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Neurotrophic Factor-Related Gene Polymorphisms and Adult Attention Deficit Hyperactivity Disorder (ADHD) Score in a High-Risk Male Population

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Adult attention deficit hyperactivity disorder (ADHD) is a widely under-reported but nevertheless common condition with a clear heritable component. Several genes have been proposed to play a role in the childhood onset of this neurodevelopmental disorder; however, association studies of persistence of ADHD into adulthood have rarely been performed. Neurotrophic factors (NTFs) are known to be involved in several aspects of neuronal development and neural plasticity in adults. They have also been linked, particularly through brain-derived neurotrophic factor (BDNF) interaction with dopamine transport, to the pathophysiology of ADHD. This study compares the genotypes of six different single nucleotide polymorphisms of genes within the neurotrophin system and their possible association with adult ADHD score in 143 high-risk male subjects referred to a forensic psychiatric unit. The genes included *NTF3*, *NTRK2* (*TrkB*), *NTRK3* (*TrkC*), *BDNF*, and $p75^{NTR}$. While none of the SNPs showed significant association with ADHD symptoms, one polymorphism within the exon of *NTF3* (rs6332) showed a trend toward an association between the A-allele and increased scores using both the retrospective childhood analysis Wender–Utah Rating Scale (WURS-k) ($P = 0.05$) and the adult ADHD assessment Wender–Reimherr interview ($P = 0.03$). This SNP is a silent mutation which might be in linkage disequilibrium with a functional risk variant for ADHD. As the association was only suggestive, however, this finding needs replication in a larger study with higher power.

KEY WORDS: neurotrophic factor; single nucleotide polymorphisms; genetic association; synaptic vesicle protein; ADHD

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INTRODUCTION

Attention Deficit/Hyperactivity disorder (ADHD) is a complex psychiatric disorder that arises due to interactions between environmental and biological influences with a strong underlying genetic aetiology [Rowland et al., 2002]. Parents (28.6%) with ADHD children previously presented symptoms of hyperactivity themselves [Biederman et al., 1990]. It is estimated that DSM-IV-defined ADHD affects between 4 and 12% of the population [Brown et al., 2001; Rösler et al., 2006]. The condition apparently arises in early childhood and persists into adolescence and sometimes into adulthood, although the hyperkinetic component is often more obvious in children and adolescents. Studies show that up to 60% of patients suffering from this disorder still show some or all of the ADHD characteristics as adults [Barkley et al., 2002]. ADHD is often associated with other psychiatric disorders making treatment more complex as one must take into account the severity of the comorbid profile [Neuman et al., 2001; Adler et al., 2005]. Individuals with ADHD are less likely to reach their academic potential when compared to healthy individuals; additionally, ADHD patients are more likely to change jobs more frequently; there is also increased drug use and explicit delinquent behavior [Barkley and Murphy 1978; Rösler et al., 2004].

Many studies have been performed on ADHD in children and adolescents due to the common belief that the patients will grow out of ADHD [Kordon et al., 2006]. A proportion of people do grow out of ADHD; however, recent studies have suggested that some adult patients continue to show ADHD symptoms albeit different from the symptoms viewed in children. ADHD diagnosis in adults is very complex; it requires retrospective consideration of childhood ADHD symptoms which can be obtained from a third party (family member or medical records) or by self-assessment. The first scale for retrospective self-assessment of ADHD symptoms was the Wender–Utah Rating Scale (WURS) [Ward et al., 1993; Wender, 1995]. The German short version of 25 questions

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(WURS-k) has been authenticated on national samples and controls [Rösler et al., 2006]. Additionally, it is desirable that the patient is given psychiatric assessment through standardized interviews such as the Wender–Reimherr Adult Attention Deficit Disorder Scale (WRAADDS) by an experienced clinician [Wender, 1995].

Prior studies have shown associations between ADHD and various genetic polymorphisms of genes involved in neurotransmitter metabolism [Domschke et al., 2005], *SNAP25*-mediated neurotransmitter release [Kustanovich et al., 2003; Feng et al., 2005] and the circadian rhythm (*CLOCK*) [Kissling et al., 2007] amongst others. Pooled data approaches or "meta-analyses" have highlighted a particularly strong association between ADHD and genes involved in dopamine transport and reception [Faraone et al., 2005; Thapar et al., 2007]. However to date, no distinct chromosomal region with a clear link to ADHD has been isolated.

