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Review article

Brain imaging genetics in ADHD and beyond – Mapping pathways from gene to disorder at different levels of complexity



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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is a common and often persistent neurodevelopmental disorder. Beyond gene-finding, neurobiological parameters, such as brain structure, connectivity, and function, have been used to link genetic variation to ADHD symptomatology. We performed a systematic review of brain imaging genetics studies involving 62 ADHD candidate genes in childhood and adult ADHD cohorts. Fifty-one eligible research articles described studies of 13 ADHD candidate genes. Almost exclusively, single genetic variants were studied, mostly focussing on dopamine-related genes. While promising results have been reported, imaging genetics studies are thus far hampered by methodological differences in study design and analysis methodology, as well as limited sample sizes. Beyond reviewing imaging genetics studies, we also discuss the need for complementary approaches at multiple levels of biological complexity and emphasize the importance of combining and integrating findings across levels for a better understanding of biological pathways from gene to disease. These may include multi-modal imaging genetics studies, bioinformatic analyses, and functional analyses of cell and animal models.

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Contents

1. Introduction	116
1.1. Identification of ADHD candidate genes	116
1.2. Brain correlates of ADHD	117
1.3. Rationale for this review	119
2. Methods	119
3. Results	122
3.1. Findings for the dopamine transporter gene (SLC6A3, DAT1)	122
3.2. Findings for the dopamine receptor D4 gene (DRD4)	133
3.3. Findings for other ADHD candidate genes	134
4. Outlook	137
4.1. Main challenges and opportunities for imaging genetics studies	138
4.2. Complementary methods for the evaluation of the mechanisms underlying ADHD risk genes	140
4.2.1. Bioinformatics approaches help to integrate findings from different types of molecular studies	140
4.2.2. Animal models provide proof of causality for genes and molecular processes found associated with ADHD	141
4.2.3. Modelling psychiatric disorders at the cellular level by using human induced pluripotent stem cell (hiPSC)-derived neurons ..	142
5. Conclusion	143

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Conflict of interest.....	143
Acknowledgements.....	143
References.....	143

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder (Faraone et al., 2015). The worldwide prevalence has been estimated at 5% in children and between 2.5 and 4.9% in adults (Polanczyk and Rohde, 2007; Simon et al., 2009). Approximately 55–75% still carry the diagnosis in adulthood or remit only partially displaying several impairments also in adulthood (Faraone et al., 2006). ADHD is characterized by age-inappropriate levels of inattention and/or hyperactivity and impulsivity (Frances, 2000), but the clinical phenotype is heterogeneous (Frances, 2000; American Psychiatric Association, 2013). Severity level and presentation of ADHD can change during a person's lifetime, with adult patients displaying less obvious symptoms of hyperactivity and impulsivity (Buitelaar et al., 2011; Haavik et al., 2010). The phenotypic heterogeneity of the disorder is apparent from a large diversity of psychiatric co-morbidities, frequently seen both in children (Biederman and Faraone, 2005; Gillberg et al., 2004; Lycett et al., 2015; Rappley, 2005; Reinhardt and Reinhardt, 2013) and in adults (Mcgough et al., 2005; Miller et al., 2007; Ollendick et al., 2008; Sobanski et al., 2007; Wilens et al., 2009).

1.1. Identification of ADHD candidate genes

The etiology of ADHD is strongly influenced by genetic factors, as demonstrated by twin and adoption studies (Faraone and Mick, 2010; Kotte et al., 2013; Thapar et al., 2013; Burt, 2009). Heritability estimates range between 70 and 90% (Faraone and Mick, 2010; Larsson et al., 2013b). Despite this substantial heritability, identification of ADHD risk genes has been challenging (Franke et al., 2009; Gizer et al., 2009). One reason for this may be that ADHD has a complex, polygenic genetic background, in which multiple genetic variants (many of them with small effects) contribute to the etiology of the disorder in most patients. Although a substantial fraction of ADHD etiology is due to genes, many environmental risk factors and potential gene-environment interactions are also linked with an increased risk for the disorder (Banerjee et al., 2007; Han et al., 2015). Furthermore, it has been shown that persistent ADHD and its paediatric form are genetically linked, but overlap only partially (Chang et al., 2013).

Multiple molecular genetic studies, employing mostly hypothesis-driven and some hypothesis-free approaches, have been used to identify ADHD risk genes. Because of the high prevalence of ADHD in the population, the search for genetic factors has mainly focused on common genetic variants, which generally have small effect sizes (Li et al., 2014; Neale et al., 2010b).

While many of the individual hypothesis-driven, candidate gene-based association studies have been underpowered, meta-analysis of those studies identified significant associations for common genetic variants in several candidate genes (Gizer et al., 2009; Faraone et al., 2005; Li et al., 2006a). Those are the dopamine and serotonin transporter encoding genes, *SLC6A3/DAT1* and *SLC6A4/5HTT*, genes coding for the D4 and D5 dopamine receptors, *DRD4* and *DRD5*, a serotonin receptor, *HTR1B*, and the gene for the synaptosomal-associated protein 25, *SNAP25*. Some additional genes (encoding dopamine beta-hydroxylase [*DBH*], adrenoceptor alpha 2A [*ADRA2A*], tryptophan hydroxylase 2 [*TPH2*], and monoamine oxidase A [*MAOA*]) were found suggestively associated with ADHD in meta-analyses (Gizer et al., 2009; Li et al., 2006a; Faraone et al., 2005). In addition, an in depth analysis of 51 genes in

a European multisite sample of 674 families with ADHD combined type probands, collected for the International Multisite ADHD Gene project (the IMAGE project), identified associations with ADHD candidate genes, such as *ADRAB2*, *DAT1*, *DRD4*, *TPH2*, and *MAOA* (Brookes et al., 2006). For more extensive reviews of ADHD candidate genes see references (Li et al., 2014; Faraone and Mick, 2010; Banaschewski et al., 2010; Franke et al., 2012; Hawi et al., 2015).

Genetic linkage studies provided a first possibility to perform hypothesis-free genetic studies in the early 2000s. However, gene identification through linkage analysis has been limited (Banaschewski et al., 2010). A meta-analysis of seven linkage studies revealed a locus on the short arm of chromosome 16 to be relevant for ADHD etiology (Zhou et al., 2008). An interesting candidate gene in the locus is cadherin 13 (*CDH13*), a gene also found in the top-ranks of several genome-wide association studies (Rivero et al., 2015). Linkage analysis also identified the latrophilin 3 (*LPHN3*) gene on chromosome 4, which was subsequently confirmed through association testing (Arcos-Burgos et al., 2010; Ribases et al., 2011). Genome-wide association studies (GWAS) of common single nucleotide polymorphisms (SNPs) have been the main hypothesis-free approach to studying the genetics of ADHD during the last ten years. However, with nine GWAS on ADHD and ADHD-symptoms published to date (Hinney et al., 2011; Lasky-Su et al., 2008; Lesch et al., 2008; Mick et al., 2010; Neale et al., 2008; Neale et al., 2010a; Stergiakouli et al., 2012; Yang et al., 2013; Sanchez-Mora et al., 2014), no locus has yet been identified that meets genome-wide levels of significance (Li et al., 2014; Neale et al., 2010b), nor has meta-analysis of these studies provided one (van Hulzen et al., 2016). An interesting genome-wide approach to identify ADHD genes has been the analysis of overlap with other psychiatric disorders. A cross-disorder GWAS across five main neuropsychiatric disorders (schizophrenia [SCZ], bipolar disorder [BD], autism spectrum disorder [ASD], major depressive disorder [MDD], and ADHD) identified five genome-wide significant findings, four of which – in/near the genes *ITIH3*, *AS3MT*, *CACNA1C*, and *CACNB2* – were shared with ADHD (Cross-Disorder Group of The Psychiatric Genomics Consortium, 2013).

Following promising results in other psychiatric disorders (Purcell et al., 2014; Cukier et al., 2014; Cruceanu et al., 2013; Kerner et al., 2013), studies of rare variants were also performed for ADHD and were successful in identifying genetic variants related to the disorder (Elia et al., 2010; Williams et al., 2010; 2012; Ramos-Quiroga et al., 2014; Lesch et al., 2011; Yang et al., 2013). Genome-wide analysis of (rare) copy number variants (CNVs) showed an enrichment of rare CNVs in patients with ADHD (Williams et al., 2010), and implicated the genes *CHRNA7* and *NPY* in ADHD etiology (Williams et al., 2012; Lesch et al., 2011), as well as genes encoding several glutamate receptors (Akutagawa-Martins et al., 2014; Elia et al., 2012), and regions on 15q11-15q13 (Valbonesi et al., 2015) and 16p13.11 (Williams et al., 2010). The picture emerging from those initial studies is that the rare variant contribution of ADHD genetics is highly heterogeneous, similar to the common variant contribution. Nevertheless, given the success of CNV studies, exome and whole-genome sequencing are now being used, allowing the identification of rare single nucleotide variants and small insertions/deletions contributing to ADHD etiology. A first study indeed found enrichment of rare variants in a predefined set of 51 candidate genes in adult patients with persistent ADHD (Demontis et al., 2016).

The genetic factors associated with ADHD are distributed across the genome, but tend to be enriched within specific functional categories. By clustering ADHD-related genes within functional networks or pathways, several biological processes have been shown to be involved in the etiology of the disorder. Top-findings of five GWASs in ADHD showed convergence on the biological process of neurite outgrowth (Poelmans et al., 2011). Comparable enrichment analyses revealed that most significantly enriched functions for the ADHD-GWAS association signals were related to nervous system development, neuron projection morphogenesis, oxogenesis, cell–cell communication, glutamatergic synapse/receptor signalling, and multicellular organismal development (Hawi et al., 2015) or neuron projections and synaptic components (Yang et al., 2013), which is consistent with a neurodevelopmental pathophysiology of ADHD. These findings were strengthened by results from a recent study, that used two GWAS datasets to identify pathways associated with ADHD by applying six pathway analysis methods (Mooney et al., 2016). Cross-method convergent results revealed a number of brain-relevant pathways, such as RhoA signaling, glycosaminoglycan biosynthesis, fibroblast growth factor receptor activity, and pathways containing potassium channel genes (Mooney et al., 2016). Another study revealed that CNVs involved in ADHD converge on biologically meaningful gene clusters related to ion channel pathways, organonitrogen compound catabolic processes, and transmembrane transport (Thapar et al., 2015). A combined analysis of ADHD candidate genes, derived both from SNP-based and CNV-based studies, showed that genes involved in biological processes, such as synaptic transmission, catecholamine metabolic processes, G-protein signalling pathways, and cell migration were over-represented among the top-findings of such studies (Cristino et al., 2014). More generally, the genome-wide analysis of five major psychiatric disorders (also including ADHD), supported a role for calcium channel signalling genes for all five disorders, suggesting that genetic variation in calcium-channel activity genes can have pleiotropic effects in the development of psychopathology (Cross-Disorder Group of The Psychiatric Genomics Consortium, 2013).

1.2. Brain correlates of ADHD

The effects of ADHD genetic risk factors on (aberrant) behaviour are likely to be mediated through effects on cell biology and brain system development and functioning. Several aspects of brain development, structure, function, and connectivity have been found altered in ADHD (Cortese et al., 2012; Greven et al., 2015; Shaw et al., 2007b; Shaw et al., 2012; van Ewijk et al., 2012; Glahn et al., 2010; Onnink et al., 2015; Mostert et al., 2016; Hoogman et al., epub head of print).

Two indirect neuroimaging techniques that have been used in imaging (genetics) studies in ADHD are positron emission tomography (PET) and single photon emission computed tomography (SPECT). Both are based on the measurement of a radionuclide's decay, during which a positron or a γ -ray is emitted, generating photons. The high sensitivity and limitless penetration depth of PET and SPECT enable imaging to examine metabolic activity, cerebral perfusion, neurotransmitter turnover, and receptor binding potentials within examined brain regions or receptor systems (Rahmim and Zaidi, 2008). Until now, the majority of recent PET studies using ADHD samples have focused on examining differences and changes in neurotransmitter binding and receptor density (Zimmer, 2009). *In vivo* imaging of the dopamine transporter (DAT) is particularly relevant for ADHD, given that DAT is the target of stimulant medications and, subsequently, a target protein for studies of pathophysiology. PET and SPECT studies have been useful in comparing striatal DAT availability between ADHD patients and controls (Jucaite et al., 2005; Spencer et al.,

2005; Ludolph et al., 2008). A meta-analysis of nine PET studies revealed that striatal DAT density was 14% higher in patients with ADHD compared to healthy controls (Fusar-Poli et al., 2012). Besides that, striatal density in people with ADHD seems to depend on previous psychostimulant exposure, with lower density in drug-naïve subjects and higher density in previously medicated patients (Fusar-Poli et al., 2012). In addition to studies exploring DAT density and binding, Volkow and co-workers examined postsynaptic dopamine receptor availability and found that medication-naïve adults with ADHD showed decreased dopamine D2/D3 receptor availability in the left caudate compared to healthy controls. Following administration of methylphenidate (MPH), the ADHD group demonstrated decreased dopamine activity in the caudate compared with controls (Volkow et al., 2007). One SPECT study investigated D2 receptor availability as a function of MPH therapy in ADHD and concluded that D2 receptor availability is significantly reduced in patients with ADHD in all four regions of the striatum (Ilgin et al., 2001).

Structural magnetic resonance imaging (sMRI) allows to non-invasively characterize the structure of the human brain. With the help of sMRI, the different magnetic properties of brain tissues are used to non-invasively map the spatial distribution of these structural properties of the human brain. Thereby, the different brain tissues (grey and white matter) and cortical and subcortical structures of the brain can be accurately mapped, and different aspects of brain structure can be quantified and compared. In general, sMRI has pointed to total brain volume and total grey matter reductions up to 3–5% in ADHD patients compared to controls (Castellanos et al., 2002; Valera et al., 2007; Greven et al., 2015). To investigate, whether these reductions are global or regional, several brain regions of interest (ROIs) have been studied. A meta-analysis reported significant volume differences in cerebellar regions, total and right cerebral volume, right caudate, and frontal brain areas (Valera et al., 2007). To investigate the most prominent changes in grey matter intensity, detected by using voxel-based morphometry (VBM) analyses, four meta-analyses have been performed to date (Ellison-Wright et al., 2008; Frodl and Skokauskas, 2012; Nakao et al., 2011). Most consistently, grey matter reductions in the ventrolateral prefrontal/insular-striatal regions, such as the right insula, putamen, globus pallidus, and caudate nucleus have been described in ADHD patients (Ellison-Wright et al., 2008; Frodl and Skokauskas, 2012; Nakao et al., 2011; Norman et al., 2016). A recent study could also show that participants with ADHD had significantly smaller grey matter volume in five clusters located in the precentral gyrus, medial and orbital frontal cortex, and (para)cingulate cortices (Bralten et al., 2015). Unaffected siblings of patients with ADHD showed intermediate volumes, significantly different from controls in four of these five clusters (all except the precentral gyrus), suggesting that the volume reductions are unlikely to be a consequence of disease, but may rather contribute to ADHD etiology (Bralten et al., 2015).

Brain differences observed in ADHD have been hypothesized to be partly attributable to a delay in maturational processes (Castellanos et al., 2002). Indeed, the few longitudinal imaging studies of ADHD patients support this hypothesis: for CT measures, Shaw and co-workers investigated growth trajectories of different points of the cortex and reported that cortical thickness maturation in participants with ADHD lagged behind that of healthy controls of approximately three years throughout the cerebrum, but most prominent in the PFC (Shaw et al., 2007a). In addition, also the SA developmental trajectory was found to be delayed in ADHD, especially in the right PFC (Shaw et al., 2012). Support for the developmental delay hypothesis in ADHD also came from cross-sectional meta-analyses of VBM studies, which found increasing age associated with more normal grey matter values in affected brain areas (Frodl and Skokauskas, 2012). The recent large mega-analysis of

subcortical regions across 60 years of the lifespan by the Enhancing Neuroimaging Genetics Through Meta Analysis (ENIGMA) ADHD Working Group extended the delayed maturation theory also to the volumes of most subcortical regions (Hoogman et al., [epub head of print](#)). First of all, they observed significant smaller volumes for the nucleus accumbens, amygdala, caudate, hippocampus, putamen, and intracranial volume (ICV) in ADHD cases relative to controls (Hoogman et al., [epub head of print](#)). Age analyses suggested different brain volume trajectories across age for patients and controls. These results from the cross-sectional lifespan analyses were consistent with the early maturation delay hypotheses of ADHD and hint at delays in brain growth and degeneration across the lifespan (Hoogman et al., [epub head of print](#); Rubia, 2007).

Next to volumetric differences observed in grey matter, white matter structure has also been found to be altered in ADHD, leading to a potential disorganization of the brain's connectivity. Diffusion tensor imaging (DTI) enables non-invasive investigations of the macrostructural integrity and orientation of white matter fibre bundles. DTI measures the directional diffusion of water molecules along neuronal membranes, allowing to map white matter pathways within the brain. One measure frequently derived from DTI is fractional anisotropy (FA). Anisotropy indicates that diffusion occurs in a directional manner, whereas isotropy indicates diffusion in all directions. Other measures derived from DTI include mean diffusivity (MD), which is an average of axial diffusivity (AD) and the perpendicular diffusivities, and radial diffusivity (RD), which is the average of perpendicular diffusivities, the mode of anisotropy, which is sensitive to crossing fibres, and the apparent diffusion coefficient, which indicates the magnitude of diffusion (Le Bihan, 2003; Le Bihan et al., 2001; Yoncheva et al., 2016). In a meta-analysis, comparing DTI findings between patients with ADHD and healthy controls, five areas with disturbed microstructural integrity in people with ADHD were highlighted, located in white matter tracts subserving the fronto-striatal-cerebellar neurocircuitry (van Ewijk et al., 2012). Most consistently, studies reported white matter anomalies in the corpus callosum in childhood ADHD (van Ewijk et al., 2014) and adult ADHD (Dramsahl et al., 2012; Onnink et al., 2015). Although the exact neurobiological meaning is not fully understood, reduced FA in the corpus callosum of adult patients with ADHD was driven by changes in RD rather than AD, suggesting that aberrant myelination is a pathophysiological factor in adult ADHD (Onnink et al., 2015). However, replication from longitudinal studies is still lacking, and the differences between patients and controls seem to be widespread and heterogeneous across studies (van Ewijk et al., 2012).

A method to investigate potential changes in brain activity is functional magnetic resonance imaging (fMRI). fMRI is primarily sensitive to the oxygenation of the blood, the so-called blood-oxygen-level-dependent (BOLD) signal. It measures brain function based on the premise that active cells consume oxygen, thereby causing changes in blood oxygenation and subsequently leading to increased blood flow, although the exact link between cell activation, oxygen saturation, and blood flow is still under debate; for review see (Hillman, 2014). Generally in fMRI, alterations in blood flow after a stimulus (e.g. a certain task) or during a resting state are measured. Comparing anatomical or functional brain measures in individuals with ADHD, their unaffected siblings, and healthy comparison subjects, is one of the best ways to examine the suitability of these neural markers as endophenotypes. With respect to functional brain studies, van Rooij et al., (2015c) recently reported a distinction in hemodynamic patterns during a stop-signal task between patients with ADHD, their unaffected siblings, and control subjects, suggesting the familial nature of these activation patterns. Thus, inhibition-related neural activation could be considered as a valuable endophenotype for ADHD. Several reviews have provided excellent overviews of

cognitive and brain (candidate) endophenotypes for ADHD (del Campo et al., 2012; Gallo and Posner, 2016; Rommelse et al., 2011). In accordance with those reports, dysregulation of structure and function of the fronto-subcortical-cerebellar pathways that control attention, response to reward, salience thresholds, inhibitory control, and motor behaviour are among the most promising endophenotype candidates, and task-based functional MRI studies in ADHD have largely focused on these neurocognitive domains. More specifically, fMRI studies using inhibitory control, working memory, and attentional tasks in patients with ADHD and healthy comparison subjects have shown underactivation of fronto-striatal, fronto-parietal, and ventral attention networks in the patients (Cortese et al., 2012). The fronto-parietal network mediates goal-directed executive processes, whereas the ventral attention network facilitates reorientation of attention towards salient and behaviourally relevant external stimuli. Meta-analyses of fMRI studies of inhibition and attention revealed that patients with ADHD have consistent functional abnormalities in two distinct domain-dissociated fronto-basal ganglia networks. These include the inferior frontal cortex, supplementary motor areas, and anterior cingulate cortex (ACC) for inhibition and the dorsolateral prefrontal cortex (PFC), parietal, and cerebellar areas for attention processes (Hart et al., 2013). Studies using reward-processing paradigms reported reduced activation of the ventral striatum of participants with ADHD in the anticipation phase of reward relative to controls (Plichta and Scheres, 2014), and differences between patients and controls have also been observed during reward receipt (von Rhein et al., 2015). Additionally, a meta-analysis of fMRI studies of timing reported consistent reductions in activation in typical areas of timing, such as the left inferior frontal gyrus (IFG)/insula, cerebellum, and the left parietal lobe in ADHD patients relative to controls (Hart et al., 2012).

