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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)

was not included in the review because it did not include genetic association results in addition to their findings of single-photon emission computed tomography or magnetic resonance imaging in OCD. This particular publication describes the protocol of an ongoing study of treatment response to either a selective serotonin reuptake inhibitor (fluoxetine) or cognitive behavioral therapy compared with controls, in which the authors plan to combine findings generated from genetics (variable number of tandem repeats in the 3′-UTR of the dopamine transporter/*SLC6A3*), neuropsychology, structural magnetic resonance imaging, and molecular neuroimaging of the dopamine transporter (Hoexter et al., 2009). Table 1 summarizes all imaging-genetic findings regarding genes associated with OCD. Of the 18 genes found to have an association with OCD listed in the table, eight (encoding *HTTLPR*, *SLC1A1*, *GRIN2B*, *DLGAP1*, *DLGAP2*, *SLC6A3*, *MOG*, and *CACNA1C*) were studied in the context of "imaging genetics" in OCD.

3.1. The serotonergic system

The first group of genetic imaging findings in OCD involves the serotonergic system. Hesse et al. (2011) reported that serotonin transporter availability in the midbrain, measured using positron emission tomography and the serotonin transporter-selective radiotracer [^{11}C]DASB, was significantly increased in OCD patients carrying the SS genotype of the *5-HTTLPR*. In addition, compared with patients with early-onset OCD or control subjects, late-onset OCD patients had significantly lower serotonin-transporter availability in the nucleus accumbens, hippocampus, occipital cortex, nucleus caudate, putamen, thalamus, and midbrain (Hesse et al., 2011). However, serotonergic binding results should be interpreted cautiously because binding effects appear to exert great impact through *5-HTTLPR* genotypes (Willeit and Praschak-Rieder, 2010). At the structural level, magnetic resonance imaging was used to demonstrate that OCD patients carrying the S allele of *5-HTTLPR* had smaller right OFC volumes than L allele carriers (Atmaca et al., 2011). At the genetic level, Lin et al. (2007) used a meta-analysis to uncover a significant association between SS genotype and OCD (odds ratio = 1.21, 95% confidence interval = 1.01–1.45, $p = 0.04$). In contrast, a recent meta-analysis that subdivided the *5-HTTLPR* L allele into the high-functioning L_A allele and the low-functioning L_G allele (Hu et al., 2006), producing a triallelic form in which the L_G allele is pooled with the S allele, reported that being an L_A allele carrier was significantly associated with OCD (odds ratio = 1.251, 95% confidence interval = 1.048–1.492, $p = 0.001$) (Taylor, 2013). Just recently, we could replicate this finding of L_A allele association with ealy onset OCD s well as within a meta-Analysis includng early and late onset OCD (Walitza et al., 2014b). However, up to now analysis of these gene variants using genetic imaging techniques in related conditions underscored the effects of the 5-*HTTLPR* S allele and brain activation. In particularly S-allele seems to play a role in the amygdala, in anxiety-related disorders and in control participants (Domschke and Dannlowski, 2010). Nevertheless, some conflicting results have been reported in the context of another psychiatric disorder, depression. In depression S-allele is considered as risk allele but two independent studies produced conflicting results. One could find abnormalities in white matter in S-carriers while the other found no effect on hippocampal volume (Alexopoulos et al., 2009; Cole et al., 2011). Up to now, no other serotonergic candidate genes have been investigated together with imaging techniques in OCD.

