Imaging genetics in neurodevelopmental psychopathology

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Abstract

Neurodevelopmental disorders are defined by highly heritable problems during development and brain growth. Attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorders (ASDs), and intellectual disability (ID) are frequent neurodevelopmental disorders, with common comorbidity among them. Imaging genetics studies on the role of disease-linked genetic variants on brain structure and function have been performed to unravel the etiology of these disorders. Here, we reviewed imaging genetics literature on these disorders attempting to understand the mechanisms of individual disorders and their clinical overlap. For ADHD and ASD, we selected replicated candidate genes implicated through common genetic variants. For ID, which is mainly caused by rare variants, we included genes for relatively frequent forms of ID occurring comorbid with ADHD or ASD. We reviewed case-control studies and studies of risk variants in healthy individuals. Imaging genetics studies for ADHD were retrieved for *SLC6A3/DAT1*, *DRD2*, *DRD4*, *NOS1*, and *SLC6A4/5HTT*. For ASD, studies on *CNTNAP2*, *MET*, *OXTR*, and *SLC6A4/5HTT* were found. For ID, we reviewed the genes *FMR1*, *TSC1 and TSC2*, *NF1*, and *MECP2*. Alterations in brain volume, activity, and connectivity were observed. Several findings were consistent across studies, implicating e.g. *SLC6A4/5HTT* in brain activation and functional connectivity related to emotion regulation. However, many studies had small sample sizes, and hypothesis-based, brain region-specific studies were common. Results from available studies confirm that imaging genetics can provide insight into the link between genes, disease-related behavior, and the brain. However, the field is still in its early stages, and conclusions about shared mechanisms cannot yet be drawn.

Keywords

ADHD; ASD; ID; brain imaging genetics; neurodevelopmental disorders

Introduction

Neurodevelopmental disorders are broadly defined as disorders in the development and growth of the brain (Goldstein 1999), but this term is largely used to describe neurological and psychiatric disorders that have their onset prior to adulthood. Most neurodevelopmental disorders are highly heritable, either caused by single genetic defects, like many of the intellectual disability (ID) disorders (Deciphering Developmental Disorders Study 2015), or with a more multifactorial background, in which several to multiple less penetrant genetic variants cause the disease in combination with environmental factors, like in many cases of autism spectrum disorders (ASDs; (Gaugler et al., 2014; Iossifov et al., 2014), as well as in attention-deficit/hyperactivity disorder (ADHD; (Faraone et al., 2015; Franke et al., 2012), oppositional defiant disorder, and conduct disorder (Salvatore and Dick 2016).

While technological advances in the last decade, especially genome-wide association studies (GWASs) and next generation sequencing, have enabled the identification of many genetic factors involved, the biological mechanisms contributing to the neurodevelopmental disorders are still largely unknown. It is thought that gene variation/mutation will alter molecular and cellular processes, which leads to altered brain development, be it structurally and/or functionally, and subsequently to altered behavior and disease symptoms (Franke et al., 2009). Measures that mediate the effects of genes on behavioral/disease phenotypes have been termed endophenotypes or intermediate phenotypes (Gottesman and Gould 2003; Kendler and Neale 2010).

Much research into the consequences of gene aberrations is performed in animal models. However, brain imaging methods like magnetic resonance imaging (MRI), electroencephalography (EEG), and magnetoencephalography (MEG) offer excellent ways to investigate the effects of genetic variation on brain structure, function, and connectivity directly in humans *in vivo*. Such 'imaging genetics' approaches can unveil the brain-biological consequences of molecular changes induced by genetic variants – both common and rare – linked to neurodevelopmental disorders. In that way they can help to understand the mechanisms through which differences in behavior arise. It has been argued that the effects of disease-linked (common) genetic variation on the brain would be larger than those on behavior and clinical phenotypes (Gottesman and Gould 2003; Rose and Donohoe 2013)), although more recent work using hypothesis-free imaging genetics approaches argues against this – at least for brain structural phenotypes (Franke et al., 2016).

Different neuroimaging methods can be used in imaging genetics studies, including different forms of structural and functional MRI as well as EEG and MEG. They have complementary characteristics enabling information to be gathered on different aspects of (gene effects on) brain anatomy and function, like location (especially MRI-based methods) and timing (especially EEG and MEG). In this review, we concentrated on those methods that have most frequently been used in imaging genetics studies of neurodevelopmental disorders, i.e. MRI-based methods evaluating gene effects on brain structure, function, and connectivity.

With structural magnetic resonance imaging (sMRI) it is possible to noninvasively characterize the structure of the human brain. Thereby, the different magnetic properties of

brain tissues are used to map the spatial distribution of these structural properties of the brain. In this way, the different brain tissues (grey and white matter) and cortical and subcortical structures of the brain can be mapped. By adapting scanning parameters, different weighting techniques of the signal can be used, such as T1-weighted imaging (used to visualise anatomy) and T2-weighted imaging (which is useful for demonstrating lesions and pathology). Different aspects of brain structure can be used for quantitative analyses. To investigate whether volumetric differences are global or regional, specific brain regions of interest (ROIs) can be selected *a priori* and studied individually. In contrast, global changes in grey or white matter intensity can be detected by using voxel-based morphometry (VBM) analyses. Next to volumetric differences observed in grey matter, structural differences of white matter connectivity can also be quantified. With the help of diffusion tensor imaging (DTI), it is possible to non-invasively investigate the macrostructural integrity and orientation of white matter fibre bundles. Thereby, the directional diffusion of water molecules along neuronal membranes is measured, allowing to map white matter connection within the brain. Multiple measures can be derived from DTI. A frequently measured parameter is fractional anisotropy (FA). Basically, anisotropy indicates that diffusion takes place in a directional manner, whereas isotropy indicates diffusion in all directions. Additional DTI-derived parameters include mean diffusivity (MD; average of axial diffusivity (AD) and perpendicular diffusivities), and radial diffusivity (RD; average of perpendicular diffusivities), the mode of anisotropy (sensitive to crossing fibres), and the apparent diffusion coefficient (indicating the magnitude of diffusion) (Le Bihan 2003; Le Bihan et al., 2001; Yoncheva et al., 2016).

Resting state functional MRI (rs-fMRI), allows to analyse the temporal correlations of neural activity across anatomically disparate brain regions and thereby to examine the functional connectivity based on spontaneous brain activity, neural organization, and circuit architecture.

To investigate potential changes in brain activity, functional magnetic resonance imaging (fMRI) can be used. Since fMRI is sensitive to the oxygenation of the blood, the so-called blood-oxygen-level-dependent (BOLD) signal can be measured. Thereby brain function is measured, based on the premise that active cells consume oxygen, thus causing changes in blood oxygenation, and subsequently leading to increased blood flow. However, the exact link between cell activation, oxygen saturation, and cerebral blood flow changes is debatable (Hillman 2014). Generally in fMRI, alterations in blood flow after e.g. a task-induced stimulus or during a resting condition are measured.

Here, we systematically reviewed the imaging genetics literature for three frequent neurodevelopmental disorders, ADHD, ASDs, and selected intellectual disability (ID) disorders. The choice for those three neurodevelopmental disorders was based on their frequent comorbidity (Vorstman and Ophoff 2013) and robustly established associations with specific genetic variants. The aim of this work was to extract core brain mechanisms affected by disease-linked genetic factors related to the individual disorders as well as their clinical overlap.

ADHD is one of the most common neurodevelopmental disorders, with a prevalence of 5–6% in childhood (American Psychiatric Association 2013; Polanczyk et al., 2007). ADHD can be clinically characterized by two core symptom domains: inattention and hyperactivity/impulsivity (American Psychiatric Association 2013; Faraone et al., 2015). Up to 60% of all patients diagnosed in childhood show ADHD symptoms and/or meet formal diagnostic criteria for the disorder in adulthood, and prevalence rates of persistent ADHD in adults range between 2.5 and 4.9% (Simon et al., 2009). ASD affects approximately 0.6% to 1% of the children, making it one of the most prevalent disorders in childhood (Elsabbagh et al., 2012). Although there are some important differences in core symptom definition, the co-occurrence between ADHD and ASD is supported by clinical (Craig et al., 2015), common biological (Rommelse et al., 2010), and non-biological risk factors (Kroger et al., 2011). Moreover, several studies identified that symptoms of autism or autistic traits appear in 20% to 30% of children with ADHD (Grzadzinski et al., 2011; Kochhar et al., 2011). Additionally, ADHD is a common comorbid disorder in children with ID, and the risk increases with increasing severity of ID (Voigt et al., 2006). Studies of children with mild and borderline ID have identified ADHD in 8% to 39% of the cases (Baker et al., 2010; Dekker and Koot 2003; Emerson 2003). ADHD is highly heritable (heritability 70–80%) (Burt 2009; Faraone et al., 2005). However, identification of ADHD risk genes has been difficult (Franke et al., 2009; Gizer et al., 2009), mainly due to ADHD's complex genetic background (Faraone et al., 2015; Franke et al., 2012). Mostly genetic variants, which occur quite frequent in the population and have generally small effects on disease risk have been investigated for their role in ADHD until today, either through candidate gene studies or hypothesis-free GWASs. Only a few of the candidate genes have been confirmed through meta-analysis (Gizer et al., 2009). However, none of the eleven GWAS (Hinney et al., 2011; Lasky-Su et al., 2008a; Lasky-Su et al., 2008b; Lesch et al., 2008; Mick et al., 2010; Neale et al., 2008; Neale et al., 2010a; Sanchez-Mora et al., 2014; Sonuga-Barke et al., 2008; Stergiakouli et al., 2012; Yang et al., 2013) nor a meta-analysis of many of them (Neale et al., 2010b) published to date, reported any genome-wide significant risk variant.

ASDs refer to a heterogeneous group of neurodevelopmental disorders diagnosed in approximately 1 of 88 children (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2008 Principal Incestigators and Centers for Disease Control and Prevention 2012). It is characterized by deficits in social behavior and language development, as well as restricted or stereotypic interests (American Psychiatric Association 2013). About 70% of individuals with ASDs have some level of ID while the remaining 30% have some disability (speech, behavior) other than cognitive dysfunction (Mefford et al., 2012). Whereas early reports estimated ASD heritability to be higher than 90% (Bailey et al., 1995; Folstein and Rutter 1977; Ritvo et al., 1985; Steffenburg et al., 1989), recent population-based studies provided an estimate of ~50% heritability (Gaugler et al., 2014; Sandin et al., 2014). ASDs are genetically highly complex, as part of the cases has oligogenic or even monogenic causes (with an important role for *de novo* mutations (Iossifov et al., 2014)), whereas the concerted action of common genetic variants of individually small effect sizes and environmental factors is likely to cause most of the disease burden of ASDs (Iossifov et al., 2014) (Gaugler et al., 2014; Zhao et al., 2007). Several of those common variants contributing to ASD risk have been identified through

hypothesis-driven studies. Until now, three GWASs have been performed for ASDs (Anney et al., 2010; Wang et al., 2009; Weiss et al., 2009), which identified a single locus on chromosome 5p14, in-between *CDH10* and *CDH9* (Wang et al., 2009). Association with this locus might be driven by markers located within the *MSNP1AS* pseudogene (Ma et al., 2009).

ID refers to a highly heterogeneous group of disorders characterized by below average intellectual functioning (IQ < 70) in conjunction with significant limitations in adaptive functioning with onset during development. ID may occur as an isolated phenomenon or accompanied with malformations, neurological signs, impairment of the special senses, seizures and behavioral disturbances (van Bokhoven 2011). ID has an estimated prevalence of approximately 2% to 3%, and approximately 0.3% to 0.5% of the population is severely handicapped (Perou et al., 2013). Comorbidity with ADHD and ASDs is frequently observed (Vorstman and Ophoff 2013). Disease etiology of ID is thought to be largely monogenic, but with many different genetic anomalies implicated (van Bokhoven 2011). Genetic causes of ID range from large cytogenetically visible chromosomal aberrations, such as trisomy 21, to translocations, subchromosomal abnormalities (such as Prader-Willi syndrome (15q11.2-q13)), copy number variations, and to single gene defects. We concentrated only on the latter in our review, based on the assumption that we can learn most from understanding effects of specific genes/variants on brain structure, function and connectivity. While in many ID disorders, a defect in a single gene can be identified as the cause of the disorder, only a few genes are hit more frequently and cause relatively common ID disorders. To prevent bias of our review by single case reports, we concentrated on those common forms of ID, especially selecting those, in which comorbidity with ADHD and ASD is common. This resulted in five ID disorders included in this review: fragile X syndrome, tuberous sclerosis, neurofibromatosis type 1, Rett syndrome, and Timothy syndrome. Fragile X syndrome (FXS), caused by genetic defects in the *FMR1* gene, is associated with a variable clinical phenotype, including intellectual disabilities with a broad range of severities. IQ is 40 on average for affected men (Merenstein et al., 1996) and normal or borderline in females (de Vries et al., 1996), who show a milder phenotype because the disorder is X-chromosome-linked. High rates of autism and autistic behaviors are seen in individuals with FXS (Hagerman et al., 2009), and 59% of FXS subjects shows ADHD symptoms (Sullivan et al., 2006). Neurofibromatosis type 1 (NF1), caused by mutations in *NF1*, is associated with the presence of usually benign neurofibromas. While IQ in general is average to low average, up to 8% of children with NF1 have an IQ below 70. Learning difficulties and neuropsychological deficits are common, and the core cognitive impairments are in visual spatial function, attention, executive function, and language skills. About 38% of children with NF1 meet diagnostic criteria for ADHD, and a substantial proportion of subjects show social deficits related to ASD (Hyman et al., 2005; Walsh et al., 2013). Tuberous sclerosis complex (TSC) is caused primarily by mutations in the genes *TSC1* and *TSC2* and is characterized by benign hamartomas in multiple organ systems, including the brain. Intellectual ability in TSC ranges from normal to profoundly impaired, and neurobehavioral abnormalities and epilepsy are common. Both ASD and ADHD are reported in about 50% of individuals with TSC, with an even higher number of diagnoses in intellectually impaired individuals (Prather and de Vries 2004). Rett syndrome, caused by

mutations in the *MECP2* gene, primarily affects females. Language problems and cognitive and motor deficits start to become obvious around the age of 6 months in the patients. Testing of cognitive dysfunction is difficult because of a characteristic absence of speech, but ASD-related features, such as avoidance of eye contact, are common (Armstrong 2005). Timothy syndrome is a multisystem disorder caused by missense mutations in the *CACNA1C* gene. Neurodevelopmental features include global developmental delays and ASDs. Average age of death is 2.5 years, usually caused by ventricular tachyarrhythmia, infection, or complications of hypoglycemia (Splawski et al., 1993).

With this review, we aimed at providing a comprehensive overview on the imaging genetics literature for the three neurodevelopmental disorders. To prevent bias, we excluded reports including less than 10 cases and focused on specific genetic variants, which for ADHD and ASDs resulted in a focus on genes/loci implicated through variants that are common in the population, and for ID, we restricted the review to the genes causing the single-gene ID disorders described above. While imaging genetics studies have been performed in patients, the underlying candidate genes and their common genetic variants are also frequently studied in healthy individuals. This allows analysis of effects of common genetic variation in candidate genes on imaging correlates in the general population and offers the opportunity to study brains not influenced by chronic disease and medication. Previous studies showed that neuroimaging correlates of common genetic variants are likely to be similar in typical and psychiatric populations (Hibar et al., 2015b). As such studies of healthy individuals may also be informative regarding the biological mechanisms leading to the diseases of interest, they were also included in this review.

Methods

Search terms

Pubmed was searched for research articles describing imaging genetics studies (April, 14th, 2015; http://www.ncbi.nlm.nih.gov/pubmed). Only studies using magnetic resonance imaging (MRI) were reviewed, specifically structural MRI (sMRI), functional MRI (fMRI), resting-state functional MRI (rs-fMRI), and diffusion tensor imaging (DTI). A general search term was created and was extended by adding the disorder (for ADHD and ASD) or syndrome name and gene (for ID) of interest. The following search term shows an example for ADHD (for [Title/Abstract]): ((((ADHD OR Attention-Deficit Hyperactivity Disorder) AND (gene* OR genetic* OR imaging genetic OR imaging genetics OR genotype OR polymorphism OR SNP OR single nucleotide polymorphism OR meta-analysis OR genome wide association OR GWA OR GWAS)) AND (structural magnetic resonance imaging OR volume OR sMRI OR voxel-based morphometry OR brain morphometry OR brain volumetry OR VBM OR functional magnetic resonance imaging OR fMRI OR diffusion tensor imaging OR diffusion imaging OR connectivity OR tractography OR DTI OR resting-state functional magnetic resonance imaging OR voxel-wise analysis OR rsfMRI)) NOT "review"[Publication Type]). For ID syndromes, the search term did not include (gene* OR genetic* OR imaging genetic OR imaging genetics OR genotype OR polymorphism OR SNP OR single nucleotide polymorphism OR meta-analysis OR genome wide association OR GWA OR GWAS), as the genes of interest were added specifically. Titles and abstracts

of the retrieved records were evaluated for relevant publications. Case-reports and reports describing less than 10 cases were excluded to prevent bias, and review articles, medical hypotheses, non-English articles, and studies on animal models were not considered (for a graphical summary of the selection procedure, please see Figure 1).

Candidate gene selection for ADHD, ASD, and ID studies

Taking into account the differences in the genetic architecture of the three neurodevelopmental disorders of interest, we defined selection criteria for the genes to be included in this review as similar as possible. The restriction to studies with 10 or more cases and single genetic variants/single-gene mutations largely defined our search strategy, which resulted in a focus on common genetic variants for ADHD and ASDs (minor allele frequency 1%); for ID disorders, this lead to the selection of relatively common forms of the disorder. For ADHD and ASDs, we selected the most promising genes containing common variants associated with the disorder based on meta-analyses, successful replication studies, and/or significant findings from hypothesis-free (genome-wide) studies.

For ADHD, we included all genes and genetic variants mentioned in Table I of the meta-analytic study by Gizer and coworkers (2009) that had reached a significant result at P 0.05 for association with ADHD. In addition to this, we also included genes with reported and replicated evidence for association with ADHD from more recent studies. These included two meta-analytic studies (Pan et al., 2015; Wu et al., 2012), a research article (Ribases et al., 2011), and the more recently observed replicated candidate genes *NOS1* and *SLC9A9* (Stergiakouli et al., 2012; Weber et al., 2015) (total number of candidate genes = 10; Table I). A recent overview of these ADHD candidate genes has been published by Hawi and colleagues (2015).

For the ASD genes, we based our selection on the review of the most consistently replicated genes harboring common variants associated with autism by Persico and Napolioni (2013). Additionally, the *CDH9/CDH10* locus was included, because it has shown genome-wide significant association with ASD (Prandini et al., 2012; Wang et al., 2009). Selection of the candidate polymorphisms in the selected genes was based on recent research articles, as meta-analyses were only available for the *OXTR* and *RELN* gene (total number of candidate genes = 11; Table II).

For the ID, the restrictions to relatively common forms of the disorder resulting from single gene mutations (as opposed to structural genetic variants involving several to many genes) as well as our aim to study potential brain mechanisms contributing to comorbidity among the three disorders lead to the inclusion of the following 5 syndromes: fragile X syndrome (*FMR1*), tuberous sclerosis (*TSC1* and *TSC2*), neurofibromatosis type 1 (*NF1*), Rett syndrome (*MECP2*), and Timothy syndrome (*CACNA1C*) (Table III). For our selection, we used Table I from Vorstman and Ophoff (2013), describing genetic anomalies associated with ID. We included all disorders with known genetic cause including a single gene (*FMR1, TSC1* and *TSC2, NF1, and CACNA1C*). Patients with these disorders also show a high rate of ASD and/or ADHD phenotypes (Vorstman and Ophoff 2013). Additionally, we included the Rett syndrome (*MECP2*), because of its known ASD- and ADHD-related features (Armstrong 2005; Rose et al., 2016; Suter et al., 2014).

