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## REVIEW ARTICLE

# The genetic blueprint of major depressive disorder: Contributions of imaging genetics studies

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### Abstract

**Objectives.** To review neuroimaging intermediate phenotypes of MDD and their relation to genetic risk variants. **Methods.** A systematic literature search of peer-reviewed English language articles using PubMed (www.pubmed.org) was performed. **Results.** Comprehensive evidence on the influence of serotonergic genes (*SLC6A4*, *HTR1A*, *MAOA*, *TPH2*) and *BDNF* on the following neural intermediate phenotypes is displayed: amygdala reactivity, coupling of amygdala-anterior cingulate cortex (ACC) activity, ACC volume, hippocampal volume and serotonin receptor 1A (5-HT<sub>1A</sub>) binding potential (BP). **Conclusions.** Intermediate phenotypes may bridge the gap between genotype and phenotype by reducing the impreciseness of psychiatric phenotypes and yield more insights into the underlying biology.

**Key words:** Major depressive disorder, genetics, pharmacogenetics, amygdala, cingulate gyrus, hippocampus, 5-HT<sub>1A</sub> receptor

### Introduction

The clinical phenotype of depression, operationalized as major depressive disorder (MDD) in DSM-IV (American Psychiatric Association 2000), is characterized by a highly variable symptom profile as well as a varying severity and course. Despite the fact that several biological treatments have proven their clear efficacy, ranging from antidepressants (Cipriani et al. 2009) to electroconvulsive therapy (Chakrabarti et al. 2010), and deep brain stimulation (Schlaepfer et al. 2010), MDD ranks among the leading causes of disease burden worldwide (Hyman 2008). Despite great strides forward regarding the understanding of the neurobiology of MDD over the last decade (Krishnan and Nestler 2010), scientific achievements failed to translate into clinical practise. Such a mismatch between scientific progress and clinical exploitation likely originated from the limited biological validity of the current behavioural conceptualization of mood disorders, thereby leading to diagnostic entities that are not well suited for

biological psychiatric research, an argument that will be in the core of this article.

### From association to imaging genetics studies

MDD is a disorder with substantial heritability ranging from 31 to 42% (Sullivan et al. 2000; Kendler et al. 2006) and is thought to be composed of complex genetic mechanisms of multiple risk genes including epistasis, imprinting, epigenetics, and gene-environment interactions (Krishnan and Nestler 2008; Caspi et al. 2010). Accordingly, the identification of gene variants increasing susceptibility of MDD has become a major goal in mood disorder research, with hundreds of behavioural and pharmacogenetic association studies reporting such a linkage (Kato and Serretti 2008; Lopez-Leon et al. 2008; Schosser and Kasper 2009). However, despite continuously increasing sample sizes, clinical association studies including thousands of cases (Willis-Owen et al. 2005; Surtees et al. 2006) still suffer from a lack of

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replication. Effects of single genes that have been linked to an increased risk of MDD have proven to be more subtle than originally expected and the study of gene–gene and gene–environment interactions suggests their pathogenetic influence to be complex (Caspi et al. 2010). Hence, the predictive value of known risk alleles is still far away from clinical exploitation for genetic or pharmacogenetic testing with respect to diagnosis or treatment.

Obviously, effects of genes do not directly translate into clinical phenotypes such as MDD, but gene variants nevertheless affect the functional or structural integrity of neural circuits through molecular and cellular mechanisms (Meyer-Lindenberg and Weinberger 2006; Meyer-Lindenberg 2010). Therefore, measures that go beyond the surface of clinical phenotypes are more appropriate for tracing the effects of such gene variants. Hence, this approach substitutes the elusive qualitative phenotypes of psychiatric disorders by quantitative biological measures, which are thought to be in tighter linkage with the underlying molecular mechanisms (Gottesman and Gould 2003). Initially, such candidate markers have been thought to exhibit heritability patterns comparable to Mendelian traits and have been termed “endophenotypes” (Gottesman and Gould 2003). However, virtually all proposed endophenotypes failed to fulfill these strict criteria and are therefore called “intermediate phenotypes” (Meyer-Lindenberg et al. 2006; Meyer-Lindenberg and Weinberger 2006). It is noteworthy that intermediate phenotypes are not specific for a certain genetic variant or even clinical diagnosis and can eventually also be detected in non-clinical samples (Meyer-Lindenberg et al. 2006; Meyer-Lindenberg and Weinberger 2006). Nevertheless, neural intermediate phenotypes measured by modern neuroimaging techniques are thought to more directly index the underlying neurobiology of complex phenotypes and hence have the intrinsic potential to bridge the gap between genes and psychiatric diagnostic phenotypes. This promising approach has demonstrated its feasibility in many studies (Meyer-Lindenberg 2010). With respect to MDD research, scientists have been able to link specific imaging intermediate phenotypes to MDD, its vulnerability factors (Pezawas et al. 2005; Cremers et al. 2010) and affective as well as cognitive symptoms (Price and Drevets 2010).

The rapidly growing field of imaging genetics utilizing neuroimaging as tool to detect the subtle neural impact of genetic variants has been able to demonstrate a tight association between several neural intermediate phenotypes and a wide array of risk alleles related to mental illness (Bigos and Weinberger 2010). Moreover, these studies suggest that risk alleles explain a significantly larger portion of variance on a brain systems level as compared to

clinical endpoints such as the diagnosis of MDD, thereby overcoming the inconclusiveness of clinical association studies by substantially increasing effect sizes. For instance, a polymorphism in the promotor region (5-HTTLPR) of the serotonin transporter gene (*SLC6A4*) accounts for up to 10% variance of amygdala activation (Munafo et al. 2008), whereas its role in predicting behavioural phenotypes such as neuroticism (Munafo et al. 2009), MDD (Risch et al. 2009; Clarke et al. 2010), or antidepressant response (Serretti et al. 2007; Taylor et al. 2010) is at least one order of magnitude lower, likely ranging around 1–3% (Serretti et al. 2007).

Traces of gene effects found in the neuroanatomy or function of healthy subjects are considered to reflect similar molecular mechanisms as being present in pathological states and therefore contribute to our understanding of the neurobiological underpinnings of psychiatric disorders (Hyman 2008). Since gene variants are selected by candidacy bearing a given *a priori* probability to be involved in the pathogenesis of (intermediate) phenotypes, the majority of studies therefore investigates genetic variants that have previously been linked to clinical phenotypes such as MDD. Although the candidate gene concept is prone to selection bias and drawn into question by the inconclusiveness found in association studies, it is nevertheless practicable and still poses the gold standard of imaging genetics. Consistently, the neural effects of candidate genes have been shown to impact on neural systems which are known to be affected during MDD and to be targeted by antidepressants (Windischberger et al. 2009), deep brain stimulation (Mayberg et al. 2005), or electroconvulsive therapy (Nordanskog et al. 2010).

In the present paper, we attempt to provide a comprehensive review of the most prominent genetic variants that have been linked to increased risk for MDD, namely serotonergic (*SLC6A4*, *HTR1A*, *MAOA*, *TPH2*) and neurotrophic (*BDNF*) genes. We will cover results of clinical phenotypes as well as intermediate phenotypes derived by neuroimaging techniques in both healthy volunteers (Table I and Figure 1) and MDD patients with concurrent major depressive episodes (MDEs).

## Material and methods

The authors performed a systematic literature search using critical keywords (amygdala, hippocampus, anterior cingulate cortex, 5-HT1A receptor, *SLC6A4*, *HTR1A*, *MAOA*, *TPH2*, *BDNF*) in PubMed (www.pubmed.gov). Imaging genetics publications (published until 08/2010) have been selected according

to the following inclusion criteria: (1) variation within serotonergic genes (*SLC6A4*, *HTR1A*, *MAOA*, *TPH2*) or *BDNF* has been associated with (2) functional or anatomical magnetic resonance imaging (MRI) or positron emission tomography (PET) measures in samples of adult healthy subjects or MDD patients with concurrent MDEs. (3) Results on established intermediate phenotypes have been extracted: amygdala reactivity, coupling of amygdala-anterior cingulate cortex (ACC) activity, ACC volume, hippocampal volume and serotonin receptor 1A (5-HT1A) binding potential (BP).

#### Intermediate phenotypes for MDD

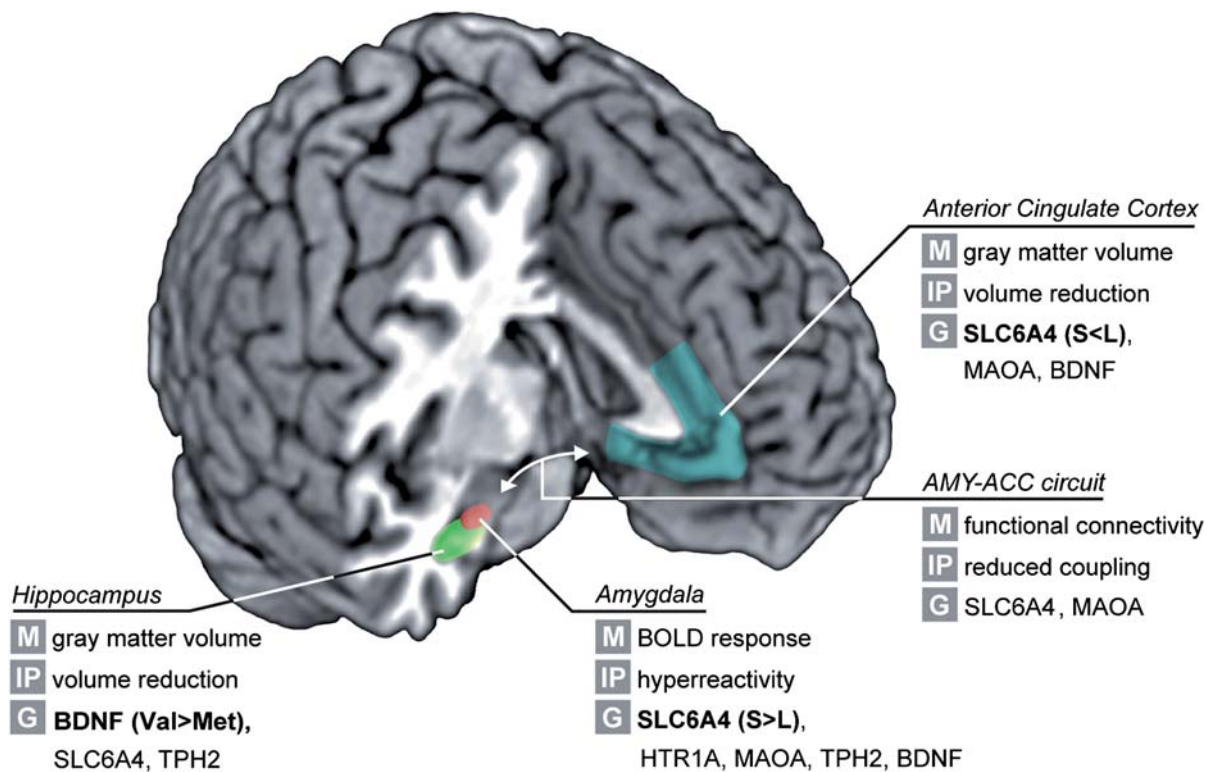
Following paragraphs will detail neural intermediate phenotypes derived by MRI and PET studies that have been linked to MDD. Figure 1 illustrates selected regions and corresponding MRI measures for which promising evidence in MDD patients with

concurrent MDEs compared to healthy controls is available: amygdala hyperreactivity, decreased coupling of amygdala-anterior cingulate cortex activity, reduced volume of the anterior cingulate cortex and hippocampus.

