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Review

The association of the BDNF Val66Met polymorphism and the hippocampal volumes in healthy humans: A joint meta-analysis of published and new data

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ABSTRACT

Background: The brain-derived neurotrophic factor (BDNF) Val66Met polymorphism (refSNP Cluster Report: rs6265) is a common and functionally relevant single nucleotide polymorphism (SNP). The gene itself, as well as the SNP rs6265, have been implicated in hippocampal learning and memory. However, imaging genetic studies have produced controversial results about the impact of this SNP on hippocampal volumes in healthy subjects.
Methods: We examined the association between the rs6265 polymorphism and hippocampal volume in 643 healthy young subjects using automatic segmentation and subsequently included these data in a meta-analysis based on published studies with 5298 healthy subjects in total.
Results: We found no significant association between SNP rs6265 and hippocampal volumes in our sample ($g = 0.05$, $p = 0.58$). The meta-analysis revealed a small, albeit significant difference in hippocampal volumes between genotype groups, such that Met-carriers had slightly smaller hippocampal volumes than Val/Val homozygotes ($g = 0.09$, $p = 0.04$), an association that was only evident when manual ($g = 0.22$, $p = 0.01$) but not automatic tracing approaches ($g = 0.04$, $p = 0.38$) were used. Studies using manual tracing showed evidence for publication bias and a significant decrease in effect size over the years with increasing sample sizes.
Conclusions: This study does not support the association between SNP rs6265 and hippocampal volume in healthy individuals. The weakly significant effect observed in the meta-analysis is mainly driven by studies with small sample sizes. In contrast, our original data and the meta-analysis of automatically segmented hippocampal volumes, which was based on studies with large samples sizes, revealed no significant genotype effect. Thus, meta-analyses of the association between rs6265 and hippocampal volumes should consider possible biases related to measuring technique and sample size.

Contents

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1. Introduction

Brain-derived neurotrophic factor (BDNF) – a member of the nerve growth factor family – plays an important role in neurogenesis and is implicated in several molecular processes in the central nervous system (Barde et al., 1982; Lu and Gottschalk, 2000; Park and Poo, 2013). BDNF is highly expressed in the hippocampus, a key region for adult neurogenesis (De Quervain and Papassotiropoulos, 2006; Milner et al., 1998), and is thought to be involved in learning and memory (Cunha et al., 2010). Pro-BDNF can induce apoptosis, while mature BDNF predominantly mediates cell survival and neuronal differentiation (Pang et al., 2004; Korte et al., 1995; Pastalkova et al., 2006). The single nucleotide polymorphism (SNP) rs6265 at codon 66 of the *BDNF* gene predicts a valine (Val) to methionine (Met) substitution in the pro-region of the protein, which is important for proper BDNF sorting. The Val66Met substitution has been investigated in a transgenic mouse model of defective BDNF secretion in hippocampal neurons (Chen et al., 2004; Egan et al., 2003). BDNF Met/Met mice have smaller hippocampal volumes, less dendritic arbor complexity of hippocampal neurons and impaired synaptic plasticity, as indicated by a decrease in NMDA-receptor-dependent long-term depression and long-term potentiation (Chen et al., 2006; Ninan et al., 2010).

Defects in synaptic plasticity and long-term potentiation, core mechanisms of hippocampus-dependent learning and memory, are thought to underlie – at least in part – neurocognitive impairments in a broad spectrum of neuropsychiatric disorders (Fusar-Poli et al., 2012; Lu et al., 2013). Another characteristic of neuropsychiatric disorders, such as schizophrenia, bipolar disorder, depression, post-traumatic stress disorders and personality disorders, is the reduction in hippocampal volume (Geuze et al., 2005; Smieskova et al., 2010; Walter et al., 2012). It is still not clear to what extent these hippocampal volume abnormalities are driven by genetic liability (Sullivan et al., 2003). One putative genetic risk factor of these alterations might be the BDNF polymorphism described above (Boulle et al., 2012; Frielingsdorf et al., 2010). The effect of this polymorphism has often been studied in healthy subjects, because in a healthy population, changes in brain volumes are independent of effects of illness or medication, and of disease-related genetic risk factors (Fusar-Poli et al., 2013; Smieskova et al., 2009).

To date findings from structural magnetic resonance imaging (sMRI) studies investigating genotype-dependent association of rs6265 SNP on hippocampal volumes are inconsistent. While three recent meta-analyses report that Met-carriers have smaller hippocampal volumes than Val/Val homozygotes (Hajek et al., 2012; Kambeitz et al., 2012; Molendijk et al., 2012a), the relation between rs6265 and hippocampal volumes is confounded by several problems: Firstly, two of these studies (Kambeitz et al., 2012; Molendijk et al., 2012a) included a variety of neurocognitive disorders, suggesting that hippocampal volumes were probably affected by burden of illness, medication or comorbid conditions and were not necessarily related to the SNP per se. Secondly, all of these meta-analyses incorporated studies with children/adolescents and elderly subjects. This can be critical, as hippocampal volumes undergo age-related changes (Karnik et al., 2010; Walhovd et al., 2011; Goodro et al., 2012). Finally, although one of the previous meta-analyses focuses exclusively on healthy subjects (Hajek et al., 2012), the analysis in this study was restricted to manual tracing of hippocampal volumes without considering automatic measurement techniques.

The present study aimed to control for these confounding factors. First, we assessed the association between the BDNF rs6265 polymorphism and hippocampal volumes using the automated tracing technique in 643 healthy young volunteers. Because the effect size of this association is known to be small (Kambeitz et al., 2012; Molendijk et al., 2012a), we then increased statistical power by means of meta-analytic techniques (Kim-Cohen et al., 2006; Munafò et al., 2009; Brandys et al., 2011). We therefore performed a systematic review of the hippocampal volumes in healthy subjects genotyped for SNP rs6265 and combined these data with our original results in a meta-analysis. Additionally, we examined the effect of potential moderators such as measuring technique, MR magnetic field strength, age, gender, ethnicity, Val/Met ratio, sample size, quality rating, hippocampal volumes normalized to intracranial volume (ICV), and publication year.

2. Material and methods

2.1. Original data of 643 healthy subjects

2.1.1. Participants

We recruited 643 healthy young subjects (383 women; age range 18–35 years, mean age ± standard deviation (SD) 22.87 ± 3.22). Participants filled in a self-rating questionnaire concerning their health status, medication, and drug consumption. All included subjects were free of any physical, neurological or psychiatric illness, and were taking no medication. 87% of the subjects were students and 91% were right-handed (see Table 1). The ethics committee of the Canton of Basel approved the experiments.