Results

Imaging genetics of ADHD candidate genes

A total of 76 records were retrieved for the ADHD search term, and a total of 16 research articles describing case-control studies were eligible for review according to our criteria. To those, we added three more recent papers from our own group ((Onnink et al., 2016; Sokolova et al., 2015; van der Meer et al., 2015); Figure 1). Most of the studies investigated a single gene (all in Caucasians), and three studies investigated multiple genes (2 in Caucasians, 1 in Asians). In addition, we obtained 295 records for the ADHD candidate gene studies in healthy population samples, of which 98 were eligible (Figure 1). Of those, 73 studies investigated a single gene (68 in Caucasians, 5 in Asians), and 25 studies tested more than one gene (1 Asian). The ADHD case-control samples consisted of both childhood/adolescent and adult samples, whereas the studies in the healthy population were largely restricted to samples of (young) adults. Single-gene findings of ADHD case-control studies and studies in the healthy population of both Caucasian and Asian ethnicities can be found in Table IV, multi-locus studies are shown in Table VI. Most of the genes investigated in brain imaging genetics studies in ADHD are from the dopaminergic and serotonergic neurotransmitter systems (*SLC6A3/DAT1, DRD2, DRD4, SLC6A4/5-HTT/SERT*). *SNAP25, DRD5, HTR1B,* and *LPHN3* had also been selected for this study, but for these genes no imaging genetics studies using MRI were found with our search terms.

The **dopamine transporter gene** *DAT1* (official name *SLC6A3*) codes for a solute carrier protein, 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. Additionally, a 30 bp VNTR in intron 8 of the gene (most common alleles with 5 and 6 repeats), 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 ADHD in children (Asherson et al., 2007; Brookes et al., 2006; Faraone et al., 2005). In contrast, the 9R/9R genotype and the 9–6 haplotype are associated with persistent ADHD (Franke et al., 2010). The sMRI and fMRI studies for *SLC6A3/DAT1*, the latter investigating several cognitive domains known to be impaired in ADHD, i.e. reward processing, working memory, and response inhibition, are summarized in Table IV and VI. The main focus of the studies for this gene has clearly been on the striatum, which shows highest gene expression.

The two sMRI case-control studies were performed in children, and both reported a smaller volume of the caudate nucleus in homozygotes for the 10R allele as compared to children with the 9R/10R genotype (Durston et al., 2005; Shook et al., 2011). A third study, including a large sample of children and adults with and without ADHD, 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 was depended on diagnostic status, since the risk haplotype affected striatal volume only in patients with ADHD (Onnink et al., 2016).

Two fMRI studies in case-control design investigated the *SLC6A3/DAT1* haplotype using reward paradigms. Independent of the genotype, a recent meta-analysis has shown that in reward-processing paradigms, most studies report lower activation of the ventral striatum in patients with ADHD in anticipation of reward than controls (Plichta and Scheres 2014). Consistent with this, a study in adolescents (including only males) found the activation of the caudate nucleus to be reduced in the ADHD group as the number of 10–6-haplotype copies increased (Paloyelis et al., 2012). The other study, in adult ADHD cases and controls (in whom the 9–6 allele is the ADHD risk allele), found no effect of *DAT1* haplotype on striatal activity (Hoogman et al., 2013). Studies in healthy adult individuals point in different directions. One found higher activation during reward anticipation in 9R-carriers (Dreher et al., 2009). Another also found increased striatal activation in 9R-carriers in a rewarded task-switching task, especially in high reward conditions (Aarts et al., 2010). A third study in healthy adults suggested that a link between reward sensitivity and striatal activation during reward anticipation is only present in 10R/10R individuals, and is lost in 9R-carriers (Hahn et al., 2011). In studies of response inhibition in children/adolescents, the 10R/10R genotype was found linked to lower (Durston et al., 2008) but also higher (Bedard et al., 2010) striatal activation. Methylphenidate was able to increase activity in the caudate nucleus (as well as a thalamocortical network and inferior frontal gyrus) during successful inhibition in healthy adult male 9R-carriers, but decreased activity in 10R/10R individuals (Kasparbauer et al., 2015). A working memory task in healthy adults elicited more activation in fronto-striatal-parietal regions in 9R/10R individuals under high memory load (Stollstorff et al., 2010). Additionally, a resting-state fMRI study in healthy adults showed stronger connectivity between midbrain (mainly striatal) and prefrontal regions in 9R/10R heterozygotes compared with 10R/10R homozygotes (Gordon et al., 2015).

Beyond striatum, *SLC6A3/DAT1* genotype effects have also been observed in fMRI studies of cortical regions, especially (pre)frontal, medial (pre-SMA, dorsal ACC), and (temporo)parietal regions (Bedard et al., 2010; Braet et al., 2011) (Table IV and VI). As expression of DAT is limited outside of striatum and cerebellum, these effects are likely due to direct or indirect connections between the regions of gene expression and the rest of the brain. This is in line with the fact that no effect of *SLC6A3/DAT1* genotype on cortical development has been observed in a longitudinal study (Shaw et al., 2007). Of particular interest might be studies showing effects of *SLC6A3/DAT1* genotype on amygdala reactivity upon exposure to threatening faces (Bergman et al., 2014) as well as on cerebellar activation during response inhibition (Durston et al., 2008). These regions are currently understudied in ADHD. A first study using DTI did not suggest a strong effect of *SLC6A3/DAT1* genotype on structural brain connectivity (Hong et al., 2015) (Table IV).

In summary, although *SLC6A3/DAT1* is one of the best-studied genes in imaging genetics literature covered in this review, existing studies do not yet clarify sufficiently the role of ADHD-linked genetic variation in brain activity and connectivity related to symptoms/cognitive deficits or their structural brain correlates. A complicating matter for this gene is the switch in ADHD risk allele from childhood to adulthood. Furthermore, interactions between genotype and diagnosis are observed in some studies, which suggest that studying effects of *SLC6A3/DAT1* in healthy individuals will not suffice to fully understand the brain mechanisms linking this gene to ADHD.

The **dopamine D2 receptor** gene (*DRD2*) codes for a G protein-coupled receptor, which inhibits adenylate cyclase (Andersen et al., 1990). Consistent with its broad expression in the brain being highest in striatum, *DRD2* plays a key role in regulating mesolimbic reward processing pathways (Usiello et al., 2000) and is also implicated in other cognitive domains, such as cognitive flexibility and learning (Puig et al., 2014). The gene has been implicated in many different psychiatric disorders, including schizophrenia and substance use disorders (Patriquin et al., 2015; Schizophrenia Working Group of the Psychiatric Genomics 2014) and is the target of several antipsychotics (Moore et al., 2014). The risk factor for ADHD is the most frequently investigated common genetic variant of *DRD2* rs1800497 (also known as Taq1A restriction fragment length polymorphism). This SNP actually lies downstream of *DRD2* in an exon of a neighboring gene, *ANKK1* (Neville et al., 2004). It affects dopamine D2 receptor expression and striatal dopamine metabolism, with the A1-allele (the ADHD risk allele) reducing the number of *DRD2* receptors (Laakso et al., 2005). No studies in ADHD case-control design are yet available for *DRD2*. The risk SNP has, however, been investigated in healthy individuals using structural and functional MRI covering the cognitive domains of reward processing, task-switching and reversal learning, working memory, emotion recognition, and language (Table IV and VI).

Structural MRI showed that the SNP affects the volume of midbrain structures, with A1-allele carriers having smaller volumes of substantia nigra (Cerasa et al., 2009), cerebellum (Wiener et al., 2014), and ACC (in interaction with *BDNF*; (Montag et al., 2010)).

Functional MRI during reversal learning tasks revealed that A1-allele carriers showed reduced response of the rostral cingulate to negative feedback and had a reduced recruitment of the right ventral striatum and right lateral occipital frontal cortex (OFC) during reversals (Jocham et al., 2009). Pharmacological fMRI in a reversal learning task showed that cabergoline (D2 receptor agonist) administration induced an allele-specific response, where A1-allele carriers showed increased neural reward responses in medial OFC, cingulate cortex, and striatum (consistent with increased D2-mediated dopamine signaling); this was coupled, however, to worse task performance and lower fronto-striatal functional connectivity (Cohen et al., 2007). The reward-related paradigms showed that A1-allele carriers exhibited increased anterior insula (Richter et al., 2013) and increased nucleus accumbens activation, the latter observed only in a three-way interaction analysis looking for differences between a placebo and bromocriptine (D2 receptor agonist) administration condition (Kirsch et al., 2006). Two multi-locus studies including the *DRD2* Taq1A variant suggested higher activation during reward anticipation, but blunted activity during reward receipt with increasing number of risk factors (Table VI).

In summary, the effects of the ADHD risk factor in *DRD2* in fMRI appear to be relatively consistent across most of the studies currently available, with stronger brain activity in parts of the wider reward processing and memory/learning circuits. It seems that this stronger activity is linked to worse functional connectivity and/or performance, thus potentially reflecting compensatory processes. Currently, no data from patients with ADHD are available.

The **dopamine D4 receptor** (encoded by the *DRD4* gene) is another 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, 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).

Structural MRI suggested that patients with ADHD carrying the 7R-allele have smaller volumes of the superior frontal and cerebellar cortex (Monuteaux et al., 2008), while no differences were found in another study (Castellanos et al., 1998) (Table IV). Interestingly, carriership of the *DRD4* 7R-allele seemed to affect cortical development in a longitudinal study, with 7R-carriers showing thinner prefrontal and parietal cortex and ADHD patients with this allele having a distinct trajectory of cortical development characterized by normalization of parietal cortical regions (Shaw et al., 2007) (Table VI). Structural connectivity was investigated in two studies in Asians using DTI, and while one did not find effects for 4R homozygotes (Hong et al., 2015), a very large recent study reported widespread increases in mean diffusivity in 5R-carriers (Takeuchi et al., 2015) (Table IV).

With the role of the D4 dopamine receptor in cognition not sufficiently characterized yet, and *DRD4* being expressed in large parts of the cortex (predominantly in frontal lobe regions, such as the OFC and ACC (Floresco and Tse 2007; Noain et al., 2006)), fMRI studies have investigated the *DRD4* gene in healthy Caucasians covering different cognitive domains, i.e. emotion processing, response inhibition, reward, stimulus-response incompatibility, and time discrimination tasks, as summarized in Table IV. Depending on the type of paradigm used in the fMRI studies, *DRD4* genotype was found to modulate brain activity in prefrontal and temporal, but also in striatal and cerebellar brain regions in the healthy adults (Table IV).

Thus, though existing evidence does not support firm conclusions, *DRD4* may mark a particular developmental trajectory in cortical brain structure related to adult outcome of ADHD, and plays a role in structural connectivity. With only one fMRI study per cognitive domain published to date, no clear picture of *DRD4* action on brain activity emerges, but those studies do clearly indicate that *DRD4* (like *DAT1*) influences brain activity beyond its regions of expression, possibly due to its effects on white matter connectivity (Takeuchi et al., 2015).

The **serotonin transporter** gene (*SLC6A4*, *5HTT*, *SERT*) 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 regulation of serotonergic activity in the brain (Lesch et al., 1996). A functional polymorphism in the promoter region of the gene (referred to as 5HTTLPR) is 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). However, allele frequencies vary across different ethnic groups (Haberstick et al., 2015). A SNP in the long allele, rs25531, can modify the activity of this allele (Lesch et al., 1996). *SLC6A4/5HTT* has been implicated in emotion regulation

as well as (emotional) memory and learning processes (Araragi and Lesch 2013; Barzman et al., 2015; Meneses and Liy-Salmeron 2012). Expression of the transporter is observed 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).

Only one recent imaging genetics study in patients with ADHD has been performed for the 5HTTLPR, showing that stress exposure, which is associated with increased ADHD severity in S-allele carriers, was associated with reduced cortical gray matter volume in precentral gyrus, middle and superior frontal gyri, frontal pole, and cingulate gyrus in these individuals. Interestingly, 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. In sMRI studies in healthy individuals, the 5HTTLPR has been associated with volume of the ACC and amygdala as well as hippocampus, though the direction of effect seemed to differ with gender and/or in interaction with environmental factors (Table IV). Few studies have looked at effects of the 5HTTLPR on structural connectivity (Table IV). A large study observed reduced connectivity of amygdala with PFC in S-allele carriers (Long et al., 2013), while another reported increased hippocampus-putamen connectivity for this genotype group (Favaro et al., 2014).

Brain activation patterns in task-based fMRI have been studied extensively for the 5HTTLPR following hallmark studies by the Weinberger lab (Hariri et al., 2005; Hariri et al., 2002). They were the first to report increased activation of the amygdala in S-allele carriers in response to negative-emotional faces. Since then, increased amygdala activation has been observed in S-allele carriers in many tasks activating the amygdala (Table IV and VI). In 2013, 34 studies investigating effects of the 5HTTLPR on amygdala activation were meta-analyzed, confirming the increased activation in S-allele carriers (although only borderline significant) (Murphy et al., 2013). However, this meta-analysis also showed strong heterogeneity between studies and a potential publication bias (towards studies reporting significant associations). Linked to the increased activation seems to be a reduced functional connectivity of the amygdala, as first observed by Pezawas and colleagues (2005) and subsequently also seen in additional studies (Table IV). Not only the amygdala, but also other cortical and subcortical brain regions (forming the 'threat circuit') seem to be influenced by 5HTTLPR genotype. A recent, replicated fMRI study, for example, also showed stronger activity in dorsomedial prefrontal cortex (dmPFC), insula, thalamus, and regions of the midbrain, in reaction to threat in S-allele carriers (Klumpers et al., 2014); interestingly, also in this study (like in the one by van der Meer and coworkers (2015)) only some of the activated regions actually mediated the genotype effects on psychophysiological responsivity to pending threats (in this case the dmPFC activation, Table IV).

Increasing evidence suggests that S-allele carriers are hypervigilant to environmental stimuli (Homberg and Lesch 2011). Potential sustained effects of environmental factors have not sufficiently been addressed in imaging genetics studies published to date. Several studies have taken stressful life events into account, and these studies suggested effects on both brain volume and activation. Only one study to date has directly looked at methylation of the promoter of the *SLC6A4/5HTT* gene, and found correlations with the volume of several regions in the 'threat circuit' of the brain, though these appeared genotype-independent

(Dannlowski et al., 2014). Also a combined PET, sMRI plus fMRI study indicated that 5HTTLPR genotype did not influence current (midbrain) serotonin transporter availability (Kobiella et al., 2011), suggesting that other factors (like environmental ones) might overrule this effect. Taking into account epigenetic effects on the *SLC6A4/5HTT* gene might thus help explain the strong heterogeneity observed in the meta-analysis of amygdala reactivity studies (Murphy et al., 2013).

In summary, functional genetic variation in the *SLC6A4/5HTT* gene is clearly linked to emotion regulation through effects on brain activation in the amygdala and the wider 'threat circuit', with those carrying the risk factor for emotional dysregulation showing increased activation in tasks related to emotion processing and learning. Those experiments link reduced availability of the transporter (at some point in development) - and thus increased serotonin signaling capacity - to increased brain activation. This increased activation seems to be linked to functional dysconnectivity, however. Whether brain volume and structural integrity are influenced by the 5HTTLPR, remains to be clarified. Importantly, genotype effects are likely to be sensitive to environmental factors.

The **nitric oxide synthase 1** (encoded by the *NOS1* gene) is an enzyme which synthesizes nitric oxide from L-arginine. Nitric oxide is a reactive free radical, which acts as a biological mediator in several processes, including dopaminergic and serotonergic neurotransmission (Kiss and Vizi 2001). The *NOS1* gene has a complex structure, including 12 alternative untranslated first exons (exon 1a-1l). In exon 1f, a functional VNTR that affects gene expression has been linked to hyperactive and impulsive behavior in humans (Reif et al., 2009; Weber et al., 2015), with the short allele being the risk factor for ADHD. In addition, a recent *Nos1* knock-out mouse model showed dysregulation of rhythmic activities mimicking ADHD-like behaviors (Gao and Heldt 2015).

So far, only one case-control study investigated the effect of the VNTR polymorphism on the brain, in his case on reward-related ventral striatal activity (Hoogman et al., 2011) (Table IV). The study revealed that homozygous carriers of the short allele of *NOS1* demonstrated higher ventral striatal activity than carriers of the other *NOS1* VNTR genotypes (Hoogman et al., 2011). This effect was comparable for both patients and healthy individuals. Similar effects of the genotype were also observed for behavioral impulsivity, with those carrying the ADHD risk factor acting more impulsive than other participants.

Imaging genetics of candidate genes for autism spectrum disorders

A total of 193 records were retrieved for the ASD search terms, and a total of six research articles were eligible for review according to our criteria. All studies investigated a single gene and were performed in Caucasian populations. For studies in the healthy population, we obtained 120 records, and 17 were included in the review (Figure 1). Twelve of those investigated a single gene in a Caucasian study sample, and five studies used Asian samples (studies for *SLC6A4/5HTT* are included in the ADHD section above). Generally, the ASD case/control samples included mainly childhood and adolescent study samples, whereas the studies in healthy population samples mostly used samples of (young) adults. From the eleven genes selected and listed in Table V, imaging genetics studies could only be retrieved for genetic variants in *CNTNAP2*, *MET*, *OXTR*, and the *SLC6A4/5HTT* gene.

The **contactin-associated protein-like 2** (CASPR2), encoded by the gene *CNTNAP2* (the largest gene in the human genome), is a neural transmembrane protein involved in neuronal-glial interactions and in clustering K^+-channels in myelinated axons; as such, it is involved in neuronal cell adhesion, migration, and the formation of neuronal networks (Rodenas-Cuadrado et al., 2014). Several single nucleotide polymorphisms (SNPs) in *CNTNAP2* have been associated with ASDs. During human brain development, *CNTNAP2* expression is broad, with highest levels in frontal and anterior lobes, striatum, and dorsal thalamus. This cortico-striato-thalamic circuitry is important for higher order cognitive functions, including speech and language, reward, and frontal executive function (Rodenas-Cuadrado et al., 2014). This is reflected in the imaging genetics studies having been performed for *CNTNAP2*, which cover studies of brain volume and structural connectivity as well as brain activity and functional connectivity during tasks related to rewarded learning and language (Table V).

Two studies performed DTI in healthy individuals. For the SNP rs2710102 it was found that carriers of the CC risk genotype showed reduced overall path length and increased small-worldness of brain-wide structural connectivity, which appeared to be a general phenomenon rather than being localized to individual tracts (Dennis et al., 2011). A large study in healthy individuals combining sMRI with DTI for the SNP rs7794745 showed that carriers of the ASD risk genotype exhibited reduced gray and white matter volume as well as reduced white matter integrity in the cerebellum, fusiform gyrus, occipital and frontal cortices; distribution of reductions was found to be sex-specific (Tan et al., 2010).

In a case-control study, an association between the SNP rs2710102 and medial prefrontal cortex activation during a rewarded implicit learning task was found, when collapsing patients and controls into one group. The non-risk allele was linked to reduced activation. Furthermore, the risk carriers had more widespread and bilateral connectivity throughout the frontal cortex and anterior temporal poles. The latter finding was confirmed in an independent healthy sample (Scott-Van Zeeland et al., 2010). An additional fMRI study using a sentence completion paradigm showed that carriers of the risk genotype for one of two SNPs had increased activation of the IFG (Broca's area), the lateral temporal cortex, or right middle temporal gyrus (Whalley et al., 2011).