3.2. The glutamatergic system

The second group of genetic imaging findings in OCD involves the glutamatergic system. So far, only candidate genes of the glutamatergic system have been replicated in both association and linkage studies of OCD. Therefore, the glutamtergic system is of special interest for imaging genetics. Arnold et al. (2009a) reported an increased thalamic volume in OCD patients with the AA genotype of the *SLC1A1* (solute carrier family 1 (neuronal/epithelial high affinity glutamate transporter), member 1) rs3056 variant. *SLC1A1* gene encodes a high-affinity excitatory amino acid transporter which is selectively expressed in the central nervous system. In contrast, Wu et al. (2012) uncovered a trend between rs301430 in *SLC1A1* and increased thalamic volume. Both observations might be caused by transcriptional alterations, because both variants lie in the 3′ untranslated region of the *SLC1A1* gene (Arnold et al., 2009a; Wendland et al., 2009). In addition to the glutamate transporter the N-methyl-D-aspartate (NMDA) receptors, a class of ionotropic glutamate receptors, are of special interest in OCD. Not only that NMDA receptor gene variants were suggested to associate with OCD (Alonso et al., 2012), dysfunction of NMDA receptors neurotransmission activity were suggested to be involved in OCD (Richter et al., 2012) as well as to mediate fear conditions (Davis, 2011). The NMDA receptor channels are heteromers, composed of three different subunits: NR1 (*GRIN1*), NR2 (*GRIN2A*, *GRIN2B*, *GRIN2C*, or *GRIN2D*). The NR2 subunit acts as the agonist binding site for glutamate and is the predominant excitatory neurotransmitter receptor in the mammalian brain. Moreover, the NMDA receptors are thought to be involved in neurodevelopmental processes of the nervous system, as with the *GRIN2B* and *GRIN2A* (Endele et al., 2010; Hall et al., 2007). Although a meta-analysis by Taylor (2013) found no association between *GRIN2B* and OCD, imaging-genetic findings suggest that *GRIN2B* affects glutamatergic concentrations in the ACC of OCD patients (Arnold et al., 2009b), as well as volumes in the ACC, OFC (Arnold et al., 2009a), and thalamus (Wu et al., 2012). Moreover, a new candidate gene for OCD risk, which encodes *DLGAP* (SAPAP-related) (Bienvenu et al., 2009; Stewart et al., 2013b; Züchner et al., 2009), was recently reported to affect ACC and OFC volume in OCD (Wu et al., 2012). The *DLGAP2* gene encoding the SAP90/PSD-95-associated protein 2 (*SAPAP2*) is located at the post-synaptic density of neuronal cells and it contributes to synaptic functioning. Such alterations might be linked to the synaptic functionality of this protein in excitatory synapses, particularly during glutamatergic synaptic transmission (Bresler et al., 2001; Wan et al., 2011, 2013; Welch et al., 2004). In contrast, the gene encoding *DLGAP2* (*SAPAP2*) has been associated with reduced OFC white matter volume in OCD (Wu et al., 2012); *DLGAP2* status has not yet been studied as a risk factor for OCD.

3.3. Dopaminergic and other genes

To date, Scherk et al. (2009) have published the only study to combine genetic imaging findings in OCD and dopaminergic genes. They investigated the influence of the VNTR polymorphism of the dopamine transporter (*DAT1/SLC6A3*) gene on the metabolic ratios NAA/choline, NAA/creatine, choline/creatine, and Ins/creatine in various brain regions using ^{1}H-magnetic resonance spectroscopy in patients with OCD or bipolar disorder and healthy controls. They found significant increases of the metabolic ratios NAA/choline and NAA/creatine in the left putamen of all subjects carrying the 10/10-repeat *DAT1* genotype (Scherk et al., 2009). They hypothesized that this increased ratio of the homozygote *DAT1* VNTR 10/10-repeat might be associated with higher dopaminergic activity in the left putamen of these individuals (Scherk et al., 2009). Nevertheless, the effects of the *DAT1* VNTR genotype on metabolic ratios were observed in all individuals irrespective of diagnostic status (Scherk et al., 2009). Therefore, there is currently no evidence of dopaminergic gene variations in neuroimaging findings in OCD. Furthermore, according to Taylors' meta-analysis (2013) no

Table 1
The most significant genetic variations associated with obsessive-compulsive disorder (OCD) and their interactions in imaging genetics.