In resting state MRI (rs-fMRI), the temporal correlations in neural activity across anatomically disparate brain regions are analysed to examine functional connectivity based on spontaneous brain activity, neural organization, and circuit architecture. Rs-fMRI studies of ADHD have mainly focused on neural circuits implicated in the disorder, especially the default-mode network (DMN), cognitive control network, and cortico-striato-thalamo-cortical loops (Posner et al., 2014). It was shown that ADHD is associated with less-pronounced or absent anti-correlations between the DMN and the cognitive control network, lower connectivity within the DMN itself, and lower connectivity within the cognitive and motivational loops of fronto-striatal circuits (Posner et al., 2014). A recent study in a large sample of adult participants with ADHD and healthy controls, showed that functional connectivity in the executive control network, and to a lesser extent also the cerebellum network, was stronger in the ADHD group (Mostert et al., 2016). Additionally, hyperactivity/impulsivity symptoms were positively correlated with the connectivity strength in these networks (Mostert et al., 2016).

Functional near-infrared spectroscopy (fNIRS) measures concentration changes of oxygenated, deoxygenated, and total haemoglobin in brain haemodynamics by measuring the absorption of near-infrared light projected through the scalp (Gervain et al., 2011). Thereby, fNIRS provides an indirect measure of neural activity based on changes in blood oxygenation due to metabolic processes within the cortex. Compared to fMRI, fNIRS is less sensitive to movement artefacts, and since the emitters and detectors can be worn in a cap, functional neural activity can be studied, while the participant is interacting with its environment. This makes fNIRS an ideal tool to study brain development, e.g. in children with ADHD (Vanderwert and Nelson, 2014). fNIRS has greater spatial resolution compared to event-related potential (ERP) or EEG techniques, however, since it is dependent on light penetration and reflection, fNIRS can only examine the cortical surface

within 2–3 cm of the scalp (Vanderwert and Nelson, 2014). The majority of fNIRS studies on ADHD investigated children with the disorder. These studies particularly focused on alterations in PFC activity during different experimental paradigms, such as Stroop tasks (Negoro et al., 2010; Xiao et al., 2012), working memory tasks (Schecklmann et al., 2010), the Trail Making Test (Weber et al., 2005), or Go/NoGo paradigms (Xiao et al., 2012; Inoue et al., 2012); they consistently pointed towards an attenuated oxygen metabolism within the frontal lobe (Ehlis et al., 2014). Studies in adult ADHD patients suggest that this hypofunctionality is persistently observed throughout development (Schecklmann et al., 2013; Ehlis et al., 2008).

The functional brain imaging techniques electroencephalography (EEG) and magnetoencephalography (MEG) have also been used for the study of ADHD (genetics). EEG directly measures electrical activity from large populations of cells and therefore offers a very good temporal resolution, far superior to fMRI. However, it has a poor spatial resolution, as electric fields smear as they pass through the skull (Ahmad et al., 2016). Every electric field also has a magnetic field, which can be detected by MEG. The spatial resolution of MEG is slightly better compared to EEG, but MEG only measures information strictly from the sulci, thus it is more limited and misses information (van Diessen et al., 2015). The frequency bands mostly studied in ADHD are theta (θ), alpha (α), and beta (β), either individually, or compared to each other (such as theta/beta power or amplitude ratio). In a resting state, (lower frequency) θ band activity can reflect drowsiness or “cortical slowing”. The α band activity is usually observed during eyes closed conditions at rest, particularly in posterior brain regions, and it is negatively associated with central nervous system arousal. In contrast, β band activity generally accompanies mental activity and concentration. The θ/β power ratio has been proposed to capture the relative contributions of two relevant frequency bands for ADHD; however, the true functional significance of this measure remains unknown (Loo and Makeig, 2012). It has been reported that patients with ADHD exhibit increased fronto-central theta (θ) band activity and increased theta-to-beta (θ/β) power ratio during rest compared to non-ADHD controls (Loo and Makeig, 2012). While (limited) discriminant validity of these EEG measures for ADHD has been suggested, significant EEG heterogeneity also exists across ADHD-diagnosed individuals (Clarke et al., 2011). In addition to differences in frequency bands, event-related potential (ERP) studies explored various aspects of brain functioning in ADHD and identified a substantial number of ERP correlates of ADHD (Johnstone et al., 2013). Robust differences between ADHD patients and healthy controls have been reported in several components related to attention (among others including orienting and vigilance), inhibitory control, and performance monitoring, such as error and reward/punishment processes (Johnstone et al., 2013). MEG studies comparing ADHD patients to healthy controls are scarce and have been geared towards investigating attention-related processes. Alterations in oscillation patterns of brain regions involved in such processes have been observed in patients (ter Huurne et al., 2013; Franzen et al., 2013; Heinrichs-Graham et al., 2014).

Importantly, the brain phenotypes found affected in people with ADHD are often moderately to highly heritable. Findings from twin studies showed that brain structure is under strong genetic control. Additionally, twin studies showed that genetic effects varied regionally within the brain, with high heritability estimates (h^2) for frontal lobe volumes ranging from 0.9 to 0.95, for region-based cortical surface areas ranging from 0.48 to 0.77, and moderate estimates for e.g. the hippocampus (h^2 -range = 0.4–0.69) (Peper et al., 2007). Surface area was predominantly more heritable than cortical thickness (h^2 -range = 0.34–0.64) (Mckay et al., 2014). Global fractional anisotropy ($h^2 = 0.55$) as well as radial diffusivity ($h^2 = 0.72$)

of white matter showed high heritability (Kochunov et al., 2015; McKay et al., 2014). Moreover, basal neural activity during a resting state condition has also been shown to be under genetic control, as functional connectivity within the default-mode network as a whole was significantly heritable ($h^2 = 0.42$) (Glahn et al., 2010). Additional examples for moderate heritabilities of neural activity are e.g. brain activation in the cerebellum and cerebral cortex during working memory tasks (h^2 -range = 0.5–0.65) (Blokland et al., 2014). Strong genetic determination has also been reported for different psychophysiological brain phenotypes measured by EEG, e.g. (Iacono et al., 2014; Smit et al., 2010), and MEG, where different frequency band heritabilities have been described by van Pelt et al., 2012.

1.3. Rationale for this review

This review aims to provide a systematic overview of brain imaging genetics studies in ADHD, as brain imaging phenotypes are frequently used as endophenotypes in ADHD research. Endophenotypes (or intermediate phenotypes) have been considered a promising strategy in order to gain more insight into the mechanisms leading from a genetic/biological basis of the disease to the full clinical phenotype (Faraone et al., 2014a). Endophenotypes are (1) those characteristics of a disorder that are linked more closely to its neurobiological substrates than its clinical symptoms (Doyle et al., 2005) and (2) share genetic susceptibility factors with the disorder itself (Gottesman and Gould, 2003). As described above, neuroimaging phenotypes, e.g. derived from sMRI (Hulshoff Pol et al., 2006) and DTI measurements (Jahanshad et al., 2013) are highly heritable. Those brain phenotypes altered in ADHD have therefore been considered key endophenotypes for the disorder, and investigating the genetic influences on these brain measures has been offered as a way for capturing underlying liability for ADHD (Dresler et al., 2014; Durston, 2010; Wu et al., 2014). Compared to existing reviews of brain imaging genetics studies in ADHD (Durston, 2003, 2010; Durston et al., 2009; Wu et al., 2014; Dresler et al., 2014), this review is more comprehensive by including both childhood and adult ADHD studies, a large spectrum of brain imaging modalities, and by investigating a more complete list of ADHD candidate genes. Beyond the systematic review, we also emphasize the need for additional approaches, describing complementary methods, which provide insight from alternative angles into the biological pathways leading from an ADHD risk gene to disease. Especially, we argue that the integration of methods at different analytical levels (e.g. *in silico*, cell, brain, cognition, and behaviour) is needed to unravel the function of ADHD candidate genes.

2. Methods

For this review, we selected genes that were previously found associated with ADHD. The selection was based on a recent review of ADHD candidate genes, which described 70 genes that are (with at least some evidence) related to ADHD risk (Li et al., 2014), see Table 1. We discarded eight genes, for which we did not find evidence for association with ADHD based on the analysis of genetic variation: *ARVCF*, *ATP2C2*, *CPLX4*, *DNM1*, *EMP2*, *IL20RA*, *MMP7*, and *TRIO* (Table 1). On November 28th 2016, we searched for all remaining 62 genes, all brain imaging modalities, and ADHD using PubMed (www.ncbi.nlm.nih.gov/pubmed) with the following search algorithm (example is shown for the *SLC6A3/DAT1* gene): (((*SLC6A3* OR solute carrier family 6 neurotransmitter transporter, member 3 protein human OR *DAT1* OR dopamine transporter gene OR dopamine transporter [All fields])) AND (gene* OR genetic* OR imaging genetic OR imaging genetics OR genotype OR polymorphism OR SNP OR single nucleotide polymorphism)) AND

Table 1
Candidate genes containing common variants associated with ADHD, adapted from (Li et al., 2014), which served to select genes for this review.

Gene	Protein	Chr position	References for genes associated with ADHD
<i>ADRA1B</i>	Adrenoceptor alpha 1B	5q33.3	Segurado et al. (2011) ^a , Hawi et al. (2013b) ^a
<i>ADRA2A</i> [*]	Adrenoceptor alpha 2A	10q25.2	Roman et al. (2003) ^a , Shiffrin et al. (2013) ^b
<i>ADRA2C</i>	Adrenoceptor alpha 2C	4p16.3	De Luca et al. (2004) ^a , Cho et al. (2008)
<i>ADRB1</i>	Adrenoceptor beta 1	10q25.3	Pascoli et al. (2005) ^d
<i>ADRB2</i>	Adrenoceptor beta 2, surface	5q31-q32	Lasky-Su et al., (2008a) ^{a,c} , Brookes et al. (2006a)
<i>ASTN2</i>	Astrotactin2	9q33	Lesch et al. (2008) ^a , Lionel et al. (2011, 2014)
<i>BCHE</i>	Butyrylcholinesterase	3q26.1-q26.2	Lesch et al. (2011) ^a , Jacob et al. (2013)
<i>BDNF</i>	Brain-derived neurotrophic factor	11p14.1	Friedel et al. (2005) ^a , Lee and Song (2015) ^b
<i>CALY</i>	Calcyon neuron-specific vesicular protein	10q26.3	Plaisancie et al. (2014) ^a
<i>CCSER1/FAM190A</i>	Coiled-coil serine-rich protein 1	4q22.1	Lantieri et al. (2010) ^{a,c}
<i>CDH13</i>	Cadherin 13	16q23.3	Lesch et al. (2008) ^a , Neale et al. (2010a) ^c
<i>CHRNA3</i>	Cholinergic Receptor, Nicotinic, Alpha 3	15q25.1	Polina et al. (2014) ^a
<i>CHRNA4</i>	Cholinergic Receptor, Nicotinic, Alpha 4	20q13.33	Guan et al. (2009) ^a , Wallis et al. (2009)
<i>CHRNA7</i>	Cholinergic Receptor, Nicotinic, Alpha 7	5q13.3 spanning <i>CHRNA7</i>	Williams et al. (2012) ^a
<i>CNTF</i>	Ciliary neurotrophic factor	11q12	Ribases et al. (2008) ^a , Tzang et al. (2014)
<i>COMT</i> [*]	Catechol-O-methyltransferase	22q11.21	Eisenberg et al. (1999) ^a , Lee and Song (2015)
<i>CPLX2</i>	Complexin 2	5q35.2	Lionel et al. (2011) ^a
<i>DBH</i>	Dopamine beta-hydroxylase (dopamine beta-mono oxygenase)	9q34	Daly et al. (1999) ^a , Gizer et al. (2009) ^b
<i>DDC</i>	Dopa decarboxylase (aromaticamino acid decarboxylase)	7p12.1	Ribases et al. (2009) ^a , Lasky-Su et al. (2008b) ^c
<i>DIRAS2</i>	DIRAS family, GTP-binding RAS-like 2	9q22.32	Reif et al. (2011) ^a
<i>DRD1</i> [*]	Dopamine receptor D1	5q34-q35	Misener et al. (2004) ^a , Ribases et al. (2012)
<i>DRD2/ANKK1</i>	Dopamine receptor D2/Ankyrin repeat and kinase domain containing 1	11q22-q23	Comings et al. (1991) ^a , Pan et al. (2015) ^b
<i>DRD3</i>	Dopamine receptor D3	3q13.3	Guan et al. (2009) ^a , Wu et al. (2012) ^b
<i>DRD4</i> [*]	Dopamine receptor D4	11p15	Lahoste et al. (1996) ^a , Gizer et al. (2009) ^b , Wu et al. (2012) ^b
<i>DRD5</i>	Dopamine receptor D5	4p16.1	Barr et al. (2001) ^a , Yang et al. (2008) ^d , Gizer et al. (2009) ^b
<i>FADS2</i>	Fatty acid desaturase 2	11q12.2	Daly et al. (1999) ^a , Gizer et al. (2009) ^b , Wu et al. (2012) ^b
<i>FTO</i>	Fat mass and obesity associated	16q12.2	Brookes et al. (2006b) ^a
<i>GDNF</i>	Glial cell derived neurotrophic factor	5p13.1-p12	Choudhry et al. (2013) ^a
<i>GPRC5B</i>	G protein-coupled receptor, class C, group 5, member B	16p12	Simchon-Tenenbaum et al. (2015) ^d , Shim et al. (2015)
<i>GRIN2A</i>	Glutamate receptor, ionotropic, N-methyl D-aspartate 2A	16p13.2	Albayrak et al. (2013) ^a
<i>GRM5</i>	Glutamate receptor, metabotropic 5	11q14.3	Turic et al. (2004) ^a
<i>GRM7</i>	Glutamate receptor, metabotropic 7	3p26-p25	Elia et al. (2010) ^a , Hinney et al. (2011) ^c , Elia et al. (2012)
<i>HES1</i>	Hes family bHLH transcription factor 1	3q28-q29	Mick et al. (2008) ^{a,c} , Elia et al. (2012), Park et al. (2014)
<i>HTR1A</i>	5-Hydroxytryptamine (serotonin) receptor 1A, G protein-coupled	5q11.2-q13	Brookes et al. (2006a) ^a , Lasky-Su et al. (2008b) ^c
<i>HTR1B</i>	5-Hydroxytryptamine (serotonin) receptor 1B, G protein-coupled	6q13	Shim et al. (2010) ^a , Zuo et al. (2015) ^d
<i>HTR1E</i>	5-Hydroxytryptamine (serotonin) receptor 1E, G protein-coupled	6q14-q15	Hawi et al. (2002) ^a , Gizer et al. (2009) ^b
<i>HTR2A</i>	5-Hydroxytryptamine (serotonin) receptor 2A, G protein-coupled	13q14-q21	Lasky-Su et al. (2008b) ^{a,c}
<i>HTR2C</i>	5-Hydroxytryptamine (serotonin) receptor 2C, G protein-coupled	Xq23	Quist et al. (2000) ^a , Lasky-Su et al. (2008a) ^c , Lasky-Su et al. (2008b) ^c
			Li et al. (2006b) ^a , Xu et al. (2009)

Table 1 (Continued)

Gene	Protein	Chr position	References for genes associated with ADHD
<i>HTR3A</i>	5-Hydroxytryptamine (serotonin) receptor 3A, G protein-coupled	11q23.1-q23.2	Hu et al. (2009) ^d
<i>HTR3B</i>	5-Hydroxytryptamine (serotonin) receptor 3B, G protein-coupled	11q23.1	Oades et al. (2008) ^a
<i>LPHN3*</i>	Latrophilin 3	4q13.1	Arcos-Burgos et al. (2010) ^a , Hwang et al., (2015) ^d , Ribases et al., (2011) ^d , Labbe et al., (2012) ^a
<i>MAOA*</i>	Monoamine oxidase A	Xp11.4-p11.3	Payton et al. (2001) ^a , Liu et al. (2011) ^d
<i>MAOB</i>	Monoamine oxidase B	Xp11.4-p11.3	Li et al. (2008) ^a , Ribases et al. (2009) ^d
<i>NOS1*</i>	Nitric oxide synthase 1	12q24.22	Reif et al. (2009) ^a , Franke et al. (2009) ^c , Weber et al. (2015) ^b
<i>PNMT</i>	Phenylethanolamine N-methyltransferase	17q12	Brookes et al. (2006a) ^a
<i>PRKG1</i>	Protein kinase, cGMP-dependent, type I	10q11.2	Neale et al. (2010a) ^a
<i>SLC1A3</i>	Solute Carrier Family 1 (Glial High Affinity Glutamate Transporter), Member 3	5p13	Turic et al. (2005) ^a , Elia et al. (2009)
<i>SLC6A2/NET1*</i>	Solute Carrier Family 6 (Neurotransmitter Transporter), Member 2	16q12.2	Bobb et al. (2005) ^a , Hohmann et al. (2015)
<i>SLC6A3/DAT1*</i>	Solute Carrier Family 6 (Neurotransmitter Transporter), Member 3; Dopamine transporter 1	5p15.3	Cook et al. (1995) ^a , Gizer et al. (2009) ^b Galili-Weisstub and Segman (2003) ^a , Gizer et al. (2009) ^b Brookes et al. (2006c) ^a , Gizer et al. (2009) ^b
<i>SLC6A4/5HTT*</i>	Solute Carrier Family 6 (Neurotransmitter Transporter), Member 4; serotonin transporter	17q11.2	Manor et al. (2001) ^a , Gizer et al. (2009) ^b , Landaas et al. (2010) ^b
<i>SLC9A9/NHE9</i>	Solute Carrier Family 9, Subfamily A, Member 9	3q24	de Silva et al. (2003) ^a , Stergiakouli et al. (2012) ^c , Mick et al., (2010) ^c
<i>SLC18A2/VMAT2</i>	Solute Carrier Family 18 (Vesicular Monoamine Transporter), Member 2	10q25	Toren et al. (2005) ^a
<i>SNAP25*</i>	Synaptosomal-associated protein, 25 kDa	20p12-p11.2	Brophy et al. (2002) ^a , Gizer et al. (2009) ^b
<i>SPOCK3</i>	Sparc/osteonectin, cwcv and kazal-like domains proteoglycan (testican) 3	4q32.3	Weber et al. (2014) ^a , Gao et al. (2015)
<i>STX1A</i>	Syntaxin 1A	7q11.2	Sanchez-Mora et al. (2013) ^d
<i>SYP</i>	Synaptophysin	Xp11.23-p11.22	Brookes et al. (2006a) ^a , Liu et al. (2013b) ^d
<i>SYT1</i>	Synaptotagmin I	12q21.2	Guan et al. (2009) ^a , Lasky-Su et al. (2008a) ^c
<i>TCERG1L</i>	Transcription elongation regulator 1-like	10q26.3	Neale et al. (2010a) ^{a,c}
<i>TH</i>	Tyrosine hydroxylase	11p15.5	Segurado et al. (2011) ^a
<i>TPH1</i>	Tryptophan hydroxylase 1	11p15.3-p14	Gizer et al. (2009) ^b
<i>TPH2*</i>	Tryptophan hydroxylase 2	12q15	Walitza et al. (2005) ^a , Sheehan et al. (2005) ^a , Gizer et al. (2009) ^b
<i>VAMP2</i>	Vesicle-associated membrane protein 2 (synaptobrevin 2)	17p13.1	Gao et al. (2015) ^a

Bold text indicates significant result at $P < 0.05$ in Gizer et al. (2009).