The **Met proto-oncogene** encoded by the *MET* gene is a cell surface receptor with tyrosine-kinase activity. In the forebrain, *MET* gene and protein expression is regulated in excitatory projection neurons during synaptogenesis (Judson et al., 2011) and is restricted to regions of temporal, occipital, and medial parietal cortex in humans. These regions are known to be of relevance to the processing of socially relevant information (Rudie et al., 2012). The effects of the ASD risk variant rs1858830 have been studied in two imaging genetics studies (Table V).

A case-control study combining fMRI (emotional face task), resting-state fMRI, and DTI modalities showed that the ASD risk genotype predicted wide-spread atypical brain activity patterns to social stimuli, with increased activation in amygdala and striatum, and impaired deactivation patterns in part of the default mode network (DMN) in the posterior cingulate cortex. In addition, reduced functional and structural connectivity was observed in temporo-

parietal regions belonging to the DMN suggesting altered white matter integrity. In general, the effects were more pronounced in the ASD group (Rudie et al., 2012). An sMRI study in a large sample of healthy individuals revealed that cortical thickness in temporal, pre- and postcentral gyri, anterior cingulate, and frontopolar cortex was reduced in risk-allele carriers, with reductions increasing with increasing number of risk alleles (Hedrick et al., 2012).

The **oxytocin receptor** (*OXTR*) gene encodes the receptor protein for oxytocin, which has an important role in the regulation of social cognition and behavior (Meyer-Lindenberg et al., 2011). So far, no imaging genetic studies were performed for risk variants in the *OXTR* gene in ASD case-control samples, but twelve studies in healthy samples were found (Table V). Various different SNPs and combinations of those were investigated, not all related to ASD risk.

Two sMRI studies showed that adolescents homozygous for the rs2254298 risk factor for psychopathology displayed an overall increased gray matter volume, but a decreased amygdala volume (Furman et al., 2011); for carriers of the rs53576 SNP, a risk factor for disorders associated with social impairment, a smaller hypothalamus gray matter volume was reported in healthy adults (Tost et al., 2010).

Functional MRI paradigms used to study *OXTR* all covered the cognitive domains of emotion processing and reward (Table V). In a face matching task, adult carriers of the rs53576 risk allele showed increased functional correlation of hypothalamus and amygdala during perceptual processing of facial emotion (Tost et al., 2010). Investigating a large group of 1445 healthy adolescents in a passive face viewing task for effects of 23 SNPs across *OXTR*, the IMAGEN Consortium found significant effects of one SNP on ventral striatal activity in a region of interest analysis. In the presence of stressful life events, this SNP modulated the occurrence of emotional problems in the participants, linking more emotional problems to reduced striatal activation; no effects of the risk variants for ASD were observed (Loth et al., 2014). A study of brain regions related to processing of social stimuli observed increased functional connectivity between such regions in adult carriers of the risk genotype for rs53576 (Verbeke et al., 2013). Functional MRI of mesolimbic structures during reward processing was modulated by the rs2268493 risk factor for ASD: young adult carriers of the risk genotype showed reduced activation in mesolimbic reward circuitry (nucleus accumbens, amygdala, insula, thalamus, and prefrontal cortical regions) during the anticipation of rewards but not during reward receipt (Damiano et al., 2014). Using a mother-child interaction task, Michalska and coworkers (2014) showed that females carrying the ASD risk genotypes for rs53576 or rs1042778 had lower brain activity in OFC, ACC, and hippocampus in response to child stimuli. When healthy adult females were tested for empathic response and associated brain activation, carriers of the rs2254298 risk factor for psychopathology showed increased responsiveness of the superior temporal sulcus to observed pain (Laursen et al., 2014). In a pharmacologic imaging genetics study in adult males, one of three SNPs modulated the response of the amygdala (only) after oxytocin inhalation, with increased activation to directed gaze and decreased activation to averted gaze under oxytocin in the carriers of the variant allele (Montag et al., 2013). This study did not find any effects of rs2254298 on brain activation.

In summary, genetic variation in the *OXTR* gene has been linked to brain activation during emotional processing. Risk factors for ASD/psychopathology appear to reduce activation during most relevant paradigms, but may increase functional connectivity during those tasks.

Four ASD case-control imaging genetics studies investigated the gene encoding the **serotonin transporter** gene (*SLC6A4*, *5HTT*) in addition to those in healthy individuals (and ADHD case-control samples) described in the section on ADHD candidate genes. Structural MRI, fMRI, and rs-fMRI were used to study the effect of either only the 5HTTLPR or the combination of this variant with rs25531 (Table V).

Whereas a VBM study did not reveal an association between total gray or white matter volume and genotype in adult patients (Raznahan et al., 2009), another sMRI study showed that in 2–4 year old boys with ASD, carriers of the 5HTTLPR S-allele had increased total cortical and frontal lobe gray matter volume (Wassink et al., 2007), suggesting an age-dependent effect of the variant.

The fMRI and rs-fMRI study, performed in overlapping samples of adolescent patients and controls, showed that carriers of alleles that mark low gene expression had increased amygdala activation during an emotional face task, an effect that was observed only in the patients (Wiggins et al., 2014b), and increased posterior-anterior connectivity during a resting-state condition in patients, where the converse was observed in the healthy group (Wiggins et al., 2012).

The findings of those case-control studies are not easily reconciled with those observed in healthy individuals (Table IV and VI), and indeed the latter two studies suggest the existence of differential effects in patients and healthy individuals.

Imaging genetics in selected intellectual disability disorders

A total of 579 records were retrieved for the ID syndromes of interest. Eighty research articles were eligible for review according to our criteria, 30 for fragile X syndrome, 24 for neurofibromatosis type 1, 22 for tuberous sclerosis complex, and four for Rett syndrome (Figure 1). No imaging studies of Timothy syndrome patients were uncovered by our search term. The reviewed imaging genetics studies in ID syndromes are presented in Table VII.

The **fragile X mental retardation 1** gene (*FMR1*) is located on the X chromosome and codes for fragile X mental retardation protein. Large expansions of a CGG repeat (>200 repeats) in the 5'- untranslated (5'UTR) region of the gene, leading to protein deficiency, are the cause of fragile X syndrome (FXS). FMR1 has a prominent role in synaptic plasticity and maturation (Saldarriaga et al., 2014). In studies including participants with the *FMR1* full mutation, brain structure was most often investigated, followed by task-based brain activation (Table VII). A few studies investigated brain structural integrity and resting-state functional connectivity. Several studies compared individuals with FXS with and without ASD or included an idiopathic autism or IQ-matched group (Table VII).

The most robust finding in investigations of brain structure in FXS is an increased caudate nucleus volume. This enlargement was observed early in development (Hazlett et al., 2009),

throughout adolescence (Bray et al., 2011; Hall et al., 2013; Lee et al., 2007) as well as in adult samples (Hallahan et al., 2011; Molnar and Keri 2014; Wilson et al., 2009). Studies comparing individuals with FXS and with ASD found increased caudate volumes in children and adults with FXS compared to children/adults with idiopathic autism (Hazlett et al., 2009; Wilson et al., 2009). Consistent volumetric abnormalities have also been found for cerebellar regions in FXS; a reduction in the volume was observed in both children and adults with FXS (Hazlett et al., 2012; Hoeft et al., 2008; Wilson et al., 2009). Several studies found cerebellar volumes to be larger in children and adults with FXS relative to individuals with autism, in whom reduced volume of cerebellar regions compared to control subjects is often seen as well (Hazlett et al., 2012; Wilson et al., 2009). Few studies have investigated white matter integrity in people with the full *FMR1* mutation, and deficits seem most prominent in fronto-striatal connections. Increased density of fibers was found in the left ventral fronto-striatal pathway in boys with FXS compared to typically developing and developmentally delayed controls (Haas et al., 2009), and differences in white matter in frontal-caudate circuits were found in females with FXS compared to controls (Barnea-Goraly et al., 2003). More widespread reductions in white matter integrity have also been observed (Villalon-Reina et al., 2013).

Cognitive and psychiatric characteristics associated with FXS include poor eye contact, repetitive motor behavior, language deficits, inattention, hyperactivity, inhibition, and anxiety (Saldarriaga et al., 2014). Functional neuroimaging studies have focused on these deficits, with a main focus on poor eye contact and behavioral inhibition. Several fMRI studies have investigated the circuitry underlying face/gaze processing in subjects with FXS, as eye-gaze avoidance is common in this population. Abnormal activation was found in several regions, including superior temporal gyrus and fusiform gyrus (Garrett et al., 2004), amygdala and insula (Watson et al., 2008), regions within the ventrolateral prefrontal cortex (vlPFC) (Holsen et al., 2008), and frontal cortex and cingulate and fusiform gyri (Bruno et al., 2014). These regions are associated with visual processing, social cognition, emotion processing, and executive functioning, indicating that eye-gaze avoidance in FXS may be linked to social anxiety. Investigating attention and inhibition, a study using a Go/No-go task found that boys with FXS show reduced activation in the right vlPFC and caudate head. The authors suggested that defective fronto-striatal signaling is a key feature of FXS, leading to impairments in executive functioning (Hoeft et al., 2007), which is in line with the altered white matter connectivity in fronto-striatal connections, described above.

The **neurofibromin 1** gene (*NF1*) located on chromosome 17q11.2 codes for neurofibromin, a protein which is thought to be a regulator of the RAS signal transduction pathway and necessary for embryonic development. Neurofibromatosis type 1 (NF1) is caused by mutations in the gene, often leading to the synthesis of truncated or otherwise non-functional proteins. We found 14 studies investigating effects of *NF1* on brain structure and four investigating brain function. Additional studies of brain structural and functional connectivity have been conducted. While most studies included children and adolescents, a few studies have included adults as well (Duarte et al., 2014; Karlsgodt et al., 2012; Pride et al., 2014; Violante et al., 2012; Wignall et al., 2010; Zamboni et al., 2007) (Table VII).

The structural brain abnormalities most commonly seen in subjects with NF1 are T2 hyperintensities and an increased brain volume. T2 hyperintensities are areas of high signal intensity on T2-weighted MR images also referred to as 'unidentified bright objects' (UBOs). Although their association with cognitive and intellectual deficits remains controversial, thalamic hyperintensities have repeatedly been associated with cognitive impairments (Payne et al., 2010). Multiple studies have investigated the characteristics of UBOs. UBOs are found in almost all children with NF1, but reports on whether their volume and number increases or decreases with age are inconsistent (Gill et al., 2006; Griffiths et al., 1999; Kraut et al., 2004). A few studies have used diffusion tensor imaging (DTI) to characterize white matter microstructure and integrity of UBOs by measuring the degree and directionality of diffusivity. Higher apparent diffusion coefficient (ADC) and (radial) diffusivity values and lower fractional anisotropy (FA) values have been found in UBOs compared to normal appearing white matter (Ertan et al., 2014; van Engelen et al., 2008). These findings can be explained by myelin deficiency and axonal damage. An increase in brain volume is observed in children with NF1, which was found to be due to increases in white matter volume (Said et al., 1996; Steen et al., 2001), gray matter volume (with an increased gray to white matter ratio especially in younger subjects (Moore et al., 2000)), or both gray and white matter volume (Karlsgodt et al., 2012). These volume increases involve temporal, parietal, occipital, and frontal regions (Duarte et al., 2014; Greenwood et al., 2005; Pride et al., 2014). In addition, the corpus callosum seems larger in cases compared to controls, which has been found in children with NF1 as well as adults, marking it as a robust finding for NF1 (Duarte et al., 2014; Moore et al., 2000; Violante et al., 2013; Wignall et al., 2010). In addition to the investigation of UBOs, DTI studies have been used to study microstructural integrity in NF1 more broadly. Increased ADC values (Ertan et al., 2014; Nicita et al., 2014; van Engelen et al., 2008) and decreased FA values (Ertan et al., 2014; Ferraz-Filho et al., 2012) are found widespread across the brain. Karlsgodt et al. also found increased radial diffusion, which may be explained by decreased myelination or axonal packing density (2012). Differences in radial diffusivity have also been observed at the genu and anterior body of the corpus callosum (Wignall et al., 2010). The change in corpus callosum size and connectivity observed in NF1 may have functional importance, as they have been associated with academic achievement and visual-spatial and motor skills (Moore et al., 2000).

Three fMRI studies have investigated visual-spatial processing in subjects with NF1, and one study investigated phonologic processing (Table VII). During visual-spatial processing, decreased activation in the primary visual cortex was found for individuals with NF1 compared to controls (Clements-Stephens et al., 2008), although an earlier study reported contrasting findings of increased posterior (occipital) cortex activation relative to lateral/inferior frontal activation (Billingsley et al., 2004). A later study did confirm that both children and adults with NF1 showed deficient activation of the low-level visual cortex during tasks specifically designed to activate magnocellular and parvocellular pathways (Violante et al., 2012). During such magnocellular-biased stimulation, NF1 patients did not deactivate regions belonging to the brain default-mode network as would be expected during cognitively demanding tasks (Violante et al., 2012).

The tumor growth suppressor genes **tuberous sclerosis 1** (*TSC1*) and **tuberous sclerosis 2** (*TSC2*) code for the hamartin and tuberin proteins, respectively. Mutations in either *TSC1* or *TSC2* disrupt the function of the GTPase-activating protein (GAP) complex formed by these proteins that regulates mTOR signaling. The neurocutaneous syndrome tuberous sclerosis complex (TSC), characterized by benign hamartomas in multiple organ systems, is caused primarily by these mutations. In the brain, the hamartomas manifest as subendymal giant cell astrocytomas, subendymal nodules (SEN), and tubers. Tubers show disrupted cortical architecture and contain a number of atypical cells. For TSC, structural MRI and DTI studies have been conducted investigating both typical neuropathological lesions, especially tubers, and normal-appearing brain matter (Table VII). A consistent imaging determinant of the cognitive phenotype in TSC has not been established. Findings of an inverse correlation of tuber number and cognitive functioning have not been consistent (Ridler et al., 2004). Tuber/brain proportion may be a better predictor of IQ than tuber load, although the age of seizure onset in patients seemed to predict cognitive functioning best (Jansen et al., 2008). However, abnormal brain structure and connectivity unrelated to tubers are likely also important factors contributing to the neurobehavioral abnormalities in TSC. Decreased white matter volume of major intrahemispheric tracts has been found in adults with TSC compared to age-matched controls, as has a decrease of gray matter volume in several cortical and subcortical structures (Ridler et al., 2001; Ridler et al., 2007). Reduced volume in the cerebellum has been associated with tuber-associated loss of the underlying parenchyma (Jurkiewicz et al., 2006; Marti-Bonmati et al., 2000). Reduced cerebellar volume was observed in all cerebellar regions in a more recent study, with strongest volume reductions in patients with a mutation in *TSC2* (Weisenfeld et al., 2013). The finding of reduced cerebellar volume is in line with mouse models showing cerebellar involvement in TSC (Reith et al., 2011). White matter abnormalities are another typical finding in TSC. DTI studies generally report increased ADC values and decreased FA values in individuals with TSC compared to controls, in tubers and white matter lesions, but also in other white matter portions (Table VII). Compared to contralateral white matter or white matter in control subjects, increased ADC values were found in cortical tubers, and higher ADC and lower FA values were found in white matter lesions (Piao et al., 2009). A recent study also found increased radial diffusivity values and decreased FA values in cortical tubers and white matter lesions (Dogan et al., 2015). Hypomyelination, gliosis, and heterotopic cells may lead to ADC and FA changes observed in such lesions (Alexander et al., 2007). Abnormalities have also been reported in normal-appearing white matter in individuals with TSC compared to control groups. Decreased FA and increased ADC, especially in corpus callosum and internal and external capsules, have been reported repeatedly (Krishnan et al., 2010; Peters et al., 2012; Simao et al., 2010). A recent whole-brain analysis of white matter connectivity showed that increased radial diffusivity exists throughout the brains of TSC patients and that interhemispheric connectivity is decreased (Im et al., 2015).

The **methyl CpG binding protein 2** gene (*MECP2*) is located on the short arm of chromosome X (Xq28) and codes for the protein MECP2. MECP2 acts as a modifier of gene expression and is highly expressed in the brain. Mutations in *MECP2* are the cause of Rett syndrome, a disorder primarily affecting female patients. Brain weight is reduced in Rett syndrome, particularly that of cerebral hemispheres. Although the anatomical basis for this

reduction is not completely clear, it has been suggested that it is caused by defective neuronal maturation for which MECP2 is essential, rather than by atrophy (Armstrong 2005). Only few imaging studies have been conducted in series of patients with Rett syndrome (Table VII). All investigated brain structure in girls. These studies confirmed a wide-spread reduction in cerebral white and gray matter volumes, the latter most pronounced in subcortical nuclei including the caudate nucleus and in prefrontal, posterior-frontal, and anterior-temporal (Reiss et al., 1993; Subramaniam et al., 1997) and parietal regions (Carter et al., 2008). Using DTI, evidence of reduced white matter integrity was found in frontal regions, corpus callosum, and internal capsule. FA was also reduced in the superior longitudinal fasciculus, but only in patients who had little or no ability to speak (Mahmood et al., 2010).

Discussion

In this review, we set out to summarize the literature on imaging genetics studies in neurodevelopmental disorders. This being a very broad field, we focused on three most frequent and often comorbid disorder spectra, ADHD, ASDs, and selected forms of ID, and we only considered MRI-based imaging genetics studies. Further restriction of the search space was achieved by focusing on genes harboring common genetic variants with the most consistent evidence for association with ADHD and ASDs, and by selecting five relatively common ID disorders with frequent ADHD/ASDs comorbidity implicating single genes. The review was driven by the wish to learn more about the mechanisms by which genetic factors influence disease-related behavior specific to the individual disorders and their clinical overlap.

At the level of the individual genes, the most extensively studied candidate gene is the *SLC6A4* (*5HTT*) gene encoding the serotonin transporter (associated with both ADHD and ASDs). Limitations regarding power of individual studies and hypothesis-driven designs aside, the fMRI-based imaging genetics literature on this gene does show a remarkably coherent picture of functional genetic variation leading to hyperactivation of the amygdala and connected areas in conjunction with functional dysconnectivity amongst those areas. However, since much of this research has been performed in healthy individuals only, the link to cognition in ADHD and ASD patients needs further investigation. Findings for *SLC6A3* (*DAT1*) and *DRD4*, which have also been studied quite often already, still lack the consistency observed for *SLC6A4* (*5HTT*), partly due to the much less restricted focus on a particular cognitive domain, and thus more 'patchy' literature.

The most consistent findings observed in all of the imaging genetics literature reviewed here are for the different genetic variants for ID. This is likely linked to the severity of the variants present in the patients, with those for ID being rare and most damaging. Consistent are finding for increased caudate volume and reduced cerebellum due to *FMR1* mutations, and for T2 hyperintensities and increased brain volume in patients carrying *NF1* mutations. However, in terms of finding overlap between different forms of ID, we find that conclusiveness of studies still is limited, as most concentrated on a limited set of (often non-overlapping) features. Tubers and T2 hyperintensities have received a lot of attention in studies of TSC and NF1, for example, although reports on their contribution to cognitive

deficits are inconsistent. In recent years, DTI studies have produced evidence that tissue microstructure and white matter connectivity patterns are affected in all ID disorders, and often in widespread brain areas. Effects on brain volumes are also often widespread, but can go in opposite directions, with reductions in total brain volume in Rett, but increases in NF1. One may conclude that while altered (structural) connectivity is likely to play a role in ID etiology, MRI at its current resolution (1.5 – 4 Tesla), does not allow a sufficiently detailed view on the brain to understand the neuroanatomical overlap between disorders (Williams and Casanova 2011).

