with Met BDNF of Val66Met BDNF (rs6265), which has been related to anxious behavior in animal models and antidepressant drug resistance (Chen et al., 2006), show reduced depolarization-induced secretion and fail to localize BDNF to secretory granules and dendritic processes (Egan et al., 2003). In accordance with these molecular mechanisms, the Met allele has been related to a smaller amygdala volume (Montag et al., 2009) possibly dependent on aging effects (Sublette et al., 2008); however, most studies have been unable to detect effects on amygdala volume (Frodl et al., 2007; Matsuo et al., 2009; Nemoto et al., 2006; Pezawas et al., 2004; Schofield et al., 2009). Counterintuitively, the Val allele has mostly been associated with increased trait anxiety (Lang et al., 2005; Sen et al., 2003; Willis-Owen et al., 2005), and similarly to morphological studies, activation studies are inconclusive, with authors reporting increased amygdala reactivity associated with the Val allele (Gasic et al., 2009) or the Met allele (Montag et al., 2008), while most studies have been unable to produce any relevant proof (Egan et al., 2003; Hariri et al., 2003; Hashimoto et al., 2008; Schofield et al., 2009).

Most imaging genetics studies have hitherto been conducted within the framework of “classical” depression concepts, such as the monoamine and neuroplasticity hypothesis; however, many more gene candidates have been suggested as important for MDD and hence likely for amygdala regulation as well (Kato, 2007). Several imaging genetics studies have focused on these candidates, such as C (−385)A FAAH (rs324420) of the fatty acid amid hydrolase gene (*FAAH*), which plays a role in the catabolism of endogenous ligands of the cannabinoid receptor and has been shown to alter amygdala reactivity in healthy subjects (Hariri et al., 2009). Analogous results were produced by a study investigating the cannabinoid receptor 1 gene (*CNR1*) in MDD (Domschke et al., 2008). Another candidate, is, rs333229 of the choline transporter gene 1 (*SLC5A7*), that indicates increased amygdala reactivity and has been associated with depression and autonomic variability in heart rate (Neumann et al., 2006). Furthermore, a microsatellite 312 bp variant (RS1) near the promoter region of the arginine vasopressin receptor 1A gene (*AVPR1A*) was related to decreased harm avoidance and increased amygdala reactivity in healthy subjects (Meyer-Lindenberg et al., 2008). Another neuropeptide – neuropeptide Y (NPY), which is released by stress – presented robust amygdala activation and increased trait anxiety via lower haplotype-driven *NPY* expression in healthy subjects (Cotton et al., 2009; Zhou et al., 2008). Moreover, markers of the gene encoding regulator of G protein signaling 2 (*RGS2*) – linked to anxious behavior in rodents – have been associated with introversion and increased

amygdala activation (Smoller et al., 2008). A(10398)G mitochondrial DNA (mtDNA), which is important for calcium regulation in neurons and probably mental illness, has been related to volumetric alterations within the amygdala (Yamasue et al., 2008). Finally, variation in two loci of D-amino acid oxidase activator G72 (*DAOA*), a gene associated with schizophrenia and bipolar disorder as well as MDD and neuroticism (Rietschel et al., 2008), has been linked to alterations in amygdala gray matter density in patients with bipolar disorder (Zuliani et al., 2009).

Advances in genetics highlight the importance of gene–gene and gene–environment interactions for understanding the complex depression phenotype. Recently, imaging genetics studies have been launched with the aim of applying such complex models derived from *in vitro* or animal studies to humans. Epistasis – gene–gene interaction – in particular reflects this sort of complex relationship. Animals genetically engineered to be hypomorphic at *BDNF* and *SLC6A4* have shown epistatic effects (Murphy et al., 2003), a finding supported by a genetically humanized mouse model demonstrating that anxiety behavior in animals carrying Met BDNF alleles is unresponsive to SSRIs and can be viewed as a pharmacological analog of 5-HTTLPR S alleles (Krishnan et al., 2007). Recently, an imaging genetics study investigating epistasis between 5-HTTLPR and Val66-Met BDNF in healthy subjects reported that the Met allele reduces the volumetric effect of the S allele on amygdala volume (Pezawas et al., 2008). With regard to amygdala activation, additive effects of the Met allele of Val158Met COMT and S/L_G alleles of 5-HTTLPR and rs25531 (Smolka et al., 2007) as well as the T allele of G(−703)T TPH2 and the S allele of 5-HTTLPR (Canli et al., 2008) were identified in healthy subjects, whereas additive effects of C(−1019)G HTR1A, 5-HTTLPR and rs25531 have been reported in a sample of MDD patients (Dannlowski et al., 2007). Furthermore, gene–environment interactions impacting amygdala activity have been demonstrated between 5-HTTLPR (Canli et al., 2006) as well as Val66Met BDNF (Gatt et al., 2009) and life stress.

