

Meta-Analysis of Brain-Derived Neurotrophic Factor p.Val66Met in Adult ADHD in Four European Populations

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Attention-deficit hyperactivity disorder (ADHD) is a multifactorial, neurodevelopmental disorder that often persists into adolescence and adulthood and is characterized by inattention, hyperactivity and impulsiveness. Before the advent of the first genome-wide association studies in ADHD, genetic research had mainly focused on candidate genes related to the dopaminergic and serotonergic systems, although several other genes had also been assessed. Pharmacological data, analysis of animal models and association studies suggest that *Brain-Derived Neurotrophic Factor (BDNF)* is also a strong candidate gene for ADHD. Several polymorphisms in *BDNF* have been reported and studied in psychiatric disorders but the most frequent is the p.Val66Met (rs6265G > A) single nucleotide polymorphism (SNP), with functional effects on the intracellular trafficking and secretion of the protein. To deal with the inconsistency raised among different case-control and family-based association studies regarding the p.Val66Met contribution to ADHD, we performed a meta-analysis of published as well as unpublished data from four different centers that are part of the International Multicentre Persistent ADHD CollaboraTion (IMpACT). A total of 1,445 adulthood ADHD patients and 2,247 sex-matched controls were available for the study. No association between the p.Val66Met polymorphism and ADHD was found in any of the four populations or in the pooled sample. The meta-analysis also showed that the overall gene effect for ADHD was not statistically significant when gender or comorbidity with mood disorders were considered. Despite the potential role of *BDNF* in ADHD, our data do not support the involvement of p.Val66Met in the pathogenesis of this neuropsychiatric disorder. © 2009 Wiley-Liss, Inc.

Key words: attention-deficit hyperactivity disorder; adult ADHD; BDNF; case-control association study; meta-analysis

INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that often persists into adolescence and adulthood and is characterized by inattention, hyperactivity and impulsiveness and causes significant social, educational and psychological problems in childhood and adulthood. Heritability of ADHD has been estimated at 39–91% and it is considered a complex disorder with genetic and environmental risk factors

[Faraone et al., 2005]. The genetic causes of ADHD are still unknown, but so far genetic research has mainly focused on candidate genes of the dopaminergic and serotonergic systems [Comings et al., 2000; Ribasés et al., 2009]. In addition to these neurotransmission pathways, neurotrophic factors, which participate in development, survival and functional maintenance of neurons, may be involved in neuroplasticity changes that take place in the central nervous system and may also contribute to the genetic predisposition to ADHD. Among these, *Brain-Derived Neurotrophic Factor (BDNF)* is a strong candidate gene. Psychostimulant and antidepressant drugs commonly used for ADHD treatment modulate the expression of *BDNF* and its specific receptor *NTRK2* [Meredith et al., 2002; Chase et al., 2007]. In addition, heterozygous *Bdnf* knockout mice display hippocampal-dependent learning deficiencies, aggressiveness, anxiety, and hyperactive locomotor behavior when compared with wild-type littermates, which interestingly can be rescued in an enriched environment [Linnarsson et al., 1997; Kernie et al., 2000; Rios et al., 2001; Chourbaji et al., 2004]. Chronic infusion of *Bdnf* into the substantia nigra of animal models alters locomotion activity, whereas its intracerebroventricular administration decreases locomotion, motility and rearing [Martin-Iverson et al., 1994; Kobayashi et al., 1997]. Finally, several association studies have tested the possible involvement of *BDNF* in ADHD, although the results are controversial. Some of these studies focus solely on *BDNF* or a few candidate genes (Table SI; [Friedel et al., 2005; Kent et al., 2005; Brookes et al., 2006; Lee et al., 2007; Schimmelmann et al., 2007; Xu et al., 2007; Conner et al., 2008; Lanktree et al., 2008; Oades et al., 2008]), whereas others are GWAS [Neale et al., 2008; Sonuga-Barke et al., 2008; Lasky-Su et al., 2008a,b; Anney et al., 2008b].

The *BDNF* gene is located at 11p13-14, is organized in 13 exons, and encodes a 247 amino acid precursor peptide (pro-BDNF) that is proteolytically cleaved to form the mature protein of 153 amino acids. Several polymorphisms of *BDNF* have been reported and studied in a number of psychiatric disorders. The most frequent is the rs6265 (p.Val66Met) SNP located within the pro-BDNF region, which goes along with increased BDNF serum concentrations in Met allele carriers [Lang et al., 2009]. Egan et al. [2003] demonstrated that although it is located in the pro-BDNF polypeptide and does not alter the intrinsic biological activity of the mature protein, the rs6265G > A sequence variant impairs the intracellular processing and secretion of the mature neurotrophin. In addition, as it was recently shown that mice also secrete proBDNF, especially

while the brain is developing, these data point towards an impact of p.Val66Met on neuronal development, especially in the hippocampus [Yang et al., 2009].