The majority of dysfunctional patterns of activation and morphometric alterations in patients with concurrent MDEs have been revealed in brain regions processing unpleasant emotions such as anxiety or sadness (Fusar-Poli et al. 2009). Since these psychopathological entities constitute core symptoms of MDD (American Psychiatric Association 2000), alterations within these emotion regions are thought to be crucial for the pathophysiology of MDD.

#### Amygdala hyperreactivity

The amygdala plays a prominent role in emotion and specifically fear processing (Costafreda et al. 2008). It has repeatedly been shown that patients suffering



**M** measure **IP** intermediate phenotype related to MDD **G** genetic impact on MRI measure

Figure 1. Reported alterations within emotion brain regions in major depressive disorder (MDD) amalgamated with analogous findings in imaging genetics studies. Only studies of patients suffering from a concurrent depressive episode are included. Imaging genetics studies are restricted to findings in healthy subjects. Genes with at least one positive report of an association are listed. Genes written in bold indicate genes for which most evidence for an impact on MRI measures is available. MRI, magnetic resonance imaging; BOLD, blood-oxygenation level dependent; AMY-ACC circuit, amygdala-anterior cingulate cortex circuit.

from MDEs display increased amygdala activation in response to aversive stimuli (Sheline et al. 2001; Siegle et al. 2002; Fu et al. 2004; Strigo et al. 2008; Suslow et al. 2010), while chronic antidepressant treatment has been reported to attenuate amygdala activation and metabolism (Sheline et al. 2001; Drevets et al. 2002; Fu et al. 2004; Arce et al. 2008; Windischberger et al. 2009). These enhanced levels of amygdala activity might represent the neural correlate of an automatic emotional processing bias leading to increases of reactivity to negative emotional cues in MDD (Suslow et al. 2010).

#### *Decreased coupling of amygdala-anterior cingulate cortex activity*

It is commonly accepted that the amygdala is not acting independently, but is embedded in multiple limbic cortical networks that are supposed to co-regulate amygdala activity during MDEs (Pezawas et al. 2005; Stein et al. 2007). Briefly, decreased coupling of the amygdala and ACC has been related to increased susceptibility for MDD (Anand et al. 2005a; Pezawas et al. 2005; Stein et al. 2007; Chen et al. 2008a; Matthews et al. 2008; Kim and Whalen 2009; Cremers et al. 2010). Additionally, chronic antidepressant treatment has been reported repeatedly to increase coupling of these structures, likely representing an increase of inhibitory control over the amygdala leading to a normalization of its hyperreactivity (Anand et al. 2005b, 2007; Chen et al. 2008a).

#### *Reduced volume of the anterior cingulate cortex and the hippocampus*

With regard to brain volume abnormalities in MDD, most consistent results are available for volume reductions of the subgenual portion of the ACC (sACC) (Drevets et al. 2008; van Tol et al. 2010) and the hippocampus (Videbech and Ravnkilde 2004; Koolschijn et al. 2009a,b; Eker and Gonul 2010), whereas volumetric measures of the amygdala are highly inconsistent (Hamilton et al. 2008). Interestingly, reduced hippocampal volume has additionally been found in individuals at risk for MDD (Rao et al. 2009; Baare et al. 2010; Chen et al. 2010) and an increase of hippocampal volume can likely be achieved by antidepressant drug treatment as suggested by animal models (Czeh et al. 2001; Kasper and McEwen 2008), or electroconvulsive therapy (Nordanskog et al. 2010).

#### *Reductions of serotonin 1A receptor binding potential*

The serotonin 1A (5-HT<sub>1A</sub>) autoreceptor is the most important release- and synthesis-controlling receptor for serotonergic neurons and has been linked to

antidepressant response rates (Richardson-Jones et al. 2010) as well as the neural processing of unpleasant emotions (Akimova et al. 2009).

The binding potential (BP) is an outcome measure of PET studies using reversibly binding radioligands and refers to both the receptor number and affinity (Innis et al. 2007). Promising results, mainly applying the radioligand [<sup>11</sup>C]WAY 100635, suggest reductions of 5-HT<sub>1A</sub> BP in diverse regions including the medial prefrontal cortex, the amygdala and hippocampus as well as the midbrain raphe nuclei to be substantially involved in the pathogenesis of MDD (Drevets et al. 1999, 2007; Sargent et al. 2000; Bhagwagar et al. 2004; Meltzer et al. 2004; Hirvonen et al. 2008).

Desensitization of 5-HT<sub>1A</sub> autoreceptors, occurring in the course of 2–3 weeks of 5-HT reuptake-blockade, is likely an important mechanism of antidepressant drug action (Richardson-Jones et al. 2010). However, PET studies in MDD samples have not revealed changes of 5-HT<sub>1A</sub> receptor BP caused by antidepressants (Moses-Kolko et al. 2007) or electroconvulsive therapy (Saijo et al. 2010). In contrast, reductions in the hippocampus, the sACC and the posterior cingulate cortex have been found in a sample of patients suffering from anxiety disorders after administration of escitalopram (Spindelegger et al. 2009).

### **Genetic impact on MDD and intermediate phenotypes**

Several lines of evidence implicate alterations within the serotonergic and neurotrophic system in the pathogenesis of MDD and the action of antidepressants (Groves 2007; Jans et al. 2007). In the following section, we will provide comprehensive information about the most relevant functional polymorphisms (gene variants that alter the expression and/or functioning of gene products) and their impact on clinical endpoints and neural intermediate phenotypes related to MDD. Figure 1 amalgamates available evidence on neural alterations in patients with concurrent MDEs as well as imaging genetics findings regarding the neural impact of functional genetic polymorphisms in healthy subjects. In contrast, table 1 summarizes specifically neural effects of upper mentioned genes assessed by MRI and PET.

#### *Serotonin transporter gene*

Drugs selectively inhibiting serotonin reuptake (SSRIs) are the first line treatment for MDD (Bauer et al. 2007). SSRIs exhibit their action by a



Table I. Imaging genetics studies reporting neural intermediate phenotypes in healthy subjects.

Measure		Amygdala BOLD			AMY-ACC FC			ACC Vol			Hippocampus Vol			5-HT <sub>1A</sub> BP		
Genes – comparison		<i>N</i> <sub>st</sub>	<i>N</i> <sub>sj</sub>	%	<i>N</i> <sub>st</sub>	<i>N</i> <sub>sj</sub>	%	<i>N</i> <sub>st</sub>	<i>N</i> <sub>sj</sub>	%	<i>N</i> <sub>st</sub>	<i>N</i> <sub>sj</sub>	%	<i>N</i> <sub>st</sub>	<i>N</i> <sub>sj</sub>	%
SLC6A4	S > L	15	652	89	–	–	–	–	–	–	–	–	–	2	54	38
	S = L	1	29	4	–	–	–	–	–	–	2	100	56	1	54	38
	S < L	1	54	7	1	94	na	3	232	100	1	77	44	1	35	24
HTR1A	C > G	1	89	62	–	–	–	–	–	–	–	–	–	–	–	–
	C = G	1	54	38	–	–	–	–	–	–	–	–	–	1	35	45
	C < G	–	–	–	–	–	–	–	–	–	–	–	–	1	43	55
MAOA	L > H	2	189	100	1	123	80	–	–	–	–	–	–	–	–	–
	L = H	–	–	–	–	–	–	1	59	38	–	–	–	–	–	–
	L < H	–	–	–	1	31	20	1	97	62	–	–	–	1	31	na
TPH2	T > G	2	51	49	–	–	–	–	–	–	–	–	–	–	–	–
	T = G	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	T < G	1	54	51	–	–	–	–	–	–	1	208	Na	–	–	–
BDNF	Val > Met	1	29	13	–	–	–	1	42	na	9	649	80	–	–	–
	Val = Met	4	153	70	–	–	–	–	–	–	2	167	20	1	53	na
	Val < Met	1	37	17	–	–	–	–	–	–	–	–	–	–	–	–

This table displays evidence on the impact of gene polymorphisms on established depression-related brain regions assessed by neuroimaging studies in healthy subjects. Shown are the number of studies (*N*<sub>st</sub>), the number of included subjects (*N*<sub>sj</sub>) and percentages (%) of the total number of subjects (*N*<sub>sj</sub>) reporting increases (>), decreases (<), or lacking differences of neuroimaging measures between alleles. AMY-ACC, amygdala-anterior cingulate cortex circuit; ACC, anterior cingulate cortex; 5-HT<sub>1A</sub>, serotonin 1A receptor; BOLD, blood oxygen level dependent; FC, functional connectivity; Vol, volume; BP, binding potential; na, not applicable. Results on 5-HT<sub>1A</sub> BP include studies using the radiotracers [<sup>11</sup>C]WAY 100635 and [<sup>18</sup>F]MPPF measuring 5-HT<sub>1A</sub> receptors in various brain regions.

blockade of the serotonin transporter (5-HTT) which is expressed by the serotonin transporter gene (*SLC6A4*). Within this gene, most attention has been paid to a variable number of tandem repeats (VNTR) polymorphism (5-HTTLPR) in the promotor region (Canli and Lesch 2007). Allele frequencies of the short (S) and the long (L) allele of 5-HTTLPR differ between certain geographical regions of the world (Chiao and Blizinsky 2010), but also inside of Europe (Noskova et al. 2008), with about 40–45% for the S allele in Caucasian samples and about 70–80% S allele carriers in East Asian samples, thereby interacting with cultural styles in a complex way (Chiao and Blizinsky 2010). In addition to this VNTR polymorphism, further genetic variability within *SLC6A4* has been detected such as a single nucleotide polymorphism (A-G substitution, rs25531) within the long (L) allele, termed L<sub>G</sub> and L<sub>A</sub> allele. Since the S and the L<sub>G</sub> allele are thought to be phenotypically similar (Hu et al. 2006), it has become common practice to integrate L<sub>G</sub> allele carriers into the S allele carrier group, commonly referred to as trial-elic 5-HTTLPR.