No	Functional group	Genetic polymorphism	Chromosomal location	Association study in OCD	Meta-analysis in OCD[a]	GWAS analysis in OCD[a]	PET/SPECT	Magnetic resonance spectroscopy	Diffusion tensor imaging	Structural MRI/fMRI
1	Serotonergic system	SLC6A4 (5-HTTLPR)	17q11.2	See meta-analysis	(Lin, 2007; Taylor, 2013; Walitza et al., 2014b)	N/Avail	SERT availability increase in *midbrain* of SS-genotypes SERT-LPR in adult OCD ($n=6$ EO-OCD, $n=13$ LO-OCD, $n=21$ control)– PET [^{11}C]DASB (Hesse et al., 2011)	N/Avail	N/Avail	Reduced *OFC* volume in S-allele in adult OCD ($n=40$ OCD, $n=40$ control)- MRI-T1 (Atmaca et al., 2011)
2		HTR2A	13q15-q21	See meta-analysis	(Taylor, 2013)	N/Avail	N/Avail	N/Avail	N/Avail	N/Avail
3		MAOA	Xp11.3	See meta-analysis	(Taylor, 2013)	N/Avail	N/Avail	N/Avail	N/Avail	N/Avail
4	Glutamatergic	SLC1A1 (Glutamate transporter)	9p24	See meta-analysis	(Taylor, 2013)	N/Avail	N/Avail	N/Avail	N/Avail	Increased *thalamic* volume of AA genotype (rs3056) in childhood & adolescent OCD ($n=31$)- MRI (Arnold et al., 2009a) Increased total *ACC* gray matter volume and decreased total *thalamic* volume in childhood & adolescent OCD ($n=20$)- MRI (Wu et al., 2012)
5		GRIK2	6q16.3	See meta-analysis	(Taylor, 2013)	(Stewart et al., 2013b)	N/Avail	N/Avail	N/Avail	N/Avail
6		GRIN2B	12p12	See meta-analysis	NOT significant (Taylor, 2013)	N/Avail	N/Avail	Reduced glutamatergic concentrations in *ACC* of GG genotype (rs1019385) in childhood & adolescent OCD ($n=16$) (Arnold et al., 2009b)	N/Avail	Increased left *OFC* and right ACC volume of A-carriers (rs1805476) in childhood & adolescent OCD ($n=31$)- MRI (Arnold et al., 2009a) Increased total *thalamic* volume in childhood & adolescent OCD ($n=20$)- MRI (Wu et al., 2012)
7		DLGAP1 (SAPAP-related)	18p11.31	See GWAS analysis	N/Avail	(Stewart et al., 2013b)	N/Avail	N/Avail	N/Avail	Increased total *ACC* volume in childhood & adolescent OCD ($n=20$)- MRI (Wu et al., 2012)
8		DLGAP2 (SAPAP-related)	8p23	See GWAS analysis	N/Avail	N/Avail	N/Avail	N/Avail	N/Avail	Reduced *OFC* white matter volume in childhood & adolescent OCD ($n=20$)- MRI (Wu et al., 2012)
9	Dopaminergic	COMT	22q11.21	See meta-analysis	Only in male OCD (Azzam and Mathews, 2003; Pooley et al., 2007; Taylor, 2013)	N/Avail	N/Avail	N/Avail	N/Avail	N/Avail

Table 1 (*Continued*)