^a Association first reported by.

^b Meta-analysis article.

^c GWAS finding.

^d Association in large sample or validation using animal model.

* Gene with at least one case-control imaging genetics study; ADHD = Attention-deficit/hyperactivity disorder, chr = chromosome.

(structural magnetic resonance imaging OR functional magnetic resonance imaging OR sMRI OR fMRI OR electroencephalography OR diffusion tensor imaging OR DTI OR resting-state functional magnetic resonance imaging OR rsfMRI OR EEG OR magnetoencephalography OR MEG OR single photon emission computed tomography OR SPECT OR positron emission tomography OR PET OR near-infrared spectroscopy OR NIRS OR volume [Title/Abstract]) AND (ADHD OR Attention-deficit/hyperactivity disorder OR [All fields] NOT "review" [Publication Type]). Titles and abstracts of the

retrieved records were evaluated for relevant publications. Studies were required to investigate genetic variants in/near the selected ADHD candidate genes, and only studies including patients with ADHD were included. Review articles, medical hypotheses, non-English articles, and studies on animal models were not considered. The preferred reporting items for systematic reviews and meta-analysis (PRISMA) diagram in Fig. 1 describes the number of articles identified and their classification.

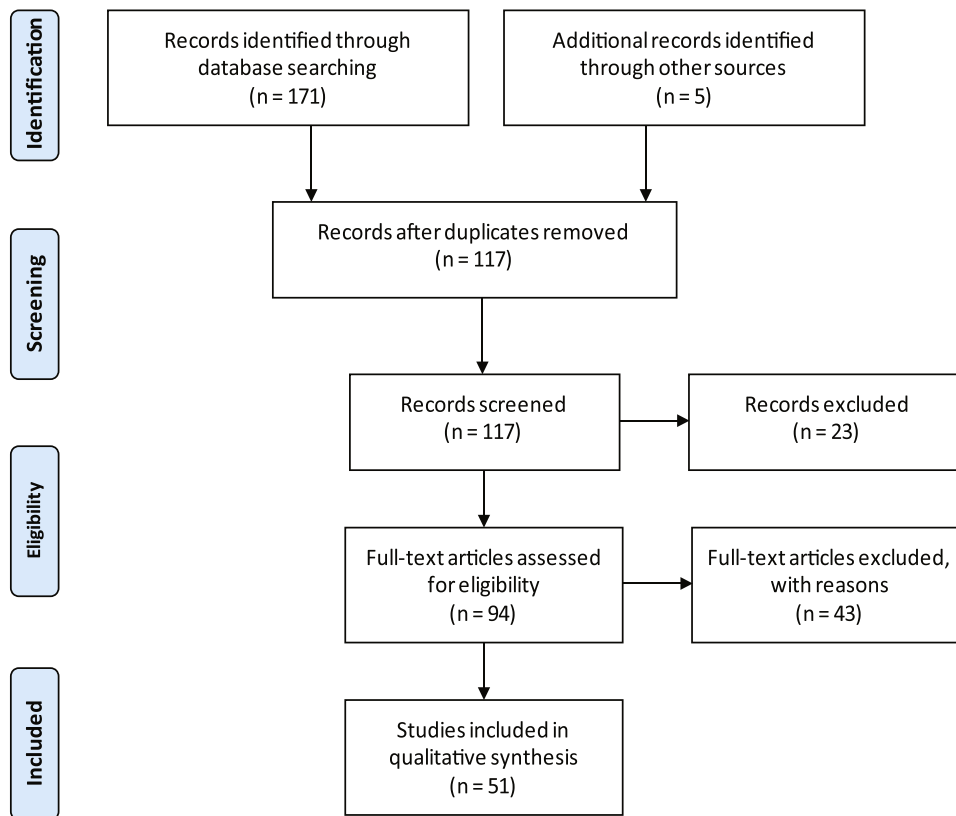


Fig. 1. Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) flowchart of the literature search and study selection for qualitative analysis. Note: see <http://www.prismastatement.org> for more information in this reporting system.

3. Results

For 25 out of the 62 ADHD candidate genes, we retrieved a total number of 171 reports linking genetic variation in/near the gene to neuroimaging by using the above mentioned search term in PubMed (Fig. 1). To those, we added two recent papers from our own group (Sokolova et al., 2015; van Ewijk et al., in revision) and three additional papers that were missing, from reading the retrieved reports (Dresler et al., 2010; Albrecht et al., 2014; Fernandez-Jaen et al., 2016). After removal of 54 duplicates, we screened 117 records and discarded an additional 66 papers, mostly because they described animal studies, did not include ADHD patients, or did not fulfil our eligibility criteria otherwise. We finally included 51 original research articles on brain imaging genetics studies for 13 ADHD candidate genes (*ADRA2A*, *COMT*, *DRD1*, *DRD4*, *HTR1B*, *LPHN3*, *MAOA*, *NOS1*, *SLC6A2/NET1*, *SLC6A3/DAT1*, *SLC6A4/5HTT*, *SNAP25*, *TPH2*; Tables 2 and 3). Most of the studies investigated a single gene (32 in Caucasians, 6 in Asians), thirteen studies investigated multiple genes (12 in Caucasians, 1 in Asians). The dopamine transporter gene (*SLC6A3/DAT1*) and the dopamine D4 receptor gene (*DRD4*) were the most frequently studied ADHD candidate genes (Tables 2 and 3).

3.1. Findings for the dopamine transporter gene (*SLC6A3*, *DAT1*)

The gene *DAT1* (official name *SLC6A3*) codes for a solute carrier protein (DAT) responsible for the reuptake of dopamine from the synaptic cleft into the presynaptic neuron, representing a primary mechanism of dopamine regulation in the striatum (Ciliax et al., 1999). The most widely studied polymorphism in *SLC6A3/DAT1* is a variable number of tandem repeat (VNTR) sequence in the 3' untranslated region (3'UTR) that is 40 base pairs (bp) in length. Most

common alleles are those with 9 and 10 repeats (9R and 10R). Additionally, a 30 bp VNTR in intron 8 of the gene (most common alleles with 5 and 6 repeats [5R and 6R]), is sometimes studied together with the 3'UTR VNTR as a haplotype. The 10R/10R genotype of the 3'UTR VNTR and the 10-6 haplotype of the two VNTRs are thought to be risk factors for childhood ADHD (Asherson et al., 2007; Brookes et al., 2006). In contrast, the 9R/9R genotype and the 9-6 haplotype are associated with persistent ADHD (Franke et al., 2010). This suggests a differential association of the gene with ADHD depending on age, and a role of *DAT1* in modulating the ADHD phenotype across the lifespan. In addition to the VNTRs, several SNPs in *DAT1* have been studied for their effect on ADHD and/or brain phenotypes.

Two studies performed PET to study the role of *DAT1* genotype on DAT availability, one using ¹¹Altropene as the ligand and one ¹¹Cocaine. In an early study investigating a very small sample of 6 patients with ADHD and 9 controls, Drgon and colleagues studied a haplotype of two SNPs (rs2652511, rs2937639) in the 5' regulatory region of the *SLC6A3/DAT1* gene, and found the CG-allele associated with ventral striatal *in vivo* DAT availability independent of diagnosis; this finding was confirmed through investigation of striatal DAT expression in post-mortem brain samples (2006). Spencer and coworkers observed that, in adults, the 9R genotype of the 3'UTR VNTR increased DAT binding in caudate nucleus both in patients and healthy controls, whereas the intron 8 VNTR and a haplotype of both variants were not associated with DAT binding (2013); (Table 3).

Four SPECT studies, using different ligands, investigated the effect of the 3'UTR VNTR on DAT availability (Table 3). Two early case-only studies, both in children with ADHD (n = 8 and 11, respectively), showed that basal ganglia DAT density was increased (Cheon et al., 2005) and that the regional cerebral blood flow (rCBF) was larger in medial frontal and left basal ganglia during

Table 2
Overview of imaging genetics studies identified per gene.

Gene	^b articles found	^b articles discarded	^b articles included	References of articles included in review.
<i>ADRA2A</i>	4	2	2	Kim et al. (2010), Park et al. (2013).
<i>BCHE</i>	1	1	0	
<i>BDNF</i>	4	4	0	
<i>CHRNA4</i>	2	2	0	
<i>CHRNA7</i>	1	1	0	
<i>COMT</i>	13	7	6	Heinzel et al. (2013), Hong et al. (2014), Shimada et al. (2015), Villemonteix et al. (2015), Kabukcu Basay et al. (2016), van Rooij et al. (2015b)
<i>DBH</i>	2	2	0	
<i>DRD1</i>	3	1	2	Bobb et al. (2005), Shaw et al. (2007a)
<i>DRD2</i>	27	27	0	
<i>DRD3</i>	1	1	0	
<i>DRD4</i>	20	9	12	Castellanos et al. (1998), Durston et al. (2005), Heinzel et al. (2013), Hong et al. (2014), Loo et al. (2010), Monuteaux et al. (2008), Shaw et al. (2007b), Szobot et al. (2005), Szobot et al. (2011), Albrecht et al. (2014), Richards et al. (2016), Schwenen et al. (2016)
<i>DRD5</i>	2	2	0	
<i>GRM5</i>	1	1	0	
<i>HTR1B</i>	1	0	1	van Rooij et al. (2015a)
<i>LPHN3</i>	2	0	2	Arcos-Burgos et al. (2010), Fallgatter et al. (2013)
<i>MAOA</i>	3	2	1	Ko et al. (2015)
<i>MAOB</i>	3	3	0	
<i>NOS1</i>	2	1	2 ^a	Hoogman et al. (2011), van Ewijk et al. (in revision)
<i>SLC6A2/NET1</i>	7	4	3	Bobb et al. (2005), Park et al. (2012), Sigurdardottir et al. (2015)
<i>SLC6A3/DAT1</i>	48	22	29 ^a	Althaus et al. (2010), Bedard et al. (2010), Braet et al. (2011), Brown et al. (2011), Brown et al. (2010), Cheon et al. (2005), Drgon et al. (2006), Durston et al. (2005), Durston et al. (2008), Hong et al. (2014), Hoogman et al. (2013), Krause et al. (2006), Loo et al. (2003), Paloyelis et al. (2012), Rohde et al. (2003), Shaw et al. (2007b), Shook et al. (2011), Spencer et al. (2013), Szobot et al. (2005), Szobot et al. (2011), Sokolova et al. (2015), Dresler et al. (2010), Onnink et al. (2016), Albrecht et al. (2014), Fernandez-Jaen et al. (2016), Fernandez-Jaen et al. (2015), Richards et al. (2016), van Rooij et al. (2015b), Schwenen et al. (2016)
<i>SLC6A4/5HTT</i>	10	6	4	van der Meer et al. (2015), Richards et al., (2016), van der Meer et al. (2016), van Rooij et al. (2015a)
<i>SNAP25</i>	7	6	1	Oner et al. (2011)
<i>SYP</i>	1	1	0	
<i>TH</i>	5	5	0	
<i>TPH2</i>	1	0	1	Baehne et al. (2009)
Total	171	110	66 ^b	

^a Papers were added manually (two recent papers from our own group (1x *NOS1*, 1x *SLC6A3/DAT1*) and three additional papers that were missing from the PubMed search (3x *SLC6A3/DAT1*).

^b This number still includes duplicate articles, since some studies investigated more than one candidate gene. No records were retrieved for the following genes: *ADRA1B*, *ADRA2C*, *ADRB1*, *ADRB2*, *ASTN2*, *CALY*, *CCSER1*, *CDH13*, *CHRNA3*, *CNTF*, *CPLX2*, *DDC*, *DIRAS2*, *FADS2*, *FTO*, *GDNF*, *GPRC5B*, *GRIN2A*, *GRM7*, *HES1*, *HTR1A*, *HTR1E*, *HTR2A*, *HTR2C*, *HTR3A*, *HTR3B*, *PNMT*, *PRKG1*, *SLC1A3*, *SLC18A2*, *SLC9A9*, *SPOCK3*, *STX1A*, *SYT1*, *TCERG1L*, *TPH1*, *VAMP2*.

a continuous performance task (CPT) in response to MPH treatment in 10R/10R-homozygotes compared to 9R-carriers (Rohde et al., 2003). A somewhat larger study in adults with ADHD did not identify a difference in striatal DAT availability between 10R/10R-homozygotes and 9R-carriers (Krause et al., 2006). Another SPECT study in boys with ADHD observed a genotypic effect of the 3'UTR VNTR variant increasing rCBF during a CPT only in the presence of risk alleles at both *SLC6A3/DAT1* (10R/10R) and *DRD4* (7R); this effect was present in the right middle temporal gyrus, an area associated with working memory and selective attention (Szobot et al., 2005); (Table 3). An interaction effect between the two polymorphisms was subsequently also shown by the same group in

adolescent patients with ADHD plus substance use disorder (Szobot et al., 2011); (Table 3). In this case, participants homozygous for the *SLC6A3/DAT1* 10R-allele and carrying the *DRD4* 7R-allele exhibited decreased DAT occupancy after MPH treatment in the right and left caudate nucleus and putamen (Szobot et al., 2011). A recent meta-analysis, including healthy subjects and patients with different psychiatric disorders including ADHD, assessed the association of the 3'UTR variant with DAT availability (Faraone et al., 2014b). The PET studies provided significant evidence that the 9R-allele was associated with increased DAT availability in human adults, independent of the diagnostic status. The SPECT studies were highly heterogeneous, but when the analysis was limited to the most

Table 3
Imaging genetics studies of ADHD candidate genes in ADHD (case-control) samples (for candidate gene list see Table 1).

Gene (s)	Variant	Imaging modality	Imaging/cognitive phenotype or task	Genotype groups compared	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
ADRA2A	rs1800544, rs553668	DTI	White matter integrity, FA values	C-allele carriers vs. GG-carriers, T-allele carriers vs. CC-carriers	53 ADHD (9.1) ^b	rs1800544 C-allele carriers: ↓ FA in right postcentral gyrus. rs553668 T-allele carriers: ↓ FA in right middle frontal cortex.	Park et al. (2013)
	rs1800544	SPECT with ^{99m} Tc-HMPAO	Regional brain perfusion	C-allele carriers vs. GG-carriers	21 ADHD (9.9) ^{a,b}	C-allele carriers: ↓ perfusion in bilateral orbitofrontal regions.	Kim et al. (2010)
COMT	rs4680	sMRI (VBM)	cerebellum, temporal lobe and IFG volume	Met-carriers vs. Val/Val-carriers	38 ADHD (10.3) 24 HC (10.1)	ADHD Met-carriers: ↓ GM volume in IFG (whole brain level) compared to HC. ADHD Val/Val: ↑ GM volume in right CN (ROI analysis) compared to ADHD Met-carriers and HC. ADHD Met-carriers: ↓ GM volume in left putamen.	Villemonteix et al. (2015)
				Met-carriers vs. Val/Val-carriers	17 ADHD (10.3) ^b 15 HC (12.8) ^b		Shimada et al. (2015)
		DTI	FA and RD values	Met-carriers vs. Val/Val-carriers	71 ADHD (10.9) 24 HC (10.8)	ADHD Val/Val: ↓ FA and ↑ RD in the right cingulum (cingulate gyrus) compared to ADHD Met-carriers and HC Val/Val.	Kabukcu Basay et al. (2016)
DRD4	exon 3 VNTR	sMRI	Superior frontal, middle frontal, anterior cingulate, and cerebellum cortices volumes TBV, PFC, cerebellum, CN, and pallidum volume	ADHD 7R-carriers vs. non-7R-carriers	24 ADHD (38.1) 19 ADHD+BPD (35.8) 20 HC (33.2)	7R- carriers: ↓ volumes of superior frontal cortex and cerebellum cortex compared to non-carriers. No effects in ADHD+BPD or HC.	Monuteaux et al. (2008)
				7R-carriers vs. non-7R-carriers	41 ADHD (9.7) 56 HC (17.6)	No volumetric differences between 7R and non 7R-carriers. No group × genotype interactions.	Castellanos et al. (1998)
		EEG	β and θ frequency bands during a CPT	7R-carriers vs. non-7R-carriers	340 children (11.1; 304 ADHD) 191 parents (44.3; 80 ADHD)	Childhood 7R-carriers: ↑ frontal θ and ↓ global β2 power. Adult 7R-carriers: similar β2 power in 'eyes closed' condition, but ↓ β2 power in 'eyes open' and CPT conditions.	Loo et al. (2010)
LPHN3	rs2305339, rs734644, rs1397547, rs1397548, haplotype	EEG	Go/No-Go task (CPT)	High risk group (2 copies of risk haplotype = AGCC) vs. low risk group	114 ADHD high risk group (34.85) 102 ADHD low risk group (34.92)	High risk group: ↑ anterior Go-centroid of P300, ↓ mean NGA.	Fallgatter et al. (2013)

Table 3 (Continued)

Gene (s)	Variant	Imaging modality	Imaging/cognitive phenotype or task	Genotype groups compared	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
	rs6551665, rs1947274, rs2345039 haplotype	Proton magnetic resonance spectroscopy (¹ H-MRS)	NAA/Cr ratio in striatum, lateral and medial thalamus, cingulate gyrus, and cerebellar vermis	Risk haplotype vs. protective haplotype	Risk haplotype: 13 ADHD, 2 HC Protective haplotype: 1 ADHD, 9 HC Different haplotypes: 8 HC	Risk haplotype carriers: ↓ NAA/Cr in left lateral thalamus, left medial thalamus, right striatum, ↑NAA/Cr in inferior–posterior cerebellar vermis. Carriers of two copies of risk haplotype had lowest levels of NAA/Cr.	Arcos-Burgos et al. (2010)
<i>MAOA</i>	rs1137070	fMRI	Working memory task	TT-carriers vs. CC-carriers	21 ADHD (23.9) ^{a,b} 19 HC (25.2) ^{a,b}	ADHD TT-carriers: ↑ activation in left inferior frontal lobe, pars opercularis.	Ko et al. (2015)
<i>NOS1</i>	Exon 1f-VNTR	DTI	WM integrity, FA and MD values	SS-carriers vs. SL/LL-carriers	178 ADHD (17.6) 122 HC (16.8)	Female SS-carriers: ↑ MD in right parietal WM tracts. Males: no difference between genotype groups. No genotype × diagnostic group interaction.	van Ewijk et al. (in revision)
<i>SLC6A2/NET1</i>	rs5569, rs28386840	fMRI	Reward anticipation task/modified MID task	SS-carriers vs. SL/LL-carriers	63 ADHD (38.3) 41 HC (38.0)	SS-carriers: ↑ activity in VS. No group × genotype interactions.	Hoogman et al. (2011)
	rs5569, rs28386840	SPECT with [^{99m} Tc] HMPAO	Cerebral perfusion in response to MPH treatment (8 weeks)	rs5569: GG-carriers vs. GA/AA-carriers; rs28386840: AA-carriers vs. AT/TT-carriers	37 ADHD (8.9) ^b	No differences in baseline clinical assessments or cerebral perfusion based on genotype. rs5569 GG-carriers: After 8 weeks of treatment hyperperfusion in right inferior temporal gyrus and middle temporal gyrus.	Park et al. (2012)
	rs28386840, rs2242246, rs15534, rs40615	PET with (S,S)-[¹⁸ F]FMeNER-D ₂	NET BP _{ND} in thalamus, midbrain with pons, putamen, and cerebellum	Minor allele carriers vs. major allele homozygotes	20 ADHD (30.8) 20 HC (30.4)	rs28386840 and rs2242446 ADHD major allele carriers (A/T): ↑ NET BP _{ND} in the thalamus compared to major allele carrying controls. No difference was detected for the minor allele between groups. rs15534 and rs40615 HC major allele carriers (C/T): ↑ NET BP _{ND} in the cerebellum compared to major allele carrying patients.	Sigurdardottir et al. (2015)
<i>SLC6A3/DAT1</i>	3' UTR VNTR	SPECT with [^{99m} Tc] TRODAT-1	Striatal DAT availability	10R/10R-carriers vs. 9R-carriers	29 ADHD (37.7)	No differences in DAT availability between 10R/10R-carriers and 9R-carriers.	Krause et al. (2006)
		SPECT with [¹²³ I]IPT in response to MPH treatment	Basal ganglia DAT density	10R/10R-carriers vs. 9R-carriers	11 ADHD (9.8) ^b	10R/10R-carriers: ↑ DAT density in basal ganglia.	Cheon et al. (2005)
		SPECT with [^{99m} Tc]-ECD in response to MPH treatment	rCBF during a CPT	10R/10R-carriers vs. 9R-carriers	8 ADHD, age range 8–12 ^a	10R/10R-carriers: ↑ rCBF in medial frontal and left basal ganglia areas in response to MPH.	Rohde et al. (2003)