Similar to the situation amongst the ID disorders, there seems to be little overlap between the findings for different genes in ADHD or ASD. This is likely to be heavily influenced by the strong focus on regions and cognitive domains of interest (consistent with the limited power of many of the studies published to date). Some overlap is seen, e.g., for *DAT1* and *DRD2*, both of which have been studied for their effects on striatal phenotypes. (Appropriately powered) brain-wide studies and phenome-wide association study (PheWAS)/RDoc-like approaches (Cuthbert and Insel 2013; Pendergrass et al., 2011) would help to determine, whether the apparent specificity of brain phenotypes for individual genes is real. An important observation is that gene expression does not predict/limit the location of effects of a genetic factor (e.g., *SLC6A3/DAT1* shows effects outside of its region of gene expression), most likely through effects on structural and/or functional connectivity.

Did the reported imaging genetics findings help us understand the comorbidity between different neurodevelopmental disorders? This would be expected, since several of the genes implicated in ID, ASD, and ADHD function in the same or overlapping molecular networks (Poelmans et al., 2011; Rudie et al., 2012; van Bokhoven 2011). However, the limited availability of genes investigated through imaging genetics to date might bias our interpretation of the data. In ID, the genes studied thus far are related to mTOR signaling, RAS signaling, and translation repression/regulation, thus functioning in very 'basal' cell signaling pathways in comparison to the genes investigated for ADHD, which regulate the dopamine and serotonin neurotransmitter systems specifically. This could explain the much more widespread cell proliferation/migration defects observed in ID, whereas in ADHD defects seem more specific, e.g. limited to individual neurotransmitter systems and or affecting cell-cell communication more acutely. ASD seems to be intermediate between the other two disorder spectra, but more studies are necessary to substantiate this view. What is already very clear from the available studies, is that the associations of genetic factors are with behavioral traits, and not with the disorders directly (e.g., (Hoogman et al., 2011). Some level of pleiotropy is highly likely, which may also form the basis of comorbidity between the neurodevelopmental disorders.

In general, we found the existing imaging genetics literature for the three neurodevelopmental disorders of our interest lacking in several aspects. Firstly, despite our focus on well-supported candidate genes, several of the selected genes had not been studied at all with MRI in humans. In several additional cases, only single studies were available for different MRI modalities (sMRI, DTI, fMRI), thus limiting the conclusiveness of the reported findings. Secondly, most imaging genetics studies, especially the earlier ones, suffer from being underpowered. The small sample sizes are severely hampering the generalization

of findings to the population the samples are meant to represent (Button et al., 2013). Although the endophenotype concept postulates that measures, which mediate a genetic effect on behavior (including some of those investigated in the imaging genetics studies), should have stronger effect sizes for gene effects than the behavioral/disease measures (Gottesman and Gould 2003), the sample size of most studies would still have to be considered too small. The problem of limited number of samples becomes evident from e.g. a recent review by Strike and coworkers. They showed that at the most lenient threshold for significance ($\alpha = 0.05$) studies with at least 1,566 participants would be needed to achieve the canonical 80% power threshold to detect a reasonable effect size (0.5% of the phenotypic variance explained) (Strike et al., 2015). Furthermore, recent work raises doubts about whether larger effect sizes can really be expected for neuroimaging (endo)phenotypes, at least for volumetric MRI measures (Franke et al., 2016; Hibar et al., 2015b). Major challenges are the large inconsistency across genetic variants tested and genotype groups compared, differences in study designs and imaging modalities, and the fact that data acquisition and analysis protocols usually were not standardized across studies. Additionally, we observed large inconsistency across studies in the way how genotypic effects were reported and recommend a standardized way of reporting results, e.g. including at least effect estimates and standard errors. Nevertheless, meta-analyses are strongly needed in order to enable definition of robust findings and realistic effect estimates. Therefore, meta-analytic studies would be beneficial for those brain measures covered by multiple studies, as it was shown for the effect of the serotonin transporter 5HTTLPR on amygdala activation (Murphy et al., 2013). Thirdly, to interpret observed links between genes, brain, and behavior properly, one needs to determine, whether a brain (endo)phenotype is really intermediate between a genetic factor and a behavioral outcome, or if it is only an epiphenomenon unrelated to the behavior of interest (Kendler and Neale 2010; Preacher and Hayes 2008). Only few studies have really studied this, e.g. by mediation analysis including environmental, behavioral, and/or physiological variables (Klumpers et al., 2014; van der Meer et al., 2015), by applying combinations of different imaging modalities (Kobiella et al., 2011; Zhang et al., 2015), or by using causal modeling (Sokolova et al., 2015). The results of those studies show that only part of the brain regions showing genotype effects actually do mediate between genetics and behavior, proving the importance of such multilevel investigations. Fourthly, age effects might also be of importance, but have been neglected in most studies. Our own work has shown, for example, that the risk factor for ADHD in *DAT1* differs between children and adults, which resulted in effects of the 9–6 VNTR haplotype on caudate nucleus volume only in adult patients (Onnink et al., 2016). Age effects have also been observed for the 5-HTTLPR variant (Wiggins et al., 2014a). Fifthly, current brain imaging genetics studies often suffer from additional limitations, such as the low ethnic diversity, as most studies included cohorts of only Caucasian origin, and gender imbalance, especially in studies of childhood ADHD and ASD that showed an over-representation of males.

An important additional aspect is that this review enabled us to look at the overlap between studies in healthy individuals and those in patients (case-control designs). An interaction between genetic variant and diagnosis was indeed observed in some studies (e.g. (Durston et al., 2008; Monuteaux et al., 2008; Wiggins et al., 2012; Wiggins et al., 2014b). With the

available limited amount of evidence it is hard to judge though, whether this is a true difference between patients and healthy individuals, or whether it is simply due to power restrictions in the samples investigated. Recent genome-wide studies investigating the genetics of brain structure as part of the ENIGMA Consortium (Thompson et al., 2014) suggest that effects are largely similar for healthy individuals and those with a psychiatric disorder (Hibar et al., 2015b; Stein et al., 2012). This means, that brain imaging genetics studies with healthy participants can be very informative in discovering related brain correlates and in understanding the biological mechanisms leading to diseases of interest.

Did we overlook important literature through the choices made in our review? We did restrict our selection of genes to study. For ASD, we did not include genes harboring rare genetic variants, while those might result in stronger effect sizes, as observed for the ID genes. However, most of the rare variants linked to ASD have only recently been identified, making the availability of imaging genetics studies (with 10 or more cases) unlikely. A similar argument holds true for our selection of ID genes, where the imaging genetics literature is largely focused on the relatively common disorder subtypes we included in our study. We also restricted our search to MRI-based studies, following a first screen of the literature showing that this was the predominant method used for imaging genetics studies of the neurodevelopmental disorders. Nevertheless, for several genes/variants, also other imaging modalities have been employed, which may provide additional insights. EEG and MEG offer a much higher time resolution than MRI, and may allow investigation of genetic influences on neuronal functioning and oscillation patterns. PET can provide information on (acute) protein availability. Especially the integration of modalities in the study of individual participants can provide deeper insights into mechanisms (e.g. (Kobiella et al., 2011)). Moreover, future studies might want to investigate additional comorbid neurodevelopmental disorders, such as conduct disorder (CD) or obsessive-compulsive disorder (OCD), once robust association of genetic variants with these disorders has been established and investigated in imaging genetics studies.

To summarize, despite the considerable numbers of imaging genetics studies in neurodevelopmental disorders available for review, this field of research should still be considered in its early stages. More genes need to be studied, and individual genes need to be investigated in larger samples, with more hypothesis-generating brain- and phenome-wide methods. Gene-environment interactions and age effects should be taken into account. While we see consistent findings for single genes and variants, gene-wide and gene-set analyses, with polygenic scores explaining more phenotypic variance and thus improving study power (Bralten et al., 2011), are likely to take the stage in the future. Several early examples reviewed here already show the promise of this work (e.g. (Nikolova et al., 2011; Passamonti et al., 2008; Stice et al., 2012). As the genes in such sets often show different gene expression patterns, (structural and functional) connectivity patterns are likely the best brain phenotypes to be studied with such approaches (see above). In the future, we are also likely to see studies approaching imaging genetics in a different way, by asking the question, whether genes contributing to brain structure/function observed in hypothesis-free, genome-wide approaches also contribute to disease-related phenotypes (Franke et al., 2016). First studies of this kind have been published for schizophrenia (Franke et al., 2016) and obsessive compulsive disorder (OCD) (Hibar et al., 2015a), based on results of findings from

the ENIGMA GWAS of brain structure (Hibar et al., 2015b; Stein et al., 2012). To successfully map the biological pathways from gene to disease, imaging genetics studies need to be combined with complementary approaches (Klein et al., in press). Recent examples for this are provided by studies by our own group, in which we investigated effects of ADHD-associated genes for their effects in the fruit fly *Drosophila melanogaster* (Klein et al., 2015; van der Voet et al., 2016), as well as the study by Jia and coworkers, in which the authors identified a genetic variant significantly associated with dysfunctional reward, a cognitive and affective deficit frequently observed in ADHD, then verified gene function in locomotion in the fruit fly model (Jia et al., 2016). In conclusion, although still in its early stages, results from studies available thus far already confirm that the imaging genetics approach is suitable to provide more insight into the link between genes, the brain, and behavior in neurodevelopmental disorders.

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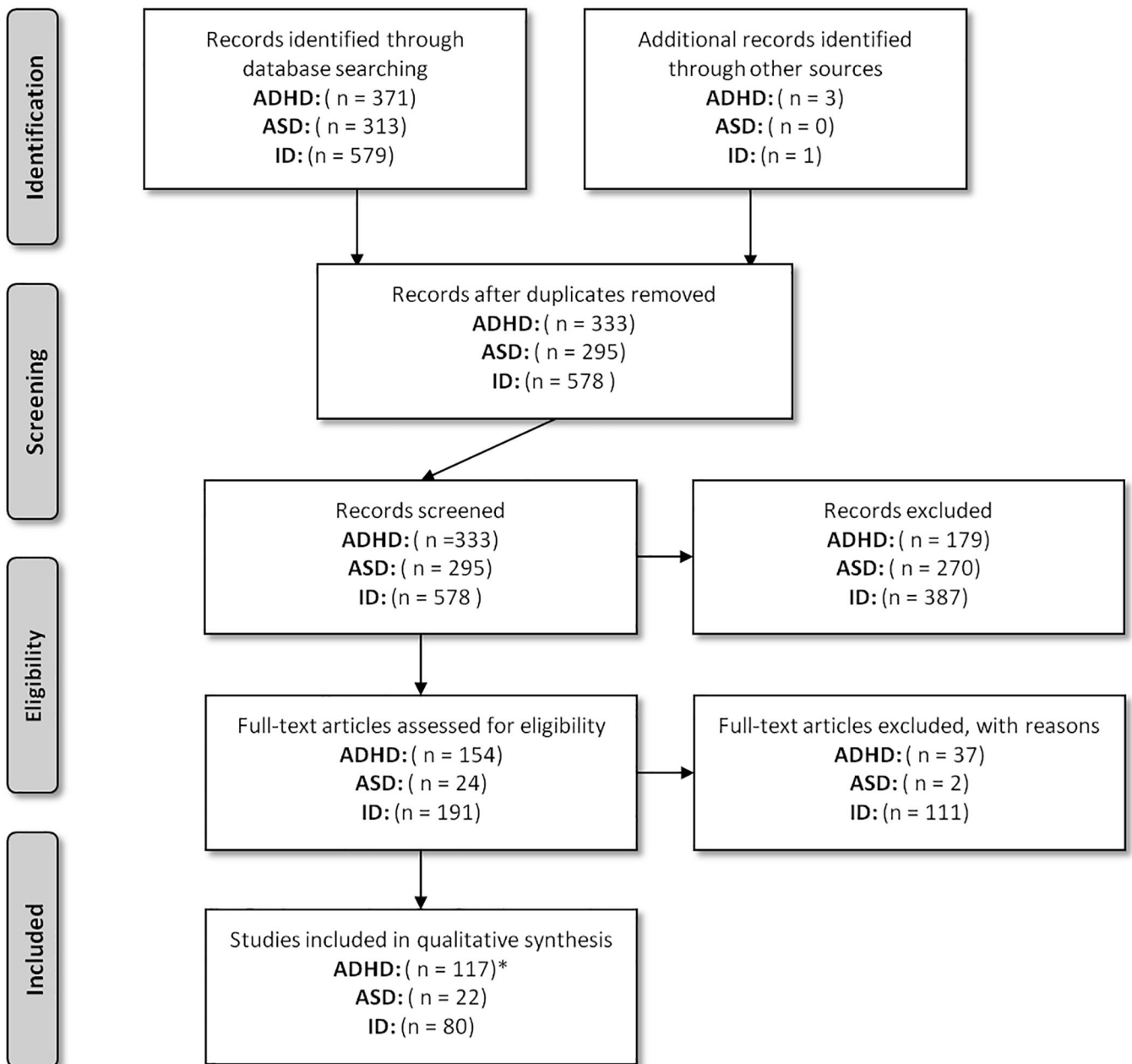
Figure 1.
Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) flowchart of the literature search and study selection for qualitative analysis. Note: see http://www.prismastatement.org/ for more information in this reporting system. ADHD = Attention-Deficit/Hyperactivity Disorder, ASD = Autism Spectrum Disorder, ID = Intellectual Disability. Records excluded for ID contain unrelated records identified by screening as well as records describing non-ID samples. * The number of studies for ADHD candidate genes also include the records for SLC6A4 (5-HTTLPR), which is also a candidate gene for ASD.

Table I:

Genes containing common variants most consistently implicated in ADHD, based on (Gizer et al. 2009) and more recent (meta-)analyses.

Gene	Protein	Associated variant/polymorphism	Risk allele	Location/chr position	References for reports of association with ADHD
DRD2/ANNK1*	Dopamine receptor D2/ Ankyrin repeat and kinase domain containing 1	Taq1A (rs1800497)	T allele = A1-allele	Exon 8/ 3' flanking/11q23	(Comings et al. 1991)[a]; (Pan et al. 2015)[b]
DRD4*	Dopamine receptor D4	**48 bp VNTR**	7 repeat (5 repeat in Asians)	Exon 3/11p15	(LaHoste et al. 1996)[a]; (Gizer et al. 2009)[b]; (Wu et al. 2012)[b]
		rs1800955	T allele	Promoter/11p15	(Barr et al. 2001)[a]; (Yang et al. 2008)[d]; (Gizer et al. 2009)[b]
DRD5	Dopamine receptor D5	**148 bp dinucleotide repeats**	148 bp allele	5' flanking/4p16	(Daly et al. 1999)[a]; (Gizer et al. 2009)[b]; (Wu et al. 2012)[b]
HTR1B	Serotonin receptor 1B, G protein-coupled	**rs6296**	G allele	Exon 1/6q14	(Hawi et al. 2002)[a]; (Gizer et al. 2009)[b]
LPHN3	Latrophilin 3	rs6551665	G allele	4q13	(Arcos-Burgos et al. 2010)[a]; (Hwang et al. 2015)[c]; (Ribases et al. 2011)[d]; (Labbe et al. 2012)[a]
		rs6858066	G allele		
NOS1*	Nitric oxide synthase 1	180–210 bp CA repeat	Short allele	Exon 1/12q24	(Reif et al. 2009)[a]; (Franke et al. 2009)[c]; (Weber et al. 2015)[b]
SLC6A3/DAT1*	Solute Carrier Family 6 (Neurotransmitter Transporter), Member 3; Dopamine transporter 1	**40 bp VNTR**	10 repeat	3' UTR/5p15	(Cook et al. 1995)[a]; (Gizer et al. 2009)[b]
		rs27072	G allele	3' UTR/5p15	(Galili-Weisstub and Segman 2003)[a]; (Gizer et al. 2009)[b]
		30 bp VNTR	6 repeat	Intron 8/5p15	(Brookes et al. 2006)[a]; (Gizer et al. 2009)[b]
SLC6A4/5HTT*	Solute carrier family 6 (neurotransmitter transporter), member 4; serotonin transporter	**5-HTTLPR**	Long allele	Promoter/17q11	(Manor et al. 2001)[a]; (Gizer et al. 2009)[b]; (Landaas et al. 2010)[b]
SLC9A9/NHE9	Solute Carrier Family 9, Subfamily A, Member 9	rs9810857	T allele	Region 3p14-q21	(de Silva et al. 2003)[a]; (Stergiakouli et al. 2012)[c]; (Mick et al. 2010)[c]
SNAP25	Synaptosomal-associated protein, 25kDa	**rs3746544**	T allele	3' UTR/20p12	(Brophy et al. 2002)[a]; (Gizer et al. 2009)[b]

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

[a] Association first reported by.

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[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; bp = base pair, chr = chromosome, CNV = copy number variation, UTR = untranslated region, VNTR = variable number tandem repeat; no imaging genetics studies found.

Table II:

Genes containing common variants most convincingly implicated in ASDs, adapted from Persico and Napolioni (2013). We added *CDH9, CDH10,* and *MSNP1AS,* because the locus harbouring these genes has shown genome-wide significant association with ASDs in GWAS (Prandini et al. 2012; Wang et al. 2009). Selection of candidate polymorphisms and risk alleles for ASD was based on recent research articles.

Gene	Protein	Associated variant/ polymorphism	Risk allele	Location/chr position	References for association with ASD
CDH9	Cadherin 9	rs4307059	C allele	Intergenic/5p14	(Wang et al. 2009)[a,c]; (Prandini et al. 2012)[d]
CDH10	Cadherin 10	rs4307059	C allele	Intergenic/5p14	(Wang et al. 2009)[a,c]; (Prandini et al. 2012)[d]
MSNP1AS	Moesin pseudogene 1, antisense	rs4307059	C allele	Intergenic/5p14	(Wang et al. 2009)[a,c]; (Prandini et al. 2012)[d]
CNTNAP2[*]	Contactin associated protein-like 2	rs7794745	T allele	Intron 2/7q35	(Arking et al. 2008)[a]; (Li et al. 2010)[d]
		rs2710102	C allele	Exon 8/7q35	(Stein et al. 2011)
EN2	Engrailed homeobox 2	rs1861972	G allele	Intron/7q36	(Gharani et al. 2004)[a]; (Benayed et al. 2005)[d]
		rs1861973	T allele	Intron/7q36	(Gharani et al. 2004)[a]; (Benayed et al. 2005)[d]
GABRB3	Gamma-aminobutyric acid (GABA) A receptor, beta 3	rs7171512	G allele	Intron/15q12	(Warrier et al. 2013)[a]
		rs7180158 (AS)	G allele	Intron/15q12	(Warrier et al. 2013)[a]
		rs7165604 (AS)	T allele	Intron/15q12	(Warrier et al. 2013)[a]
		rs12593579 (AS)	C allele	Intron/15q12	(Warrier et al. 2013)[a]
		rs9806546 (EQ)	G allele	Intron/15q12	(Warrier et al. 2013)[a]
		rs11636966 (EQ)	T allele	Intron/15q12	(Warrier et al. 2013)[a]
ITGB3	Integrin, beta 3 (platelet glycoprotein IIIa, antigen CD61)	rs12603582	T allele	Intron 11/17q21.32	(Napolioni et al. 2011)[a]; (Schuch et al. 2014)[d]
		rs15908	A allele	Exon 9/17q21.32	(Schuch et al. 2014)[a]
MET[*]	Met proto-oncogene (hepatocyte growth factor receptor)	rs1858830	C allele	Promoter/7q31	(Campbell et al. 2006)[a]; (Sousa et al. 2009)[d]; (Thanseem et al. 2010)[d]; (Zhou et al. 2011)[d]

Gene	Protein	Associated variant/ polymorphism	Risk allele	Location/chr position	References for association with ASD
OXTR	Oxytocin receptor	rs7632287	A allele	3′ flanking/3p25	(Tansey et al. 2010) [a]; (LoParo and Waldman 2014) [b]; (Campbell et al. 2011) [d]
		rs237887	A allele	Intron3/3p25	(Liu et al. 2010) [a]; (LoParo and Waldman 2014) [b]
		rs2268491	T allele	Intron3/3p25	(Liu et al. 2010) [a]; (LoParo and Waldman 2014) [b]
		rs2254298	A allele	Intron3/3p25	(Wu et al. 2005) [a]; (LoParo and Waldman 2014) [b]; (Liu et al. 2010) [d]; (Nyffeler et al. 2014) [d]
		rs2268493	C allele	Intron3/3p25	(Yrigollen et al. 2008) [a]; (Campbell et al. 2011) [d]; (Di Napoli et al. 2014) [d]
		rs53576	A allele	Intron3/3p25	(Wu et al. 2005) [a]; (Nyffeler et al. 2014) [d]
		rs2268494	T allele	Intron3/3p25	(Lerer et al. 2008) [a]
RELN	Reelin	rs362691	Population specific?	Exon 22/7q22	(Wang et al. 2014) [b]
		rs362780	G allele	Intron 41/7q22	(Holt et al. 2010) [a]
		rs736707	Population specific?	Intron 59/7q22	(Sharma et al. 2013) [a]
		rs2073559	T allele	Intron 11/7q22	(Ashley-Koch et al. 2007) [a]
SLC6A4/5HTT[*]	Serotonin transporter	5-HTTLPR	Long allele	Promoter/17q11.2	(Nyffeler et al. 2014) [d]; (Gadow et al. 2013)

[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

ASD = Autism spectrum disorder, AS = Asperger's syndrome, chr = chromosome, EQ = empathy quotient); no imaging genetics studies found.