No	Functional group	Genetic polymorphism	Chromosomal location	Association study in OCD	Meta-analysis in OCD[a]	GWAS analysis in OCD[a]	PET/SPECT	Magnetic resonance spectroscopy	Diffusion tensor imaging	Structural MRI/fMRI
10		SLC6A3 (DAT1)	5p15.3	See meta-analysis	(Taylor, 2013)	N/Avail	N/Avail	10-repeat homozygotes exhibit higher NAA/choline and NAA/creatine in the left *putamen*- Adult bipolar disorder ($n=30$)+OCD ($n=17$) & Control ($n=16$) (Scherk et al., 2009)	N/Avail	N/Avail
11		DRD3	3q13.3	See meta-analysis	(Taylor, 2013)	N/Avail	N/Avail	N/Avail	N/Avail	N/Avail
12		DRD2	11q23	See meta-analysis	NOT significant (Taylor, 2013)	N/Avail	N/Avail	N/Avail	N/Avail	N/Avail
13	Others	BTBD3	20p12.2	See GWAS analysis	N/Avail	(Stewart et al., 2013b)	N/Avail	N/Avail	N/Avail	N/Avail
14		FAIM2	12q13	See GWAS analysis	N/Avail	(Stewart et al., 2013b)	N/Avail	N/Avail	N/Avail	N/Avail
15		BDNF	11p13	See meta-analysis	NOT significant (Taylor, 2013)	N/Avail	N/Avail	N/Avail	N/Avail	N/Avail
16		MOG	6p22.1	One family-based OCD study ($n=160$) (Zai et al., 2004)	N/Avail	N/Avail	N/Avail	N/Avail	N/Avail	*Total white matter* volumes of OCD patients were larger than those of healthy controls, particularly in patients carrying the *MOG* G511C (Val142Leu) Val/Val genotype. Adult OCD ($n=30$) and Control ($n=30$).- MRI (Atmaca et al., 2010)
17		CACNA1C	12p13.3	N/Avail	N/Avail	N/Avail	N/Avail	N/Avail	N/Avail	Amygdala gray matter volume was affected in hemisphere and diagnosis of SZ ($n=21$) versus controls ($n=16$), and was genotype-specific for rs1006737, while no effect was found in OCD ($n=7$) or bipolar disorder ($n=28$)- MRI (Wolf et al., 2013)
18		GPRC6A	6q22.1	See GWAS analysis	N/Avail	(Stewart et al., 2013b)	N/Avail	N/Avail	N/Avail	N/Avail

ACC, anterior cingulate cortex; BDNF, **brain-derived neurotrophic factor;** BTBD3, BTB (POZ) domain containing 3; COMT, catechol-O-methyltransferase; DAT, dopamine transporter; DLGAP, discs, large (*Drosophila*) homolog-associated protein; DRD2, dopamine D2 receptor; DRD3, dopamine D3 receptor; EO-OCD, early-onset OCD; FA, fractional anisotropy; FAIM2, **Fas apoptotic inhibitory molecule 2;** fMRI, functional magnetic resonance imaging; GNAQ, guanine nucleotide-binding protein (G protein), q polypeptide; GNG2, guanine nucleotide-binding protein (G protein), gamma 2; GPRC6A, G-protein coupled receptor family C group 6 member A; GRIK2, glutamate receptor, ionotropic, kainate 2; GRIN2B, glutamate receptor, ionotropic, N-methyl D-aspartate 2B; HTR2A, serotonin receptor 2A; 5-HTTLPR, serotonin transporter promoter polymorphism; LO-OCD, late-onset OCD; MAOA, monoamine oxidase A; MRI, magnetic resonance imaging; N/Avail, Not available; **NAA,** N-acetylaspartate; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; PET, positron emission tomography; SAPAP, SAP90/PSD-95-associated protein; SERT, serotonin transporter; 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; SPECT, single-photon emission computed tomography.

[a] Findings of significant or nominal association with OCD.

association between OCD and dopaminergic genes – such as the *DAT1* VNTR gene variant – could be confirmed and only very small effect sizes have been shown for *DAT1* in OCD so far (see review Brem et al., 2014).