Cingulate cortex—The cingulate cortex (CC), a belt-shaped cortical area wrapped around the corpus callosum, is of critical importance for both emotion processing and depression models and has become an outstanding example of the powerful convergence of brain imaging and numerous other neuroscientific disciplines (Vogt, 2009). Based on structural, circuitry-related, imaging and pharmacological studies, the CC can be split up into four distinct anatomical regions: anterior cingulate (ACC, primary limbic cortex), midcingulate (MCC, premotor limbic cortex), posterior cingulate (PCC, limbic association cortex) and retrosplenial cortex (RCC, memory access) (Palomero-Gallagher et al., 2009). One of the primary reasons for differentiating between ACC and MCC lies in the profound connections with the amygdala, which is a unique trait of the ACC and highlights the specific importance of this region for emotion processing (Vogt, 2009). Furthermore, these four regions are subdivided into eight subregions encompassing several cytoarchitectonic areas frequently reflected in imaging studies (Vogt, 2009). With regard to emotion processing, both ACC regions – the subgenual ACC (sACC) implicated in autonomic control and the perigenual ACC (pACC) implicated in emotional and autonomic integration – as well as the anterior MCC (aMCC) implicated in approach/avoidance processing are of primary importance (Vogt, 2009). It is noteworthy that the sACC, the rostral parts of the pACC as well as the

medial orbitofrontal cortex (mOFC) are sometimes also referred to as the ventromedial prefrontal cortex (vmPFC), a large region encompassing the ventral area of the medial prefrontal cortex primarily associated with decision-making (Koenigs and Grafman, 2009).

Since the first reports of increased metabolism (Drevets et al., 1997) and decreased tissue volume in the sACC of MDD patients (Ongur et al., 1998), a tremendous amount of clinical research has been dedicated to this field (Drevets et al., 2008b). The sACC, which exhibits the highest 5-HTT and 5-HT_{1A} density of the human cortex (Gaspar et al., 2003), has been related to the processing of negative mood, treatment response to SSRIs, deep brain stimulation, electro-convulsive therapy as well as cognitive behavioral therapy (Drevets et al., 2008b) and thus qualifies as a primary research target for MDD (Ressler and Mayberg, 2007).

Abnormalities in the sACC have frequently been reported to be more pronounced in subjects with a family history of mood disorders (Boes et al., 2008; Hajek et al., 2008; McDonald et al., 2004; Ongur et al., 1998), suggesting a profound genetic background for the characteristics thus observed. Given the high expression of 5-HTT within the ACC, studies investigating 5-HTTLPR in healthy controls reported S-allele-associated increases of basal metabolism (Graff-Guerrero et al., 2005) and blood-flow in response to visceral pain (Fukudo et al., 2009) as well as decreases of cerebral blood-flow under resting-state conditions (Rao et al., 2007). Despite the lack of any fMRI paradigm robustly engaging the ACC and specifically the sACC, several studies showed increased activation in S allele carriers of 5-HTTLPR (Dannlowski et al., 2008; Friedel et al., 2009; Passamonti et al., 2008; Roiser et al., 2009; Smolka et al., 2007), whereas only one study reported opposing effects (Shah et al., 2009). Hence, MRI studies primarily focused on the impact of *SLC6A4* on ACC anatomy, as suggested by the well-known and important role of 5-HT during brain development (Gaspar et al., 2003). A structural imaging study in a large sample of healthy subjects revealed S-allele-moderated gray matter volume loss in the ACC, exhibiting maximum effects within the sACC (Pezawas et al., 2005), similarly to other human studies recording S-allele-associated volume loss in the ACC or sACC (Canli et al., 2005b; Frodl et al., 2008a) as well as a non-human primate study with a rhesus macaque orthologue of 5-HTTLPR (rh5-HTTLPR) (Jedema et al., 2010). Despite current evidence in healthy humans and non-human primates, patient studies are as yet inconclusive, with authors reporting S-allele-driven increases of ACC activation in mood disorder patients under (Benedetti et al., 2007) and without (Dannlowski et al., 2008) treatment conditions, while others found decreased activation (Shah et al., 2009) or have been unable to detect any difference (Friedel et al., 2009; Frodl et al., 2008a). In addition, other monoaminergic genetic variants, such as the MAOA-L allele of *MAOA*, have been related to volume loss (Meyer-Lindenberg et al., 2006) as well as decreased activation in fMRI studies (Meyer-Lindenberg et al., 2006; Passamonti et al., 2008) in the ACC, and specifically the sACC in healthy controls. However, negative or opposing volumetric findings exist in underpowered (Cerasa et al., 2008a) or gender-restricted non-Caucasian (Lee and Ham, 2008a) samples. Furthermore, studies suggest monoaminergic genetic impact of Val158Met COMT with decreased activation in Val allele carriers (Smolka et al., 2007; Williams et al., 2010), whereas in a small sample the Val allele has been associated with a failure of deactivation (Pomarol-

Clotet et al., 2010). In addition, the C allele of C(178)T HTR3A of the 5-HT_{3A} receptor gene (*HTR3A*) has been found to increase ACC activation (Iidaka et al., 2005).