To deal with the inconsistency raised among different case-control and family-based association studies regarding the contribution of *BDNF* p.Val66Met to ADHD, we aimed to perform a meta-analysis of published as well as unpublished case-control data from four different centers (Germany, The Netherlands, Norway and Spain) integrated in the International Multicentre persistent ADHD CollaboraTion (IMpACT), which focuses its interest on adulthood ADHD.

MATERIALS AND METHODS

Patients and Controls

In total, 1,445 adult ADHD patients and 2,447 controls of Caucasian origin from four European countries (Spain, Germany, Norway, and The Netherlands) were recruited by members of the International Multicentre Persistent ADHD CollaboraTion (IMpACT). Consensus eligibility criteria for the current study across all sites were a diagnosis of ADHD according to the diagnostic criteria of DSM-IV (Diagnostic and Statistical Manual for Mental Disorders-IV), onset before the age of 7 years via retrospective diagnosis (which was confirmed by a family member, wherever possible), lifelong persistence and current diagnosis. Patients were extensively examined by experienced psychiatrists in adult ADHD using open and semi-structured interviews. Other psychiatric disorders were evaluated with the Structured Clinical Interview of DSM-IV for axis-I and axis-II disorders (SCID-I, SCID-II) or semi-structured interviews. Severity of ADHD in adulthood was measured by means of standards rating scales. Most of the clinical sample has been described before [Bekker et al., 2005; Kooij et al., 2005; Jacob et al., 2007; Franke et al., 2008; Johansson et al., 2008; Ramos-Quiroga et al., 2008; Ribasés et al., 2008]. Diagnosis was blind to genotype (see Table SII for a detailed description of the instruments and procedures used by the different sites).

Most controls (except for the Norwegian samples and part of the German samples, see Table SII) were screened for the presence of ADHD and those scoring high on symptoms of the disorder were excluded.

The study was approved by the ethics committee of each participating institution and informed consent was obtained from all subjects in accordance with the Helsinki Declaration.

DNA Isolation and Genotyping

Genomic DNA was isolated either from saliva using the Oragene™ DNA Self-Collection kit from DNA Genotek (DNA Genotek Inc., Ottawa, Canada) or from peripheral blood lymphocytes by the salting-out procedure [Miller et al., 1988].

Germany and Norway: genotyping of rs6265 was accomplished using the Sequenom MassArray genotyping platform (Sequenom, San Diego, CA).

Netherlands: The rs6265 polymorphism was genotyped using TaqMan-based genotyping. Genotyping was carried out in a volume of 10 μ l containing 10 ng of genomic DNA, 5 μ l of ABgene Mastermix (2 \times ; ABgene Ltd., Hamburg, Germany), 0.125 μ l of the

Taqman assay (assay ID: Taqman assay: C_11592758_10; reporter 1: VIC-C-allele; reporter 2: FAM-T-allele; Applied Biosystems, Nieuwerkerk a/d IJssel, The Netherlands) and 3.875 μ l of H₂O. Amplification was performed on a 7500 Fast Real-Time PCR System starting with 15 min at 95°C, followed by 50 cycles of 15 sec at 95°C and 1 min at 60°C. Genotypes were scored using the algorithm and software supplied by the manufacturer (Applied Biosystems).

Spain: rs6265 was genotyped with the SNPlex platform (Applied Biosystems, Foster City, CA) at the Barcelona node of the Centro Nacional de Genotipado (CeGen, www.cegen.org) as previously described [Tobler et al., 2005].