Atmaca et al. (2010) recently published a study that combined magnetic resonance imaging measurements with analysis of the myelin oligodendrocyte glycoprotein (*MOG*) gene polymorphism, which was of interest in the context of OCD because of the positive results of a family-based association study (Zai et al., 2004). The work of Atmaca et al. (2010) demonstrated that the total white matter volumes of OCD patients were larger than those of healthy controls, particularly among patients carrying the *MOG* G511C (Val142Leu) Val/Val genotype. Similarly, a publication by Wolf et al. (2013) combined the magnetic resonance imaging technique with the examination of a polymorphism (rs1006737) in a gene that encodes the alpha-1C subunit of the L-type voltage-gated calcium channel (*CACNA1C*), which has been implicated in structural and functional variation in the amygdala in healthy people as well as in patients with bipolar disorder or schizophrenia (Jogia et al., 2011; Perrier et al., 2011; Tesli et al., 2013; Wessa et al., 2010). Nevertheless, up to now, there are no association studies between *CACNA1C* and OCD; however, there is some indication of an association with the predisposition to develop schizophrenia (Green et al., 2010; Nyegaard et al., 2010) or bipolar disorder (Ferreira et al., 2008; Sklar et al., 2008), as well as increased signs of depression, anxiety, or obsessive-compulsive thoughts (Erk et al., 2010; Roussos et al., 2011). In healthy volunteers, carriers of the *CACNA1C* risk variant exhibited alterations in hippocampal and anterior cingulate cortex activation as measured by functional magnetic resonance imaging (Erk et al., 2010). In addition to the above findings, a significant higher psychopathology scores for obsessive-compulsive thoughts in the risk allele carriers were found, correlating negatively with the observed regional brain activation (Erk et al., 2010). Wolf et al. (2013) investigated whether amygdala volumes differed between hemispheres, diagnostic groups (schizophrenia, bipolar disorder, OCD, and healthy controls), or genotype groups, and examined the interaction of these three parameters. They were able to demonstrate effects of hemisphere and diagnosis of schizophrenia versus controls, in which amygdala gray matter volume was affected and was genotype-specific for *CACNA1C*; however, no alterations in amygdala gray matter of OCD and association with genotypic changes were observed in the OCD group (Wolf et al., 2013).

When we expanded our search to include general publications discussing "imaging genetics" and comorbid psychiatric disorders or healthy controls involving the 16 genes in Table 1, most of these genes were significantly associated both with OCD as such (in pure genetic association studies) and with brain imaging data in non-OCD pathologies, with the exception of four genes (encoding *DRD3*, *GRIK2*, *BTBD3*, and *FAIM2*) that exhibited genetic associations with OCD, but have not yet been studied in the context of imaging genetics (Suppl. Table S1). This analysis added 43 publications to our systemic review. The preponderance of publications investigated polymorphisms in the *DAT1*, *COMT*, *BDNF*, and the serotonin transporter (*SERT/HTTLPR/SLC6A4*), mostly in populations other than OCD patients. The reports of imaging-genetics associations were conflicting, particularly in investigations involving *BDNF* polymorphism.

4. Discussion

To date, only eight imaging genetics studies that investigate the association between OCD and genetic variation have been published. Most of these genetic associations have been proven by meta-analysis and/or GWAS (Table 1). By adding studies with comorbid psychiatric disorders and healthy controls, we extended the publication collection to include other associated genes in the context, which have been found to be associated with OCD (e.g. *BDNF*, *COMT*), but which have not yet been investigated with imaging techniques in OCD. This very small collection of studies underscores the lack of knowledge in this research field, particularly regarding OCD.

Although only a small number of studies investigated OCD, their findings provide interesting insights into the genetic specificity of neural impairments. The OFC, ACC, striatal and thalamic regions have often been shown to be associated with OCD (Brem et al., 2012, 2014; Montigny et al., 2013; Peng et al., 2012; Radua et al., 2010). Regions of these cortico-striato-thalamic loops also seems to be sensitive to specific genetic variations (Fig. 1). The OFC and the midbrain surrounding the raphe nuclei have been associated with variants of the *5-HTTLPR*. The raphe nuclei are well known to incorporate serotonergic neurons that project to several cortical regions. One of the main target regions of these projections is the OFC (Cools et al., 2008), which is well known for decision making and learning (Hauser et al., 2014; Hunt et al., 2012; Kable and Glimcher, 2007), and is impaired in OCD (Cavedini et al., 2006; Graybiel and Rauch, 2000; Sachdev and Malhi, 2005). Additional support for a serotonergic involvement comes from pharmacological treatment and in vivo studies: serotonergic medication is the first choice pharmacological treatment with high effect sizes and serotonergic depletion induced OCD-like behaviors in monkeys (Clarke et al., 2004, 2005, 2007) and in humans (Seymour et al., 2012). However, it must be noted that the imaging genetics studies did only focus on serotonin transporter gene (*5-HTTLPR*) variants and up to now did not include other serotonergic gene variants (e.g. serotonin receptors, metabolizing enzymes). Moreover, within the *5-HTTLPR* they did not yet differentiate between the different *5-HTTLPR* variants, i.e. the L_G and L_A carries (Hu et al., 2006). Such a differentiation, however, has been shown to have strong functional implications (Hesse et al., 2011; Willeit and Praschak-Rieder, 2010) and might also affect cortical regions.