Neurotrophic factors (NTFs) or neurotrophins are proteins that regulate the survival and differentiation of selective populations of neurons during embryonic development. Neurotrophins are crucial for many aspects of central nervous system development and function including roles in the maintenance of neural plasticity, the ability of neural circuits to undergo changes in function or organization due to previous activity and novel axonal growth, guidance, and regeneration [Hünnerkopf et al., 2007; Lynch et al., 2007]. Neurotrophin 3 in particular has been implicated in the survival of adult neurons and regulation of the enteric nervous system. The neurotrophins bind, with high affinity to tyrosine kinase (Trk) receptors including a strong brain-derived neurotrophic factor (BDNF) interaction with *NTRK2* (*TrkB*) and a high affinity *NTF3* interaction with *NTRK3* (*TrkC*). Neurotrophins also bind with low affinity to p75 (nerve growth factor (NGFB) receptor) with diverse functions including retrograde transport of the neurotrophin or increased affinity of the neurotrophin for the Trk receptors [Blochl and Blochl, 2007]. Mutations in the genes encoding for neurotrophins could be a causative factor resulting in a number of neuropsychiatric disorders [Thome et al., 1997; Hattori et al., 2002; Kent et al., 2005]. Neurotrophins have been shown to play a possible role in the pathophysiology of ADHD in a study of *BDNF* gene knockout mice [Monteggia et al., 2004; Monteggia et al., 2007]. BDNF is known to play a part in midbrain dopaminergic function when it interacts with the dopamine transporter (DAT), which is already thought to be important in the pathology of ADHD [Tsai, 2007]. The decreased levels of central BDNF are shown to play a part in the hyperactive behavior of the mice [Tsai, 2007]; however, some studies of the association between BDNF and ADHD have been negative, including that of the common valine allele of the Val66Met polymorphism [Schimmelmann et al., 2007]. As ADHD is thought to be a neurodevelopmental disorder, an NTFs involvement is likely to be very important in the pathophysiology of this common disorder [Syed et al., 2007] and in a very recent article, it has been suggested that 1 of 10 SNPs from genes related to the NTF-family may have an association with childhood ADHD [Syed et al., 2007]. Our study, therefore, assesses the link between six single nucleotide polymorphisms within the promoter region and exon of *NTF3*, exons of *BDNF* and $p75^{NTR}$, the promoter region of *NTRK2* (*TrkB*), and in the 3′-UTR of *NTRK3* (*TrkC*) with comprehensively assessed scores of adult ADHD in 143 high-risk subjects.

MATERIALS AND METHODS

The study focused on 143 male adults, consecutively referred for psychiatric examination to the Institute of Forensic Psychiatry of Saarland University. Given the association of ADHD with high rates of social maladaptation in later life, this was a high-risk population for ADHD [Rösler et al., 2004]. Average age was 31.3 ± 11.7 (SD). ADHD symptoms were assessed according to their relative ADHD-scores following ADHD self-report scales (WURS-k for the retrospective assessment of childhood and ADHS-SB for the assessment of current ADHD symptoms), the Wender–Reimherr interview, which is the German validated version of the WRAADDS and validated background data. Comorbid disorders were diagnosed according to DSM-IV and ICD-10 criteria, using modified, standardized checklists as reported by Rösler et al. [2004]. Since the ethnic heterogeneity of an analyzed sample may notably affect the observed allele frequencies [Dvornyk et al., 2004], all of the subjects in this study were Caucasians of Western European origin and German background. The study was approved by the local Ethical Committee, as previously outlined [Kissling et al., 2007]. To assure uniformity of data collection, all subjects underwent the same evaluation, after providing written informed consent and explanation of the aims of the study. No subjects with a diagnosis of current substance dependence, acute schizophrenia, major depression/bipolar disorder, or any other severe Axis-I diagnosis according to DSM-IV as well as subjects with the diagnosis of mental retardation ($IQ < 70$) were admitted to participate in the study.