In addition, a few other human imaging studies have reported nonmonoaminergic genetic effects on ACC development and function. One study showed a volume decrease of the ACC in Met allele carriers of Val66Met BDNF in a sample of healthy subjects and bipolar patients (Matsuo et al., 2009), while another study reported this type of volume decrease in Japanese Cys allele carriers of Ser704Cys (rs821616) of the disrupted-in-schizophrenia 1 gene (*DISC1*) (Hashimoto et al., 2006), which has been linked to MDD as well as schizophrenia by various markers (Hashimoto et al., 2006; Schosser et al., 2010). Further genetic variants of genes, such as *SLC5A7* (Neumann et al., 2006), TREK1 (*KCNK2*) (Dillon et al., 2010), and Period 3 (*PER3*) (Vandewalle et al., 2009), have been found to impact on cingulate activation in healthy controls; the same holds for *CLOCK* (Benedetti et al., 2008) in patients. Finally, genes of the Wnt signaling pathway, which regulate aspects of neurodevelopment and neuroplasticity, have been shown to be associated with volume alterations in the ACC (Inkster et al., 2010).

Similar to the amygdala, epistatic effects have also been investigated in the ACC. One author reported that Val66Met BDNF interacts epistatically with 5-HTTLPR, presumably affecting the development and integrity of this neural system (Pezawas et al., 2008). Specifically, this study found that the Met BDNF allele protects against the adverse developmental effects of 5-HTTLPR S alleles, which the ancestral Val BDNF allele potentiates. With respect to activation studies, one author reported that MAOA-H leads to an increase of S-allele-associated activity in the ACC (Passamonti et al., 2008), whereas another author detected additive effects of 5-HTTLPR and Val158Met COMT on ACC, MCC and PCC (Smolka et al., 2007). Finally, gene–environment interactions have been identified for Val66Met BDNF, but not for 5-HTTLPR (Gatt et al., 2009).

Orbitofrontal cortex—The OFC, which receives numerous sensory inputs and is heavily interconnected with the amygdala, ventral striatum and ACC, mirrors reward or affective values of primary reinforcers and integrates representations of other stimuli in order to estimate expected reward, therefore acting as a key structure in emotion processing and decision-making (Rolls and Grabenhorst, 2008). Interestingly, the OFC and ACC have a lot of similarities, as both structures are implicated in reinforcement-guided decision-making, emotion and social behavior, share connections to the ventral striatum and the amygdala, and might therefore be involved in similar tasks (Rushworth et al., 2007). Similar to the ACC in mood disorder patients, volume loss and metabolic increases have also been reported for the medial and lateral posterior OFC (Drevets et al., 2008a).

Genetic impact of monoaminergic genes has also been shown for 5-HTTLPR, reporting S-allele-induced increases of OFC perfusion by visceral pain induction (Fukudo et al., 2009) as well as S-allele-induced volume loss (Canli et al., 2005b). Further evidence stems from *MAOA*, demonstrating an increase of OFC volume in healthy male MAOA-L allele carriers and a decrease of activation of the lateral OFC in both genders (Meyer-Lindenberg et al., 2006), similarly to volumetric (Cerasa et al., 2008a) and functional (Passamonti et al., 2008) replication studies. By the same token, it has been suggested by studies in Turner syndrome

patients (Cutter et al., 2006; Good et al., 2003) that the *MAOB* gene is related to OFC volume. With respect to Val158Met COMT, increased OFC activation (Bishop et al., 2006; Pomarol-Clotet et al., 2010) and volume (Cerasa et al., 2008b) have been reported for the Val allele, whereas one functional study reported the opposite (Dreher et al., 2009). Taq1A (rs1800497), a D_2-receptor-linked polymorphism located in ankyrin repeat and kinase domain containing 1 gene (*ANKK1*), has demonstrated diminished lateral OFC activation in healthy carriers of the A1 allele (Cohen et al., 2005; Jocham et al., 2009), a region associated with increased response to aversive stimuli in the Val/Val genotype of Val66Met BDNF (Gasic et al., 2009). Furthermore, an increased OFC response has been found in healthy carriers of the low risk haplotype of TREK1 (*KCNK2*) (Dillon et al., 2010).

Epistasis of 5-HTTLPR and Val66Met BDNF has also been shown for the OFC, which was related to a significant BDNF effect in S allele carriers, leading to OFC volume decrease in the presence of a Met allele for a sample of healthy individuals at high risk for alcohol dependence (Hill et al., 2009). Another study investigated interactions between Val158Met COMT and a VNTR polymorphism in the dopamine transporter 1 gene (*SLC6A3*), which detected maximum OFC activation in healthy subjects with 9-repeat DAT1 allele and COMT Met/Met genotype, a finding putatively related to high dopamine levels (Dillon et al., 2010; Dreher et al., 2009).