The S allele has been related to lower 5-HTT expression in humans cell lines *in vitro* (Heils et al. 1996; Bradley et al. 2005). Accordingly, 5-HTTLPR is thought to affect 5-HTT expression in the human brain, with the S allele leading to higher extracellular concentrations of serotonin in the synaptic

cleft (Canli and Lesch 2007), though direct evidence for this assumption is lacking, since 5-HT concentration cannot be directly assessed in the living human brain. *In vivo*, several PET studies applying the 5-HTT sensitive radioligand [<sup>11</sup>C]DASB have demonstrated decreased serotonin transporter BP in the midbrain in S allele carriers as compared to individuals homozygous for the L allele (Praschak-Rieder et al. 2007; Reimold et al. 2007; Kalbitzer et al. 2009). However, inconsistency of results indicates that 5-HTTLPR might only marginally contribute to the transmembrane availability of 5-HTT proteins and therefore only exhibits subtle direct effects on serotonergic neurotransmission in the human adult brain (Murthy et al. 2010). Nevertheless, serotonin plays a significant modulating role during brain development (Gaspar et al. 2003). Hence, even minor increases of synaptic 5-HT concentration due to 5-HTTLPR may impact on the migration of serotonergic and non-serotonergic neurons along growth cones and thereby determine brain wiring and indirectly activation patterns of neural circuitries (Ansorge et al. 2004; Riccio et al. 2009).

First evidence for an impact of 5-HTTLPR genotype on behaviour came from the report of an association between S allele carrier status and enhanced levels of anxiety-related traits (e.g., neuroticism) (Lesch et al. 1996). Unfortunately,

several replications failed (Munafo et al. 2009), likely suggesting that direct genetic effects on personality are much smaller than originally thought. With regard to a direct effect of the 5-HTTLPR genotype on depression susceptibility, numerous studies have been conducted and one recent meta-analysis supports the presence of a small effect for an increased risk of MDD (Clarke et al. 2010), whereas others could not detect any effect at all (Lasky-Su et al. 2005; Risch et al. 2009). While evidence for a direct association between 5-HTTLPR genotype and risk for MDD is weak (Clarke et al. 2010), reports of gene–environment interactions between 5-HTTLPR genotype and environmental adversity causing stress sensitivity and susceptibility for MDD now substantially contribute to the current discussion on how genes might shape behaviour (Caspi et al. 2010). The original report (Caspi et al. 2003), however, was followed by both replications and nonreplications and has been drawn into question by meta-analytical data (Munafo et al. 2009; Risch et al. 2009). Specifically, recently criticised issues with regard of the chosen study design may be accountable for this inconclusiveness (Uher and McGuffin 2010).

In contrast, MRI studies investigating the impact of 5-HTTLPR on amygdala activity in response to negative stimuli have revealed more consistent results (Munafo et al. 2008) and report healthy S allele carriers to show higher levels of amygdala activity as compared to individuals homozygous for the L allele (Hariri et al. 2002, 2005; Bertolino et al. 2005; Canli et al. 2005b; Heinz et al. 2005; Lee et al. 2005; Pezawas et al. 2005; Smolka et al. 2007; Dannlowski et al. 2008, 2009; Friedel et al. 2009; Williams et al. 2009; Gillihan et al. 2010). One study in an Asian sample revealed opposing results (Lee and Ham 2008b) and we are aware of only one study to date, which found no difference (Surguladze et al. 2008). Similar to healthy volunteers, studies in patients with concurrent MDEs have replicated S-allele-associated increases of amygdala activation (Dannlowski et al. 2007, 2008; Friedel et al. 2009). Notably, studies investigating 5-HTTLPR influence on amygdala baseline perfusion are inconclusive (Viviani et al. 2010; Canli et al. 2006; Rao et al. 2007).

Genetic mechanisms do not only affect regional brain activity, but also shape the neural circuitries in which these regions participate. Accordingly, the 5-HTTLPR genotype has been shown to impact on the amygdala-ACC circuit, with healthy S allele carriers demonstrating reductions of functional coupling (FC) as compared to individuals with L/L genotype (Pezawas et al. 2005). Moreover,

activity of the sACC and the amygdala has been demonstrated to be positively correlated, whereas inverse functional coupling has been reported between the pregenual portion of the ACC (pACC) and the amygdala (Pezawas et al. 2005; Stein et al. 2007). Hence, reductions of functional coupling within this neural circuit may reflect genetically driven decreases of inhibitory influences on the amygdala corresponding to the aforementioned finding of increased amygdala reactivity. This has further been underlined by data showing that the magnitude of FC between the sACC and the amygdala predicts trait anxiety scores to a remarkable extent (Pezawas et al. 2005). Moreover, a single MRI study applying diffusion tensor imaging has associated the S allele with microstructural alterations in the uncinate fasciculus, a white matter tract that connects the amygdala to the prefrontal cortex (Pacheco et al. 2009). This finding supports the idea that subtle alterations of white matter architecture may contribute to reductions of functional coupling between the sACC and the amygdala among S allele carriers.

With respect to effects of 5-HTTLPR on ACC volume, S-allele-associated gray matter volume loss has been described, exhibiting the largest effects within the sACC portion (Canli et al. 2005b; Pezawas et al. 2005; Frodl et al. 2008a), a region for which the highest cortical 5-HTT densities have been found (Varnas et al. 2004). There is also recent evidence that this finding holds true for non-human primates (Jedema et al. 2010).

With regard to hippocampal volume, results surprisingly suggest that 5-HTTLPR exhibits opposing effects in healthy controls and MDD samples. Indeed, reductions of hippocampal gray and white matter volume have been found to be relatively pronounced in symptomatic patients homozygous for the L allele as compared to S allele carriers (Frodl et al. 2004; Frodl et al. 2008b), while healthy L allele homozygotes exhibit relatively larger hippocampal volumes (Frodl et al. 2008b). This relationship may be further complicated by an interaction with childhood stress (Frodl et al. 2010).

Applying the 5-HT<sub>1A</sub> radioligand [<sup>11</sup>C]WAY 100635, healthy S allele carriers demonstrated lower levels of 5-HT<sub>1A</sub> receptor BP as compared to L/L homozygotes (David et al. 2005). However, replication studies failed (Borg et al. 2009), or reported opposing results for the cingulate cortex (Lee et al. 2005). Additionally, studies applying another radiotracer, [<sup>18</sup>F]MPPF, demonstrated female volunteers with S/S genotype to exhibit higher levels of [<sup>18</sup>F]MPPF BP in several brain regions, but not the raphe nuclei (Lothe et al. 2009).

*Serotonin receptor 1A gene*

High levels of the serotonin receptor 1A (5-HT<sub>1A</sub>) are expressed in a number of depression-related brain regions including the cerebral cortex, the hippocampus, the amygdala and the raphe nuclei (Ito et al. 1999). Somatodendritic 5-HT<sub>1A</sub> autoreceptors, which are mainly located on neurons in the midbrain raphe nuclei, are thought to mediate the negative feedback inhibition of these neurons and hence to uniquely impact on serotonergic neurotransmission of forebrain areas (Sharp et al. 2007). Furthermore, a strong inverse relationship between 5-HT<sub>1A</sub> autoreceptor density and neural activity in the amygdala has been found in healthy participants (Fisher et al. 2006), thereby linking two of the aforementioned intermediate phenotypes for MDD, amygdala hyperactivity and reductions of 5-HT<sub>1A</sub> density.

The G allele of C(-1019)G (rs6295), a single nucleotide polymorphism (SNP) within the promoter region of the 5-HT<sub>1A</sub> gene (*HTR1A*), has been associated with MDD, suicidality (Lemondé et al. 2003) and trait anxiety (Strobel et al. 2003). On a molecular level, the G allele reduces binding of transcriptional repressors presumably leading to enhanced 5-HT<sub>1A</sub> receptor expression, which eventually results in reductions of serotonergic neurotransmission (Lemondé et al. 2003).

Evidence on the influence of the C(-1019)G SNP on amygdala reactivity is sparse, with one study reporting G allele associated reductions of amygdala reactivity to threatening stimuli (Fakra et al. 2009), whereas a study in an Asian sample found no effect (Lee and Ham 2008b).

Supporting its role as a functional SNP, the G allele has been found to be associated with increased 5-HT<sub>1A</sub> receptor BP in the raphe nuclei (Parsey et al. 2006). Because 5-HT<sub>1A</sub> receptors on neurons of the raphe nuclei are inhibitory, an increase of 5-HT<sub>1A</sub> density possibly causes less 5-HT release in serotonergic projection regions. However, others could not detect genetically-driven alterations of 5-HT<sub>1A</sub> receptor BP (David et al. 2005).

*Monoamine oxidase A gene*

Monoamine oxidase A (MAOA) is a key enzyme of monoaminergic neurons which catalyzes the degradation of biogenic amines, preferentially of 5-HT and norepinephrine. According to this crucial role for serotonergic neurotransmission, altered levels of MAOA in the brain have been discussed to be involved in the pathogenesis of MDD. PET studies have revealed evidence for elevated MAOA levels during MDEs in several emotion processing regions including the prefrontal and cingulate cortex, or

subcortical regions such as the hippocampus (Meyer et al. 2006).

A VNTR polymorphism in the promoter region of the X-chromosome-linked *MAOA* gene results in a highly active MAOA-H allele and a less active MAOA-L allele (Sabol et al. 1998). However, available evidence from PET studies applying the radiotracer [11C]clorgyline *in vivo* suggests no differences in brain MAOA activity in healthy male adults (Fowler et al. 2007; Alia-Klein et al. 2008). Association studies have revealed an increased frequency of the longer MAOA-H alleles in MDD samples (Schulze et al. 2000; Yu et al. 2005). Besides, variation within the MAOA gene has predominantly been associated with antisocial, impulsive and aggressive behaviour, especially in the context of familial adversity and maltreatment during childhood (Caspi et al. 2002; Kim-Cohen et al. 2006).

With regard to amygdala reactivity in response to aversive stimuli, healthy MAOA-L carriers have been found to show relatively increased activity as compared to individuals homozygous for MAOA-H in both European and Asian samples (Meyer-Lindenberg et al. 2006; Lee and Ham 2008).

On the level of brain systems, the MAOA-L allele has been shown to increase functional coupling of a neural pathway between the ventromedial prefrontal cortex (vmPFC), including the ACC, and the amygdala. Interestingly, the magnitude of FC between these regions has also been associated with increased levels of harm avoidance (Buckholtz et al. 2008). In the same line, decreases of FC between the ACC and the amygdala have been reported for healthy and depressed MAOA-H carriers (Dannowski et al. 2009b).

The MAOA-L allele has also been related to volume loss of the entire ACC in healthy volunteers (Meyer-Lindenberg et al. 2006), however others failed to replicate this finding (Cerasa et al. 2008). A single study investigated the possible impact of the MAOA genotype on 5-HT<sub>1A</sub> receptor BP (Mickey et al. 2008). Moreover, female MAOA-H carriers have been found to be associated with greater 5-HT<sub>1A</sub> BP, whereas no difference was found in men.

