

ADHD and autism: differential diagnosis or overlapping traits? A selective review

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Abstract According to DSM-IV TR and ICD-10, a diagnosis of autism or Asperger Syndrome precludes a diagnosis of attention-deficit/hyperactivity disorder (ADHD). However, despite the different conceptualization, population-based twin studies reported symptom overlap, and a recent epidemiologically based study reported a high rate of ADHD in autism and autism spectrum disorders (ASD). In the planned revision of the DSM-IV TR, dsm5 (www.dsm5.org), the diagnoses of autistic disorder and ADHD will not be mutually exclusive any longer. This provides the basis of more differentiated studies on overlap and distinction between both disorders. This review presents data on comorbidity rates and symptom overlap and discusses common and disorder-specific risk factors, including recent proteomic studies. Neuropsychological findings in the areas of attention, reward processing, and social cognition are then compared between both disorders, as these cognitive abilities show overlapping as well as specific impairment for one of both disorders. In addition, selective brain imaging findings are reported. Therapeutic options are summarized, and new approaches are discussed. The review concludes with a prospectus on open questions for research and clinical practice.

Keywords ADHD · Autism · Risk factor · Reward · Empathy · Brain imaging · Genetics · Proteomics

Introduction

According to DSM-IV TR and ICD-10, a diagnosis of autism or Asperger Syndrome precludes a diagnosis of attention-deficit/hyperactivity disorder (ADHD). However, despite the different conceptualization, population-based twin studies reported symptom overlap (Reiersen et al. 2007; Ronald et al. 2008), and a recent epidemiologically based study reported a high rate of ADHD in autism and autism spectrum disorders (ASD) (Simonoff et al. 2008). In the planned revision of the DSM-IV TR, dsm5 (www.dsm5.org), the diagnoses of autistic disorder and ADHD will not be mutually exclusive any longer. This provides the basis of more differentiated studies on overlap and distinction between both disorders. To date, many studies on ASD did not differentiate individuals with high and low ADHD symptoms, despite a clear clinical differentiation in psychopathological symptom load (Holtmann et al. 2007). Vice versa, most studies on ADHD did not differentiate between children with or without different possible comorbid disorders (Freitag et al. 2010a; Taurines et al. 2010b).

This review first presents data on comorbidity rates and symptom overlap; it then discusses common and disorder-specific risk factors as well as proteomic findings. Neuropsychological findings in the areas of attention, reward processing, and social cognition are then compared between both disorders, as these cognitive abilities show overlapping as well as specific impairment for one of both disorders. In addition, selective brain imaging findings are reported. Therapeutic options are summarized and new approaches are discussed. The review concludes with a

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prospectus on open questions for research and clinical practice.

Methods

A systematic search of studies on ASD and ADHD was performed, using the databases PubMed and PsycInfo. The following key words were used: “autism”, “ASD”, “ADD”, and “ADHD” combined with “epidemiological”, “attention”, “hyperactivity”, “impulsivity”, “re-ward”, “social cognition”, “theory-of-mind”, “review”, “genetic”, “proteomic”, “brain imaging”, and “MRI”. Only recent studies since 2006 were included into the review, and a focus was put on reporting additional information to three recent reviews on the same topic (Gargaro et al. 2011; Rommelse et al. 2010, 2011) to avoid redundancy. Titles and abstracts were screened by subjective criteria. Studies that compared individuals with ASD and ADHD directly were given priority.

Diagnosis and comorbidity

Differential diagnosis and symptom overlap

ICD-10 and DSM-IV TR diagnostic criteria of ADHD, comprising symptoms of inattention, hyperactivity, and impulsivity, and ASD, comprising difficulties in social interaction, communication, and stereotyped behavior, do not overlap. However, clinically, inattentive, and hyperactive symptoms are often reported in individuals with ASD, and children and adolescents with ADHD often suffer from problems in social interaction with peers. The only epidemiologically based study on comorbid disorders in ASD reported a 30 % prevalence of comorbid ADHD (Simonoff et al. 2008) but did not differentiate between the three DSM-IV TR-based subtypes. Studies in clinical samples with ASD have differentiated between ADHD subtypes and have observed a prevalence of approximately 20 % inattentive and 10 % combined ADHD subtype in children with ASD (Gjevik et al. 2011; Leyfer et al. 2006). No population-based study on ASD diagnoses in children with a primary clinical diagnosis of ADHD has been performed to date. In a subgroup of children with ADHD, increased autistic symptoms were reported, measured predominantly by the Social Responsiveness Scale SRS (Grzadzinski et al. 2011; Reiersen et al. 2007) or the Social Communication Questionnaire SCQ (Kroger et al. 2011; Mulligan et al. 2009).

Models of comorbidity

The prevalence of 30 % of ADHD in ASD is approximately 6 times higher than the prevalence of ADHD in

children and adolescents worldwide (Polanczyk et al. 2007). Also, autistic symptoms in children with ADHD are higher than in healthy control children (Mulligan et al. 2009). These findings preclude a co-occurrence of both disorders by chance. Other models of comorbidity comprise the following (Rhee et al. 2008):

1. Three independent disorders ASD, ADHD, and combined ASD+ADHD.
2. Two disorders are alternate manifestations of the same underlying risk factor(s).
3. Specific risk factors for both disorders are correlated (several submodels do exist, for which specific correlation patterns can be modeled).
4. The presence of one disorder increases the risk of the other disorder (multiformity, again different forms can be modeled).

Studies on risk factors, biological, neuropsychological, and brain imaging findings support many of these comorbidity models. In addition, it may be possible—as both, ADHD and ASD are heterogeneous disorders—that different subtypes within and across disorders do exist, for example, a subtype of ADHD combined with atypical autism (Mandy et al. 2011), which may also show specific underlying risk factors.

Risk factors

Genetic risk factors

ASD as well as ADHD are both highly heritable neurodevelopmental disorders, and about 70–80 % of the phenotypic variance of each disorder may be explained by genetic factors (Faraone et al. 2005; Freitag et al. 2010b; Lichtenstein et al. 2010). Family based studies showed increased ASD symptoms in affected and non-affected siblings of ADHD patients, which indicates familiarity of the co-occurrence of ASD and ADHD symptoms (Mulligan et al. 2009). According to twin studies, which used questionnaire-based data on ADHD and ASD symptoms, about 50–70 % of the co-variance of ASD and ADHD symptoms may be explained by shared additive genetic factors (Reiersen et al. 2008; Ronald et al. 2008). A recent review has discussed the topic of shared heritability in ASD and ADHD in detail (Rommelse et al. 2010). In the following chapter—after a brief revision of key findings of candidate and linkage analyses—mainly recent results of genome-wide association studies (GWAS) of single-nucleotide polymorphisms (SNPs) and rare copy number variants (CNVs) as well as network/pathway analyses will be presented.

Linkage and candidate gene association studies

Until recently, genetic research in ADHD and ASD mainly focused on linkage and candidate gene association studies to elucidate their genetic basis. In family based linkage studies, genetic variation throughout the genome is evaluated to identify polymorphic loci that segregate with a phenotype. In subsequent candidate gene association studies, genes in replicated linkage regions were screened for mutations or common variants as potential genetic risk factors. With these study designs, due to genetic and clinical heterogeneity of ASD and ADHD as well as lack of power of most studies, little progress has been made in the identification of underlying genetic risk variants.

When focusing on shared genetic underpinnings in ASD and ADHD, limited evidence for overlapping linkage loci mapping genes with possible pleiotropic effect emerged. The most promising findings were 5p13, 9q33 as well as 16p13 (Rommelse et al. 2010; Smalley et al. 2002). In a genome-wide QTL linkage approach, autistic traits in ADHD patients of the IMAGE study (1143 ADHD subjects, 1453 siblings) were mapped (Nijmeijer et al. 2010). One locus on 15q24 was described, where pleiotropic genetic risk factors for ASD and ADHD may be located.

As potential-specific candidate genes for ADHD, in a 2009 meta-analysis (functional) variants predominantly in dopaminergic and serotonergic genes were described (Gizer et al. 2009). For ASD, association was replicated with rare and common variants in a large number of candidate genes (Abrahams and Geschwind 2010; Freitag et al. 2010b; Geschwind 2011; Rommelse et al. 2010). Several variants in candidate genes of ADHD also have been examined for their potential association with ASD: variants in *DAT1*, *DRD3*, *DRD4*, catechol-*O*-methyltransferase (*COMT*) and monoamine oxidase A (*MAOA*). Only *DRD3* and *MAOA*—variants were nominally associated with ASD symptoms (Rommelse et al. 2010). Results on other genetic variants of interest in ADHD were undetermined or negative with regard to a modulating role in ASD. No ASD-specific candidate genes have been systematically studied for association with ADHD to date.

In this selective review, results of linkage and candidate gene association studies are not discussed in further detail. Please refer to the following recent reviews: (Rommelse et al. 2010)—shared heritability of ASD and ADHD; (Banaschewski et al. 2010; Franke et al. 2011; Gizer et al. 2009; Sharp et al. 2009; Stergiakouli et al. 2012; Wallis et al. 2008)—genetics of ADHD; (Bill and Geschwind 2009; Freitag et al. 2010b; Gupta and State 2007; Huang and Santangelo 2008; Losh et al. 2008; State and Levitt 2011; Yang and Gill 2007)—genetics of ASD.

Genome-wide association studies (GWAS)

Due to technical advances in CHIP-based genotyping and bioinformatics, the most recent studies in ASD and ADHD were based on genome-wide approaches, studying association of single-nucleotide polymorphisms (SNPs) and rare copy number variations (CNVs) with the phenotype, and describing involved biological pathways. Currently, sequencing studies are under way, but results have not been published.

Genome-wide SNP association studies

Overall, predominantly negative results emerged from GWAS and associated meta-analyses on common SNPs in ADHD (Elia et al. 2012; Hinney et al. 2011; Mick et al. 2010; Neale et al. 2010; Stergiakouli et al. 2012). As an example for suggestive association with ADHD, the cadherin 13 gene (*CDH13*) might be mentioned, coding for a protein that regulates neural cell adhesion and cell migration via activation of small GTPases. This finding was also supported by results from family based linkage studies (Lesch et al. 2008).

Similarly in ASD, GWAS on common genetic variants (SNPs) have not yielded independently replicated positive results (Devlin et al. 2011), although a few suggestive risk alleles with small effect sizes have been reported on 5p15 [mapping semaphorin 5A (*SEMA5A*) and the taste receptor, type 2, member 1 genes (*TAS2R1*) (Weiss et al. 2009)] and on 5p14.1, the region between *CDH10* and *CDH9* (coding for neuronal cell adhesion molecules of the above named cadherin family (Ma et al. 2009; Wang et al. 2009)). Furthermore, on chromosome 20p12.1 association with a SNP in the MACRO domain containing 2 gene (*MACROD2*) (Anney et al. 2010) was observed but not replicated (Curran et al. 2011). *MACROD2* codes for a protein important in numerous biological processes, among others axonal outgrowth and metabotropic glutamate receptor signaling (Devlin et al. 2011). Negative findings from GWAS may arise from differences in genotyping methods and platforms, insufficient sample sizes for risk alleles of small effect or heterogeneity of included phenotypes and gene-environmental effects.

Regarding overlapping findings for ASD and ADHD, among the not significantly associated top-findings of GWAS in ADHD cohorts, SNPs in the following genes may also increase ASD symptoms (Franke et al. 2009; Rommelse et al. 2010): *CDH13* (chr. 16), neuron navigator 2 (*NAV2*, chr. 11), doublesex and mab-3-related transcription factor 2 (*DMRT2*, chr. 9), fragile histidine triad (*FHIT*, chr. 3), mannosidase, alpha, class 2A, member 2 (*MAN2A2*, 15q26.1), astrotactin 2 (*ASTN2*, 9q33.1), dynamin 1 (*DNM1*, 9q34.11), matrix metalloproteinase 24 (*MMP24*, 20q11), potassium

voltage-gated channel, Shaw-related subfamily, member 1 (*KCNK1*, 11p15.1), glypican 6 (*GPC6*, 13q31.3), integrin alpha 11 (*ITGA11*, 15q23), solute carrier organic anion transporter family, member 3A1 (*SLCO3A1*, chr. 15), and heparine sulfatase 2 (*SULF2*, chr. 20). Similarly, several SNPs related to ASD might also be of interest for ADHD, such as the above-mentioned SNPs on 5p14.1 (between *CDH9* and *CD10*), and in the leucine-rich repeat containing 1 (*LRRCL1*, 6p12.1), elastin (*ELN*, chr. 7), and synaptotagmin XVII genes (*SYT17*, 16p12.3). These findings support the notion of potential pleiotropy of some common variants, increasing the risk of both disorders.

Genome-wide CNV studies

Technological advances in microarray-based comparative genomic hybridization recently allowed the detection of small cytogenetic abnormalities, so-called copy number variants (CNVs). CNVs are either inherited or de novo-mutated segments of DNA, longer than 1 kb, with a variable copy number compared with a reference genome, that may occur as deletion, insertion, duplication, or as a complex multisite variant (Feuk et al. 2006). CNVs may be of etiological importance by changing the coding gene sequence, the rate of gene transcription or unmasking recessive mutations. Within the context of ADHD and ASD, predominantly rare, large CNVs were studied, as these likely confer the highest risk of both disorders and are less frequent in healthy control populations.

In several studies on ADHD and control cohorts, concordantly enrichment of large (>100 kb respective >500 kb), rare (<1 % population frequency) CNVs in ADHD was reported (Elia et al. 2010, 2012; Williams et al. 2010, 2012). An excess of duplications was replicated on chromosome 16p13.11 and 15q13.3 (Williams et al. 2010, 2012). In a recent study, enrichment of rare recurrent CNVs affecting glutamatergic genes was replicated in two large samples of European descent (Elia et al. 2012). An additional gene network analysis described enrichment for genes related to the metabotropic glutamate receptor family in about 10 % of the ADHD individuals. Neuropeptide Y (NPY) and further possible candidate loci of rare CNVs were described in another study (Lesch et al. 2011). A possible link between ADHD, metabolic dysregulation, and NPY was further supported by increased NPY plasma concentrations in NPY duplication carriers as well as modulated activation patterns linked with reward and emotion processing in fMRI analyses.

Recent genome-wide CNV studies also revealed an enrichment of rare CNVs in autistic cohorts in comparison with healthy controls (Bucan et al. 2009; Glessner et al. 2009; Kumar et al. 2008, 2010; Marshall et al. 2008; Mefford et al. 2008; Moessner et al. 2007; Pinto et al.

2010; Sebat et al. 2007; Weiss et al. 2008). Replicated rare CNVs were observed in the following regions: 1q21, 2p16.3 (e.g., *NRXN1*), 3p25-26 (e.g., contactin 4, *CNTN4*), 7q36.2 (e.g., dipeptidyl-peptidase 6, *DPP6*), 15q11-13 (e.g., ubiquitin protein ligase E3A, *UBE3A*; olfactory receptor, family 4, subfamily M, member 2, *OR4M2*; olfactory receptor, family 4, subfamily N, member 4, *OR4N4*); 16p11.2 (e.g., mitogen-activated protein kinase 3, *MAPK3*; MYC-associated zinc finger protein (purine-binding transcription factor), *MAZ*; double C2-like domains, alpha, *DOC2A*; seizure-related 6 homolog (mouse)-like 2, *SEZ6L2*; HIRA-interacting protein 3, *HIRIP3*; interleukin 6, *IL6*); 22q11.2; X (e.g., DEAD box polypeptide 51, *DDX51*—patched domain containing 1, *PTCHD1*); 22q13.3 (e.g., *SHANK3*) (Freitag et al. 2012a).

Results of CNV studies supported evidence of a shared heritability in ADHD and ASD: In ADHD cohorts, CNV enrichment was observed at loci linked with autism. Common genetic risk regions were reported for 1p36, 1q21.1, 15q11.2–q13.1, 15q13.3, 16p11.2, and 22q11, respectively, for the genes *CNTN4*, *SUMF1* (sulfatase modifying factor 1), *NLG1*, *AUTS2* (autism susceptibility candidate 2), *UBE3A*, and *DPP6* (Elia et al. 2012; Glessner et al. 2009; Marshall et al. 2008; Weiss et al. 2008; Williams et al. 2010, 2012). Further studies additionally support an overlap of CNVs at numerous loci relevant for ASD, intellectual disability, and schizophrenia (Guilmatre et al. 2009; Williams et al. 2010). Thus, several neurodevelopmental disorders besides ADHD seem to be influenced by shared biologic pathways and possibly pleiotropic genetic variants relevant for ASD.

Pathway and network analyses

Recent publications aimed at integrating findings on common and rare genetic variants, gene expression data, animal models, etc. using sophisticated bioinformatic tools to unravel pathophysiological pathways and networks of genes that may contribute to the development of ADHD and ASD.

Integrating findings from several GWAS in ADHD and combining bioinformatic pathway analyses with systematic literature research revealed that 45 of 85 top-ranked ADHD candidate genes encode proteins fitting into a neurodevelopmental network that is involved in directed neurite outgrowth, a finding that was further supported by data from animal models (Poelmans et al. 2011). Several of these network proteins are also directly modulated by the first choice medication for treating ADHD, psychostimulants. Stergiakouli et al. (2012) integrated findings from a genome-wide analysis of SNP and large rare CNVs of 727 children with ADHD and 5,081 comparison subjects. Although none of the SNPs reached genome-wide significance,

13 biological pathways were identified with converging enrichment for SNP association as well as rare CNVs, among these, cholesterol-related and CNS development pathways.