Table 3 (Continued)

Gene (s)	Variant	Imaging modality	Imaging/cognitive phenotype or task	Genotype groups compared	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
	3' UTR, intron 8 VNTR, and haplotype	PET with [¹¹ C] altropane	DAT binding in CN	9R-carriers vs. 10R/10R-carriers; 6R-carriers vs. 5R/5R-carriers	34 ADHD (32.8) 34 HC (27.7)	ADHD and HC 9R-carriers: ↑ DAT binding in CN. No association between intron 8 polymorphism or 3'-UTR-intron 8 haplotype with DAT binding.	Spencer et al. (2013)
	rs2652511, rs2937639 haplotype	PET with [¹¹ C] cocaine	Ventral striatal DAT expression	CG-haplotype (rs2652511C-allele and rs2937639 G-allele carriers) vs. rest	6 ADHD 9 HC	CG-haplotype: No effect on diagnosis. Haplotype was more frequent in individuals with high DAT expression.	Drgon et al. (2006)
	3'UTR and intron 8 VNTR haplotype	sMRI	Bilateral striatal volumes (nucleus accumbens, CN, and putamen)	Three DAT1 alleles (10/10 genotype, and the haplotypes 10–6 and 9–6)	118 ADHD (35.9) 111 HC (37) 301 ADHD (17.2) 186 HC (16.6) 1718 HC (26.1)	Adult ADHD 9–6 haplotype carriers ↑ 5.9% larger striatum volume relative to participants not carrying this haplotype (in adult ADHD patients only). Effect was not replicated in adolescent case-control and adult population-based cohort.	Onnink et al. (2016)
	3' UTR VNTR	sMRI	Cingulate cortex thickness	10R/10R-carriers vs. 9R-carriers	98 ADHD (10.9)	10R/10R-carriers: ↑ thickness in right cingulate gyrus and right BA 24.	Fernandez-Jaen et al. (2016)
	3' UTR VNTR	sMRI	PFC thickness	10R/10R-carriers vs. 9R-carriers	63 ADHD (10.9)	10R/10R-carriers: ↓ cortical thickness in right BA 46 (lateral PFC). No other prefrontal ROI differed significantly.	Fernandez-Jaen et al. (2015)
	3' UTR VNTR	sMRI	CN volume	9R-carriers vs. 10R/10R-carriers	33 ADHD (10.5) 26 HC (10.6)	9R-carriers: ↑ volumes of CN.	Shook et al. (2011)
	3'UTR and intron 8 VNTR haplotype	fMRI	Striatal activity during reward anticipation task	9-6 haplotype carriers vs. non 9-6 haplotype carriers	87 ADHD (38.3) 77 HC (38)	No differences in striatal activity compared with non 9-6 haplotype carriers nor 9R- and 10R/10R-carriers.	Hoogman et al. (2013)
					87 ADHD (38.3) 77 HC (38); same as above	Bayesian Constraint-based Causal Discovery (BCCD) algorithm confirmed that there is no direct link between <i>DAT1</i> genetic variability and brain activation, but suggested an indirect link mediated through inattention symptoms and diagnostic status of ADHD.	Sokolova et al. (2015)

Table 3 (Continued)

Gene (s)	Variant	Imaging modality	Imaging/cognitive phenotype or task	Genotype groups compared	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
			VS and CN activity during reward-predicting cues	<i>SLC6A3</i> 10-6 dosage (2 copies vs. <2 copies)	29 ADHD (combined type; 15.8) ^a 30 HC (15.6) ^a	ADHD: Activation in CN ↓ as number of copies ↑, but in control group reverse was found.	Paloyelis et al. (2012)
	3' UTR VNTR	fMRI	Working memory task	9R-carriers vs. 10R/10R-carriers	53 ADHD (35.7) 38 HC (31.2)	9R-carriers: ↓ left medial PFC activation compared to 10R/10R-carriers. Group × genotype interaction showed that 10R/10R-ADHD patients had ↑ activity in pre-SMA/dorsal ACC compared to HC.	Brown et al. (2011)
			Go/No-Go task	10R/10R-carriers vs. 9R-carriers	20 ADHD (14.1) 38 HC (13.12)	10R/10R carriers: ↑ activity in frontal, medial, and parietal regions during response inhibition compared to 9R-carriers; ↓ error response in the parahippocampal gyrus.	Braet et al. (2011)
				10R/10R-carriers vs. 9R-carriers	33 ADHD (11.1)	10R/10R carriers: ↑ activity in left striatum, right dorsal premotor cortex, and temporoparietal cortical junction compared to 9R-carriers.	Bedard et al. (2010)
				9R-carriers vs. 10R/10R-carriers	10 ADHD (14.6) ^a 10 unaffected siblings (14.8) ^a 9 HC (15.3) ^a	9R-carriers: ↑ activity in CN and ↓ in cerebellar vermis compared to 10R/10R-carriers. Group × genotype interaction: effect in CN is observed in ADHD and unaffected siblings, but not HC.	Durston et al. (2008)
			Multi-source interference task	10R/10R-carriers vs. 9R-carriers	42 ADHD (35.4)	9R-carriers: ↓ activity in dorsal ACC compared to 10R/10R-carriers.	Brown et al. (2010)
		EEG	Go/No-Go task	10R/10R-carriers vs. 9R-carriers	161 ADHD (35.6) 109 HC (35.8)	ADHD 9R-carriers: ↓ NGA (indicating impaired cognitive response control); No genotype effect in control group	Dresler et al. (2010)
			Feedback-based learning task; measuring ERPs	10R/10R-carriers vs. 9R-carriers	27 ADHD (11.5) 18 PDD (11.3) 20 HC (11.5)	10R/10R-carriers: ↓ Pe to errors and ↓ SPN in anticipation of negative feedback, particularly with learning.	Althaus et al. (2010)
		EEG, single dose of 10 mg MPH (double-blind, placebo-controlled)	Sustained attention and vigilance task	10R/10R-carriers vs. 9R-carriers	27 ADHD (10.1)	10R/10R-carriers: medication-related EEG changes of ↑ central and parietal β power, ↓ right frontal θ power, ↓ θ/β ratios. 9R-carriers: showed opposite pattern.	Loo et al. (2003)

Table 3 (Continued)

Gene (s)	Variant	Imaging modality	Imaging/cognitive phenotype or task	Genotype groups compared	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
<i>SLC6A4/5HTT</i>	5-HTTLPR	sMRI (VBM)	GM volume	S-carriers vs. LL-carriers	291 ADHD 78 subthreshold ADHD 332 HC; Average age: 17 years	S-carriers: stress exposure is associated with ↓ GM volume in precentral gyrus, middle and superior frontal gyri, frontal pole, and cingulate gyrus. Association of GxE interaction with ADHD symptom count was mediated by GM volume in frontal pole and anterior cingulate gyrus only.	van der Meer et al. (2015)
<i>SNAP25</i>	rs1051312, rs3746544	fNIRS	MPH treatment-related hemodynamic changes during interference condition of Stroop task	rs1051312: TT- vs. TC/CC-carriers, rs3746544: TT- vs. TG/GG-carriers; 4 groups for interaction analysis	15 ADHD (26.1) 16 ADHD (9.7)	rs1051312 TT-carriers: ↓ right [HHb] with treatment rs3746544 TT-carriers: changes in genotype right [HbO2] and [HHb] as well as left [HHb]. Interaction analysis – participants with rs1051312 CC/TC and rs3746544 GG/TG: ↑ right [HHb] with MPH use. Interaction analysis – participants with rs1051312 TT and rs3746544 TT or rs1051312 TT and rs3746544 GG/TG: ↓ right prefrontal [HHb] with MPH use.	Oner et al. (2011)
<i>TPH2</i>	rs4570625, rs11178997	EEG	Go/No-Go task (CPT)	rs4570625: GG- vs. T-carriers, rs11178997: TT- vs. TA-carriers	124 ADHD (34.7) 84 HC (34.8)	rs11178997 TT-carriers and rs4570625 GG-carriers: ↓ NGA in both HC and ADHD. No group × genotype interactions.	Baehne et al. (2009)
<i>SLC6A3/DAT1, DRD4</i>	3' UTR VNTR, exon 3 VNTR	SPECT with [^{99m} Tc]TRODAT-1 in response to MPH treatment	Striatal DAT binding potential	10/10R-carriers vs. 9R-carriers; 7R-carriers vs. non-7R-carriers; 10/10R+7R-carriers vs. rest	17 ADHD/SUDs, age range 15–21 years ^a	10/10R-carriers: no effect on DAT occupancy after MPH treatment. 7R-carriers: no effect on DAT occupancy after MPH treatment. 10/10R+7R-carriers: ↓ DAT occupancy after MPH treatment in right and left CN and putamen.	Szobot et al. (2011)
		SPECT with [^{99m} Tc]ECD	rCBF during a CPT	10/10R-carriers vs. 9R-carriers; 7R-carriers vs. non-7R-carriers; 10/10R+7R-carriers vs. rest	34 ADHD (11.6) ^a	10/10R-carriers: no effect on rCBF. 7R-carriers: no effect on rCBF. 10/10R+7R-carriers: ↑ rCBF in right middle temporal gyrus area.	Szobot et al. (2005)
		sMRI	PFC GM and CN volume	9R-carriers vs. 10R/10R-carriers, 4R/4R-carriers vs. rest	26 ADHD (12.1) 26 unaffected siblings (11.6) 20 HC (10.7); all ^a	<i>SLC6A3</i> ADHD 10/10R-carriers: ↓ CN volumes <i>DRD4</i> unaffected siblings 7R-carriers: ↑ prefrontal GM volume. No effects on CN, or TBV. No interactions between ADHD status and genotype.	Durstun et al. (2005)

Table 3 (Continued)

Gene (s)	Variant	Imaging modality	Imaging/cognitive phenotype or task	Genotype groups compared	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
	3'UTR and intron 8 VNTR haplotype, exon 3 VNTR	sMRI	Striatum, frontal cortex, and hippocampus volumes	10-6 haplotype carriers vs. non-10-6 haplotype carriers, 7R-carriers vs. non-7R-carriers	316 ADHD (17.2) 187 HC (16.5)	<i>SLC6A3</i> 10-6 haplotype-carriers: ↓ left striatal volume, irrespective of treatment. <i>DRD4</i> 7R-carriers: frontal cortex volume is associated with stimulant treatment at younger age.	Schweren et al. (2016)
<i>SLC6A3/DAT1, DRD4, SLC6A4/5HTT</i>		sMRI	Total GM, caudate, and putamen volume	9R-carriers vs. rest, 7R-carriers vs. rest, S-allele-carriers vs. rest	368 high ADHD severity (17.3) 374 low ADHD severity (16.8)	For total GM, differential age effects were found for <i>SLC6A3</i> 9R- and <i>SLC6A4</i> L/L carriers, depending on the amount of positive peer affiliation. For putamen volume, <i>DRD4</i> 7R-carriers and <i>SLC6A3</i> 10/10 homozygotes showed opposite age relations. Results were independent of ADHD severity.	Richards et al. (2016)
<i>SLC6A3/DAT1, DRD4, DRD1</i>	3' UTR VNTR, exon 3 VNTR, rs4532	sMRI; longitudinal study (mean follow-up, 6 years)	Cortical thickness	9R-carriers vs. 10R/10R-carriers, 7R-carriers vs. non-7R-carriers, C-allele carriers vs. non-C-allele carriers	105 ADHD (10.1; 13.1; 15.9) 103 HC (10.0; 12.4; 14.4)	<i>SLC6A3</i> 9R-carriers: No effect on cortical development. <i>DRD4</i> 7R-carriers: thinner right orbitofrontal/inferior prefrontal and posterior parietal cortex. ADHD 7R-carriers: distinct trajectory of cortical development; normalization of right parietal cortical region. <i>DRD1</i> : No effect of genotype on clinical outcome or cortical development.	Shaw et al. (2007b)
<i>SLC6A3/DAT1, DRD4, COMT</i>	3' UTR VNTR, exon 3 VNTR, rs4680	DTI	WM integrity, FA values	9R-carriers vs. 10R/10R-carriers; 4R/4R-carriers vs. rest; Met-carriers vs. Val/Val	58 stimulant- and atomoxetine-naïve ADHD (8.7) ^b	<i>SLC6A3</i> 9R-carriers: no effect on WM integrity <i>DRD4</i> 4R/4R-carriers: no effect on WM integrity. Met-carriers: ↓ Network of WM connections linking 18 brain regions	Hong et al. (2014)

Table 3 (Continued)

Gene (s)	Variant	Imaging modality	Imaging/cognitive phenotype or task	Genotype groups compared	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
<i>SLC6A3/DAT1, COMT</i>	3'UTR and intron 8 VNTR haplotype, rs37020, rs460000, rs4680	fMRI	Stop-signal task	10-6 haplotype-carriers vs. non-10-6 haplotype-carriers; rs37020: CC vs. rest; rs460000: GG vs. rest; Val/Val vs Met-carriers	185 ADHD (17.3) 111 unaffected siblings (17.3) 124 HC (16.5)	No genotype × ADHD interaction effects. <i>SLC6A3</i> 10-6 haplotype-homozygotes: ↑ activity related to successful stop-trials in pre-supplementary motor areas, ↓ activity in superior frontal and temporal pole areas. rs37020 AA-carriers: ↓ activity during failed stop-trials in IFG, pre-supplementary motor areas, and post-central gyrus. rs4680 Val/Val-carriers: ↓ activity during successful stop-trials in thalamus, frontal pole, and left IFG; ↑ activity in hippocampus during failed stop-trials.	van Rooij et al. (2015b)
<i>SLC6A3/DAT1, DRD4</i>	3'UTR and intron 8 VNTR haplotype, exon 3 VNTR	EEG	CPT	10-6 haplotype-carriers vs. non-10-6 haplotype-carriers; 7R-carriers vs. non-7R-carriers	94 ADHD; 31 HC; age range 8–16 ; all ^a	<i>SLC6A3</i> 10-6 haplotype-carriers: ↑ activity related to inhibitory response control (Nogo-P3) <i>DRD4</i> 7R-carriers: ↓ activity related to attentional orienting (Cue-P3) and cognitive or response preparation (CNV). No genotype × ADHD interactions.	Albrecht et al. (2014)
<i>DRD4, COMT</i>	exon 3 VNTR, rs4680	EEG	Go/No-Go task	7R-carriers vs. non-7R-carriers; Val/Val vs. Val/Met vs. Met/Met-carriers	181 ADHD (35.3, age range: 18–60) 114 HC	Single genes and diagnosis had no effect on neural correlates of prefrontal response control (NGA). <i>DRD4</i> VNTR and <i>COMT</i> SNP epistatically interacted on NGA.	Heinzel et al. (2013)

Table 3 (Continued)

Gene (s)	Variant	Imaging modality	Imaging/cognitive phenotype or task	Genotype groups compared	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
<i>DRD1</i> , <i>SLC6A2/NET1</i>	rs4532 and rs265981, rs998424 and rs3785157	sMRI	TCV, volumes of total GM and WM, CN, cerebellum, frontal, temporal, parietal lobes	2 and 3 genotype groups per SNP	114 ADHD (9) 79 HC (16)	<i>DRD1</i> and <i>NET1</i> SNPs: No genotype effects on GM or WM volume and no group × genotype interactions.	Bobb et al. (2005)
<i>SLC6A4/5HTT</i> , <i>HTR1B</i>	5-HTTLPR, rs6296	fMRI	Stop-signal task	3 genotype groups per variant	184 ADHD (17.3) 111 unaffected siblings (17.3) 124 HC (16.5)	<i>SLC6A4</i> SS-genotype group: ↓ activation in frontal nodes and ↑ activation in posterior nodes. <i>HTR1B</i> genotype: associated with differential activation in anterior cingulate, occipital, inferior temporal, and cerebellar regions during successful stop trials. No associations between <i>SLC6A4</i> and <i>HTR1B</i> variants and ADHD or ADHD-related neural activation.	van Rooij et al. (2015a)
<i>SLC6A4/5HTT</i> , <i>NR3C1</i>	5-HTTLPR, rs6189, rs6198	sMRI	GM volume	S-allele carriers vs. rest; NR3C1 risk haplotype-carriers (rs6189G and rs6198G) vs. rest	539 ADHD, unaffected siblings, and HC combined (17.2)	NR3C1 risk haplotype-carriers : ↑ positive relation between stress exposure and ADHD severity; which was stronger for <i>SLC6A4</i> L-allele homozygotes. Interactions were reflected in GM volume of cerebellum, parahippocampal gyrus, intracalcarine cortex, and angular gyrus.	van der Meer et al. (2016)

BP = binding potential, BP_{ND} = nondisplaceable binding potential, BPD = bipolar disorder, CN = caudate nucleus, CPT = continuous performance test, dACC = dorsal anterior cingulate cortex, DAT = dopamine transporter, DTI = Diffusion tensor imaging, ECD = ethyl-cysteinate-dimer, EEG = electroencephalography, ERP = event related potential, FA = fractional anisotropy, fMRI = functional magnetic resonance imaging, fNIRS = functional near-infrared spectroscopy, HC = healthy control, IFG = inferior frontal gyrus, NAA/Cr = ratio of N-acetylaspartate to creatine, NAcc = nucleus accumbens, NGA = NoGo-anteriorization, PDD = Pervasive Developmental Disorder, Pe = error-related positivity, PET = positron emission tomography, PFC = prefrontal cortex, pre-SMA = pre-supplementary motor area, rCBF = regional cerebral blood flow, RD = radial diffusivity, ROI = region of interest, sMRI, structural magnetic resonance imaging, SPECT = single-photon emission tomography, SPN = stimulus-preceding negativity, SUD = substance use disorder, TBV = total brain volume, TCV = total cerebral volume, UTR = untranslated region, VBM = voxel-based morphometry, VNTR = variable number tandem repeat, VS = ventral striatum, 4R = 4 repeat allele, 5R = 5 repeat allele, 7R = 7 repeat allele, 9R = 9 repeat allele, 10R = 10 repeat allele, [Hb] = deoxyhemoglobin, [HbO₂] = oxygenated hemoglobin, [^{99m}Tc] = technetium-99; ¹H MRS = Proton magnetic resonance spectroscopy, [^{99m}Tc]-HMPAO = technetium-^{99m} hexamethylpropylene amine oxime.

^a Only males.

^b Asian sample.

commonly used ligand, stratification by affection status dramatically reduced heterogeneity and revealed a significant association of the 9R allele with increased DAT availability for healthy subjects. The authors concluded that in humans, the 3'UTR polymorphism of *SLC6A3/DAT1* regulates dopamine activity in the striatal brain regions independent of the presence of neuropsychiatric illness.