Statistical Analysis

We first assessed Hardy-Weinberg equilibrium (HWE) in the control groups from each IMpACT node using a χ^2 test. To determine the best genetic model to be used we estimated the three possible odds ratios (ORs) and their 95% confidence intervals (CI): OR1 (Val/Val vs. Met/Met), OR2 (Val/Val vs. Val/Met) and OR3 (Met/Met vs. Val/Met) in the pooled sample (Table SIII). Thus, if OR1 = OR3 \neq 1 and OR2 = 1, a recessive model is suggested; OR1 = OR2 \neq 1 and OR3 = 1 indicates a dominant model; and OR1 > OR3 > 1 (or OR1 < OR2 < 1 and OR1 < OR3 < 1) suggests a codominant model. Prior to the pooling of the four individual studies, we compared genotype and allele frequencies among cases and controls from each separate IMpACT node using a χ^2 test with the SNPAssoc R package [Gonzalez et al., 2007]. To combine the individual study results, we conducted meta-analyses using the Meta R package (cran.r-project.org/web/packages/meta/index.html). We first tested for heterogeneity among studies using the Q-statistic, which is a weighted sum of the squares of the deviations of individual study OR estimates from the overall estimate. When the ORs are homogeneous, Q follows a χ^2 distribution with $r - 1$ (r is the number of studies) degrees of freedom (df). If $P_Q < 0.10$, the heterogeneity was considered to be statistically significant [Lau et al., 1997; Fleiss, 1981]. Inconsistency across studies was quantified with the I^2 metric ($I^2 = Q - df/Q$), which can be interpreted as the percentage of total variation across several studies due to heterogeneity. I^2 takes values between 0% and 100%, with higher values denoting a greater degree of heterogeneity (0–25%: no heterogeneity; 25–50% moderate heterogeneity; 50–75%: large heterogeneity; 75–100% extreme heterogeneity) [Zintzaras and Hadjigeorgiou, 2004]. When no heterogeneity was present, the pooled OR was estimated using fixed-effects model (Mantel and Haenszel, 1959). Otherwise, random effects models (Laird and Mosteller, 1990) were applied to obtain the pooled OR. Random effects modeling assumes a genuine diversity in the results of various studies and it incorporates a between-study variance into the calculations (Whitehead, 2002). The results of the association tests are given as pooled ORs (which estimate the genotype-induced risk of adult ADHD), with the corresponding 95% confidence intervals (CIs). $P < 0.05$ was considered statistically significant. Additionally, we conducted other meta-analytical studies in which we split the sample by gender or by clinical subtype (combined and inattentive). Because ADHD is highly comorbid with mood disorders and *BDNF* has been extensively tested for association with this psychiatric entity [Gratacòs et al., 2007;

Verhagen et al., 2008], we also considered ADHD patients with and without mood disorders.

RESULTS

A total of 1,445 adult ADHD patients and 2,247 controls from four IMpACT nodes were available for the meta-analysis. Table I shows the clinical description of the samples included in the study. Genotype distributions of the p.Val66Met SNP showed no significant departure from HWE when each control group as well as the pooled control sample were considered ($P > 0.05$). No significant differences were observed when genotype or allele frequencies of the p.Val66Met SNP were compared between ADHD patients from each country and their sex-matched unrelated controls (Table II). To determine the best genetic model we calculated the three ORs. The estimated ORs in the pooled sample were $OR_1 = 0.93$ (95% CI: 0.66–1.31), $OR_2 = 0.99$ (95% CI: 0.86–1.14), and $OR_3 = 1.07$ (95% CI: 0.75–1.52). No heterogeneity was detected for OR_1 , OR_2 , or OR_3 across samples ($P = 0.43$, $P = 0.35$, and $P = 0.51$, respectively) (Table SIII). The fact that none of the ORs significantly deviated from 1 did not allow to choose a particular genetic model based on the pattern of the odds ratios. Thus, comparisons of genotype frequencies between cases and controls were performed under different models (codominant, dominant, recessive, overdominant, and log-additive). The dominant one was eventually selected for the meta-analysis because (1) it was the one that produced lower P -values in most comparisons, (2) it produced the lowest Akaike Information Criterion (AIC) values, and (3) it was the only one to show nominal P -values in some particular comparisons (see below). Therefore, a Met66 dominant model with fixed effects was used to perform a meta-analysis, which showed a lack of a statisti-

cally significant effect of the p.Val66Met *BDNF* SNP on adulthood ADHD ($P = 0.86$; $OR = 0.99$ (95% CI: 0.86–1.13); Table III).

We then considered the combined and inattentive subtypes separately and we did not observe statistically significant effects of p.Val66Met *BDNF* on ADHD subtypes in either of the four populations (Table SIV). The pooled analysis under a fixed-effects model showed no significant effect of the polymorphism on ADHD subtypes either (Table IV). The hyperactive/impulsive subtype was not studied because of the limited sample size (6.43% from the total sample; Table I).

The separate analysis of males and females displayed a nominal association between p.Val66Met and ADHD in females from the Spanish cohort ($P = 0.0363$, $OR = 0.50$ (95% CI: 0.26–0.96); Table SV). Nevertheless, after having discarded heterogeneity, the pooled analysis under a fixed-effects model showed that the overall gene effect on ADHD was neither statistically significant in females ($P = 0.51$; $OR = 0.93$ (95% CI: 0.75–1.14)) nor in males ($P = 0.72$; $OR = 1.03$ (95% CI: 0.85–1.24); Table V).