Comprehensive pathway analysis based on GWAS and rare CNV data in ASD by different methods replicated gene networks implicated in synaptogenesis (Gilman et al. 2011; Marshall and Scherer 2012), cell proliferation, projection and motility, and in GTPase/Ras signaling cascades (Gilman et al. 2011; Pinto et al. 2010). Other studies additionally reported gene networks implicated in glyco-biology (van der Zwaag et al. 2009) and oxytocin-related pathways (Lee et al. 2012). A recent study (Ben-David and Shifman 2012) first constructed gene networks based on gene expression data of the Allen Human Brain Atlas project to describe modules associated with specific neuronal cell types and processes. Common and rare variants previously reported to be associated with ASD were assessed for enrichment in specific modules derived from the gene expression data. ASD-associated genetic variants were enriched in two neuronal modules, one predominantly expressed during infancy and related to neuronal plasticity and neurogenesis, the other one expressed throughout all ages and enriched with synaptic genes.

No study directly compared gene network analysis of ADHD and ASD samples, using results on common and/or rare genetic variants in both disorders. From the above-mentioned studies, it is likely that genes implicated in synaptogenesis and in different aspects of neuronal growth and differentiation may be relevant for both disorders.

Genetic risk factors: conclusion

Summarizing current data of molecular genetic approaches in ADHD give support to the neurotransmitter hypothesis, but also extend research interest to several other neuro-biological pathways that include cell division, cell adhesion, neuronal migration, and neuronal plasticity. These findings build a bridge to pathophysiological processes that are discussed in ASD, such as neuronal migration, growth, and dendritic spine development as well as excitatory and inhibitory neurotransmission (Freitag 2012).

Integrating findings from recent GWAS and CNV studies, various genetic effects show an influence on ASD and ADHD symptoms or diagnoses. On the one hand, rare de novo or inherited risk factors, such as mutations or rare CNVs, clearly increase susceptibility for the disorders and may also go along with a more severe phenotype. On the other hand, common risk alleles of mild-to-moderate effect only interfere with involved gene networks and increase the risk of a neurodevelopmental disorder in interplay with other genetic and/or environmental risk factors. Furthermore, similar etiological pathways may be involved in

phenotypically distinct outcomes: Some of the risk alleles seem to demonstrate a pleiotropic effect, resulting either in an ASD or ADHD phenotype (Romanos et al. 2008; Freitag et al. 2012a; Marshall and Scherer 2012; Williams et al. 2012); others are likely to be disorder-specific risk factors.

Recent complementing findings also emphasize the role of epigenetic effects (such as DNA methylation and chromatin interactions) in the etiopathogenesis of neurodevelopmental disorders (LaSalle 2011; Nguyen et al. 2010). Diverse environmental factors may induce such reversible changes to genomic function that are independent of the DNA sequence, leading to long-term modifications in phenotypes (Mill and Petronis 2008).

Non-genetic biological risk factors

Compared with the magnitude of genetic studies in ASD and ADHD, non-genetic biological risk factors besides the well-known male preponderance in both disorders were rarely studied. The current heritability estimates of ASD and ADHD also imply the relevance of environmental risk factors for both disorders (Lichtenstein et al. 2010). Some studies have started to focus on these aspects and are summarized here.

Some environmental, biological risk factors increase the risk of ASD as well as ADHD, which supports the idea that both disorders may be alternate manifestations of the same underlying risk factors. Recent population-based studies reported increased rates of inattentive and ASD symptoms in 11 year old, previously preterm children below 26 weeks of pregnancy (Johnson et al. 2010), which also was replicated for adults with ADHD (Halmoy et al. 2011). In addition, several pregnancy-related risk factors simultaneously seem to increase the risk of ASD and combined ADHD diagnosis or symptoms, as the use of valproic acid (Cohen et al. 2011; Rasalam et al. 2005), maternal diabetes (Lyll et al. 2011; Nomura et al. 2012), pre-eclampsia (Mann et al. 2010; Mann and McDermott 2011) or viral or bacterial infections (Atladdottir et al. 2010a; Mann and McDermott 2011) during pregnancy (Table 1). Most of these risk factors have been studied only recently, and—besides preterm birth resp. very low birth weight—are not well replicated. The risk associated with these common biological risk factors seems to lie between OR/RR/HR 1.1 and 2 for both disorders. However, more population-based studies need to be performed to replicate these findings and to establish well based odds ratios resp. relative risk estimates associated with the respective risk factors.

Disorder-specific risk factors seem to be maternal use of SSRI during pregnancy for ASD (Croen et al. 2011) and bupropion for ADHD (Figuroa 2010). Both psychotropic medications may specifically influence neuronal development during pregnancy. Similarly, studies on maternal

Table 1 Overlapping and specific non-genetic biological risk factors—results from selected epidemiological or register-based studies

Risk factor	ASD	Reference ASD	ADHD	Reference ADHD
Parental age	Fathers ≥ 50 years old versus ≤ 29 years old: RR 2.2 (95 %-CI 1.3–3.9)	Hultman et al. (2011)	Mothers ≤ 21 years old versus > 21 years old: OR 1.8 (95 %-CI 1.3–2.7)	Galera et al. (2011)
<i>Pregnancy risk factors</i>				
Pre-pregnancy obesity	<i>Not assessed</i>		Inattention overweight/obese mothers versus normal weight: OR 2.0/2.1 (95 %-CI 1.2–3.4/1.2–4.8)	Rodriguez et al. (2008), Rodriguez (2010)
Maternal infectious disease	Viral infection 1st trimester: HR 2.98 (95 %-CI 1.29–7.15) bacterial infection 2nd trimester: HR 1.4 (95 %-CI 1.1–1.9)	Atladdottir et al. (2010b)	Maternal genito-urinary infection OR 1.3 (95 %-CI 1.2–1.4)	Mann and McDermott (2011)
Maternal autoimmune disease	Psoriasis OR 2.7 (95 %-CI 1.3–5.8)	Croen et al. (2005)	Maternal thyroid peroxidase antibodies (OR = 1.77, 95 % CI: 1.15–2.72)	Ghassabian et al. (2012)
Maternal psychotropic medication	Valproic acid (clinical study only): ASD in 9 % of exposed children SSRI: OR 2.2 (95 %-CI 1.4–4.3)	Croen et al. (2011), Rasalam et al. (2005)	Valproic acid bupropion: OR 3.6 exclusion: SSRI	Clinical studies only (Cohen et al. 2011; Figueroa 2010)
Maternal smoking	<i>Excluded</i>	Lee et al. (2011)	Several studies: risk factor for comorbid conduct disorder and hyperactive-impulsive symptoms $1 < OR < 2$	Galera et al. (2011), Linnet et al. (2005), Romano et al. (2006), Sciberras et al. (2011)
Maternal diabetes	OR 1.8 (95 % CI 1.3–2.3)	Lyall et al. (2011)	OR > 2 ; interaction with low socio-economic status	Nomura et al. (2012)
Pre-eclampsia	OR 1.7 (95 %-CI 1.3–2.3)	Mann et al. (2010)	OR 1.2 (95 %-CI 1.1–1.3)	Mann and McDermott (2011)
<i>Perinatal risk factors</i>				
Pre-term birth	11 y.o. children < 26 weeks gestation: 8 versus 0 % in term-born classmates	Johnson et al. (2010)	11 y.o. children < 26 weeks gestation: 11.5 versus 2.9 % (inattentive subtype) adults < 28 weeks gestation: RR = 5	Johnson et al. (2010), Halmoy et al. (2011)

autoimmune disorders during pregnancy have reported different associated disorders (psoriasis with ASD; thyroid antibodies with ADHD). Again, these risk factors have to be replicated before any firm conclusion can be drawn.

Well-replicated ADHD-specific biological risk factors are pre-pregnancy obesity, increasing the risk of combined ADHD resp. inattention symptoms (Rodriguez et al. 2008; Rodriguez 2010), and smoking during pregnancy, which is a specific risk factor for hyperactive-impulsive behavior and also increases the risk of comorbid conduct disorder and aggressive behavior in children with ADHD (Freitag et al. 2012b; Galera et al. 2011; Linnet et al. 2005; Sciberras et al. 2011). Pre-pregnancy obesity has not yet been studied, whereas smoking during pregnancy was excluded as risk factor for ASD (Lee et al. 2011).

For ASD, increased paternal age has been replicated as specific risk factor (Hultman et al. 2011), whereas younger maternal age seems to be an ADHD-specific risk factor (Galera et al. 2011; Gustafsson and Kallen 2011). The exact mechanism, how these risk factors exert their influence on the developing brain, has not yet been studied in detail.

Non-genetic psychosocial risk factors

For ASD, non-genetic psychosocial risk factors have not been described, whereas for ADHD, several psychosocial risk factors have been strongly replicated in longitudinal studies. A prospective association does exist between familial conflicts/divorce, maternal depression, paternal dissociative personality disorder, and low socio-economic status of the family increasing rates of the ADHD combined subtype as well as inattentive and hyperactive-impulsive symptoms (Galera et al. 2011; Larsson et al. 2011; Sciberras et al. 2011). Thus, these psychosocial risk factors seem to be specific for ADHD and also may increase ADHD symptoms in children with ASD. With regard to psychosocial risk factors, an independence of the three disorders ASD, ADHD, and combined ASD+ADHD can be proposed. The relevance of psychosocial risk factors for comorbid ADHD in ASD has been shown by a population-based study, in which higher area deprivation was a specific risk factor for comorbid ADHD in children with ASD (Simonoff et al. 2008). Interestingly, in children with ADHD and increased ASD symptoms, familial risk factors in one study were predictive of more ASD symptoms (Kroger et al. 2011), which either indicates some relevance of psychosocial risk factors for ASD symptoms in general or the possibility that increased ASD symptoms in ADHD may represent a specific ADHD subtype but not the same disorder as ASD without ADHD symptoms.

Risk factors: conclusion

The different risk factor patterns with regard to genetic, non-genetic and psychosocial risk factors support different models of comorbidity for ADHD and ASD. It seems to be likely that comorbidity in some individuals is caused by overlapping genetic (e.g., large, rare CNVs) or overlapping non-genetic biological risk factors (e.g., low birth weight). The combination of independent disorder-specific risk factors by chance may cause the co-occurrence in other individuals (e.g., psychosocial risk factors or smoking during pregnancy for ADHD plus ASD-specific genetic risk factor, or ADHD-specific genetic risk factor plus ASD-specific non-genetic biological risk factor). In addition, it also is likely that some disorder-specific risk factors may be correlated, as for example, some biological risk factors (e.g., infectious diseases or diabetes during pregnancy) with psychosocial risk factors (Ross et al. 2010), thus increasing the risk of co-occurrence of both disorders.

Proteomics

Recently, proteomic technologies have been applied to psychiatric research in an attempt to systematically analyze the “proteome” (all expressed proteins in a tissue at a specific point in time). Proteomics may be used in a hypothesis-driven way, characterizing candidate proteins in ADHD and ASD research, or in a hypotheses-generating approach (“screening”) without a priori assumptions about candidate molecules. However, currently only scarce results on proteomics in ASD and ADHD research are available in the literature (see Table 2).

One main advantage of proteomic technologies is the determination of molecular modifications at the level of proteins. Complexity and diversity increase from genes to their final products via alternative mRNA splicing and post-translational modifications, therefore the transcription of a single gene results in multiple proteins that may vary in their structure and function. By analyzing proteins, proteomic research is probably closer to the underlying pathophysiological processes in ASD and ADHD than pure genetic approaches.

Proteomics, mainly based on mass spectrometry, allows for the analysis of protein expression levels, amino acid structures, post-translational modifications (e.g., phosphorylation, oxidation, glycosylation) and protein–protein interactions in diverse tissues in an automated, technology-driven large-scale mode of protein analysis. Often proteomic projects are complemented by transcriptomic or metabolomic methods, which aim at the analysis of transcripts/mRNA (Hegde et al. 2003) and metabolites/small

Table 2 Proteomic findings in ASD and ADHD

	Tissue/condition	Proteins	Methods	Reference
ASD	fmr1 -/- mouse in vitro	132 differentially expressed proteins, among others: dynamin1, N-ethylmaleimide sensitive fusion protein attachment protein (SNAP)-beta, syntaxin binding protein 1, calbindin 2, CDCrel-1AI	SILAC	Liao et al. (2008)
	Human total brain gray matter	Glyoxalase 1	2D-PAGE	Junaid et al. (2004)
	Human serum	apoB100 prec; complement factor H-related protein prec; complement C1q subcomponent, C chain prec; fibronectin 1 isoform 1 preproprotein, cold-insoluble globulin	LC-ESI MS/MS Spin filters LC-ESI MS/MS	Corbett et al. (2007)
ASD+ADHD	Human serum	3 MALDI-ToF-Peaks at 4.4 kDa, 5.15 kDa, 10.38 kDa for group distinction	Magnetic beads MALDI-ToF-MS	Taurines et al. (2010a)
ADHD	DBA/2J mice, striatum, DAT proteome	20 proteins associated with DAT: ras GRF2, rho GEF, synapsin 1, dynamin 1, synaptojanin 2, adapter protein 1 beta, neurocan, brevicin precursor, KV 4.3 M, KV 2.1, cystic fibrosis transmembrane conductance regulator, tubulin, actin, kinesin-related protein KIF3b, aczonin, similar to mitochondrial aconitase, fructose bis phosphate aldolase, triose phosphate isomerase, Par-3, Brca 2	IP LC-ESI-MS/MS Western Blot, in silico analysis	Maiya et al. (2007)
	Wig rat total protein frontal cortex, striatum and midbrain	19 differentially expressed proteins: chain A, 14-3-3 protein epsilon, dihydropyrimidinase-related protein-2, collapsin response mediator protein 4, 14-3-3 protein zeta, phosphatidylethanolamine binding protein, fragile histidine triad protein, brain glycogen phosphorylase, phosphoglycerate mutase 1, triosephosphate isomerase 1 protein, pyruvate dehydrogenase E1 alpha 1, dynamin 1, N-ethylmaleimide sensitive fusion protein attachment protein-beta, syntaxin binding protein 1, calbindin 2 (calretinin), solution structure of calcium-calmodulin N-terminal domain, Tu translation elongation factor, acidic ribosomal phosphoprotein PO, CDCrel-1AI, heat shock protein HSP 90-alpha	2D-PAGE MALDI-ToF-MS Q-ToF-MS/MS LC-ESI-MS/MS RT-PCR DNA microarray chip	Hirano et al. (2008)

2D-PAGE 2-dimensional sodium dodecyl sulfate polyacrylamide gel electrophoresis, DAT dopamine transporter, IP immuno precipitation, MALDI-ToF matrix-assisted laser desorption/ionization time of flight, MS mass spectrometry, Prec. precursor, Q-ToF quadrupole time of flight, RT-PCR reverse transcription quantitative polymerase chain reaction, SILAC stable isotope labeling

molecules that are relevant in biochemical networks (Oldiges et al. 2007).

In the following sections only those studies are included that use modern mass spectrometric technologies to analyze the proteome.

Proteomics in animal model and in vitro studies

Searching for pathophysiologically relevant candidates, proteomic methods were used to characterize differences in mRNA and protein expression in animal models for ASD and ADHD.

In a proposed model for ADHD, the Wig rat, protein expression was determined in the frontal cortex, striatum and midbrain (Hirano et al. 2008). Among nineteen up- or down-regulated proteins, five were involved in neurotransmitter release (dynamitin, N-ethylmaleimide sensitive fusion protein attachment protein (SNAP)-beta, syntaxin binding protein 1, calbindin 2, and CDCrel-1AI). The other differentially expressed proteins played a role in energy metabolism, cellular transport processes, protein synthesis, cytoskeleton and cell rescue. Some of them had previously been discussed in studies involving neurodegenerative diseases and diverse psychiatric disorders. In the context of autism, involvement of heat shock protein 90 alpha (Evers et al. 2002) in stress response, and the Ca²⁺ binding protein calbindin 2 has already been debated (Levav-Rabkin et al. 2010).

Another study aimed at characterizing the Dopamine transporter (DAT1) proteome, as the DAT1 is a key target of methylphenidate (Maiya et al. 2007). For their proteomic approach, DAT1 and interacting proteins were isolated from the striatum of DBA/2J (DBA) mice and 20 DAT1-associated proteins were identified, among others phosphoprotein synapsin Ib—which plays a role in neurotransmitter release.

To study pathophysiology of ASD, synaptic protein expression patterns were assessed in in vitro cultured primary cortical neurons from *fmr1* ^{-/-} mouse, as the resulting phenotype, fragile X syndrome, is often associated with autistic features (Liao et al. 2008). More than one hundred differentially expressed proteins fell into a variety of functional categories, including those regulating synaptic formation and morphology, neurotransmission and dendritic mRNA transport. One dysregulated protein was catenin-like protein, ARVCF, a gene product that is deleted in velocardiofacial syndrome, which is also associated with autistic features (Kates et al. 2007). Furthermore, reduced expression of the *Kcnma1α* gene was observed, which encodes the alpha-subunit of the large conductance Ca²⁺-activated K⁺ (BKCa) channel, a synaptic regulator of neuronal excitability. This is in line with former reports on a possible association between a functional defect of the BKCa channel and autistic features in association with mental retardation (Laumonnier et al. 2006).

