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Review article

Imaging genetics studies on monoaminergic genes in major depressive disorder

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ABSTRACT

Although depression is the leading cause of disability worldwide, current understanding of the neurobiology of depression has failed to be translated into clinical practice. Major depressive disorder (MDD) pathogenesis is considered to be significantly influenced by multiple risk genes, however genetic effects are not simply expressed at a behavioral level. Therefore the concept of endophenotype has been applied in psychiatric genetics. Imaging genetics applies anatomical or functional imaging technologies as phenotypic assays to evaluate genetic variation and their impact on behavior. This paper attempts to provide a comprehensive review of available imaging genetics studies, including reports on genetic variants that have most frequently been linked to MDD, such as the monoaminergic genes (serotonin transporter gene, monoamine oxidase A gene, tryptophan hydroxylase-2 gene, serotonin receptor 1A gene and catechol-O-methyl transferase gene), with regard to key structures involved in emotion processing, such as the hippocampus, amygdala, anterior cingulate cortex and orbitofrontal cortex.

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1. Introduction

Depression is the leading cause of disability worldwide in terms of total years lost due to disability. Depressive disorders often recur, and can also lead to suicide, with almost 1 million lives being lost nowadays yearly due to suicide. Depression is a multifaceted illness, characterized by a highly variable symptom profile as well as a varying severity and course. As the neurobiology of depression complexly involves multiple biochemical, genetic, and environmental factors, scientific achievements on the understanding of the neurobiology of depression, have failed to be translated into clinical practice (Scharinger et al., 2011).

Abbreviations: SLC6A4, serotonin transporter gene; 5-HTTLPR, serotonin transporter-linked polymorphic region; MAOA, monoamine oxidase A gene; MAOA-uVNTR, monoamine oxidase A upstream variable number of tandem repeats; TPH2, tryptophan hydroxylase-2 gene; HTR1A, serotonin receptor 1A gene; COMT, catechol-O-methyl transferase gene; MDD, major depressive disorder; HC, healthy control; BOLD, blood-oxygen-level dependent; FC, functional connectivity; ACC, anterior cingulate cortex; OFC, orbitofrontal cortex; GWA, genome-wide association; SLC6A15, neutral amino acid transporter gene; BDNF, brain derived-neurotrophic factor gene; FKBP5, FK506 binding protein 5 gene; NR3C1, glucocorticoid receptor gene.

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The heritability of major depressive disorder (MDD) is estimated to range from 31 to 42% (Kendler et al., 2006), and although genetic linkage and association studies have not been able to identify strong and consistent MDD susceptibility genes (Krishnan and Nestler, 2008), MDD pathogenesis is considered to be significantly influenced by multiple risk genes (Lopez-Leon et al., 2008). However, the genetic architecture of depression is complex and genetic effects are not simply expressed at a behavioral level (Meyer-Lindenberg and Weinberger, 2006). Hence genes do not directly encode for psychiatric diagnoses or symptoms as genetic effects do not translate directly into psychiatric phenotypes (Pezawas and Meyer-Lindenberg, 2010). Therefore the concept of endophenotype has been applied in psychiatric genetics. An endophenotype is a measurable component of neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological nature, unseen by the unaided eye, along the pathway between disease and distal genotype (Gottesman and Gould, 2003). The term intermediate phenotype has been used interchangeably, however traits that are not sufficiently heritable to meet endophenotype criteria have been referred to as intermediate phenotypes (Meyer-Lindenberg and Weinberger, 2006). Intermediate phenotypes of neuroanatomical nature have been visualized by neuroimaging techniques such as functional magnetic resonance imaging (fMRI), morphometric MRI, diffusion tensor imaging, single photon emission computed tomography (SPECT), and positron emission tomography (PET).

Imaging genetics is a form of genetic association analysis, that applies anatomical or functional imaging technologies as phenotypic assays to evaluate genetic variation and their impact on behavior (Hariri and Weinberger, 2003). As gene variants are considered to affect neural circuits through molecular and cellular mechanisms (Meyer-Lindenberg, 2010), imaging genetics has mapped neural phenotypes as a function of genotype (Scharinger et al., 2010), in an attempt to further the understanding of biological mechanisms mediating genetically driven variations. Results of previous imaging genetics studies support the notion that effects of risk genes that shape the structure or function of brain circuits involved in emotion processing (Canli et al., 2009), lead to individual differences in behavior, mood, or cognition (Hariri et al., 2006). As MDD pathology is known to be associated with deficits in the monoaminergic system, monoaminergic genes such as serotonin transporter gene (SLC6A4), monoamine oxidase A gene (MAOA), tryptophan hydroxylase-2 gene (TPH2), serotonin receptor 1A gene (HTR1A) and catechol-O-methyl transferase gene (COMT) have repeatedly been studied, with results suggesting these genes to shape the brain and render it susceptible to depression (Lopez-Munoz and Alamo, 2011). Brain areas, such as the hippocampus, amygdala, anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) have been found to be under the influence of depression-related gene variants (Price and Drevets, 2010).