Table III:

Genes causing prevalent and well-studied single-gene ID disorders with behavioral and cognitive overlap with ADHD and/or ASD.

Gene	Protein	Chr position	Associated ID disorder	Reported rate of ASD-related phenotype	Reported rate of ADHD-related phenotype
FMR1	Fragile X mental retardation protein	Xq27	Fragile X syndrome	30% [Hagerman and others 2009]	59% [Sullivan and others 2006]
NF1	Neurofibromin	17q11	Neurofibromatosis type 1	40% [Walsh and others 2013]	38% [Hyman and others 2005]
TSC1	Hamartin	9q34	Tuberous sclerosis complex	50% [Prather and de Vries 2004]	30-60% [D'Agati and others 2009]
TSC2	Tuberin	16p13			
MECP2	Methyl-CpG-binding protein 2	Xq28	Rett syndrome	42-58% [Wulffaert and others 2009]	unknown
CACNA1C	Voltage-dependent L-type calcium channel subunit alpha-1C	12p13	Timothy syndrome	60% [Splawski and others 2004]	unknown

Phenotypic overlap as adapted from [Vorstman and Ophoff 2013]; ID= intellectual disability; ASD= Autism spectrum disorder; ADHD= Attention deficit/hyperactivity disorder; Chr= chromosome; no imaging genetics studies found.

Table IV:

Imaging genetics studies in ADHD case-control samples and ADHD candidate genes studies in the healthy population (for selection of candidate genes see Table I).

Gene	Variant	Imaging modality	Imaging/cognitive phenotype	Genotype groups compared	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
DRD2	DRD2/ANKK1-Taq1a (rs1800497, T allele = A1 allele)	sMRI (VBM)	Global GM volume	A1- carriers vs. A2/A2-carriers	70 HC (30.7)	A1- carriers: ↓ part of midbrain, encompassing substantia nigra bilaterally	(Cerasa et al. 2009)
		sMRI (VBM)	GM and WM volume	A1- carriers vs. A2/A2-carriers	25 HC (25)	A1-carriers: ↓ Volume in cerebellar cluster	(Wiener et al. 2014)
		fMRI	Temporal or color discrimination task			A1-carriers: ↑ Activation in striatum and right dorsolateral PFC	
			Reward anticipation paradigm	A1- carriers vs. A2/A2-carriers	24 HC (25.7)	↑ Nucleus accumbens activation in three-way interaction analysis from placebo to bromocriptine (D2 receptor agonist); ↑ performance under bromocriptine in A1- carriers.	(Kirsch et al. 2006)
			Striatal activation in response to receiving palatable food (2 fMRI paradigms)	A1- carriers vs. A2/A2-carriers	fMRI 1: 43 HC (20.4)[†] fMRI 2: 33 HC (15.7)[†]	↑ Negative relation between striatal response to food receipt and BMI. A1-non-carriers : striatal activation in response to food intake was positively related to weight gain (negatively related to weight gain for A1-carriers).	(Stice et al. 2008)
			Emotional face task	A1/A1-carriers vs. A1/A2-carriers vs. A2/A2-carriers	45 HC (23.2)[†§]	TaqIA genotype modifies activations in putamen, ACC, and amygdala in response to negative facial stimuli (higher signal intensity in homozygous groups (A1/A1 + A2/A2) than in heterozygous group (A1/A2)).	(Lee et al. 2011)
			Flanker task with a motivation manipulation	A1- carriers vs. A2/A2-carriers	32 HC (22.9)	A1- carriers: ↓ Interference effects to reward alone (as compared to reward + punishment) and ↑ anterior insula activation	(Richter et al. 2013)
			Task-switching paradigm	A1-non-carriers vs. A1-carriers	48 HC (22)	A1 non-carriers: ↑ Task-switching costs, ↑ prefrontal switching activity in inferior frontal junction area, and ↑ functional connectivity in dorsal frontostriatal circuits	(Stelzel et al. 2010)
			Feedback-based reversal learning task	A1- carriers vs. A2/A2-carriers	22 HC (age range 20-31)	A1- carriers in placebo condition: ↓ neural responses to positive feedback; cabergoline: ↑ neural reward responses in medial OFC, cingulate cortex, and striatum, but ↓ task performance and frontostriatal functional connectivity	(Cohen et al. 2007)

Gene	Variant	Imaging modality	Imaging/cognitive phenotype	Genotype groups compared	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
			Probabilistic reversal learning task	A1- carriers vs. A2/A2-carriers	28 HC (26.1)‡	A1- carriers: no graded increase in RCZ activity to preceding negative feedback; ↓ recruitment of right VS and right lateral OFC during reversals.	(Jocham et al. 2009)
			"Wug" test (knowledge of grammar, opposed to vocabulary)	A2/A2-carriers vs. A1- carriers	22 HC (22)	A2/A2-carriers: ↑ At concatenative (but not analogical) grammar learning; ↑ striatal responses	(Wong et al. 2013)
DRD4	exon 3 VNTR	sMRI	Superior frontal, middle frontal, anterior cingulate, and cerebellum cortices volumes	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)
			TBV, PFC, cerebellum, CN and pallidum volume	7R-carriers vs. non-7R-carriers	41 ADHD (9.7) 56 HC (17.6)	No volumetric differences between 7R-carriers and non-7R-carriers. No group × genotype interactions.	(Castellanos et al. 1998)‡
		DTI	WM integrity	5R- carriers vs. non 5R-carriers	765 HC (20.7)§	5R-carriers: ↑ MD in widespread GM and WM areas of cerebral cortex, and subcortical areas	(Takeuchi et al. 2015)
		fMRI	Activity related to N-back paradigm			5R-carriers : ↓ Task-induced deactivation in precuneus areas in both attention-demanding working memory task and sensorimotor task; similar patterns were observed in posterior cingulate cortex and areas around midbrain and hippocampus.	
		fMRI	MID task	7R-carriers vs. non 7R-carriers	78 HC (16.3)	DRD4 status moderated relation between Behavioral Inhibition (BI) and activation in CN. 7R-carriers: ↑ striatal response to incentive cues. DRD4 genotype influenced relations among neural response to incentives, early childhood BI and anxiety.	(Perez-Edgar et al. 2014)
			Emotional rating task	4R/7R-carriers vs. 4R/4R-carriers	26 HC (23.3)	4R/7R-carriers: ↑ activity in response to unpleasant images compared to neutral images in right temporal lobe.	(Gehricke et al. 2015)
			Go/No-go task	7R-carriers vs. non 7R-carriers	62 HC (18)	7R-carriers "No-Go" trials:, ↓ activation in right anterior PFC/IFG, left premotor cortex, and right occipital/ cerebellar areas (7-repeat status accounted for ca. 5-6% of variance in BOLD response during "No-Go" trials).	(Mulligan et al. 2014)
			Combined stimulus-response Incompatibility Task (IC) and Time Discrimination Task (TT)	7R-non-carriers vs. 7R-carriers	26 HC (11.4)	7R-non-carriers: ↑activation of left middle and IFG in IC and ↑cerebellar activation in TT; ↑functional connectivity between left IFG and ACC during IC and between cerebellar activation and IFG and ACC during TT.	(Gilsbach et al. 2012)

Gene	Variant	Imaging modality	Imaging/cognitive phenotype	Genotype groups compared	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
NOS1	Exon 1f-VNTR	fMRI	Reward anticipation task/ modified MID task	SS-carriers vs. SL/LL-carriers	63 ADHD (38.3) 41 HC (38.0)	SS-carriers: ↑ in VS. No group × genotype interactions.	(Hoogman et al. 2011)
SLC6A3/DAT1	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	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	VS and CN activity during reward-predicting cues	*SLC6A3* 10-6 dosage (2 copies vs. <2 copies)	29 ADHD (combined type; 15.8)[‡] 30 HC (15.6)[‡]	ADHD: Activation in CN ↓ as number of copies ↑, but in control group reverse was found.	(Paloyelis et al. 2012)
			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)
				9-6 haplotype carriers vs. non 9-6 haplotype carriers	87 ADHD (38.3) 77 HC (38); same as above	Bayesian Constraint-based Causal Discovery (BCCD) algorithm confirmed that there is no evidence of a direct link between *DAT1* genetic variability and brain activation, but suggested an indirect link mediated through inattention symptoms and diagnostic status of ADHD	(Sokolova et al. 2015)
	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)[‡]	9R-carriers: ↑ activity in CN and ↓ in cerebellar vermis compared to 10R/10R-carriers. Group × genotype	(Durston et al. 2008)

Gene	Variant	Imaging modality	Imaging/cognitive phenotype	Genotype groups compared	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
					10 unaffected siblings (14.8)[‡] 9 HC (15.3)[‡]	interaction: effect in CN is observed in ADHD and unaffected siblings, but not HC.	(Brown et al. 2010)
	3' UTR VNTR	rs-fMRI	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.	
			Striatal FC	9R/10R-carriers vs. 10R/10R carriers	50 HC (20.4)	9R/10R-carriers: stronger connectivity between dorsal CN and insula, dorsal anterior cingulate, and dorsolateral prefrontal regions, as well as between VS and ventrolateral PFC, compared with 10R/10R-carriers.	(Gordon et al. 2015)
		fMRI	Modified version of the MID task	10R/10R-carriers vs. 9R carriers	53 HC (29)	10R/10R-carriers: strong positive correlation between reward sensitivity and reward-related VS activity (relationship is absent in 9R-carriers).	(Hahn et al. 2011)
			Exposure to threatening faces	10R/10R-carriers vs. 9R-carriers	85 HC (45.2)	9R-carriers: ↑ amygdala reactivity compared with 10R/10R-carriers.	(Bergman et al. 2014)
			Go/No-Go task under influence of 40 mg MPH or placebo	9R-carriers vs. 10R/10R- carriers	50 HC (23.7)[‡]	9R-carriers: MPH induced ↑ activation during successful no-go trials compared with oddball trials in thalamocortical network 10R/10R-carriers: ↓ activation in thalamocortical network. Same pattern was observed in CN and IFG (successful no-go trials compared with successful go trials).	(Kasparbauer et al. 2015)
			Pre-cued task-switching task	9R-carriers vs. 10R/10R- carriers	20 HC (21.6)	9R-carriers: ↑ventromedial striatum activation during reward anticipation compared with 10R/10R-carriers; ↑ influence of anticipated reward on switch costs, and ↑activity in dorsomedial striatum during task switching in anticipation of high reward relative to low reward in 9R-carriers.	(Aarts et al. 2010)
			Verbal n-back task	9R/10R-carriers vs. 10R/10R-carriers	20 HC (10.4)	9R/10R-carriers: ↑ performance accuracy, ↑ activation in frontalstriatal-parietal regions in high but not low runs compared with 10R/10R-carriers. Genotype × load interaction in right CN. 9R/10R-carriers: ↑ activation in striatal and parietal regions under high compared to low load, and genotype differences (9R/10R>10R/10R) were evident only under high load. 10R/10R-carriers: ↑ activation of substantial nigra/ subthalamic nuclei under low than high load and genotype differences (10R/10R>9R/10R) were evident only under low load.	(Stollstorff et al. 2010)

Gene	Variant	Imaging modality	Imaging/cognitive phenotype	Genotype groups compared	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
SLC6A4/5HTT	5-HTTLPR	sMRI (VBM)	GM volume	S-carriers vs. LL	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 cingulated gyrus. Association of G × E interaction with ADHD symptom count was mediated by GM volume in frontal pole and anterior cingulated gyrus only.	(van der Meer et al. 2015)
	5-HTTLPR	sMRI	Amygdala	SS vs. SL vs. LL	138 HC (41.2)	SS-carriers × anxiety: ↑ right amygdala volume (only in females)	(Cerasa et al. 2014)
			Hippocampus	S-carriers vs. LL	56 HC (71)	↓ Hippocampal volume in interaction with increased waking cortisol levels	(O'Hara et al. 2007)
				SS/SL vs. LL	357 HC (24.3)	S-carriers: ↓ hippocampal volume (females only); ↓ hippocampal volume correlated with severe CA (males only)	(Everaerd et al. 2012)
				S-carriers vs. LL	51 HC (~21)	↑ Left hippocampal volumes in woman ↓ Left hippocampal volumes in men	(Price et al. 2013)
				LL vs. SS/SL	159 HC (69.5)	LL-carriers × stress: ↓ hippocampal volume	(Zannas et al 2013)
			Multiple regions	S-carriers vs. LL	113 HC (37.6)	↓ GM volume of right IFG, left anterior cingulate, and superior temporal gyrus	(Selvaraj et al. 2011)
	5-HTTLPR, rs25531	sMRI	Total GM volume	SS vs. LL, S' vs. L'	58 HC (18.5)	No significant association with total GM volume	(Walsh et al. 2014)
	5-HTTLPR, rs25531, AluJb methylation of promoter	sMRI (VBM)	Hippocampus, amygdala, insula, anterior cingulated gyrus	S' vs. L' quantitative methylation score	Sample 1: 94 HC (36.9) Sample 2: 95 HC (34.2)	No significant association of genotype. Strong association of methylation and hippocampal GM volume; amygdala, insula, and CN showed similar associations, genotype-independent.	(Dannlowski et al. 2014)
	5-HTTLPR	sMRI (VBM)	GM volume	S-carriers vs. LL	sMRI: 114 HC (32.8) fMRI: 94 HC (31.3) (26 included in both)	S-carriers (VBM): ↓GM volume in limbic regions, particularly perigenual ACC and medial amygdala.	(Pezawas et al. 2005)
		fMRI	perceptual processing of fearful stimuli			S-carriers (fMRI): ↓ of amygdala- perigenual ACC connectivity, particularly in rostral ACC; ↓ structural covariance between amygdala and rostral ACC	
		fMRI	GM volume, attentional interference task	S-carriers vs. LL	41 HC (adults)	S-carriers (VBM): ↑ volume in left cerebellum LL (VBM): ↑ volume in left superior and medial frontal gyri, left anterior cingulated, and right IFG	(Canli et al. 2005)

Gene	Variant	Imaging modality	Imaging/cognitive phenotype	Genotype groups compared	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
						S-carriers (fMRI): ↑ activation in response to negative, relative to neutral, words in right amygdala (driven by ↓ activation to neutral stimuli, rather than ↑ activation to negative stimuli); for negative-neutral contrast ↑ activation most prominent in insula, putamen, and CN	
		sMRI (VBM)	Hippocampus, amygdala	S-carriers vs. LL, interaction with SLEs	48 HC (24.7);	S-carriers: no correlation of hippocampus and amygdala volume with SLEs. LL-carriers: positive correlation in GM volume with SLEs.	(Canli et al. 2006)
		fMRI	Face-stimuli			Negative correlation between SLEs and amygdala and hippocampus activation in response to face stimuli in S-carriers; positive correlation in LL-carriers.	
		rs-fMRI	FC between amygdala and hippocampus; absolute CBF at rest		21 HC for perfusion scan	GxE effect altered FC between hippocampus and putamen. Interaction effect of 5-HTTLPR genotype and life stress on resting level activation in amygdala and hippocampus (positive correlation in S-group and negative correlation in L-group).	
		sMRI	GM volume resting CBF	SS vs. LL	26 HC (20.3)	SS-carriers: No effect on amygdala and ventromedial PFC volume	(Rao et al. 2007)
		rs-fMRI				SS-carriers: ↑ resting CBF in amygdala and ↓ CBF in ventromedial PFC	
		DTI	WM integrity	L-carriers vs. SS	233 HC (22.7) §	L-carriers: ↓ anatomical connectivity between amygdala and PFC through uncinate fasciculus.	(Long et al. 2013)
		rs-fMRI	TC			L-carriers: ↓ FC between right amygdala and right frontal pole.	
	5-HTTLPR, rs25531	DTI	Structural connectivity	S'-carriers × SLE vs. L'L' × SLE	34 HC (25.6) †	↑ Structural connectivity between hippocampus and putamen (seed-based).	(Favaro et al. 2014)
		rs-fMRI	FC			↑ Positive correlation of co-activation of right parahippocampus and posterior cingulate cortex with SLEs (seed-based).	
	5-HTTLPR	rs-fMRI	Task-free activity	SS vs. LL	30 HC (20.3)	↑ Negative correlation of right amygdala activity and depressive symptoms	(Gillihan et al. 2011)
			FC	SS vs. L-carriers	200 HC (22.1) ‡§	SS-carriers: ↑ fractional amplitude of low-frequency fluctuation in amygdala; ↓ rsFC between amygdala and various regions (including insula, Heschl's gyrus, lateral occipital cortex, superior temporal gyrus, hippocampus) and ↑ rsFC between amygdala and various regions (including supramarginal gyrus and middle frontal gyrus)	(Zhang et al. 2015)

Gene	Variant	Imaging modality	Imaging/cognitive phenotype	Genotype groups compared	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
	5-HTTLPR, rs25531	rs-fMRI	FC	S'S' vs. S'L' vs. L'L'	39 HC (14.8)	↓ Superior medial frontal cortex connectivity ↓ Age-related increase in FC between posterior hub and superior medial frontal cortex	(Wiggins et al. 2012)
	5-HTTLPR	fMRI	Sadness induction - regulation to normal emotion	SS vs. LL	30 HC (20.3)	↑ Amygdala activity during mood recovery.	(Gillihan et al. 2010)
			Emotion regulation task	S-carriers vs. LL	37 HC (22.6) †	↑ Right amygdala reactivity to fearful faces. ↑ Signal reductions in right amygdala during regulation of fear. ↑ Modulatory influence of cognitive regulation on FC between amygdala and bilateral ventrolateral PFC, left medial OFC, subgenual ACC and rostral ACC.	(Schardt et al. 2010)
				SS vs. LL	30 HC (20.3), same sample as above	↑Anti-correlation between amygdala and posterior cingulate cortex/precuneus during mood recovery.	(Fang et al. 2013)
	5-HTTLPR, rs25531	fMRI	Emotion regulation task	S'S' vs. L'L'	30 HC (20.5)	↓ Posterior insula and prefrontal brain activation during passive perception of negative emotional information. ↑ Prefrontal activation and anterior insula activation during down- and upregulation of negative emotional responses.	(Firk et al. 2013)
	5-HTTLPR	fMRI	Mood induction, sadness (film)	S-carriers vs. LL	48 HC (8.3)	↑ Right putamen, right CN, right rostro-ventral ACC, left CN, and left putamen in sad mood.	(Fortier et al. 2010)
				S-carriers vs. LL	49 HC (12) †	↑ Earlier rise of left amygdala activation as sad mood increases.	(Furman et al. 2011)
	5-HTTLPR	rs-fMRI	FC	LL vs. SS	38 HC (20.4) §	↑ Regional homogeneity in right amygdala; no effects on FC of right amygdala.	(Li et al. 2012)
		fMRI	Emotional processing			No difference in amygdala activity in response to negative stimuli.	
	5-HTTLPR, rs25531	fMRI	Emotion processing task	S'S' vs. S'L' vs. L'L' (treatment with escitalopram)	36 HC (25.1) †	↑Left amygdala activation with escitalopram treatment linearly related to 5-HTTLPR S' allele load for negative stimuli increased.	(Outhred et al. 2014)
	5-HTTLPR	fMRI	Emotional face task	S-carriers vs. LL	28 HC	S-carriers: ↑ right amygdala activity	(Hariri et al. 2002)
				S-carriers vs. LL	92 HC (30.5)	S-carriers: ↑ right amygdala activity	(Hariri et al. 2005)

