DOI 10.1007/s00702-005-0366-5
J Neural Transm (2006) 113: 929–938

Journal of Neural Transmission
Printed in Austria

Inferring candidate genes for Attention Deficit Hyperactivity Disorder (ADHD) assessed by the World Health Organization Adult ADHD Self-Report Scale (ASRS)

M. Reuter[1], **P. Kirsch**[2], and **J. Hennig**[1]

[1] Department of Psychology, and
[2] Department of Psychiatry, University of Giessen, Germany

Received March 8, 2005; accepted August 28, 2005
Published online December 14, 2005;

Summary. The present study tests the psychometric properties and validity of the German version of the World Health Organization Adult Attention Deficit Hyperactivity Disorder (ADHD) Self-Report Scale (ASRS), which is a short screening instrument for use in the general population. Furthermore, two candidate genes for ADHD, the COMT VAL158MET and the 5-HT2a T102C polymorphisms, were tested for associations with the ASRS subscales inattention and hyperactivity/impulsivity in $N = 203$ healthy subjects.

The ordinal CFA yielded a two-factorial model corroborating the structure of the official English WHO version. Genetic analysis revealed an association between the VAL allele of COMT and the inattention scale ($F_{(1, 201)} = 7.20$, $p = 0.008$), the hyperactivity/impulsivity scale ($F_{1, 201} = 4.30$, $p = 0.039$), and the total ASRS scale ($F_{(2, 201)} = 7.64$, $p = 0.006$) with highest scores in carriers of the MET/MET genotype. The C-allele of 5-HT2a was significantly associated with the hyperactivity/impulsivity scale ($F_{(1, 201)} = 5.52$, $p = 0.020$) and the total ASRS scale ($F_{(1, 201)} = 4.21$, $p = 0.042$) with highest scores in carriers of the TT genotype.

The data provide evidence for the structural as well as for the external validity of the ASRS.

Keywords: ADHD, COMT, 5-HT2a, ASRS.

Introduction

Attention-Deficit Hyperactivity Disorder (ADHD) is a psychiatric disorder that is characterized by inattention, hyperactivity and impulsivity. Although the diagnosis of ADHD is more frequent in children, there is agreement that ADHD can also be reliably diagnosed in adults (Murphy, 1996). The symptoms of ADHD in adulthood are similar to those observed in children. Longitudinal studies have demonstrated that ADHD once diagnosed in childhood persists into adulthood in 10–60% of the cases (Weiss et al., 1985; Mannuzza et al., 1993; Biederman et al., 2000).

Family and twin studies (e.g. Faraone and Biederman, 1998; Levy et al., 1997) that have demonstrated the high heritability of ADHD, with heritability estimates of around 60–88% (Thapar, 2002), have stimulated studies from molecular genetics trying to identify

chromosomal regions harboring genes linked to ADHD or to identify candidate genes for ADHD.

Until now two genome scans with respect to ADHD were available in an US sample consisting of 270 sib-pairs from 204 families (Ogdie et al., 2003) and a Dutch sample based on 164 sib-pairs from 106 families (Bakker et al., 2003). Although the average age of affected children in both samples was comparable (11.1 vs. 10 years) there were differences between the two samples with respect to sex ratio, comorbidity with conduct disorder and socioeconomic status. Although both studies partly identified different chromosomal regions linked to ADHD, both studies identified a region on chromosome 5p13 with a LOD score >1. This region is located close to the dopamine transporter gene DAT1 (SLC6A3) which has been proven as a promising candidate gene for ADHD in a meta-analysis by Maher et al. (2002). Besides the DAT gene the dopamine receptor genes DRD4 and DRD5 and the dopamine beta-hydroxylase gene (DBH) have been shown to be associated with ADHD across several studies (for a review see Kirley et al., 2002; Heiser et al., 2004). Most of the candidate genes identified so far were involved in the dopamine metabolism but also candidate genes of the serotonergic (5-HT) system, the 5-HT transporter gene (5-HTTLPR) and the 5-HT2a receptor gene, have been reported to be associated with ADHD (Seeger et al., 2001; Zoroglu et al., 2002; Levitan et al., 2002).

Although the effects of most of the above mentioned genes seem to be rather robust also negative findings have been reported. The problem when trying to identify candidate genes for ADHD is the heterogeneity of the syndrome. On a phenomenological level one could discriminate patients who display all three diagnostic criteria or patients who exhibit one or two of these in a more pronounced way than the other(s). Therefore, it is justified to assume that different gene loci underlie the sub-dimensions of ADHD.