Eight sMRI studies for *SLC6A3/DAT1* were performed thus far (Table 3). Two studies reported a smaller volume of the striatal caudate nucleus in homozygotes for the 10R allele when compared to children with the 9R/10R genotype (Durstun et al., 2005; Shook et al., 2011). While Durstun and coworkers found this effect to be most pronounced in children with ADHD, rather than their unaffected siblings or healthy comparison subjects, the overall genotype effect was independent of diagnosis. Two recent studies investigated cortical thickness in children and adolescents with ADHD. Fernández-Jaén and colleagues suggested that thickness of the lateral PFC and the cingulate cortex might be influenced by the presence of the 10R-allele (2015; 2016). Interestingly, homozygotes for the 10R allele showed increased thickness in the right cingulate gyrus (Fernandez-Jaen et al., 2016), but decreased cortical thickness in the lateral PFC (Fernandez-Jaen et al., 2015). In addition, a large observational study in an adolescent cohort revealed that irrespective of stimulant treatment, left striatal volume was reduced in participants with ADHD carrying one 10-6 haplotype (Schworen et al., 2016). A recent cross-sectional sMRI study included three cohorts (a childhood/adolescent ADHD case-control sample, an adult ADHD case-control sample, and an adult population-based sample) and showed that only in the adult ADHD case-control cohort, carriers of the *DAT1* adult ADHD risk haplotype 9-6 had a 5.9% larger striatum volume relative to participants not carrying this haplotype. The effect varied by diagnostic status, with the risk haplotype affecting striatal volumes only in patients with ADHD (Onnink et al., 2016). A longitudinal study did not reveal any effect of *SLC6A3/DAT1* genotype on cortical thickness (Shaw et al., 2007b), consistent with the predominant expression of *DAT1* in subcortical (striatal) structures (and cerebellum). A recent gene-environment (GxE) interaction study reported differential age effects for *SLC6A3/DAT1* 9R-allele carriers for total grey matter volume and for *SLC6A3/DAT1* 10R-allele homozygotes on putamen volume, depending on positive peer affiliation (Richards et al., 2016) (Table 3). These findings were independent of ADHD severity. The presence of such differential age-dependent GxE effects might explain the diverse and sometimes opposing results of genetic and environmental effects on brain phenotypes (Richards et al., 2016). A single DTI study was performed in a sample of children with ADHD to assess *DAT1*'s effect on structural connectivity (Table 3). However, the investigated 3'UTR VNTR genotype did not appear to affect white matter integrity (Hong et al., 2014).

In total, nine fMRI studies were performed to investigate the effect of *SLC6A3/DAT1* genotype on brain activity related to different tasks, most often examining reward processing and different aspects of executive functioning (Table 3). The studies included childhood, adolescent, and adult ADHD samples. Three fMRI studies investigated the role of the *SLC6A3/DAT1* VNTR haplotype using reward-processing paradigms. Reward processing is altered in ADHD, and meta-analysis has shown that activation of the ventral striatum in anticipation of reward is lower in patients with ADHD than in controls (Plichta and Scheres, 2014). In a study in male adolescents, the activation of the caudate nucleus within the ventral striatum was found reduced in the ADHD group as the number of 10-6 haplotype copies increased (Paloyelis et al., 2012). A sizeable study in adult ADHD cases and controls, on the other hand, found no effect of *SLC6A3/DAT1* haplotype on striatal activity (Hoogman et al., 2013). The latter dataset was re-analyzed using a Bayesian constraint-based causal discovery algorithm; this analysis suggested that any links between the genetic haplotype in *DAT1* and

reward anticipatory brain activity may be indirect only, mediated through inattention symptoms (Sokolova et al., 2015).

In studies of response inhibition, tested through a Go/No-Go task in children and adolescents, the 10R/10R genotype was found to be linked to higher (Bedard et al., 2010), but also lower (Durstun et al., 2008) striatal activation. Interestingly, Durstun and colleagues observed genotypic effects in the caudate nucleus in the patients and their unaffected siblings, but not in healthy controls (2008). Beyond the striatum, *SLC6A3/DAT1* genotype effects were also found in additional brain regions, such as during cerebellar activation in children with ADHD (Durstun et al., 2008), and in frontal, medial, and parietal regions, where activity was increased during response inhibition in adolescents homozygous for the 10R allele (Braet et al., 2011). Increased activity in the (temporo-)parietal regions in homozygous carriers of the 10R-allele was also observed in a second study, in addition to increased activity in the right dorsal premotor cortex (Bedard et al., 2010). The effects of the *SLC6A3/DAT1* haplotype and rs37020 genotype on neural activation during response inhibition have been investigated as well (van Rooij et al., 2015b) (Table 3). Homozygous carriers of the *SLC6A3* 10-6 haplotype exhibited increased activity related to successful stop-trials in pre-supplementary motor areas and reduced activity in superior frontal and temporal pole areas, whereas homozygous carriers of the rs37020 A-allele showed reduced activity during failed stop-trials in the IFG, pre-supplementary motor areas, and post-central gyrus (van Rooij et al., 2015b). Despite these wide-spread effects on neural activation changes of the response inhibition network, these changes were independent of ADHD diagnostic status (van Rooij et al., 2015b). As expression of *DAT1* is limited outside of striatum and cerebellum, these latter effects are likely due to direct or indirect connections between the regions of gene expression and the rest of the brain.

A working memory task in adult participants elicited increased activity in the dorsal ACC in patients homozygous for the 10R allele, whereas this genotype caused reduced activity in controls (Brown et al., 2011). Additionally, the authors showed a marginal association of the *SLC6A3/DAT1* genotype with task-related suppression in the left medial PFC (Brown et al., 2011). Also in a multi-source interference task, the 10R/10R homozygotes had increased activity in the dorsal ACC compared to carriers of the 9R-allele (Brown et al., 2010). The dorsal ACC is thought to play a crucial role in numerous cognitive control functions including attention modulation, competition monitoring, complex motor control, novelty, error detection, working memory, anticipation of cognitively demanding tasks, and the modulation of reward-based decision making (Shenhav et al., 2013). Functional abnormalities associated with the dorsal ACC have been repeatedly reported in ADHD (Cao et al., 2009; Castellanos et al., 2008; Tamm et al., 2004; Zang et al., 2007; Tian et al., 2006), and the results above suggest that these effects might be most pronounced in 10R-allele homozygotes, which constitute approximately 71.9% of the Caucasian population (Doucette-Stamm et al., 1995).

No studies in patients have yet investigated effects of *DAT1* genotype on functional brain connectivity assessed through resting state fMRI. A single study in healthy participants using seed-based analysis revealed that carriers of the 9R-allele showed stronger connectivity between dorsal caudate nucleus and insula, dorsal ACC, and dorsolateral prefrontal regions, as well as between ventral striatum and centrolateral prefrontal cortex, suggesting wide-spread effects of the *SLC6A3/DAT1* genotype on functional connectivity of striatal structures with the rest of the brain (Gordon et al., 2015).

Four EEG studies in ADHD childhood samples investigated the effects of *SLC6A3/DAT1* variation (Table 3). One study examined the influence of the common 9R and 10R alleles on prefrontal brain functioning and cognitive response control in participants

with adult ADHD and healthy controls (Dresler et al., 2010). By means of a Go-NoGo task (CPT) they inspected a neurophysiological marker of cognitive response control (NoGo-anteriorization, NGA). The NGA is an endophenotypic marker of prefrontal functioning, reflecting neural correlates of both response inhibition and execution in a Go-NoGo test situation (Fallgatter and Strik, 1999). It is a topographic event-related potential parameter quantifying the brain's electrical field frontalization during motor inhibition (NoGo, when compared with response execution Go). As such, the NGA reflects "NoGo" activation of the medial PFC (anterior cingulate cortex, ACC) (Fallgatter et al., 2002). The NGA and the electrical field frontalization during NoGo trials have been found reduced in patients with ADHD (as well as those with schizophrenia) compared with healthy controls, reflecting diminished activation of the medial PFC in these patient groups (Fallgatter and Muller, 2001; Fallgatter et al., 2005). In the study of *SLC6A3/DAT1* genotype carriers of the 9R-allele within the ADHD group showed significantly reduced NGA, whereas no influence of genotype was observed in the control group (Dresler et al., 2010). A second EEG study investigated the effect of the 10-6 haplotype on response control, by using a CPT task in a childhood case-control sample (Albrecht et al., 2014). Independent of ADHD diagnosis, 10-6 haplotype-carriers exhibited elevated brain activity related to inhibitory response control (Albrecht et al., 2014). Another study investigated the effect of the *SLC6A3/DAT1* 3'UTR genotype on neurophysiological correlates of performance monitoring by measuring event-related potentials (ERPs) during a feedback-based learning task. The authors showed that 10R/10R homozygotes had a smaller error-related positivity (Pe) response to errors and a smaller stimulus-preceding negativity (SPN) in the anticipation of negative feedback, especially with learning (Althaus et al., 2010), suggesting that *SLC6A3/DAT1* genotype influences a system that is sensitive to aversive stimuli and their conscious processing (Althaus et al., 2010). The third EEG study investigated MPH medication-related changes on cortical power spectra during a sustained attention and vigilance task in a patient-only sample. ADHD patients have been shown to have increased frontocentral θ band activity and increased θ/β ratio compared to non-ADHD controls during rest (Loo and Makeig, 2012). Generally, the β band activity has been associated with attentional arousal, and it has been suggested that the θ/β ratio may reflect increased impulsivity and difficulty negotiating the speed-accuracy trade-off (faster speed but poorer performance) in ADHD (Loo and Makeig, 2012). In their study of *DAT1* genetic variation during MPH treatment, the authors reported that those children with ADHD homozygous for the 10R-allele, exhibited medication-related cortical changes of increased central and parietal β power, decreased right frontal θ power, and lower θ/β ratios; 9R carriers showed the opposite pattern (Loo et al., 2003).

Summarizing, sMRI studies (as well as PET/SPECT by definition) find *SLC6A3/DAT1* genotype effects mainly in regions, in which the gene is preferentially expressed. These local effects can have widespread consequences on brain activity, as fMRI and EEG studies reveal. However, it is still unclear how the PET/SPECT findings, such as high DAT binding and density in nucleus accumbens and dorsal striatum (Kuczenski and Segal, 2002; Segal and Kuczenski, 1997) or the differences observed in brain activity are related to structural volume differences in the specific brain regions of ADHD patients. Therefore, studies could benefit from combining different imaging methodologies. The effects of genotype are often observed independent of diagnostic status, as would be expected for bona fide risk factors. Additionally, credibility of most of the existing studies can be questioned, since many of them are limited by their small sample sizes (Mier et al., 2010; Munafò et al., 2008). The actual neuroanatomical and brain activity-based mechanisms by which *SLC6A3/DAT1* genotype increases ADHD risk remain to be clarified, as the results of studies published thus far are too patchy

(and based on too small samples) to allow a coherent story to be defined. Moreover, links with cognitive performance and behaviour have often not been investigated. A further complicating matter for the interpretation of studies on *SLC6A3/DAT1* is the switch in ADHD risk allele from childhood to adulthood. Longitudinal studies or at least cross-sectional studies including large samples of both children and adult participants (preferably also including persistent and remitted forms of ADHD) are therefore needed to advance the field.

3.2. Findings for the dopamine receptor D4 gene (*DRD4*)

The **dopamine D4 receptor**, encoded by *DRD4*, is a G protein-coupled receptor and belongs to the dopamine D2-like receptor family (Oldenhof et al., 1998). The most widely studied *DRD4* polymorphism in ADHD has been the 48 bp VNTR in exon 3 of the gene, with the 2-, 4-, and 7-repeat alleles being the most common alleles. Allele frequencies vary significantly across ethnic groups (Chang et al., 1996; van Tol et al., 1992), and the ADHD risk allele in the Caucasian population (7R) seems to be a different one from that in Asians (Nikolaidis and Gray, 2010; Wang et al., 2004; Li et al., 2006a). The *DRD4* 48 bp VNTR seems to show differential association with ADHD in children, where it may be one of the strongest risk factors among the common genetic variants (Gizer et al., 2009), and adults, where no association with the disorder could be observed (Sanchez-Mora et al., 2011), though it might occur as part of gene-environment interactions (Sanchez-Mora et al., 2015). *DRD4* is abundantly expressed in areas of the brain affected in ADHD, including frontal lobe regions, such as the orbitofrontal cortex and anterior cingulate (Lahti et al., 1995; De La Garza and Madras, 2000; Li et al., 2007b); the risk allele has been found to affect receptor binding and to produce a blunted response to dopamine (Asghari et al., 1995), although the functionality of the *DRD4* VNTR has recently been challenged by meta-analysis (Pappa et al., 2015). The exon 3 VNTR has been the sole target of imaging genetic studies involving patients with ADHD, in which different imaging modalities have been used (Table 3).

An early sMRI study in children and adolescents did not report differences between carriers and non-carriers of the 7R-allele in selected regional and global brain volumes (Castellanos et al., 1998). A second study observed smaller prefrontal grey matter volumes in children homozygous for the 4R-allele, an effect that appeared particularly pronounced in unaffected siblings of patients with ADHD (Durstun et al., 2005). In contrast, adult patients carrying the 7R-allele were found to have smaller volumes of the superior frontal and cerebellar cortex (Monuteaux et al., 2008). In a longitudinal study, *DRD4* genotype also affected cortical development (by measuring cortical thickness), with 7R-carriers showing thinner prefrontal and parietal cortex; patients with ADHD carrying this allele had a distinct trajectory of cortical development characterized by normalization of parietal cortical regions (Shaw et al., 2007b). Additionally, an observational cohort study evaluating the effects of cumulative stimulant treatment, revealed associations between treatment and frontal and hippocampal volume dependent on *DRD4* genotype and age (Schworen et al., 2016). More specifically, carriers of the 7R-allele showed decreased frontal cortex volume at younger age and lower treatment levels, whereas left hippocampal volume was increased in those with treatment at younger age (Schworen et al., 2016) (Table 3). By studying GxE interaction effects, carriers of the 7R-allele were found to have larger putamen volumes over age when exposed to high positive peer affiliation (Richards et al., 2016). This result was independent of ADHD severity. Effects of *DRD4* genotype on structural brain connectivity were investigated in a single study in Asian children with ADHD, resulting in a report of no effects for 4R-homozygotes (Hong et al., 2014). A very large recent study in healthy participants

($n = 765$) revealed an absence of significant effects of the *DRD4* 5R-allele on FA as well (Takeuchi et al., 2015). However, widespread changes in another measure of structural connectivity, mean diffusivity (MD), were observed, with increased MD in 5R-carriers in grey and white matter areas of the cerebral cortex, and in subcortical areas including the globus pallidus, amygdala, midbrain areas, and the brain stem (Takeuchi et al., 2015).

An EEG study administering a CPT as a measure of response inhibition and sustained attention, reported that children with the 7R-allele showed increased frontal θ and reduced global β power. Similar effects of *DRD4* genotype were also apparent on the β frequency band in the parents (Loo et al., 2010); in both generations, carriers of the 7R-allele had reduced cortical activation upon performing the CPT task compared to participants not carrying this allele (Loo et al., 2010). Similarly, Albrecht and colleagues also applied the CPT to a childhood case-control sample and reported significant effects of the 7R-allele on ERP components. Specifically, they observed reduced activity related to attentional orienting and cognitive or response preparation in 7R-carriers (2014). This effect was found to be independent of an ADHD diagnosis (Albrecht et al., 2014). Extrapolating to behaviour, a recent meta-analysis showed that longer *DRD4* variants (including the 7R-allele) were associated with lower levels of executive functioning (Pappa et al., 2015). In contrast to the continuous performance measure, an EEG study of inhibition applying another Go/No-Go task to adults with and without ADHD did not find an effect of *DRD4* genotype on the NGA neural correlate of prefrontal response control (Heinzel et al., 2013). However, in this study, an epistatic interaction between the *DRD4* VNTR and a SNP in the *COMT* gene (rs4680; Val/Met) was observed for the NGA; in homozygous carriers of the *DRD4* 7R-allele, the NGA followed a more pronounced U-relationship based on an increasing number of *COMT* Met-alleles compared with 7R-heterozygotes. In *COMT* Val/Met carriers, *DRD4* 7R-homozygosity was associated with decreased NGA compared with 7R-heterozygosity. This interaction could be localized to the right premotor and supplementary motor areas (Heinzel et al., 2013). These findings were independent of diagnostic status.

Thus, though existing evidence does not support firm conclusions about the pathways from gene to disease, genotypic variability in *DRD4* may affect brain structure and/or activity and mark a particular developmental trajectory in cortical brain structure related to adult outcome of ADHD.

3.3. Findings for other ADHD candidate genes

Adrenergic neurotransmitter systems influence attentional processes and certain aspects of executive control (Arnsten, 2006), and the gene encoding the **alpha-2A adrenergic receptor** (*ADRA2A*) has been found to be a candidate gene for ADHD. The alpha-2A adrenergic receptor is the most prevalent noradrenergic receptor in the PFC (Park et al., 2005; Arnsten et al., 1996). Two variants appear to be risk factors for ADHD, the rs1800544 SNP in the promoter region, for which the G-allele was considered risk-increasing (Park et al., 2005), and the rs553668 SNP in the promoter region, for which the T-allele was considered the risk allele (Park et al., 2005). However, meta-analyses have not confirmed associations with ADHD risk for either SNP (Gizer et al., 2009). Alpha-2 adrenoceptors have also been implicated in other major neuropsychiatric diseases that are often comorbid with ADHD, such as major depressive disorder and schizophrenia (Langer, 2015).

Genotypic effects of *ADRA2A* on the brain were studied in only two studies of Asian children with ADHD. A SPECT study showed that carriers of the non-risk allele for rs1800544 exhibited reduced perfusion in bilateral orbitofrontal regions (Kim et al., 2010). A DTI study investigated the effect of both SNPs (rs1800544 and rs553668) on white matter integrity. Carriers of the rs553668 non-

risk-allele (C-allele) showed reduced fractional anisotropy (FA) in the right postcentral gyrus, whereas carriers of the rs553668 T-allele (non-risk group) showed reduced FA in the right middle frontal cortex (Park et al., 2013).

The **Catechol-O-methyl-transferase** enzyme (encoded by the *COMT* gene, located at 22q11.21) is involved in the degradation of the catecholamines dopamine and norepinephrine. It is highly expressed in the frontal lobe regions, where it is responsible for the regulation of dopamine levels (Hong et al., 1998). Studies investigating the association between *COMT* and ADHD have largely focused on a functional SNP (rs4860) in exon 4 that leads to an amino acid substitution (valine \rightarrow methionine). This polymorphism has been shown to considerably affect *COMT* enzyme activity, such that homozygous carriers of the valine-allele show 3–4 times higher activity than homozygous carriers of the methionine-allele, resulting in decreased dopamine availability in valine homozygotes (Chen et al., 2004). An initial small study suggested that the valine-allele was associated with increased risk for ADHD (Eisenberg et al., 1999), although a recent meta-analysis failed to confirm this association (Lee and Song, 2015). The functional *COMT* rs4680 variant also seems relevant to other psychiatric and cognitive phenotypes. A recent study evaluating the association of the *COMT* genotype with schizophrenia in a systematic review and meta-analysis in 32,816 subjects, revealing a significant association (Gonzalez-Castro et al., 2016). Another recent meta-analysis revealed an association of the *COMT* genotype and reward learning, suggesting that variability in dopamine signalling associated with *COMT* rs4680 influences individual differences in reward processing, which may potentially contribute to psychopathology characterized by reward dysfunction, such as ADHD (Corral-Frias et al., 2016).