Gene	Variant	Imaging modality	Imaging/cognitive phenotype	Genotype groups compared	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
				S-carriers vs. LL	29 HC (40) ‡	S-carriers: ↑ activation of amygdala and ↑ coupling between amygdala and ventromedial PFC.	(Heinz et al. 2005)
				SS vs. SL vs. LL	29 HC (37.5)	↑ Activity in right fusiform gyrus to fearful faces. ↑Positive FC between amygdala and fusiform gyrus and between right fusiform gyrus and right ventrolateral PFC.	(Surguladze et al. 2008)
				S-carriers vs. LL	21 HC (15)	↑ Left amygdala activation in response to anger.	(Battaglia et al. 2012)
5-HTTLPR, rs25531		fMRI	Emotional face task	S'-carriers vs. L'L'	44 HC (30.3)	↑ Right amygdala responses to sad faces.	(Dannlowski et al. 2010)
				L'L' vs. S'S'	30 HC (26.6)	No association with amygdala reactivity. ↓ Subgenual cingulate cortex activation in response to fearful faces.	(O'Nions et al. 2011)
		sMRI	Amygdala volume	S'-carriers vs. L'L'	54 HC (41.6)	↓ Amygdala volume Path analysis suggests effects on left amygdala volume are mediated by right amygdala volume but not through (midbrain) 5-HTT availability.	(Kobiella et al. 2011)
		PET	5-HTT availability			No genotype effect on (midbrain) 5-HTT availability.	
		fMRI	Amygdala activation			↑ Left amygdala activation in response to emotional stimuli.	
				S'S' vs. L'L	67 HC (18.6)	↑ Left amygdala reactivity in multivariate analysis; additive effects of recent SLEs.	(Walsh et al. 2012)
				S'S' vs. L'-carriers, interaction with SLEs	44 HC (26.8) ‡	↑ Bilateral amygdala activation in response to fearful faces. Interaction with SLEs: highest activity in S'S with SLEs for fearful faces in bilateral amygdala.	(Alexander et al. 2012)
		rs-fMRI		S'S' vs. L'-carriers	48 HC (14.8)	↓ Connectivity between right amygdala and ventromedial PFC with age.	(Wiggins et al. 2014)
		fMRI				↑ Amygdala activation with age (age range 9-19 years)	
				S'-carriers vs. L'L' (bright-light intervention)	30 HC (24.3) ‡	Bright-light dose positively associated with intra-prefrontal (medial PFC coupling with medial PFC seed) functional coupling only in S'-carriers.	(Fisher et al. 2014)
5-HTTLPR		fMRI	Perceptual task of threatening stimuli	S-carriers vs. LL	14 HC phobic-prone (32.7)	S-carriers: ↑ activity in right amygdala	(Bertolino et al. 2005)

Gene	Variant	Imaging modality	Imaging/cognitive phenotype	Genotype groups compared	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
					14 HC eating disorders prone (34.3)		
		fMRI	Emotional face task with approach-avoidance	S-carriers vs. LL	48 HC (22.5)‡	↑ Amygdala activity originating from reduced prefrontal inhibitory regulation.	(Volman et al. 2013)
			Emotional face-emotional word conflict task	S-carriers vs. LL	26 HC (70.5)	↓ Connectivity between dorsal ACC and pregenual ACC for incongruent face-word combination.	(Waring et al. 2014)
	5-HTTLPR, rs25531	fMRI	Emotional face task with self-referential and emotion labeling conditions	S-carriers vs. LL, SLE interaction	45 HC (23.3)	↑ Amygdala activation and ↓ FC of amygdala with subgenual ACC in self-referential processing vs. emotion labeling. Negative correlation of bilateral amygdala activation during self-referential with SLEs in S-carriers; positive correlation in LL; pattern opposite during emotion labeling.	(Lemogne et al. 2011)
			Emotional face- word conflict task (Stroop-like task)	S'-carriers vs. L'L'	42 HC (~20)	↓ Recruitment of prefrontal control regions and superior temporal sulcus during conflict when task-irrelevant information was positively-valenced. ↑ Recruitment of these regions during conflict when task-irrelevant information was negatively-valenced.	(Stollstorff et al. 2013)
	5-HTTLPR	fMRI	Pain rating task	LL vs. SS	50 HC (24.9)†	↑ Positive linear effect of target pain in posterior cerebellum.	(Laursen et al. 2014)
			(un)predictable electric shocks	SS vs. L-carriers	51 HC (22)†	↑ Activity of amygdala, hippocampus, anterior insula, thalamus, pulvinar, CN, precuneus, ACC, and mPFC during threat anticipation. ↑ Positive coupling between mPFC activation and anxiety experience; L-carriers show ↑ negative coupling between insula and success of regulating anxiety.	(Drabant et al. 2012)
				S- carriers vs. LL	99 HC (21.9)‡ 69 HC (33.4)	S-carriers: ↑ dorsomedial PFC, anterior insula, bed nucleus of stria terminalis, thalamus and midbrain activation with increasing threat conditions across both samples.	(Klumpers et al. 2014)
	5-HTTLPR, rs25531	fMRI	Modified Flanker task	S'-carriers vs. L'L'	33 HC (23.4)	↑ Error-related rostral ACC activation. ↓ Conflict-related dorsal ACC activation.	(Holmes et al. 2010)
			Decision making task	S'S' vs. L'L'	30 HC (26.6)	↑ Amygdala activation during decisions made counter to, relative to decisions made in accord with, the frame effect (gain or loss).	(Roiser et al. 2009)

Gene	Variant	Imaging modality	Imaging/cognitive phenotype	Genotype groups compared	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
						Anterior cingulate-amygdala coupling during choices to made in counter to, relative to those made in accord with, the frame effect only observed in L'L'.	
			n-back task	S'S' vs. S'L' vs. L'L'	33 HC (37) [†]	↑ Bilateral prefrontal activation in right and left IFG pars triangularis with increasing S-allele count.	(Jonassen et al. 2012)
5-HTTLPR		fMRI	Source memory task	S-carriers vs. LL	23 HC (66.8) [17 (23.3), not analyzed for genotype effects in fMRI]	↓ Activity in left IFG, middle frontal gyrus and anterior paracingulate cortex.	(Pacheco et al. 2012)
			Food / non-food pictures	LL vs. S-carriers	28 HC (25.5)	↑ Left posterior cingulate cortex activity for food pictures.	(Kaurijoki et al. 2008)
5-HTTLPR, rs25531		fMRI	Differential fear conditioning	S'S' vs. L'-carriers	47 HC (26.8) [‡]	↑ Activity in fear network: amygdala (right), insula, thalamus (left) and occipital cortex for conditioned stimulus. Interaction with SLEs: ↑ activity in right insula and left occipital cortex in S'S'.	(Klucken et al. 2013)

ACC = anterior cingulated cortex, ADHD = attention-deficit/hyperactivity disorder, BCCD = Bayesian Constraint-based Causal Discovery, BI = Behavioral Inhibition, BMI = Body mass index, BOLD = blood oxygen level–dependent, BPD = bipolar disorder, CA = childhood adversity, CBF = cerebral blood flow, CN = caudate nucleus, FC = functional connectivity, fMRI = functional magnetic resonance imaging, GM = gray matter, HC = healthy control, IC = Incompatibility Task, IFG = inferior frontal gyrus, MD = mean diffusivity, MID task = monetary incentive delay task, MPH = methylphenidate, OFC = orbitofrontal cortex, PET = positron emission tomography, PFC = prefrontal cortex, RCZ = rostral cingulate zone, rsFC = resting-state functional connectivity, SLE = stressful life events, SMA = supplementary motor area, sMRI = structural magnetic resonance imaging, TBV = total brain volume, TT = Time Discrimination Task, VBM = voxel-based morphometry, VS = ventral striatum, WM = white matter

[†] only females

[‡] only males

[§] Asian sample

S' = functional S-allele (S or LG), L' = functional L'-allele (LA); in gray case-control studies

Table V:

Imaging genetics studies in ASDs case-control samples and ASDs candidate genes studies in the healthy population (for selection of candidate genes see Table II).

Gene	Polymorphism	Imaging modality	Imaging/cognitive phenotype	Genotype groups compared	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
CNTNAP2	rs2710102	fMRI	Reward-guided implicit learning task (fronto-striatal circuits)	C-allele carriers vs. non-risk-carriers	Discovery sample: 16 ASD (12.4) [‡] 16 HC (12.3) [‡]	Non-risk group (collapsed across patients and controls): ↓ Activity in medial PFC during reward feedback processing; Risk group: ↑ long-range anterior-posterior connectivity between medial PFC, medial occipital, and ventral temporal cortices.	(Scott-Van Zeeland et al. 2010)
				C-allele carriers vs. non-risk-carriers	Replication sample: 39 HC (13)	Non-risk-group: ↑ long-range anterior-posterior functional connectivity between mPFC, medial occipital, and ventral temporal cortices.	
	rs2710102	DTI	Whole-brain fiber tractography (graph theory analyses)	CC-carriers vs. CT/TT-carriers	328 HC (23.4); twins from 189 families	CC-carriers: ↓ path length, ↑ small-worldness and global efficiency in whole-brain analyses, and ↑ eccentricity (maximum path length) in 60 of the 70 nodes in regional analyses.	(Dennis et al. 2011)
	rs7794745	sMRI	WM and GM morphology	TT-carriers vs. AT/AA-carriers	314 HC	TT-carriers: ↓ GM and WM volume in cerebellum, fusiform gyrus, occipital and frontal cortices. Male TT-carriers: ↓ GM in right frontal pole in right rostral fronto-occipital fasciculus.	(Tan et al. 2010)
		DTI	WM integrity			TT-carriers: ↓ FA in cerebellum, fusiform gyrus, occipital and frontal cortices. Male TT-carriers: ↓FA in right rostral fronto-occipital fasciculus. Female TT-carriers: ↓ FA of anterior thalamic radiation.	
	rs7794745, rs2710102	fMRI	Language task	Risk group (T- and C-allele) vs. non-risk group	66 HC (20.54)	Risk group: ↑ activation in right IFG (Broca's area homologue) and right lateral temporal cortex.	(Whalley et al. 2011)
MET	rs1858830	fMRI	Emotional faces task (n = 144), DMN functional connectivity (n = 71), WM structural connectivity (n = 84).	CC-carriers vs. CG-carriers vs. GG-carriers (non-risk)	75 ASD (13.1) 87 HC (12.5)	Risk genotype predicted wide-spread atypical fMRI activation (↑ amygdala and striatum) and deactivation patterns (↓ mainly posterior cingulate cortex) to social stimuli. Effects were more pronounced ASD group, especially within heterozygous risk group.	(Rudie et al. 2012)
		rs-fMRI				Risk genotype: ↓ Functional and structural connectivity in temporo-parietal regions (within DMN)	

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Gene	Polymorphism	Imaging modality	Imaging/cognitive phenotype	Genotype groups compared	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
		DTI				Risk genotype: Altered WM integrity	
	rs1858830	sMRI	Measures of cortical thickness (CT) development	CC-carriers vs. CG-carriers vs. GG-carriers	222 HC (9-22)	C-carriers: ↓CT (lowest in CC group) in superior and middle temporal gyri, ventral precentral and postcentral gyri, and anterior cingulate bilaterally, and in right frontopolar cortex.	(Hedrick et al. 2012)
OXTR	rs2254298	sMRI	Amygdala volume, TBV	GG-carriers vs. GA-carriers	51 HC (13)[†]	GG-carriers: ↑GM volume, ↓amygdala volumes. VBM analysis revealed ↑volume in region of dorsomedial ACC in GG-carriers and ↑in posterior brainstem in G/A-carriers	(Furman et al. 2011)
		sMRI (VBM)	Global brain measures (GM, WM, TBV)	AA-carriers vs. AG-carriers vs. GG-carriers	135 HC (28.8)[§]	Male A-allele carrier: ↓GM volume in right insula (neuroanatomical correlate of ALTs).	(Saito et al. 2014)
	rs1042778, rs2254298, rs237887, rs918316, rs2268493, rs53576, rs2268495	sMRI	Amygdala and hippocampus volume, TBV	rs2254298: AA-carriers vs. AG-carriers vs. GG-carriers	208 HC (33.9)[§]	rs2254298: A-allele carriers: ↑bilateral amygdala volume. Two 3-SNP haplotypes (including rs2254298 G-allele), showed associations with ↓bilateral amygdala volume.	(Inoue et al. 2010)
	rs53576	sMRI (VBM)	Global brain measures (GM, WM, TBV)	AA-carriers vs. GG/GA-carriers	290 HC (23.7)[§]	Female AA-carriers: ↓amygdala volumes bilaterally (especially centromedial subregion, with a trend of allele-load-dependence)	(Wang et al. 2014)
		rs-fMRI	rsFC			↓ Resting-state functional coupling between PFC and amygdala bilaterally (allele-load-dependent trend).	
		rs-fMRI	Functional connectivity density (FCD) using a voxel-wise, data-driven approach	Male AA-carriers vs. male G-allele carriers	270 HC (24.2)[§]	FCD of hypothalamus exhibited main effect of genotype (↓FCD in male AA homozygotes). Gender-by-genotype interaction in resting-state FC (rsFC) between hypothalamic region and left dorsolateral PFC, but no main effect of genotype (↓rsFC in male AA homozygotes).	(Wang et al. 2013)
		sMRI (VBM)	Regional alterations in GM volume	GG-carriers vs. GA-carriers vs. AA-carriers	VBM: 212 HC (29.9) fMRI: 228 HC (31.9) (98 overlap)	A-allele carriers: ↓hypothalamus GM volume	(Tost et al. 2010)
		fMRI	Face-matching task			A-allele carriers: ↓amygdala activation, ↑functional correlation of hypothalamus and amygdala during perceptual processing of facial	

Gene	Polymorphism	Imaging modality	Imaging/cognitive phenotype	Genotype groups compared	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
	23-tagging SNPs (including rs7632287, rs237887, rs2268491, rs2254298, rs2268494)	fMRI	Animated angry faces task	rs237915: CC-carriers vs. CT/TT-carriers	1445 HC (14.4)	emotion (specifically in male risk allele carriers lower levels of reward dependence predicted). CC-carriers: ↓ VS activity (related to more peer problems).	(Loth et al. 2014)
	rs53576	fMRI	Others' suffering task	GG-carriers vs. AA-carriers	60 HC (20.2)[§]	GG-carriers: hierarchical regression analyses revealed ↑ associations between interdependence and empathic neural responses in insula, amygdala, and superior temporal gyrus.	(Luo et al. 2015)
		fMRI	Emotional-valenced stimuli task	GG-carriers vs. AG/AA-carriers	21 HC (34)	GG-carriers: ↑ functional connectivity between regions of interest. Bilateral amygdala and medial PFC show ↑ influence on other brain regions; bilateral pars opercularis, left amygdala, and left medial PFC are more receptive to activity in other brain regions.	(Verbeke et al. 2013)
	rs1042778, rs2268493, rs237887	fMRI	MID task	rs2268493: TT-carriers vs. CT/CC-carriers	31 HC (23.6)	rs2268493 TT-carriers: ↓ Activation in mesolimbic reward circuitry (nucleus accumbens, amygdala, insula, thalamus and prefrontal cortical regions) during anticipation of rewards but not during outcome phase.	(Damiano et al. 2014)
	rs53576, rs1042778	fMRI	Mother-child interaction task	3 genotype groups per SNP	40 HC [†]	Both rs53576 and rs1042778 were associated with both positive parenting and hemodynamic responses to child stimuli in OFC, ACC, and hippocampus (rs53576 GG group showed lowest hemodynamic response).	(Michalska et al. 2014)
	rs2268498, rs180789, rs401015	fMRI, doubleblind placebo-controlled crossover study	Social-emotional and gaze processing task; amygdala activation after intranasal oxytocin self-administration	rs401015: CT-carriers vs. TT-carriers	55 HC (24.9) [‡]	rs401015 modulated right amygdala activity under influence of oxytocin (CT-carriers: ↑ amygdala activity).	(Montag et al. 2013)
SLC6A4/5HTT	5-HTTLPR	sMRI (VBM)	Total GM and WM volume	LL vs. LS vs. SS	43 ASD (30)	No associations between total GM or WM volume and genotype.	(Raznahan et al. 2009)
		sMRI (longitudinal)	Cerebral cortical and cerebellar GM and WM volume	SS vs. SL vs. LL	44 ASD (3.4) [‡]	S-carriers: ↑ cortical and frontal lobe GM	(Wassink et al. 2007)

Gene	Polymorphism	Imaging modality	Imaging/cognitive phenotype	Genotype groups compared	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
	5-HTTLPR, rs25531	rs-fMRI	Functional connectivity	Low vs. high expressing	54 ASD (13.7) 66 HC (14.5)	Low expressing genotypes (SS, SL$_G$, L$_G$–L$_G$): ↑ posterior-anterior connectivity in ASD group (converse for HC).	(Wiggins et al. 2012)
		fMRI	Emotional faces task	Low vs. high expressing	44 ASD (13.5) 65 HC (14.7)	Low expressing genotypes (SS, SL$_G$, L$_G$–L$_G$): ↑ amygdala activation in ASD group.	(Wiggins et al. 2014)

ACC = anterior cingulate cortex, ALT = autistic-like traits, CA = childhood adversity, CN = caudate nucleus, CT = cortical thickness, CV = cortical volume, DMN = default mode network, DTI = diffusion tensor imaging, GM = gray matter, FC = functional connectivity, FCD = functional connectivity density, HC = healthy control, IFG = inferior frontal gyrus, MID = monetary incentive delay task, mPFC = medial prefrontal cortex, OFC = orbitofrontal cortex, PFC = prefrontal cortex, ROI = region of interest, rsFC = resting-state functional connectivity, SA = surface area, SLE = stressful life events, sMRI = structural magnetic resonance imaging, STS = superior temporal sulcus, VBM = voxel-based morphometry, VS = ventral striatum, WM = white matter, TBV = total brain volume

[†] only females

[‡] only males

[§] Asian sample

in gray only case-control studies; for *SLC6A4* studies in healthy individuals see Tables IV and VI (ADHD).

Table VI:

Imaging genetics studies in ADHD and ASDs case-control samples and candidate genes studies in the healthy population studying more than one single gene.

