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Imaging genetics in obsessive-compulsive disorder: Linking genetic variations to alterations in neuroimaging

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ABSTRACT

Obsessive-compulsive disorder (OCD) occurs in ~1–3% of the general population, and its often rather early onset causes major disabilities in the everyday lives of patients. Although the heritability of OCD is between 35 and 65%, many linkage, association, and genome-wide association studies have failed to identify single genes that exhibit high effect sizes. Several neuroimaging studies have revealed structural and functional alterations mainly in cortico-striato-thalamic loops. However, there is also marked heterogeneity across studies. These inconsistencies in genetic and neuroimaging studies may be due to the heterogeneous and complex phenotypes of OCD. Under the consideration that genetic variants may also influence neuroimaging in OCD, researchers have started to combine both domains in the field of imaging genetics. Here, we conducted a systematic search of PubMed and Google Scholar literature for articles that address genetic imaging in OCD and related disorders (published through March 2014). We selected 8 publications that describe the combination of imaging genetics with OCD, and extended it with 43 publications of comorbid psychiatric disorders. The most promising findings of this systematic review point to the involvement of variants in genes involved in the serotonergic (5-*HTTLPR*, *HTR2A*), dopaminergic (*COMT*, *DAT*), and glutamatergic (*SLC1A1*, *SAPAP*) systems. However, the field of imaging genetics must be further explored, best through investigations that combine multimodal imaging techniques with genetic profiling, particularly profiling techniques that employ polygenetic approaches, with much larger sample sizes than have been used up to now.

Contents

Abbreviations: ACC, anterior cingulate cortex; BDNF, brain-derived neurotrophic factor; COMT, catechol-O-methyltransferase; DAT, dopamine transporter; DLGAP, discs large (*Drosophila*) homolog-associated protein; GWAS, genome-wide association study; 5-HTTLPR, serotonin transporter-linked polymorphic region; MTL, medial temporal lobe; NAA, N-acetylaspartate; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; SAPAP, SAP90/PSD-95-associated protein; PRISMA, systematic reviews and meta-analysis; SLC1A1, solute carrier family 1 (neuronal/epithelial high affinity glutamate transporter); SLC6A3, solute carrier family 6 (neurotransmitter transporter dopamine) member 3; SLC6A4, solute carrier family 6 (neurotransmitter transporter serotonin) member 4.

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1. Introduction

Obsessive-compulsive disorder (OCD) is a heterogeneous psychiatric disorder characterized by clinically significant recurrent, intrusive, and disturbing thoughts (obsessions) and by repetitive behaviors that are aimed at reducing anxiety or dread (compulsions) (American Psychiatric Association, 2000, 2013). It is estimated that the lifetime prevalence of OCD is 1–3% in the general population (Flament et al., 1988; Fontenelle and Hasler, 2008), suggesting that each of our social networks may contain family members, friends, or colleagues that live with this often debilitating condition (Ayuso-Mateos, 2006). The rather high burden of OCD and its elusive etiology emphasize the urgent need for additional research into the neurobiological pathways that cause the disorder and the identification of biomarkers for its prediction and prevention (Fineberg et al., 2012).

A variety of imaging techniques have allowed researchers to delve deep into the brains of OCD patients to seek out aberrations in the neural circuits that control behavior. The most consistent impairments have been found in cortico-striato-thalamic loops (Brem et al., 2012; Maia et al., 2008; van den Heuvel et al., 2010; Walitza et al., 2014a), which connect regions of the neocortex with the striatum and the thalamus to form important feedback loops that regulate neural activity. The cortico-striato-thalamic loops are centrally involved in motor, cognitive, and affective processes, and are assumed to be causally related to OCD symptom generation (Brem et al., 2012; van den Heuvel et al., 2010). Structural magnetic resonance imaging studies have revealed that mainly areas of the medial prefrontal wall – which contains the anterior cingulate cortex (ACC) and adjacent areas -, orbitofrontal cortex (OFC), striatum, and thalamus are impaired in OCD (Huyser et al., 2009; Menzies et al., 2008; Montigny et al., 2013; Peng et al., 2012; Radua et al., 2010). Studies that used diffusion tensor imaging to investigate the integrity of fiber connections have revealed that these prefrontal areas (e.g., ACC and OFC) exhibit altered structural connectivity (Peng et al., 2012; Piras et al., 2013). Similar regions have also been identified using functional neuroimaging, mainly during error processing, inhibition, and decision-making tasks, but also during rest (Brem et al., 2012; Harrison et al., 2013; Huyser et al., 2009). Despite these overlapping findings, it must be noted that the neuroimaging findings in OCD vary widely across studies, and it is not possible to attribute OCD to a single dysfunctional region or network. This heterogeneity is most likely caused by a rather broad spectrum of OCD phenotypes regarding symptomatology, severity, and (last but not least) by the different genetic background. Therefore, the integration of neuroimaging and genetic methods should not only focus on patients' phenotypes, but also on an endophenotypic analysis of unaffected relatives; such integration may improve basic research findings.