We then separated ADHD patients according to comorbidity with mood disorders and observed nominal association between *BDNF* and ADHD with mood disorders in some of the populations (Germany, genotypes: $P = 0.035$, $OR = 1.33$ (95% CI: 1.02–1.75) and alleles: $P = 0.035$, $OR = 1.28$ (95% CI: 1.01–1.64); Table SVI) and without mood disorders in others (Netherlands: genotypes: $P = 0.047$, $OR = 0.60$ (95% CI: 0.36–0.99); Table SVI). However, after discarding heterogeneity, the meta-analysis under a fixed-effects model showed that the overall gene effect was not significant in any of the two clinical groups considered (ADHD with mood disorders: $P = 0.24$, $OR = 1.11$ (95% CI: 0.93–1.31); ADHD without mood disorders: $P = 0.20$, $OR = 0.88$ (95% CI: 0.73–1.07); Table VI).

TABLE I. Descriptive Characteristics of the IMpACT Samples: Adult ADHD Patients and Controls Without ADHD From Four European Countries

Study	Germany	Netherlands	Norway	Spain ^a	Pool
Cases					
Female	282 (46.45%)	95 (50%)	208 (47.7%)	58 (23.5%)	643 (44.49%)
Male	325 (53.54%)	96 (50%)	228 (52.29%)	153 (76.5%)	802 (55.50%)
Total	607	191	436	211	1,445
ADHD subtype					
Combined type	408 (67.21%)	172 (90.07%)	230 (52.75%)	139 (65.87%)	949 (65.67%)
Hyperactive/impulsive type	48 (7.90%)	5 (2.61%)	30 (6.88%)	10 (4.73%)	93 (6.43%)
Inattentive type	151 (24.87%)	14 (7.32%)	73 (16.74%)	62 (29.4%)	300 (20.76%)
Sub-threshold	—	—	97 (22.24%)	—	97 (6.71%)
Unknown	—	—	6 (1.39%)	—	6 (0.43%)
Age (mean and SD)	31 (10.26)	42 (10.7)	34 (10.6)	35 (10.17)	35 (4,6)
Mood disorders	323 (53.21%)	119 (62.30%)	299 (68.57%)	81 (38.38%)	822 (56.8%)
Controls					
Female	390 (46.42%)	243 (50%)	237 (47.78%)	116 (27.29%)	986 (43.8%)
Male	450 (53.57%)	243 (50%)	259 (52.2%)	309 (72.7%)	1261 (56.1%)
Total	840	486	496	425	2,247
Age (mean and SD)	31 (10.4)	62 (18.06)	27 (7.2)	43 (16.36)	40 (15.7)

^aPublished data [Ribasés et al., 2008].

TABLE II. Comparison of Genotype and Allele Frequencies of the BDNF p.Val66Met Polymorphism in 1,445 Adulthood ADHD Patients and 2,247 Sex-Matched Unrelated Controls From Four European Countries

	Genotypes ^a										Alleles ^b				
	Cases, n (%)					Controls, n (%)					Genotype AG + AA vs. GG		Allele A vs. allele G		
	AA	AG	GG	Sum	AA	AG	GG	Sum	P	OR (95% CI)	P	OR (95% CI)	P		
Germany	25 (4.1)	189 (31.1)	393 (64.7)	607	39 (4.6)	284 (33.8)	517 (61.5)	840	0.45	0.88 (0.53–1.47)	0.63	1.14 (0.92–1.42)	0.21	1.12 (0.93–1.35)	0.22
Netherlands	5 (2.6)	67 (35.1)	119 (62.3)	191	12 (2.5)	152 (31.3)	322 (66.3)	486	0.62	1.06 (0.37–3.06)	0.91	0.84 (0.59–1.19)	0.33	0.88 (0.65–1.18)	0.38
Norway	22 (5.0)	132 (30.3)	282 (64.7)	436	17 (3.4)	155 (31.2)	324 (65.3)	496	0.46	1.50 (0.78–2.86)	0.21	0.97 (0.74–1.26)	0.83	0.93 (0.74–1.17)	0.53
Spain	10 (4.7)	79 (37.4)	122 (57.8)	211	18 (4.2)	141 (33.2)	266 (62.6)	425	0.51	1.12 (0.51–2.48)	0.24	0.81 (0.58–1.14)	0.24	0.86 (0.65–1.13)	0.28
Pool	62 (4.3)	467 (32.3)	916 (63.4)	1,445	86 (3.8)	732 (32.6)	1,429 (63.6)	2,247	0.77	1.13 (0.81–1.57)	0.48	0.99 (0.86–1.13)	0.90	0.98 (0.87–1.1)	0.72

^aAA = Met/Met; AG = Met/Val; GG = Val/Val.