Proteomic studies like these in both animal and in vitro models may help to identify potential disease candidates for further hypothesis-driven genetic studies or protein characterization in vivo.

Postmortem and peripheral protein expression in humans

Currently, only limited and preliminary results are available from proteomic approaches in ASD and ADHD individuals with regard to postmortem and peripheral qualitative or quantitative protein expression.

Protein abnormalities in eight autopsied ASD brains were reported by one study (Junaid et al. 2004). One protein with differences in polarity between patients and controls was identified as glyoxalase (Glo) I, and a decrease in Glo1 enzyme activity in ASD brains was demonstrated. Additional *GLO1* gene/mRNA sequencing pointed to a SNP (C419A) in association with ASD. Association of gene variants in *GLO1* and ASD was furthermore confirmed in independent ASD and control samples. A defect in Glo1 enzyme activity, that has a major role in the detoxification of the highly reactive methylglyoxal, might prenatally impact on neurogenesis and therefore susceptibility for ASD.

In a proteomics study in peripheral tissue in ASD, the serum proteome was analyzed in a group of autistic children aged 4–6 years in comparison with healthy developing controls for differentially expressed proteins and reported altered levels of apolipoprotein (apo) B100 and the following complement factors: complement factor H-related protein, complement C1q and fibronectin 1 (Corbett et al. 2007). In this study, comorbidity with ADHD was not accounted for.

Changes in peripherally circulating proteins in ASD were confirmed by another proteomic pilot study that aimed at a comparison of the serum proteome by the assessment and comparison of mass spectrometric peak patterns, not primarily at the identification of single, differentially expressed proteins (Taurines et al. 2010a). About half of the included ASD patients were diagnosed with a comorbid ADHD. Using matrix-assisted laser desorption/ionization time of flight-MS (MALDI-TOF-MS), three MALDI-ToF peaks could be revealed that differentiated the ASD sample from healthy controls (peaks at 4.4, 5.15 and 10.38 kDa). After sub-grouping ASD patients into children with and without comorbid ADHD (ASD/ADHD+, ASD/ADHD-), one peak at about 10.4 kDa distinguished the ASD/ADHD+ patients from both controls and ASD/ADHD- patients and therefore might constitute a characteristic for ADHD or the comorbid condition. Subsequent identification studies are in line with Corbett et al.'s findings of dysregulated peripheral apo levels (unpublished data).

Proteomics: conclusion

Following these first, proteomic, mass spectrometric studies, some candidates for ASD and ADHD have been suggested and new molecules of interest have been proposed. However, to elucidate pathophysiological, underlying pathways and comorbidity models of ADHD and ASD, further studies are necessary. No conclusions on specific models of comorbidity can currently be drawn from proteomic studies. Results on protein expression abnormalities in the blood of ASD (+ADHD) patients will have to be replicated and validated in sufficiently large samples, with thorough phenotyping of ASD, ADHD and the comorbid condition. In the pilot studies, modern and easily manageable, clinically applicable proteomics methods were established to characterize the proteome in peripheral tissue. Findings from such studies might contribute to define biomarkers or biomarker sets for ASD and ADHD. Such disease markers may be defined as characteristics which, after validation, are used to assess objectively normal, biological, pathogenetic processes or pharmacological responses to therapeutic interventions. One of the ambitious goals of biomarker research in relation to ASD and ADHD might be the early differential diagnosis of the partially overlapping phenotypes; a crucial precondition for an early behavior-modifying therapeutic intervention. A further promising option might be the chance to predict drug response and monitor therapy in the individual and therefore allow for a more personalized therapy on the basis of the distinct protein profile.

Selective neuropsychological findings

Attention

Clinically and neuropsychologically defined attention problems as one of the core deficits in individuals with ADHD have been frequently reported in several studies. Beyond that, children with ASD are also known to show difficulties in attention and executive function (Corbett et al. 2009; Gargaro et al. 2011; Happe et al. 2006; Sinzig et al. 2008a). Apart from comparisons between one clinical and one typically developing sample, direct comparisons between both disorders were studied in order to identify overlapping and distinctive characteristics concerning attention function.

In general, executive functions (EF) are widely recognized as an umbrella term for domains as planning, cognitive flexibility, working memory and response inhibition (Pennington and Ozonoff 1996). In a model combining EF and attention function (Norman and Shallice 1986), the superior control system, called supervisory attentional

system (SAS), includes several EF domains which are relevant for automatic or conscious selection of actions as a function of task complexity.

Directly related to the SAS are different aspects of attention function (AF). Van Zomeren and Brouwer (Van Zomeren and Brouwer 1994), who continued to develop Posner and Rafal's attention model (Posner and Rothbart 2007), proposed a division into two broad dimensions, namely 'intensity' and 'selectivity', which can be further divided into different subdomains. The intensity aspect of attention includes alertness and sustained attention, whereas selectivity contains focused, divided, visual-spatial and shift of attention (Sturm and Zimmermann 2000).

Children with ASD typically show impairments in the form of perseverative errors in the aforementioned EF measuring cognitive flexibility, planning or shifting, assessed by the Tower of Hanoi or Wisconsin Card Sorting Test (Corbett et al. 2009; Happe et al. 2006; Pellicano 2007). In individuals with ADHD, executive dysfunction has also been found, even though the central domains that seem to be impaired differ from those that have been reported for children with autism (Corbett et al. 2009). With regard to inhibition abilities, there is clear evidence that individuals with ADHD are affected by a deficit in their inhibitory control (Happe et al. 2006; Sinzig et al. 2008a), usually tested by Go/No-Go or stop signal tasks. In contrast, in children with pure ASD without ADHD, findings are unequivocal: In comparison with typically developing control samples or children with ADHD both normal inhibitory function (Buhler et al. 2011; Happe et al. 2006; Sinzig et al. 2008b) and impaired abilities (Christ et al. 2007; Corbett et al. 2009; Johnson et al. 2007) have been reported.

Most of the published studies concentrated on investigating EF in individuals with ADHD and ASD, whereas assessments of more basal attention domains as the ones that were suggested by Van Zomeren and Brouwer (1994) are rare. For a recent review discussing EF impairments in ASD and ADHD in detail, see Gargaro et al. (2011).

Regarding sustained attention, deficits have been particularly reported for individuals with ADHD (Corbett and Constantine 2006; Johnson et al. 2007; Tucha et al. 2006, 2009). Typical findings are a higher rate of errors and an increased variability of reaction time in comparison with typically developing peers. Only little research has been published on sustained attention in children with ASD. A few studies directly compared ADHD, ASD and typically developing groups using sustained attention tasks among others (Corbett and Constantine 2006; Corbett et al. 2009; Johnson et al. 2007), and found diverging results. Johnson et al. (2007) reported a performance comparable to typically developing individuals in the ASD group, whereas ADHD children showed impaired sustained attention

abilities. However, Corbett and Constantine (2006) and Corbett et al. (2009) found intact performance in sustained attention in both disorders.

As an interesting example for studies that directly compare participants with ADHD and ASD serves the study from Sinzig et al. (2008a). They included four groups of children (ADHD, ASD without comorbid ADHD, ASD with comorbid ADHD, and typically developing controls) in order to contrast their performance in working memory and several attention/EF tasks. As expected, they found impairments of the ADHD group in inhibition and working memory, whereas the ASD children showed reduced planning and flexibility, although only ASD participants with comorbid ADHD showed difficulties in the flexibility task. Interestingly, the children with ASD and comorbid ADHD performed comparably to those who had a pure ADHD diagnosis. This seems to support the notion of three separate disorders, ADHD, ASD, and ADHD+ASD, with the combined disorder showing typical “additive” impairments in computerized attention tasks of both disorders.

Regarding attention function, the heterogeneity of results for children with ADHD and/or ASD may be due to the diversity of tests implemented in the different studies. Furthermore, sample inclusion criteria may have influenced results. For example, the majority of subjects in Corbett et al. (2009) study consisted of children with high functioning autism, whereas Happe et al. (2006) and Sinzig et al. (2008a, b) predominantly investigated children with Asperger syndrome. Moreover, it should be noted, that the age range varied from early childhood to adulthood. Additionally, in most studies individuals with ASD with comorbid ADHD symptoms were excluded.

There is a strong need to continue investigating attention function in children with ASD and ADHD, especially by including participants with both, high autism and coexisting ADHD symptoms, to draw further conclusions on models of comorbidity based on neuropsychological performance. In addition, the findings of specific or overlapping impairments are relevant for the development of new, targeted treatment options for the disorders, either the single or the comorbid condition.

Reward processing

Besides executive function impairment, aberrant reward processing was postulated as a central neuropsychological impairment in ADHD by the dual-pathway-model (Sonuga-Barke 2002). Children and adults with ADHD were found to differ in their reaction to rewards in studies adopting behavioral, neuroimaging, electrophysiological, and psychophysiological measures (Luman et al. 2005; Rubia et al. 2009a, b; van Meel et al. 2011). In subjects with ADHD

compared to typically developing controls, hypoactivation of the neural reward system, especially the nucleus accumbens, was found in response to anticipated reward in fMRI and PET studies (Stark et al. 2011; Volkow et al. 2011). A robust result of the research focussing on motivational markers in ADHD is the finding of delay aversion, that is, participants with ADHD prefer small and immediate reward instead of larger delayed reward (Castellanos et al. 2006; Luman et al. 2005; Marco et al. 2009). Interestingly, if children with ADHD can expect highly valuable rewards, they choose the delayed reward as often as controls (Marx et al. 2011b). Also, IQ was identified to be a meaningful mediator that has to be taken into account in studies of reward processing (Wilson et al. 2011).

In addition, the effect of reinforcement on performance in children with ADHD differs between studies and tasks. Reinforcement was found to positively influence children’s reaction time variability, yet to the same extent in children with ADHD and controls (Epstein et al. 2011). Other studies found a negative influence of reward on temporal information processing (Luman et al. 2009). Current research indicates that the kind of reward has an impact on its effectiveness in enhancing performance in children with ADHD compared to controls: In a go/no-go task, children with ADHD showed smaller false alarm rates than controls when reinforced by social stimuli. However, monetary reward had an influence on reaction times: While children with ADHD reacted more slowly under monetary reward condition, controls showed reduced reaction times (Kohls et al. 2009a, b).

Due to the high comorbidity rates between ADHD and ASD, the specificity of aberrant reward processing for ADHD has been under debate. Comparative studies including participants with ADHD as well as ASD found children with ADHD to show delay aversion, while children with ASD did not differ from controls (Antrop et al. 2006). In a learning experiment, authors manipulated the frequency and magnitude of monetary reinforcement and compared children with ADHD, ASD and controls. No difference between groups was found regarding reinforcement amount. Compared to controls, performance of the children with ADHD was not influenced by reinforcement frequency, while children with ASD showed an intermediate performance between children with ADHD and controls. However, this result may be due to the fact that ADHD symptoms were present in more than 70 % of the children with ASD, but were not accounted for in the statistical analysis (Luman et al. 2009). In a well conducted study that compared the impact of type and amount of reward on performance in a reaction time task, authors compared children with ADHD, ASD and typically developing controls. They excluded participants with clinically relevant ADHD symptoms from the ASD group. Results indicate

that groups did not differ in their performance in response to the amount of reward, and that reward in general had a positive influence on performance independent from group. At the same time, participants of both clinical groups reacted faster when reinforced by monetary compared to social reward, which was not true for controls (Demurie et al. 2011b).

Studies concentrating on reward processing in ASD found larger effects of monetary reward compared to social reward in a reaction time task in adults with ASD as well as in the control group. However, participants with ASD differed from controls in their activation of reward-related neural structures in both conditions (Dichter et al. 2012; Schmitz et al. 2008). A general difference in reward processing that was independent from the type of reward was found in an electrophysiological study, which was conducted with children (Kohls et al. 2011). Contrary to results from behavioral studies, at first sight, these results may suggest, that participants with ASD show a general aberrant neural reward processing independently from reward type. However, there is also evidence for comparable neural reward processing in subjects with ASD compared to controls (Larson et al. 2011) as well as evidence for a more pronounced difference in the processing of social compared to monetary rewards in subjects with ASD, which indicates not only a general, but also a specific difference in processing of social reward (Scott-Van Zeeland et al. 2010).

In summary, altered reward processing in subjects with ADHD can be seen as a core characteristic of this disorder, and results of current research support models of ADHD focussing on motivational differences in addition to models focussing on executive functioning deficits. Comparative studies found similarities as well as differences in reward processing between participants with ADHD and ASD. Most studies indicate an aberrant reward processing in ASD, too, but presumably to a lower extent than in ADHD. Regarding both disorders, the effect of the type of reward remain unclear. Studies differentiating monetary and social rewards yield complementary results for ADHD as well as for ASD. Therefore, more research on this topic within reward processing in ADHD and ASD as well as more comparative studies are needed to clarify these research questions.

Social cognition

Social cognition comprises a large range of skills such as de- and encoding of social cues, memory for and retrieval of social information, and the processing of such information. For ASD, a deficit in special fields of social cognition is assumed to represent a potential endophenotype with underlying abnormal development of neural networks

(Cheng et al. 2011; Derntl and Habel 2011; Domes et al. 2008; Hadjikhani et al. 2006; Pelphrey et al. 2011). Yet, taking a closer look at research results regarding social cognition in ASD, considerable differences in the extent to which different aspects have been investigated emerge. While some areas of social cognition have been studied intensively, others are rather un-investigated. Regarding ADHD, some social cognition deficits have also been shown, but to a fewer extent and less consistently. Taking into account the potential impact of this field of research, we highlight some of the most important fields of social cognition and their relevance for ASD as well as ADHD.

Social perception

Emotion recognition can be seen as a core function of social information encoding. Children with ASD have been found to be impaired in the recognition of emotions in a large number of studies (Golan et al. 2007; Kuusikko et al. 2009). They not only differ in emotion recognition competence but also in autonomic responses regarding heart rate and respiration to emotional expressions (Bal et al. 2010). Different mechanisms have been discussed to underlie emotion recognition impairments in ASD. Studies on eye gaze and visual attention reported inconsistent findings (Back et al. 2007; Speer et al. 2007). Also, the role of the neuropeptide oxytocin has been studied: Application of oxytocin not only improves emotion recognition performance in non-clinical participants but also in subjects with ASD (Guastella et al. 2010).

Nevertheless, some studies failed to find general differences in emotion recognition in children with ASD compared to controls or found differences only for specific emotional expressions, complex stimulus materials or younger age groups (Jones et al. 2011; Rump et al. 2009; Schwenck et al. 2011a).

Despite of high comorbidity, few of these studies have taken comorbid ADHD symptoms into account. Past research also yields evidence for impaired emotion recognition in children and adults with ADHD (Kats-Gold et al. 2007; Uekermann et al. 2010; Yuill and Lyon 2007). Electrophysiological research indicates deficits in early face processing in subjects with ADHD (Ibanez et al. 2011). Furthermore, in adults with ADHD, subtype differences were found regarding emotion recognition ability. Inattention, not impulsivity and hyperactivity, predicted these impairments (Miller et al. 2011). On the contrary, no subtype differences were observed in children (Schwenck et al. 2011b). One study compared children with ADHD, with ASD and ADHD, pure ASD and a control group regarding emotion recognition competence (Sinzig et al. 2008b). The authors found children of both groups with ADHD diagnosis to be more impaired in affect recognition

than children with pure ASD or the control group. Emotion recognition ability did not correlate with neither ASD- nor ADHD symptoms, but with the specific neurocognitive functions inhibition and sustained attention. According to these results, ADHD symptoms and specific functions of attention should be taken into account when assessing emotion recognition abilities in participants with ASD.

Self-perception

Self-perception constitutes an important brick between social perception and socially adjusted action. While physical self-awareness and a sense of physical agency seem to be unimpaired in subjects with ASD, there is evidence for a diminished psychological self-awareness (David et al. 2010; Lind 2010; Lou 2012; Williams 2010). Studies on psychological self-awareness in ASD show a delayed self-recognition indicated by the usage of first-person pronouns (Lind and Bowler 2009) and a reduced awareness of own feelings (Silani et al. 2008) and intentions (Williams and Happe 2010).

Research on self-perception in ADHD is rare and has addressed questions other than in ASD research. No comparative studies have been conducted to date. The majority of studies addressed the question of self-regulation competencies, rather than self-awareness, which have been found to be impaired in children with ADHD (Lou 2012). Studies that focused on self-perception in ADHD found children with ADHD to show a positively biased self-perception (McQuade et al. 2011b; Ohan and Johnston 2011). Positively biased self-perception in the field of academic performance and social skills were related to deficits in executive functions. On the other hand, longitudinal research indicates loss of positive self-perception in children with ADHD to be related to depressive symptoms (McQuade et al. 2011a).