This paper attempts to provide a comprehensive review of available imaging genetics studies, including reports on genetic variants that have most frequently been linked to increased risk for MDD, such as the monoaminergic genes (SLC6A4, MAOA, TPH2, HTR1A, COMT), with regard to key structures being involved in emotion processing, such as the hippocampus, amygdala, ACC and OFC. In addition, all data was summarized in Table 1.

2. Imaging genetics studies of MDD

The majority of neuroimaging studies on patients with depression have reported a dysfunction in the activation and alteration in structure of brain regions processing emotion (Fusar-Poli et al., 2009). Reduced volume or thickness of the hippocampus, ACC and OFC, amygdala hyper-reactivity and decreased coupling of amygdala-ACC activity have most widely been reported (Scharinger et al., 2011). Evidence of depression-related gene variants influencing brain systems involved in emotion processing in MDD is accumulating (Scharinger et al., 2010), hence encourages the imaging genetics approach in the exploration of the neurobiology of depression.

Alterations within the monoaminergic system have been implicated in the pathogenesis of MDD (Groves, 2007; Jans et al., 2007). Therefore polymorphisms of genes related to the monoaminergic system have been associated with MDD and their impact has been described in distinct brain regions and circuits (Hariri and Weinberger, 2003). A polymorphism is a common variant or allele of a given gene that is present in over 1% of the population (Canli et al., 2005b, 2009). Different types of polymorphisms exist, such as single nucleotide polymorphisms (SNPs), insertions/deletions of nucleotide sequences, variable number of tandem repeats (VNTRs), and copy number variations (CNVs). Polymorphisms may alter the expression and/or functioning of gene products and therefore have impact on clinical outcomes and neural intermediate phenotypes related to MDD (Hariri et al., 2006).

2.1. Serotonin transporter gene (SLC6A4)

The human gene encoding the serotonin transporter (5-HTT) is located on chromosome 17q11.1–17q12, spans 31 kb and consists of 14 exons (Serretti et al., 2007). The primary molecular target for selective serotonin reuptake inhibitors (SSRIs) is 5-HTT, which is responsible for serotonin reuptake at the terminals and cell bodies of serotonergic neurons (Blakely et al., 1998). One of the polymorphic sites in this gene is an insertion/deletion in the 5′-flanking promoter region (serotonin transporter-linked polymorphic region, 5-HTTLPR) (Michaelovsky et al., 1999). 5-HTTLPR results in a short (s) versus long (l) polymorphism (Lenze et al., 2010), with the l allele having a 44-bp insertion of tandem repeat elements in the promoter region, and the s allele lacking this 44-bp insertion (Lesch et al., 1996). The l and s variants of the promoter polymorphism have been reported to have functional differences in modulating transcription of the 5-HTT gene as well as subsequent 5-HTT availability (Heils et al., 1996). Some reports describe an association between depression and the s/s genotype (Bellivier et al., 1998; Cervilla et al., 2006; Gutierrez et al., 1998; Kunugi et al., 1997; Ramasubbu et al., 2006), while other studies have failed to report such an association (Collier et al., 1996; Furlong et al., 1998; Stober et al., 1996).

Previous imaging genetics studies have reported 5-HTTLPR exhibiting opposing effects on MDD patients and healthy controls (Frodl et al., 2008). Patients homozygous for the l allele had significantly reduced bilateral hippocampal volumes than patients homozygous for the s allele. However in healthy controls, homozygosity for the s allele was related to reduced hippocampal volume (Frodl et al., 2008). Also MDD patients who carried a s allele and also had a positive history for emotional neglect were shown to develop smaller hippocampal volumes, compared to patients who only had either an environmental or genetic risk factor (Frodl et al., 2010). Recent studies investigating the interaction effects on hippocampal volume between 5-HTTLPR and environmental adversity, have reported increased negative impact of life events on hippocampal volume in s allele carriers (Rabl et al., 2014). In adolescents, increasing copies of s alleles were found to predict smaller hippocampal volume, which in turn was associated with increased risk of experiencing a first onset of MDD (Little et al., 2014). Also gender was reported to influence 5-HTTLPR effects on the hippocampus in healthy individuals, with female s allele carriers being associated with increased depressive symptoms and larger hippocampal volumes, and male s allele carriers being associated with smaller hippocampal volumes and increased depressive symptoms (Price et al., 2013).

Activity of the amygdala was significantly greater in healthy subjects who carried the s allele when matching fearful and angry facial expressions (Hariri et al., 2002, 2005), and a positive relationship between amygdala activity and number of s alleles in healthy individuals was reported (Bertolino et al., 2005). Increased amygdala activation/response to negative words (Canli et al., 2005b), masked emotional faces

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