Two very small sMRI studies, both using VBM, examined the genotypic effect of rs4680 on the brain in children with and without ADHD (Table 3). Villemonteix and colleagues observed that children with ADHD and at least one methionine-allele had reduced grey matter volume in the insula/IFG relative to children without ADHD (2015). In an additional ROI analysis within the small ADHD group only ($n = 34$), the study showed that those children with ADHD who were homozygous for the valine-allele had increased grey matter volume in the caudate nucleus compared to ADHD children carrying the methionine-allele, and also compared to children without ADHD (Villemonteix et al., 2015). A second sMRI study in a Japanese childhood sample also found a relation of *COMT* genotype with striatal volume pointing in the same direction, as the authors showed that the smaller grey matter volume observed in the left putamen in children with ADHD was moderated by the methionine-allele, whose carriers showed smaller volume than the valine homozygotes (Shimada et al., 2015). Effects of *COMT* on structural connectivity were investigated by two DTI studies. One study in Asian children with ADHD revealed that carriers of the methionine-allele showed a weakened network of white matter connections linking 18 different brain regions (Hong et al., 2014) (Table 3). This finding is in line with a report on healthy participants, showing that the methionine-allele was associated with impaired structural maturation of brain white matter connectivity (Thomason et al., 2010). Based on these findings, Hong and coworkers formulated the hypothesis that higher dopamine availability may inhibit myelination (2014). Recently, Kabukcu Basay and colleagues reported that children with ADHD, who were homozygous for the Valine-allele, had reduced FA and increased RD values in the right cingulum bundle (2016). This indicates demyelination effects in the white matter connections between the cingulate cortex to the PFC, premotor regions, cortical association areas in the parietal and occipital lobes, thalamus, and hippocampus (Kabukcu Basay et al., 2016). The cingulate cortex is known to be involved in complex cognitive processing (Bush et al., 2000) and functions that are believed to be impaired in ADHD (Bush, 2011; Makris et al., 2008).

A single fMRI study investigated the association of *COMT* rs4680 genotype on task performance and whole-brain neural activation during response inhibition (van Rooij et al., 2015b). Although the *COMT* Val158Met variant resulted in differential activation patterns during successful and failed stop-trials in the combined ADHD-control sample, no interactions between genetic effects and ADHD diagnostic status were observed in any of the whole-brain fMRI results (van Rooij et al., 2015b) (Table 3). This indicates that genetic variation in the *COMT* gene exerts large-scale effects on neural activation changes of the response inhibition network, but these changes are independent of ADHD.

The single EEG study of *COMT* in ADHD, using a Go/No-Go task in adults with and without ADHD, did not reveal an effect of *COMT* genotype on brain activity individually. However, an epistatic interaction of *DRD4* × *COMT* genotype on neurophysiological correlates of prefrontal function was observed (Heinzel et al., 2013). In homozygous carriers of the *DRD4* 7R allele, the anteriorization of the NoGo response (NGA, explained above) followed a more pronounced U-relationship with increasing numbers of Met alleles compared with 7R heterozygotes. In *COMT* Val/Met carriers, *DRD4* 7R homozygotes showed a significantly decreased NGA compared with 7R heterozygotes. The genotype-dependent effects on the NGA were localized in the right premotor and supplementary motor area. The epistatic interactions were independent of ADHD diagnosis (Heinzel et al., 2013). Given the role of fronto-striatal circuits and dopamine in reward processing (Plichta and Scheres, 2014; von Rhein et al., 2015), an important domain of impairment in ADHD (see above), it is surprising that no studies have yet investigated the role of *COMT* in brain activity related to reward anticipation and receipt.

The **dopamine D1 receptor** (encoded by the *DRD1* gene) is the most abundant dopamine receptor subtype in the brain; it is highly expressed in the striatum and cerebral cortex (Bergson et al., 1995). Common genetic variation in the *DRD1* gene (rs5326) has been associated with schizophrenia risk (Pan et al., 2014) and impaired cognition in patients with bipolar disorder (Zhao et al., 2015), both often found comorbid with ADHD. Several studies explored associations between ADHD and genetic variants of *DRD1*, such as SNPs rs4532 and rs265981 (Bobb et al., 2005). In the initial study, participants with ADHD were more likely than healthy controls to have the C-allele or rs4532 and the A-allele of rs265981 (Bobb et al., 2005). However, results of a meta-analysis of rs4532 did not support its association with ADHD (Wu et al., 2012), and also replication for rs265981 is still pending. Nevertheless, two sMRI studies investigated the effect of genetic variation in *DRD1* on cortical thickness (Shaw et al., 2007b) and on brain volume (Bobb et al., 2005). Neither study found an effect of *DRD1* genotype or group × genotype interactions (Table 3).

The **5-Hydroxytryptamine receptor 1B** (encoded by the *HTR1B* gene) is the most widely studied serotonin receptor gene in relation to ADHD. *HTR1B* is a G protein-coupled receptor that inhibits cyclic AMP formation (Murphy et al., 1998). It is highly expressed in the dorsal raphe nucleus, which is involved in the sleep/wake cycle, and to lesser degrees in the striatum and frontal regions, such as the dorsolateral PFC (Ichikawa et al., 2005). The initial study, investigating 273 nuclear families with ADHD, reported preferential transmission of the rs6296 G-allele to ADHD probands (Hawi et al., 2002). Results of a meta-analysis supported this association between childhood ADHD and rs6296 genotype (Gizer et al., 2009). A single fMRI study investigated the relationship of rs6296 genotype with neural correlates of response inhibition, using a stop-signal task in a childhood sample (van Rooij et al., 2015a). The rs6296 genotype was associated with widespread differential activation during successful and failed stop trials (Table 3). However, the direction of these effects was inconsistent, with both increased and decreased activation for the GG genotype being observed in

frontal and posterior nodes, and the differential activation patterns were independent of ADHD diagnosis (van Rooij et al., 2015a).

The **latrophilin 3 gene** (*LPHN3*; official name Adhesion G Protein-Coupled Receptor L3 [ADGRL3]) codes for a member of the LPHN subfamily of G-protein-coupled receptors (GPCRs). Subtype 3 is the most brain-specific LPHN (Sugita et al., 1998; Ichtchenko et al., 1998) and is expressed in regions implicated in ADHD, i.e. the caudate nucleus, cerebellum, amygdala, and cerebral cortex (Arcos-Burgos et al., 2010). *LPHN3* was identified as an ADHD risk gene downstream of genetic linkage studies in multicaser families from a genetic isolate. In multisite association studies, initially, a haplotype of three SNPs (rs6551665, rs1947274, and rs2345039) was shown to be associated with ADHD (Arcos-Burgos et al., 2010). The association of *LPHN3* genotypes with ADHD has been replicated in children (rs6551665) (Hwang et al., 2015) and adults with ADHD (multiple markers) (Ribases et al., 2011). By use of proton magnetic resonance spectroscopy (¹H-MRS), Arcos-Burgos and colleagues showed that individuals carrying the *LPHN3* susceptibility haplotype exhibited a decreased ratio of N-acetylaspartate to creatine (NAA/Cr ratio) in the left lateral and medial thalamus as well as the right striatum, and an increased ratio in inferior-posterior cerebellar vermis; this suggested that the maintenance of neuron viability is altered in those carrying the ADHD risk haplotype (2010). Since the ADHD susceptibility haplotype itself did not cause any significant coding region changes or canonical splice site alterations, it was suggested that non-coding variations may be likely contributors to ADHD (Domene et al., 2011).

Although *LPHN3* is among the best-supported candidate genes for ADHD, thus far, imaging genetics studies of the gene are still limited in the literature. No studies on structural or connectivity alterations related to the risk variant of the gene in patients with ADHD have been published yet, nor have any fMRI studies. An EEG study using a Go/No-Go task revealed that adult patients with ADHD carrying a 'high-risk' *LPHN3* haplotype (comprised out of rs2305339, rs734644, rs1397547, and rs1397548) showed a more anterior Go-centroid of the P300, had a reduced NGA, and had worse behavioural task performance due to more omission errors (Fallgatter et al., 2013).

Monamine oxidase A, encoded by *MAOA*, is an enzyme, which catalyzes the oxidative deamination of amines, such as dopamine, norepinephrine, and serotonin. For this gene located on the X-chromosome, studies have largely focused on a functional 30 bp VNTR 1.2 kb upstream of the gene, which has been previously associated with impulsivity and aggression (Caspi et al., 2002; Manuck et al., 2000). The polymorphism consists of alleles of 2, 3, 3.5, 4, and 5 repeat copies, and evidence suggests that the 2 and 3 repeat ('low-activity/MAOA-L') alleles are less efficiently transcribed than the longer ('high-activity/MAOA-H') alleles (Deckert et al., 1999). Although the *MAOA* gene has received a lot of attention as a candidate gene for ADHD given the prior findings for impulsivity, a meta-analysis did not indicate a significant association between ADHD and the high activity alleles of the VNTR (Gizer et al., 2009). A SNP, rs1137070 (located in exon 14), has also been reported to contribute to impulsivity and the outcome of ADHD (Li et al., 2007a; Liu et al., 2011). Especially, the C-allele of rs1137070 has been associated with high ADHD scores and poor outcomes (Li et al., 2007a).

With evidence for a role of *MAOA* in aggression being more consistent than for ADHD (e.g. (Brunner et al., 1993; Caspi et al., 2002; Byrd and Manuck, 2014)), imaging genetics studies have largely concentrated on population groups other than patients with ADHD, e.g. (Holz et al., 2016; Meyer-Lindenberg et al., 2006). A recent fMRI study forms an exception. Using a phonological working memory task in male Asian adults with and without ADHD, the authors showed that the effect of *MAOA* (rs1137070 T- versus C-allele) interacted with diagnosis in the left inferior frontal lobe, pars opercularis (Table 3); further analysis demonstrated that the increased

brain activation observed in this region in patients was only significantly different to controls among those hemizygous for the T-allele (Ko et al., 2015).

The *NOS1* gene codes for **nitric oxide synthase 1**, an enzyme that synthesizes nitric oxide from L-arginine. Nitric oxide is a reactive free radical, which can act as a biological mediator in several processes, including dopaminergic and serotonergic neurotransmission (Kiss and Vizi, 2001) and neurite outgrowth (Chen et al., 2006). The *NOS1* gene has a complex structure, including 12 alternative untranslated first exons (exon 1a–1l). In exon 1f, a VNTR that affects gene expression has been linked to hyperactive and impulsive behaviour in humans (Reif et al., 2009; Weber et al., 2015); the short allele was shown to be the risk factor for ADHD, especially in females.

No studies have yet reported effects of *NOS1* on brain structure. A recent case-control DTI study of structural connectivity in adolescents revealed that female homozygous carriers of the ADHD risk allele showed higher MD values in several major white matter tracts of the brain compared with long allele carriers. This effect was present in both female patients and controls (van Ewijk et al., in revision). The white matter tracts found affected by *NOS1* genotype overlap with those earlier found associated with ADHD (Onnink et al., 2015; van Ewijk et al., 2012; Wu et al., 2016). Since higher MD values can be indicative of demyelination, lower axonal density, or axonal degeneration, homozygosity of the short allele might thus be a risk factor for aberrant development of white matter tracts involved in ADHD etiology.

NOS1 exon 1f is particularly highly expressed in striatum. Therefore, the single study of gene effects on brain function investigated the effect of the VNTR on ventral striatal activity during reward anticipation using fMRI (Hoogman et al., 2011) (Table 3). The study revealed that homozygous carriers of short alleles of *NOS1* demonstrated higher ventral striatal activity than carriers of the other *NOS1* VNTR genotypes (Hoogman et al., 2011). Again, this effect was independent of diagnostic status. Similar effects of the genotype were also observed for behavioural impulsivity, with those carrying the ADHD risk factor acting more impulsive than other participants. As the authors did not perform mediation studies, it remains to be investigated, whether the observed genotype effects on brain connectivity and/or activity directly link to behavioural effects.

The **norepinephrine transporter** gene (*SLC6A2*, *NET1*) codes for a protein responsible for the reuptake of norepinephrine (as well as dopamine) from the synaptic cleft back into the presynaptic neuron (Pacholczyk, 1991). The gene is highly expressed in the frontal lobes (Stahl, 2003). Candidate gene studies of *SLC6A2/NET1* selected numerous SNPs to test for association, but conflicting results have been reported, with each study yielding evidence of association, but differing in which specific SNPs were associated with ADHD (Gizer et al., 2009).

A SPECT study examined the effects of rs5569 and rs28386840 on cerebral perfusion in response to MPH treatment in Asian children with ADHD (Table 3) (Park et al., 2012). At baseline, no differences were observed, but after eight weeks of MPH treatment increased regional brain perfusion in the right inferior temporal gyrus and middle temporal gyrus in homozygous carriers of the rs5569 G-allele was demonstrated (Park et al., 2012). Given that no previous studies had reported a significant association between this polymorphism and ADHD, no 'risk' allele was indicated. A PET study reported the influence of four genetic variants within the transporter gene on *in vivo* norepinephrine transporter binding in adults with and without ADHD (Table 3) (Sigurdardottir et al., 2015); the authors found differences in cerebellar and thalamic norepinephrine transporter binding depending on genotype between adult patients and controls (Sigurdardottir et al., 2015). For the two SNPs rs28386840 and rs2242446, patients carrying

the major alleles (A/T) showed increased norepinephrine transporter binding in the thalamus compared to controls carrying the major alleles. For the SNPs rs15534 and rs40615, controls carrying the major alleles (C/T) showed increased norepinephrine transporter binding in the cerebellum compared to patients carrying the major alleles (Sigurdardottir et al., 2015). In the patients with ADHD, a high correlation between hyperactivity/impulsivity symptoms and norepinephrine transporter binding in the cerebellum was detected, an effect which was strongly moderated by genotype (Sigurdardottir et al., 2015).

With this knowledge on SNP functionality related to ADHD, studies using additional imaging modalities are warranted, but thus far, only a single sMRI study investigated the effect of genetic variation in *SLC6A2/NET1* on brain volume (Table 3). No effect of *SLC6A2/NET1* genotype (for SNPs rs998424 and rs3785157—different SNPs from those having been investigated through PET and SPECT) and no group x genotype interactions were reported (Bobb et al., 2005).

The **serotonin transporter** gene (*5HTT*, *SERT*; official name *SLC6A4*) codes for a solute carrier protein responsible for the reuptake of serotonin from the synaptic cleft back into the presynaptic neuron, which is the primary mechanism for regulating serotonergic activity in the brain (Lesch et al., 1996). A functional polymorphism exists in the promoter region of this gene (5HTTLPR) in the form of a 44-bp insertion/deletion yielding short (S) and long (L) alleles. The long variant is associated with more rapid serotonin reuptake, resulting in lower levels of active serotonin (Lesch et al., 1996). A SNP in the long allele, rs25531, additionally modifies its activity (Lesch et al., 1996). *SLC6A4/5HTT* has been implicated in emotion regulation, (emotional) memory, and learning processes (Araragi and Lesch, 2013; Barzman et al., 2015; Meneses and Liy-Salmeron, 2012). The serotonin transporter is expressed in regions implicated in attention, memory, and motor activities, such as the amygdala, hippocampus, thalamus, putamen, and ACC (Frankle et al., 2004; Oquendo et al., 2007). The 5HTTLPR has been extensively studied for its role in depression and anxiety – especially in the context of environmental adversity, with the S-allele being the risk allele (Caspi et al., 2003; Oo et al., 2016). For ADHD, the evidence for association is more limited, although an earlier meta-analysis provided significant evidence of an association between ADHD (in children) and the 'long' variant of 5HTTLPR (Gizer et al., 2009). However, an international multicentre study reported a slight, non-significant overrepresentation of the S-allele in adult patients with ADHD (Landaas et al., 2010).

Given the evidence for *SLC6A4* as a depression gene, imaging genetics research has largely concentrated on non-ADHD samples; in healthy individuals, functional genetic variation in the *SLC6A4/5HTT* gene has been linked to emotion regulation through effects on brain activation in the amygdala and the wider 'threat circuit', while effects on regional brain volumes are inconsistent (Klein et al., under review; Jonassen and Landro, 2014). Three sMRI studies have been performed for 5HTTLPR in ADHD thus far, all investigating GxE interactions. The initial study showed that the interaction between exposure to environmental stress and carrier status of the 5HTTLPR S-allele, which was linked to increased ADHD severity in a longitudinal study of ADHD families (van der Meer et al., 2014), was associated with reduced cortical grey matter volume in the precentral gyrus, middle and superior frontal gyri, frontal pole, and cingulate gyrus in S-allele carriers compared with participants homozygous for the L-allele (van der Meer et al., 2015). Importantly, this paper showed that only some of these regions, the frontal pole and the ACC, actually mediated the effects of the gene-environment interaction on ADHD severity. Similarly, van der Meer and colleagues reported that individuals carrying the *NR3C1* risk haplotype, who were homozygous for the 5HTTLPR L-allele, showed a negative relation between stress and grey matter vol-

ume (2016). However, no mediation effects were found, meaning that the local effects of these interaction on grey matter volume did not significantly explain their association with ADHD severity (van der Meer et al., 2016). Such studies testing the mediation of effects through the observed brain phenotypes (as opposed to those just being epiphenomena of the genetic variation) are largely lacking in the imaging genetics literature thus far, but are critically needed to map gene to disease pathways. However, sample sizes will have to be substantial to allow valid conclusions to be drawn from such studies. Another sMRI study used the same dataset and revealed that, in agreement with age-related reductions of total grey matter volume found in longitudinal studies (Brain Development Cooperative, 2012; Raznahan et al., 2014), participants scoring high on positive peer affiliation and carrying two 5HTTLPR L-alleles had smaller total grey matter volumes with age (Richards et al., 2016). Moreover, participants with the same genotype, but low positive peer affiliation had larger GM volumes with age (Richards et al., 2016). These findings were independent of ADHD severity and were in line with a longitudinal study reporting regional GM reductions with age in adolescents exposed to high positive maternal behavior, but increased putamen volumes when exposed to maternal aggression (Whittle et al., 2014).

In contrast to the sMRI studies, which investigated GxE effects related to stress and social environments, the only fMRI study focused on the relationship between 5HTTLPR genetic variation and neural correlates of response inhibition using a stop-signal task (van Rooij et al., 2015a) (Table 3). Using a childhood sample, van Rooij and colleagues revealed that homozygous carriers of the 5HTTLPR S-allele showed decreased activation in the frontal nodes and increased activation in the posterior nodes in successful stop trials (2015a). However, no significant associations were found between differential neural activation and ADHD diagnosis or ADHD severity (van Rooij et al., 2015a).

The **synaptosomal-associated protein 25** (encoded by the *SNAP25* gene) is involved in axonal growth and synaptic plasticity, as well as in the docking and fusion of synaptic vesicles in presynaptic neurons necessary for the regulation of neurotransmitter release (Sollner et al., 1993). Several studies have tested for linkage and association between *SNAP25* and ADHD, and these studies have consistently genotyped multiple SNPs within the gene rather than focusing on any single polymorphism. An early meta-analysis of SNP rs3746544 suggested *SNAP25* as ADHD risk gene (Faraone et al., 2005). A more recent meta-analysis of rs3746544 also provided evidence of a modest but significant association between childhood ADHD and the T-allele, whereas no evidence of association with rs1051312 was found (Gizer et al., 2009).

Again, only a single imaging genetics study is currently available for this gene. In this case, the interaction of MPH treatment-related hemodynamic changes with genetic variation in *SNAP25* (rs3746544 and rs1051312) was studied in small samples of children and adults with ADHD on and off single dose MPH using fNIRS (Table 3). Through fNIRS, brain haemodynamics in prefrontal cortices can be measured, since brain activation causes increased cerebral blood flow, but not all of this oxygenated blood is used, therefore oxygenated haemoglobin increases and deoxyhaemoglobin decreases during e.g. sustained attention (Villringer and Chance, 1997). Homozygous carriers of the rs3746544 T-allele exhibited changes in right oxygenated haemoglobin and right as well as left deoxyhaemoglobin levels. Additionally, homozygous carriers of the rs1051312 T-allele showed decreased right prefrontal deoxyhaemoglobin with treatment. Combination of the genotypes also showed interaction effects on right prefrontal deoxyhaemoglobin levels (Oner et al., 2011).