Demographic data show typical features of a delinquent sample with poor school education (no regular school education: 14.1%; $\leq$9 years of education: 68.8%; >9 years of education: 17.2%), low rate of vocational training (53.1%) and typical marital status (single: 57.0%; divorced: 20.3%; married: 22.7%). The rate of prior convictions was 50.4%. Criminal offences comprised a wide spectrum: the most frequent (>5%) were sexual offenses (18.2%), physical injury (16.8%), property offences (9.8%), robbery (8.4%), homicide (8.4%) and fraud (5.6%), and drug offences (5.0%). 55 subjects had a WURS-k score $\geq$30, indicating a history of ADHD in childhood [Retz-Junginger et al., 2003]. As expected, current and childhood ADHD symptoms were highly prevalent in this forensic study population. The mean WURS-k score of the entire group was 25.7 (SD 15.5). Of the subjects with a WURS-k score $\geq$30, 37/55 (67.3%) still fulfilled DSM-IV diagnostic criteria for ADHD (DSM-IV 314.00 and 314.01), whereas 18/55 (32.79%) subjects were diagnosed with "ADHD, in partial remission" (DSM-IV 314.9). Subjects with lifetime ADHD and persistent ADHD did not differ from non-ADHD subjects regarding prevalence of violent behavior according to a common definition ($\chi^2 = .563$, $P = 0.45$ and $\chi^2 = .380$, $P = 0.54$, respectively) [Retz et al., 2004].

Substance use disorders (41.3%) and personality disorders (32.2%) were the most prevalent psychiatric lifetime diagnoses according to DSM-IV criteria in this forensic sample. Cluster B personality disorders were present in 25.9%, personality disorders of clusters A and C in 6.3% of the sample. Other psychiatric lifetime diagnoses were less frequent and comprised a history of psychotic disorder (7.0%), paraphilia (5.6%), affective disorder (2.1%), neurotic disorder and disorder of impulse control (3.5%).

Ten milliliter EDTA-stabilized venous blood samples were taken and stored immediately after collection at −20°C until analysis. Genomic DNA was extracted from whole blood of each subject using the commercial Invisorb® Blood Giga Kit (Invitek, Berlin, Germany) and concentration was adjusted using a PicoGreen fluorometric assay (Molecular Probes/Invitrogen, Carlsbad, CA). Polymerase chain reaction (PCR) was performed with primers and PCR conditions optimized as described [Kissling et al., 2007]; the resulting products were genotyped with RFLP analysis. With the exception of rs4930767 ($P = 0.079$) all genotypes were in Hardy–Weinberg equilibrium (HWE; assessed by the open-source program FINETTI which is in the public domain and accessible via the website http://ihg.gsf.de/cgibin/hw/hwa1.pl).

TABLE I. Allele Frequencies, Average Psychometric Scores, and Probability Analyses (±SD) for Each of the Six Single Nucleotide Polymorphisms Analyzed