ADHD/ASD candidate gene (polymorphism)	Additional gene(s) studied	Imaging modality	Imaging/cognitive phenotype	Genotype groups compared (candidate genes or interaction)	Samples size (mean age in years)	Primary results (main effect of candidate gene genotype or interaction)	Reference
SLC6A3 (3' UTR VNTR), *DRD4* (exon 3 VNTR)	---	sMRI	PFC gray matter 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 ‡	*SLC6A3* 9R-carriers: ↑ CN volumes *DRD4* 4R/4R-carriers: ↓ prefrontal GM volume. No effects on CN, or TBV. No interactions between ADHD status and genotype.	(Durston et al. 2005)
	DRD1	sMRI; longitudinal study (mean follow-up, 6 years)	Cortical thickness	9R-carriers vs. 10R/ 10R-carriers, 7R-carriers vs. non-7R-carriers	105 ADHD (10.1; 13.1; 15.9) 103 HC (10.0; 12.4; 14.4)	*SLC6A3* 9R-carriers: No effect on cortical development. *DRD4* 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.	(Shaw et al. 2007)
	COMT	DTI	WM integrity, FA values	9R-carriers vs. 10R/ 10R-carriers; 4R/4R-carriers vs. rest	58 stimulant- and atomoxetine-naïve ADHD (8.7) §	*SLC6A3* 9R-carriers: no effect on WM integrity *DRD4* 4R/4R-carriers: no effect on WM integrity.	(Hong et al. 2015)
SLC6A3 (3' UTR VNTR)	*COMT*	fMRI	Episodic memory task	9R-carriers vs. 10R/ 10R-carriers	49 HC (22.7)	9R-carriers: ↑ midbrain activation (right substantia nigra and the ventral tegmental area)	(Schott et al. 2006)
			N-back task	9R/9R-carriers × val/ val-carriers	75 HC (19.6)	No effects on brain activation were found for each genotype independently. Val/val and 9R/9R subjects show highest activation dorsolateral prefrontal region.	(Caldu et al. 2007)
			Response inhibition (stop-signal) task	9R-carriers vs. 10R/ 10R-carriers	43 HC (22.7)	*SLC6A3* 9-allele carriers: ↑ activation during inhibition in subthalamic nucleus and (pre-Supplementary motor area	(Congdon et al. 2009)
			Reward anticipation task	9R-carriers vs. 10R/ 10R-carriers; val-carriers vs. met/met-carriers	22 HC (27.9)	*SLC6A3* 9R- carriers: highest activity in CN and VS during reward anticipation and in lateral PFC and midbrain at time of reward delivery. Interaction *SLC6A3* and *COMT*: *DAT1* 9R-allele carriers and *COMT* met/met-allele carriers showing highest activation in VS and lateral PFC during reward anticipation and in lateral prefrontal and orbitofrontal cortices, and in midbrain at time of reward delivery.	(Dreher et al. 2009)

ADHD/ASD candidate gene (polymorphism)	Additional gene(s) studied	Imaging modality	Imaging/cognitive phenotype	Genotype groups compared (candidate genes or interaction)	Samples size (mean age in years)	Primary results (main effect of candidate gene genotype or interaction)	Reference
	TREK, COMT	fMRI	MID task	9R-carriers vs. 10R/10R-carriers	32 HC (21.7)	TREK1 and SLC6A3/COMT genotypes were independently related to basal ganglia responses to gains.	(Dillon et al. 2010)
	COMT	fMRI	Fear conditioning, extinction and reacquisition task	9R-carriers vs. 10R/10R-carriers	69 HC [‡]	9R-carriers: ↑ learning rates and stronger hemodynamic appetitive prediction error signals in VS.	(Raczka et al. 2011)
SLC6A4 (5-HTTLPR)	BDNF	sMRI	Global GM volume	S-carriers × val/val	111 HC (32.60)	↓ ACC volume	(Pezawas et al. 2008)
SLC6A4 (5-HTTLPR, rs25531, STin2)	OXTR, STMN1	sMRI	Amygdala volume	SS vs. SL vs. LL.	139 HC (22) [‡]	SLC6A4 risk alleles are associated with ↓ amygdala volumes.	(Stjepanovic et al. 2013)
SLC6A4 (5-HTTLPR)	COMT	sMRI (VBM)	Global GM volume	S-carriers vs. LL-carriers × met-carriers vs. val/val-carriers	91 HC (33)	Interaction: ↓GM volume of bilateral parahippocampal gyrus, amygdala, hippocampus, vermis of cerebellum and right putamen/insula	(Radua et al. 2014)
SLC6A4 (5-HTTLPR, rs25531)	TPH2	fMRI	MID task	L'L' vs. S'-carriers	89 HC (27.8)	L'L'-carriers: positive association with amygdala-hippocampus activity and trait anxiety score.	(Hahn et al. 2013)
SLC6A4 (5-HTTLPR)	MAOA	fMRI	Response inhibition task	S-carriers vs. LL	35 HC (32.1) [‡]	S-carriers: ↑ activation in ACC Allele–allele interaction: ↑ BOLD activity in ACC.	(Passamonti et al. 2008)
SLC6A4 (5-HTTLPR, rs25531)	COMT	fMRI	Emotion processing task	S'S'-carriers and L'L'-carriers × val/val –carriers and met/met-carriers	48 HC (41.2) [‡]	Interaction effects in amygdala, hippocampal and limbic cortical regions elected by unpleasant stimuli. No additive or interaction effects.	(Smolka et al. 2007)
			Emotional face task	S'-carriers vs. L'L' met/met vs. val-carriers	54 HC (24.1)	S'-carriers : ↑right amygdala activity in response to angry stimuli.	(Lonsdorf et al. 2011)
SLC6A4 (5-HTTLPR)	TPH2, HTR1A, HTR2A	fMRI	Emotional face task	L-carriers vs. SS	55 HC (23.3) [†§]	L-carriers: ↑Bilateral amygdala activation in response to angry faces	(Lee and Ham 2008)
SLC6A4 (5-HTTLPR, rs25531)	COMT	fMRI	Emotional face task	S'S'-carriers and L'L'-carriers × met/met-carriers and val-carriers	91 HC (32.5)	Interaction: ↓Reciprocal connectivity within bilateral fusiform and inferior occipital regions, right superior temporal gyrus and superior temporal sulcus, bilateral inferior and middle PFC and right amygdala, in fear processing conditions.	(Surguladze et al. 2012)

ADHD/ASD candidate gene (polymorphism)	Additional gene(s) studied	Imaging modality	Imaging/cognitive phenotype	Genotype groups compared (candidate genes or interaction)	Samples size (mean age in years)	Primary results (main effect of candidate gene genotype or interaction)	Reference
SLC6A4 (5-HTTLPR)	TPH2	fMRI	Emotional face task	S-carriers and LL-carriers × TPH2	49 HC (24.0)	Interaction: ↑ activation of putamen and amygdala, most robust for visuospatial and negatively valenced stimuli	(Canli et al. 2008)
SLC6A4 (5-HTTLPR, rs25531)	BDNF	fMRI	Emotion processing	S-carriers vs. LL; interaction val/met	28 HC (24.49) †	S-carriers: ↑rostral ACC and amygdala activation during presentation of emotional images. S-carriers and met-carriers: ↑ activation in rostral ACC and amygdala.	(Outhred et al. 2012)
DRD2 (A1 allele)	BDNF	sMRI	Global GMV	A1-carriers × met-carriers	161 HC (27.29)	Interaction: ↓GM volume of ACC	(Montag et al. 2010)
DRD4 (rs1800955)	COMT	fMRI	Gambling paradigm featuring unexpectedly high monetary gains and losses	CC-carriers vs. TT-carriers	53 HC (21.2)	CC-carriers: ↑ responses in anterior insula and cingulate cortex.	(Camara et al. 2010)
DRD2 (rs1800497), DRD4 (exon 3 VNTR)	---	fMRI	Imagined intake of palatable foods, unpalatable foods, glasses of water (pictures).	A1-carriers and 7R-carriers	44 HC (15.6) †	↓ Activation of frontal operculum, lateral OFC, and striatum in response to imagined intake of palatable foods (vs. unpalatable food or water), predicted future ↑ in body mass for those with A1 or 7R-allele.	(Stice et al. 2010)
SLC6A3 (3' UTR VNTR), DRD2 (rs1800497)	COMT	fMRI	Cue-target reading paradigm	A1-carriers vs. A2/A2, 9R-carriers vs. 10R/10R, met/met vs. val/met vs. val/val	71 HC (27.6) ‡	DRD2 polymorphism did not affect results. 10R-carriers: ↑ dorsal IFG activation. Linear effect of COMT val/met and DAT1 9R/10R on preparatory activity in left IFG pointed to negative interaction between tonic lateral prefrontal and phasic subcortical DA.	(Arnold et al. 2015)
DRD2 (rs1800497), DRD4 (exon 3 VNTR), SLC6A3 (3' UTR VNTR and intron 8 VNTR)	ADRA1A, ADRA1B, ADRA1D, ADRA2A, ADRA2B, ADRB1, ADRB2, ADRB3, COMT, DBH, DDC, DRD1, DRD3, DRD5, SLC6A2, TH	fMRI	Stop-signal task	SLC6A3 rs37020 (T-carriers vs. GG-carriers)	50 HC (22.1)	Activity in frontal regions (anterior frontal, superior frontal and superior medial gyri) and CN varied additively with T-allele of rs37020.	(Cummins et al. 2012)

ADHD/ASD candidate gene (polymorphism)	Additional gene(s) studied	Imaging modality	Imaging/cognitive phenotype	Genotype groups compared (candidate genes or interaction)	Samples size (mean age in years)	Primary results (main effect of candidate gene genotype or interaction)	Reference
DRD2 (rs1800497), **DRD4** (rs1799732), **DRD4** (exon 3 VNTR) **SLC6A3** (3' UTR VNTR)	COMT	fMRI	Receipt and anticipated receipt of palatable food and monetary reward	Individual risk genotypes and multilocus score	160 HC (15.3)	Individuals with 5 'risk' genotypes: did not show ↓ activation of DA-based reward regions. DRD4-L vs. DRD4-S genotype: ↓ middle occipital gyrus activation in response to monetary reward. Multilocus composite score: ↑ number of 'risk' genotypes ↓ activation in putamen, CN, and insula in response to monetary reward.	(Stice et al. 2012)
			Card guessing game task	Multilocus DA profile	69 HC (44.5)	↑ Reactivity correlated with ↑ number of risk factors. Multilocus DA profile scores accounted for 10.9% of inter-individual variability in reward-related VS reactivity. None of individual polymorphisms accounted for significant variability.	(Nikolova et al. 2011)
SLC6A4 (5-HTTLPR, rs25531), **OXTR** (rs2268498 and rs53576)	---	fMRI	Empathic performance task (facial responses of target person to electric stimulation)	SS-carriers vs. LL-carriers; rs2268498: CC- vs. CT- vs. TT-carriers; rs53576: AA- vs. AG- vs. GG-carriers	50 HC (24.9) [†]	rs2268498 CC-carriers: high empathic accuracy was associated with ↑ responsiveness of right STS to observed pain.	(Laursen et al. 2014)

ACC = anterior cingulate cortex, ADHD = Attention deficit/hyperactivity disorder, BOLD = blood oxygen level–dependent, CN = caudate nucleus, DA = dopamine, DTI = diffusion tensor imaging, FA = fractional anisotropy, fMRI = functional magnetic resonance imaging, GMV = gray matter volume, HC = healthy control, MID task = monetary incentive delay task, OFC = orbitofrontal cortex, PFC = prefrontal cortex, sMRI = structural magnetic resonance imaging, UTR = untranslated region, TBV = total brain volume, VAC task = variable attentional control task, VNTR = variable number tandem repeat, VS = ventral striatum, VSWM = visuospatial working memory, WM = white matter

[†] only females

[‡] only males

[§] Asian sample

in gray only case-control studies

Table VII:

Imaging genetics studies in intellectual disability syndromes (fragile X syndrome (*FMR1*), tuberous sclerosis (*TSC1* and *TSC2*), neurofibromatosis type 1 (*NF1*), and Rett syndrome (*MECP2*)). No studies for Timothy syndrome (*CACNA1C*) were retrieved in our search of the literature.

Disorder	Gene	Imaging modality	Imaging phenotype	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
Fragile X syndrome	*FMR1* full mutation	sMRI	Quantitative morphometry	Subgroups of 51 FXS; 120 HC	↑ CN volume, and lateral ventricle (in males).	(Reiss et al. 1995)
			Hippocampus and amygdala volume	10 FXS (5 ‡ (6.3); 5 † (9.0)); 10 HC (5 ‡ (6.4); 5 † (8.7))	↑ Right hippocampal volume.	(Kates et al. 1997)
			Regional brain volumes	10 FXS (9.0); 10 HC (8.5)	↑ CN and ventricular volumes.	(Kaplan et al. 1997)
			Tissue volumes	10 FXS (9.1); 10 HC (8.5)	↑ CN GM volume.	(Reiss et al. 1998)
			TBM	36 FXS (14.66); 33 HC (14.67)	↑ CN and lateral ventricle volumes, and trend-level parietal and temporal WM ↑.	(Lee et al. 2007)
			GM VBM and manual tracing; multivariate pattern classification	51 FXS (35 months); 32 HC (29.7 months); 18 DD (34.8 months) ‡	↓ GM volumes in regions including hypothalamus, insula, medial and lateral PFC. Spatial patterns that discriminated FXS from other groups included a medial to lateral gradient of increased and decreased regional brain volumes in posterior vermis, amygdala, and hippocampus.	(Hoeft et al. 2008)
			CN, hippocampus, putamen, amygdala volume	52 FXS (2.9); 63 ASD (2.8); 19 DD (3.0); 31 HC (2.6) ‡	↑ CN volume compared to all control groups. FXS: ↓ amygdala volume. ASD: ↑ amygdala volume.	(Hazlett et al. 2009)
			VBM of regional GM	10 FXS (28.9); 10 ASD (30.1); 10 HC (29.4)	FXS: ↑ GM volumes within frontal, parietal, temporal, and cingulate gyri, and in CN and cerebellum compared to ASD. FXS: ↑ GM volumes in frontal gyri and CN and ↓ GM volumes in cerebellar, parietal and temporal regions compared to HC. ASD: ↑ GM volumes in frontal and temporal gyri compared to FXS and ↓ GM cerebellar volumes compared to HC.	(Wilson et al. 2009)
			Total and regional insular volumes	11 FXS (5 † (15.3); 6 ‡ (16.3)); 8 HC ((5 † (16.5); 3 ‡ (13.3)); 11 DD (6 † (16.4); 5 ‡ (16.0))	↓ Total, anterior and posterior insular volumes compared to HC and DD.	(Cohen et al. 2011)

Disorder	Gene	Imaging modality	Imaging phenotype	Primary results (main effect of genotype)	Samples size (mean age in years)	Reference
			Univariate VBM; multivariate pattern classification and clustering.	↓ (for FXS) and ↑ (for ASD) volumes of frontal and temporal GM and WM regions (including medial PFC, OFC, superior temporal region, temporal pole, amygdala, insula, and dorsal cingulum) compared to HC. Overall pattern of brain structure in ASD resembles that of HC more than FXS.	52 FXS (2.90); 63 ASD (2.77); 31 HC (2.55); 19 DD (2.96)[‡]	(Hoeft et al. 2011)
			Regional brain bulk volumes (stereology) and GM and WM volume (VBM)	↑ CN, parietal lobes and right brainstem bulk volume. ↓ Left frontal lobe volume. ↑ GM volumes of fronto-striatal regions including CN. ↑ WM in regions extending from brainstem to parahippocampal gyrus, and from left cingulate cortex to CC.	17 FXS (30); 18 HC (35)[‡]	(Hallahan et al. 2011)
			Age-related change in regional brain volumes	Consistent FXS related volume differences in CN compared to HC across adolescence. Aberrant maturation of PFC gyri.	59 FXS (36[†] (16.0); 23[‡] (15.2)) (19 with longitudinal data); 83 HC (47[†] (15.8); 36[‡] (15.5)) (17 with longitudinal data)	(Bray et al. 2011)
			Cortical volume, thickness, complexity, surface area and gyrification index	FXS: ↑Cortical volume, thickness and complexity compared to HC. FXS+ASD: ↑ Left parietal lobe volume, ↓ gyrification specifically in the left temporal and a trend for ↓ right frontal surface area compared to FXS.	11 FXS (9.16) (6 FXS; 5 FXS +ASD); 10 HC (8.25)[‡]	(Meguid et al. 2012)
			Total brain, regional (lobar) and subcortical volumes; brain growth	FXS: ↑ Global brain volumes compared to HC but not ASD. ↑ Temporal lobe WM, cerebellar GM, and CN volume compared to ASD. ↓ Amygdala volume compared to ASD. Rate of brain growth from 2 to 5 years similar to HC.	53 FXS (2.9); 68 ASD (2.8); 19 DD (3.0); 31 HC (2.6)[‡]	(Hazlett et al. 2012)
			Relationship repetitive behaviors and CN volume	FXS: Positive correlation of self-injury with CN volume. ASD: Positive correlation of compulsive behaviors with CN volume.	41 FXS+ASD (4.6) (16 FXS+ASD (4.8); 30 ASD (4.7)[‡]	(Wolff et al. 2013)
			CN volume and topography	↑ CN compared to both control groups, with ↑ bilateral CN radial distance, ↑ dorsolateral CN head and ventromedial CN body radial distances.	48 FXS (21.3); 28 IQ-matched controls (19.5); 36 HC (19.7)	(Peng et al. 2014)
			CN and hippocampal volume	FXS: ↑ Hippocampus and CN volume compared to HC. HI: ↓ Hippocampal volumes.	14 FXS+ASD (22.6); 17 HI (22.0); 25 HC (21.6)[‡]	(Molnar and Keri 2014)
		DTI	Whole-brain, frontal-caudate, and sensory-motor tract FA	↓ FA in WM in fronto-striatal pathways and parietal sensory-motor tracts.	10 FXS (16.7); 10 HC (17.1)[†]	(Barnea-Goraly et al. 2003)

Disorder	Gene	Imaging modality	Imaging phenotype	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
			Ventral frontostriatal WM	17 FXS (2.8); 13 HC (2.3); 8 DD (3.0) ‡†	↑ Density of fibers localized in left ventral frontostriatal pathway.	(Haas et al. 2009)
			Voxel-based comparison of anisotropy and diffusivity	18 FXS (11.01); 25 22q11.2DS (10.75); 17 TS (10.56); 41 HC (10.6) †	FXS: ↓ FA in posterior limbs of internal capsule, posterior thalami, and precentral gyrus.	(Villalon-Reina et al. 2013)
		sMRI	GM density (VBM)	17 FXS (17.5); 16 HC (16.3)	↑ GM density in bilateral caudate head, left hippocampus, left planum temporale, left angular gyrus, and left superior parietal lobule. ↓ GM density in bilateral insular cortex, precuneus cortex, thalamus, and subgenual cingulate cortex.	(Hall et al. 2013)
		rs-fMRI	Fractional Amplitude (fALFF); functional connectivity (group ICA and dual regression)		↓ Functional connectivity in salience, precuneus, left executive control, language, and visuospatial networks. ↓fALFF in bilateral insular, precuneus, and ACC.	
		fMRI	ROI activation during 1-back and 2-back visuospatial working memory tasks	10 FXS; 15 HC †	No change in activation between 1-back and 2-back tasks in IFG, middle frontal gyrus, superior parietal lobule, and supramarginal gyrus, while HCs showed ↑ activation.	(Kwon et al. 2001)
			Activation during a counting Stroop task	14 FXS; 14 HC † (15.4) †	↓ Activation in orbitofrontal gyrus, insular cortex, superior temporal gyrus. No activation in inferior/superior parietal lobe as seen in HC.	(Tamm et al. 2002)
			FG and STS activation in response to face and gaze stimuli	11 FXS (16.4); 11 HC (15.5) †	↓ Left STS activation to all stimuli. No greater FG activation to forward faces compared to angled faces as seen in HC.	(Garrett et al. 2004)
			Go/nogo task	10 FXS (15.4); 10 DD (14.6); 10 HC (16.7) ‡	↓ Activation in right ventrolateral PFC and right caudate head, and ↑ left ventrolateral PFC activation compared with both control groups. Positive correlation between task performance and activation in left ventrolateral PFC.	(Hoeft et al. 2007)
			Emotional attribution task	10 FXS (16.4); 10 HC (15.6) †	↓ ACC activation for neutral compared to scrambled faces. ↓ CN activation for sad compared to scrambled faces. FXS: ↑ Negative correlation between IQ and insula activation for neutral compared to scrambled faces. HC: ↑ Positive correlation between IQ and ACC activation for neutral compared to scrambled faces.	(Hagan et al. 2008)
			Activation during face encoding	11 FXS (18.5); 11 HC (18.7)	↓ Activation of prefrontal regions including medial and superior frontal cortex during successful face encoding. Negative correlation social anxiety and brain activity during face encoding.	(Holsen et al. 2008)