Table 1
Overview of included subjects.

	Val/Val	*N* Val/Val	Val/Met and Met/Met	*N* Val/Met and Met/Met	Statistics	*p*-Value	Effect size*
Age [mean ± SD]	22.75 ± 3.22	413	23.10 ± 3.23	230	$F = 1.72$ df = 1	0.19	0.003
Sex							
Women		254		129	$x^2 = 1.80$	0.18	0.053
Men		159		101	df = 1		
Profession							
In education		361		198	$x^2 = 0.69$	0.71	0.033
Working		35		24	df = 2		
Not in education and without job		12		6			
Handedness							
Right		376		210	$x^2 = 0.01$	0.91	0.004
Left		37		20	df = 1		

* Partial eta (η^2) is reported for age differences, whereas Cramers V is indicated for sex, profession and handedness differences.

Written informed consent was obtained from all subjects prior to participation.

2.1.2. Genotyping

DNA was extracted from saliva samples collected with the Oragene DNA sample collection kit using standard procedures (DNA Genotek Inc., Ontario, Canada). DNA samples were processed on the Affymetrix® Genome-Wide Human SNP Array 6.0. in one centralized microarray facility. rs6265 (refSNP Cluster Report: rs6265) is represented on the array (AFFY|SNP_A-2038925). Generation of SNP calls and array quality control were performed using the Affymetrix Genotyping Console Software 3.0 (Affymetrix Inc.). According to the manufacturer's recommendation, contrast quality control (QC) was chosen as QC metric, using the default value of 0.4. All samples passing QC criteria were subsequently genotyped using the Birdseed (v2) algorithm. Genotypic outliers were identified using Bayesian clustering algorithm (Bellenguez et al., 2012) and excluded (for more details see supplementary material).

2.1.3. Image acquisition and extraction of hippocampal volumes

We acquired an anatomical sequence with a radio-frequency pulses and rapid gradient-echo (MPRAGE) sequence. For this sequence, we used the following acquisition parameters: TE (echo time) = 3.37 ms, FOV (field of view) = 25.6 cm, acquisition matrix = 256 × 256 × 176, voxel size: 1 mm × 1 mm × 1 mm. Using a midsaggital scout image, 176 contiguous axial slices were placed along the anterior–posterior commissure (AC–PC) plane covering the entire brain with a TR = 2000 ms ($\theta = 8$ degrees).

Segmentations of cortical and subcortical structures were retrieved from FreeSurfer 4.5 and labeling was based on the Desikan–Killiany Atlas (Desikan et al., 2006). We extracted raw volumes for both hippocampi for $n = 805$ subjects. Left and right hippocampal volumes were corrected separately for ICV, age, sex and differences due to software and gradient updates by using the *z*-transformed residuals of a linear regression. Afterwards we did a separate outlier-control for both hippocampal sides (mean ± 3.5 SD). For all subjects with complete dataset, we then calculated the corrected mean value of both hippocampal volumes. For a subgroup of $n = 643$ subjects we had additional genetic information regarding BDNF genotype. The corrected volumetric data of these subjects were included in all further analyses.

2.1.4. Association analysis

For the genetic association analysis, we used the WG-Permer software (www.wg-permer.org), with analysis of variance for quantitative phenotypes. This software corrects nominal *p*-values for multiple testing on a permutation-based procedure according to Westfall and Young (Westfall, 1993).

One-way analyses of variance (ANOVA) and chi-square tests were used to test for differences between genotype groups of age, sex, profession and handedness. These statistical analyses were performed with SPSS (IBM SPSS Statistics, Version 20, 2011). Values are presented as mean ± SD (see Table 1).

2.2. Meta-analysis

2.2.1. Literature search and inclusion criteria

Electronic searches were conducted using PubMed and Embase, considering all publications until the end of December 2012 with the following search terms: "BDNF Val66Met" AND "MRI" and "rs6265" AND "MRI". Additionally, a retrospective search was carried out on the reference lists of the included articles. This resulted in 86 publications, for which the abstracts were screened (more information is presented in Fig. 1). In this meta-analysis, we included healthy groups only. Firstly, we extracted studies addressing the relation between hippocampal volumes and the SNP. Secondly, the papers were filtered according to the following criteria: (a) published in a peer-reviewed journal, (b) reporting a relation between the SNP rs6265 and sMRI, (c) showing hippocampal data. A total of 27 publications met these criteria, whereof from one recent genome-wide association study (GWAS) data of 5 cohorts were obtained (Stein et al., 2012). Altogether a total

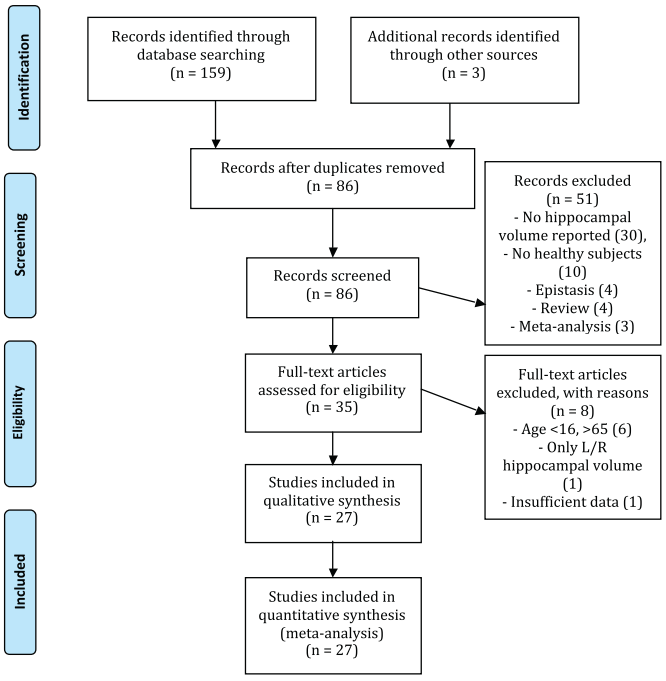

Fig. 1. Flow chart of the search strategy and included studies for meta-analysis.

of 32 samples, 31 previously published and our own data, were included in this meta-analysis. Criteria for exclusion were: mean age of participants (<15 or >65 years), not clearly defined healthy control group, overlapping datasets, and only left or only right hippocampal volume reported. The authors were contacted when information essential for the calculation of effect sizes was missing. Both measuring techniques, i.e. automated and manual tracing, were included. We followed the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) guidelines (Moher et al., 2010).