Processing of social information

Without any doubt, theory of mind (ToM) is the concept most intensely analyzed within social information processing in ASD. A large number of studies found children with autism to be impaired in ToM (Flood et al. 2011; Lind and Bowler 2010; Marsh and Hamilton 2011; Pellicano 2010; Schwenck et al. 2011a; Senju 2011), and the most severe impairments were found in ecologically valid tasks (Roeyers and Demurie 2010). Since ToM competencies were found to be related to executive functioning performance (Ahmed and Stephen 2011; Pellicano 2007), it was discussed whether ToM deficiencies are a potential endophenotype for both disorders, ADHD and ASD. Studies comparing ADHD and ASD, respectively, controlling for

ADHD symptomatology in children with ASD, observed a negative relationship between ToM performance and ASD symptoms, but not with ADHD symptoms (Ames and White 2011; Demurie et al. 2011a; Yang et al. 2009). A recent review on ToM competencies in children with ADHD concluded, that ToM abilities are not impaired. Thus, ToM impairments are no potential endophenotype for ADHD in contrast to ASD (Geurts et al. 2010). Structural brain abnormalities exclusively found for ASD were discussed to be associated with ToM impairments. As opposed to children with ADHD, children with ASD showed increased gray matter volume near the right temporo-parietal junction (Brieber et al., 2007).

Another field of the processing of social information is memory performance for social cues. No studies directly comparing participants with ASD and ADHD have been conducted to date. Regarding ASD, studies indicate impaired autobiographical memory (Lind 2010), which presumably is directly linked with ToM performance (Adler et al. 2010). While children with ASD were not found to show reduced recognition performance for non-social stimulus material, they performed worse, compared to controls, in identifying the source of their memory: Control children were significantly better in specifying whether they themselves or the experimenter had named a picture card that had to be remembered later (Lind and Bowler 2009). In this study children with ASD comparably to control children showed the so-called self-enhancement-effect which means that they showed better memory performance for pictures they had labeled themselves compared to those the experimenter had labeled. On the contrary, another study did not find the self-enhancement effect in children with ASD (Henderson et al. 2009). Confronted with a memory task for human faces, children as well as adults with ASD were found to be less accurate in their confidence ratings regarding their memory performance than controls (Wilkinson et al. 2010).

Regarding ADHD, research on memory performance primarily focused on memory for non-social stimuli. Since different research questions have been addressed so far, it is difficult to compare ADHD study results with ASD research. However, comparably to ASD, there is some evidence for impaired autobiographical memory in children with ADHD, too (Klein et al. 2011). Furthermore, with regard to emotional content, children with ADHD show comparable memory performance for stimuli with positive and negative valence, while they perform worse than controls when exposed to neutral stimuli (Krauel et al. 2009). At the same time, participants with ADHD are more easily distracted by emotional cues, which results in reduced memory performance (Marx et al. 2011a).

Social cognition: conclusion

Summarizing results from social cognition research in ASD and ADHD, it can be concluded, that despite the unchallenged relevance of the topic on the one hand and high comorbidity rates between the disorders on the other hand, there is still a striking lack of comparative studies in this field of research. Regarding social perception, difficulties in emotion recognition were found in both disorders, while a comparative study found these difficulties to be related to special functions of attention, and children with ADHD to be more impaired than those with pure ASD. The overlap in research addressing the processing of social information can be found in ToM-research. Here, results indicate a specific impairment in children with ASD, while ToM-impairment seems to be unrelated to ADHD symptomatology. Studies on other fields of social cognition research like memory or self-perception addressed different questions in research on ADHD and ASD, which makes it difficult to compare results. Therefore, there is still a lot to be learned by comparative studies in this promising field of research.

Selective brain imaging findings

Although shared and distinct neuropsychological as well as genetic findings have been studied in ASD and ADHD, neuroimaging studies which compare both conditions are lacking. Currently, conclusions about specific and shared brain imaging findings can only be drawn from studies performed separately in both clinical entities (Gargaro et al. 2011). None of the neuroimaging studies to date have controlled for ADHD symptoms in studies on ASD and vice versa.

Neuroimaging studies in children with ADHD have shown consistent abnormalities relative to control subjects in the inferior frontostriatal and frontocerebellar circuitries that mediate cognitive control functions that are impaired in the disorder (Bush 2011; Castellanos et al. 2009; Dickstein et al. 2006; Durston et al. 2011; Rubia 2011). Thus, structural MRI studies found reduced volume and cortical thickness in inferior prefrontal cortex, but also in other frontal cortical regions, as well as in parieto-temporal regions, the basal ganglia, the splenium of the corpus callosum, and the cerebellum. Diffusion tensor imaging studies have provided evidence for abnormalities in multiple white matter tracts in cingulate and frontostriatal, as well as frontoparietal, frontocerebellar, and parieto-occipital white matter tracts in ADHD. Functional imaging studies have shown a reduced activation in ADHD in the inferior prefrontal cortex, anterior cingulate, caudate nucleus, and temporo-parietal regions during tasks of

motor response, inhibition and attention. Furthermore, ADHD children have also shown reduced activation in dorsal and ventrolateral prefrontal, cingulate, and cerebellar brain regions during temporal processing. Moreover, some studies have tested for neurofunctional deficits in children with ADHD during tasks of motivation, finding abnormalities in ventral striatum, orbitofrontal, and cingulate cortices during reward-related processes. Studies on functional connectivity during the resting state have revealed a reduced connectivity in ADHD children related to healthy controls in frontostriatal, frontoparietal, temporo-parietal, and frontocerebellar networks. All these findings point to a specific dysfunction in fronto-striato-cerebellar and frontoparietal networks in ADHD.

In children, adolescents and adults with ASD (Amaral et al. 2008; Anagnostou and Taylor 2011; Mueller et al. 2011; Philip et al. 2012; Stanfield et al. 2008) structural MRI studies have revealed consistent findings of accelerated brain volume growth in early childhood, resulting in increased gray and white matter volume throughout adolescence, and a reduced volume of the corpus callosum (Freitag et al. 2009). Inconsistent findings have been reported with respect to local volume reductions or increases in the cerebellum, amygdala, caudate nuclei and cingulate cortex as well as parts of the frontal, temporal, and parietal lobes, the thalamus and brainstem. In addition, DTI studies in children and adults have shown disturbances of fronto-striatal, fronto-temporal and fronto-occipital white matter tracts (Ameis et al. 2011; Bode et al. 2011; Langen et al. 2012). Studies using functional MRI have demonstrated attenuated BOLD signals for basic as well as complex information processing tasks. In simple motor and perceptual tasks, patients with ASD have been characterized by an abnormal activation in primary sensory and motor cortices as well as the thalamus. In executive, language, and social cognition tasks, ASD patients have shown activation differences to healthy subjects in the middle and inferior frontal gyrus, superior temporal gyrus, inferior parietal lobe as well as in the fusiform gyrus during face processing. Functional connectivity studies, based on fMRI data, have consistently demonstrated abnormal patterns of connectivity within different networks such as the default mode network, networks of language processing, executive functions and social cognition with decreased cortical-cortical connectivity and increased connectivity between subcortical and cortical regions.

It seems likely that ASD represents a disorder with more general abnormalities and atypical connectivity compared to ADHD. In addition, a number of common structures emerge from the aforementioned studies, which seem to be involved in both ADHD and ASD: the medial frontal and prefrontal cortex, as well as structures of the default mode network.

Only a few neuroimaging studies directly compared individuals with ADHD and ASD to elicit disorder-specific findings. None of the studies, however, systematically controlled for ADHD symptoms in ASD or did include a combined ASD+ADHD group.

A structural MRI study in 15 children and adolescents with ASD, 15 age matched ADHD patients and 15 healthy peers described common gray matter reductions in the left medial temporal lobe and increased gray matter volumes in the left inferior parietal cortex in both disorders (Brieber et al. 2007). In addition, increased gray matter volume in the right temporo-parietal junction was only observed in ASD individuals. It has been suggested that the common gray matter abnormalities are likely to be related to common neuropsychological deficits in ASD and ADHD such as memory, executive and attention function. ASD-specific gray matter changes were associated with impaired social cognitive abilities.

Another study correlated radiate white matter volume within the primary motor cortex using anatomical MRI with motor performance in 20 children with ASD, 36 healthy children and 20 children with ADHD (Mostofsky et al. 2007). In healthy children, white matter volume predicted better motor skills. The opposite effect was observed in children with ASD: increased white matter volume predicted poorer motor skills. No significant correlations were found for ADHD. In between-group comparison, the only differences for correlation coefficients between white matter volume and motor performance were found for ASD compared with both healthy and ADHD children. The authors suggested that the abnormal association between radiate white matter volume and functional motor skill impairment may be related to specific global pattern of brain abnormality in ASD.

A recent fMRI study investigated haemodynamic changes during a vigilance task with a progressively increasing load of sustained attention in 20 boys with ADHD, 20 age and IQ matched ASD and 20 healthy boys using functional MRI (Christakou et al. 2012). ADHD and ASD boys showed reduced activation relative to controls in bilateral striato-thalamic regions, left dorsolateral prefrontal cortex and superior parietal cortex. Both groups also displayed increased precuneus activation compared with controls. In healthy subjects, haemodynamic changes in precuneus negatively correlated with the activation in the dorsolateral prefrontal cortex (DLPFC). This correlation was not found in both patient groups suggesting reduced deactivation of a task-related default mode network in both disorders. Underactivation in the left DLPFC was more pronounced in ADHD relative to ASD boys, which furthermore was associated with sustained performance measures that were only impaired in ADHD patients. In contrast, ASD boys showed disorder-specific enhanced

cerebellar activation relative to both ADHD and control boys. The study provides evidence that shared deficits in ADHD and ASD are likely to be related to fronto-striato-parietal activation and default mode suppression, and differences between disorders may comprise a more severe DLPFC dysfunction in ADHD and fronto-striato-cerebellar dysregulation in ASD.

The findings of these studies have to be replicated in different age groups and also in females with ADHD and ASD, who rarely were assessed in neuroimaging studies. In addition, studies directly comparing the three clinical groups, ASD, ADHD, and ASD with ADHD need to be done to elicit the specific impairments associated with the single or the combined disorders.

Therapeutic aspects

For most disorders in child and adolescent psychiatry, a multimodal therapy is the recommended treatment. Nevertheless, according to current scientific findings, the composition of therapeutic modules and key aspects of this multimodal treatment differ between disorders. Although both, ADHD and ASD are largely caused by biological factors, treatment strategies of choice differ and furthermore depend on the profile of comorbid disorders for each group. Only few specific studies on a targeted treatment for children, adolescents and adults with comorbid ADHD and ASD have been performed to date. In addition, the differential or common neuropsychological strengths and weaknesses or risk factors have only rarely been addressed by specific therapeutic approaches.

To date surprisingly few controlled studies have been undertaken to evaluate different psychosocial treatments for ADHD (Murphy 2005). In contrast, medical therapeutic options in ADHD are well researched. The first line treatment for ADHD is methylphenidate treatment, which showed superior effects on ADHD symptoms compared to behavioral therapy in a large randomized controlled trial (Jensen et al. 2001b). With regard to comorbid disorders, additional psychotherapeutic modules are indicated depending on the pattern of comorbidity and risk factors (Jensen et al. 2001a). A recently published meta-analysis showed large effect sizes of methylphenidate (alone or in combination with CBT) on ADHD symptoms, while CBT alone showing moderate effect sizes. Comorbid ODD/CD symptoms and social behavior were also improved by medication alone or in combination with CBT with large effect sizes. Less improvement was observed with CBT, and no effect on academic performance was observed by both treatments (van der Oord et al. 2008). A critical aspect of past research on ADHD treatment is that most studies concentrated on young school aged children without

considering developmental aspects. Treatment indication might differ from preschool to adulthood, which should be addressed by future research. Furthermore, future studies should take into account the different subtypes of the disorder, since subtypes may respond differently to different treatments.

Methylphenidate also is clearly effective in treating children with ASD and hyperactive symptoms or comorbid ADHD, but a lower daily dose is generally required (Aman et al. 2005). In addition, atomoxetine also alleviates ADHD symptoms in both disorders (Arnold et al. 2006; Hanwella et al. 2011).

With respect to other specific comorbid disorders, ADHD children with comorbid anxiety or conduct disorder show a better outcome when methylphenidate and behavioral therapy are combined (March et al. 2000). Similarly, ADHD with comorbid depression should be treated by a combination of methylphenidate and behavioral therapy, but also the additional use of SSRIs is an option. The empirical basis for these combined therapies, however, is still scarce. A combined pharmacotherapy is recommended in those cases in which the comorbid symptomatology persists after the target symptomatology has been diminished. Targets of the additional psychosocial treatment are social and academic problems (Daviss 2008). According to the results of the TADS study, adolescents with depression and comorbid disorders showed best response rates to a treatment of SSRI and CBT (Curry et al. 2006). However, the kind of comorbid disorder was not differentiated in this study; thus no specific recommendation on ADHD comorbid with depression can be drawn from this study.

A new therapeutic approach for ADHD and ASD is bio- or neurofeedback-therapy. In ADHD, randomized—controlled studies reported effects of EEG neurofeedback especially aiming at the theta/beta ratio on the reduction of inattentive and impulsive symptoms (Arns et al. 2009). No such studies have been performed in ASD to date (Holtmann et al. 2011).

Omega-3 fatty acids may improve ADHD symptoms, but large randomized-controlled studies need to be done (Richardson 2012). A recent Cochrane review did not find any evidence for an effect of Omega-3 fatty acids in ASD (James et al. 2011).

In preschool children with ASD, the treatment of choice is behaviorally based early intervention (Freitag 2010; Ospina et al. 2008). No such studies have been performed in children with ADHD. Comprehensive programs as well as treatments that target specific areas of behavior have been shown to reduce problematic behavior in children with ASD and to enhance communication and social skills (Vismara and Rogers 2010). Treatments were shown to be most effective if they were applied before the age of 5 years and with an intensity of at least 15 h per week for

at least 2 years. Under these conditions significant improvements in IQ, communication and social functioning were shown in different studies (Ospina et al. 2008). Still, despite this treatment intensity, not all children with ASD improve with therapy (Howlin 2005), and a comparison of different approaches has rarely been performed (Ospina et al. 2008). In addition, most health or social systems cannot afford the expenses associated with treatments of such intensity. Therefore, high quality research on additional, more targeted approaches needs to be done.

In older school aged children with ASD, autism-specific social skills training leads to improved social responsiveness (Kasari et al. 2012; White et al. 2007), whereas in ADHD, social skills training did not result in improved social skills nor reduced ADHD symptoms (Storebo et al. 2011). Some social skills trainings in ASD have also included parents as coaches in the social skills training, but a direct comparison of social skills training with or without parental support has not been done (Frankel and Whitham 2011). A recent study showed that the kind of comorbidity may influence the efficacy of social skills training in ASD: While children with ASD and comorbid symptoms of anxiety improved by a social skills training, children with ASD and comorbid ADHD did not (Antshel et al. 2011). Despite of the generally promising results, the aim of future research should be to prove long-term effects and generalization of interventions effects.

Additional therapeutic options in ASD are several psychotropic drugs, which specifically can improve comorbid disorders or symptoms, for example, hyperactivity (see above), aggressive and stereotyped behavior as well as sleeping problems. Several recent reviews summarized the findings on psychopharmacotherapy in ASD (Coury 2010; Freitag 2012). Additional studies are required to develop targeted psychopharmacotherapy for the core symptoms of ASD, intellectual disability, and comorbid disorders or symptoms. Especially, the recent genetic and proteomic findings need to be translated into more specific psychopharmacological approaches for both disorders, ASD and ADHD.

Beyond methylphenidate and atomoxetine therapy, no specific studies on targeted treatment for children, adolescents and adults with comorbid ADHD and ASD have been performed to date. In addition, the differential or common neuropsychological strengths and weaknesses or risk factors have only rarely been addressed by specific therapeutic approaches.

Conclusions

The present review aimed at selectively presenting and discussing overlapping and specific symptoms of ADHD

and ASD as well as associated risk factors, biological and neuropsychological processes. Due to the vast literature on both disorders, the review focused on selected aspects with an emphasis on studies including a comparison of both disorders. Several open questions remain regarding overlapping and distinct risk factors, especially with regard to genetic and environmental risk factors and their specific mediating mechanisms. Proteomic research is just in its infancy, and further studies are necessary to be able to distinguish the disorders or specific subtypes of the disorders for better diagnosis and treatment. A specific pattern of psychosocial risk factors emerged for ADHD, whereas ASD seems to be affected by more severe and specific impairments of social cognition, and a distinct brain structure and function. The results from basic research have yet to be translated into even more specific and individualized therapeutic approaches for the disorders ASD, ADHD, and ASD+ADHD.