^bA = Met; G = Val.

DISCUSSION

To our knowledge, this is the first meta-analysis performed to evaluate the association between *BDNF* and adulthood ADHD. No evidence of association was found between the p.Val66Met variation and this neuropsychiatric disorder. Although most of the previous studies considered childhood ADHD samples (Table SI), our results are in agreement with those described by Friedel et al. [2005] in 88 childhood ADHD patients and 96 controls, Schimmelmann et al. [2007] in 468 children from 294 families comprising one or more affected sibs, Lee et al. [2007] in 315 ADHD children from 266 nuclear families, or Brookes et al. [2006] in 674 DSM-IV combined type probands with 808 siblings, in which no association between the p.Val66Met SNP and ADHD was detected. However, other association studies have reported a possible contribution of *BDNF* to ADHD (Table SI). In this regard, Kent et al. [2005] demonstrated a preferential paternal transmission of the p.Val66 allele in 341 childhood ADHD trios and Xu et al. [2007] found no association between p.Val66Met and ADHD but showed evidence for a decreased transmission of the $-270T/p.Val66$ haplotype in two independent samples of ADHD child probands. In addition, two studies considered the *BDNF* gene in adulthood ADHD and while Lanktree et al. [2008] found evidence for a p.Val66 contribution, Conner et al. [2008] showed no association between this polymorphism and adult ADHD scores (Table SI). Two genome-wide association studies (GWAS) have been reported in ADHD so far, one of them in 343 adult ADHD patients and 304 controls using a DNA pooling approach [Lesch et al., 2008] and the other one in 958 affected family trios with child ADHD sibs considering either ADHD as a categorical trait or related quantitative measures such as ADHD symptoms, age at onset of ADHD symptoms or conduct problems [Neale et al., 2008; Lasky-Su et al., 2008a,b; Anney et al., 2008b]. All of them included the p.Val66Met variation (rs6265) and other polymorphic sites within the *BDNF* gene, but they did not achieve genome-wide significance.

All these conflicting findings may either reflect that the variant is not associated with ADHD or, alternatively, that the results vary because of factors such as reduced statistical power due to limited sample sizes in some of the reported studies (Table SI), genetic heterogeneity introduced or increased by different diagnostic criteria, different frequencies of ADHD subtypes, comorbidity and/or distinct ethnic origin among the studied samples, as differences in *BDNF* allelic frequencies have been reported among ethnic groups [Shimizu et al., 2004]. The lack of association between *BDNF* and adulthood ADHD detected in our study, however, raises several considerations:

- (1) Genetic effects for common variants may be reduced and difficult to detect in association studies of small sample sizes. The present meta-analysis, that considers relatively large well-characterized clinical samples that fulfilled DSM-IV criteria for ADHD and were evaluated using a common set of diagnostic instruments, improves the statistical power to detect association (>95%) with respect to the analyses of previous datasets. Our strategy also allowed examination of heterogeneity between the different series of patients and controls included in the study. In this regard, we did not detect heterogeneity of ORs

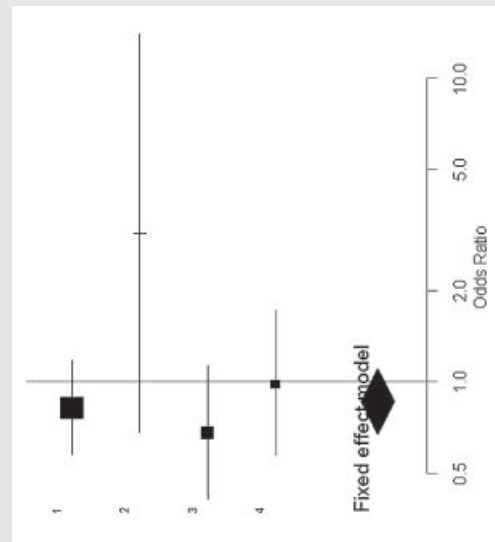
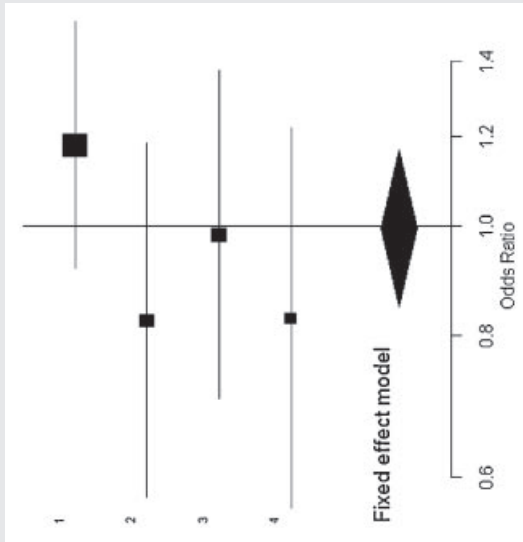
TABLE III. Genetic Effect of the p.Val166Met Polymorphism on Adulthood ADHD Using a Fixed-Effects Model

