ADHD Atten Def Hyp Disord
DOI 10.1007/s12402-012-0086-2

REVIEW ARTICLE

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

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Received: 2 April 2012 / Accepted: 26 June 2012

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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Published online: 01 August 2012

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-occurence of both disorders by chance. Other models of comorbity 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-nucelotide 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 metallopeptidase 24 (*MMP24*, 20q11), potassium

voltage-gated channel, Shaw-related subfamily, member 1 (*KCNC1*, 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 (*LRRC1,* 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)*, NLGN1, 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 glycobiology (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 neurobiological 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 (Lyall et al. 2011; Nomura et al. 2012), pre-eclampsia (Mann et al. 2010; Mann and McDermott 2011) or viral or bacterial infections (Atladottir 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 (Figueroa 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)
Pregnancy risk factors				
Pre-pregnancy obesity	*Not assessed*		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)	Atladottir et al. (2010b)	Maternal genito-urinary infection OR 1.3 (95 %-CI 1.2–1.4)	Mann and McDermott (2011)
Maternal auto-immune 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 buproprion: OR 3.6 exclusion: SSRI	Clinical studies only (Cohen et al. 2011; Figueroa 2010)
Maternal smoking	*Excluded*	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)
Perinatal risk factors				
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 pregancy, 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 dissocial 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 LC-ESI MS/MS	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	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 I, dynamin I, synaptojanin 2, adapter protein 1 beta, neurocan, brevican 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-dimentional 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 (dynamin1, 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 Ca^{2+} 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 Ca^{2+}-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 impairements 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 been 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, temporoparietal, 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 prefronal 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 Conchrane 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.

Acknowledgments The study was partly supported by the EU/BMBF grant 01EW1105 to Christine Freitag.

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