One of the most influential neuropsychological theories on ADHD is the disinhibition theory postulated by Barkley (1997). The model holds that the critical impairment in ADHD is an insufficient response inhibition which can also be seen as a disturbance of executive functioning. Executive functioning is primarily located in the prefrontal cortex and evidence from neuropsychological (for an overview on adult ADHD, see Hervey et al., 2004) as well as neuroimaging studies (e.g. Zametkin et al., 1990) has demonstrated prefrontal disturbances in ADHD.

The most promising candidate gene for prefrontal functioning encompassing cognitive processes like attention and working memory is the catechol-O-methyltransferase (COMT) VAL158MET polymorphism (Egan et al., 2001; Malhorta et al., 2002; Joober et al., 2002; Goldberg et al., 2003). COMT is an enzyme which plays a crucial role in the metabolism of catecholamines by inactivating them in the synaptic cleft. A single nucleotide polymorphism (SNP), a $G \rightarrow A$ transition in codon 158 of the COMT gene located at the q11 band of human chromosome 22, results in 3 to 4-fold difference in COMT enzyme activity (Lachman et al., 1996) by coding for the synthesis of the amino acid methionine (MET) instead of valine (VAL). Heterozygotes (VAL/MET genotype) have intermediate levels of COMT activity (Lachman et al., 1996; Syvänen et al., 1997). Egan et al. (2001) reported better working memory performance in carriers of the MET/MET genotype. Using an n-back task Goldberg et al. (2003) also found the best working memory performance in carriers of the MET/MET genotype and worst performance in carriers with the VAL/VAL genotype. In line with these findings Malhorta et al. (2002) found that subjects with only the low-activity MET allele made significantly

fewer perseverative errors on the Wisconsin Card Sorting Test, which is a task of prefrontal cognition, than did subjects with the VAL allele. This finding could be corroborated in healthy controls and in schizophrenic patients (Joober et al., 2002). Interestingly Mattay et al. (2003) reported better results in carriers of the VAL allele and a decline in the MET/MET group in a working memory task after a pharmacological challenge with the DA-agonistic substance amphetamine. The decline in performance in the MET/MET group after amphetamine intake suggests that the association between performance and DA levels has an inverted 'U' shape characteristic, i.e. activation of the DA system by working memory load and amphetamine pushes these subjects beyond their optimal activation level.

The COMT gene is an attractive candidate gene for ADHD because a) the above cited studies have demonstrated the effect of the COMT gene on prefrontal executive functions which are impaired in patients with ADHD and b) neurobiological studies have suggested that altered DA function may contribute to the etiology of ADHD (for a review see Faraone and Biederman, 1998) and c) DA agonistic substances like methylphenidate are successful in the pharmacological treatment of ADHD (for a review see Leonard et al., 2004) and COMT plays a major role in the degrading of DA. Some studies have already tested the COMT gene for a possible association with ADHD. The results were predominately negative (Barr et al., 1999; Payton et al., 2001; Turic et al., 2005; Bellgrove et al., 2005). Only one study found an association between the COMT gene and ADHD (Eisenberg et al., 1999). Studies trying to extrapolate the positive findings on the relationship between the COMT gene and prefrontal cognitive functions observed in healthy subjects and schizophrenics on patients with ADHD were rather unsuccessful (Eisenberg et al., 1999; Taerk et al., 2004; Mills et al., 2004). Only Bellgrove et al. (2005) reported positive results, however, contrary to the findings in healthy subjects and schizophrenic patients. The MET allele of the VAL158MET polymorphism impaired prefrontally mediated cognition, whereas best performance was observed in carriers of the VAL/VAL genotype.

The second symptom of ADHD, hyperactivity, is related to the DA system in the same way as attention. Animal studies have demonstrated the effects of dopaminergic drugs on locomotor activity (Piazza et al., 1990). Furthermore, a lack of central DA is observed in patients with Morbus Parkinson, a disease characterized by a severe motor impairment. In normal subjects, extraverts, who seem to be characterized by higher DA levels (Depue et al., 1994) are prone to engage in activities and show faster reaction times (Doucet and Stelmack, 1997). These findings suggest that dopaminergic genes form a common molecular basis for ADHD as well as for hyperactivity in normal subjects.

Neurobiological studies indicate that the third component of ADHD, impulsivity, is related to the serotonergic (5-HT) system. For example, results from neurochemical studies show that impulsivity besides aggression and depression are marked by a dysfunctional serotonergic system (e.g. Asberg and Traskman, 1981; Brown and Linnoila, 1990; Coccaro, 1992; Hennig et al., 1997, 1998). Therefore, genes of the 5-HT system are possible candidate genes for ADHD.