2.2.2. Data extraction

The following variables were extracted: First author name, publication year, number of independent samples per study. For each independent sample, we extracted sample size of genotype subgroups, ethnicity, gender, mean age of sample, Hardy–Weinberg equilibrium (HWE; calculated, when not reported), genotyping method, structural MRI measurement technique, direction of effect, field strength of MR scanner, mean hippocampal volumes and standard deviation, *t*-statistic, *F*-statistic and *p*-values per genotype, and whether the hippocampal volumes were normalized to ICV. To sustain statistical independence, one single effect size per sample was used for this meta-analysis.

2.2.3. Quality assessment

Using an 11-item checklist adapted from (Karg et al., 2011) the quality of the included studies was evaluated. In detail, the criteria were: (1) Funding – role in analysis and interpretation of data, (2) Sample size, (3) Clear inclusion criteria for participants, (4) Reported allele distribution, (5) Ethnicity assessed, (6) If mixed ethnicity: discussion of problems, (7) IQ/educational level available, (8) Inter- and intrarater reliability, (9) Report of HWE, (10) Sample in HWE and (11) Additional descriptive data including age, gender, genotyping method, magnetic field strength of scanner. For each category 0, 1 or 2 points were given. Finally, the included studies were rated according to the sum of the points and characterized as high (above 80% of the maximal sum of points), moderately high (60–79%), moderate (40–59%), moderately low (20–39%), and low quality studies (below 19%) (for more details see supplementary tables S1 and S2).

2.2.4. Data analysis

Data were entered into an electronic database and quantitative meta-analysis was performed using the R 2.15.2 software (R Core Team, 2012). The effect size was calculated using Hedge's *g*, which provides an unbiased standardized mean difference that incorporates a correction for small sample sizes (Lipsey and Wilson, 2000). Hedge's g values above 0.2, 0.5 and 0.8 correspond to small, medium and large effect sizes respectively. Hedge's g was calculated using data of mean hippocampal volumes, standard deviations and sample sizes. Where these data were not available, we employed the *t*-statistic, *F*-statistic or *p*-values, together with the corresponding sample sizes. A positive value of the effect size reflected larger hippocampal volumes in the Val/Val homozygotes than for the Met-carriers of the SNP rs6265. We employed a random-effects model with the DerSimonian-Laird estimator using the metafor package (DerSimonian and Laird, 1986; Wolfgang Viechtbauer, 2010). The random-effects model shows more flexibility with respect to effect size variability between studies and study populations (Cooper et al., 2009), as it incorporates the between-study variance τ^2. And in case of high between-study heterogeneity, the random-effects model compared to the fixed-effects model is the model of choice (Ioannidis et al., 2007).

Cochran's *Q* test was then used to calculate between-group heterogeneity; the magnitude of heterogeneity was assessed by I^2 (Higgins and Thompson, 2002). I^2 is an estimate of variability across studies based on heterogeneity rather than chance, ranging from 0 to 100%. Values above 25%, 50% and 75% corresponded to low, moderate and high heterogeneity respectively (Higgins and Thompson, 2002). Furthermore, potential publication bias was investigated by funnel plot asymmetry and Egger's regression test (Egger et al., 1997). In case of a bias, "the trim and fill" method was used subsequently to identify and correct for publication bias detected by an asymmetric funnel plot (Duval and Tweedie, 2000). A series of meta-regression analyses was carried out to assess the impact of possibly moderating study design characteristics such as publication year, age of participants, gender ratio, ethnicity, Val/Met ratio, sample size, quality rating, magnetic field strength, hippocampal volumes normalized to intracranial volume and applied hippocampal measuring techniques. Most studies used a dominant allele approach, but two studies reported an additive allele comparison (Agartz et al., 2006; Gruber et al., 2012). Nevertheless, these were treated equivalently in this analysis.

3. Results

3.1. Association analysis of 643 healthy subjects

Of the 643 subjects, 413 were homozygous for the Val allele, 204 were heterozygous Val/Met, and 26 were homozygous for Met allele. Met-carriers were taken together in a single group. Genotype groups did not differ according to age, sex, profession and handedness (see Table 1). All 643 subjects had complete genotype information. The genotype distribution did not deviate from the Hardy–Weinberg equilibrium ($p = 0.90$).

As shown in Fig. 2, there were no significant genotype-dependent differences in the z-transformed scores of the left (Val/Val homozygous 0.029 ± 0.97 ($n = 413$), Met-carriers 0.001 ± 0.98 ($n = 230$); $p = 0.25$, see Fig. 2), right (Val/Val homozygous 0.048 ± 0.96 ($n = 413$), Met-carriers 0.043 ± 1.05 ($n = 230$); $p = 0.12$, see Fig. 2) and mean hippocampal volume (Val/Val homozygous 0.041 ± 0.97 ($n = 413$), Met-carriers 0.023 ± 1.01 ($n = 230$); $p = 0.15$, see Fig. 2). The difference between genotypes in mean hippocampal volumes resulted in a non-significant *g* of 0.05 ($p = 0.58$). We did not observe a main effect of age or sex as well as no

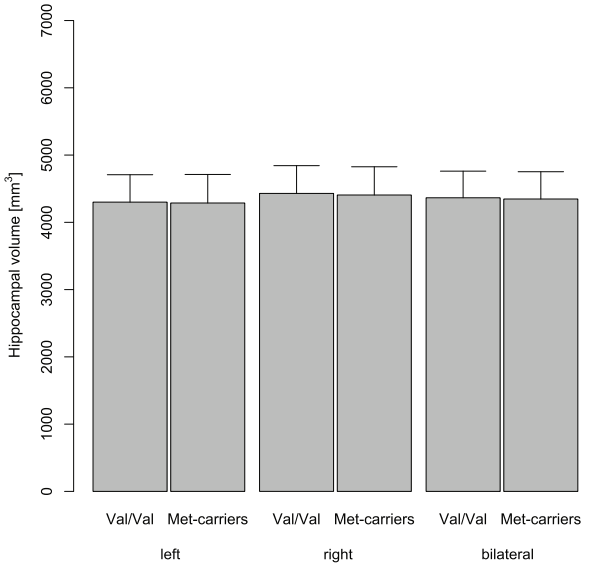

Fig. 2. Barplot showing left, right and mean bilateral hippocampal volumes [mm^3] ± standard deviation of our original data. Neither the left, right nor mean bilateral hippocampus showed a significant difference between 230 Met-carriers and 413 Val/Val homozygotes.

interaction effect of sex and rs6265 genotype groups on hippocampal volumes (see supplementary methods and supplementary table S3).