Study	Cases		Controls						
	GG	Total	GG	Total	Weight (%)	OR M-H, fixed, 95% CI	z	P	OR M-H, fixed, 95% CI
1. Germany	393	607	517	840	37.95	1.14 (0.92–1.42)			
2. Netherlands	119	191	322	486	17.00	0.84 (0.59–1.19)			
3. Norway	282	436	324	496	26.57	0.97 (0.74–1.27)			
4. Spain	122	211	266	425	18.48	0.81 (0.58–1.14)			
Fixed-effects model	916	1,445	1,429	2,247	100	0.98 (0.86–1.13)			

Test of heterogeneity: $I^2 = 3.84$, $df = 3$, $P = 0.28$; $I^2 = 21.9\%$ (0–88%).

TABLE IV. Genetic Effect of the p.Val66Met Polymorphism on (a) Adulthood ADHD, Combined Subtype (949 Cases and 2,247 Controls) and Adulthood ADHD, Inattentive Subtype (299 Cases and 2,247 Controls), Using a Fixed-Effects Model

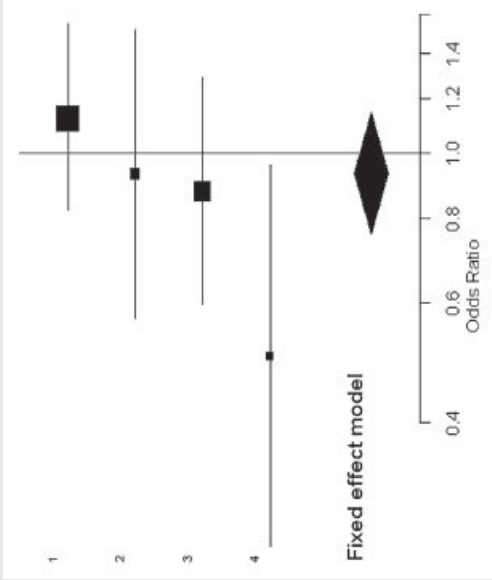
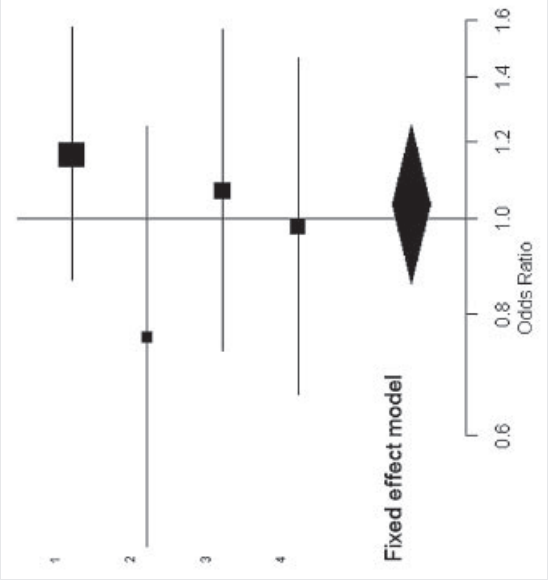
Study	Cases				Controls				
	GG	Total	GG	Total	Weight (%)	OR M-H, fixed, 95% CI	z	P	OR M-H, fixed, 95% CI
(a)									
1. Germany	274	407	534	840	37.51	1.18 (0.91–1.51)			
2. Netherlands	106	172	321	486	21.21	0.82 (0.57–1.18)			
3. Norway	155	230	336	496	22.86	0.98 (0.70–1.37)			
4. Spain	79	140	259	425	18.42	0.83 (0.56–1.22)			
Fixed-effects model	614	949	1450	2,247	100	0.99 (0.84–1.16)	-0.05	0.95	
(b)									
1. Germany	89	151	534	840	51.24	0.82 (0.57–1.17)			
2. Netherlands	12	14	321	486	1.97	3.08 (0.68–13.9)			
3. Norway	43	73	336	496	27.17	0.68 (0.41–1.12)			
4. Spain	37	61	259	425	19.62	0.98 (0.57–1.71)			
Fixed-effects model	181	299	1450	2,247	100	0.86 (0.67–1.10)	-1.16	0.24	



^aTest of heterogeneity: $I^2 = 3.67$, $df = 3$, $P = 0.29$; $I^2 = 18.3\%$ (0–87.5%).