In a recent study Kooik et al. (2004) have demonstrated in a population-based sample of 1813 adults that the ADHD DSM-IV rating scale (Du Paul et al., 1998) has good construct validity as indicated by a robust three factor solution in a confirmatory factor analysis (CFA). The three factors, inattention, hyperactivity and impulsivity were identical with the DSM-IV criteria for ADHD corroborating the assumption that personali-

ty dimensions within a normal range and psychopathological (personality) disorders have one common underlying dimension (Donnelly, 1998). Investigating the relation between the ''big five'' personality dimensions and ADHD, Nigg et al. (2002) as well as Parker et al. (2004) found associations between agreeableness, conscientiousness and neuroticism and ADHD symptoms. In line with these findings, Kessler et al. (2005) have constructed the World Health Organization Adult ADHD Self-Report Scale (ASRS), which is a short screening scale for use in the general population. If the assumption holds that personality dimensions – marked by inattention, hyperactivity, and impulsivity – and ADHD have one common underlying dimension then the ASRS scores should be normally distributed in the general population.

The aim of the present study is to validate the World Health Organization Adult ADHD Self-Report Scale (ASRS) by detecting candidate genes for the total scale and its subscales inattention and hyperactivity/impulsivity. Based on the considerations mentioned above we tested one gene locus related to inattention as well as to hyperactivity, the COMT VAL158MET polymorphism and one gene locus related to impulsivity, the 5-HT2a T102C receptor polymorphism. Since there was no German version of the ASRS available until now (there only exists a German 6-item screener version), we also wanted to test the structure and the reliability of our newly constructed German version of the ASRS.

Material and methods

Sample

Subjects were N = 203 members of the *Giessen Gene Brain Behavior Project* (GGBBP) data bank (n = 160 women and n = 43 men; age: M = 24.12, SD = 6.07. This data bank presently contains over 800 subjects (more than 500 healthy subjects and 300 patients with a psychiatric diagnosis of alcoholism or eating disorder) who are willing to participate in experimental studies investigating the molecular basis of behavior. Participants in the present study were those healthy Caucasian subjects of German origin who had filled in the German version of the ASRS in a first screening study. The study was approved by the ethics committee of the German Psychological Association.

Construction and validation of the German version of the World Health Organization Adult ADHD Self-Report Scale (ASRS)

The German version of the ASRS is a translation of the original 18 item ASRS scale by Kessler et al. (2005). It is based on the criteria for ADHD from the DSM-IV-TR (American Psychiatric Association, 2000) but measures frequencies of the symptoms. By means of a Likert scale of 0–4 (0 = never, 1 = seldom, 2 = sometimes, 3 = often, 4 = very often) participants/patients answer how often the ADHD symptoms occur. The first nine items form the inattention scale and items 10–18 the hyperactivity/impulsivity scale. If the sum score for one of the two scales is <17 then it is unlikely to have ADHD, if it is between 17 and 23 then it is likely to have ADHD and a score greater or equal 24 indicates that it is highly likely to have ADHD.

Before the application of the German version it was retranslated by a bilingual psychologist and critically tested with respect to its content. In a second step a confirmatory factor analysis (CFA) was calculated by means of LISREL 8.51 (Jöreskog and Sörbom, 2001) to validate the two-factorial structure of the ASRS suggested by Kessler et al. (2005). The proposed factors were inattention and hyperactivity/impulsivity. Due to the fact that the data were ordinal we analyzed the model based on polychoric correlation matrices (PM) and asymptotic covariance matrices (AC). The parameter estimates were calculated by the Maximum Likelihood (ML) method because the sample size was too small to get robust estimates with the Weighted Least Squares method (WLS) (Olsson, 2000). The use of the PM and AC matrices yields the Satorra-Bentler Scaled Chi-Square test statistic which takes non-normality of data into account (Hu et al., 1992). Furthermore, reliabilities in terms of Cronbach's alpha were calculated by SPSS 11.5.