Tryptophan hydroxylase 2 catalyzes the reaction of tryptophan to 5-hydroxytryptophan, which is subsequently decarboxylated to form the neurotransmitter serotonin. Two isoforms of tryptophan

hydroxylase have been identified (encoded by the *TPH1* and *TPH2* genes). The *TPH2* gene codes for a rate-limiting enzyme in the production of serotonin in serotonergic neurons in the midbrain raphe nuclei, while *TPH1* seems to be involved in synthesizing serotonin in peripheral tissues (Walther et al., 2003). For several SNPs of the *TPH2* gene, an association with ADHD was found (Brookes et al., 2006; Sheehan et al., 2005; Walitza et al., 2005). For rs4570625, the G-allele was shown to be transmitted more often to offspring with ADHD (Walitza et al., 2005). For rs1178997, the T-allele was identified as the risk allele for ADHD (Walitza et al., 2005). However, the initial findings could not be replicated in a larger, multicentre study (Brookes et al., 2006). Mouse models in conjunction with approaches focusing on *TPH2* variants in humans described a role of serotonin in brain development and in disorders related to negative emotionality, aggression, antisocial behaviour, and bipolar disorder (Waider et al., 2011; Gao et al., 2012, 2016). The *TPH2* gene has also been a candidate for the investigation of gene by environment interaction studies, in depression and suicidal behaviour as well as in aggression; for review see (Mandelli and Serretti, 2013; Lesch et al., 2012).

As the evidence for a role of *TPH2* in ADHD is limited, only a single imaging genetics study involving patients with this disorder has yet been performed for this gene. This EEG study investigated the genotypic effect of the two SNPs of the *TPH2* gene mentioned above (rs4570625 and rs1178997) on the NGA during a Go/NoGo task in adult patients with ADHD and healthy individuals (Table 3). Risk alleles of each of the SNPs were found associated with a reduction in the NGA in both participant groups, indicating an effect on ADHD-relevant prefrontal brain function independent of a specific psychiatric diagnosis (Baehne et al., 2009). These promising first findings may warrant further analysis of *TPH2* variants, especially in combination with adverse environmental factors.

4. Outlook

In this review we set out to summarize the current literature on imaging genetics studies of candidate genes involving patients with ADHD. As no genome-wide association studies have yet reported loci/genes with significant evidence for association with ADHD, we used a liberal definition of a candidate (having shown association with the disorder in at least one earlier study) and used an adapted version of the list of ADHD candidate genes recently compiled by Li et al. (2014). Of the 62 candidate genes selected for review, we found that only 12 had been studied with any brain imaging technique in an ADHD population. For most of those 12, only a very limited number of studies was available. The two most frequently studied ADHD candidate genes were the *SLC6A3/DAT1* and *DRD4* genes, and even for those two genes most findings await replication.

Brain imaging phenotypes offer an important level of investigation in mapping the biological pathways from gene to disease. Brain structure, function, and connectivity can provide endophenotypes (or intermediate phenotypes) for a disease (Gottesman and Gould, 2003). As those brain endophenotypes are thought to lie in-between a genetic factor and the clinical phenotype, it has been argued that effect sizes for effects of genes on those brain phenotypes may be larger than the ones for effects on behaviour. However, for structural brain phenotypes (i.e. brain volumes) and for structural connectivity, this has been refuted by recent large-scale studies; see (Franke et al., 2016; Jahanshad et al., in preparation). For brain activity measured by fMRI, comparisons of cognitive and brain imaging studies for several genetic variants (Rose and Donohoe, 2013) and evidence from meta-analyses (Mier et al., 2010; Murphy et al., 2013) suggests that effect sizes might be larger. However, it is still unclear, how large the effects of publication bias on those results are (Murphy et al., 2013). Never-

theless, power estimates indicate that several hundred samples are needed, while the majority of studies discussed in this review had less than 50 participants per group (see Table 3). This has implications for the generalizability/replicability of positive findings (as the sample investigated may not sufficiently well represent the population it was sampled from) as well as harbouring the risk of false-negative findings (Button et al., 2013). Importantly, the term endophenotype has also often been misused in recent years, as for many of the so-called endophenotypes, the required criteria have not all been investigated. As such, many of the endophenotypes may not be intermediates between gene and behavioural phenotype, but rather be simple markers of disease (Kendler and Neale, 2010). Assessing, whether a brain phenotype observed for a risk genotype really mediates between the risk variant and the behavioural/clinical phenotype has been done in hardly any of the papers reviewed here. The paper by van der Meer and colleagues, in which such an analysis has been performed, shows the importance of such mediation analyses, as only a subgroup of the brain substrates of the gene-environment interaction investigated was also linked to ADHD severity (2015).

Shortly summarizing the results of the review, our understanding of the mechanisms underlying the action of genetic risk factors for ADHD is still limited. A promising start has been made. We see, for example, that *SLC6A3/DAT1* genotype regulates dopamine activity in striatal regions implicated in ADHD neurobiology (Spencer et al., 2013). Genetic variants also appear to affect brain structure and function beyond the regions of gene expression (Hong et al., 2014; van der Meer et al., 2014; Villemonteix et al., 2015), which is likely due to effects on structural and/or functional connectivity. Some studies reported differential genotype effects for ADHD patients and controls, whereas others did not observe genotype by diagnosis interactions (Table 3). However, such findings have not been replicated yet, and genotype effects may differ in the context of other ADHD-related risk factors.

As there is room for improvement of study designs, and research focusing on new ADHD candidate genes identified through hypothesis-free, genome-wide association studies will soon be needed, we address main challenges and opportunities for imaging genetics studies in the following paragraph. Additionally, since imaging genetics approaches cannot explain the full complexity of a biological system such as the human brain, we also highlight additional levels of investigation and methodologies that can complement the insights provided by imaging genetics studies.

4.1. Main challenges and opportunities for imaging genetics studies

The size of individual studies is potentially the biggest challenge in imaging genetics today, as also discussed above. Given the small (to potentially modest) effect sizes to be expected (Franke et al., 2016; Murphy et al., 2013; Rose and Donohoe, 2013), larger samples are essential in order to gain the necessary statistical power.

Common confounding factors encountered in the published brain imaging genetics studies are mainly related to the study sample itself, and many are aggravated by the limited sample sizes used.

False-negative findings may occur due to the large variability of the ADHD phenotype. Additionally, comorbidities occur frequently in ADHD (Kessler et al., 2006; McGough et al., 2005; Wilens et al., 2009), and differences in medication use may further increase phenotypic heterogeneity (Schworen et al., 2013). Together with the low effect sizes of individual common genetic variants and limited sample sizes, phenotypic heterogeneity in a sample challenges the discovery of effects. Meaningful subtyping of this heterogeneous condition to decrease phenotypic heterogeneity and maximize power might therefore be helpful. Besides that, potential differ-

ences of effects between age groups, with gender distribution, intelligence levels, and between ethnicities can still make it challenging to replicate and generalize findings.

Although most genetic risk factors investigated here were derived from studies of ADHD in children, our review shows that imaging genetics studies have employed childhood, adolescent, and adult ADHD samples. Knowing about the age-dependence of the genetic contribution to ADHD (Chang et al., 2013; Pingault et al., 2015), which e.g. results in differential association of *SLC6A3/DAT1* (Franke et al., 2010) and *DRD4* (Sanchez-Mora et al., 2011) with ADHD in children and adults, makes the definition of appropriate research questions highly important. Only one study thus far used a longitudinal approach, with a follow-up period of six years (Shaw et al., 2007b). Longitudinal samples are best suited to investigate potential age-dependent changes in the effects of genetic factors on the brain, and therefore more longitudinal studies of ADHD including imaging and genetic assessments are needed. This is especially important in light of a recent discussion on whether not only the onset of ADHD can occur in adulthood, but also whether childhood-onset and adult-onset ADHD may be distinct syndromes or trajectories (Agnew-Blais et al., 2016; Caye et al., 2016; Faraone and Biederman, 2016; Moffitt et al., 2015). Therefore, longitudinal studies including participants with remitted versus persistent ADHD, can help us in understanding the genetic and neurobiological correlates of this multifactorial disorder.

All of the imaging genetics studies reviewed here employed hypothesis-driven approaches. This means, that candidate genetic variants were only investigated in relation to specified candidate brain phenotypes and by this it severely limits our ability to create new knowledge on genetic effects on the brain. Even main effects of a variant may have been missed, as our ability to define the right hypotheses is hampered by the still so limited understanding of ADHD etiology. Besides that, most studies investigated single genetic variants (SNPs or VNTRs), although we know that frequently more than one risk allele exists in a single gene/locus; see e.g. (Schizophrenia Working Group of the Psychiatric Genomics Consortium et al., 2014). Also, only few studies looked for epistatic or gene-environment interaction effects.

In the face of limited sample sizes available for an imaging genetics study, data reduction strategies might help to preserve power. By moving to gene-based mass-univariate and multivariate statistics, it is possible to test the combined effect of multiple genetics variants in a single test statistic. Such models thus reduce the number of statistical tests, e.g. through gene-wide analyses, and – by explaining more phenotypic variance – may enable the discovery of gene effects that would have been otherwise undetectable with single variant methods (Hibar et al., 2011; Bralten et al., 2011, 2013). Alternatively – or rather in addition – analyses of multiple genetic factors may be performed in the context of international collaborations, like ENIGMA and CHARGE (Psaty et al., 2009; Thompson et al., 2014) or using the publicly available data from large national research efforts (like the UK Biobank; <http://www.ukbiobank.ac.uk/>). These are mainly population studies, but since ADHD is currently viewed as an extreme on a continuum of population traits (Larsson et al., 2013a; Chen et al., 2008), we can learn a lot from studies performed in healthy individuals. While for this review, we specifically selected studies that had included patients with ADHD, it is indeed apparent also from those studies that genes affect traits rather than disorders (Hoogman et al., 2011). We have referred to some relevant studies in healthy individuals already in the previous sections. An additional example is an fMRI study investigating a genetic variant in *SNAP25*, which was found associated with altered activation of the posterior cingulate cortex during a working memory task, a finding that was replicated in a second, independent sample (Soderqvist et al., 2010). With working memory being one of the cognitive domains affected in ADHD (Alderson et al., 2013),

this finding can contribute to unravelling the biological pathways from gene to disease. However, some studies have also suggested differential genotype effects in subjects with ADHD and healthy participants (Durston et al., 2008; Monuteaux et al., 2008; Onnink et al., 2016). In those cases, imaging genetics studies in healthy participants will not reveal the full spectrum of the genetic effects, and studies in patients are warranted. The ENIGMA-ADHD Working Group, with its sample spanning 60 years of the human lifespan (Hoogman et al., [epub head of print](#)), is an important resource for the investigation of diagnosis-specific effects.

There are a number of additional areas, in which we foresee that imaging genetics studies will profit from technical advances as well as recent insights into disease etiology. Importantly, a new GWAS meta-analysis is now underway by the ADHD Working Group of the Psychiatric Genomics Consortium (PGC) and the Danish iPSYCH consortium, which will provide several bona fide ADHD risk genes identified in hypothesis-free analyses (PGC and iPSYCH ADHD working groups, [in preparation](#)). Those will be interesting targets for investigation through imaging genetics approaches. In addition, the introduction of next generation sequencing (NGS) technology in psychiatric research will allow us to go beyond studying SNPs and VNTRs. It is likely that also more rare genetic variants, identified through exome and whole-genome sequencing will find their way into imaging genetics studies, e.g. through mutational load or burden tests (Medland et al., 2014).

Most imaging genetics studies in the field of ADHD have used MRI as their main brain imaging technique. For subcortical brain structures, grey matter volume has been the most frequently investigated characteristic. For the cortex, measurements of surface area (SA) and cortical thickness (CT) were found to be genetically and phenotypically rather independent (Winkler et al., 2010). Volume has been shown to be more closely related to SA than CT (Winkler et al., 2010). Therefore, it has been suggested that SA and CT measurements should be considered separately in imaging genetics studies (Winkler et al., 2010), in addition or instead of cortical volume. Until now, only very few studies have made use of this opportunity, however. Because of its low invasiveness, high spatial resolution, and wide availability of MRI scanners, this technique dominates the brain imaging field. Imaging genetic studies investigating genetic variation in the *SLC6A2/NET1*, *SLC6A3/DAT1*, and *DRD4* also used PET and SPECT (Table 3). These modalities enable direct localization and quantification of e.g. binding capacities of transporters and receptors, but are quite invasive. An alternative method for investigating the neurochemistry of the brain *in vivo* might be proton magnetic resonance spectroscopy (¹H-MRS), which allows for non-invasive quantification of several neurometabolites, such as N-acetylaspartate, (phospho-) creatine, choline, myo-inositol, glutamate and glutamine, and gamma aminobutyric acid (GABA) (Naaijen et al., 2015). While no significant differences in GABA levels were found in ADHD compared with controls (Schur et al., 2016), a possible increased signal of a combination of glutamate, glutamine, and GABA in the striatum of ADHD patients was observed, as well as an increased signal in the ACC in a paediatric ADHD sample and a reduced signal in an adult ADHD sample; reviewed by (Naaijen et al., 2015). The neurodevelopmental changes in fronto-striatal glutamatergic circuits across the lifespan suggested by this might be interesting targets for future imaging genetics studies. By combining different methods, it should be possible to create a comprehensive picture of how polymorphisms in ADHD-related genes affect the brain at chemical, structural, and functional levels. To date, also no MEG genetics studies has been reported. The high temporal resolution of this modality might be of great additional value in understanding genetic effects on brain function. Resting-state fMRI studies are also still lacking from the imaging genetics literature. Especially the combination and integration of different modalities in the study of individual

participants may provide more comprehensive insights into gene effects (Kobiella et al., 2011). With respect to functional brain markers that might serve as a useful endophenotype, it is crucial to use a functional contrast that isolates brain activity specifically associated with the cognitive process of interest. For example, stop/NoGo and Go conditions in traditional stop-signal/Go-NoGo tasks not only differ in the involvement of response inhibition, but also in other processes such as novelty/probability of occurrence and perceptual processing (Boehler et al., 2010; Sanchez-Carmona et al., 2016). Results of a recent study highlight the importance of controlling for the different strategies adopted by participants to perform selective stopping tasks before analyzing brain activation patterns (Sanchez-Carmona et al., 2016). Thus, activity emerging from a functional contrast (e.g., Go versus NoGo) will probably reflect a mixture of different processes. This is an important issue to be considered, when interpreting task-based fMRI studies and designing new studies.

Another opportunity to improve the design of imaging genetics studies is the use of mediation and moderation analyses. In mediation analysis, a causal explanation for the effect of an independent on a dependent variable is statistically modelled. The assumption of causality is important in this type of analysis and thus should be justified by a plausible biological theory or appropriate experimental constraints. In moderation analysis, the influence of a third variable on the association of an independent and dependent variable is modelled. The simple moderation and mediation models can be combined to account for more complex data structures and biological models (Hayes and Scharkow, 2013; van der Meer et al., 2014). Such models have e.g. been employed in psychological (Aram et al., 2010; Graziano et al., 2011) and medical research questions (Nigg et al., 2008), but could be also promising for analyses of the pathway from genes to phenotypes in complex disorders, such as ADHD, which involves different biological and non-biological factors acting synergistically during an individual's developmental trajectory (Bale et al., 2010; Krain and Castellanos, 2006). Indeed, van der Meer and coworkers recently used such analyses to inspect the moderation of the effect of stress on ADHD severity by the 5HTTLPR genetic variant. The researchers could show that an interaction of 5HTTLPR genotype and stress was associated with ADHD severity (van der Meer et al., 2014), and that this gene-environment interaction had several substrates in the brain. Importantly however, only a subset of those substrates did really mediate the effects of the gene-environment interaction, whereas others were epiphenomena (van der Meer et al., 2015).

While imaging genetics studies with the goal of mapping pathways from gene to disease up to now have always started with the selection of the candidate gene/variant to study, the advances brought about by international consortia now start to allow entirely data-driven approaches to be used for imaging genetics. For example, we have recently developed a comprehensive pipeline for the analysis of genetic overlap of GWAS results for disease risk (in that case schizophrenia risk data from the PGC) and the GWAS results for brain volume (Franke et al., 2016). The latter was based on data from the ENIGMA consortium (Stein et al., 2012; Medland et al., 2014; Thompson et al., 2014), in which MRI scans and genome-wide genotyping data from up to 30,717 individuals were analysed, and several genetic factors contributing to the volumes of specific brain structures were identified (Hibar et al., 2015). Finding such overlap between disease risk variants and those for brain phenotypes would be indicative of etiologic sharing, and would thus directly flag the pathways from gene to disease (Franke et al., 2016). For their previous studies, ENIGMA used mainly regional brain volume measures (Hibar et al., 2015; Stein et al., 2012), but one can also envisage more comprehensive voxel-wise genome-wide scans (vGWAS) to examine evidence for associations across the genome at each voxel in the brain image (Stein et al., 2010). While these

approaches still are limited by the fact that a stringent correction for type I errors dramatically increases the threshold for statistical significance (as genomes and images are both highly dimensional), data reduction strategies are being devised that can preserve power in such settings (Medland et al., 2014). With respect to the different imaging modalities, structural MRI and DTI seem to be best suited for larger collaborations and data sharing, but also fMRI imaging genetics meta-analyses have been shown to be feasible (Mier et al., 2010; Murphy et al., 2013). First analyses of overlap between ADHD GWAS findings and results of the ENIGMA volume analyses are currently underway (Klein et al., in preparation).

4.2. Complementary methods for the evaluation of the mechanisms underlying ADHD risk genes

Imaging genetics analyses of the human brain provide information on the effect of ADHD risk genes/variants on brain structure, activity, and connectivity, but other levels of investigation are needed to provide a more complete picture (Fig. 2). We also need information about the molecular networks, in which an ADHD gene acts, and the cellular processes that are affected by it. In the following section we highlight different methodologies and approaches that can be used to shed light on these additional levels of complexity contributing to the mechanisms underlying the effects of ADHD genes on behaviour and disease.

4.2.1. Bioinformatics approaches help to integrate findings from different types of molecular studies

Bioinformatics is a broad field of research, which can support our efforts to map pathways from gene to disease in several different ways. A first goal to be pursued through bioinformatics analyses is the clarification of the actual effects of risk variants on gene expression and regulation. Risk variants for a disease are often found in non-protein coding sequences, and therefore the molecular consequences are difficult to evaluate (Paul et al., 2014; Civelek and Lusis, 2014). We will not go into this type of bioinformatics analyses any deeper, but would want to point the interested reader to a recent example for a comprehensive bioinformatic follow-up study demonstrating how to elucidate the mechanisms by which a genetic risk variant (e.g. rs1344706; *ZNF408A* gene) confers susceptibility to disease, in this case schizophrenia and bipolar disorder (Hess et al., 2015).