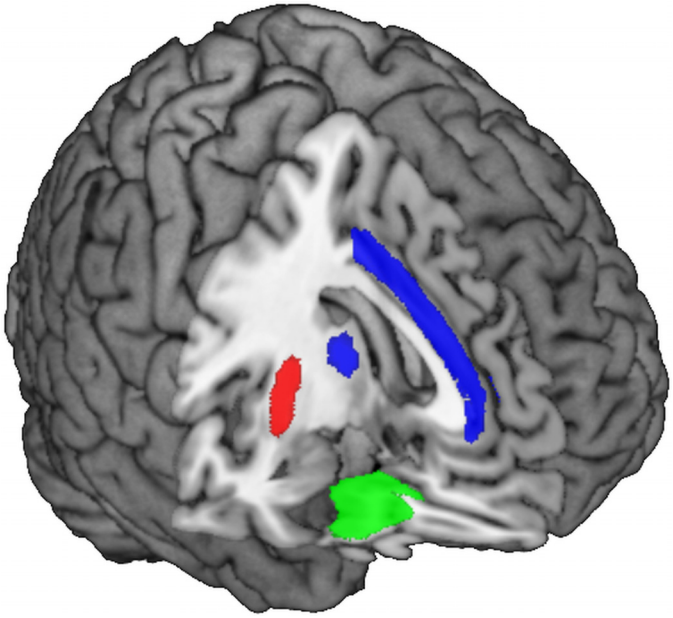

Fig. 1. Schematic illustration of regions influenced by genetic variations in obsessive-compulsive disorder. Variants of the serotonergic system have been shown to influence the orbitofrontal cortex (*green*) and the raphe nuclei (not shown). Glutamatergic gene variations also influence the orbitofrontal cortex; they affect the anterior cingulate cortex and the thalamus (*both blue*). Dopaminergic genes appear to influence the putamen (*red*). All of these regions are also assumed to be impaired in patients with obsessive-compulsive disorder relative to healthy control participants.

Less is known about the impact of dopaminergic gene variations on neuroimaging in OCD. Only one dopaminergic study incorporated OCD patients into its imaging genetics analysis (Scherk et al., 2009). The study found that the metabolism of NAA in the left putamen was modulated by variations of the *DAT1* gene. However this genetic variant is only weakly associated with OCD. So the effect could be unspecific for OCD but more specific for the variant by itself.

Glutamatergic neurons are the most prevalent excitatory neurons across the entire cortex and play a crucial role in the cortico-striato-thalamic loops. In OCD, several regions of the cortico-striato-thalamic loops appear to be affected by variations in glutamatergic genes. Similarly, as in serotonergic genes, the OFC demonstrates sensitivity to variations in glutamatergic genes. An investigation of whether there is an interaction between the variations of serotonergic, dopaminergic and glutamatergic genes or whether these genes have independent effects on the OFC would be of great interest. Glutamatergic genes also influence the thalamus and the ACC. Both regions are assumed to play a role in the cortico-striato-thalamic loop dysfunction in OCD (Brem et al., 2012; Huyser et al., 2009). The ACC appears to be very consistently involved OCD, mainly in the context of conflict, error, and feedback processing (Albrecht et al., 2008; Botvinick et al., 2004; Bush, 2010; Hauser et al., 2014; Rushworth et al., 2004).