Hippocampus—Located in the medial temporal lobe, the ‘seahorse’-shaped hippocampus is a macroscopic structure that is composed of distinct histological subregions and is interconnected with the entorhinal cortex, the parahippocampal cortex and the perirhinal cortex, receiving input from the ends of many cortical processing streams, such as the cerebral association cortex including visual and auditory temporal lobe association cortical areas, the prefrontal cortex and the parietal cortex. Moreover, the hippocampus receives inputs from the amygdala and orbitofrontal cortex, which suggests a specific role in emotion processing (Rolls, 2007). With regard to cognitive functions, the hippocampus has been predominantly associated with explicit memory functions (Burwell, 2000; Rolls and Kesner, 2006) as well as with stress responsivity (Lopez et al., 1999). Similar to the abovementioned regions, the hippocampus is also a key region in mood disorder research (Phillips et al., 2003a,b), since hippocampal volume loss has frequently been reported in MDD and can be reversed with antidepressant drug therapy in animal models (Kasper and McEwen, 2008). As MDD development has been clinically related to stress exposure and the hippocampus is among the brain regions most sensitive to the deleterious effects of stress (McEwen, 2001), extensive work has focused on the interplay between neural stress response and hippocampal function and development (de Kloet et al., 2005).

Although monoamines exert an impact on adult hippocampal neurogenesis (Lledo et al., 2006), only a few authors reported an increase of hippocampal activation (Smolka et al., 2007) or blood-flow (Fukudo et al., 2009) as well as volume loss (Frodl et al., 2008a) associated with the S allele of 5-HTTLPR, while the vast majority of studies investigating 5-HTTLPR neglected alterations in the hippocampus or reported negative results in healthy subjects (Frodl et al., 2004, 2008b). Similarly, little is known about 5-HTTLPR effects in MDD patients, and, counterintuitively, reports showing L-allele-associated hippocampal volume loss exist (Frodl et al., 2008a,b, 2004). However, addressing the likely relationship

between 5-HTTLPR and hippocampal aging one study comparing early with late-onset depression found an L-allele-driven volume reduction only in the late-onset group (Taylor et al., 2005), whereas another study reported lacking effects (Hickie et al., 2007). With regard to *MAOA*, two studies demonstrated increased hippocampal activation in healthy MAOA-L carriers (Lee and Ham, 2008a; Meyer-Lindenberg et al., 2006). Furthermore, studies investigating Val158Met COMT effects in healthy subjects have shown Val-allele-associated decreases in hippocampal volume (Cerasa et al., 2008b; Ehrlich et al., this issue; Honea et al., 2009; Taylor et al., 2007) and activation (Drabant et al., 2006; Krach et al., this issue; Smolka et al., 2007; Smolka et al., 2005); the latter bears similarities to several studies of prefrontal regions supporting the "worrier/warrior" hypothesis of Val158Met COMT (Mier et al., 2009). However, morphological alterations could not be replicated in healthy Japanese (Ohnishi et al., 2006). In addition, one author demonstrated that healthy Tyr carriers of His452Tyr (rs6314) within the 5-HT_{2A} receptor gene (*HTR2A*) exhibit smaller hippocampal volumes (Filippini et al., 2006).

However, the major bulk of evidence regarding hippocampal development and function in imaging genetics studies is available for *BDNF*, which was shown to modulate hippocampal plasticity and hippocampal-dependent memory and learning (Egan et al., 2003) and is considered being related to hippocampal stress sensitivity as well as the emergence of mood disorders (Berton et al., 2006). Healthy carriers of the defective Met allele of Val66Met BDNF have been associated with decreased hippocampal volume (Bueller et al., 2006; Chepenik et al., 2009; Frodl et al., 2007; Matsuo et al., 2009; Montag et al., 2009; Nemoto et al., 2006; Pezawas et al., 2004; Schofield et al., 2009; Szeszko et al., 2005) and neuroticism-dependent effects (Joffe et al., 2009), whereas only a minority of studies reported lacking effects (Jessen et al., 2009; Koolschijn et al., in press). Functional studies in healthy subjects demonstrating the impact of Val66Met BDNF on hippocampal activation found an association of the Val allele with increased hippocampal activity (Hariri et al., 2003; Hashimoto et al., 2008), while others presented contrary results (Egan et al., 2003; Schofield et al., 2009). With regard to patient studies, hippocampal volume reduction has also been reported for Met carriers, independent of clinical diagnosis (Chepenik et al., 2009; Frodl et al., 2007), whereas one author was unable to replicate those findings (Jessen et al., 2009).