Genetic analyses

DNA was extracted from buccal cells to avoid a selective exclusion of subjects with blood and injection phobias. Purification of genomic DNA was performed with a standard commercial extraction kit (High Pure PCR Template Preparation Kit; Roche Diagnostics,

Mannheim, Germany). Genotyping of the two single nucleotide polymorphisms (SNPs) was performed by real time PCR using fluorescence melting curve detection analysis by means of the Light Cycler System (Roche Diagnostics, Mannheim, Germany). The primers and hybridization probes used (TIB MOLBIOL, Berlin, Germany) and the PCR protocols were as follows:

For COMT: forward primer: 5′-GGGCCTACTGTGGC TACTCA-3′; reverse primer: 5′-GGCCCTTTTTCCAG GTCTG-3′; anchor hybridization probe: 5′-LCRed640-TGTGCATGCCTGACCCGTTGTCA-phosphate-3′; sensor hybridization probe: 5′-ATTTCGCTGGCAT GAAGGACAAG-fluorescein-3′. The PCR run comprised 55 cycles of denaturation (95°C, 0 s, ramp rate 20°C s^{-1}), annealing (57°C, 10 s, ramp rate 20°C s^{-1}) and extension (72°C, 10 s, ramp rate 20°C s^{-1}) which followed an incubation period of 10 min to activate the FastStart Taq DNA Polymerase of the reaction mix (Light Cycler FastStart DNA Master Hybridization Probes, Roche Diagnostics, Mannheim, Germany). After amplification a melting curve was generated by holding the reaction time at 40°C for 2 min and then heating slowly to 95°C with a ramp rate of 0.2°C s^{-1}. The fluorescence signal was plotted against temperature to yield the respective melting points (Tm) of the two alleles. Tm for the VAL allele was 59.00°C and 64.50°C for the MET allele.

For 5-HT2A: forward primer: 5′-CTTATATGTGT GAGTCTGAGTGG-3′; reverse primer: 5′-CCATGA TGACGAGTATGTTT-3′; anchor hybridization probe: 5′-LCRed640-CTTCTGATGCATTTAACTGGACAGT CG-phosphate-3′; sensor hybridization probe: 5′-GAC TTTAACTCCGGAGAAGCTAAC-fluorescein-3′. The PCR run comprised 55 cycles of denaturation (95°C, 0 s, ramp rate 20°C s^{-1}), annealing (60°C, 10 s, ramp rate 20°C s^{-1}) and extension (72°C, 10 s, ramp rate 20°C s^{-1}) which followed an incubation period of 10 min to activate the FastStart Taq DNA Polymerase of the reaction mix (Light Cycler FastStart DNA Master Hybridization Probes, Roche Diagnostics, Mannheim, Germany). After amplification a melting curve was generated by holding the reaction time at 40°C for 2 min and then heating slowly to 95°C with a ramp rate of 0.2°C s^{-1}. The fluorescence signal was plotted against temperature to yield the respective melting points (Tm) of the two alleles. Tm for the T allele was 56.80°C and 63.40°C for the C allele.

Results

The reliabilities (Cronbach's alpha) for the two subscales inattention (0.75) and impulsivity (0.77) as well as for the total ASRS (0.82) were satisfactory. The results of the CFA confirmed the two-factorial model suggested by Kessler et al. (2005) (see Fig. 1). The fit of the model was very good (Satorra-Bentler Scaled Chi-Square = 125.20, df = 134, $p = 0.695$; RMSEA < 0.001). The factor intercorrelation was 0.61 indicating a common second order factor which makes it legitimate to sum up all 18 items to yield a total ASRS score. According to the ASRS manual, in the present sample 61.1% of the subjects were unlikely to have ADHD, 34% were likely to have ADHD and 4.9% were highly likely to have ADHD. There were no gender differences with respect to the ASRS scales observable (all F-values <1).

The genotype and allele frequencies for the COMT and the 5-HT2a polymorphisms are presented in Table 1. Both SNPs were in Hardy-Weinberg Equilibrium (COMT: $\chi^2 = 0.081$, df = 1, $p > 0.05$; 5-HT2a: $\chi^2 = 0.241$, df = 1, $p > 0.05$). Results of the genetic analyses yielded a main effect of the COMT polymorphism on inattention ($F_{(2, 200)} = 4.15$, $p = 0.017$) and on the total ASRS scale ($F_{(2, 200)} = 3.76$, $p = 0.025$). The effects of the COMT gene were even more pronounced if the alleles were evaluated. The VAL allele was significantly associated with inattention ($F_{(1, 201)} = 7.20$, $p = 0.008$), hyperactivity/impulsivity ($F_{1, 201} = 4.30$, $p = 0.039$) and the total ASRS scale ($F_{(2, 201)} = 7.64$, $p = 0.006$). Carriers of the MET/MET genotype (VAL−) had highest scores on all scales.

With respect to the 5-HT2a polymorphism T102C there was a significant main effect of the C allele on the hyperactivity/impulsivity scale ($F_{(1, 201)} = 5.52$, $p = 0.020$) and on the total ASRS scale ($F_{(1, 201)} = 4.21$, $p = 0.042$). Subjects homozygous for the T allele had highest scores on the ASRS scales. In the absence of a significant epistasis effect (gene–gene interaction), both SNPs together explained 5.8% of the variance of the total ASRS scores.