*Tryptophan hydroxylase 2 gene*

In serotonergic neurons, neural tryptophan hydroxylase 2 (TPH2) is the rate limiting enzyme for the synthesis of serotonin (Walther et al. 2003) and has been discussed to play an important role for the pathogenesis of MDD, since higher levels of TPH2 mRNA and protein have been found in the raphe nuclei in MDD patients who committed suicide while being depressed (Bach-Mizrahi et al. 2006).



Several variants within the *TPH2* gene have been reported to impact *TPH2* expression (Scheuch et al. 2007; Haghighi et al. 2008), serotonin synthesis (Zhang et al. 2004) and susceptibility to MDD (Zhang et al. 2005; Zhou et al. 2005). Furthermore, variation within *TPH2* has been related to anxiety- and depression- associated personality traits and emotional instability (Gutknecht et al. 2007).

With regard to intermediate phenotypes for MDD, the T allele of G(-703)T *TPH2* (rs4570625) has been related to increases of amygdala reactivity in healthy volunteers (Brown et al. 2005; Canli et al. 2005a), whereas opposing effects have been found in an Asian sample (Lee and Ham 2008b). Moreover, a recent study has revealed volume reductions within the hippocampus in healthy T allele carriers as compared to G allele homozygotes (Inoue et al. 2010).

#### *Brain-derived neurotrophic factor*

Neurotrophins influence a wide range of cellular processes in the central nervous system such as neural survival or synaptic plasticity. Their effects are mediated by different neurotrophin receptors and dependent on the form of the neurotrophin (pro- versus mature) (Lu et al. 2005). Decrease of brain-derived neurotrophic factor (BDNF) (Bocchio-Chiavetto et al. 2010), especially in the hippocampus, has been suggested to play an important role in the pathogenesis of MDD (Groves 2007; Mossner et al. 2007). Notably, both BDNF and serotonin are increasingly recognized to regulate the development and plasticity of neural circuits and to interact epistatically (Martinowich and Lu 2008; Pezawas et al. 2008).

A substantial number of different SNPs within the *BDNF* gene has been identified and associated with MDD (Licinio et al. 2009). Nevertheless, most attention has been paid to Val66Met *BDNF* (rs6265) which has been reported to influence the activity-dependent secretion of BDNF (Egan et al. 2003). Clinical association studies with MDD have been inconsistent, with meta-analytical data drawing a direct relationship into question (Chen et al. 2008a,b; Verhagen et al. 2010). With regard to anxiety-related traits, meta-analytical evidence suggests an association between the Met allele and lower levels of neuroticism (Frustraci et al. 2008).

Imaging genetics studies have revealed inconsistent results on the possible impact of Val66Met on amygdala reactivity, with one study reporting the Val allele (Gasic et al. 2009), and one suggesting the Met allele (Montag et al. 2008) to be associated with increased neural activity of the amygdala. Consistently, most studies have not detected any influence (Egan et al. 2003; Hariri et al. 2003; Hashimoto et al. 2008; Schofield et al. 2009). With regard to

brain structure, a single study reported a volume decrease of the ACC in healthy Met allele carriers (Matsuo et al. 2009).

More evidence exists with respect to hippocampal volume, which has very consistently been found to be decreased in healthy volunteers carrying the Met allele (Pezawas et al. 2004; Szeszko et al. 2005; Bueler et al. 2006). Only a minority could not detect an effect (Jessen et al. 2009; Koolschijn et al. 2009a). Similar findings arguing for Met allele-associated hippocampal volume reductions have been found in MDD samples (Frodl et al. 2007; Chepenik et al. 2009). However, others failed to replicate these findings (Gonul et al. 2010; Jessen et al. 2009).

With regard to 5-HT<sub>1A</sub> BP, we are aware of one single study not revealing any impact on Val66Met *BDNF*. However, applying the 5-HTT radiotracer [<sup>11</sup>C]MADAM, the Val allele has been demonstrated to be associated with higher BPs (Henningsson et al. 2009).

#### **Discussion and future directions**

Currently and also in next generation of psychiatric diagnostics, MDD is operationalized exclusively by clinical parameters and psychopathological symptoms without consideration of its neural underpinnings (American Psychiatric Association 2000). Beyond its clinical application, the nosological framework for MDD substantially guides current biological psychiatric research. Specifically, classical association and pharmacogenetic studies follow this behaviour-based concept, as they directly examine associations between genes and a behavioural phenotype that is defined by diagnostic categories using symptom-based rating scales (e.g., the Hamilton Depression Rating Scale) (Della Pasqua et al. 2010).

As detailed above, this approach has mainly been carried out for single candidate genes based on *a priori* assumptions and resulted in inconsistent findings (Kato and Serretti 2008; Lopez-Leon et al. 2008). More recent approaches such as genome-wide association (GWA) studies (Cichon et al. 2009) are overcoming the selection bias that is inherent to hypothesis-driven candidate studies by investigating associations with thousands of proxy markers spanning the whole genome in order to locate functional loci for MDD (Shyn et al. 2009; McMahon et al. 2010; Muglia et al. 2010; Shi et al. 2011) or antidepressant response (Ising et al. 2009; Adkins et al. 2010; Garriock et al. 2010; Uher et al. 2010). However, the statistical analysis of such enormous data sets bears several statistical pitfalls related to multiple comparison problems as well as statistical sensitivity and specificity (Pezawas and Meyer-Lindenberg 2010).

Genetic risk profiles follow the idea of summarizing variation within thousands of loci on the genome in order to assess their collective impact on clinical phenotypes. Accordingly, such a genetic risk score has recently been tested for MDD, but revealed the predictive value for MDD to be not greater than 0.7–1%, although it has been based on a set of initially 181,582 SNPs (Demirkan et al. 2010). It is obvious that even such recent approaches are by no means valuable for clinical decision making, since they barely bear information superior to the patients' medical history.

Nevertheless, such studies deliver useful information: A variant of the above mentioned score based on half of the SNPs could capture 2.1% of the variance for anxiety, suggesting a common genetic basis with MDD (Demirkan et al. 2010). This highlights an important observation that constantly accompanies research on genetics in psychiatric disorders: gene polymorphisms are not specifically linked to certain phenotypes, but influence risk for different disorders (Green et al. 2010; Huang et al. 2010). However, this is no great surprise, since there is even a substantial overlap between psychiatric diagnostic categories on the level of symptoms that is reflected by high rates of comorbidity, such as the co-occurrence of MDD and anxiety disorders (Kessler et al. 2005).

Patients differ in their clinical presentation within a specific diagnostic category and therefore likely suffer from distinct susceptibility factors. Accordingly, the high inconsistencies found in classical association and pharmacogenetic studies may – along with factors such as epistasis and gene–environment interactions – primarily result from high levels of biological heterogeneity as subjects are solely included based on their vaguely biological-related clinical phenotypes. The concept of endophenotypes has been enthusiastically acclaimed as a strategy to deal with this dilemma. Unsurprisingly, the non-specificity inherent to clinical phenotypes can also be found with regard to intermediate phenotypes. Reductions of 5-HT<sub>1A</sub> BP or volume decrease of the ACC have not only been found in samples of MDD, but also in patients assigned to anxiety disorders (Neumeister et al. 2004; Lanzenberger et al. 2007; van Tol et al. 2010). The same holds true for amygdala hyperactivity that occurs in various psychiatric phenotypes including social phobia and Tourette's syndrome (Birbaumer et al. 1998; Neuner et al. 2010) and hippocampus volume, which is also an intermediate phenotype of schizophrenia (Honea et al. 2008). This picture will presumably get even more sophisticated, the more state-of-the-art neuroimaging methods are applied to other clinical phenotypes. This non-specificity suggests that intermediate phenotypes are not well suited as quantitative

biomarkers for current psychiatric diagnostic categories. In contrast, they may be most advantageous as substitutes for clinical phenotypes in the quest for valid biologically defined psychiatric diagnostic entities. Recent approaches such as the Research Domain Criteria (RDoC) framework are first attempts to liberate psychiatric research from its nosological boundaries and may bridge the gap to a biologically based classification of mental illness (Miller 2010)

Intermediate phenotypes that are non-specific to a certain psychiatric diagnostic entity further suggest shared pathogenetic pathways, that may also implicate shared pathways for treatment: As an example, anxiety disorders and MDD are both associated with increased amygdala response and can be treated with SSRIs, which in turn have been shown to modulate amygdala activity (Fu et al. 2004; Windischberger et al. 2009). For this purpose, upcoming neuroimaging studies that map the effects of antidepressants on the level of intermediate phenotypes such as amygdala reactivity or 5-HT<sub>1A</sub> BP will certainly yield useful insights (Spindelegger et al. 2009; Windischberger et al. 2009). Hopefully, the dissection of psychopathological syndromes in their shared and unique neurobiological components reflected by intermediate phenotypes may finally enable the “functional approach” and improve diagnosis and treatment by “denosologization” of biological psychiatry, an issue already discussed over twenty years ago (van Praag et al. 1987).