Although OCD has a strong genetic background and high familiality (Pauls, 2008; van Grootheest et al., 2005; Walitza et al., 2010), the identification of single causal gene variants has remained difficult. Many molecular-genetic studies of OCD have investigated candidate genes, including those that encode proteins involved in serotonergic [e.g. the *SLC6A4*/serotonin transporter-linked polymorphic region (*5-HTTLPR*)], dopaminergic [e.g. catechol-O-methyltransferase (*COMT*)], and glutamatergic systems (e.g. *SLC1A1* and *DLGAP1*), as well as other systems (e.g. neurotrophic pathways, cell adhesion, and synaptic plasticity). A recent meta-analysis of association studies confirmed that several risk genes are significantly associated with OCD (Taylor, 2013). Moreover, a recent first genome-wide association study (GWAS) discovered several new candidates (Stewart et al., 2013b). According to the GWAS, the lowest two *P*-values were located within the *DLGAP1* gene, a member of the neuronal postsynaptic density complex. However, thus far neither linkage studies nor GWAS have identified any candidate genes with a large effect size. Given that many psychiatric disorders are a complex result of a variety of genetic and environmental factors, each genetic variant accounts for only a small increment in risk of developing the disorder. Therefore, multi-gene risk factors are currently hypothesized to be better predictors for complex disorders (Hibar et al., 2011; International Schizophrenia et al., 2009; Meda et al., 2012).

In the last decade, technological advances in neuroimaging and molecular genetics have facilitated the implementation of imaging genetics, a new strategy that enables to identify the effects of susceptibility genes on the brain (Domschke and Dannlowski, 2010; Pine et al., 2010; Willeit and Praschak-Rieder, 2010). Notably, genetic susceptibility effects are mediated by molecular and cellular mechanisms, which in turn modulate behavioral phenotypes by affecting the structural and functional properties of neural circuits (Atmaca et al., 2011; Hesse et al., 2011; MacMaster, 2010; Wu et al., 2012). Therefore, such translational studies that implement genetics and imaging techniques may reveal the etiology of OCD more precisely (MacMaster, 2010). The combination of genetic variants and imaging techniques has recently been explored as a tool for personalized medicine and the specificity of imaging findings (Biffi et al., 2010; Hibar et al., 2011; Kohannim et al., 2012; Meda et al., 2012; Nikolova et al., 2011; Stice et al., 2012). In this systematic review, we present an exploration, to our knowledge for the first time, of the current literature involving imaging genetics in OCD. We discuss the main results and limitations of these investigations.

2. Experimental procedures

We conducted a systematic review using the preferred reporting items for systematic reviews and meta-analysis criteria (PRISMA) (Liberati et al., 2009; Moher et al., 2009). Articles were searched to include studies that described imaging genetics in OCD (see PRISMA flow diagram in Supplementary Figure S1). In order to expand the literature search results, a second step included psychiatric disorders known to be often comorbid to OCD (Kichuk et al., 2013) (e.g. Tourette and tic disorder, anxiety, panic, substance abuse, bipolar disorder, and depression) or healthy controls. No limits on publication date or publication status were imposed. Articles were identified in PubMed and Google Scholar. The final search was launched on March 6th, 2014. For more details regarding the literature search and keywords, see Supplementary Figure S1. The reference list from each extracted article was reviewed to add manuscripts of potential interest. Two authors (E.G. and S.W.) conducted these searches independently. A total of 718 articles were identified in the first step using the keywords cited in supplementary Figure S1. Sixty-three of these articles were selected; they referred to "imaging-genetics" studies in OCD and for the second step also the comorbid disorders or more specifically referred to the effects of genes that were associated with OCD on neuroimaging findings in patients with comorbid psychiatric disorders.

3. Results

We began the search by looking for all publications that involved "imaging genetics" in OCD. This stipulation led to the retrieval of a small collection of manuscripts describing association analyses of genetic variants with neuroimaging techniques in OCD ($n = 8$). The present study focused on the most significant and nominally significant genes associated with OCD as inclusion criteria by cross-referencing these publications with GWAS and meta-analyzed genetic association (Azzam and Mathews, 2003; Lin, 2007; Pooley et al., 2007; Stewart et al., 2013a, 2013b; Taylor, 2013; Walitza et al., 2014b). A publication by Hoexter et al. (2009)