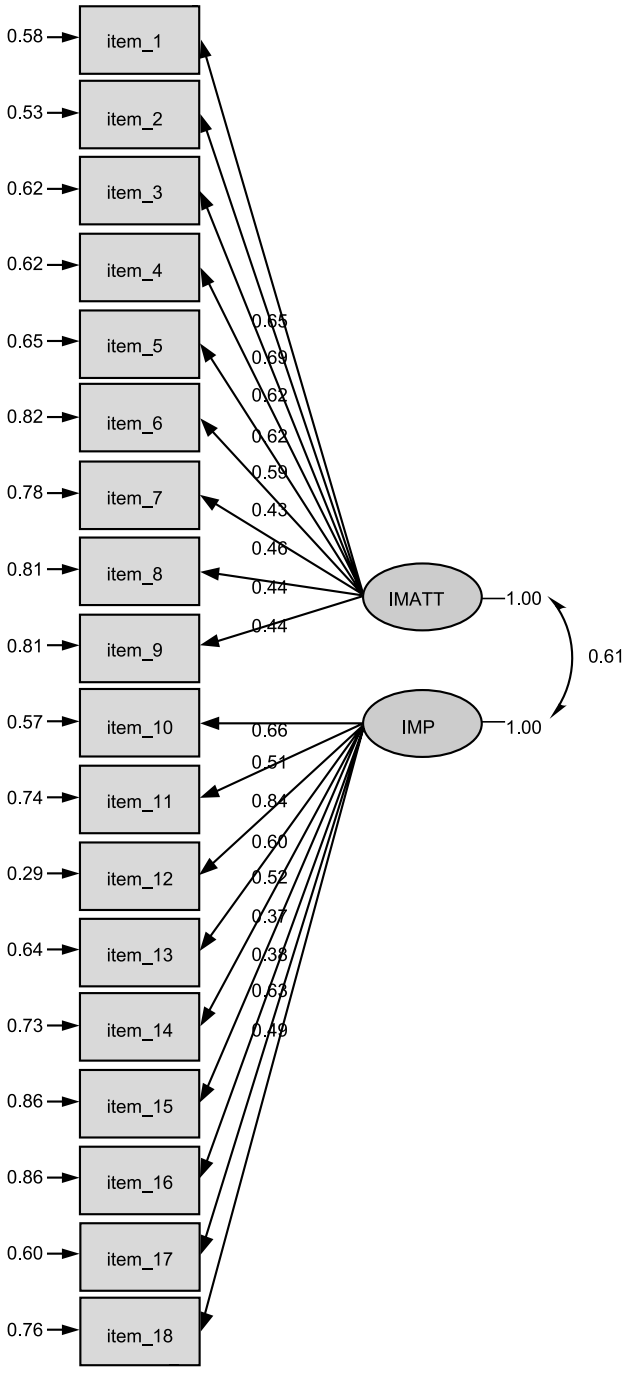

Fig. 1. Results of the confirmatory factor analysis (CFA). Support for the two-factorial structure of the ASRS. Satorra-Bentler Scaled Chi-Square = 125.20, df = 134, p = 0.695; RMSEA < 0.001

Discussion

The aim of the present paper was twofold. First we wanted to test the reliability and construct validity of the German version of the World Health Organization Adult ADHD Self-Report Scale (ASRS) and second we wanted to test two candidate genes for

Table 1. Genotype and allele frequencies of the COMT VAL158MET and the 5-HT2a T102C polymorphisms and descriptive statistics (Mean, SEM) and results of the ANOVAs with respect to the ASRS

	n	Inattention	Hyperactivity/ impulsivity	ASRS total
COMT genotypes sig.		0.017	n.s.	0.025
VAL/VAL	45	13.96 (0.68)	13.42 (0.81)	27.38 (1.32)
VAL/MET	99	13.49 (0.38)	12.69 (0.42)	26.18 (0.67)
MET/MET	59	15.45 (0.66)	14.56 (0.80)	30.01 (1.24)
COMT VAL-allele sig.		0.008	0.039	0.006
VAL− (MET/MET)	59	15.45 (0.66)	14.56 (0.80)	30.01 (1.24)
VAL+ (VAL/MET, VAL/VAL)	144	13.64 (0.34)	12.92 (0.39)	26.56 (0.62)
5-HT2a genotypes sig.		n.s.	n.s.	n.s.
TT	39	14.85 (0.58)	15.12 (0.78)	29.97 (1.19)
CT	96	13.79 (0.47)	13.10 (0.50)	26.90 (0.80)
CC	68	14.30 (0.57)	12.82 (0.67)	27.12 (1.09)
5-HT2a C-allele sig.		n.s.	0.020	0.042
C− (TT)	39	14.85 (0.58)	15.12 (0.78)	29.97 (1.19)
C+ (CT, CC)	164	14.00 (0.36)	12.98 (0.40)	26.99 (0.65)

ADHD, COMT and 5-HT2a, for possible associations with the ASRS to support the external validity of the ASRS.