143 Subjects		ADHD-SB (self-report) questionnaire data			WURS-k (self-report)	Wender–Reimherr interview
SNP [gene; position]	Genotype (N)	ADHD, total symptom score	ADHD, inattentive symptom score	ADHD, hyperactive/impulsive symptom score	WURS-k score	Wender–Reimherr total score
rs6332 [*NTF3*; exon III]	AA (32)	14.9 ± 2.0	6.9 ± 1.1	8.0 ± 1.1	27.9 ± 2.6	18.8 ± 2.0
	AG (77)	13.7 ± 1.3	6.2 ± 0.7	7.5 ± 0.7	25.6 ± 1.7	17.7 ± 1.3
	GG (34)	12.6 ± 1.9	6.4 ± 1.0	6.1 ± 1.0	21.8 ± 2.5	14.5 ± 2.0
	(DF = 2) T, *P*-value	1.36, 0.48	0.91, 0.61	1.33, 0.48,	5.74, 0.05*	6.99, 0.03*
rs4930767 [*NTF3*; promoter]	CC (40)	12.9 ± 1.8	6.5 ± 1.0	6.4 ± 1.0	23.1 ± 2.3	16.1 ± 1.8
	CT (61)	13.3 ± 1.4	5.8 ± 0.8	7.6 ± 0.8	26.8 ± 1.9	17.5 ± 1.5
	TT (42)	15.1 ± 1.7	7.3 ± 0.9	7.7 ± 0.9	25.1 ± 2.3	17.8 ± 1.8
	(DF = 2) T, *P*-value	0.77, 0.67	1.45, 0.47	0.95, 0.61	1.39, 0.49	0.65, 0.70
rs1017412 [*NTRK3*; 3'-UTR]	AA (62)	13.5 ± 1.4	6.6 ± 0.8	6.9 ± 0.8	24.2 ± 1.9	17.7 ± 1.5
	AG (67)	13.4 ± 1.4	5.9 ± 0.7	7.4 ± 0.7	26.1 ± 1.8	16.3 ± 1.4
	GG (14)	16.4 ± 3.0	8.2 ± 1.6	8.2 ± 1.6	26.0 ± 3.9	18.9 ± 3.1
	(DF = 2) T, *P*-value	1.31, 0.42	2.29, 0.24	0.08, 0.91	0.13, 0.87	0.15, 0.84
rs1212171 [*NTRK2*; promoter]	CC (26)	15.9 ± 2.3	7.4 ± 1.2	8.5 ± 1.2	27.9 ± 3.0	17.6 ± 2.4
	CT (69)	12.6 ± 1.4	5.7 ± 0.8	6.9 ± 0.8	24.3 ± 1.9	17.9 ± 1.5
	TT (47)	14.0 ± 1.6	6.6 ± 0.9	7.4 ± 0.9	26.3 ± 2.1	16.1 ± 1.7
	(DF = 2) T, *P*-value	1.39, 0.47	1.52, 0.43	1.72, 0.41	0.73, 0.65	0.35, 0.82
rs6265 [*BDNF*; exon]	AA/AG (59)**	13.0 ± 1.5	5.9 ± 0.8	7.1 ± 0.8	23.9 ± 1.9	16.1 ± 1.5
	GG (84)	14.2 ± 1.2	6.8 ± 0.7	7.4 ± 0.7	26.2 ± 1.6	17.9 ± 1.3
	(DF = 1) T, *P*-value	0.14, 0.71	0.44, 0.51	0.02, 0.89	0.71, 0.40	0.34, 0.56
rs2072446 [$p75^{NTR}$; exon IV]	CC (132)	13.8 ± 1.0	6.4 ± 0.5	7.4 ± 0.5	25.3 ± 1.3	16.9 ± 1.0
	CT (10)	12.0 ± 3.5	6.4 ± 1.9	5.5 ± 1.9	23.6 ± 4.6	19.6 ± 3.6
	(DF = 1) T, *P*-value	0.12, 0.73	0.002, 0.97	1.23, 0.27	0.04, 0.84	1.18, 0.28

T-values, *P*-values, and degrees of freedom (DF) are included.
*While not significant, these *P*-values might suggest a possible trend towards association.
**For rs6265, only five individuals were AA homozygous. Therefore, AA and AG were grouped together.

Descriptive data between genotypes were compared by non-parametric analysis of variance (ANOVA) or χ^2 tests. Possible confounding variables (criterion $P < 0.10$) associated with a specific genotype were controlled for in further analyses. As the distribution of the rating scale values was markedly skewed from a normal distribution, non-parametric analyses were performed to assess the association of the genotypes with the severity of the ADHD self-assessment and Wender–Reimherr interview. These non-parametric analyses of covariance (ANCOVA) were computed by the SAS-macro npar (www.ams.med.uni-goettingen.de/projekte/makros/index.html) with adjustment for age and history of personality disorder (as described above). Bonferroni-adjustment for multiple testing resulted in critical P-value < 0.008 indicating significance of the findings.