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## Statement of Interest

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## References

- Adkins DE, Aberg K, McClay JL, Hettema JM, Kornstein SG, Bukszar J, et al. 2010. A genomewide association study of citalopram response in major depressive disorder—a psychometric approach. *Biol Psychiatry* 68(6):25–27.
- Akimova E, Lanzenberger R, Kasper S. 2009. The serotonin-1A receptor in anxiety disorders. *Biol Psychiatry* 66(7):627–635.
- Alia-Klein N, Goldstein RZ, Kriplani A, Logan J, Tomasi D, Williams B, et al. 2008. Brain monoamine oxidase A activity predicts trait aggression. *J Neurosci* 28(19):5099–5104.
- Anand A, Li Y, Wang Y, Wu J, Gao S, Bukhari L, Mathews VP, et al. 2005a. Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. *Biol Psychiatry* 57(10):1079–1088.
- Anand A, Li Y, Wang Y, Wu J, Gao S, Bukhari L, et al. 2005b. Antidepressant effect on connectivity of the mood-regulating circuit: an FMRI study. *Neuropsychopharmacology* 30(7):1334–1344.
- Anand A, Li Y, Wang Y, Gardner K, Lowe MJ. 2007. Reciprocal effects of antidepressant treatment on activity and connectivity of the mood regulating circuit: an FMRI study. *J Neuropsychiatry Clin Neurosci* 19(3):274–282.
- Ansorge MS, Zhou M, Lira A, Hen R, Gingrich JA. 2004. Early-life blockade of the 5-HT transporter alters emotional behavior in adult mice. *Science* 306(5697):879–881.
- American Psychiatric Association. 2000. Diagnostic and statistical manual of mental disorders. 4th ed. Text revision. Washington, DC: American Psychiatric Association.
- Arce E, Simmons AN, Lovero KL, Stein MB, Paulus MP. 2008. Escitalopram effects on insula and amygdala BOLD activation during emotional processing. *Psychopharmacology (Berlin)* 196(4):661–672.
- Baare WF, Vinberg M, Knudsen GM, Paulson OB, Langkilde AR, Jernigan TL, et al. 2010. Hippocampal volume changes in healthy subjects at risk of unipolar depression. *J Psychiatr Res*, in press.
- Bach-Mizrahi H, Underwood MD, Kassir SA, Bakalian MJ, Sibille E, Tamir H, et al. 2006. Neuronal tryptophan hydroxylase mRNA expression in the human dorsal and median raphe nuclei: major depression and suicide. *Neuropsychopharmacology* 31(4):814–824.
- Bauer M, Bschor T, Pfennig A, Whybrow PC, Angst J, Versiani M, et al. 2007. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders in Primary Care. *World J Biol Psychiatry* 8(2):67–104.
- Bertolino A, Arciero G, Rubino V, Latorre V, De Candia M, Mazzola V, et al. 2005. Variation of human amygdala response during threatening stimuli as a function of 5-HTTLPR genotype and personality style. *Biol Psychiatry* 57(12):1517–1525.
- Bhagwagar Z, Rabiner EA, Sargent PA, Grasby PM, Cowen PJ. 2004. Persistent reduction in brain serotonin 1A receptor binding in recovered depressed men measured by positron emission tomography with [<sup>11</sup>C]WAY-100635. *Mol Psychiatry* 9(4):386–392.
- Bigos KL, Weinberger DR. 2010. Imaging genetics—days of future past. *Neuroimage* 53(3):804–809.
- Birbaumer N, Grodd W, Diedrich O, Klose U, Erb M, Lotze M, et al. 1998. fMRI reveals amygdala activation to human faces in social phobics. *NeuroReport* 9:1223–1226.
- Bocchio-Chiavetto L, Bagnardi V, Zanardini R, Molteni R, Nielsen MG, Placentino A, et al. 2010. Serum and plasma BDNF levels in major depression: a replication study and meta-analyses. *World J Biol Psychiatry* 11(6):763–773.
- Borg J, Henningsson S, Saijo T, Inoue M, Bah J, Westberg L, et al. 2009. Serotonin transporter genotype is associated with cognitive performance but not regional 5-HT1A receptor binding in humans. *Int J Neuropsychopharmacol* 12(6):783–792.
- Bradley SL, Dodelzon K, Sandhu HK, Philibert RA. 2005. Relationship of serotonin transporter gene polymorphisms and haplotypes to mRNA transcription. *Am J Med Genet B Neuropsychiatr Genet* 136B(1):58–61.
- Brown SM, Peet E, Manuck SB, Williamson DE, Dahl RE, Ferrell RE, et al. 2005. A regulatory variant of the human tryptophan hydroxylase-2 gene biases amygdala reactivity. *Mol Psychiatry* 10(9):884–888, 805.
- Buckholtz JW, Callicott JH, Kolachana B, Hariri AR, Goldberg TE, Genderson M, et al. 2008. Genetic variation in MAOA modulates ventromedial prefrontal circuitry mediating individual differences in human personality. *Mol Psychiatry* 13(3):313–324.
- Bueller JA, Aftab M, Sen S, Gomez-Hassan D, Burmeister M, Zubieta JK. 2006. BDNF Val66Met allele is associated with reduced hippocampal volume in healthy subjects. *Biol Psychiatry* 59(9):812–815.
- Canli T, Lesch KP. 2007. Long story short: the serotonin transporter in emotion regulation and social cognition. *Nat Neurosci* 10(9):1103–1109.
- Canli T, Congdon E, Gutknecht L, Constable RT, Lesch KP. 2005a. Amygdala responsiveness is modulated by tryptophan hydroxylase-2 gene variation. *J Neural Transm* 112(11):1479–1485.
- Canli T, Omura K, Haas BW, Fallgatter A, Constable RT, Lesch KP. 2005b. Beyond affect: a role for genetic variation of the serotonin transporter in neural activation during a cognitive attention task. *Proc Natl Acad Sci USA* 102(34):12224–12229.
- Canli T, Qiu M, Omura K, Congdon E, Haas BW, Amin Z, et al. 2006. Neural correlates of epigenesis. *Proc Natl Acad Sci USA* 103(43):16033–16038.
- Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, et al. 2002. Role of genotype in the cycle of violence in maltreated children. *Science* 297(5582):851–854.
- Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. 2003. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 301(5631):386–389.
- Caspi A, Hariri AR, Holmes A, Uher R, Moffitt TE. 2010. Genetic sensitivity to the environment: the case of the serotonin transporter gene and its implications for studying complex diseases and traits. *Am J Psychiatry* 167(5):509–527.
- Cerasa A, Gioia MC, Labate A, Lanza P, Magariello A, Muglia M, et al. 2008. MAO A VNTR polymorphism and variation in human morphology: a VBM study. *Neuroreport* 19(11):1107–1110.
- Chakrabarti S, Grover S, Rajagopal R. 2010. Electroconvulsive therapy: a review of knowledge, experience and attitudes of patients concerning the treatment. *World J Biol Psychiatry* 11(3):525–537.
- Chen CH, Suckling J, Ooi C, Fu CH, Williams SC, Walsh ND, et al. 2008a. Functional coupling of the amygdala in depressed patients treated with antidepressant medication. *Neuropsychopharmacology* 33(8):1909–1918.
- Chen L, Lawlor DA, Lewis SJ, Yuan W, Abdollahi MR, Timpson NJ, et al. 2008b. Genetic association study of BDNF in depression: finding from two cohort studies and a meta-analysis. *Am J Med Genet B Neuropsychiatr Genet* 147B(6):814–821.



- Chen MC, Hamilton JP, Gotlib IH. 2010. Decreased hippocampal volume in healthy girls at risk of depression. *Arch Gen Psychiatry* 67(3):270–276.
- Chepenik LG, Fredericks C, Papademetris X, Spencer L, Lacadie C, Wang F, et al. 2009. Effects of the brain-derived neurotrophic growth factor val66met variation on hippocampus morphology in bipolar disorder. *Neuropsychopharmacology* 34(4):944–951.
- Chiao JY, Blizinsky KD. 2010. Culture-gene coevolution of individualism-collectivism and the serotonin transporter gene. *Proc Biol Sci* 277(1681):529–537.
- Cichon S, Craddock N, Daly M, Faraone SV, Gejman PV, Kelsoe J, et al. 2009. Genomewide association studies: history, rationale, and prospects for psychiatric disorders. *Am J Psychiatry* 166(5):540–556.
- Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, et al. 2009. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* 373(9665):746–758.
- Clarke H, Flint J, Attwood AS, Munafo MR. 2010. Association of the 5-HTTLPR genotype and unipolar depression: a meta-analysis. *Psychol Med* 40(11):1767–1778.
- Costafreda SG, Brammer MJ, David AS, Fu CH. 2008. Predictors of amygdala activation during the processing of emotional stimuli: a meta-analysis of 385 PET and fMRI studies. *Brain Res Rev* 58(1):57–70.
- Cremers HR, Demenescu LR, Aleman A, Renken R, van Tol MJ, van der Wee NJ, et al. 2010. Neuroticism modulates amygdala-prefrontal connectivity in response to negative emotional facial expressions. *Neuroimage* 49(1):963–970.
- Czeh B, Michaelis T, Watanabe T, Frahm J, de Biurrun M, van Kampen M, et al. 2001. Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. *Proc Natl Acad Sci USA* 98(22):12796–12801.
- Dannlowski U, Ohrmann P, Bauer J, Kugel H, Baune BT, Hohoff C, et al. 2007. Serotonergic genes modulate amygdala activity in major depression. *Genes Brain Behav* 6(7):672–676.
- Dannlowski U, Ohrmann P, Bauer J, Deckert J, Hohoff C, Kugel H, et al. 2008. 5-HTTLPR biases amygdala activity in response to masked facial expressions in major depression. *Neuropsychopharmacology* 33(2):418–424.
- Dannlowski U, Konrad C, Kugel H, Zwitterlood P, Domschke K, Schoning S, et al. 2009a. Emotion specific modulation of automatic amygdala responses by 5-HTTLPR genotype. *Neuroimage* 53(3):893–898.
- Dannlowski U, Ohrmann P, Konrad C, Domschke K, Bauer J, Kugel H, et al. 2009b. Reduced amygdala-prefrontal coupling in major depression: association with MAOA genotype and illness severity. *Int J Neuropsychopharmacol* 12(1):11–22.
- David SP, Murthy NV, Rabiner EA, Munafo MR, Johnstone EC, Jacob R, et al. 2005. A functional genetic variation of the serotonin (5-HT) transporter affects 5-HT1A receptor binding in humans. *J Neurosci* 25(10):2586–2590.
- Della Pasqua O, Santen GW, Danhof M. 2010. The missing link between clinical endpoints and drug targets in depression. *Trends Pharmacol Sci* 31(4):144–152.
- Demirkan A, Penninx BW, Hek K, Wray NR, Amin N, Aulchenko YS, et al. 2010. Genetic risk profiles for depression and anxiety in adult and elderly cohorts. *Mol Psychiatry* 16(7):773–783.
- Drevets WC, Frank E, Price JC, Kupfer DJ, Holt D, Greer PJ, et al. 1999. PET imaging of serotonin 1A receptor binding in depression. *Biol Psychiatry* 46(10):1375–1387.
- Drevets WC, Bogers W, Raichle ME. 2002. Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. *Eur Neuropsychopharmacol* 12(6):527–544.
- Drevets WC, Thase ME, Moses-Kolko EL, Price J, Frank E, Kupfer DJ, et al. 2007. Serotonin-1A receptor imaging in recurrent depression: replication and literature review. *Nucl Med Biol* 34(7):865–877.
- Drevets WC, Savitz J, Trimble M. 2008. The subgenual anterior cingulate cortex in mood disorders. *CNS Spectr* 13(8):663–81.
- Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, et al. 2003. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* 112(2):257–269.
- Eker C, Gonul AS. 2010. Volumetric MRI studies of the hippocampus in major depressive disorder: Meanings of inconsistency and directions for future research. *World J Biol Psychiatry* 11(1):19–35.
- Fakra E, Hyde LW, Gorka A, Fisher PM, Munoz KE, Kimak M, et al. 2009. Effects of HTR1A C(-1019)G on amygdala reactivity and trait anxiety. *Arch Gen Psychiatry* 66(1):33–40.
- Fisher PM, Meltzer CC, Ziolkowski SK, Price JC, Moses-Kolko EL, Berga SL, et al. 2006. Capacity for 5-HT1A-mediated autoregulation predicts amygdala reactivity. *Nat Neurosci* 9(11):1362–1363.
- Fowler JS, Alia-Klein N, Kriplani A, Logan J, Williams B, Zhu W, et al. 2007. Evidence that brain MAO A activity does not correspond to MAO A genotype in healthy male subjects. *Biol Psychiatry* 62(4):355–358.
- Friedel E, Schlagenhauf F, Sterzer P, Park SQ, Bermpohl F, Strohle A, et al. 2009. 5-HTT genotype effect on prefrontal-amygdala coupling differs between major depression and controls. *Psychopharmacology (Berlin)* 205(2):261–271.
- Frodl T, Meisenzahl EM, Zill P, Baghai T, Rujescu D, Leinsinger G, et al. 2004. Reduced hippocampal volumes associated with the long variant of the serotonin transporter polymorphism in major depression. *Arch Gen Psychiatry* 61(2):177–183.
- Frodl T, Schule C, Schmitt G, Born C, Baghai T, Zill P, et al. 2007. Association of the brain-derived neurotrophic factor Val66Met polymorphism with reduced hippocampal volumes in major depression. *Arch Gen Psychiatry* 64(4):410–416.
- Frodl T, Koutsouleris N, Bottlender R, Born C, Jager M, Morgensthaler M, et al. 2008a. Reduced gray matter brain volumes are associated with variants of the serotonin transporter gene in major depression. *Mol Psychiatry* 13(12):1093–1101.
- Frodl T, Zill P, Baghai T, Schule C, Rupprecht R, Zetzsche T, et al. 2008b. Reduced hippocampal volumes associated with the long variant of the tri- and diallelic serotonin transporter polymorphism in major depression. *Am J Med Genet B Neuropsychiatr Genet* 147B(7):1003–1007.
- Frodl T, Reinhold E, Koutsouleris N, Donohoe G, Bondy B, Reiser M, et al. 2010. Childhood stress, serotonin transporter gene and brain structures in major depression. *Neuropsychopharmacology* 35(6):1383–1390.
- Frustaci A, Pozzi G, Gianfagna F, Manzoli L, Boccia S. 2008. Meta-analysis of the brain-derived neurotrophic factor gene (BDNF) Val66Met polymorphism in anxiety disorders and anxiety-related personality traits. *Neuropsychobiology* 58(3–4):163–170.
- Fu CH, Williams SC, Cleare AJ, Brammer MJ, Walsh ND, Kim J, et al. 2004. Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study. *Arch Gen Psychiatry* 61(9):877–889.
- Fusar-Poli P, Placentino A, Carletti F, Landi P, Allen P, Surguladze S, et al. 2009. Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. *J Psychiatry Neurosci* 34(6):418–432.