Besides BDNF, several other genes have been related to hippocampal alterations in the context of mood disorders. Genetic variation (Ser704Cys) in *DISC1* exhibited increased hippocampal response in Ser allele carriers (Callicott et al., 2005; Di Giorgio et al., 2008), whereas, with regard to morphology, studies are inconclusive (Callicott et al., 2005; Di Giorgio et al., 2008; Hashimoto et al., 2006). Another genetic variation (rs58575285) in the ionotropic kainate 4 glutamate receptor gene (*GRIK4*), which has been associated with bipolar disorder, demonstrated increased hippocampal activation in healthy participants carrying the Del allele (Whalley et al., 2009a,b). Similar findings have been reported by studies investigating *NPY* (Zhou et al., 2008), *PER3* (Vandewalle et al., 2009), and the neurotrophin receptor 3 gene (*NTRK3*) (Otnaess et al., 2009). Researchers have further demonstrated that a genetic variant (rs6438552) in *GSK3B* (Inkster et al., 2009) as well as other Wnt pathway-related genes (Inkster et al., this issue) impact on hippocampal volume in MDD patients, but not in healthy controls. Furthermore, two genetic variants (rs833070,

rs2146323) in the vascular endothelial growth factor gene (*VEGF*), which is of importance for adult hippocampal neurogenesis, have revealed some morphometric impact (Blumberg et al., 2008). Finally, genetic alteration in *DAOA* has been linked to altered activation in the parahippocampal gyrus (Jansen et al., 2009) and hippocampus (Goldberg et al., 2006) in healthy subjects.

Reports on hippocampal alterations resulting from epistatic effects of mood disorder genes are limited. Two studies suggest epistatic effects of Val158Met COMT and a VNTR polymorphism of the dopamine transporter (*SLC6A3*) with hippocampus activation correlating positively with the number of COMT Met alleles and SLC6A3 10-repeat alleles (Bertolino et al., 2008) as well as additive effects of Val158Met COMT and 5-HTTLPR showing the highest response in carriers of both Val/Val and L_A/L_A genotype (Smolka et al., 2007). Furthermore, reports on gene–environment interactions are available for 5-HTTLPR, showing a modulation of S allele effects on hippocampal connectivity, resting activation as well as hippocampal volume by life stress (Canli et al., 2006), whereas Met carriers of Val66Met BDNF exposed to greater early-life stress exhibited smaller hippocampal volumes (Gatt et al., 2009).

Neural systems of mood disorders

The development of tools to study imaging data on a brain systems level, which has become a standard procedure within the neuroimaging community over the last couple of years (Rubinov and Sporns, in press), triggered a new era in understanding the complexity of brain function and its relationship to human behavior and mental illness (Ramnani et al., 2004). The importance of a brain systems level understanding of brain function is highlighted by the fact that behavior is orchestrated by the engagement of a variety of specialized and interconnected brain regions. Such a systems level view of human behavior is specifically important for the understanding of emotion processing, since the limbic system is among the anatomically most complex brain systems. Due to the large number of interconnections between structures of the limbic system, it has been necessary in imaging studies to dissect this system into smaller neural systems, which has been proven to be a promising approach for imaging genetics studies (Meyer-Lindenberg, 2009).

One of these subsystems is the amygdala–ACC circuitry (Ressler and Mayberg, 2007), which has been postulated to be composed of feedforward projections from the amygdala to the sACC and feedback projections from the pACC/aMCC back to the amygdala (Pezawas et al., 2005). This circuitry being implicated in depressive illness (Wang et al., 2009) likely corresponds to anatomical interconnections such as the uncinatus and cingulum bundle (Pezawas et al., 2005). Since 5-HT probably impacts the formation of growth cones (Gaspar et al., 2003) and cell migration (Riccio et al., 2009) in humans, it has been hypothesized that 5-HTTLPR exerts an impact on the development and function of this neural circuitry (Pezawas et al., 2005). In a large-scale imaging study in healthy subjects, it has been demonstrated that the S allele leads to a decrease in structural covariance and functional connectivity between amygdala and sACC (Pezawas et al., 2005). Since those findings are commonly interpreted as aspects of neural wiring, it has been suggested that the S allele putatively decreases anatomical connections between the amygdala and sACC, leading to a

diminished functional coupling between those two structures and hence resulting in a disinhibition of the feedback loop being reflected in increased amygdala activity (Pezawas et al., 2005). These results are in accordance with other functional (Dannlowski et al., 2007; Friedel et al., 2009; Heinz et al., 2005; Roiser et al., 2009) and anatomical studies (Pacheco et al., 2009) of patients or healthy subjects reporting S allele effects on amygdala–mPFC coupling, which has been related to trait anxiety via functional connectivity (Pezawas et al., 2005) and fractional anisotropy (Kim and Whalen, 2009). It is noteworthy that it has been suggested that S-allele-induced amygdala hyperreactivity can be down-regulated by cognitive control mechanisms affecting this circuitry during non-automatic processing of threatening stimuli (Schardt et al., this issue). Notably, the anatomical impact of the S allele has also been reported for orthologous rh5-HTTLPR in rhesus monkeys in the corresponding brain regions (Jedema et al., 2010). Furthermore, effects of epistasis between 5-HTTLPR and Val66Met BDNF have been studied in a large sample of healthy subjects, demonstrating that the Met allele counteracts S-allele-induced structural reductions of amygdala–sACC coupling (Pezawas et al., 2008). Furthermore, some evidence exists for gene–gene interaction between *SLC6A4* and *HTR1A* (Dannlowski et al., 2007). While studies investigating this specific circuitry in patients are still scarce (Houenou et al., 2007), it has been reported by studies of acute MDD that connectivity between amygdala and mPFC varies depending on the genotype and is associated with depressive symptomatology (Friedel et al., 2009) as well as global functioning, duration of episodes and lifetime hospitalization (Dannlowski et al., 2007).