^bTest of heterogeneity: $I^2 = 3.87$, $df = 3$, $P = 0.27$; $I^2 = 22.6\%$ (0–88.4%).

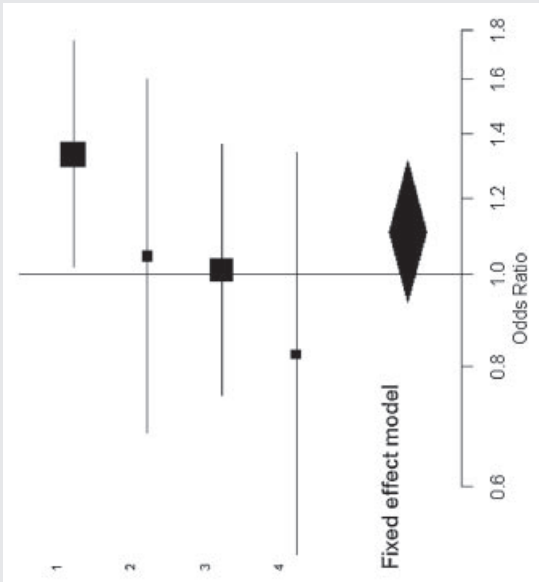
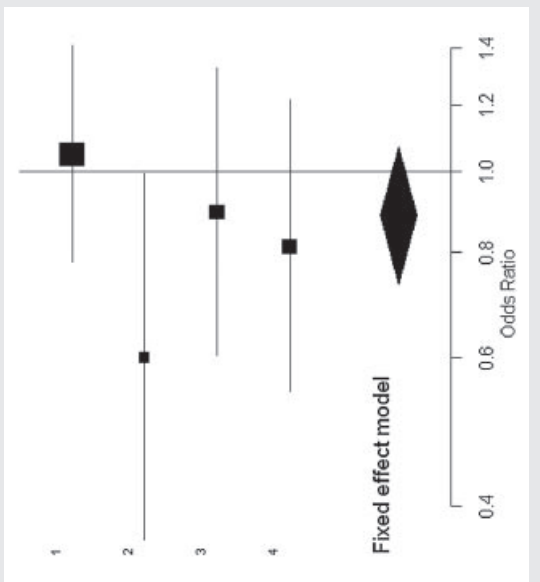
TABLE V. Genetic Effect of the p.Val66Met Polymorphism on (a) Females (643 Cases and 986 Controls) and (b) Males (802 Cases and 1261 Controls) with Adulthood ADHD Using a Fixed-Effects Model

Study	Cases				Controls				
	GG	Total	GG	Total	Weight (%)	OR M-H, fixed, 95% CI	z	P	OR M-H, fixed, 95% CI
(a) ^a									
1. Germany	180	282	238	390	38.91	1.13 [0.82–1.54]			
2. Netherlands	59	95	155	243	17.78	0.93 [0.56–1.51]			
3. Norway	128	208	153	237	29.62	0.87 [0.59–1.29]			
4. Spain	30	58	79	116	13.69	0.50 [0.26–0.95]			
Fixed-effects model	397	643	625	986	100	0.93 [0.75–1.14]	-0.66	0.51	
									
(b) ^b									
1. Germany	213	325	279	450	37.08	1.16 [0.86–1.56]			
2. Netherlands	60	96	167	243	16.31	0.75 [0.46–1.24]			
3. Norway	154	228	171	259	23.90	1.07 [0.73–1.56]			
4. Spain	92	153	187	309	22.71	0.98 [0.66–1.46]			
Fixed-effects model	519	802	804	1261	100	1.03 [0.85–1.24]	0.36	0.72	

^aTest of heterogeneity: $Q = 2.23$, $df = 3$, $P = 0.52$; $I^2 = 40\%$ [0–79.6%].

^bTest of heterogeneity: $Q = 2.23$, $df = 3$, $P = 0.52$; $I^2 = 40\%$ [0–79.6%].

TABLE VI. Genetic Effect of the p.Val166Met Polymorphism on (a) Adulthood ADHD With Mood Disorders (822 Cases and 2,247 Controls) and (b) Adulthood ADHD Without Mood Disorders (580 Cases and 2,247 Controls) Using a Fixed-Effects Model

Study	Cases			Controls					
	GG	Total	GG	Total	Weight (%)	OR M-H, fixed, 95% CI	z	P	OR M-H, fixed, 95% CI
(a) ^b									
1. Germany	220	323	517	840	36.23	1.33 (1.01; 1.75)			
2. Netherlands	80	119	322	486	16.42	1.04 (0.68; 1.60)			
3. Norway	196	299	324	496	33.21	1.01 (0.74; 1.36)			
4. Spain	47	81	266	425	14.14	0.82 (0.50; 1.33)			
Fixed-effects model	543	822	1,429	2,247	100	1.10 (0.93; 1.31)	1.17	0.24	
									