- Garriock HA, Kraft JB, Shyn SI, Peters EJ, Yokoyama JS, Jenkins GD, et al. 2010. A genomewide association study of citalopram response in major depressive disorder. *Biol Psychiatry* 67(2):133–138.
- Gasic GP, Smoller JW, Perlis RH, Sun M, Lee S, Kim BW, et al. 2009. BDNF, relative preference, and reward circuitry responses to emotional communication. *Am J Med Genet B Neuropsychiatr Genet* 150B(6):762–781.
- Gaspar P, Cases O, Maroteaux L. 2003. The developmental role of serotonin: news from mouse molecular genetics. *Nat Rev Neurosci* 4(12):1002–1012.
- Gillihan SJ, Rao H, Wang J, Detre JA, Breland J, Sankoorikal GM, et al. 2010. Serotonin transporter genotype modulates amygdala activity during mood regulation. *Soc Cogn Affect Neurosci* 5(1):1–10.
- Gonul AS, Kitis O, Eker MC, Eker OD, Ozan E, Coburn K. 2010. Association of the brain-derived neurotrophic factor Val66Met polymorphism with hippocampus volumes in drug-free depressed patients. *World J Biol Psychiatry* 12(2):110–118.
- Gottesman II, Gould TD. 2003. “The endophenotype concept in psychiatry: etymology and strategic intentions.” *Am J Psychiatry* 160(4):636–645.
- Green EK, Grozeva D, Jones I, Jones L, Kirov G, Caesar S. 2010. The bipolar disorder risk allele at CACNA1C also confers risk of recurrent major depression and of schizophrenia. *Mol Psychiatry* 15(10):1016–1022.
- Groves JO. 2007. Is it time to reassess the BDNF hypothesis of depression? *Mol Psychiatry* 12(12):1079–1088.
- Gutknecht L, Jacob C, Strobel A, Kriegebaum C, Muller J, Zeng Y, et al. 2007. Tryptophan hydroxylase-2 gene variation influences personality traits and disorders related to emotional dysregulation. *Int J Neuropsychopharmacol* 10(3):309–320.
- Haghighi F, Bach-Mizrahi H, Huang YY, Arango V, Shi S, Dwork AJ, et al. 2008. Genetic architecture of the human tryptophan hydroxylase 2 Gene: existence of neural isoforms and relevance for major depression. *Mol Psychiatry* 13(8):813–820.
- Hamilton JP, Siemer M, Gotlib IH. 2008. Amygdala volume in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. *Mol Psychiatry* 13(11):993–1000.
- Hariri AR, Mattay VS, Tessitore A, Kolachana B, Fera F, Goldman D, et al. 2002. Serotonin transporter genetic variation and the response of the human amygdala. *Science* 297(5580):400–403.
- Hariri AR, Goldberg TE, Mattay VS, Kolachana BS, Callicott JH, Egan MF, et al. 2003. Brain-derived neurotrophic factor val66-met polymorphism affects human memory-related hippocampal activity and predicts memory performance. *J Neurosci* 23(17):6690–6694.
- Hariri AR, Drabant EM, Munoz KE, Kolachana BS, Mattay VS, Egan MF, et al. 2005. A susceptibility gene for affective disorders and the response of the human amygdala. *Arch Gen Psychiatry* 62(2):146–152.
- Hashimoto R, Moriguchi Y, Yamashita F, Mori T, Nemoto K, Okada T, et al. 2008. Dose-dependent effect of the Val66Met polymorphism of the brain-derived neurotrophic factor gene on memory-related hippocampal activity. *Neurosci Res* 61(4):360–367.
- Heils A, Teufel A, Petri S, Stober G, Riederer P, Bengel D, et al. 1996. Allelic variation of human serotonin transporter gene expression. *J Neurochem* 66(6):2621–2624.
- Heinz A, Braus DF, Smolka MN, Wrase J, Puls I, Hermann D, et al. 2005. Amygdala-prefrontal coupling depends on a genetic variation of the serotonin transporter. *Nat Neurosci* 8(1):20–21.
- Henningsson S, Borg J, Lundberg J, Bah J, Lindstrom M, Ryding E, et al. 2009. Genetic variation in brain-derived neurotrophic factor is associated with serotonin transporter but not serotonin-1A receptor availability in men. *Biol Psychiatry* 66(5):477–485.
- Hirvonen J, Karlsson H, Kajander J, Lepola A, Markkula J, Rasi-Hakala H, et al. 2008. Decreased brain serotonin 5-HT1A receptor availability in medication-naïve patients with major depressive disorder: an in-vivo imaging study using PET and [carbonyl-11C]WAY-100635. *Int J Neuropsychopharmacol* 11(4):465–476.
- Honea RA, Meyer-Lindenberg A, Hobbs KB, Pezawas L, Mattay VS, Egan MF, et al. 2008. Is gray matter volume an intermediate phenotype for schizophrenia? A voxel-based morphometry study of patients with schizophrenia and their healthy siblings. *Biol Psychiatry* 63(5):465–474.
- Hu XZ, Lipsky RH, Zhu G, Akhtar LA, Taubman J, Greenberg BD, et al. 2006. Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. *Am J Hum Genet* 78(5):815–826.
- Huang J, Perlis RH, Lee PH, Rush AJ, Fava M, Sachs GS, et al. 2010. Cross-disorder genomewide analysis of schizophrenia, bipolar disorder, and depression. *Am J Psychiatry* 167(10):1254–1263.
- Hyman SE. 2008. A glimmer of light for neuropsychiatric disorders. *Nature* 455(7215):890–893.
- Innis RB, Cunningham VJ, Delforge J, Fujita M, Gjedde A, Gunn RN, et al. 2007. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *J Cereb Blood Flow Metab* 27(9):1533–1539.
- Inoue H, Yamasue H, Tochigi M, Takei K, Suga M, Abe O, et al. 2010. Effect of tryptophan hydroxylase-2 gene variants on amygdalar and hippocampal volumes. *Brain Res* 1331:51–57.
- Ising M, Lucae S, Binder EB, Bettecken T, Uhr M, Ripke S, et al. 2009. A genomewide association study points to multiple loci that predict antidepressant drug treatment outcome in depression. *Arch Gen Psychiatry* 66(9):966–975.
- Ito H, Halldin C, Farde L. 1999. Localization of 5-HT1A receptors in the living human brain using [carbonyl-11C]WAY-100635: PET with anatomic standardization technique. *J Nucl Med* 40(1):102–109.
- Jans LA, Riedel WJ, Markus CR, Blokland A. 2007. Serotonergic vulnerability and depression: assumptions, experimental evidence and implications. *Mol Psychiatry* 12(6):522–543.
- Jedema HP, Gianaros PJ, Greer PJ, Kerr DD, Liu S, Higley JD, et al. 2010. Cognitive impact of genetic variation of the serotonin transporter in primates is associated with differences in brain morphology rather than serotonin neurotransmission. *Mol Psychiatry* 15(5):512–522, 446.
- Jessen F, Schuhmacher A, von Widdern O, Guttenthaler V, Hofels S, Suliman H, et al. 2009. No association of the Val66Met polymorphism of the brain-derived neurotrophic factor with hippocampal volume in major depression. *Psychiatr Genet* 19(2):99–101.
- Kalbitzer J, Frokjaer VG, Erritzoe D, Svarer C, Cumming P, Nielsen FA, et al. 2009. The personality trait openness is related to cerebral 5-HTT levels. *Neuroimage* 45(2):280–285.
- Kasper S, McEwen BS. 2008. Neurobiological and clinical effects of the antidepressant tianeptine. *CNS Drugs* 22(1):15–26.
- Kato M, Serretti A. 2008. Review and meta-analysis of antidepressant pharmacogenetic findings in major depressive disorder. *Mol Psychiatry* 15(5):473–500.
- Kendler KS, Gatz M, Gardner CO, Pedersen NL. 2006. A Swedish national twin study of lifetime major depression. *Am J Psychiatry* 163(1):109–114.
- Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. 2005. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 62(6):617–627.
- Kim-Cohen J, Caspi A, Taylor A, Williams B, Newcombe R, Craig IW, et al. 2006. MAOA, maltreatment, and gene-environment