Further studies highlight that this circuitry is affected by functional variation of multiple genes, such as the MAOA-L-allele of MAOA uVNTR, which was shown to be associated with increases in sACC-mediated vmPFC–amygdala connectivity, a finding that correlates positively with harm avoidance and negatively with reward dependence (Buckholtz et al., 2008). Decreases of amygdala–pACC and amygdala–aMCC connectivity have also been reported in a smaller sample of healthy MAOA-H subjects, whereas MAOA-H MDD patients showed the weakest amygdala–prefrontal coupling, indicating a longer and more severe course of disease (Dannlowski et al., 2009). Finally, C(178)T HTR3A of the 5-HT_{3A} receptor gene (*HTR3A*) (Iidaka et al., 2005) and rs1344706 in *ZNF804A* that has been related to bipolar disorder, were found to profoundly affect the functional connectivity (Esslinger et al., 2009) of the amygdala–ACC circuitry, whereas DISC1 was reported as being related to reduced white matter tracts comprising this circuitry (Hashimoto et al., 2006).

Knowledge of genetic impact on other mood circuitries is limited, but some evidence exists that the MAOA-L genotype of MAOA uVNTR reduces functional coupling of the amygdala–OFC circuitry in healthy males (Meyer-Lindenberg et al., 2006), which appears to also apply to the Val allele of Val158Met COMT for both genders (Drabant et al., 2006).

Conclusions

Since the introduction of imaging genetics as a research tool (Hariri and Weinberger, 2003), a dramatically increasing number of scientists are applying this approach to mood disorder studies, thereby facilitating the understanding of how genes and interacting factors affect the

OMPFC and interconnected structures, such as the amygdala, OFC, ACC and hippocampus (Price and Drevets, 2009).

Imaging genetics studies corroborate the crucial role of monoaminergic genetic variation as functional or developmental regulators of the amygdala (e.g. *SLC6A4*, *TPH2*, *HTR1A*, *COMT*), OFC (e.g. *MAOA*, *COMT*), ACC (e.g. *SLC6A4*, *MAOA*, *COMT*), AMY–mPFC circuitry (e.g. *SLC6A4*, *MAOA*) and hippocampus (e.g. *MAOA*, *COMT*) in healthy subjects (see Fig. 1). However, the hippocampus appears to be under strong direct genetic control of further and non-monoaminergic genes, such as *BDNF* and *DISC1*, likely reflecting its specific role in memory formation (see Fig. 1). As detailed above, many more genes have been reported to affect OMPFC structures and networks in single studies, and doubtlessly more evidence will emerge over the next couple of years. Thus, further replications will be necessary in order to draw final conclusions. In addition, imaging genetics studies have emphasized the validity of complex disease models of depression, including epistasis as well as gene–environment interactions, which are likely more suitable to reflect the highly complex neurobiology of mood disorders. Such models may be considered more appropriate for studies in patient populations, which are currently sparse and inconclusive.

So far, candidate gene selection has been primarily based on *a priori* assumptions derived from preclinical and association studies, and imaging genetics studies have repeatedly shown small effect sizes, which was frequently attributed to the genetic complexity of mood disorders. This raises the question of whether genes with significantly stronger effects on the OMPFC than the currently known candidates exist, which might be conceivably more important for emotion processing and, consequently, for mood disorders. Recent advances in ‘agnostic’ genome-wide association (GWA) studies (Baum et al., 2008; Ising et al., 2009; The Wellcome Trust Case Control Consortium, 2007) promise such insights, and imaging genetics studies have begun to adopt these new GWA techniques optimized for gene discovery (Potkin et al., 2009a,b,c,d; Stein et al., 2010) and are starting to investigate new candidate genes derived from GWA studies (Esslinger et al., 2009). While GWA imaging genetics studies are still in their infancy, a clear weakness with regard to statistical confirmation exists, and strategies on how to deal with problems of multiple testing in connection with such enormous data sets are still under development, this approach will likely be helpful for drawing final conclusions regarding expected effect sizes in imaging genetics studies and might equally contribute to the discovery of new candidate genes for mood disorders.