RESULTS

Genotypic frequencies for each of the polymorphisms analyzed are summarized in Table I with the relative ADHD scores measured using the ADHS-SB self-report questionnaire, WURS-k self-report data and the Wender–Reimherr interview data. The data include the absolute genotype frequencies for each polymorphism, the average score for each genotype and a P-value calculation of significance. Following Bonferroni correction, these showed no significant differences for any of the genotypes. The "silent" Pro>Pro *NTF3* exon I polymorphism (rs6332), however, resulted in P-values of 0.05 and 0.03 for association with the WURS-k and Wender–Reimherr diagnostic instruments, respectively. This indicates a trend for association of one or more A-alleles of rs6332 with increased ADHD scores.

DISCUSSION

NTFs play a role in neurogenesis during development as well as the regulation of neural plasticity in adults. In childhood ADHD, the *NGFB* polymorphism rs6330 did show association in one study, whereas the *NTF3* polymorphisms rs6332 and rs4930767 did not [Syed et al., 2007].

This study compared six polymorphisms of NTF and NTF-related genes and their possible association with "increased ADHD scores" of 143 volunteer male subjects referred to a forensic psychiatric unit, therefore with an increased propensity for ADHD, using current standard assessment measures. Those polymorphisms were located in the exon III and promoter regions of *NTF3* (rs6332 and rs4930767, respectively), the 3′-UTR of *NTRK3* (rs1017412), the promoter region of *NTRK2* (rs1212171), and the exons of *BDNF* and of $p75^{NTR}$ (rs6265 and rs2072446, respectively).

None of the six SNPs had significant association with increased ADHD scores; however, the rs6332 A > G polymorphism was on the borderline for the WURS-k and Wender–Reimherr instruments. This was not the case for the other questionnaires; however, these are widely considered to be less reliable. Significance was only lost once the Bonferroni multiple testing effect was taken into consideration suggesting a possible trend toward ADHD susceptibility with the A-allele as a risk factor. The lack of association for this SNP (rs6332) and ADHD in a previous study [Syed et al., 2007] may reflect the sample population size, differences in the relative diagnostic analysis of ADHD-score or may represent a negation of this polymorphism as a factor in adult ADHD. Further studies would be necessary to confirm or refute this association and as with all such studies, these genetic associations are tempered by the suggestion that ADHD has a dimensional or continuous phenotype rather than a distinct genetic aetiology [Thapar et al., 2006]. rs6332 is a silent Pro-Pro genetic variation, suggesting limited biological relevance of the mutation itself, although codon usage must be taken into account, while the rs4930767 polymorphism in the promoter region of the same gene showed no association with any measure of ADHD. As rs4930767 was not at HWE, the apparent lack of association is less significant; however, the data suggest that if the rs6332-association with ADHD-scores were confirmed through increased sample size, we would expect the polymorphism to be in linkage disequilibrium with biologically relevant markers rather than having a direct causative role. It is important to acknowledge that the lack of an association between the SNPs and ADHD scores in our study does not exclude a role for the investigated genes containing these SNPs in the pathophysiology of this disease. Additionally, possible gene × gene interaction and haploblock data analyses in future studies may elucidate linked or co-inherited effects of a number of similar or closely located genes.

As the subjects assessed in this study were recruited from a forensic sample with high rates of conduct problems and antisocial personality disorder, the results cannot be generalized.

To our knowledge, this is the first study evaluating a possible role of several NTF-related gene polymorphisms in adult ADHD, focusing on six genetic sequence variations.

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REFERENCES

Adler CM, Delbello MP, Mills NP, Schmithorst V, Holland S, Strakowski SM. 2005. Comorbid ADHD is associated with altered patterns of neuronal activation in adolescents with bipolar disorder performing a simple attention task. Bipolar Disord 7(6):577–588.

Barkley RA, Fischer M, Smallish L, Fletcher K. 2002. The persistence of attention-deficit/hyperactivity disorder into young adulthood as a function of reporting source and definition of disorder. J Abnorm Psychol 111(2):279–289.

Barkley RA, Murphy JV. 1978. Pseudodeterioration of intelligence in children. Ann Neurol 4(4):388.