3.2. Description of studies and cohorts included in the meta-analysis

A total of 4655 subjects in 32 datasets were selected for this random-effects meta-analysis (Agartz et al., 2006; Bueller et al., 2006; Cerasa et al., 2010; Chepenik et al., 2009; Cole et al., 2011; Dutt et al., 2009; Frodl et al., 2007; Gatt et al., 2009; Gonul et al., 2011; Gruber et al., 2012; Jessen et al., 2009; Joffe et al., 2009; Koolschijn et al., 2010; Molendijk et al., 2012b; Montag et al., 2009; Nemoto et al., 2006; Pezawas et al., 2004; Richter-Schmidinger et al., 2011; Sanchez et al., 2011; Schofield et al., 2009; Smith et al., 2012; Soliman et al., 2010; Stein et al., 2012; Stern et al., 2008; Szeszko et al., 2005; Takahashi et al., 2008; Yang et al., 2012). All 27 included studies were published between 2004 and 2012. This structural MRI meta-analysis comprises 1771 Met-carriers and 2884 Val/Val homozygotes. For an overview of all included samples, see Table 2. Ethnicity was reported in 26 samples, of which 19 were performed on a Caucasian sample, 2 on a Japanese sample, 1 on a Chinese sample and 4 on a sample of mixed ethnicity. The overall mean age of all datasets providing this information was 31.65 ± 9.0. The Hardy–Weinberg equilibrium did not deviate in 28 datasets, whereas in 3 datasets this parameter could not be calculated due to insufficient data. Quality analysis showed that most of the included studies were of high or moderate quality (44% high and 48% moderate scores, supplementary table S1 and table S2).

3.3. Meta-analysis of one original and 31 previously published samples

Meta-analysis of all datasets ($k = 32$) showed evidence for significant, albeit weak association between hippocampal volumes and SNP rs6265 ($g = 0.09$, se = 0.04, 95% CI = [0.01–0.17], $Z = 2.08$, $p = 0.0376$, see Fig. 3A and table S4), with indications of significant between-study heterogeneity ($I^2 = 38.24\%$, Q(df = 31) = 50.20, $p = 0.02$). The effect was in the direction of slightly smaller hippocampal volumes for Met-carriers than for Val/Val homozygotes. Visual inspection of the funnel plot indicated evidence for potential publication bias (Fig. 3B, table S4). This was quantitatively confirmed by significant regression intercept in Egger's regression test ($p = 0.0075$). The trim and fill procedure suggested 8 missing studies on the left side of the funnel plot and a corrected non-significant Hedge's g of 0.02 (95% CI = [−0.07–0.11], Fig. 3B). Meta-regression analysis did not reveal any effect for age of participants ($\beta = -0.08$, $F(1,30) = 0.18$, $p = 0.67$), gender ratio ($\beta = 0.13$, $F(1,30) = 0.48$, $p = 0.49$), ethnicity of the subjects ($\beta = 0.26$, $F(1,25) = 1.83$, $p = 0.19$), Val/Met ratio ($\beta = 0.14$, $F(1,24) = 0.48$, $p = 0.50$), sample size ($\beta = -0.23$, $F(1,30) = 1.71$, $p = 0.20$), quality rating ($\beta = -0.32$, $F(1,24) = 2.74$, $p = 0.11$), magnetic field strength ($\beta = -0.22$, $F(1,28) = 1.49$, $p = 0.23$), or hippocampal volumes normalized to ICV ($\beta = -0.01$, $F(1,30) = 0.002$, $p = 0.96$). However, the analysis of the meta-regressions indicated a potential source for bias related to measurement techniques ($\beta = 0.43$, $F(1,29) = 6.55$, $p = 0.02$) (see Fig. 3C and table S4) and year of publication ($\beta = -0.38$, $F(1,30) = 5.01$, $p = 0.03$) (see Fig. 3A, cumulative meta-analysis, and table S4).

3.4. Effect of moderators

To further disentangle the moderating effect of the measurement technique, samples were subsequently subdivided into manually and automatically segmented volumes of the hippocampi. One study using semi-automated analysis was excluded from further analysis (Sanchez et al., 2011), leaving 13 samples with manual tracing ($n = 829$ subjects) and 18 samples using automated segmentation ($n = 4426$ subjects). The detected small effect size estimate of manual tracing samples indicated significantly smaller hippocampal volumes for Met-carriers compared to Val/Val subjects ($g = 0.22$, se = 0.09, 95% CI = [0.05–0.39], $Z = 2.51$, $p = 0.0121$, $I^2 = 38.12\%$, $Q(\mathrm{df} = 12) = 19.39$, $p = 0.08$, Trim and fill: 5 missing studies on left side of the funnel plot and a corrected non-significant g of 0.08, see Fig. 4A and table S4). The meta-analysis of the manual tracing samples revealed significant publication bias (Egger's test: $z = 3.24$, $p = 0.0012$), significant between-study heterogeneity and a significant moderator effect only for the sample size ($\beta = -0.72$, $F(1,11) = 12.07$, $p = 0.01$). Analysis of the relation between years of publication and effect size revealed a significant decrease in the effect sizes with increasing sample size over the years, but only for manual tracing samples (see Fig. 5). In contrast, the overall effect size of the samples using automatic measurement techniques showed no significant genotype effect ($g = 0.04$, se = 0.05, 95% CI = [−0.05–0.13], $Z = 0.89$, $p = 0.3751$, $I^2 = 37.87\%$, $Q(\mathrm{df} = 17) = 27.36$, $p = 0.05$, see Fig. 4B and table S4).

4. Discussion

In this paper, we present a joint analysis of the relation between the BDNF SNP rs6265 and the hippocampal volumes in healthy young subjects. Specifically, we first explored whether hippocampal volumes of 643 healthy individuals differed between Val/Val homozygotes and Met-carriers. These data were further incorporated into a meta-analysis of previously published studies subsuming a total of 5298 healthy subjects.