(b) ^b									
1. Germany	151	241	517	840	37.58	1.04 (0.77; 1.40)			
2. Netherlands	39	72	322	486	16.62	0.60 (0.36; 0.99)			
3. Norway	86	137	324	496	22.79	0.89 (0.60; 1.32)			
4. Spain	75	130	266	425	23.01	0.81 (0.54; 1.21)			
Fixed-effects model	351	580	1,429	2,247	100	0.88 (0.73; 1.06)	-1.26	0.20	
									

^aTest of heterogeneity: $I^2 = 3.64$, $df = 3$, $P = 0.30$; $I^2 = 17.6\%$ [0–87.4%].

^bTest of heterogeneity: $I^2 = 3.71$, $df = 3$, $P = 0.29$; $I^2 = 19\%$ [0–89.6%].

or evidence that a single study accounted for the significance or magnitude of the pooled study.

- (2) The proportions of the different ADHD subtypes differ among the reported studies. Thus, while most patients described by Kent et al. [2005] (81%) or Xu et al. [2007] (100% UK and 78% Taiwan) were combined ADHD, a lower proportion was seen in the other studies (<70%), including the present meta-analysis (66%). If the *BDNF* contribution to ADHD was subtype-specific, these differences could account for the distinct results between studies.
- (3) Gender differences among studies may also explain controversial results, as a recent study suggests that hyperactivity may be gender-specific [Kim et al., 2007]. In this regard, male *BDNF* conditional knock-out mice exhibit hyperactivity, whereas females display normal locomotor activity with a prominent increase in depression-like behaviors [Monteggia et al., 2007]. Although we found nominal association between *BDNF* and ADHD in Spanish females, the pooled analysis stratified for gender showed that the overall gene effect on ADHD was not statistically significant.
- (4) Other studies have reported a gene-specific parent of origin effect in ADHD. In this regard, Kent et al. [2005] demonstrated a significant preferential paternal transmission of the p.Val66 allele to children with ADHD. Nevertheless, other groups did not find evidence for a preferential paternal transmission of *BDNF* risk alleles in ADHD [Kim et al., 2007; Anney et al., 2008a]. This aspect, however, could not be assessed in the present case-control association study.
- (5) Genetic variants in *BDNF* have generally been linked to a number of other psychiatric phenotypes, that may share genetic risk factors with ADHD, such as schizophrenia, eating disorders, bipolar disorder or depression [Neves-Pereira et al., 2002; Sklar et al., 2002; Green et al., 2006; Gratacòs et al., 2007; Verhagen et al., 2008; Duncan et al., 2009]. Since comorbidity with these disorders is frequently observed in ADHD (e.g., substantial proportion of our ADHD sample showed comorbidity with mood disorders (56.8%)), in contrast to most of the previous studies we tested directly whether this comorbidity might bias association results for ADHD [Kent et al., 2005; Xu et al., 2007; Lanktree et al., 2008]. Although we observed a nominal association between *BDNF* and ADHD with mood disorders (in the German sample) or without mood disorders (in the Dutch sample), the pooled analysis showed that the overall gene effect was not significant in any of these two groups.
- (6) Most of the previous studies reporting a *BDNF* contribution to the susceptibility to ADHD include only children samples, which may suggest a childhood-specific association between this neurotrophic factor and ADHD. Only one study reports association between *BDNF* and adult ADHD, although the sample size is limited [Lanktree et al., 2008]. In this regard, our group identified a childhood-specific association between ADHD and the *BDNF* specific receptor, *NTRK2* [Ribasés et al., 2008] that might support a differential genetic component in childhood ADHD with or without remission of the phenotype across life span.
- (7) Although it has been reported that the p.Val66Met polymorphism alters the intracellular trafficking and activity-depen-

dent secretion of *BDNF* [Egan et al., 2003], this SNP may not be functionally involved in ADHD, although it is still possible that other *BDNF* sequence variants do contribute to the phenotype.

In conclusion, although *BDNF* remains as a candidate risk factor for ADHD, we found no evidence of association between the p.Val66Met SNP and adulthood ADHD using a meta-analysis strategy in large well-characterized clinical samples from four European populations. Further dissection of clinical phenotypes as well as full genetic coverage, in terms of LD, of the *BDNF* gene in larger cohorts of children as well as adult patients may improve our knowledge about the involvement of *BDNF* in the susceptibility to this complex neuropsychiatric disorder.

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