- interaction predicting children's mental health: new evidence and a meta-analysis. *Mol Psychiatry* 11(10):903–913.
- Kim MJ, Whalen PJ. 2009. The structural integrity of an amygdala-prefrontal pathway predicts trait anxiety. *J Neurosci* 29(37):11614–11618.
- Koolschijn PC, van Haren NE, Bakker SC, Hoogendoorn ML, Pol HE, Kahn RS. 2009a. Effects of brain-derived neurotrophic factor Val66Met polymorphism on hippocampal volume change in schizophrenia. *Hippocampus* 20(9):1010–1017.
- Koolschijn PC, van Haren NE, Lensvelt-Mulders GJ, Hulshoff Pol HE, Kahn RS. 2009b. Brain volume abnormalities in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. *Hum Brain Mapp* 30(11):3719–3735.
- Krishnan V, Nestler EJ. 2008. The molecular neurobiology of depression. *Nature* 455(7215):894–902.
- Krishnan V, Nestler EJ. 2010. Linking molecules to mood: new insight into the biology of depression. *Am J Psychiatry* 167(11):1305–1320.
- Lanzenberger RR, Mitterhauser M, Spindelegger C, Wadsak W, Klein N, Mien LK, et al. 2007. Reduced serotonin-1A receptor binding in social anxiety disorder. *Biol Psychiatry* 61(9):1081–1089.
- Lasky-Su JA, Faraone SV, Glatt SJ, Tsuang MT. 2005. Meta-analysis of the association between two polymorphisms in the serotonin transporter gene and affective disorders. *Am J Med Genet B Neuropsychiatr Genet* 133B(1):110–115.
- Lee BT, Ham BJ. 2008a. Monoamine oxidase A-uVNTR genotype affects limbic brain activity in response to affective facial stimuli. *Neuroreport* 19(5):515–519.
- Lee BT, Ham BJ. 2008b. Serotonergic genes and amygdala activity in response to negative affective facial stimuli in Korean women. *Genes Brain Behav* 7(8):899–905.
- Lee M, Bailer UF, Frank GK, Henry SE, Meltzer CC, Price JC, et al. 2005. Relationship of a 5-HT transporter functional polymorphism to 5-HT1A receptor binding in healthy women. *Mol Psychiatry* 10(8):715–716.
- Lemondé S, Turecki G, Bakish D, Du L, Hrdina PD, Bown CD, et al. 2003. Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide. *J Neurosci* 23(25):8788–8799.
- Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, et al. 1996. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* 274(5292):1527–1531.
- Licinio J, Dong C, Wong ML. 2009. Novel sequence variations in the brain-derived neurotrophic factor gene and association with major depression and antidepressant treatment response. *Arch Gen Psychiatry* 66(5):488–497.
- Lopez-Leon S, Janssens AC, Gonzalez-Zuloeta Ladd AM, Del-Favero J, Claes SJ, Oostra BA, et al. 2008. Meta-analyses of genetic studies on major depressive disorder. *Mol Psychiatry* 13(8):772–785.
- Lothe A, Boni C, Costes N, Gorwood P, Bouvard S, Le Bars D, et al. 2009. Association between triallelic polymorphism of the serotonin transporter and [18F]MPPF binding potential at 5-HT1A receptors in healthy subjects. *Neuroimage* 47(2):482–492.
- Lu B, Pang PT, Woo NH. 2005. The yin and yang of neurotrophin action. *Nat Rev Neurosci* 6(8):603–614.
- Martinowich K, Lu B. 2008. Interaction between BDNF and serotonin: role in mood disorders. *Neuropsychopharmacology* 33(1):73–83.
- Matsuo K, Walss-Bass C, Nery FG, Nicoletti MA, Hatch JP, Frey BN, et al. 2009. Neuronal correlates of brain-derived neurotrophic factor Val66Met polymorphism and morphometric abnormalities in bipolar disorder. *Neuropsychopharmacology* 34(8):1904–1913.
- Matthews SC, Strigo IA, Simmons AN, Yang TT, Paulus MP. 2008. Decreased functional coupling of the amygdala and supragenual cingulate is related to increased depression in unmedicated individuals with current major depressive disorder. *J Affect Disord* 111(1):13–20.
- Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. 2005. Deep brain stimulation for treatment-resistant depression. *Neuron* 45(5):651–660.
- McMahon FJ, Akula N, Schulze TG, Muglia P, Tozzi F, Detera-Wadleigh SD, et al. 2010. Meta-analysis of genome-wide association data identifies a risk locus for major mood disorders on 3p21.1. *Nat Genet* 42(2):128–131.
- Meltzer CC, Price JC, Mathis CA, Butters MA, Ziolkowski SK, Moses-Kolko E, et al. 2004. Serotonin 1A receptor binding and treatment response in late-life depression. *Neuropsychopharmacology* 29(12):2258–2265.
- Meyer-Lindenberg A. 2010. Intermediate or brainless phenotypes for psychiatric research? *Psychol Med* 40(7):1057–1062.
- Meyer-Lindenberg A, Weinberger DR. 2006. Intermediate phenotypes and genetic mechanisms of psychiatric disorders. *Nat Rev Neurosci* 7(10):818–827.
- Meyer-Lindenberg A, Buckholtz JW, Kolachana B, A RH, Pezawas L, Blasi G, Wabnitz A, et al. 2006. Neural mechanisms of genetic risk for impulsivity and violence in humans. *Proc Natl Acad Sci USA* 103(16):6269–6274.
- Meyer JH, Ginovart N, Boovariwala A, Sagrati S, Hussey D, Garcia A, et al. 2006. Elevated monoamine oxidase A levels in the brain: an explanation for the monoamine imbalance of major depression. *Arch Gen Psychiatry* 63(11):1209–1216.
- Mickey BJ, Ducci F, Hodgkinson CA, Langenecker SA, Goldman D, Zubieta JK. 2008. Monoamine oxidase A genotype predicts human serotonin 1A receptor availability in vivo. *J Neurosci* 28(44):11354–11359.
- Miller G. 2010. Psychiatry. Beyond DSM: seeking a brain-based classification of mental illness. *Science* 327(5972):1437.
- Montag C, Reuter M, Newport B, Elger C, Weber B. 2008. The BDNF Val66Met polymorphism affects amygdala activity in response to emotional stimuli: evidence from a genetic imaging study. *Neuroimage* 42(4):1554–1559.
- Moses-Kolko EL, Price JC, Thase ME, Meltzer CC, Kupfer DJ, Mathis CA, et al. 2007. Measurement of 5-HT1A receptor binding in depressed adults before and after antidepressant drug treatment using positron emission tomography and [11C] WAY-100635. *Synapse* 61(7):523–530.
- Mossner R, Mikova O, Koutsilieri E, Saoud M, Ehli AC, Muller N, et al. 2007. Consensus paper of the WFSBP Task Force on Biological Markers: biological markers in depression. *World J Biol Psychiatry* 8(3):141–174.
- Muglia P, Tozzi F, Galwey NW, Francks C, Upmanyu R, Kong XQ, et al. 2010. Genome-wide association study of recurrent major depressive disorder in two European case-control cohorts. *Mol Psychiatry* 15(6):589–601.
- Munafò MR, Brown SM, Hariri AR. 2008. Serotonin transporter (5-HTTLPR) genotype and amygdala activation: a meta-analysis. *Biol Psychiatry* 63(9):852–857.
- Munafò MR, Freimer NB, Ng W, Ophoff R, Veijola J, Miettunen J, et al. 2009. 5-HTTLPR genotype and anxiety-related personality traits: a meta-analysis and new data. *Am J Med Genet B Neuropsychiatr Genet* 150B(2):271–281.
- Murthy NV, Selvaraj S, Cowen PJ, Bhagwagar Z, Riedel WJ, Peers P, et al. 2010. Serotonin transporter polymorphisms (SLC6A4 insertion/deletion and rs25531) do not affect the availability of 5-HTT to [11C] DASB binding in the living human brain. *Neuroimage* 52(1):50–54.
- Neumeister A, Bain E, Nugent AC, Carson RE, Bonne O, Luckenbaugh DA, et al. 2004. Reduced serotonin type 1A receptor binding in panic disorder. *J Neurosci* 24(3):589–591.