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References

- Abrahams BS, Geschwind DH (2010) Connecting genes to brain in the autism spectrum disorders. *Arch Neurol* 67:395–399
- Adler N, Nadler B, Eviatar Z, Shamay-Tsoory SG (2010) The relationship between theory of mind and autobiographical memory in high-functioning autism and Asperger syndrome. *Psychiatry Res* 178:214–216
- Ahmed FS, Stephen ML (2011) Executive function mechanisms of theory of mind. *J Autism Dev Disord* 41:667–678
- Aman MG, Arnold LE, Ramadan Y, Witwer A, Lindsay R, McDougle CJ, Posey DJ, Swiezy N, Kohn A, McCracken JT, Shah B, Cronin P, McGough J, Lee JSY, Scahill L, Martin A, Koenig K, Carroll D, Young C, Lancor A, Tierney E, Ghuman J, Gonzalez NM, Grados M, Vitiello B, Ritz L, Chuang S, Davies M, Robinson J, McMahon D (2005) Randomized, controlled, crossover trial of methylphenidate in pervasive developmental disorders with hyperactivity. *Arch Gen Psychiatry* 62:1266–1274
- Amaral DG, Schumann CM, Nordahl CW (2008) Neuroanatomy of autism. *Trends Neurosci* 31:137–145
- Ameis SH, Fan J, Rockel C, Voineskos AN, Lobaugh NJ, Soorya L, Wang AT, Hollander E, Anagnostou E (2011) Impaired structural connectivity of socio-emotional circuits in autism spectrum disorders: a diffusion tensor imaging study. *PLoS One* 6:e28044
- Ames CS, White SJ (2011) Are ADHD traits dissociable from the autistic profile? Links between cognition and behaviour. *J Autism Dev Disord* 41:357–363
- Anagnostou E, Taylor MJ (2011) Review of neuroimaging in autism spectrum disorders: what have we learned and where we go from here. *Mol Autism* 2:4
- Anney R, Klei L, Pinto D, Regan R, Conroy J, Magalhaes TR, Correia C, Abrahams BS, Sykes N, Pagnamenta AT, Almeida J, Bacchelli E, Bailey AJ, Baird G, Battaglia A, Berney T, Bolshakova N, Bolte S, Bolton PF, Bourgeron T, Brennan S, Brian J, Carson AR, Casallo G, Casey J, Chu SH, Cochrane L, Corsello C, Crawford EL, Crossett A, Dawson G, de JM, Delorme R, Drmic I, Duketis E, Duque F, Estes A, Farrar P, Fernandez BA, Folstein SE, Fombonne E, Freitag CM, Gilbert J, Gillberg C, Glessner JT, Goldberg J, Green J, Guter SJ, Hakonarson H, Heron EA, Hill M, Holt R, Howe JL, Hughes G, Hus V, Iglizoi R, Kim C, Klauck SM, Kolevzon A, Korvatska O, Kustanovich V, Lajonchere CM, Lamb JA, Laskawiec M, Leboyer M, Le CA, Leventhal BL, Lionel AC, Liu XQ, Lord C, Lotspeich L, Lund SC, Maestrini E, Mahoney W, Mantoulan C, Marshall CR, McConachie H, McDougle CJ, McGrath J, McMahon WM, Melhem NM, Merikangas A, Migita O, Minshew NJ, Mirza GK, Munson J, Nelson SF, Noakes C, Noor A, Nygren G, Oliveira G, Papanikolaou K, Parr JR, Parrini B, Paton T, Pickles A, Piven J, Posey DJ, Poustka A, Poustka F, Prasad A, Ragoussis J, Renshaw K, Rickaby J, Roberts W, Roeder K, Roge B, Rutter ML, Bierut LJ, Rice JP, Salt J, Sansom K, Sato D, Segurado R, Senman L, Shah N, Sheffield VC, Soorya L, Sousa I, Stoppioni V, Strawbridge C, Tancredi R, Tansey K, Thiruvahindrapuram B, Thompson AP, Thomson S, Tryfon A, Tsiantis J, van EH, Vincent JB, Volkmar F, Wallace S, Wang K, Wang Z, Wassink TH, Wing K, Wittmeyer K, Wood S, Yaspan BL, Zurawiecki D, Zwaigenbaum L, Betancur C, Buxbaum JD, Cantor RM, Cook EH, Coon H, Cuccaro ML, Gallagher L, Geschwind DH, Gill M, Haines JL, Miller J, Monaco AP, Nurnberger JI, Jr., Paterson AD, Pericak-Vance MA, Schellenberg GD, Scherer SW, Sutcliffe JS, Szatmari P, Vicente AM, Vieland VJ, Wijsman EM, Devlin B, Ennis S, Hallmayer J (2010) A genome-wide scan for common alleles affecting risk for autism. *Hum Mol Genet* 19:4072–4082
- Antrop I, Stock P, Verte S, Wiersma JR, Baeyens D, Roeyers H (2006) ADHD and delay aversion: the influence of non-temporal stimulation on choice for delayed rewards. *J Child Psychol Psychiatry* 47:1152–1158
- Antshel KM, Polacek C, McMahon M, Dygert K, Spenceley L, Dygert L, Miller L, Faisal F (2011) Comorbid ADHD and anxiety affect social skills group intervention treatment efficacy in children with autism spectrum disorders. *J Dev Behav Pediatr* 32:439–446
- Arnold LE, Aman MG, Cook AM, Witwer AN, Hall KL, Thompson S, Ramadan Y (2006) Atomoxetine for hyperactivity in autism spectrum disorders: placebo-controlled crossover pilot trial. *J Am Acad Child Adolesc Psychiatry* 45:1196–1205
- Arns M, de Ridder S, Strehl U, Bretelet M, Coenen A (2009) Efficacy of neurofeedback treatment in ADHD: the effects on inattention, impulsivity and hyperactivity: a meta-analysis. *Clin EEG Neurosci* 40:180–189
- Atladdottir HO, Thorsen P, Ostergaard L, Schendel DE, Lemcke S, Abdallah M, Parner ET (2010a) Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders. *J Autism Dev Disord* 40:1423–1430
- Atladdottir HO, Thorsen P, Schendel DE, Ostergaard L, Lemcke S, Parner ET (2010b) Association of hospitalization for infection in childhood with diagnosis of autism spectrum disorders: a Danish cohort study. *Arch Pediatr Adolesc Med* 164:470–477
- Back E, Ropar D, Mitchell P (2007) Do the eyes have it? Inferring mental states from animated faces in autism. *Child Dev* 78:397–411
- Bal E, Harden E, Lamb D, Van Hecke AV, Denver JW, Porges SW (2010) Emotion recognition in children with autism spectrum disorders: relations to eye gaze and autonomic state. *J Autism Dev Disord* 40:358–370
- Banaschewski T, Becker K, Scherag S, Franke B, Coghill D (2010) Molecular genetics of attention-deficit/hyperactivity disorder: an overview. *Eur Child Adolesc Psychiatry* 19:237–257
- Ben-David E, Shifman S (2012) Networks of neuronal genes affected by common and rare variants in autism spectrum disorders. *PLoS Genet* 8:e1002556

- Bill BR, Geschwind DH (2009) Genetic advances in autism: heterogeneity and convergence on shared pathways. *Curr Opin Genet Dev* 19:271–278
- Bode MK, Mattila ML, Kiviniemi V, Rahko J, Moilanen I, Ebeling H, Tervonen O, Nikkinen J (2011) White matter in autism spectrum disorders—evidence of impaired fiber formation. *Acta Radiol* 52:1169–1174
- Brieber S, Neufang S, Bruning N, Kamp-Becker I, Remschmidt H, Herpertz-Dahlmann B, Fink GR, Konrad K (2007) Structural brain abnormalities in adolescents with autism spectrum disorder and patients with attention deficit/hyperactivity disorder. *J Child Psychol Psychiatry* 48:1251–1258
- Bucan M, Abrahams BS, Wang K, Glessner JT, Herman EI, Sonnenblick LI, Alvarez Retuerto AI, Imielinski M, Hadley D, Bradfield JP, Kim C, Gidaya NB, Lindquist I, Hutman T, Sigman M, Kustanovich V, Lajonchere CM, Singleton A, Kim J, Wassink TH, McMahon WM, Owley T, Sweeney JA, Coon H, Nurnberger JI, Li M, Cantor RM, Minshew NJ, Sutcliffe JS, Cook EH, Dawson G, Buxbaum JD, Grant SF, Schellenberg GD, Geschwind DH, Hakonarson H (2009) Genome-wide analyses of exonic copy number variants in a family-based study point to novel autism susceptibility genes. *PLoS Genet* 5:e1000536
- Buhler E, Bachmann C, Goyert H, Heinzl-Gutenbrunner M, Kamp-Becker I (2011) Differential diagnosis of autism spectrum disorder and attention deficit hyperactivity disorder by means of inhibitory control and ‘theory of mind’. *J Autism Dev Disord* 41:1718–1726
- Bush G (2011) Cingulate, frontal, and parietal cortical dysfunction in attention-deficit/hyperactivity disorder. *Biol Psychiatry* 69:1160–1167
- Castellanos FX, Sonuga-Barke EJ, Milham MP, Tannock R (2006) Characterizing cognition in ADHD: beyond executive dysfunction. *Trends Cogn Sci* 10:117–123
- Castellanos FX, Kelly C, Milham MP (2009) The restless brain: attention-deficit hyperactivity disorder, resting-state functional connectivity, and intrasubject variability. *Can J Psychiatry* 54:665–672
- Cheng Y, Chou KH, Fan YT, Lin CP (2011) ANS: aberrant neurodevelopment of the social cognition network in adolescents with autism spectrum disorders. *PLoS One* 6:e18905
- Christ SE, Holt DD, White DA, Green L (2007) Inhibitory control in children with autism spectrum disorder. *J Autism Dev Disord* 37:1155–1165
- Christakou A, Murphy CM, Chantiluke K, Cubillo AI, Smith AB, Giampietro V, Daly E, Ecker C, Robertson D, Murphy DG, Rubia K (2012) Disorder-specific functional abnormalities during sustained attention in youth with attention deficit hyperactivity disorder (ADHD) and with autism. *Mol Psychiatry* [Epub ahead of print]
- Cohen MJ, Meador KJ, Browning N, Baker GA, Clayton-Smith J, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW (2011) Fetal antiepileptic drug exposure: motor, adaptive, and emotional/behavioral functioning at age 3 years. *Epilepsy Behav* 22:240–246
- Corbett BA, Constantine LJ (2006) Autism and attention deficit hyperactivity disorder: assessing attention and response control with the integrated visual and auditory continuous performance test. *Child Neuropsychol* 12:335–348
- Corbett BA, Kantor AB, Schulman H, Walker WL, Lit L, Ashwood P, Rocke DM, Sharp FR (2007) A proteomic study of serum from children with autism showing differential expression of apolipoproteins and complement proteins. *Mol Psychiatry* 12:292–306
- Corbett BA, Constantine LJ, Hendren R, Rocke D, Ozonoff S (2009) Examining executive functioning in children with autism spectrum disorder, attention deficit hyperactivity disorder and typical development. *Psychiatry Res* 166:210–222
- Coury D (2010) Medical treatment of autism spectrum disorders. *Curr Opin Neurol* 23:131–136
- Croen LA, Grether JK, Yoshida CK, Odouli R, Van de Water J (2005) Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorders: a case-control study. *Arch Pediatr Adolesc Med* 159:151–157
- Croen LA, Grether JK, Yoshida CK, Odouli R, Hendrick V (2011) Antidepressant use during pregnancy and childhood autism spectrum disorders. *Arch Gen Psychiatry* 68:1104–1112
- Curran S, Bolton P, Rozsnyai K, Chiochetti A, Klauck SM, Duketis E, Poustka F, Schlitt S, Freitag CM, Lee I, Muglia P, Poot M, Staal W, De Jonge MV, Ophoff RA, Lewis C, Skuse D, Mandy W, Vassos E, Fossdal R, Magnusson P, Hreidarsson S, Saemundsen E, Stefansson H, Stefansson K, Collier D (2011) No association between a common single nucleotide polymorphism, rs4141463, in the MACROD2 gene and autism spectrum disorder. *Am J Med Genet B Neuropsychiatry Genet* 156B:633–639
- Curry J, Rohde P, Simons A, Silva S, Vitiello B, Kratochvil C, Reinecke M, Feeny N, Wells K, Pathak S, Weller E, Rosenberg D, Kennard B, Robins M, Ginsburg G, March J (2006) Predictors and moderators of acute outcome in the treatment for adolescents with depression study (TADS). *J Am Acad Child Adolesc Psychiatry* 45:1427–1439
- David N, Aumann C, Bewernick BH, Santos NS, Lehnhardt FG, Vogeley K (2010) Investigation of mentalizing and visuospatial perspective taking for self and other in Asperger syndrome. *J Autism Dev Disord* 40:290–299
- Daviss WB (2008) A review of co-morbid depression in pediatric ADHD: etiology, phenomenology, and treatment. *J Child Adolesc Psychopharmacol* 18:565–571
- Demurie E, De Corel M, Roeyers H (2011a) Empathic accuracy in adolescents with autism spectrum disorders and adolescents with attention-deficit/hyperactivity disorder. *Res Autism Spectr Disord* 5:126–134
- Demurie E, Roeyers H, Baeyens D, Sonuga-Barke E (2011b) Common alterations in sensitivity to type but not amount of reward in ADHD and autism spectrum disorders. *J Child Psychol Psychiatry* 52:1164–1173
- Derntl B, Habel U (2011) Deficits in social cognition: a marker for psychiatric disorders? *Eur Arch Psychiatry Clin Neurosci* 261(Suppl 2):S145–S149
- Devlin B, Melhem N, Roeder K (2011) Do common variants play a role in risk for autism? Evidence and theoretical musings. *Brain Res* 1380:78–84
- Dichter GS, Richey JA, Rittenberg AM, Sabatino A, Bodfish JW (2012) Reward circuitry function in autism during face anticipation and outcomes. *J Autism Dev Disord* 42:147–160
- Dickstein SG, Bannon K, Castellanos FX, Milham MP (2006) The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis. *J Child Psychol Psychiatry* 47:1051–1062
- Domes G, Kumbier E, Herpertz-Dahlmann B, Herpertz SC (2008) Social cognition in autism. A survey of functional imaging studies. *Nervenarzt* 79:261–274
- Durston S, van Belle J, de Zeeuw P (2011) Differentiating frontostriatal and fronto-cerebellar circuits in attention-deficit/hyperactivity disorder. *Biol Psychiatry* 69:1178–1184
- Elia J, Gai X, Xie HM, Perin JC, Geiger E, Glessner JT, D’arcy M, deBerardinis R, Frackelton E, Kim C, Lantieri F, Muganga BM, Wang L, Takeda T, Rappaport EF, Grant SF, Berrettini W, Devoto M, Shaikh TH, Hakonarson H, White PS (2010) Rare structural variants found in attention-deficit hyperactivity disorder are preferentially associated with neurodevelopmental genes. *Mol Psychiatry* 15:637–646
- Elia J, Glessner JT, Wang K, Takahashi N, Shtir CJ, Hadley D, Sleiman PM, Zhang H, Kim CE, Robison R, Lyon GJ, Flory JH,