Hippocampal volume is a heritable quantitative trait (estimates vary between 40 and 69%). Hence, several studies have analyzed the association between candidate genes, such as BDNF, and the hippocampus (Goldman et al., 2008; Peper et al., 2007; Sullivan et al., 2001). However, the studies investigating the association between BDNF SNP rs6265 and hippocampal volumes report inconsistent findings. Some studies observe BDNF-dependent differences in hippocampal volumes (Bueller et al., 2006; Montag et al., 2009; Pezawas et al., 2004; Schofield et al., 2009), whereas others do not find an association (Agartz et al., 2006; Cerasa et al., 2010; Chepenik et al., 2009; Cole et al., 2011; Dutt et al., 2009; Frodl et al., 2007; Gatt et al., 2009; Gruber et al., 2012; Jessen et al., 2009; Joffe et al., 2009; Koolschijn et al., 2010; Molendijk et al., 2012b; Nemoto et al., 2006; Richter-Schmidinger et al., 2011; Sanchez et al., 2011; Smith et al., 2012; Soliman et al., 2010; Stein et al., 2012; Stern et al., 2008; Szeszko et al., 2005; Takahashi et al., 2008; Yang et al., 2012). The results based on our own data as well as the meta-analysis across studies applying automatic hippocampal segmentation do not support an association between rs6265 and hippocampal volumes.

Several studies report BDNF-dependent volume differences in the hippocampus of patients with neuropsychiatric disorders such as bipolar disorder and schizophrenia (Chepenik et al., 2009; Szeszko et al., 2005) as well as between healthy controls and patients of the same genotype (Chepenik et al., 2009; Gonul et al., 2011; Koolschijn et al., 2010; Smith et al., 2012). Other studies in patient populations found no association of the rs6265 polymorphism and hippocampal volumes (Agartz et al., 2006; Cerasa et al., 2010; Cole et al., 2011; Dutt et al., 2009; Frodl et al., 2007; Gruber et al., 2012; Jessen et al., 2009; Molendijk et al., 2012b; Takahashi et al., 2008). Two recent meta-analyses did not find a significant association of SNP rs6265 and hippocampal structure in neuropsychiatric disorders, including schizophrenia, bipolar disorder, depressive and anxiety disorders (Kambeitz et al., 2012; Molendijk et al., 2012a). However, the meta-analyses were not conducted separately per psychiatric disease category and treatment

Table 2
Overview of included imaging genetics samples.

Author	Year	*n*	Age [mean ± SD]	Females/ males	Met/Met	Val/Met or Met-carriers	Val/Val	HWE	Genotyping method	Norm. to ICV	Magnet field strength	Direction of effect	Hippocampal measuring technique
Agartz et al. (Agartz et al., 2006)	2006	104	41.6 ± 8.9	35/69	4	27	73	y°	Pyrosequencing	+	1.5 T	Met/Met < Val/Met < Val/Val	Manual tracing
Bueller et al. (Bueller et al., 2006)	2006	36	27.1 ± 6.6	22/14	0	15	21	y°	PCR-RFLP	+	1.5 T	Met/Val < Val/Val	Manual tracing
Cerasa et al. (Cerasa et al., 2010)	2010	139	36.0 ± 13.4	82/57	7	51	81	y°	PCR-RFLP	–	1.5 T	Met-carriers < Val/Val	SPM99: ROI
Chepenik et al. (Chepenik et al., 2009)	2009	18	28 ± 12	12/6	0	6	12	y°	TaqMan	–	1.5 T	Met-carriers < Val/Val	Manual tracing
Cole et al. (Cole et al., 2011)	2011	109	33.0 ± 9.2	54/55	4	37	68	y	PCR-RFLP or TaqMan	+	1.5 T	Met-carriers > Val/Val	Manual tracing
Dutt et al. (Dutt et al., 2009)	2009	60	40.8 ± 15.1	33/28	–	17	43	y	SNuPe technology	–	1.5 T	Met-carriers < Val/Val	Manual tracing
Frodl et al. (Frodl et al., 2007)	2007	60	41.6 ± 12.3	29/31	1	19	40	y	RT-PCR	–	1.5 T	Met-carriers < Val/Val	Manual tracing
Gatt et al. (Gatt et al., 2009)	2009	89	36.2 ± 12.7	28/61	–	26	63	y	PCR-RFLP	–	1.5 T	Met-carriers > Val/Val	SPM2: VBM: ROI
Gonul et al. (Gonul et al., 2011)	2011	40	29.8 ± 6.4	17/23	0	16	24	y	RT-PCR	–	1.5 T	Met-carriers < Val/Val	Manual tracing
Gruber et al. (Gruber et al., 2012)	2012	39	38.2 ± 12.8 *	49/57 *	3	12	24	y	PCR-RFLP	+	1.5 T	Met/Met > Val/Met > Val/Val	Manual tracing
Jessen et al. (Jessen et al., 2009)	2009	84	43.9 ± 8.7	40/44	–	29	55	?	TaqMan	–	1.5 T and 3 T	Met-carriers < Val/Val	Manual tracing
Joffe et al. (Joffe et al., 2009)	2009	113	36.8 ± 13.1 *	224/243 *	2	43	68	y	PCR-RFLP	–	1.5 T	Met-carriers > Val/Val	SPM2: VBM: ROI
Koolschijn et al. (Koolschijn et al., 2010)	2010	90	38.2 ± 13.6	34/56	5	26	59	y	Illumina Bead Array	–	1.5 T	Met-carriers > Val/Val	Manual tracing
Millan Sanchez et al. (Sanchez et al., 2011)	2011	43	57.0 ± 0.9 *	22/122 *	–	19	24	?	Illumina Bead Array	–	1.5 T	Met-carriers > Val/Val	Surgical Navigation Technologies
Molendijk et al. (Molendijk et al., 2012b)	2012	31	37.4 ± 10.1 *	100/57 *	0	10	21	y°	Four genotyping array	–	3.0 T	Met/Val < Val/Val	SPM5: VBM: ROI
Montag et al. (Montag et al., 2009)	2009	87	23.9 ± 4.8	63/24	6	27	54	y	RT-PCR	+	1.5 T	Met-carriers < Val/Val	SPM5: VBM: ROI
Nemoto et al. (Nemoto et al., 2006)	2006	109	36.2 ± 12.1	71/38	17	51	41	y	TaqMan	–	1.5 T	Met-carriers < Val/Val	SPM2: VBM: ROI
Pezawas et al. (Pezawas et al., 2004)	2004	111	32.6 ± 9.3	55/56	–	42	69	?	Genotyped	+	1.5 T	Met-carriers < Val/Val	SPM2: VBM: ROI
Richter-Schmidinger et al. (Richter-Schmidinger et al., 2011)	2011	135	24.6 ± 3.2	91/44	11	40	84	y°	PCR-RFLP	–	1.5 T	Met-carriers > Val/Val	Manual tracing