Disorder	Gene	Imaging modality	Imaging phenotype	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
			Whole-brain and ROI activation during directed or averted eye gaze stimuli	13 FXS (15.5); 10 DD (16.1); 13 HC (15.0) [‡]	↓ PFC activation and ↑ left insula activation to direct eye gaze stimuli. ↑ Sensitization in left amygdala with successive exposure to direct gaze compared to controls.	(Watson et al. 2008)
			Auditory temporal discrimination task	10 FXS (18.7); 10 HC (14.7) [†]	↑ Activation in a left-lateralized network including left medial frontal gyrus, left superior and middle temporal gyrus, left cerebellum, and left brainstem (pons).	(Hall et al. 2009)
			Brain activity during a gaze habituation task	30 FXS (20.9); 25 HC (19.0)	↓ Neural habituation and significant sensitization in cingulated gyrus, fusiform gyrus and frontal cortex in response to gaze stimuli.	(Bruno et al. 2014)
Neurofibromatosis type 1	NF1	sMRI	Cerebral GM and WM	22 NFI; 20 HC	↑ Brain volume, especially WM.	(Said et al. 1996)
			Number, volume, distribution and change in time of UBOs	46 NF1 (7.8) (28[♂]; 18[♀])	UBOs found in 93% of subjects, localized most commonly in GP (30.4%), cerebellum (23.5%), and midbrain (16.2%). ↑ UBO number and volume between 4 to 10 years with a reduction in subjects aged 10+ years.	(Griffiths et al. 1999)
			24 ventricular and parenchymal dimensions and area calculations	27 NFI (8.8) (20[♂]; 7[♀]); 43 HC (5.9) (22[♂];21[♀])	↑ Bicaudate width, biatrial width, and biparietal diameter, but not hemispheric length. ↑ Iter measures, descending sigmoid sinus, and ↑ brainstem height (age-specific).	(DiMario et al. 1999)
			TBV, GM, WM, CSF, CC regions and hyperintensities	52 NF1 (10.9); 19 HC (9.8)	↑ TBV due to ↑ GM volume. ↑ CC size. ↑ Group differences in GM to WM ratio in younger compared to older subjects.	(Moore et al. 2000)
			Morphometric and volumetric measures of (midline) structures; GM and WM volume	18 NF1 (range 6.2-14.7); 60 HC (range 4.5-16.1)	↑ Bilateral hyperintensities and ↑ midline structure size in macrocephalic compared to normocephalic NF1. ↑ Brain volume and WM volume but not GM or ventricular volume in macrocephalic subjects compared to HC.	(Steen et al. 2001)
			Surface area, GM volume, and asymmetry of the PT and PP	24 NF1 (11.1); 24HC (11.8)	↓ Left PT surface area and GM volume and ↑ symmetry between left and right PT in NF1 boys compared to NFI girls and HC.	(Billingsley et al. 2002)
			Number of affected regions, UBO volume and number	12 NFI (13.0)	UBO prevalent in GP/internal capsule. ↓UBO locations, number and/or volume for all regions except cerebellar hemispheres between ages 7 to 12 years and ↑ during adolescence.	(Kraut et al. 2004)

Disorder	Gene	Imaging modality	Imaging phenotype	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
			GM and WM volumes	36 NF1 (9.3); 39 HC (9.5)	↑ GM volumes predominantly in temporal, parietal and occipital regions and WM volumes predominantly in frontal lobe.	(Greenwood et al. 2005)
			Frequency, signal characteristics and localization of T2 hyperintensities at different ages	103 NF1 (13.9)	↓ Frequency, size, and intensity of T2 hyperintensities in BG and cerebellum/brainstem with age. No differences in hemispheric lesions with age.	(Gill et al. 2006)
			Regional subcortical volumes; cortical volume, thickness, surface area and gyrification	14 NF1 (11.3); 14 HC (11.9)	↑ Volume of thalami, right CN and middle CC. ↓ Gyrification indices in frontal and temporal lobes, insula, cingulate cortex, parietal and occipital regions. No differences in cortical volume, thickness and surface area.	(Violante et al. 2013)
			SVM; VBM	21 NF1 (11.1); 29 HC; 18 NF1 (33.1); 31 HC (35.0)	SVM classifiers correctly classified 94% of cases (sensitivity 92%; specificity 96%).	(Duarte et al. 2014)
			GM and WM volume	16 NF1 (29.8); 16 HC (33.1)	↓ GM volume of superior frontal gyrus, orbital gyrus and right STG ↑ GM volume in frontal, temporal,parietal and limbic lobes	(Pride et al. 2014)
		sMRI	TBV; CC morphology	10 NF1 (range 20-68): 10 HC (range 21-64)	No differences in TBV. ↑ CC length (10%), CC area (20%).	(Wignall et al. 2010)
		DTI	CC diffusion characteristics		↑ Minor eigenvalues at genu of CC.	
			GM and WM volume	14 NF1 (24); 12 HC (22.7)	↑ GM and WM volume.	(Karlsgodt et al. 2012)
			TBSS		↓ FA and radial diffusion and ↑ ADC with greatest magnitude in frontal lobe.	
		DTI	FA and ADC brainstem, basal ganglia, thalamus, CC, and frontal and parietooccipital WM regions	10 NF1 (25.8); 10 HC (26.3)	↑ ADC and ↓ FA in all regions of interest.	(Zamboni et al. 2007)
			Diffusion characteristics (ADC, FA, A(m), eigenvalues) healthy and disordered brain matter	50 NF1 ((21 female (12.2); 29 male (12.3)); 8 HC	↑ ADC and eigenvalues in UBO compared to normal-appearing sites ↑ ADC in normal-appearing sites compared to HC. No differences in FA or A(m) in most regions.	(van Engelen et al. 2008)
			FA BG, cerebellum, pons, thalamus	44 NF1(12.8); 20 HC (14.1)	↓ Bilateral cerebellar and thalamic FA.	(Ferraz-Filho et al. 2012)
			FA, ADC CN, putamen, GP, thalamus	14 NF1 (16.3) (8 with UBOs; 6 without UBOs and 9 <18	↑ ADC in CN, putamen, GP, thalamus.	(Nicita et al. 2014)

Disorder	Gene	Imaging modality	Imaging phenotype	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
				years;5 > 18 years); 8 HC (16.1)		
			ADC,FA, RD, eigenvalues for 7 GM and 8WM ROIs; WM trajectories for adjacent WM tracts of NBOs	14 NF1 (7.2); HC	↑ ADC and eigenvalues in GM and WM UBOs compared to contralateral normal-appearing sites and HC and ↓ FA compared to HC. Three out of 18 UBOs disrupt WM tracts. ↑ ADC, lambda(2) and radial diffusivity of WM UBOs in patients with neurological symptoms compared to patients without.	(Ertan et al. 2014)
		fMRI	Activity in ten ROIs during phonologic processing	15 NF1 (14.4); 15 HC (15.3)	Inferior and dorsolateral PFC activation relative to posterior activation ↑ during auditory phonologic processing and ↓ during orthographic processing.	(Billingsley et al. 2003)
			Occipital and parietal cortex activity during visual-spatial processing	15 NF1 (14.4); 15 HC (15.3)	↑ Posterior cortex activation relative to lateral and inferior frontal activation.	(Billingsley et al. 2004)
			Activation in frontal, temporal, parietal, and occipital regions during visuospatial processing	13 NF1 (9.8); 13 HC (9.8)	↑ Left instead of right hemisphere activation. ↓ Activation in primary visual cortex.	(Clements-Stephens et al. 2008)
			Early cortical visual pathway and DN activation during visual stimuli activating magnocellular and parvocellular pathways	15 NF1 (11.7); 24 HC (12.0); 13 NF1 (33.1)†; 15 HC (32.7)†	↓ Activation of low-level visual cortex. ↓ Deactivation or ↑ activation of midline regions of DN during magnocellular– biased stimulation.	(Violante et al. 2012)
		rs-fMRI	Ventral ACC, amygdala, OFC, PCC RSFC	14 NF1 (12.5); 30 HC (12.3)	↑ Connectivity between: left ventral ACC and frontal cortex, insula, and subcortical areas (CN, putamen); left amygdala and frontal cortex, insula, supramarginal gyrus, and PCC/ precuneus; left OFC and frontal and subcortical areas (CN, pallidum).	(Loitfelder et al. 2015)
Tuberous sclerosis complex	TSC1/ TSC2	sMRI	Number and location of cerebellar tubers and volumes of underlying parenchyma	34 TSC (8.9)	Mean tuber number was 14.3 and 44.1% of subjects showed both cerebral and cerebellar tubers and had more global cortical lesions than subjects with cerebral tubers only. ↓ Focal volume associated with tubers in cerebellum.	(Marti-Bonmati et al. 2000)
			GM, WM and CSF volume	10 TSC (41.5); 8 HC (40.0)	↓ GM volume in medial temporal lobes, posterior cingulate gyrus, thalamus, BG and right fronto-parietal cortex. ↓ Of limbic and subcortical GM volume negatively correlated with tuber count. ↓ WM of longitudinal fasciculi and other major intrahemispheric tracts. ↑ Cerebellar WM.	(Ridler et al. 2001)

Disorder	Gene	Imaging modality	Imaging phenotype	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
			Tuber distribution and lesion load	25 TSC (39.0)	Highest tuber frequency in frontal lobes and highest tuber density in parietal regions with variation in tuber density but no lateralization of tubers. Nodules were located predominantly in CN. Tuber and nodule volumes positively correlated. ↑Tuber volume in subjects with a history of epilepsy.	(Ridler et al. 2004)
			Characteristics of cerebellar lesions	73 TSC (range 0–28 years)	16.4% of TSC subjects showed cerebellar lesions. Six subjects showed atrophy of cerebellar parenchyma around tubers.	(Jurkiewicz et al. 2006)
			GM, WM and CSF volume and lesion load	25 TSC (39.3); 25 HC (34.3)	↓Subcortical GM volume in regions including thalamus, BG, insula, and cerebellum. ↓WM in intrahemispheric tracts.	(Ridler et al. 2007)
			Tuber number and tuber/ brain proportion	58 TSC (20.6)(19 *TSC1* (25.0); 34 *TSC2* (19.0))	↑Tubers and tuber/brain proportion in *TSC2* compared to *TSC1* subjects and in subjects with a mutation deleting or directly inactivating tuberin GAP domain compared to subjects with an intact GAP domain.	(Jansen et al. 2008a)
			Tuber number and tuber/ brain proportion as determinants of seizures and cognitive function	61 TSC (17.9) (14 *TSC1*; 30 *TSC2*)	Tuber/brain proportion was inversely related to age at seizure onset and intelligence.	(Jansen et al. 2008b)
			Presence of SENs and SGCTs	81 TSC (28)	15% of TSC subjects showed SGCTs. 62% showed SENs, 24% of which also showed SGCTs. ↑SGCT volume at follow-up.	(Michelozzi et al. 2013)
			Cerebellar volume	36 TSC (9.7)(19 *TSC2*; 7 *TSC1*); HC (9.7)	↓Cerebellar volume, with strongest effect in subjects with *TSC2* mutations.	(Weisenfeld et al. 2013)
			(Cyst-like) tuber/ brain proportion and tuber number in relation to age at seizure onset	23 TSC (12.4)	Tuber/brain proportion and number of tubers, but not cyst-like tuber/brain proportion and number of cyst-like tubers, were negatively correlated with age at seizure onset.	(Nakata et al. 2013)
		DTI	ADC, FA of epileptogenic tubers	15 TSC	↑ADC values in subtuber WM in epileptogenic tubers compared to nonepileptogenic tubers.	(Chandra et al. 2006)
			ADC of NAWM in frontal, parietal and occipital lobes, and pons	23 TSC (12); 18 HC	↑ADC values in frontal WM and pons for age group between 96 and 144 months and in right parietal and occipital WM for subjects older than 144 months.	(Arulrajah et al. 2009)
			ADC, FA in tubers and WM lesions	14 TSC (15.1)	↑ADC values in cortical tubers. ↑ADC values and ↓FA values in WM lesions compared with contralateral regions.	(Piao et al. 2009)

Disorder	Gene	Imaging modality	Imaging phenotype	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
			FA, diffusion characteristics in ROIs in or adjacent to cortical tubers in epileptogenic and non-epileptogenic zones	12 TSC (8.2)	↓ FA of cortical tubers in epileptogenic compared to non-epileptogenic zones. ↑ Radial diffusivity and ↓ FA in NAWM in epileptogenic zones compared to non-epileptogenic zones.	(Widjaja et al. 2010)
			FA, trace, eigenvalues CC and internal capsules, in relation to tuber load	12 TSC (9.2); 23 HC (11.1)	Tubers were found in frontal lobes (144), parietal lobes (64), temporal lobes (42), occipital lobes (57) and insular cortex (7). ↓ FA, ↑ trace and average lambda(3) in CC and ↑ trace in internal capsules. Tuber volume correlated with multiple DTI characteristics in CC and internal capsules.	(Simao et al. 2010)
			Diffusion characteristics geniculocalcarine tract, internal capsule, temporal gyri and splenium of the CC	10 TSC (range 1.5-25 years); 6 HC (range 1.1-25 years)	↓ FA in geniculocalcarine tracts and splenium of CC. ↓ Axial diffusivity in internal capsule, STG, and geniculocalcarine tracts. ↑ Mean and radial diffusivity in splenium of CC.	(Krishnan et al. 2010)
			FA, mean radial and axial diffusivities of CC	40 TSC (7.2) (12 with ASD); 29 HC (7.7)	↓ Average FA and ↑ diffusivity values in CC. ↓ Average FA in TSC +ASD compared to HC and TSC −ASD subjects (who showed no differences).	(Peters et al. 2012)
			Diffusion characteristics in major tracts	16 TSC (13.0); 12 HC (15.3)	↓ FA and axial diffusivity in wide-spread WM regions. ↓ Number of fibers and number of tract points of commissural fibers, projection fibers and major WM tracts.	(Wong et al. 2013)
			Diffusion characteristics of RMLs, tubers, SENs, cerebellar lesions and SGCT and NAWM	30 TSC (15.5); 16 HC (7 children (9); 9 adults (36))	Mean of 47 RMLs, 27 tubers, and 10 SENs per TSC subject. Inverse correlation of RML FA and MD. No differences NAWM FA and MD.	(van Eeghen et al. 2013)
			FA dorsal language circuit tract	38 TSC (10 TSC + ASD; 17 TSC − ASD); 24 HC	↓ FA values in dorsal language circuit tract. ↓ FA in WM close to Geschwind's territory and WM close to Broca's area in TSC +ASD compared to TSC −ASD subjects.	(Taquet et al. 2014)
			FA, ADC, axial and radial diffusivity of tubers and WM lesions	18 TSC (9.3)	↓ FA and ↑ ADC and axial and radial diffusivity values in tubers compared to contralateral normal regions. ↑ Radial diffusivity and ↓ FA in WM lesions.	(Dogan et al. 2015)
			Global and regional WM connectivity	20 TSC (range 3-24 years)(11 TSC+ DD; 9 TSC − DD; 20 HC (range 2-23 years)	↓ Interhemispheric connectivity. ↑ MD, positively correlated with tuber load severity. ↑ MD in TSC + DD subjects compared to TSC − DD subjects.	(Im et al. 2015)
Rett syndrome	MECP	sMRI	TBV, cortical GM and WM, subcortical gray nuclei, CSF volumes	11 RTT (10.1); 15 HC (11.2) [†]	↓ Cerebral volume ↓ Loss of GM in comparison to WM, with largest decrease in frontal regions and CN and midbrain volume.	(Reiss et al. 1993)

Disorder	Gene	Imaging modality	Imaging phenotype	Samples size (mean age in years)	Primary results (main effect of genotype)	Reference
			TBV, cortical GM and WM, subcortical GM, CSF and posterior fossa volumes	20 RTT (9.8); 20 HC (9.0) [†]	↓ GM volume most pronounced in prefrontal, posterior-frontal, and anterior-temporal regions. ↓ WM volume uniformly throughout brain. ↓ CN volume. No differences in midbrain volumes.	(Subramaniam et al. 1997)
			Absolute and relative changes in GM and WM volumes	23 RTT (8.6) (12 more severe (8.8); 10 less severe (8.3)); 25 HC (8.9) [†]	↓ Absolute volume throughout the brain ↓ Relative parietal lobe GM volume, particularly dorsal. ↓ Cortical WM volume. ↓ Anterior frontal lobe volumes in more severely affected subjects.	(Carter et al. 2008)
		DTI	Regional FA	32 RTT (5.5); 37 HC (6.1) [†]	↓ FA in genu and splenium of CC and external capsule, and regions of cingulate, internal capsule, posterior thalamic radiation, and frontal WM. No differences in visual pathways. ↓ FA in superior longitudinal fasciculus in patients who were nonverbal or speaking only single words.	(Mahmood et al. 2010)

22q11.2DS= 22-q11.2 deletion syndrome, ACC= anterior cingulate cortex, ADC= apparent diffusion coefficient, A(m)= axial anisotropy, ASD= autism spectrum disorder, BG=basal gangli, CC= corpus callosum, CN= caudate nucleus, CSF= cerebrospinal fluid, DD= developmental delay, DN= default network, DTI = diffusion tensor imaging, FA= fractional anisotropy, fALFF =fractional amplitude of low-frequency fluctuations, FG= fusiform gyrus, fMRI= functional MRI, FXS= fragile X syndrome, GAP= GTPase activating protein, GM= grey matter, GP= globus pallidum, HI= hypoxic injury, IFG= inferior frontal gyrus, IPL= inferior parietal lobule, IPS= intraparietal sulcus, MCP= middle cerebellar peduncle, MD= mean diffusivity, MTI=magnetization transfer imaging, NAWM= normal-appearing white matter, NF1= neurofibromatosis 1, OFC= orbitofrontal cortex, PCC= posterior cingulate cortex, PFC= prefrontal cortex, PP= planum parietale, PT= planum temporale, RML= radial migration lines, ROI= region of interest, RSFC= resting state functional connectivity; RTT= Rett syndrome, SCP= superior cerebellar peduncle, SEN= subependymal nodule, SGCT= subependymal giant cell tumour, sMRI= structural MRI, STG= superior temporal gyrus, STS= superior temporal sulcus, SVM= support vector machines, SWM= spatial working memory, T1= timepoint 1, T2= timepoint 2, TBM = tensor-based morphometry, TBV= total brain volume, TPJ= temporoparietal junction, TS= turner syndrome, TSC= tuberous sclerosis, TWM = temporal working memory, UBO = unidentified bright objects, VBM= voxel based morphometry, WM= white matter

[†] female

[‡] male