- Bradfield JP, Imielinski M, Hou C, Frackelton EC, Chiavacci RM, Sakurai T, Rabin C, Middleton FA, Thomas KA, Garris M, Mentch F, Freitag CM, Steinhausen HC, Todorov AA, Reif A, Rothenberger A, Franke B, Mick EO, Roeyers H, Buitelaar J, Lesch KP, Banaschewski T, Ebstein RP, Mulas F, Oades RD, Sergeant J, Sonuga-Barke E, Renner TJ, Romanos M, Romanos J, Warnke A, Walitzka S, Meyer J, Palmason H, Seitz C, Loo SK, Smalley SL, Biederman J, Kent L, Asherson P, Anney RJ, Gaynor JW, Shaw P, Devoto M, White PS, Grant SF, Buxbaum JD, Rapoport JL, Williams NM, Nelson SF, Faraone SV, Hakonarson H (2012) Genome-wide copy number variation study associates metabotropic glutamate receptor gene networks with attention deficit hyperactivity disorder. *Nat Genet* 44:78–84
- Epstein JN, Brinkman WB, Froehlich T, Langberg JM, Narad ME, Antonini TN, Shiels K, Simon JO, Altaye M (2011) Effects of stimulant medication, incentives, and event rate on reaction time variability in children with ADHD. *Neuropsychopharmacology* 36:1060–1072
- Evers M, Cunningham-Rundles C, Hollander E (2002) Heat shock protein 90 antibodies in autism. *Mol Psychiatry* 7(Suppl 2):S26–S28
- Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, Sklar P (2005) Molecular genetics of attention-deficit/hyperactivity disorder. *Biol Psychiatry* 57:1313–1323
- Feuk L, Carson AR, Scherer SW (2006) Structural variation in the human genome. *Nat Rev Genet* 7:85–97
- Figueroa R (2010) Use of antidepressants during pregnancy and risk of attention-deficit/hyperactivity disorder in the offspring. *J Dev Behav Pediatr* 31:641–648
- Flood AM, Julian HD, Wallis P (2011) An investigation into social information processing in young people with Asperger syndrome. *Autism* 15:601–624
- Franke B, Neale BM, Faraone SV (2009) Genome-wide association studies in ADHD. *Hum Genet* 126:13–50
- Franke B, Faraone SV, Asherson P, Buitelaar J, Bau CH, Ramos-Quiroga JA, Mick E, Grevet EH, Johansson S, Haavik J, Lesch KP, Cormand B, Reif A (2011) The genetics of attention deficit/hyperactivity disorder in adults, a review. *Mol Psychiatry* [Epub ahead of print]
- Frankel F, Whitham C (2011) Parent-assisted group treatment for friendship problems of children with autism spectrum disorders. *Brain Res* 1380:240–245
- Freitag CM (2010) Empirically based early intervention programs for children with autistic disorders—a selective literature review. *Z Kinder Jugendpsychiatr Psychother* 38:247–256
- Freitag CM (2012) Autistic disorders—the state of the art and recent findings: epidemiology, aetiology, diagnostic criteria, and therapeutic interventions. *Z Kinder Jugendpsychiatr Psychother* 40:139–149
- Freitag CM, Luders E, Hulst HE, Narr KL, Thompson PM, Toga AW, Krick C, Konrad C (2009) Total brain volume and corpus callosum size in medication-naïve adolescents and young adults with autism spectrum disorder. *Biol Psychiatry* 66:316–319
- Freitag CM, Rohde LA, Lempp T, Romanos M (2010a) Phenotypic and measurement influences on heritability estimates in childhood ADHD. *Eur Child Adolesc Psychiatry* 19:311–323
- Freitag CM, Staal W, Klauk SM, Duketis E, Waltes R (2010b) Genetics of autistic disorders: review and clinical implications. *Eur Child Adolesc Psychiatry* 19:169–178
- Freitag CM, Asherson P, Hebebrand J (2012a) Behavioural genetics of childhood disorders. *Curr Top Behav Neurosci*
- Freitag CM, Hanig S, Schneider A, Seitz C, Palmason H, Retz W, Meyer J (2012b) Biological and psychosocial environmental risk factors influence symptom severity and psychiatric comorbidity in children with ADHD. *J Neural Transm* 119:81–94
- Galera C, Cote SM, Bouvard MP, Pingault JB, Melchior M, Michel G, Boivin M, Tremblay RE (2011) Early risk factors for hyperactivity-impulsivity and inattention trajectories from age 17 months to 8 years. *Arch Gen Psychiatry* 68:1267–1275
- Gargaro BA, Rinehart NJ, Bradshaw JL, Tonge BJ, Sheppard DM (2011) Autism and ADHD: how far have we come in the comorbidity debate? *Neurosci Biobehav Rev* 35:1081–1088
- Geschwind DH (2011) Genetics of autism spectrum disorders. *Trends Cogn Sci* 15:409–416
- Geurts H, Broeders M, Nieuwland MS (2010) Thinking outside the executive functions box: theory of mind and pragmatic abilities in attention deficit/hyperactivity disorder. *Eur J Dev Psychol* 7:135–151
- Ghassabian A, Bongers-Schokking JJ, de Rijke YB, van MN, Jaddoe VW, de Muinck Keizer-Schrama SM, Hooijkaas H, Hofman A, Visser W, Roman GC, Visser TJ, Verhulst FC, Tiemeier H (2012) Maternal thyroid autoimmunity during pregnancy and the risk of attention deficit/hyperactivity problems in children: the generation R study. *Thyroid* 22:178–186
- Gilman SR, Iossifov I, Levy D, Ronemus M, Wigler M, Vitkup D (2011) Rare de novo variants associated with autism implicate a large functional network of genes involved in formation and function of synapses. *Neuron* 70:898–907
- Gizer IR, Ficks C, Waldman ID (2009) Candidate gene studies of ADHD: a meta-analytic review. *Hum Genet* 126:51–90
- Gjevik E, Eldevik S, Fjaeran-Granum T, Sponheim E (2011) Kiddie-SADS reveals high rates of DSM-IV disorders in children and adolescents with autism spectrum disorders. *J Autism Dev Disord* 41:761–769
- Glessner JT, Wang K, Cai G, Korvatska O, Kim CE, Wood S, Zhang H, Estes A, Brune CW, Bradfield JP, Imielinski M, Frackelton EC, Reichert J, Crawford EL, Munson J, Sleiman PM, Chiavacci R, Annaiah K, Thomas K, Hou C, Glaberson W, Flory J, Otieno F, Garris M, Soorya L, Klei L, Piven J, Meyer KJ, Anagnostou E, Sakurai T, Game RM, Rudd DS, Zurawiecki D, McDougale CJ, Davis LK, Miller J, Posey DJ, Michaels S, Kolevzon A, Silverman JM, Bernier R, Levy SE, Schultz RT, Dawson G, Owley T, McMahon WM, Wassink TH, Sweeney JA, Nurnberger JI, Coon H, Sutcliffe JS, Minshew NJ, Grant SF, Bucan M, Cook EH, Buxbaum JD, Devlin B, Schellenberg GD, Hakonarson H (2009) Autism genome-wide copy number variation reveals ubiquitin and neuronal genes. *Nature* 459:569–573
- Golan O, Baron-Cohen S, Hill JJ, Rutherford MD (2007) The ‘reading the mind in the voice’ test-revised: a study of complex emotion recognition in adults with and without autism spectrum conditions. *J Autism Dev Disord* 37:1096–1106
- Grzadzinski R, Di MA, Brady E, Mairena MA, O’Neale M, Petkova E, Lord C, Castellanos FX (2011) Examining autistic traits in children with ADHD: does the autism spectrum extend to ADHD? *J Autism Dev Disord* 41:1178–1191
- Guastella AJ, Einfeld SL, Gray KM, Rinehart NJ, Tonge BJ, Lambert TJ, Hickie IB (2010) Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. *Biol Psychiatry* 67:692–694
- Guilmatre A, Dubourg C, Mosca AL, Legallic S, Goldenberg A, Drouin-Garraud V, Layet V, Rosier A, Briault S, Bonnet-Brilhault F, Laumonnier F, Odent S, Le VG, Joly-Helas G, David V, Bendavid C, Pinoit JM, Henry C, Impallomeni C, Germano E, Tortorella G, Di RG, Barthelemy C, Andres C, Faivre L, Frebourg T, Saugier VP, Campion D (2009) Recurrent rearrangements in synaptic and neurodevelopmental genes and shared biologic pathways in schizophrénia, autism, and mental retardation. *Arch Gen Psychiatry* 66:947–956
- Gupta AR, State MW (2007) Recent advances in the genetics of autism. *Biol Psychiatry* 61:429–437

- Gustafsson P, Kallen K (2011) Perinatal, maternal, and fetal characteristics of children diagnosed with attention-deficit-hyperactivity disorder: results from a population-based study utilizing the Swedish Medical Birth Register. *Dev Med Child Neurol* 53:263–268
- Hadjikhani N, Joseph RM, Snyder J, Tager-Flusberg H (2006) Abnormal activation of the social brain during face perception in autism. *Hum Brain Mapp*
- Halmoy A, Klungsoyr K, Skjaerven R, Haavik J (2011) Pre- and perinatal risk factors in adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry*
- Hanwella R, Senanayake M, de SV (2011) Comparative efficacy and acceptability of methylphenidate and atomoxetine in treatment of attention deficit hyperactivity disorder in children and adolescents: a meta-analysis. *BMC Psychiatry* 11:176
- Happé F, Booth R, Charlton R, Hughes C (2006) Executive function deficits in autism spectrum disorders and attention-deficit/hyperactivity disorder: examining profiles across domains and ages. *Brain Cogn* 61:25–39
- Hegde PS, White IR, Debouck C (2003) Interplay of transcriptomics and proteomics. *Curr Opin Biotechnol* 14:647–651
- Henderson HA, Zahka NE, Kojkowski NM, Inge AP, Schwartz CB, Hileman CM, Coman DC, Mundy PC (2009) Self-referenced memory, social cognition, and symptom presentation in autism. *J Child Psychol Psychiatry* 50:853–861
- Hinney A, Scherag A, Jarick I, Albayrak O, Putter C, Pechlivanis S, Dauvermann MR, Beck S, Weber H, Scherag S, Nguyen TT, Volckmar AL, Knoll N, Faraone SV, Neale BM, Franke B, Cichon S, Hoffmann P, Nothen MM, Schreiber S, Jockel KH, Wichmann HE, Freitag C, Lempp T, Meyer J, Gilsbach S, Herpertz-Dahlmann B, Sinzig J, Lehmkuhl G, Renner TJ, Warnke A, Romanos M, Lesch KP, Reif A, Schimmelmann BG, Hebebrand J (2011) Genome-wide association study in German patients with attention deficit/hyperactivity disorder. *Am J Med Genet B Neuropsychiatry Genet* 156B:888–897
- Hirano M, Rakwal R, Shibato J, Sawa H, Nagashima K, Ogawa Y, Yoshida Y, Iwahashi H, Niki E, Masuo Y (2008) Proteomics- and transcriptomics-based screening of differentially expressed proteins and genes in brain of Wig rat: a model for attention deficit hyperactivity disorder (ADHD) research. *J Proteome Res* 7:2471–2489
- Holtmann M, Bolte S, Poustka F (2007) Attention deficit hyperactivity disorder symptoms in pervasive developmental disorders: association with autistic behavior domains and coexisting psychopathology. *Psychopathology* 40:172–177
- Holtmann M, Steiner S, Hohmann S, Poustka L, Banaschewski T, Bolte S (2011) Neurofeedback in autism spectrum disorders. *Dev Med Child Neurol* 53:986–993
- Howlin P (2005) The effectiveness of interventions for children with autism. *J Neural Transm Supp* 101–119
- Huang CH, Santangelo SL (2008) Autism and serotonin transporter gene polymorphisms: a systematic review and meta-analysis. *Am J Med Genet B Neuropsychiatry Genet* 147B:903–913
- Hultman CM, Sandin S, Levine SZ, Lichtenstein P, Reichenberg A (2011) Advancing paternal age and risk of autism: new evidence from a population-based study and a meta-analysis of epidemiological studies. *Mol Psychiatry* 16:1203–1212
- Ibanez A, Petroni A, Urquina H, Torrente F, Torralva T, Hurtado E, Guex R, Blenkman A, Beltrachini L, Muravchik C, Baez S, Cetkovich M, Sigman M, Lischinsky A, Manes F (2011) Cortical deficits of emotional face processing in adults with ADHD: its relation to social cognition and executive function. *Soc Neurosci* 6:464–481
- James S, Montgomery P, Williams K (2011) Omega-3 fatty acids supplementation for autism spectrum disorders (ASD). *Cochrane Database Syst Rev* CD007992
- Jensen PS, Hinshaw SP, Kraemer HC, Lenora N, Newcorn JH, Abikoff HB, March JS, Arnold LE, Cantwell DP, Conners CK, Elliott GR, Greenhill LL, Hechtman L, Hoza B, Pelham WE, Severe JB, Swanson JM, Wells KC, Wigal T, Vitiello B (2001a) ADHD comorbidity findings from the MTA study: comparing comorbid subgroups. *J Am Acad Child Adolesc Psychiatry* 40:147–158
- Jensen PS, Hinshaw SP, Swanson JM, Greenhill LL, Conners CK, Arnold LE, Abikoff HB, Elliott G, Hechtman L, Hoza B, March JS, Newcorn JH, Severe JB, Vitiello B, Wells K, Wigal T (2001b) Findings from the NIMH multimodal treatment study of ADHD (MTA): implications and applications for primary care providers. *J Dev Behav Pediatr* 22:60–73
- Johnson KA, Robertson IH, Kelly SP, Silk TJ, Barry E, Daibhis A, Watchorn A, Keavey M, Fitzgerald M, Gallagher L, Gill M, Bellgrove MA (2007) Dissociation in performance of children with ADHD and high-functioning autism on a task of sustained attention. *Neuropsychologia* 45:2234–2245
- Johnson S, Hollis C, Kochhar P, Hennessy E, Wolke D, Marlow N (2010) Psychiatric disorders in extremely preterm children: longitudinal finding at age 11 years in the EPICure study. *J Am Acad Child Adolesc Psychiatry* 49:453–463
- Jones CR, Pickles A, Falcato M, Marsden AJ, Happe F, Scott SK, Sauter D, Tregay J, Phillips RJ, Baird G, Simonoff E, Charman T (2011) A multimodal approach to emotion recognition ability in autism spectrum disorders. *J Child Psychol Psychiatry* 52:275–285
- Junaid MA, Kowal D, Barua M, Pullarkat PS, Sklower BS, Pullarkat RK (2004) Proteomic studies identified a single nucleotide polymorphism in glyoxalase I as autism susceptibility factor. *Am J Med Genet A* 131:11–17
- Kasari C, Rotheram-Fuller E, Locke J, Gulsrud A (2012) Making the connection: randomized controlled trial of social skills at school for children with autism spectrum disorders. *J Child Psychol Psychiatry* 53:431–439
- Kates WR, Antshel KM, Fremont WP, Shprintzen RJ, Strunge LA, Burnette CP, Higgins AM (2007) Comparing phenotypes in patients with idiopathic autism to patients with velocardiofacial syndrome (22q11 DS) with and without autism. *Am J Med Genet A* 143A:2642–2650
- Kats-Gold I, Besser A, Priel B (2007) The role of simple emotion recognition skills among school aged boys at risk of ADHD. *J Abnorm Child Psychol* 35:363–378
- Klein SB, Gangi CE, Lax ML (2011) Memory and self-knowledge in young adults with ADHD. *Self Identity* 10:213–230
- Kohls G, Herpertz-Dahlmann B, Konrad K (2009a) Hyperresponsiveness to social rewards in children and adolescents with attention-deficit/hyperactivity disorder (ADHD). *Behav Brain Funct* 5:20
- Kohls G, Peltzer J, Herpertz-Dahlmann B, Konrad K (2009b) Differential effects of social and non-social reward on response inhibition in children and adolescents. *Dev Sci* 12:614–625
- Kohls G, Peltzer J, Schulte-Ruther M, Kamp-Becker I, Remschmidt H, Herpertz-Dahlmann B, Konrad K (2011) Atypical brain responses to reward cues in autism as revealed by event-related potentials. *J Autism Dev Disord* 41:1523–1533
- Krauel K, Duzel E, Hinrichs H, Rellum T, Santel S, Baving L (2009) Emotional memory in ADHD patients with and without comorbid ODD/CD. *J Neural Transm* 116:117–120
- Kroger A, Hanig S, Seitz C, Palmason H, Meyer J, Freitag CM (2011) Risk factors of autistic symptoms in children with ADHD. *Eur Child Adolesc Psychiatry* 20:561–570
- Kumar RA, Karamohamed S, Sudi J, Conrad DF, Brune C, Badner JA, Gilliam TC, Nowak NJ, Cook EH Jr, Dobyns WB, Christian SL (2008) Recurrent 16p11.2 microdeletions in autism. *Hum Mol Genet* 17:628–638