Table 2 (*Continued*)

Author	Year	*n*	Age [mean ± SD]	Females/ males	Met/Met	Val/Met or Met-carriers	Val/Val	HWE	Genotyping method	Norm. to ICV	Magnet field strength	Direction of effect	Hippocampal measuring technique
Schofield et al. (Schofield et al., 2009)	2009	161	32.6 ± 13	75/106	6	59	96	y	PCR-RFLP	–	1.5 T	Met-carriers < Val/Val	SPM2: VBM: whole brain
Smith et al. (Smith et al., 2012)	2012	39	21.2 ± 4.6	19/20	8	10	21	y	TaqMan	–	1.5 T	Met-carriers < Val/Val	FreeSurfer: ROI
Soliman et al. (Soliman et al., 2010)	2010	70	24.9 ± 4.6	34/36	3	32	35	y°	TaqMan	+	3.0 T	Met-carriers > Val/Val	FreeSurfer: ROI
Stern et al. (Stern et al., 2008)	2008	50	31.7 ± 10.5	17/33	0	12	38	y°	TaqMan	+	3.0 T	Met/Val < Val/Val	FreeSurfer: ROI
Szeszko et al. (Szeszko et al., 2005)	2005	25	27.1 ± 6.7	15/10	0	10	15	y	TaqMan	+	1.5 T	Met/Val < Val/Val	Manual tracing
Takahashi et al. (Takahashi et al., 2008)	2008	29	24.2 ± 6.1	12/17	5	11	13	y	PCR-RFLP	+	1.5 T	Met-carriers < Val/Val	Manual tracing
Yang et al. (Yang et al., 2012)	2012	61	20.5 ± 0.9 *	27/34	17	29	15	y	PCR-Sequencing	–	3.0 T	Met-carriers < Val/Val	FSL-VBM
BFS cohort (Stein et al., 2012)	2012	220	24.0 ± 7.7	115/105	6	82	132	y	Illumina Omni Express	–	1.5 T	Met-carriers > Val/Val	FSL FIRST
BIG cohort (Stein et al., 2012)	2012	1281	22.8 ± 3.3 *	735/546	62	411	808	y	Affymetrix microarray	–	1.5 T and 3 T	Met-carriers > Val/Val	FSL FIRST
MooDS cohort (Stein et al., 2012)	2012	221	33.1 ± 10.0	119/102	–	81	140	y	Illumina Human610-Quad	–	3.0 T	Met-carriers > Val/Val	FreeSurfer
TOP cohort (Stein et al., 2012)	2012	190	35.8 ± 9.7	91/99	8	55	127	y	Affymetrix Human SNP 6.0	–	1.5 T	Met-carriers > Val/Val	FreeSurfer
QTIM cohort (Stein et al., 2012)	2012	811	23.1 ± 2.8	506/305	37	254	520	y	Illumina 610 K	–	4.0 T	Met-carriers < Val/Val	FSL FIRST

HWE, Hardy–Weinberg equilibrium; ICV, intracranial volume; Met, methionine, ROI, region of interest; Val, valine; VBM, voxel-based morphometry; association study cohorts included in Stein et al. (34): BFS, Bipolar Family Study; BIG, Brain Imaging Genetic Study; MooDS, Mood Disorders and Schizophrenia; TOP, Thematically Organized Psychosis Study; QTIM, Queensland Twin Imaging Measures; *, reported of larger sample only; ?, not possible to calculate;°, calculated of raw data.