The reliabilities as well as the factor structure tested by a CFA model proved the quality of the German ASRS. It has to be emphasized that the CFA model applied took into account the ordinal quality of the data. Most CFA models reported in the literature treat ordinal data as metric variables, thereby adulterating the nature of the data which leads to incorrect parameter estimates.

In this study we derived candidate genes for ADHD by focusing on the basic symptoms of ADHD, namely inattention, hyperactivity, and impulsivity. Since the ASRS is a questionnaire that is constructed to screen for ADHD in the normal population, it is implicitly based on the assumption that there is one common underlying continuum between ADHD and the three symptoms observed in healthy subjects in a mild form. Therefore genes which have been found to be related to attention, activity and impulsivity were likely to be associated with the ASRS scales. It was hypothesized that the COMT gene was related to inattention and hyperactivity because the DA system has been shown to at least partly represent the neurochemical basis of these two constructs and that the serotonergic 5-HT2a gene was related to impulsivity due to its moderating influence on impulse control.

Results could corroborate our hypotheses. The COMT VAL158MET SNP was strongly related to inattention and had also a significant influence on the hyperactivity/impulsivity scale and the 5-HT2a T102C polymorphism was significantly associated with the hyperactivity/impulsivity scale but not with inattention. Both genes together explained 5.8% of the variance of the total ASRS scale which means, a heritability of 50% for ADHD assumed, nearly 12% of the genetic variance of ADHD could be explained by the COMT VAL158MET and the 5-HT2a T102C polymorphisms.

In carriers of the MET/MET (VAL−) genotype inattention scores were significantly higher than in carriers of the VAL-allele (VAL+). This finding is in line with the study by Bellgrove et al. (2005) who reported impaired prefrontally mediated cognition in a sustained attention task in carriers of the MET-allele in a sample of children and adults

with ADHD. The experimental data by Bellgrove et al. (2005) as well as our own self-report data suggest that the MET-allele or especially the MET/MET genotype is associated with higher inattention in ADHD subjects whereas other studies reported better cognitive functioning for carriers of the MET-allele in schizophrenic patients (Egan et al., 2001; Joober et al., 2002; Goldberg et al., 2003) or healthy adults (Malhorta et al., 2002). Our results indicate a dissociation of the effect of the COMT gene polymorphism on attentional processes in ADHD prone subjects and persons with other psychiatric disorders like schizophrenia. However, the neurobiological mechanism underlying this dissociation remains unclear and has to be further investigated.

Highest scores in hyperactivity/impulsivity could be observed in carriers of the TT-genotype. This result corroborates previous findings reporting an association between the 5-HT2a gene and ADHD (Levitan et al., 2002) or impulsive traits (Preuss et al., 2001). Binding experiments revealed lower receptor binding in carriers of the "C" allele (Turecki et al., 1999). Therefore, a higher receptor binding capacity in TT subjects might be an adaptation to lower 5-HT levels that have been reported to be associated to low impulse control (e.g. Brown and Linnoila, 1991).

Given the small sample size, the reported genetic associations for the ASRS are preliminary and have to be corroborated in an independent sample. Nevertheless the psychometric as well as the genetic data indicate that the ASRS seems to be a useful diagnostic tool for the assessment of ADHD in adult subjects.

References

American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders, fourth edn, text revision. American Psychiatric Association, Washington DC

Asberg M, Traskman L (1981) Studies of CSF 5-HIAA in depression and suicidal behaviour. Adv Exp Med Biol 133: 739–752

Bakker SC, van der Meulen EM, Buitelaar JK, Sandkuijl LA, Pauls DL, Monsuur AJ, van't Slot R, Minderaa RB, Gunning WB, Pearson PL, Sinke RJ (2003) A whole-genome scan in 164 Dutch sib pairs with attention-deficit/hyperactivity disorder: suggestive evidence for linkage on chromosomes 7p and 15q. Am J Hum Gen 72: 1251–1260

Barkley RA (1997) Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull 121: 65–94