- Neuner I, Kellermann T, Stocker T, Kircher T, Habel U, Shah JN, et al. 2010. Amygdala hypersensitivity in response to emotional faces in Tourette's patients. *World J Biol Psychiatry* 11(7):858–872.
- Nordanskog P, Dahlstrand U, Larsson MR, Larsson EM, Knutsson L, Johanson A. 2010. Increase in hippocampal volume after electroconvulsive therapy in patients with depression: a volumetric magnetic resonance imaging study. *J ECT* 26(1):62–67.
- Noskova T, Pivac N, Nedic G, Kazantseva A, Gaysina D, Faskhutdinova G, et al. 2008. Ethnic differences in the serotonin transporter polymorphism (5-HTTLPR) in several European populations. *Prog Neuropsychopharmacol Biol Psychiatry* 32(7):1735–1739.
- Pacheco J, Beevers CG, Benavides C, McGeary J, Stice E, Schnyer DM. 2009. Frontal-limbic white matter pathway associations with the serotonin transporter gene promoter region (5-HTTLPR) polymorphism. *J Neurosci* 29(19):6229–6233.
- Parsey RV, Oquendo MA, Ogden RT, Olvet DM, Simpson N, Huang YY, et al. 2006. Altered serotonin 1A binding in major depression: a [carbonyl-C-11]WAY100635 positron emission tomography study. *Biol Psychiatry* 59(2):106–113.
- Pezawas L, Meyer-Lindenberg A. 2010. Imaging genetics: Progressing by leaps and bounds. *Neuroimage* 53 (3):801–803.
- Pezawas L, Verchinski BA, Mattay VS, Callicott JH, Kolachana BS, Straub RE, et al. 2004. The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. *J Neurosci* 24(45):10099–10102.
- Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, Kolachana BS, et al. 2005. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. *Nat Neurosci* 8(6):828–834.
- Pezawas L, Meyer-Lindenberg A, Goldman AL, Verchinski BA, Chen G, Kolachana BS, et al. 2008. Evidence of biologic epistasis between BDNF and SLC6A4 and implications for depression. *Mol Psychiatry* 13(7):709–716.
- Praschak-Rieder N, Kennedy J, Wilson AA, Hussey D, Boovariwala A, Willeit M, et al. 2007. Novel 5-HTTLPR allele associates with higher serotonin transporter binding in putamen: a [(11)C] DASB positron emission tomography study. *Biol Psychiatry* 62(4):327–331.
- Price JL, Drevets WC. 2010. Neurocircuitry of mood disorders. *Neuropsychopharmacology* 35(1):192–216.
- Rao H, Gillihan SJ, Wang J, Korczykowski M, Sankoorikal GM, Kaercher KA, et al. 2007. Genetic variation in serotonin transporter alters resting brain function in healthy individuals. *Biol Psychiatry* 62(6):600–606.
- Rao U, Chen LA, Bidesi AS, Shad MU, Thomas MA, Hammen CL. 2009. Hippocampal changes associated with early-life adversity and vulnerability to depression. *Biol Psychiatry* 67(4):357–364.
- Reimold M, Smolka MN, Schumann G, Zimmer A, Wrase J, Mann K, et al. 2007. Midbrain serotonin transporter binding potential measured with [(11)C]DASB is affected by serotonin transporter genotype. *J Neural Transm* 114(5):635–639.
- Riccio O, Potter G, Walzer C, Vallet P, Szabo G, Vutsits L, et al. 2009. Excess of serotonin affects embryonic interneuron migration through activation of the serotonin receptor 6. *Mol Psychiatry* 14(3):280–290.
- Richardson-Jones JW, Craig CP, Guiard BP, Stephen A, Metzger KL, Kung HF, et al. 2010. 5-HT1A autoreceptor levels determine vulnerability to stress and response to antidepressants. *Neuron* 65(1):40–52.
- Risch N, Herrell R, Lehner T, Liang KY, Eaves L, Hoh J, et al. 2009. Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. *J Am Med Assoc* 301(23):2462–2471.
- Sabol SZ, Hu S, Hamer D. 1998. A functional polymorphism in the monoamine oxidase A gene promoter. *Hum Genet* 103(3):273–279.
- Saijo T, Takano A, Suhara T, Arakawa R, Okumura M, Ichimiya T, et al. 2010. Effect of electroconvulsive therapy on 5-HT1A receptor binding in patients with depression: a PET study with [(11)C]WAY 100635. *Int J Neuropsychopharmacol* 13(6):785–791.
- Sargent PA, Kjaer KH, Bench CJ, Rabiner EA, Messa C, Meyer J, et al. 2000. Brain serotonin1A receptor binding measured by positron emission tomography with [(11)C]WAY-100635: effects of depression and antidepressant treatment. *Arch Gen Psychiatry* 57(2):174–180.
- Scheuch K, Lautenschlager M, Grohmann M, Stahlberg S, Kirchheiner J, Zill P, et al. 2007. Characterization of a functional promoter polymorphism of the human tryptophan hydroxylase 2 gene in serotonergic raphe neurons. *Biol Psychiatry* 62(11):1288–1294.
- Schlaepfer TE, George MS, Mayberg H. 2010. WFSBP Guidelines on brain stimulation treatments in psychiatry. *World J Biol Psychiatry* 11(1):2–18.
- Schofield PR, Williams LM, Paul RH, Gatt JM, Brown K, Luty A, et al. 2009. Disturbances in selective information processing associated with the BDNF Val66Met polymorphism: evidence from cognition, the P300 and fronto-hippocampal systems. *Biol Psychol* 80(2):176–188.
- Schosser A, Kasper S. 2009. The role of pharmacogenetics in the treatment of depression and anxiety disorders. *Int Clin Psychopharmacol* 24(6):277–288.
- Schulze TG, Muller DJ, Krauss H, Scherk H, Ohlraun S, Sygailo YV, et al. 2000. Association between a functional polymorphism in the monoamine oxidase A gene promoter and major depressive disorder. *Am J Med Genet* 96(6):801–803.
- Serretti A, Kato M, De Ronchi D, Kinoshita T. 2007. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with selective serotonin reuptake inhibitor efficacy in depressed patients. *Mol Psychiatry* 12(3):247–257.
- Sharp T, Boothman L, Raley J, Queree P. 2007. Important messages in the 'post': recent discoveries in 5-HT neurone feedback control. *Trends Pharmacol Sci* 28(12):629–636.
- Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, Mintun MA. 2001. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biol Psychiatry* 50(9):651–658.
- Shi J, Potash JB, Knowles JA, Weissman MM, Coryell W, Scheftner WA, et al. 2011. Genome-wide association study of recurrent early-onset major depressive disorder. *Mol Psychiatry* 16(2):193–201.
- Shyn SI, Shi J, Kraft JB, Potash JB, Knowles JA, Weissman MM. 2009. Novel loci for major depression identified by genome-wide association study of Sequenced Treatment Alternatives to Relieve Depression and meta-analysis of three studies. *Mol Psychiatry* 16(2):202–215.
- Siegle GJ, Steinhauer SR, Thase ME, Stenger VA, Carter CS. 2002. Can't shake that feeling: event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. *Biol Psychiatry* 51(9):693–707.
- Smolka MN, Buhler M, Schumann G, Klein S, Hu XZ, Moayer M, et al. 2007. Gene-gene effects on central processing of aversive stimuli. *Mol Psychiatry* 12(3):307–317.
- Spindelegger C, Lanzenberger R, Wadsak W, Mien LK, Stein P, Mitterhauser M, et al. 2009. Influence of escitalopram treatment on 5-HT 1A receptor binding in limbic regions in patients with anxiety disorders. *Mol Psychiatry* 14(11):1040–1050.

- Stein JL, Wiedholz LM, Bassett DS, Weinberger DR, Zink CF, Mattay VS, et al. 2007. A validated network of effective amygdala connectivity. *Neuroimage* 36(3):736–745.
- Strigo IA, Simmons AN, Matthews SC, Craig AD, Paulus MP. 2008. Association of major depressive disorder with altered functional brain response during anticipation and processing of heat pain. *Arch Gen Psychiatry* 65(11):1275–1284.
- Strobel A, Gutknecht L, Rothe C, Reif A, Mossner R, Zeng Y, et al. 2003. Allelic variation in 5-HT1A receptor expression is associated with anxiety- and depression-related personality traits. *J Neural Transm* 110(12):1445–1453.
- Sullivan PF, Neale MC, Kendler KS. 2000. Genetic epidemiology of major depression: review and meta-analysis. *Am J Psychiatry* 157(10):1552–1562.
- Surguladze SA, Elkin A, Ecker C, Kalidindi S, Corsico A, Giampietro V, et al. 2008. Genetic variation in the serotonin transporter modulates neural system-wide response to fearful faces. *Genes Brain Behav* 7(5):543–551.
- Surtees PG, Wainwright NW, Willis-Owen SA, Luben R, Day NE, Flint J. 2006. Social adversity, the serotonin transporter (5-HTTLPR) polymorphism and major depressive disorder. *Biol Psychiatry* 59(3):224–229.
- Suslow T, Konrad C, Kugel H, Rumstadt D, Zwieterlood P, Schoning S, et al. 2010. Automatic mood-congruent amygdala responses to masked facial expressions in major depression. *Biol Psychiatry* 67(2):155–160.
- Szeszko PR, Lipsky R, Mentschel C, Robinson D, Gunduz-Bruce H, Sevy S, et al. 2005. Brain-derived neurotrophic factor val66-met polymorphism and volume of the hippocampal formation. *Mol Psychiatry* 10(7):631–636.
- Taylor MJ, Sen S, Bhagwagar Z. 2010. Antidepressant response and the serotonin transporter gene-linked polymorphic region. *Biol Psychiatry* 68(6):536–543.
- Uher R, McGuffin P. 2010. The moderation by the serotonin transporter gene of environmental adversity in the etiology of depression: 2009 update. *Mol Psychiatry* 15(1):18–22.
- Uher R, Perroud N, Ng MY, Hauser J, Henigsberg N, Maier W, et al. 2010. Genome-wide pharmacogenetics of antidepressant response in the GENDEP project. *Am J Psychiatry* 167(5):555–564.
- van Praag HM, Kahn RS, Asnis GM, Wetzler S, Brown SL, Bleich A, et al. 1987. Denosologization of biological psychiatry or the specificity of 5-HT disturbances in psychiatric disorders. *J Affect Disord* 13(1):1–8.
- van Tol MJ, van der Wee NJ, van den Heuvel OA, Nielen MM, Demenescu LR, Aleman A, et al. 2010. Regional brain volume in depression and anxiety disorders. *Arch Gen Psychiatry* 67(10):1002–1011.
- Varnas K, Halldin C, Hall H. 2004. Autoradiographic distribution of serotonin transporters and receptor subtypes in human brain. *Hum Brain Mapp* 22(3):246–260.
- Verhagen M, van der Meij A, van Deurzen PA, Janzing JG, Arias-Vasquez A, Buitelaar JK, et al. 2010. Meta-analysis of the BDNF Val66Met polymorphism in major depressive disorder: effects of gender and ethnicity. *Mol Psychiatry* 15(3):260–271.
- Videbech P, Ravnkilde B. 2004. Hippocampal volume and depression: a meta-analysis of MRI studies. *Am J Psychiatry* 161(11):1957–1966.
- Viviani R, Sim EJ, Lo H, Beschoner P, Osterfeld N, Maier C, et al. 2010. Baseline brain perfusion and the serotonin transporter promoter polymorphism. *Biol Psychiatry* 67(4):317–322.
- Walther DJ, Peter JU, Bashammakh S, Hortnagl H, Voits M, Fink H, et al. 2003. Synthesis of serotonin by a second tryptophan hydroxylase isoform. *Science* 299(5603):76.
- Williams LM, Gatt JM, Schofield PR, Olivieri G, Peduto A, Gordon E. 2009. ‘Negativity bias’ in risk for depression and anxiety: brain-body fear circuitry correlates, 5-HTT-LPR and early life stress. *Neuroimage* 47(3):804–814.
- Willis-Owen SA, Turri MG, Munafo MR, Surtees PG, Wainwright NW, Brixey RD, et al. 2005. The serotonin transporter length polymorphism, neuroticism, and depression: a comprehensive assessment of association. *Biol Psychiatry* 58(6):451–456.
- Windischberger C, Lanzenberger R, Holik A, Spindelegger C, Stein P, Moser U, et al. 2009. Area-specific modulation of neural activation comparing escitalopram and citalopram revealed by pharmacofMRI: a randomized cross-over study. *Neuroimage* 49(2):1161–1170.
- Yu YW, Tsai SJ, Hong CJ, Chen TJ, Chen MC, Yang CW. 2005. Association study of a monoamine oxidase a gene promoter polymorphism with major depressive disorder and antidepressant response. *Neuropsychopharmacology* 30(9):1719–1723.
- Zhang X, Beaulieu JM, Sotnikova TD, Gainetdinov RR, Caron MG. 2004. Tryptophan hydroxylase-2 controls brain serotonin synthesis. *Science* 305(5681):217.
- Zhang X, Gainetdinov RR, Beaulieu JM, Sotnikova TD, Burch LH, Williams RB, et al. 2005. Loss-of-function mutation in tryptophan hydroxylase-2 identified in unipolar major depression. *Neuron* 45(1):11–16.
- Zhou Z, Roy A, Lipsky R, Kuchipudi K, Zhu G, Taubman J, et al. 2005. Haplotype-based linkage of tryptophan hydroxylase 2 to suicide attempt, major depression, and cerebrospinal fluid 5-hydroxyindoleacetic acid in 4 populations. *Arch Gen Psychiatry* 62(10):1109–1118.