Imaging genetics studies have provided a proof of concept in mood disorder research by indicating and detailing how “classical” candidate genes impact brain circuitries of emotion processing *in vivo* in humans. These results support major hypotheses of depression and moreover suggest alternative mechanisms. Further progress in the field of imaging genetics research is on the horizon given the large number of genes being currently under investigation along with the development of more sophisticated techniques, which will be helpful in unraveling the uncertainties of mood disorder neurobiology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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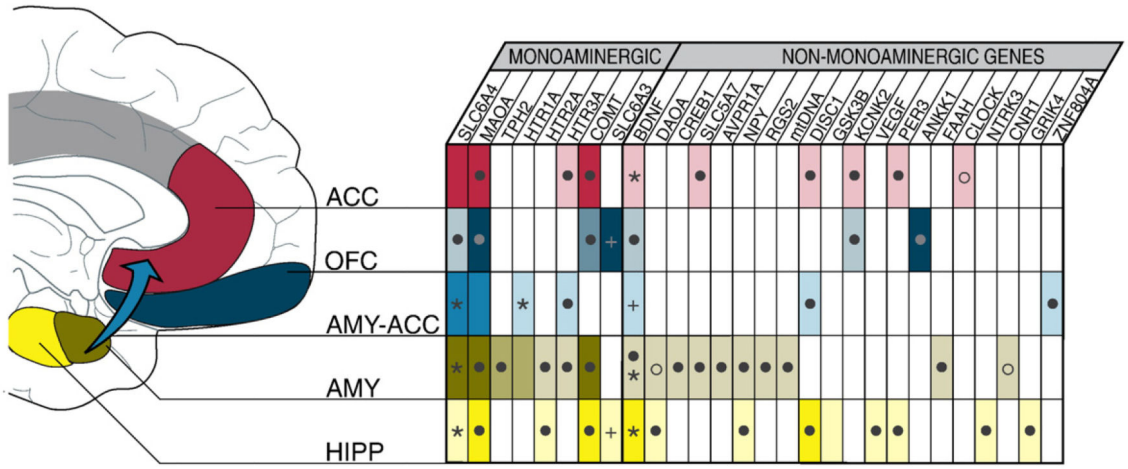

Fig. 1.

Summary of the genetic impact of mood disorder risk genes on volumetric and BOLD measures in healthy subjects and mood disorder patients. BOLD, blood-oxygen level dependent. ○, only studies in mood disorder samples available; ●, only studies in healthy samples available; +, only gene–gene interaction reported; *, gene–environment interaction reported; three classes of color opacity display available evidence (from light to dark): 30% single study or support index <0.5; 60% support index 0.5–0.75; 100% support index N0.75; further details on the calculation of the support index can be found in Supplementary data; ACC, anterior cingulate cortex; OFC, orbitofrontal cortex; AMY–ACC, amygdala–anterior cingulate cortex circuitry; AMY, amygdala; HIPP, hippocampus. Gene nomenclature corresponds to OMIM (Online Mendelian Inheritance in Man).

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Table 1

Reported impact of mood disorder risk genes on brain morphology in healthy subjects.

Genes	Comparison	Amygdala			ACC			OFC			Hippocampus		
		N_{st}	N_{sj}	W_s (%)	N_{st}	N_{sj}	W_s (%)	N_{st}	N_{sj}	W_s (%)	N_{st}	N_{sj}	W_s (%)
SLC6A4	S>L 1	37	4.5	–		–	–	–	–	–	–	–	–
	S<L	3	302	91.7	3	232	100.0	1	41	n.a.	1	77	27.8
	L=S	1	45	3.8	–	–	–	–	–	–	2	100	72.2
MAOA	L>H	–	–	–	–	–	–	2	101^{+}	78.6	–	–	–
	L<H	1	97	n.a.	1	97	62.2	–	–	–	–	–	–
	L=H	–	–	–	1	59*	37.8	1	55^{+}	21.4	–	–	–
HTR2A	His>Tyr	–	–	–	–	–	–	–	–	–	1	76	n.a.
COMT	Met>Val	3	203	100.0	–	–	–	–	–	–	4	353	94.9
	Met<Val	–	–	–	–	–	–	1	53	n.a.	–	–	–
	Met=Val	–	–	–	–	–	–	–	–	–	1	76	5.1
BDNF	Met<Val	1	87	2.0	1	42	n.a.	–	–	–	9	649	94.6
	Met=Val	5	483	98.0	–	–	–	–	–	–	2	167	5.4
mtDNA	A>G	1	118	n.a.	–	–	–	–	–	–	–	–	–
DISC1	Ser>Cys	–	–	–	1	108	n.a.	–	–	–	1	71	34.0
	Ser<Cys	–	–	–	–	–	–	–	–	–	1	157	11.8
	Ser=Cys	–	–	–	–	–	–	–	–	–	1	108	54.2
PER3	4/4>5/5				1	29	n.a.				1	29	n.a
VEGF	T<C	–	–	–	–	–	–	–	–	–	1	47	n.a.
	A<C	–	–	–	–	–	–	–	–	–	1	47	n.a.