Biederman J, Faraone SV, Keenan K, Knee D, Tsuang MT. 1990. Family-genetic and psychosocial risk factors in DSM-III attention deficit disorder. J Am Acad Child Adolesc Psychiatry 29(4):526–533.

Blochl A, Blochl R. 2007. A cell-biological model of p75(NTR) signaling. J Neurochem 102: 289–305.

Brown RT, Freeman WS, Perrin JM, Stein MT, Amler RW, Feldman HM, Pierce K, Wolraich ML. 2001. Prevalence and assessment of attention-deficit/hyperactivity disorder in primary care settings. Pediatrics 107(3): E43.

Domschke K, Sheehan K, Lowe N, Kirley A, Mullins C, O'Sullivan R, Freitag C, Becker T, Conroy J, Fitzgerald M, et al. 2005. Association analysis of the monoamine oxidase A and B genes with attention deficit hyperactivity disorder (ADHD) in an Irish sample: Preferential transmission of the MAO-A 941G allele to affected children. Am J Med Genet B Neuropsychiatr Genet 134B(1):110–114.

Dvornyk V, Long JR, Xiong DH, Liu PY, Zhao LJ, Shen H, Zhang YY, Liu YJ, Rocha-Sanchez S, Xiao P, et al. 2004. Current limitations of SNP data from the public domain for studies of complex disorders: A test for ten candidate genes for obesity and osteoporosis. BMC Genet 5:4.

Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, Sklar P. 2005. Molecular genetics of attention-deficit/hyperactivity disorder. Biol Psychiatry 57(11):1313–1323.

Feng Y, Crosbie J, Wigg K, Pathare T, Ickowicz A, Schachar R, Tannock R, Roberts W, Malone M, Swanson J, Kennedy JL, Barr CL. The SNAP25 gene as a susceptibility gene contributing to attention-deficit hyperactivity disorder. Mol Psychiatry 2005. 10(11):998–1005, 973.

Hattori M, Kunugi H, Akahane A, Tanaka H, Ishida S, Hirose T, Morita R, Yamakawa K, Nanko S. 2002. Novel polymorphisms in the promoter region of the neurotrophin-3 gene and their associations with schizophrenia. Am J Med Genet 114(3):304–309.

Hünnerkopf R, Strobel A, Gutknecht L, Brocke B, Lesch KP. 2007. Interaction between BDNF Val66Met and dopamine transporter gene variation influences anxiety-related traits. Neuropsychopharmacology 32: 2552–2560.

Kent L, Green E, Hawi Z, Kirley A, Dudbridge F, Lowe N, Raybould R, Langley K, Bray N, Fitzgerald M, et al. 2005. Association of the paternally transmitted copy of common valine allele of the Val66Met polymorphism of the brain-derived neurotrophic factor (BDNF) gene with susceptibility to ADHD. Mol Psychiatry 10(10):939–943.

Kissling C, Retz W, Wiemann S, Coogan A, Clement R, Hünnerkopf R, Conner A, Freitag C, Rösler M, Thome J. 2007. A polymorphism at the 3′-untranslated region of the clock gene is associated with adult attention-deficit hyperactivity disorder. Am J Med Genet B Neuropsychiatr Genet (in press).

Kordon A, Kahl KG, Wahl K. 2006. A new understanding of attention-deficit disorders-beyond the age-at-onset criterion of DSM-IV. Eur Arch Psychiatry Clin Neurosci 256 (Suppl 1):i47–i54.

Kustanovich V, Merriman B, Mcgough J, Mccracken JT, Smalley SL, Nelson SF. 2003. Biased paternal transmission of SNAP-25 risk alleles in attention-deficit hyperactivity disorder. Mol Psychiatry 8(3):309–315.

Lynch G, Kramar EA, Rex CS, Jia Y, Chappas D, Gall CM, Simmons DA. 2007. Brain-derived neurotrophic factor restores synaptic plasticity in a knock-in mouse model of Huntington's disease. J Neurosci 27(16):4424–4434.

Monteggia LM, Barrot M, Powell CM, Berton O, Galanis V, Gemelli T, Meuth S, Nagy A, Greene RW, Nestler EJ. 2004. Essential role of brain-derived neurotrophic factor in adult hippocampal function. Proc Natl Acad Sci USA 101(29):10827–10832.