Taken together, the published imaging genetics studies provide evidence that OCD patients cannot be understood and therefore treated as a homogeneous group in neuroimaging analyses. Rather, there seems to be significant cerebral variability between specific gene variations in OCD patients. Importantly, regions which are found to be associated with genetic variants often also differ between OCD patients and controls, which might mean that the differences observed between patients and controls are also driven by a specific genetic subgroup. Given that genetic variations are not yet used for between-group matching, ordinary group differences might be influenced by the prevalence of specific genetic variations within each group. Therefore, inconsistencies in genetic profiles might also (partially) explain inconsistencies among neuroimaging studies that focus on OCD.

One major limitation thus far is that most studies used small sample sizes and unequally sized genetic subgroups. Genetic association studies (esp. GWAS) are known to require extremely large sample sizes to detect significant genetic contributions to psychiatric disorders. This is mainly due to the fact that genetic variants have only small effect sizes, and that such genome-wide studies need rigorous statistical correction mechanisms. Due to the high costs in neuroimaging, it is still much more common to study smaller groups of approx. 20 subjects per group. In such small groups, however, the effect sizes of genetic variants are highly likely not to be detectable. Only very recently, large multi-national initiatives started to investigate imaging genetics with large sample sizes (e.g. ENIGMA, IMAGEN, ADNI, CHARGE, Medland et al., 2014; Thompson et al., 2014).

An additional challenge in imaging genetics is caused by the pre-selection of genes and brain regions. Due to the small sample sizes, researchers are forced to pre-select candidate genes as well as brain regions-of-interest to reduce the burden of multiple comparison correction. Although such an approach is valid and has been used in most of the studies reported here, it also biases the results to certain extend. Namely, it restricts findings to the prior hypothesis and hinders the detection of novel effects and interactions. The pre-selection of cortico-striatal-loop networks, for example, does not allow investigating (potentially stronger) effects outside of these loops. Furthermore, it assumes that the neural differences between different genotypes in OCD are within the same networks that show differences between OCD patients and controls.

Also from a genetics point of view, candidate genes which are known to be related to OCD do not necessarily predict neural alterations. This has been shown in the first meta-analysis imaging genetic GWAS of the hippocampus (Stein et al., 2012). In a vast sample of subjects, the authors did not find a strong relation between hippocampal volume and candidate genes. Rather, they found associations between previously not predicted SNPs and hippocampal volume (Stein et al., 2012). Such studies, however, are only feasible in very large samples of patients and controls and by using adequate statistical methods (Kochunov et al., 2014; Medland et al., 2014).

Current research has focused on alterations in serotonergic and glutamatergic systems. The imaging genetics findings in OCD related to the *5-HTTLPR* are still rather preliminary, and many factors, such as comorbidity, ethnicity, therapy, sex, age (neuro-developmental factors), and age of onset, should be considered in future studies. Although the genetic studies show one of the highest effect sizes for association of the glutamatergic system and OCD, only few groups have reported findings related to imaging genetics in OCD and genetic variants of glutamatergic genes (Arnold et al., 2009a, 2009b; Wu et al., 2012). The results of these investigations coincide with findings from meta-analyses and GWAS; taken together, these observations support the involvement of the glutamatergic system in OCD (Stewart et al., 2013a, 2013b; Taylor, 2013). The existing literature on imaging-genetic studies with respect to OCD provides evidence of increasing specificity of brain structure and/or activity findings exerted by variants in genes involved in the serotonergic (5-HTTLPR, HTR2A) and glutamatergic (SLC1A1, SAPAP) systems.