Barr CL, Wigg K, Malone M, Schachar R, Tannock R, Roberts W, Kennedy JL (1999) Linkage study of catechol-O-methyltransferase and attention-deficit hyperactivity disorder. Am J Med Gen 88: 710–713

Bellgrove MA, Domschke K, Hawi Z, Kirley A, Mullins C, Robertson IH, Gill M (2005) The methionine allele of the COMT polymorphism impairs prefrontal cognition in children and adolescents with ADHD. Exp Brain Res [Epub ahead of print 2005 Jan 15]

Biederman J, Mick E, Faraone SV (2000) Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. Am J Psychiatry 157: 816–818

Brown GL, Linnoila MI (1990) CSF serotonin metabolite (5-HIAA) studies in depression, impulsivity, and violence. J Clin Psychiatry 51 [Suppl]: 31–41

Coccaro EF (1992) Impulsive aggression and central serotonergic system function in humans: an example of a dimensional brain-behavior relationship. Int Clin Psychopharmacol 7: 3–12

Depue RA, Luciana M, Arbisi P, Collins P, Leon A (1994) Dopamine and the structure of personality: relation of agonist-induced dopamine activity to positive emotionality. J Pers Soc Psychol 67: 485–498

Donnelly JP (1998) A continuum model of personality disorder. Psychol Rep 83: 387–391

Doucet C, Stelmack RM (2000) An event related potential analysis of extraversion and individual differences in cognitive processing speed and response execution. J Pers Soc Psychol 78: 956–964

Faraone SV, Biederman J (1998) Neurobiology of attention-deficit hyperactivity disorder. Biol Psychiatry 44: 951–958

Heiser P, Friedel S, Dempfle A, Konrad K, Smidt J, Grabarkiewicz J, Herpertz-Dahlmann B, Remschmidt H, Hebebrand J (2004) Molecular genetic aspects of attention-deficit/hyperactivity disorder. Neurosci Biobehav Rev 28: 625–641

Hennig J, Opper C, Huwe S, Netter P (1997) The antagonism of ipsapirone induced biobehavioral

responses by +/− pindolol in high and low impulsives. J Neural Transm 104: 1027–1035

Hennig J, Kroeger A, Meyer B, Prochaska H, Krien P, Huwe S, Netter P (1998) Personality correlates of +/− pindolol induced decreases in prolactin. Pharmacopsychiatry 31: 19–24

Hervey AS, Epstein JN, Curry JF (2004) Neuropsychology of adults with attention-deficit/hyperactivity disorder: a meta-analytic review. Neuropsychol 18: 485–503

Hu L-T, Bentler TM, Kano Y (1992) Can test statistics in covariance structure analysis be trusted? Psychol Bull 112: 351–362

Jöreskog KG, Sörbom D (2001) LISREL 8.51. Scientific Software International, Lincolnwood, IL

Joober R, Gauthier J, Lal S, Bloom D, Lalonde P, Rouleau G, Benkelfat C, Labelle A (2002) Catechol-O-methyltransferase Val-108/158-Met gene variants associated with performance on the Wisconsin Card Sorting Test. Arch Gen Psychiatry 59: 662–663

Kessler RC, Adler L, Ames M, Delmer O, Faraone S, Hiripi E, Howes MJ, Jin R, Secnik K, Spencer T, Ustun TB, Walters EE (2005) The World Health Organization Adult ADHD Self-Report Scale (ASRS): a short screening scale for use in the general population. Psychol Med 35: 245–256

Kirley A, Hawi Z, Daly G, McCarron M, Mullins C, Millar N, Waldman I, Fitzgerald M, Gill M (2002) Dopaminergic system genes in ADHD: toward a biological hypothesis. Neuropsychopharmacology 27: 607–619

Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski CL, Weinshilboum RM (1996) Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics 6: 243–250

Leonard BE, McCartan D, White J, King DJ (2004) Methylphenidate: a review of its neuropharmacological, neuropsychological and adverse clinical effects. Hum Psychopharmacol 19: 151–180

Levitan RD, Masellis M, Basile VS, Lam RW, Jain U, Kaplan AS, Kennedy SH, Siegel G, Walker ML, Vaccarino FJ, Kennedy JL (2002) Polymorphism of the serotonin-2A receptor gene (HTR2A) associated with childhood attention deficit hyperactivity disorder (ADHD) in adult women with seasonal affective disorder. J Affect Disord 71: 229–233

Levy F, Hay DA, McStephen M, Wood C, Hons WI (1997) Attention-deficit hyperactivity disorder: a category or a continuum? Genetic analysis of a large-scale twin study. J Child Adol Psychiatry 36: 737–744