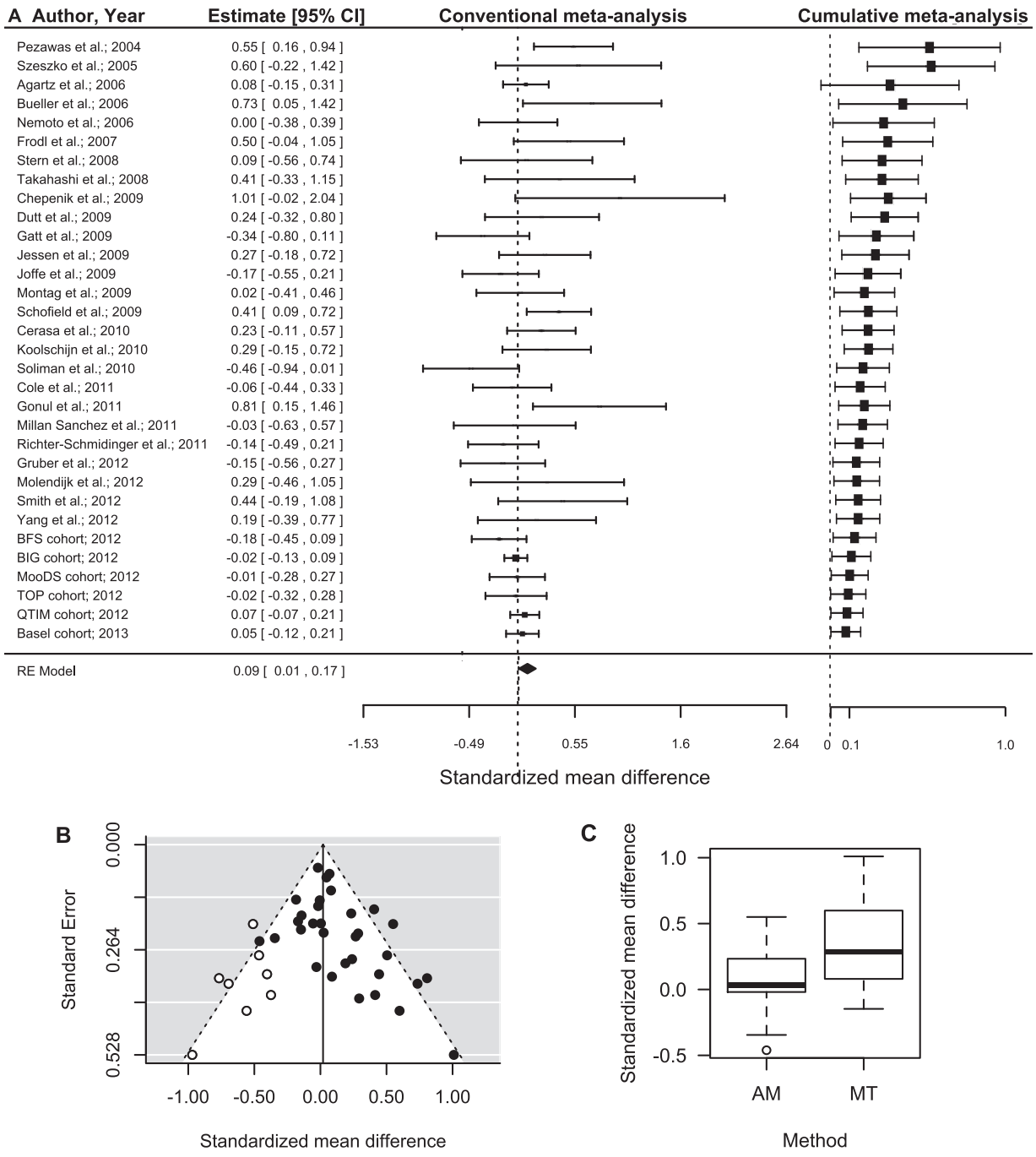

Fig. 3. (A) Forest plots of random-effects meta-analysis assessing hippocampal volumes with structural MRI and the BDNF SNP rs6265. Positive effect sizes indicate larger hippocampi in the Val allele subjects than with the Met allele subjects. The forest plot of a cumulative meta-analysis shows the change of the evidence over time. Dashed lines indicate zero line. (B) Funnel plot with additional trim and fill procedure where white dots indicate the missing studies to correct for potential publication bias. (C) Meta-regression analysis of the hippocampal measuring technique and the effect of the SNP rs6265, MT: manual tracing, AM: automatic measurement.

effects may have influenced the hippocampal volumes (Fusar-Poli et al., 2013).

Inconsistent findings in studies of healthy subjects and psychiatric patients raise the question if BDNF-dependent structural hippocampal differences are specific for different developmental stages. Until now, only few studies have addressed this issue by investigating the relationship between BDNF and hippocampal volumes in neonates, children and adolescents and also elderly. Two studies have not observed BDNF-dependent differences in hippocampal volumes in children and adolescents (age range 8–19) (Mueller et al., 2013; Toro et al., 2009). In contrast, Knickmeyer and colleagues find rs6265-dependent differences in hippocampal volumes in neonates (Knickmeyer et al., 2013). However, in order to investigate the influence of developmental stages on BDNF-dependent effects, additional longitudinal studies will be necessary. For instance, Knickmeyer and colleagues will implement a follow-up design, collecting data over several time points (at age 1, 2, 4 and 6 years of age) (Knickmeyer et al., 2013). Moreover, several studies report hippocampal volume reductions in aging (Driscoll et al., 2003; Erickson et al., 2010; Malykhin et al., 2008; Raz et al., 2010). Erikson and colleagues investigated the relationship between serum BDNF levels, age, hippocampal volume and

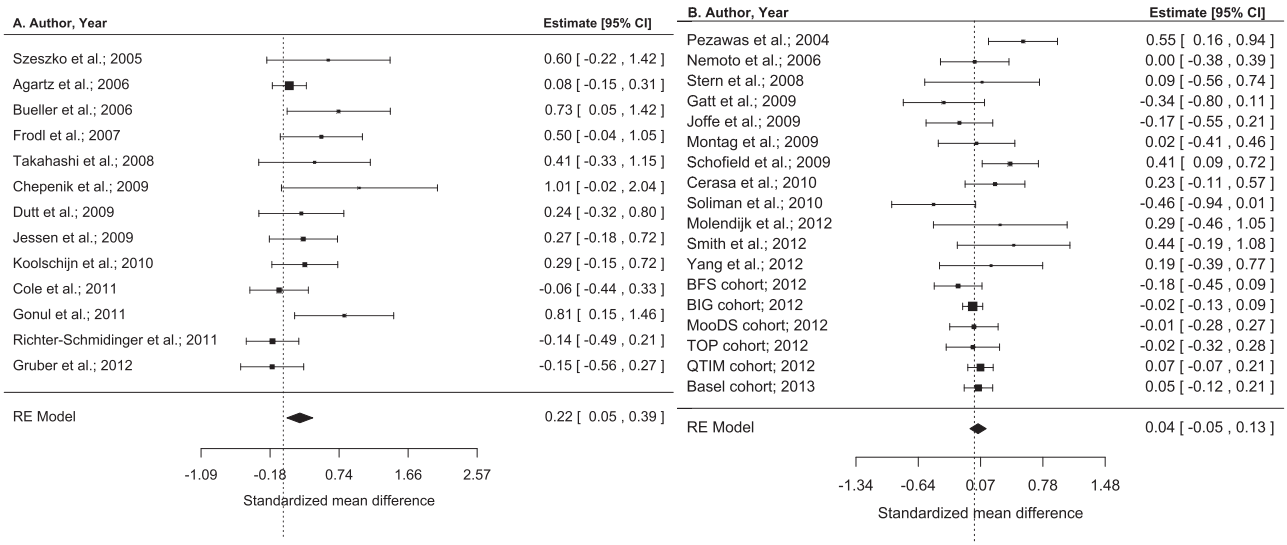

Fig. 4. Forest plots of BDNF SNP rs6265 of structural MRI studies assessing potential publication bias arising from the applied hippocampus analysis technique. (A) Manual traced hippocampus; (B) Hippocampus volumes evaluated by automatic measurement; positive effect sizes indicate larger hippocampi in the Val allele subjects compared to the Met-carriers. Dashed lines indicate zero line.

memory performance (Erickson et al., 2010). Age was associated with reduced hippocampal volumes as well as reduced BDNF serum levels and poorer memory performance. In his review, Von Bohlen und Halbach suggests a role of BDNF in age-dependent processes in the hippocampus (Von Bohlen und Halbach, 2010). However, studies investigating the association of rs6265 with hippocampal volumes in also aged populations report inconsistent results (Brooks et al., 2014; Karnik et al., 2010; Sanchez et al., 2011).

The importance of the hippocampus in learning and memory is well established (Squire and Wixted, 2011) and it has been suggested that BDNF plays a role in these processes (Baj et al., 2013; Cunha et al., 2010). Even though we did not find BDNF-dependent differences in hippocampal volumes, the absence of difference on the anatomical level does not rule out that BDNF modulates other processes in the hippocampus. Indeed, two studies included in this meta-analysis provide support for BDNF-dependent differences in hippocampal activation during memory paradigms in the absence of structural differences (Cerasa et al., 2010; Molendijk et al., 2012b), which is further supported by additional studies analyzing functional MRI data (Dennis et al., 2011; Egan et al., 2003; Hariri et al., 2003; Hashimoto et al., 2008). However, the meta-analysis by Kambeitz and colleagues did not find an association between rs6265 and hippocampus-mediated memory activation, which might be explained by the large variety of paradigms combining working and episodic memory processes (Kambeitz et al., 2012). Moreover, meta-analyses assessing an association between rs6265 and declarative memory performance revealed contradictory results (Kambeitz et al., 2012; Mandelman and Grigorenko, 2012).