It must be noted that for the discussion and interpretation of the main results of this systematic review, the interacting and moderating effects of the heterogeneous phenotype should be addressed in more detail. OCD is now described in the DSM-5 as an obsessive-compulsive spectrum disorder separately to anxiety disorders, in contrast to the previous DSM-IV criteria (American Psychiatric Association, 2013). Nevertheless, there is a broad phenotype range within OCD and its related disorders regarding symptomatology and comorbidity, as well as regarding de novo and high-familiality cases. The content of obsessions and compulsions often concerns contamination, but can also be focused on aggression, symmetry, precision, and religious or sexual themes; mixed types and changes among these symptoms are also common (Geller et al., 1998; Walitza et al., 2011). Leckman et al. (2001) were the first to use item-level factor analysis (cleaning/washing, checking, symmetry/exactness, and hoarding/saving) to describe a set of symptom dimensions that have been validated by multiple other studies (Delorme et al., 2006; Kichuk et al., 2013). Later studies showed high stability of these symptom dimensions over time. In addition, a study of heritability estimates showed that symptom dimensions display different strong genetic background, shared environmental variance with each other and with symptom severity. The authors presumed that the results supported the utility of both OCD diagnosis and symptom dimensions in genetic research and clinical contexts (Katerberg et al., 2010). According to the DSM-5, the clinician must e.g. assign a sub-classification of the OCD depending on the patient's degree of insight. The patient's level of insight is associated with severity and highly associated with therapy response. Furthermore, now the subtypes of OCD with and without tic disorder (present or in the past) must be classified (American Psychiatric Association, 2013). This is in accordance with observations that tic-related OCD is a very common but special phenotype that includes more males with early onset OCD and more relatives affected with OCD and/or tic disorders. Tic-related OCD does not respond as positively to serotonergic-based medication alone, and more often requires augmentation strategies using atypical antipsychotic medications.

One major point is that only very few imaging and genetic studies were able to include only drug-naïve patients. Most studies should be assumed to include at least a few patients that were on medications, ideally at stable dosages. It is obvious that these different phenotypes and conditions interact with imaging and/or genetic findings as well as with imaging genetic studies. Therefore, the use of larger sample sizes with phenotypes that are more homogeneous, as well as the use of endophenotypic approaches (Manoach and Agam, 2013) that include unaffected relatives, might help to deal with limitation factors caused by the heterogeneous phenotypes.

Nevertheless, to date, only univariate analyses using one gene variant and one brain region of interest at a time have been used for imaging genetics in OCD. Recently, several studies of patients with schizophrenia, patients with Alzheimer's disease, and healthy controls implemented a combination of imaging techniques and GWAS findings to identify polygenetic risk loads that affect specific brain structures, functions, or connectivity (Bedenbender et al., 2011; Mattingsdal et al., 2013; Meda et al., 2012; Medland et al., 2014; Nymberg et al., 2013; Whalley et al., 2013). These large scale-data analyses employed various analytic techniques, such as polygenic scoring (International Schizophrenia et al., 2009), pathway enrichment analysis (Mattingsdal et al., 2013), multivariate parallel independent component analysis (Meda et al., 2012), clustering analysis, weight voxel co-activation network analysis, and principal component analysis (Nymberg et al., 2013). These techniques are still being developed, but hold great promise for the investigation of genetic and neuronal factors underlying human behavior, particularly psychiatric disorders. Even more promising, the recently launched ENIGMA2 project (successor of the ENIGMA consortium) will also include OCD and related disorders in its mega-meta-analysis studies of GWAS and neuroimaging. This hopefully will result in new insights in how genetic variations influence functional and structural alterations in OCD (Thompson et al., 2014).

In summary, only a small number of imaging studies that study OCD also investigated imaging genetics. Such investigations have the ability to offer insight into brain alterations, permitting glimpses of how genetic changes may affect brain structure, chemistry, and ultimately function. However, there is clearly a great need for additional large multimodal imaging-genetic studies that assess OCD, especially investigations that implement polygenetic approaches in order to identify biomarkers for better prediction and prognosis.

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Contributors

Edna Grünblatt and Susanne Walitza managed the literature searches, discussed the results, and wrote the first draft. Tobias Hauser participated in the discussion of the results and writing of the manuscript. All authors contributed substantively to the development of the content of this paper and have approved the final manuscript.

Conflicts of interest and financial disclosure

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pneurobio.2014.07.003.

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