Maher BS, Marazita ML, Ferrell RE, Vanyukov MM (2002) Dopamine system genes and attention deficit hyperactivity disorder: a meta-analysis. Psychiat Genet 12: 207–215

Malhotra AK, Kestler LJ, Mazzanti C, Bates JA, Goldberg T, Goldman D (2002) A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. Am J Psychiatry 159: 652–654

Mannuzza S, Klein RG, Bessler A, Malloy P, LaPadula M (1993) Adult outcome of hyperactive boys. Educational achievement, occupational rank, and psychiatric status. Arch Gen Psychiatry 50: 565–576

Murphy K (1996) Adults with attention deficit hyperactivity disorder: assessment and treatment considerations. Sem Speech Lang 17: 245–253

Nigg JT, John OP, Blaskey LG, Huang-Pollock CL, Willicut EG, Hinshaw SP, Pennington B (2002) Big five dimensions and ADHD symptoms: links between personality traits and clinical symptoms. J Pers Soc Psychol 83: 451–469

Ogdie MN, Macphie IL, Minassian SL, Yang M, Fisher SE, Francks C, Cantor RM, McCracken JT, McGough JJ, Nelson SF, Monaco AP, Smalley SL (2003) A genomewide scan for attention-deficit/hyperactivity disorder in an extended sample: suggestive linkage on 17p11. Am J Hum Genet 72: 1268–1279

Olsson UH (2000) The performance of ML, GLS, and WLS estimation in structural equation modeling under conditions of misspecification and nonnormality. Structural Equation Modeling 4: 557–595

Parker JDA, Majeski SA, Collin VT (2004) ADHD symptoms and personality: relationships with the five-factor model. Pers Indiv Differ 36: 977–987

Payton A, Holmes J, Barrett JH, Hever T, Fitzpatrick H, Trumper AL, Harrington R, McGuffin P, O'Donovan M, Owen M, Ollier W, Worthington J, Thapar A (2001) Examining for association between candidate gene polymorphisms in the dopamine pathway and attention-deficit hyperactivity disorder: a family-based study. Am J Med Gen 105: 464–470

Piazza PV, Deminiere JM, Maccari S, Mormede P, Le Moal M, Simon H (1990) Individual reactivity to novelty predicts probability of amphetamine self-administration. Behav Pharmacol 1: 339–345

Preuss UW, Koller G, Bondy B, Bahlmann M, Soyka M (2001) Impulsive traits and 5-HT2A receptor promoter polymorphism in alcohol dependents: possible association but no influence of personality disorders. Neuropsychobiology 43: 186–191

Seeger G, Schloss P, Schmidt MH (2001) Functional polymorphism within the promotor of the serotonin transporter gene is associated with severe hyperkinetic disorders. Mol Psychiatry 6: 235–238

Syvänen AC, Tilgmann C, Rinne J, Ulmanen I (1997) Genetic polymorphism of catechol-O-methyltransferase (COMT): correlation of genotype with individual variation of S-COMT activity and comparison of the allele frequencies in the normal population and parkinsonian patients in Finland. Pharmacogenetics 7: 65–71

Turecki G, Briere R, Dewar K, Antonetti T, Lesage AD, Seguin M, Chawky N, Vanier C, Alda M, Joober R, Benkelfat C, Rouleau GA (1999) Prediction of level of serotonin 2A receptor binding by serotonin receptor 2A genetic variation in postmortem brain samples from subjects who did or did not commit suicide. Am J Psychiatry 156: 1456–1458

Turic D, Williams H, Langley K, Owen M, Thapar A, O'Donovan MC (2005) A family based study of catechol-O-methyltransferase (COMT) and attention deficit hyperactivity disorder (ADHD). Am J Med Gen B 133: 64–67

Weiss G (1985) Followup studies on outcome of hyperactive children. Psychopharmacol Bull 21: 169–177

Zametkin A, Nordahl T, Gross M, King C, Semple W, Rumsey J, Hamburger S, Cohen R (1990) Cerebral glucose metabolism in adults with hyperactivity of childhood onset. N Engl J Med 323: 1361–1366

Zoroglu SS, Erdal ME, Alasehirli B, Erdal N, Sivasli E, Tutkun H, Savas HA, Herken H (2002) Significance of serotonin transporter gene 5-HTTLPR and variable number of tandem repeat polymorphism in attention deficit hyperactivity disorder. Neuropsychobiology 45: 176–181

Authors' address: Dr. M. Reuter, Department of Psychology, Justus-Liebig-University of Giessen, Otto-Behaghel-Strasse 10F, 35394 Giessen, Germany, e-mail: martin.reuter@psychol.uni-giessen.de