Bioinformatics can also help to unravel the molecular networks and cellular processes that an ADHD risk gene is involved in. ADHD-associated genetic factors are distributed throughout the genome; however, they have been found to be enriched within functional categories. This clustering of ADHD-related genes within functional networks or pathways has helped to identify biological processes of importance to ADHD etiology. As also mentioned earlier, through those bioinformatics studies we learned that functions related to nervous system development, cell migration, neuron projection morphogenesis/neurite outgrowth, oxogenesis, cell–cell communication, glutamatergic synapse/receptor

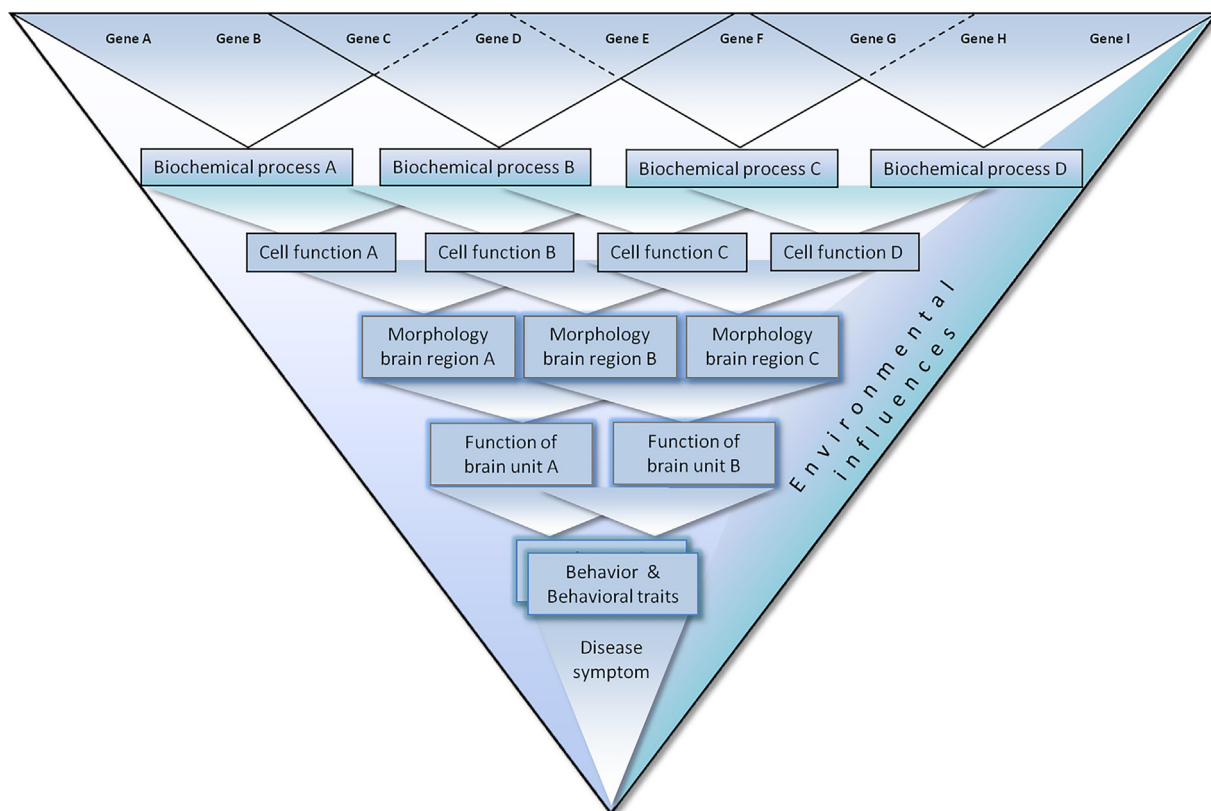


Fig. 2. This schematic representation of the endophenotype concept shows the pathway from gene to disease at different levels of complexity in psychiatric genetics. The figure has been modified from a previous publication (Fig. 1, (Franke et al., 2009)). Polygenic (schematically depicted by gene A–I) is involved in causing disease symptoms. A reduced number of genes is involved in disease-related endophenotypes. These can be studied at various biological levels, e.g. biochemical processes and cell function can be assessed by biological assays in cell or animal models by measuring e.g. neuron morphology or synaptic functioning. Neuroimaging methods (structural and functional) can be applied to assess relevant endophenotypes at the level of brain morphology ('Morphology brain region A–C'). Endophenotypes, related to the 'function of brain units', can be e.g. investigated by functional MRI or through performance measurements on neuropsychological tests. Aberrations at this level can result in altered behavior and disease-related behavioral traits, that subsequently lead to disease symptoms. Environmental influences can impact on all levels and need more attention in future studies. Bioinformatic pathway and network analyses can help to integrate data from various sources and to identify molecular networks or cellular processes in which ADHD-related genes are enriched.

signalling, multicellular organismal development, RhoA signalling, glycosaminoglycan biosynthesis, fibroblast growth factor receptor activity, ion (potassium) channel function, transmembrane transport, as well as synaptic transmission, catecholamine metabolic processes, G-protein signalling and organonitrogen compound catabolic processes are enriched in the results of hypothesis-free, genome-wide ADHD-GWAS and CNV studies (Poelmans et al., 2011; Hawi et al., 2015; Yang et al., 2013; Cristino et al., 2014; Mooney et al., 2016; Thapar et al., 2015). Those studies mainly used childhood ADHD data; little is yet known about biological pathways leading to persistence of ADHD. A first, small-scale GWAS of rare and common genetic variants in adults with persistent ADHD showed that the top SNPs implicated biological pathways involved in the regulation of gene expression, cell adhesion, and inflammation (Zayats et al., 2015). The Network and Pathway Analysis Subgroup of the PGC focussed on common pathways underlying additional, ADHD-related psychiatric disorders in adults, i.e. schizophrenia, major depression, and bipolar disorder (The Network Pathway Analysis Subgroup of The Psychiatric Genomics Consortium, 2015). Histone methylation processes (playing important roles in the regulation of gene expression) showed the strongest association, and the researchers also found significant evidence for involvement of immune and neuronal signalling pathways and for processes occurring at the postsynaptic density (The Network Pathway Analysis Subgroup of The Psychiatric Genomics Consortium, 2015).

Comprehensive studies applied to the ADHD-related autism spectrum disorders (ASD) point out, how the combination and integration across several molecular modalities can advance our knowledge about pathways from gene to disease. For example, systematic integration of findings from multiple levels of genomics data and studies of mouse models highlighted the period of fetal development and the processes of chromatin structure, neurite outgrowth, steroidogenesis, synaptic function, and neuron-glia signalling (Poelmans et al., 2013; Chen et al., 2015). Additional studies revealed that ASD genes grouped together in terms of functional annotations, protein–protein interactions and coexpression (Voineagu et al., 2011; Ben-David and Shifman, 2012; O’roak et al., 2012; Neale et al., 2012), and gene interaction and coevolutionary patterns (Gilman et al., 2011). By integrating gene expression data representing normal human fetal development, developmental timing and cellular specificity of the molecular pathways disrupted in ASD could be clarified (Willsey et al., 2013; Parikshak et al., 2013). Such integrative studies are still lacking for ADHD, but highly warranted in order to shed more light on the onset and neurodevelopmental trajectory of the disorder.

4.2.2. Animal models provide proof of causality for genes and molecular processes found associated with ADHD

The complexity and crucial role of the brain in the human body largely restrict studies in humans to the described non-invasive imaging methods for investigating brain structure and function. However, to fully understand the role of a disease gene in the fine-tuning of this sophisticated organ, we also need to be able to manipulate genes and monitor the effects of such manipulation on molecular and cellular processes. For this, animal models are indispensable. They can be genetically modified to enable determination of causality, have a natural complexity of the nervous system, and allow a tight control of environmental influences, including diet and drug delivery (Lange et al., 2012; van der Voet et al., 2016). During the last decades, studies were performed on several ADHD animal models, including monkey (Ma et al., 2005; Seu et al., 2009), rat (Ruocco et al., 2014; Williams et al., 2009b; Russell et al., 1995), mouse (Wallis et al., 2012; Zhu et al., 2014; Zimmermann et al., 2015; Zhu et al., 2014; Zimmermann et al., 2015), zebrafish (Lange et al., 2012), and fruit fly (van der Voet et al., 2016). The particu-

larity of each model, like the different levels of complexity of the nervous system, provide complementary information to the broad picture of ADHD.

Most studies in monkeys were mainly based on drug administration to stimulate/inhibit certain brain regions or neurotransmitter receptors and to study its effect on a nearly as sophisticated brain structure as the human (Ma et al., 2005; Seu et al., 2009).

The rat and mouse models additionally provided evidence for involvement of genes in ADHD (Gainetdinov et al., 1999; Simchon et al., 2010; Wallis et al., 2012; Zhuang et al., 2001; Zimmermann et al., 2015; Zhuang et al., 2001; Zimmermann et al., 2015). This was done by measuring face-valid hyperactivity, inattentiveness, or impulsivity, and also looking for physiological and histological abnormalities in reverse and forward genetic approaches. Reverse genetic approaches are employed for disease candidate genes identified in human studies; the orthologues of the observed human genes are manipulated in the animal model to evoke measurable phenotypes and to study their involvement on cellular and/or behavioural levels (Rivero et al., 2013; Wallis et al., 2012). Forward genetics use the opposite tactic by studying inbred animal strains for ADHD-associated conducts, and analysing their protein expression pattern and behaviour (Dimatelis et al., 2015; Womersley et al., 2015; Li et al., 2007b). In reverse genetics approaches, early studies proved the involvement of candidate genes from association studies in ADHD, e.g. by showing ADHD-like behavioural phenotypes in *Dat1* knock-out mice and the coloboma mouse showing a mutation in *Snap25* (Heyser et al., 1995; Giros et al., 1996). Most knock-out and transgenic mouse models targeted genes involved in dopamine transmission. These mutant models provide an excellent opportunity to evaluate the contribution of dopamine-related processes to brain pathophysiology, to analyse the neuronal circuits and molecular mechanisms involved in the action of ADHD medication, and to test novel treatments for ADHD; for review see (Leo and Gainetdinov, 2013). More recent studies of a mouse model containing a null mutation of the latrophilin 3 gene (*Lphn3*), which showed a hyperactive phenotype in an open field test, revealed that this ADHD candidate gene is involved in gene expression regulation of monoamine signalling genes, such as dopamine and serotonin receptors and transporters, neurotransmitter metabolism genes, and neural development genes (Wallis et al., 2012). Additionally, actin depolymerising factor and n-cofilin double mutant mice displayed hyperlocomotion, impulsivity, impaired working memory, and disturbed morphology of striatal excitatory synapses, accompanied by strongly increased glutamate release (Zimmermann et al., 2015). Of note, the hyperlocomotion and impulsivity were reversed by methylphenidate (Zimmermann et al., 2015).

While reverse genetics approaches are most often applied in ADHD research to date, forward genetics has led to new models to study ADHD, like the spontaneous hypertensive rat (SHR), which was created to study hypertension by inbreeding albino Wistar rats showing elevated blood pressure (Okamoto and Aoki, 1963). These rats also showed deficits in attention, and ADHD-associated conducts, such as increased impulsivity and hyperactivity, and are therefore widely employed as a model for ADHD (Li et al., 2007b; Williams et al., 2009a,c,b). Studies of the molecular and cellular characteristics of this forward genetic model have provided evidence that proteins involved in energy metabolism, neurotransmitter function, neural development, and myelination are differently expressed in the striatum and PFC (Dimatelis et al., 2015; Womersley et al., 2015). The observed changes in the striatal energy metabolism support the neuroenergetics hypothesis of Killeen et al. (2013), which states that inadequate neuronal energy supply can lead to ADHD symptoms (2013). Moreover, the GABAergic system was shown to be involved in ADHD-like behaviour of SHR rats by investigating the physiological response of GABA on hippocampal

slices and finding GABA significantly altered during early-life stress in these animals (Sterley et al., 2013b,a).

Novel animal models for the study of ADHD include zebrafish (*Danio rerio*) and the fruit fly (*Drosophila melanogaster*) (Lange et al., 2012; van der Voet et al., 2016). These models have the great advantage of being relatively inexpensive, having a wide range of genomic tools available, and being highly suitable for fast, high throughput studies of (candidate) genes. The combination of those characteristics, with the availability of valid and quantifiable phenotypic readouts for ADHD-relevant traits makes these animal models a potent addition to non-invasive studies in humans. Even though both zebrafish and fruit fly diverged from the human lineage early in evolution, there is still a high level of conservation of neuronal genes; for example, in a screen for intellectual disability genes, more than 70% of candidate genes had an unambiguous orthologue in the fruit fly (Oortveld et al., 2013; van der Voet et al., 2014). Also genes involved in the phenotypic manifestation of hyperactivity were crucial during early evolution and thus can be found in species with a much simpler nervous system. Several studies show the strength of such models. In zebrafish, e.g. the orthologues of the human ADHD candidate genes *LPHN3*, *PER1*, and *PER2* have been studied and shown to cause hyperactivity (Huang et al., 2015; Lange et al., 2012; Wang et al., 2015a). The *lphn3.1* mutant fish showed, besides the behavioural phenotypes, misplaced dopaminergic neurons in the brain (Lange et al., 2012). Functional studies on *Per2* null mutants in zebrafish showed differential expression of the circadian clock genes *aanat2* and *bmal1b* and indicated the involvement of *Per2* in the circadian regulation (Wang et al., 2015a). In addition, *per1b* mutant fish display hyperactive and impulsivity-like behaviours and low levels of dopamine, of which hyperactivity could be rescued by ADHD medication (Huang et al., 2015). It could be shown that the circadian clock has direct influence on the structure and abundance of dopaminergic neurons and lower expression of transcription factors directly regulating development, maintenance and differentiation of these neurons (Huang et al., 2015). In the fruit fly, manipulation of the orthologues of the dopamine-related genes *DAT1* and *LPHN3*, caused characteristic darkness-dependent hyperactivity, an ADHD-like behaviour (van der Voet et al., 2016). Also in those models, ADHD medication was able to reverse the behavioural phenotype (van der Voet et al., 2016). Finally, the vacuolar protein sorting-associated protein 4A (*VPS4A*) in the striatal node was significantly associated with dysfunctional reward, a cognitive (e.g. poor inhibitory control or timing estimation), but also affective (e.g. delay aversion or hyposensitivity to reward) deficit observed in ADHD (Jia et al., 2016). The orthologue was studied in the fruit fly, showing that flies with an overexpression of *Vps4* have a reduced overall activity similar to a *Drd1* knockout fly, while a knockdown of *Vps4* leads to hyperactivity, suggesting the involvement of *VPS4A* in the regulation of *DRD1*-mediated activity (Jia et al., 2016).

At the level of animal models, the integration of knowledge from models of different evolutionary complexity will optimally support the elucidation of gene to disease pathways, as it is already apparent from the initial study of *LPHN3* orthologues across mouse, zebrafish, and fruit fly.

4.2.3. Modelling psychiatric disorders at the cellular level by using human induced pluripotent stem cell (hiPSC)-derived neurons

ADHD is a multifactorial disorder, and in most patients, several to multiple genetic factors are likely to contribute to disease. Animal models are mostly based on highly penetrant single gene mutations, which limits the translation of findings from molecular and cellular levels to the human situation. A human model, especially one derived from a patient him-/herself, might therefore be preferable in certain situations. Until recently, the only way to study cellular processes and molecular pathways in patient brain

cells was through post-mortem material. Due to the scarceness of available post-mortem brain tissues, only a very limited number of studies was performed to date, concentrated on demonstrating an influence of ADHD-related genetic variants on gene expression (Weber et al., 2015; Hawi et al., 2013a; Brookes et al., 2010, 2007). Fortunately, cell reprogramming technology has been developed throughout the past decade, which provides a powerful tool to simulate neural developmental processes *in vitro* in a petri dish (Brennand et al., 2015b; Takahashi et al., 2007; Yu et al., 2007). Neurons from both healthy individuals and psychiatric patients can be derived by (1) reprogramming human skin fibroblasts or blood mononuclear cells into induced pluripotent stem cells (iPSCs) and then differentiating these into neurons (Zhang et al., 2013), or by (2) directly reprogramming skin fibroblasts into neural stem cells or neurons (Pang et al., 2011; Vadodaria et al., 2015; Brennand and Gage, 2012). The human induced pluripotent stem cell (hiPSC)-derived neurons from a patient then have a genetic background identical to the disorder state, and thereby provide the possibility to characterize the effects of the cocktail of genetic perturbations leading to disease in this patient (Brennand et al., 2015a; Madison et al., 2015; O'shea and Mcinnis, 2015; Wang et al., 2015b; Lim et al., 2015). Such effects may be specific to cell types and/or specific developmental stages (Duan, 2015; Hockemeyer and Jaenisch, 2016). Moreover, a temporal analysis of disease initiation and progression can be performed in the cell type(s) most relevant to a disorder (Brennand et al., 2012). For example, studying hiPSC neurons from patients with disease-associated large CNVs provides the opportunity to perform comprehensive molecular analyses of the effects of these large CNVs in several cell lineages (Urban and Purmann, 2015). Until now, several studies were published using hiPSC-derived neurons from patients with ASD, schizophrenia, or bipolar disorder (Marchetto et al., 2010; Ananiev et al., 2011; Urbach et al., 2010; Sheridan et al., 2011; Chiang et al., 2011; Brennand et al., 2011; Wen et al., 2014). For example, hiPSC-derived neurons from patients with schizophrenia were shown to have synapse deficits and transcriptional dysregulation (Wen et al., 2014). Additionally, by comparing hiPSC-derived neurons from patients with bipolar disorder and controls, alterations in key components of the microRNA processing pathway were identified, potentially altering neuronal cell fate determination (O'shea and Mcinnis, 2015). To overcome confounding effects of variable genetic backgrounds, when comparing cells from patients to those from healthy controls, genome-editing technology can be applied (Duan, 2015), such as Zinc-finger nucleases (ZFN) (Reinhardt et al., 2013), transcription activator-like effector nucleases (TALEN) (Wen et al., 2014), and recently developed clustered regularly interspaced short palindromic repeats (CRISPR) (Ran et al., 2013; Wang et al., 2015b; Liu et al., 2016). Such genome-editing enables the generation of isogenic hiPSC-derived neurons that differ only at the genetic site of interest (Ding et al., 2013; Bedell et al., 2012; Choi et al., 2013). In this way, specific mutations can be either introduced in control cells or corrected in patient cells to investigate causality (Duan, 2015; Hendriks et al., 2016).

Beyond mechanistic insights, hiPSC neurons might also serve as a platform for high throughput screening to identify novel therapeutics for psychiatric disorders (Schadt et al., 2014). For example, the ability to test drugs to rescue synaptic deficiency in Rett syndrome neurons has been demonstrated (Brennand et al., 2012). Generally, it is suggested that these cell models are suited for longitudinal observations, studying on-off-medication effects, and investigating the mechanisms of comorbid disorders in individual patients (O'shea and Mcinnis, 2015).

A current limitation of hiPSC-based models is the high heterogeneity of the derived differentiated neuronal populations (Gore et al., 2011; Hu et al., 2010; Lister et al., 2011; Osafune et al., 2008). Although almost pure glutamatergic neurons can be dif-

ferentiated from hiPSCs, the differentiation efficiency for other types of neurons, such as dopaminergic, GABAergic, serotonergic, or cholinergic neurons, is relatively low, which can cause variability in the outcome of *in vitro* experiments (Swistowski et al., 2010; Vadodaria et al., 2015; Zhang et al., 2013; Liu et al., 2013a; Hu et al., 2016). Therefore, ideally a comparison of several hiPSC-derived neuronal lines from multiple patients should be performed (Brennand and Gage, 2012). It seems advantageous to model the psychiatric disorders in a pure, specified type of neuron; however, it is also reasonable to carry out investigations at the network level in different types of neurons interacting, better mimicking the multi-dimensional integration in the brain through 3D culture systems or brain 'organoids', which are currently being developed (Kim et al., 2015; Lancaster et al., 2013).

Based on the above, it is clear that the reprogramming technology will revolutionize our use of model systems. Although still very much under development, and not yet applied to ADHD risk genes, first results for other psychiatric disorders already suggest that valuable findings about molecular and cellular pathways from gene to disease can be derived from iPSC-derived neurons.

5. Conclusion

Results from studies described in this review show that imaging genetics approaches are highly suitable to provide more insight into the pathways from gene to behaviour via the brain in ADHD. However, this field is clearly still in its early stages. Inconsistency of findings, due to the use of relatively small sample sizes, clinical and biological heterogeneity of ADHD, methodological differences in study design, and analysis methodology, make it difficult, yet, to draw firm conclusions about effects of genes on brain morphology, function, and connectivity. Individual genes need to be investigated more extensively and in larger samples, and additional genes need to be studied – preferably focussing on those implicated in ADHD through genome-wide, hypothesis-free approaches. We emphasize that a combination and integration of imaging genetics studies with complementary approaches at different levels of biological complexity – including bioinformatics as well as cell and animal models – will be necessary to fully map the biological pathways from gene to disease.

Conflict of interest

None of the authors report conflicts of interest. Barbara Franke discloses having received educational speaking fees from Merz and Shire.

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