- Kumar RA, Sudi J, Babatz TD, Brune CW, Oswald D, Yen M, Nowak NJ, Cook EH, Christian SL, Dobyns WB (2010) A de novo 1p34.2 microdeletion identifies the synaptic vesicle gene RIMS3 as a novel candidate for autism. *J Med Genet* 47:81–90
- Kuusikko S, Haapsamo H, Jansson-Verkasalo E, Hurtig T, Mattila ML, Ebeling H, Jussila K, Bolte S, Moilanen I (2009) Emotion recognition in children and adolescents with autism spectrum disorders. *J Autism Dev Disord* 39:938–945
- Langen M, Leemans A, Johnston P, Ecker C, Daly E, Murphy CM, Dell'acqua F, Durston S, Murphy DG (2012) Fronto-striatal circuitry and inhibitory control in autism: findings from diffusion tensor imaging tractography. *Cortex* 48:183–193
- Larson MJ, South M, Krauskopf E, Clawson A, Crowley MJ (2011) Feedback and reward processing in high-functioning autism. *Psychiatry Res* 187:198–203
- Larsson H, Dilshad R, Lichtenstein P, Barker ED (2011) Developmental trajectories of DSM-IV symptoms of attention-deficit/hyperactivity disorder: genetic effects, family risk and associated psychopathology. *J Child Psychol Psychiatry* 52:954–963
- LaSalle JM (2011) A genomic point-of-view on environmental factors influencing the human brain methylome. *Epigenetics* 6:862–869
- Laumonnier F, Roger S, Guerin P, Molinari F, M'rad R, Cahard D, Belhadj A, Halayem M, Persico AM, Elia M, Romano V, Holbert S, Andres C, Chaabouni H, Colleaux L, Constant J, Le Guennec JY, Briault S (2006) Association of a functional deficit of the BKCa channel, a synaptic regulator of neuronal excitability, with autism and mental retardation. *Am J Psychiatry* 163:1622–1629
- Lee BK, Gardner RM, Dal H, Svensson A, Galanti MR, Rai D, Dalman C, Magnusson C (2011) Brief report: maternal smoking during pregnancy and autism spectrum disorders. *J Autism Dev Disord*
- Lee TL, Raygada MJ, Rennert OM (2012) Integrative gene network analysis provides novel regulatory relationships, genetic contributions and susceptible targets in autism spectrum disorders. *Gene* 496:88–96
- Lesch KP, Timmesfeld N, Renner TJ, Halperin R, Roser C, Nguyen TT, Craig DW, Romanos J, Heine M, Meyer J, Freitag C, Warnke A, Romanos M, Schafer H, Walitza S, Reif A, Stephan DA, Jacob C (2008) Molecular genetics of adult ADHD: converging evidence from genome-wide association and extended pedigree linkage studies. *J Neural Transm* 115:1573–1585
- Lesch KP, Selch S, Renner TJ, Jacob C, Nguyen TT, Hahn T, Romanos M, Walitza S, Shoichet S, Dempfle A, Heine M, Boreatti-Hummer A, Romanos J, Gross-Lesch S, Zerlaut H, Wulsch T, Heinzl S, Fassnacht M, Fallgatter A, Allolio B, Schafer H, Warnke A, Reif A, Ropers HH, Ullmann R (2011) Genome-wide copy number variation analysis in attention-deficit/hyperactivity disorder: association with neuropeptide Y gene dosage in an extended pedigree. *Mol Psychiatry* 16:491–503
- Levav-Rabkin T, Melamed O, Clarke G, Farber M, Cryan JF, Dinan TG, Grossman Y, Golan HM (2010) A sensitive period of mice inhibitory system to neonatal GABA enhancement by vigabatrin is brain region dependent. *Neuropsychopharmacology* 35:1138–1154
- Leyfer OT, Folstein SE, Bacalman S, Davis NO, Dinh E, Morgan J, Tager-Flusberg H, Lainhart JE (2006) Comorbid psychiatric disorders in children with autism: interview development and rates of disorders. *J Autism Dev Disord* 36:849–861
- Liao L, Park SK, Xu T, Vanderklis P, Yates JR III (2008) Quantitative proteomic analysis of primary neurons reveals diverse changes in synaptic protein content in *fmr1* knockout mice. *Proc Natl Acad Sci USA* 105:15281–15286
- Lichtenstein P, Carlstrom E, Rastam M, Gillberg C, Anckarsater H (2010) The genetics of autism spectrum disorders and related neuropsychiatric disorders in childhood. *Am J Psychiatry*
- Lind SE (2010) Memory and the self in autism: a review and theoretical framework. *Autism* 14:430–456
- Lind SE, Bowler DM (2009) Recognition memory, self-other source memory, and theory-of-mind in children with autism spectrum disorder. *J Autism Dev Disord* 39:1231–1239
- Lind SE, Bowler DM (2010) Episodic memory and episodic future thinking in adults with autism. *J Abnorm Psychol* 119:896–905
- Linnet KM, Wisborg K, Obel C, Secher NJ, Thomsen PH, Agerbo E, Henriksen TB (2005) Smoking during pregnancy and the risk for hyperkinetic disorder in offspring. *Pediatrics* 116:462–467
- Losh M, Sullivan PF, Trembath D, Piven J (2008) Current developments in the genetics of autism: from phenome to genome. *J Neuropathol Exp Neurol* 67:829–837
- Lou HC (2012) Paradigm shift in consciousness research: the child's self-awareness and abnormalities in autism, ADHD and schizophrenia. *Acta Paediatr* 101:112–119
- Luman M, Oosterlaan J, Sergeant JA (2005) The impact of reinforcement contingencies on AD/HD: a review and theoretical appraisal. *Clin Psychol Rev* 25:183–213
- Luman M, van Meel CS, Oosterlaan J, Sergeant JA, Geurts HM (2009) Does reward frequency or magnitude drive reinforcement-learning in attention-deficit/hyperactivity disorder? *Psychiatry Res* 168:222–229
- Lyall K, Pauls DL, Spiegelman D, Ascherio A, Santangelo SL (2011) Pregnancy complications and obstetric suboptimality in association with autism spectrum disorders in children of the Nurses' Health Study II. *Autism Res* [Epub ahead of print]
- Ma D, Salyakina D, Jaworski JM, Konidari I, Whitehead PL, Andersen AN, Hoffman JD, Slifer SH, Hedges DJ, Cukier HN, Griswold AJ, McCauley JL, Beecham GW, Wright HH, Abramson RK, Martin ER, Hussman JP, Gilbert JR, Cuccaro ML, Haines JL, Pericak-Vance MA (2009) A Genome-wide Association Study of Autism Reveals a Common Novel Risk Locus at 5p14.1. *Ann Hum Genet* 73:263–273
- Maiya R, Ponomarev I, Linse KD, Harris RA, Mayfield RD (2007) Defining the dopamine transporter proteome by convergent biochemical and in silico analyses. *Genes Brain Behav* 6:97–106
- Mandy W, Charman T, Gilmour J, Skuse D (2011) Toward specifying pervasive developmental disorder-not otherwise specified. *Autism Res* 4:121–131
- Mann JR, McDermott S (2011) Are maternal genitourinary infection and pre-eclampsia associated with ADHD in school-aged children? *J Atten Disord* 15:667–673
- Mann JR, McDermott S, Bao H, Hardin J, Gregg A (2010) Pre-eclampsia, birth weight, and autism spectrum disorders. *J Autism Dev Disord* 40:548–554
- March JS, Swanson JM, Arnold LE, Hoza B, Conners CK, Hinshaw SP, Hechtman L, Kraemer HC, Greenhill LL, Abikoff HB, Elliott LG, Jensen PS, Newcorn JH, Vitiello B, Severe J, Wells KC, Pelham WE (2000) Anxiety as a predictor and outcome variable in the multimodal treatment study of children with ADHD (MTA). *J Abnorm Child Psychol* 28:527–541
- Marco R, Miranda A, Schlotz W, Melia A, Mulligan A, Muller U, Andreou P, Butler L, Christiansen H, Gabriels I, Medad S, Albrecht B, Uebel H, Asherson P, Banaschewski T, Gill M, Kuntsi J, Mulas F, Oades R, Roeyers H, Steinhausen HC, Rothenberger A, Faraone SV, Sonuga-Barke EJ (2009) Delay and reward choice in ADHD: an experimental test of the role of delay aversion. *Neuropsychology* 23:367–380
- Marsh LE, Hamilton AF (2011) Dissociation of mirroring and mentalising systems in autism. *Neuroimage* 56:1511–1519
- Marshall CR, Scherer SW (2012) Detection and characterization of copy number variation in autism spectrum disorder. *Methods Mol Biol* 838:115–135
- Marshall CR, Noor A, Vincent JB, Lionel AC, Feuk L, Skaug J, Shago M, Moessner R, Pinto D, Ren Y, Thiruvahindrapuram B,

- Fiebig A, Schreiber S, Friedman J, Ketelaars CE, Vos YJ, Ficcioglu C, Kirkpatrick S, Nicolson R, Sloman L, Summers A, Gibbons CA, Teebi A, Chitayat D, Weksberg R, Thompson A, Vardy C, Crosbie V, Luscombe S, Baatjes R, Zwaigenbaum L, Roberts W, Fernandez B, Szatmari P, Scherer SW (2008) Structural variation of chromosomes in autism spectrum disorder. *Am J Hum Genet* 82:477–488
- Marx I, Domes G, Havenstein C, Berger C, Schulze L, Herpertz SC (2011a) Enhanced emotional interference on working memory performance in adults with ADHD. *World J Biol Psychiatry* 12(Suppl 1):70–75
- Marx I, Pieper J, Berger C, Hassler F, Herpertz SC (2011b) Contextual influence of highly valued rewards and penalties on delay decisions in children with ADHD. *J Behav Ther Exp Psychiatry* 42:488–496
- McQuade JD, Hoza B, Waschbusch DA, Murray-Close D, Owens JS (2011a) Changes in self-perceptions in children with ADHD: a longitudinal study of depressive symptoms and attributional style. *Behav Ther* 42:170–182
- McQuade JD, Tomb M, Hoza B, Waschbusch DA, Hurt EA, Vaughn AJ (2011b) Cognitive deficits and positively biased self-perceptions in children with ADHD. *J Abnorm Child Psychol* 39:307–319
- Mefford HC, Sharp AJ, Baker C, Itsara A, Jiang Z, Buysse K, Huang S, Maloney VK, Crolla JA, Baralle D, Collins A, Mercer C, Norga K, de RT, Devriendt K, Bongers EM, de LN, Reardon W, Gimelli S, Bena F, Hennekam RC, Male A, Gaunt L, Clayton-Smith J, Simoncic I, Park SM, Mehta SG, Nik-Zainal S, Woods CG, Firth HV, Parkin G, Fichera M, Reitano S, Lo GM, Li KE, Casuga I, Broomer A, Conrad B, Schwerzmann M, Raber L, Gallati S, Striano P, Coppola A, Tolmie JL, Tobias ES, Lilley C, Armengol L, Spyschaert Y, Verloof P, De CA, Goossens L, Mortier G, Speleman F, van BE, Nelen MR, Hochstenbach R, Poot M, Gallagher L, Gill M, McClellan J, King MC, Regan R, Skinner C, Stevenson RE, Antonarakis SE, Chen C, Estivill X, Menten B, Gimelli G, Gribble S, Schwartz S, Sutcliffe JS, Walsh T, Knight SJ, Sebat J, Romano C, Schwartz CE, Veltman JA, de Vries BB, Vermeesch JR, Barber JC, Willatt L, Tassabehji M, Eichler EE (2008) Recurrent rearrangements of chromosome 1q21.1 and variable pediatric phenotypes. *N Engl J Med* 359:1685–1699
- Mick E, Todorov A, Smalley S, Hu X, Loo S, Todd RD, Biederman J, Byrne D, Dechairo B, Guiney A, McCracken J, McGough J, Nelson SF, Reiersen AM, Wilens TE, Wozniak J, Neale BM, Faraone SV (2010) Family-based genome-wide association scan of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 49:898–905
- Mill J, Petronis A (2008) Pre- and peri-natal environmental risks for attention-deficit hyperactivity disorder (ADHD): the potential role of epigenetic processes in mediating susceptibility. *J Child Psychol Psychiatry* 49:1020–1030
- Miller M, Hanford RB, Fassbender C, Duke M, Schweitzer JB (2011) Affect recognition in adults with ADHD. *J Atten Disord* 15: 452–460
- Moessner R, Marshall CR, Sutcliffe JS, Skaug J, Pinto D, Vincent J, Zwaigenbaum L, Fernandez B, Roberts W, Szatmari P, Scherer SW (2007) Contribution of SHANK3 mutations to autism spectrum disorder. *Am J Hum Genet* 81:1289–1297
- Mostofsky SH, Burgess MP, Gidley Larson JC (2007) Increased motor cortex white matter volume predicts motor impairment in autism. *Brain* 130:2117–2122
- Mueller S, Keeser D, Reiser MF, Teipel S, Meindl T (2011) Functional and structural MR imaging in neuropsychiatric disorders, part 2: application in schizophrenia and autism. *AJNR Am J Neuroradiol*
- Mulligan A, Anney RJ, O'Regan M, Chen W, Butler L, Fitzgerald M, Buitelaar J, Steinhausen HC, Rothenberger A, Minderaa R, Nijmeijer J, Hoekstra PJ, Oades RD, Roeyers H, Buschgens C, Christiansen H, Franke B, Gabriels I, Hartman C, Kuntsi J, Marco R, Meidad S, Mueller U, Psychogiou L, Rommelse N, Thompson M, Uebel H, Banaschewski T, Ebstein R, Eisenberg J, Manor I, Miranda A, Mulas F, Sergeant J, Sonuga-Barke E, Asherson P, Faraone SV, Gill M (2009) Autism symptoms in attention-deficit/hyperactivity disorder: a familial trait which correlates with conduct, oppositional defiant, language and motor disorders. *J Autism Dev Disord* 39:197–209
- Murphy K (2005) Psychosocial treatments for ADHD in teens and adults: a practice-friendly review. *J Clin Psychol* 61:607–619
- Neale BM, Medland S, Ripke S, Anney RJ, Asherson P, Buitelaar J, Franke B, Gill M, Kent L, Holmans P, Middleton F, Thapar A, Lesch KP, Faraone SV, Daly M, Nguyen TT, Schafer H, Steinhausen HC, Reif A, Renner TJ, Romanos M, Romanos J, Warnke A, Walitza S, Freitag C, Meyer J, Palmason H, Rothenberger A, Hawi Z, Sergeant J, Roeyers H, Mick E, Biederman J (2010) Case-control genome-wide association study of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 49:906–920
- Nguyen A, Rauch TA, Pfeifer GP, Hu VW (2010) Global methylation profiling of lymphoblastoid cell lines reveals epigenetic contributions to autism spectrum disorders and a novel autism candidate gene, RORA, whose protein product is reduced in autistic brain. *FASEB J* 24:3036–3051
- Nijmeijer JS, Arias-Vasquez A, Rommelse NN, Altink ME, Anney RJ, Asherson P, Banaschewski T, Buschgens CJ, Fliers EA, Gill M, Minderaa RB, Poustka L, Sergeant JA, Buitelaar JK, Franke B, Ebstein RP, Miranda A, Mulas F, Oades RD, Roeyers H, Rothenberger A, Sonuga-Barke EJ, Steinhausen HC, Faraone SV, Hartman CA, Hoekstra PJ (2010) Identifying loci for the overlap between attention-deficit/hyperactivity disorder and autism spectrum disorder using a genome-wide QTL linkage approach. *J Am Acad Child Adolesc Psychiatry* 49:675–685
- Nomura Y, Marks DJ, Grossman B, Yoon M, Loudon H, Stone J, Halperin JM (2012) Exposure to gestational diabetes mellitus and low socioeconomic status: effects on neurocognitive development and risk of attention-deficit/hyperactivity disorder in offspring. *Arch Pediatr Adolesc Med* [Epub ahead of print]
- Norman DA, Shallice T (1986) Attention to action: willed and automatic control of behaviour
- Ohan JL, Johnston C (2011) Positive illusions of social competence in girls with and without ADHD. *J Abnorm Child Psychol* 39:527–539
- Oldiges M, Lutz S, Pflug S, Schroer K, Stein N, Wiendahl C (2007) Metabolomics: current state and evolving methodologies and tools. *Appl Microbiol Biotechnol* 76:495–511
- Ospina MB, Krebs SJ, Clark B, Karkhanavaj M, Hartling L, Tjosvold L, Vandermeer B, Smith V (2008) Behavioural and developmental interventions for autism spectrum disorder: a clinical systematic review. *PLoS One* 3:e3755
- Pellicano E (2007) Links between theory of mind and executive function in young children with autism: clues to developmental primacy. *Dev Psychol* 43:974–990
- Pellicano E (2010) The development of core cognitive skills in autism: a 3-year prospective study. *Child Dev* 81:1400–1416
- Pelphrey KA, Shultz S, Hudac CM, Vander Wyk BC (2011) Research review: constraining heterogeneity: the social brain and its development in autism spectrum disorder. *J Child Psychol Psychiatry* 52:631–644
- Pennington BF, Ozonoff S (1996) Executive functions and developmental psychopathology. *J Child Psychol Psychiatry* 37:51–87
- Philip RC, Dauvermann MR, Whalley HC, Baynham K, Lawrie SM, Stanfield AC (2012) A systematic review and meta-analysis of