Genotypes of genes can be found in the text of this article. Gene nomenclature corresponds to OMIM (Online Mendelian Inheritance in Man), corresponding RefSNP accession numbers are mentioned in the text. S or L of *SLC6A4* comprises the biallelic or triallelic classification of 5-HTTLPR. ACC, anterior cingulate cortex; OFC, orbitofrontal cortex; N_{st}, number of studies; N_{sj}, number of subjects; W_s, support index weighted for number of studies and number of subjects (formula available in Supplementary data); n.a., not applicable;

*, males only;

$^{+}$, females only.

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Table 2

Reported impact of mood disorder risk genes on BOLD signal in healthy subjects.

Genes	Comparison	Amygdala			ACC			OFC			Hippocampus		
		N_{st}	N_{sj}	W_s (%)	N_{st}	N_{sj}	W_s (%)	N_{st}	N_{sj}	W_s (%)	N_{st}	N_{sj}	W_s (%)
SLC6A4	S>L	13	601	98.5	5	166	94.5	–	–	–	1	48	n.a.
	S<L	1	54^+	1.0	1	48	5.5	–	–	–	–	–	–
	L=S	1	29	0.5	–	–	–	–	–	–	–	–	–
MAOA	L>H	2	189	100.0	1	47^+	11.7	–	–	–	2	189	100.0
	L<H	–	–	–	2	177	88.3	2	177	100.0	–	–	–
TPH2	T>G	2	51	65.0	–	–	–	–	–	–	–	–	–
	T<G	1	54^+	35.0	–	–	–	–	–	–	–	–	–
HTR1A	C>G	1	89	61.8	–	–	–	–	–	–	–	–	–
	C=G	1	54^+	38.2	–	–	–	–	–	–	–	–	–
HTR2A	T>C	1	54^+	n.a.	–	–	–	–	–	–	–	–	–
HTR3A	C>T	1	26	n.a.	1	26	n.a.	–	–	–	–	–	–
COMT	Met>Val	3	129	67.6	2	94	87.8	1	27	25.2	4	268	100.0
	Met<Val	1	74	13.7	1	27	12.2	2	40	74.8	–	–	–
	Met=Val	1	101	18.7	–	–	–	–	–	–	–	–	–
CREB1	C<T	1	28	n.a.	–	–	–	–	–	–	–	–	–
BDNF	Met>Val	1	37^+	5,46	–	–	–	–	–	–	2	58	38.9
	Met<Val	1	29	4,28	–	–	–	1	29	n.a.	2	95	61.1
	Met=Val	4	153	90,27	–	–	–	–	–	–	–	–	–
FAAH	A<C	1	82	n.a.	–	–	–	–	–	–	–	–	–
SLC5A7	G>T	1	32	n.a.	1	32	n.a.	–	–	–	–	–	–
AVPR1A	320<312 bp	1	121	n.a.	–	–	–	–	–	–	–	–	–
NPY	Low>High	1	71	n.a.	–	–	–	–	–	–	1	71	n.a.
RGS2	G>C	1	55	n.a.	–	–	–	–	–	–	–	–	–
DISC1	Ser>Cys	–	–	–	–	–	–	–	–	–	2	122	100.0
GRIK4	Del>In	–	–	–	–	–	–	–	–	–	1	42	n.a.
KCNK2	Low>High	–	–	–	1	31	n.a.	1	31	n.a.	–	–	–

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Genes	Comparison	Amygdala			ACC			OFC			Hippocampus		
		N_{st}	N_{sj}	W_s (%)	N_{st}	N_{sj}	W_s (%)	N_{st}	N_{sj}	W_s (%)	N_{st}	N_{sj}	W_s (%)
ANKK1	A1<A2	–	–	–	–	–	–	2	42	100.0	–	–	–
STMN1	T>C	–	–	–	1	42	n.a.	–	–	–	–	–	–
	G>T	–	–	–	1	42	n.a.	–	–	–	–	–	–
DAOA	A>T	–	–	–	–	–	–	–	–	–	1	14	n.a.
	High<Low	–	–	–	–	–	–	–	–	–	1	83	n.a.
NTRK3	G>C	–	–	–	–	–	–	–	–	–	1	36	n.a.

Genotypes of genes can be found in the text of this article. Gene nomenclature corresponds to OMIM (Online Mendelian Inheritance in Man), corresponding RefSNP accession numbers are mentioned in the text. S or L of *SLC6A4* comprises the biallelic or triallelic classification of 5-HTTLPR. BOLD, blood-oxygen level dependent; ACC, anterior cingulate cortex; OFC, orbitofrontal cortex; N_{St}, number of studies; N_{Sj}, number of subjects; W_S, support index weighted for number of studies and number of subjects (formula available in Supplementary data); n.a., not applicable;

$^{+}$, females only.