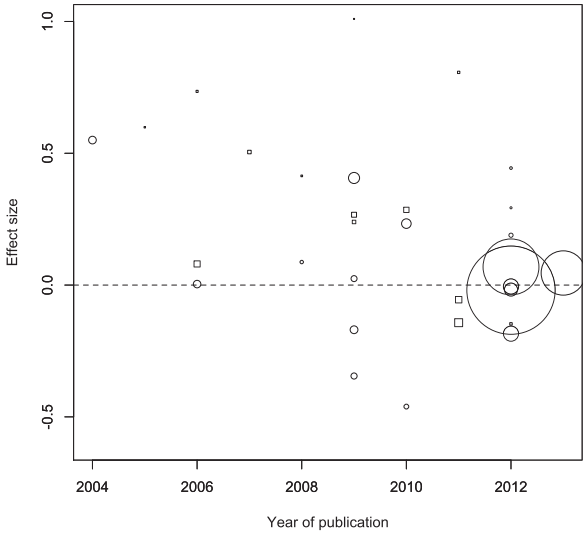

Fig. 5. Scatter plot showing the relation between effect size and year of publication for the association of the hippocampal volume and BDNF SNP rs6265. The size of the shapes indicates the sample size of each study. Squares represent the studies that traced the hippocampus manually; circles represent the studies that measured the hippocampus automatically. Dashed line indicates zero line.

In our meta-analysis we observed an effect of the applied measuring technique (manually traced vs. automatically measured hippocampal volumes) after we investigated the effect of several moderators due to significant between-study heterogeneity and publication bias. First, the overall meta-analysis showed a weakly ($g = 0.09$) significant association between hippocampal volumes and SNP rs6265. In particular, Val/Val homozygotes had significantly larger hippocampal volumes than Met-carriers. The direction of the effect is in accordance with recent meta-analyses of healthy subjects (Hajek et al., 2012; Kambeitz et al., 2012; Molendijk et al., 2012a), but the effect size in this study was considerably smaller. To further disentangle the dissociable effect of these two measurement approaches, subsequent analyses were conducted after separating the samples by the hippocampus measuring technique. We found that Met-carriers had smaller hippocampal volumes than Val/Val homozygotes ($g = 0.22$) when the hippocampi were manually segmented. In contrast, we did not find a significant genotype effect with automatic segmentation ($g = 0.04$). This latter result is consistent with the findings of our original sample in 643 healthy subjects, where we used the automatic segmentation technique from FreeSurfer and also with the results of a recent GWAS analysis in 5776 healthy subjects (Stein et al., 2012). Even though manual segmentation is generally considered as the gold standard due to the precise delineation of anatomical structures, the increasing sample size of imaging studies renders the process of manual segmentation less practicable, as it is both costly and time consuming. Several studies compared manual and different automatic segmentation methods and report comparable accuracy, sensitivity and reproducibility (Bergouignan et al., 2009; De Boer et al., 2010; Doring et al., 2011; Morey et al., 2009).

Specifically, automated segmentation of the hippocampus using FreeSurfer shows higher correlations with manual segmentation compared to FSL/First (Doring et al., 2011; Morey et al., 2009). Nonetheless, it has been shown that, compared to manual segmentation, FreeSurfer and FSL overestimate hippocampal volumes (Doring et al., 2011; Morey et al., 2009) while they are underestimated by SACHA (Bergouignan et al., 2009). However, our meta-analysis across studies using only manual tracing samples revealed a publication bias, between-study heterogeneity and a moderator effect for the sample size. These effects were further studied in detail to investigate the relation between sample size and publication year. We showed that effect sizes shrink as a function of publication year and sample size. In contrast to the findings of previous meta-analyses (Kambeitz et al., 2012; Molendijk et al., 2012a), this decrease in effect size could not be attributed to publication year alone, but was also linked to an increase in sample size.

Several limitations of our analyses need to be considered. In our meta-analysis, we could not address laterality differences or differences in specific hippocampal sub-regions as many of the included studies only report total hippocampal volumes. Furthermore, we explicitly focused on the impact of the rs6265 polymorphism on hippocampal volumes in healthy subjects, without considering the effect of other SNPs, gene-gene interactions (Honea et al., 2009) or gene-environment interactions (Gatt et al., 2009; Gerritsen et al., 2012). This is of particular relevance, as the impact of the BDNF SNP rs6265 on hippocampal volume could be modified by other SNPs that have already been shown to impact the volume of the hippocampus, such as the Val159Met polymorphism of catecholamine-O-methyltransferase (COMT) (Cerasa et al., 2008; Dutt et al., 2009; Ehrlich et al., 2010; Honea et al., 2009; Taylor et al., 2007), an SNP of ZNF804a (Donohoe et al., 2011; Wei et al., 2012) or the intergenic variant rs7294919 (Stein et al., 2012). Finally, we did not observe a main effect of sex and age on hippocampal volumes, nor did we observe an interaction effect of sex and genotype on hippocampal volumes. Other studies found sex- (Cahill, 2006; Goldstein et al., 2001; Liu et al., 2010; Ruigrok et al., 2013), and age-dependent differences in hippocampal volumes (Driscoll et al., 2003; Malykhin et al., 2008; Raz et al., 2010). Since the association of rs6265 and age-dependent hippocampal changes revealed controversial results (Brooks et al., 2014; Karnik et al., 2010; Sanchez et al., 2011) and the role of sex in this association is not well understood, it would be interesting if future studies would address these questions. Potential reasons for the absence of such effects in our original study are the applied correction for intracranial volume and the limited age-range of our sample.

In summary, the present study does not support the association between SNP rs6265 and hippocampal volumes in healthy individuals. The weak effect observed in the meta-analysis is mainly driven by studies with small sample sizes applying manual segmentation of hippocampi. Our findings confirm the results of previous results based on a large sample size. Moreover, our findings demonstrate an effect of measuring techniques, publication year and sample size.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2014.03.011.

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