- the fMRI investigation of autism spectrum disorders. *Neurosci Biobehav Rev* 36:901–942
- Pinto D, Pagnamenta AT, Klei L, Anney R, Merico D, Regan R, Conroy J, Magalhaes TR, Correia C, Abrahams BS, Almeida J, Bacchelli E, Bader GD, Bailey AJ, Baird G, Battaglia A, Berney T, Bolshakova N, Bolte S, Bolton PF, Bourgeron T, Brennan S, Brian J, Bryson SE, Carson AR, Casallo G, Casey J, Chung BH, Cochrane L, Corsello C, Crawford EL, Crossett A, Cytrynbaum C, Dawson G, de JM, Delorme R, Drmic I, Duketis E, Duque F, Estes A, Farrar P, Fernandez BA, Folstein SE, Fombonne E, Freitag CM, Gilbert J, Gillberg C, Glessner JT, Goldberg J, Green A, Green J, Guter SJ, Hakonarson H, Heron EA, Hill M, Holt R, Howe JL, Hughes G, Hus V, Iglizzi R, Kim C, Klauck SM, Kolevzon A, Korvatska O, Kustanovich V, Lajonchere CM, Lamb JA, Laskawiec M, LeBoyer M, Le CA, Leventhal BL, Lionel AC, Liu XQ, Lord C, Lotspeich L, Lund SC, Maestrini E, Mahoney W, Mantoulan C, Marshall CR, McConachie H, McDougle CJ, McGrath J, McMahon WM, Merikangas A, Migita O, Minschew NJ, Mirza GK, Munson J, Nelson SF, Noakes C, Noor A, Nygren G, Oliveira G, Papanikolaou K, Parr JR, Parrini B, Paton T, Pickles A, Pilorge M, Piven J, Ponting CP, Posey DJ, Poustka A, Poustka F, Prasad A, Ragoussis J, Renshaw K, Rickaby J, Roberts W, Roeder K, Roge B, Rutter ML, Bierut LJ, Rice JP, Salt J, Sansom K, Sato D, Segurado R, Sequeira AF, Senman L, Shah N, Sheffield VC, Soorya L, Sousa I, Stein O, Sykes N, Stoppioni V, Strawbridge C, Tancredi R, Tansley K, Thiruvahindrapuram B, Thompson AP, Thomson S, Tryfon A, Tsiantis J, van EH, Vincent JB, Volkmar F, Wallace S, Wang K, Wang Z, Wassink TH, Webber C, Weksberg R, Wing K, Wittmeyer K, Wood S, Wu J, Yaspan BL, Zurawiecki D, Zwaigenbaum L, Buxbaum JD, Cantor RM, Cook EH, Coon H, Cuccaro ML, Devlin B, Ennis S, Gallagher L, Geschwind DH, Gill M, Haines JL, Hallmayer J, Miller J, Monaco AP, Nurnberger Jr, Paterson AD, Pericak-Vance MA, Schellenberg GD, Szatmari P, Vicente AM, Vieland VJ, Wijsman EM, Scherer SW, Sutcliffe JS, Betancur C (2010) Functional impact of global rare copy number variation in autism spectrum disorders. *Nature* 466:368–372
- Poelmans G, Pauls DL, Buitelaar JK, Franke B (2011) Integrated genome-wide association study findings: identification of a neurodevelopmental network for attention deficit hyperactivity disorder. *Am J Psychiatry* 168:365–377
- Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA (2007) The worldwide prevalence of ADHD: a systematic review and meta-regression analysis. *Am J Psychiatry* 164:942–948
- Posner MI, Rothbart MK (2007) Research on attention networks as a model for the integration of psychological science. *Annu Rev Psychol* 58:1–23
- Rasalam AD, Hailey H, Williams JH, Moore SJ, Turmpenny PD, Lloyd DJ, Dean JC (2005) Characteristics of fetal anticonvulsant syndrome associated autistic disorder. *Dev Med Child Neurol* 47:551–555
- Reiersen AM, Constantino JN, Volk HE, Todd RD (2007) Autistic traits in a population-based ADHD twin sample. *J Child Psychol Psychiatry* 48:464–472
- Reiersen AM, Constantino JN, Grimmer M, Martin NG, Todd RD (2008) Evidence for shared genetic influences on self-reported ADHD and autistic symptoms in young adult Australian twins. *Twin Res Hum Genet* 11:579–585
- Rhee SH, Willcutt EG, Hartman CA, Pennington BF, DeFries JC (2008) Test of alternative hypotheses explaining the comorbidity between attention-deficit/hyperactivity disorder and conduct disorder. *J Abnorm Child Psychol* 36:29–40
- Richardson AJ (2012) Review: omega-3 fatty acids produce a small improvement in ADHD symptoms in children compared with placebo. *Evid Based Ment Health* 15:46
- Rodriguez A (2010) Maternal pre-pregnancy obesity and risk for inattention and negative emotionality in children. *J Child Psychol Psychiatry* 51:134–143
- Rodriguez A, Miettunen J, Henriksen TB, Olsen J, Obel C, Taanila A, Ebeling H, Linnet KM, Moilanen I, Jarvelin MR (2008) Maternal adiposity prior to pregnancy is associated with ADHD symptoms in offspring: evidence from three prospective pregnancy cohorts. *Int J Obes (Lond)* 32:550–557
- Roeyers H, Demurie E (2010) How impaired is mind-reading in high-functioning adolescents and adults with autism? *Eur J Dev Psychol* 7:123–134
- Romano E, Tremblay RE, Farhat A, Cote S (2006) Development and prediction of hyperactive symptoms from 2 to 7 years in a population-based sample. *Pediatrics* 117:2101–2110
- Romanos M, Freitag C, Jacob C, Craig DW, Dempfle A, Nguyen TT, Halperin R, Walitza S, Renner TJ, Seitz C, Romanos J, Palmason H, Reif A, Heine M, Windemuth-Kieselbach C, Vogler C, Sigmund J, Warnke A, Schafer H, Meyer J, Stephan DA, Lesch KP (2008) Genome-wide linkage analysis of ADHD using high-density SNP arrays: novel loci at 5q13.1 and 14q12. *Mol Psychiatry* 13:522–530
- Rommelse NN, Franke B, Geurts HM, Hartman CA, Buitelaar JK (2010) Shared heritability of attention-deficit/hyperactivity disorder and autism spectrum disorder. *Eur Child Adolesc Psychiatry* 19:281–295
- Rommelse NN, Geurts HM, Franke B, Buitelaar JK, Hartman CA (2011) A review on cognitive and brain endophenotypes that may be common in autism spectrum disorder and attention-deficit/hyperactivity disorder and facilitate the search for pleiotropic genes. *Neurosci Biobehav Rev* 35:1363–1396
- Ronald A, Simonoff E, Kuntsi J, Asherson P, Plomin R (2008) Evidence for overlapping genetic influences on autistic and ADHD behaviours in a community twin sample. *J Child Psychol Psychiatry* 49:535–542
- Ross NA, Gilmour H, Dasgupta K (2010) 14-year diabetes incidence: the role of socio-economic status. *Health Rep* 21:19–28
- Rubia K (2011) “Cool” inferior frontostriatal dysfunction in attention-deficit/hyperactivity disorder versus “hot” ventromedial orbitofrontal-limbic dysfunction in conduct disorder: a review. *Biol Psychiatry* 69:e69–e87
- Rubia K, Halari R, Cubillo A, Mohammad AM, Brammer M, Taylor E (2009a) Methylphenidate normalises activation and functional connectivity deficits in attention and motivation networks in medication-naïve children with ADHD during a rewarded continuous performance task. *Neuropharmacology* 57:640–652
- Rubia K, Smith AB, Halari R, Matsukura F, Mohammad M, Taylor E, Brammer MJ (2009b) Disorder-specific dissociation of orbitofrontal dysfunction in boys with pure conduct disorder during reward and ventrolateral prefrontal dysfunction in boys with pure ADHD during sustained attention. *Am J Psychiatry* 166:83–94
- Rump KM, Giovannelli JL, Minschew NJ, Strauss MS (2009) The development of emotion recognition in individuals with autism. *Child Dev* 80:1434–1447
- Schmitz N, Rubia K, Van AT, Daly E, Smith A, Murphy DG (2008) Neural correlates of reward in autism. *Br J Psychiatry* 192:19–24
- Schwenck C, Mergenthaler J, Keller K, Zech J, Salehi S, Taurines R, Romanos M, Schecklmann M, Schneider W, Warnke A, Freitag CM (2011a) Empathy in children with autism and conduct disorder: group-specific profiles and developmental aspects. *J Child Psychol Psychiatry* [Epub ahead of print]
- Schwenck C, Schmitt D, Sievers S, Romanos M, Warnke A, Schneider W (2011b) Cognitive and emotional empathy in children with ADHD and conduct disorder. *Z Kinder Jugendpsychiatri Psychother* 39:265–276
- Sciberras E, Ukoumunne OC, Efron D (2011) Predictors of parent-reported attention-deficit/hyperactivity disorder in children aged

- 6–7 years: a national longitudinal study. *J Abnorm Child Psychol* 39:1025–1034
- Scott-Van Zeeland AA, Dapretto M, Ghahremani DG, Poldrack RA, Bookheimer SY (2010) Reward processing in autism. *Autism Res* 3:53–67
- Sebat J, Lakshmi B, Malhotra D, Troge J, Lese-Martin C, Walsh T, Yamrom B, Yoon S, Krasnitz A, Kendall J, Leotta A, Pai D, Zhang R, Lee YH, Hicks J, Spence SJ, Lee AT, Puura K, Lehtimäki T, Ledbetter D, Gregersen PK, Bregman J, Sutcliffe JS, Jobanputra V, Chung W, Warburton D, King MC, Skuse D, Geschwind DH, Gilliam TC, Ye K, Wigler M (2007) Strong association of de novo copy number mutations with autism. *Science* 316:445–449
- Senju A (2011) Spontaneous theory of mind and its absence in autism spectrum disorders. *Neuroscientist* [Epub ahead of print]
- Sharp SI, McQuillin A, Gurling HM (2009) Genetics of attention-deficit hyperactivity disorder (ADHD). *Neuropharmacology*
- Silani G, Bird G, Brindley R, Singer T, Frith C, Frith U (2008) Levels of emotional awareness and autism: an fMRI study. *Soc Neurosci* 3:97–112
- Simonoff E, Pickles A, Charman T, Chandler S, Loucas T, Baird G (2008) Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. *J Am Acad Child Adolesc Psychiatry* 47:921–929
- Sinzig J, Bruning N, Morsch D, Lehmkuhl G (2008a) Attention profiles in autistic children with and without comorbid hyperactivity and attention problems. *Acta Neuropsychiatrica* 20:207–215
- Sinzig J, Morsch D, Bruning N, Schmidt MH, Lehmkuhl G (2008b) Inhibition, flexibility, working memory and planning in autism spectrum disorders with and without comorbid ADHD-symptoms. *Child Adolesc Psychiatry Ment Health* 2:4
- Smalley SL, Kustanovich V, Minassian SL, Stone JL, Ogdie MN, McGough JJ, McCracken JT, MacPhie IL, Francks C, Fisher SE, Cantor RM, Monaco AP, Nelson SF (2002) Genetic linkage of attention-deficit/hyperactivity disorder on chromosome 16p13, in a region implicated in autism. *Am J Hum Genet* 71:959–963
- Sonuga-Barke EJ (2002) Psychological heterogeneity in AD/HD—a dual pathway model of behaviour and cognition. *Behav Brain Res* 130:29–36
- Speer LL, Cook AE, McMahon WM, Clark E (2007) Face processing in children with autism: effects of stimulus contents and type. *Autism* 11:265–277
- Stanfield AC, McIntosh AM, Spencer MD, Philip R, Gaur S, Lawrie SM (2008) Towards a neuroanatomy of autism: a systematic review and meta-analysis of structural magnetic resonance imaging studies. *Eur Psychiatry* 23:289–299
- Stark R, Bauer E, Merz CJ, Zimmermann M, Reuter M, Plichta MM, Kirsch P, Lesch KP, Fallgatter AJ, Vaitl D, Herrmann MJ (2011) ADHD related behaviors are associated with brain activation in the reward system. *Neuropsychologia* 49:426–434
- State MW, Levitt P (2011) The conundrums of understanding genetic risks for autism spectrum disorders. *Nat Neurosci* 14:1499–1506
- Stergiakouli E, Hamshere M, Holmans P, Langley K, Zaharieva I, Hawi Z, Kent L, Gill M, Williams N, Owen MJ, O'Donovan M, Thapar A (2012) Investigating the contribution of common genetic variants to the risk and pathogenesis of ADHD. *Am J Psychiatry* 169:186–194
- Storebo OJ, Skoog M, Damm D, Thomsen PH, Simonsen E, Gluud C (2011) Social skills training for attention deficit hyperactivity disorder (ADHD) in children aged 5 to 18 years. *Cochrane Database Syst Rev* CD008223
- Sturm W, Zimmermann P (2000) Aufmerksamkeitsstörungen
- Taurines R, Dudley E, Conner AC, Grassl J, Jans T, Guderian F, Mehler-Wex C, Warnke A, Gerlach M, Thome J (2010a) Serum protein profiling and proteomics in autistic spectrum disorder using magnetic bead-assisted mass spectrometry. *Eur Arch Psychiatry Clin Neurosci* 260:249–255
- Taurines R, Schmitt J, Renner T, Conner AC, Warnke A, Romanos M (2010b) Developmental comorbidity in attention-deficit/hyperactivity disorder. *Atten Defic Hyperact Disord* 2:267–289
- Tucha O, Walitza S, Mecklinger L, Sontag TA, Kubber S, Linder M, Lange KW (2006) Attentional functioning in children with ADHD—predominantly hyperactive-impulsive type and children with ADHD—combined type. *J Neural Transm* 113:1943–1953
- Tucha L, Tucha O, Walitza S, Sontag TA, Laufkotter R, Linder M, Lange KW (2009) Vigilance and sustained attention in children and adults with ADHD. *J Atten Disord* 12:410–421
- Uekermann J, Kraemer M, Abdel-Hamid M, Schimmelmann BG, Hebebrand J, Daum I, Wiltfang J, Kis B (2010) Social cognition in attention-deficit hyperactivity disorder (ADHD). *Neurosci Biobehav Rev* 34:734–743
- van der Oord S, Prins PJ, Oosterlaan J, Emmelkamp PM (2008) Efficacy of methylphenidate, psychosocial treatments and their combination in school-aged children with ADHD: a meta-analysis. *Clin Psychol Rev* 28:783–800
- van der Zwaag B, Franke L, Poot M, Hochstenbach R, Spierenburg HA, Vorstman JA, van DE, De Jonge MV, Verbeek NE, Brilstra EH, van 't SR, Ophoff RA, van Es MA, Blauw HM, Veldink JH, Buizer-Voskamp JE, Beemer FA, van den Berg LH, Wijmenga C, van Amstel HK, van EH, Burbach JP, Staal WG (2009) Genenetwork analysis identifies susceptibility genes related to glycolysis in autism. *PLoS ONE* 4:e5324
- van Meel CS, Heslenfeld DJ, Oosterlaan J, Luman M, Sergeant JA (2011) ERPs associated with monitoring and evaluation of monetary reward and punishment in children with ADHD. *J Child Psychol Psychiatry* 52:942–953
- Van Zomeren AH, Brouwer WH (1994) Clinical neuropsychology of attention
- Vismara LA, Rogers SJ (2010) Behavioral treatments in autism spectrum disorder: what do we know? *Annu Rev Clin Psychol* 6:447–468
- Volkow ND, Wang GJ, Newcorn JH, Kollins SH, Wigal TL, Telang F, Fowler JS, Goldstein RZ, Klein N, Logan J, Wong C, Swanson JM (2011) Motivation deficit in ADHD is associated with dysfunction of the dopamine reward pathway. *Mol Psychiatry* 16:1147–1154
- Wallis D, Russell HF, Muenke M (2008) Review: genetics of attention deficit/hyperactivity disorder. *J Pediatr Psychol* 33:1085–1099
- Wang K, Zhang H, Ma D, Bucan M, Glessner JT, Abrahams BS, Salyakina D, Imielinski M, Bradfield JP, Sleiman PM, Kim CE, Hou C, Frackelton E, Chiavacci R, Takahashi N, Sakurai T, Rappaport E, Lajonchere CM, Munson J, Estes A, Korvatska O, Piven J, Sonnenblick LI, Alvarez Retuerto AI, Herman EI, Dong H, Hutman T, Sigman M, Ozonoff S, Klin A, Owley T, Sweeney JA, Brune CW, Cantor RM, Bernier R, Gilbert JR, Cuccaro ML, McMahon WM, Miller J, State MW, Wassink TH, Coon H, Levy SE, Schultz RT, Nurnberger JI, Haines JL, Sutcliffe JS, Cook EH, Minshew NJ, Buxbaum JD, Dawson G, Grant SF, Geschwind DH, Pericak-Vance MA, Schellenberg GD, Hakonarson H (2009) Common genetic variants on 5p14.1 associate with autism spectrum disorders. *Nature* 459:528–533
- Weiss LA, Shen Y, Korn JM, Arking DE, Miller DT, Fossdal R, Saemundsen E, Stefansson H, Ferreira MA, Green T, Platt OS, Ruderfer DM, Walsh CA, Altshuler D, Chakravarti A, Tanzi RE, Stefansson K, Santangelo SL, Gusella JF, Sklar P, Wu BL, Daly MJ (2008) Association between microdeletion and microduplication at 16p11.2 and autism. *N Engl J Med* 358:667–675
- Weiss LA, Arking DE, Daly MJ, Chakravarti A (2009) A genome-wide linkage and association scan reveals novel loci for autism. *Nature* 461:802–808

- White SW, Keonig K, Scahill L (2007) Social skills development in children with autism spectrum disorders: a review of the intervention research. *J Autism Dev Disord* 37:1858–1868
- Wilkinson DA, Best CA, Minshew NJ, Strauss MS (2010) Memory awareness for faces in individuals with autism. *J Autism Dev Disord* 40:1371–1377
- Williams D (2010) Theory of own mind in autism: evidence of a specific deficit in self-awareness? *Autism* 14:474–494
- Williams D, Happe F (2010) Recognising ‘social’ and ‘non-social’ emotions in self and others: a study of autism. *Autism* 14:285–304
- Williams NM, Zaharieva I, Martin A, Langley K, Mantripragada K, Fossdal R, Stefansson H, Stefansson K, Magnusson P, Gudmundsson OO, Gustafsson O, Holmans P, Owen MJ, O’Donovan M, Thapar A (2010) Rare chromosomal deletions and duplications in attention-deficit hyperactivity disorder: a genome-wide analysis. *Lancet* 376:1401–1408
- Williams NM, Franke B, Mick E, Anney RJ, Freitag CM, Gill M, Thapar A, O’Donovan MC, Owen MJ, Holmans P, Kent L, Middleton F, Zhang-James Y, Liu L, Meyer J, Nguyen TT, Romanos J, Romanos M, Seitz C, Renner TJ, Walitza S, Warnke A, Palmason H, Buitelaar J, Rommelse N, Vazquez AA, Hawi Z, Langley K, Sergeant J, Steinhausen HC, Roeyers H, Biederman J, Zaharieva I, Hakonarson H, Elia J, Lionel AC, Crosbie J, Marshall CR, Schachar R, Scherer SW, Todorov A, Smalley SL, Loo S, Nelson S, Shtir C, Asherson P, Reif A, Lesch KP, Faraone SV (2012) Genome-wide analysis of copy number variants in attention deficit hyperactivity disorder: the role of rare variants and duplications at 15q13.3. *Am J Psychiatry* 169:195–204
- Wilson VB, Mitchell SH, Musser ED, Schmitt CF, Nigg JT (2011) Delay discounting of reward in ADHD: application in young children. *J Child Psychol Psychiatry* 52:256–264
- Yang MS, Gill M (2007) A review of gene linkage, association and expression studies in autism and an assessment of convergent evidence. *Int J Dev Neurosci* 25:69–85
- Yang J, Zhou S, Yao S, Su L, McWhinnie C (2009) The relationship between theory of mind and executive function in a sample of children from mainland China. *Child Psychiatry Hum Dev* 40:169–182
- Yuill N, Lyon J (2007) Selective difficulty in recognising facial expressions of emotion in boys with ADHD. General performance impairments or specific problems in social cognition? *Eur Child Adolesc Psychiatry* 16:398–404