Monteggia LM, Luikart B, Barrot M, Theobold D, Malkovska I, Nef S, Parada LF, Nestler EJ. 2007. Brain-derived neurotrophic factor conditional knockouts show gender differences in depression-related behaviors. Biol Psychiatry 61(2):187–197.

Neuman RJ, Heath A, Reich W, Bucholz KK, Madden PAF, Sun L, Todd RD, Hudziak JJ. 2001. Latent class analysis of ADHD and comorbid symptoms in a population sample of adolescent female twins. J Child Psychol Psychiatry 42(7):933–942.

Retz W, Retz-Junginger P, Supprian T, Thome J, Rösler M. 2004. Association of serotonin promoter gene polymorphism with violence: Relation with personality disorders, impulsivity and childhood ADHD psychopathology. Behav Sci Law 22(3):415–425.

Retz-Junginger P, Retz W, Blocher D, Stieglitz RD, Georg T, Supprian T, Wender PH, Rösler M. 2003. Reliability and validity of the Wender–Utah-rating-scale short form. Retrospective assessment of symptoms for attention deficit/hyperactivity disorder. Nervenarzt 74(11):987–993.

Rösler M, Retz W, Retz-Junginger P, Hengesch G, Schneider M, Supprian T, Schwitzgebel P, Pinhard K, Dovi-Akue N, Wender P. et al. 2004. Prevalence of attention deficit-/hyperactivity disorder (ADHD) and comorbid disorders in young male prison inmates. Eur Arch Psychiatry Clin Neurosci 254(6):365–371.

Rösler M, Retz W, Thome J, Schneider M, Stieglitz RD, Falkai P. 2006. Psychopathological rating scales for diagnostic use in adults with attention-deficit/hyperactivity disorder (ADHD). Eur Arch Psychiatry Clin Neurosci 256 (Suppl 1):i3–i11.

Rowland AS, Lesesne CA, Abramowitz AJ. 2002. The epidemiology of attention-deficit/hyperactivity disorder (ADHD): A public health view. Ment Retard Dev Disabil Res Rev 8(3):162–170.

Schimmelmann BG, Friedel S, Dempfle A, Warnke A, Lesch KP, Walitza S, Renner TJ, Romanos M, Herpertz-Dahlmann B, Linder M, et al. 2007. No evidence for preferential transmission of common valine allele of the Val66Met polymorphism of the brain-derived neurotrophic factor gene (BDNF) in ADHD. J Neural Transm 114(4):523–526.

Syed Z, Dudbridge F, Kent L. 2007. An investigation of the neurotrophic factor genes GDNF, NGF, and NT3 in susceptibility to ADHD. Am J Med Genet B Neuropsychiatr Genet 144B(3):375–378.

Thapar A, Langley K, O'Donovan M, Owen M. 2006. Refining the attention deficit hyperactivity disorder phenotype for molecular genetic studies. Mol Psychiatry 11(8):714–720.

Thapar A, Langley K, Owen MJ, O'Donovan MC. 2007. Advances in genetic findings on attention deficit hyperactivity disorder. Psychol Med 37: 1681–1692.

Thome J, Durany N, Palomo A, Foley P, Harsanyi A, Baumer A, Hashimoto E, Cruz-Sanchez FF, Riederer P. 1997. Variants in neurotrophic factor genes and schizophrenic psychoses: No associations in a Spanish population. Psychiatry Res 71(1):1–5.

Tsai SJ. 2007. Attention-deficit hyperactivity disorder may be associated with decreased central brain-derived neurotrophic factor activity: Clinical and therapeutic implications. Med Hypotheses 68(4):896–899.

Ward MF, Wender PH, Reimherr FW. 1993. The Wender Utah rating scale: An aid in the retrospective diagnosis of childhood attention deficit hyperactivity disorder. Am J Psychiatry 150(6):885–890.

Wender EH. 1995. Attention-deficit hyperactivity disorders in adolescence. J Dev Behav Pediatr 16(3):192–195.