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- Impact of rs6265 on hippocampal volumes in neuropsychiatric patients.
- Meta-analysis showed no association of hippocampus and genotype in patients.
- For both genotypes, patients had smaller hippocampal volumes than healthy controls.

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BDNF Val66Met polymorphism and hippocampal volume in neuropsychiatric disorders: A systematic review and meta-analysis

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Abstract

Background: Brain-derived neurotrophic factor (BDNF) is a neurotrophin involved in neurogenesis and synaptic plasticity in the central nervous system, especially in the hippocampus, and has been implicated in the pathophysiology of several neuropsychiatric disorders. Its Val66Met polymorphism (refSNP Cluster Report: rs6265) is a functionally relevant single nucleotide polymorphism affecting the secretion of BDNF and is implicated in differences in hippocampal volumes.

Methods: This is a systematic meta-analytical review of findings from imaging genetic studies on the impact of the rs6265 SNP on hippocampal volumes in neuropsychiatric patients with major depressive disorder, anxiety, bipolar disorder or schizophrenia.

Results: The overall sample size of 18 independent clinical cohorts comprised 1695 patients. Our results indicated no significant association of left (Hedge's g=0.08, p=0.12), right (g=0.07, p=0.22) or bilateral (g=0.07, p=0.16) hippocampal volumes with BDNF rs6265 in neuropsychiatric patients. There was no evidence for a publication bias or any demographic, clinical, or methodological moderating effects.

Both Val/Val homozygotes (g=0.32, p=0.004) and Met-carriers (g=0.20, p=0.004) from the patient sample had significantly smaller hippocampal volumes than the healthy control sample with the same allele. The magnitude of these effects did not differ between the two genotypes.

Conclusion: This meta-analysis suggests that there is no association between this BDNF polymorphism and hippocampal volumes. For each BDNF genotype, the hippocampal volumes were significantly lower in neuropsychiatric patients than in healthy controls.

Keywords: BDNF Val66Met, rs6265, Brain-derived Neurotrophic Factor, BDNF, MRI, Structural, Hippocampus, Neuropsychiatric Patients, Depression, Anxiety Disorders, Bipolar Disorder, Schizophrenia, Meta-analysis

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1. Introduction

Hippocampal atrophy is a common characteristic of neuropsychiatric disorders, such as major depressive disorder, bipolar disorder, anxiety disorders and schizophrenia (Buehlmann et al., 2010; Fusar-Poli et al., 2007; Geuze et al., 2005; Kempton MJ et al., 2011; Shepherd et al., 2012). The hippocampus has been intensely studied, as it is involved in learning and memory-dependent processes (Kandel, 2001; McDonald and Hong, 2013; Preston and Eichenbaum, 2013) and due to the occurrence of cognitive impairment in neuropsychiatric disorders (Bora et al., 2010; Bourne et al., 2013; Fusar-Poli et al., 2012; Schaefer et al., 2013; Snyder, 2013).

Brain-derived neurotrophic factor (BDNF) is a widely investigated marker in neuropsychiatric disorders and may be important in the pathophysiology of depression (Buchmann et al., 2013; Karege et al., 2002; Lang and Borgwardt, 2013; Shimizu et al., 2003), bipolar disorder (Cunha et al., 2006) and schizophrenia (Niitsu et al., 2014; Numata et al., 2006). BDNF protein is involved in neurogenesis and neuroplasticity in the brain. Proper BDNF signalling requires both pro-BDNF and mature BDNF. BDNF concentrations can be measured in serum, plasma or whole blood. These concentrations are highly correlated with those in cerebrospinal fluid, as BDNF crosses the blood-brain barrier (Pan et al., 1998; Pillai et al., 2010). Several meta-analyses have shown that there may be a correlation between low BDNF levels and the emergence of depression (Fernandes et al., 2014; Molendijk et al., 2014), bipolar disorder (Fernandes et al., 2014, 2011; Lin, 2009) and schizophrenia (Fernandes et al., 2014; Green et al., 2011). The critical role of BDNF in neuropsychiatric diseases is further reflected by the fact that its level can be increased by neuropsychiatric medications, such as antidepressants, mood stabilisers and antipsychotics (Choi et al., 2006; Dmitrzak-Weglarz et al., 2008; El-Hage et al., 2014; Grande et al., 2014; Hong et al., 2003; Perkovic et al., 2014; Ricken et al., 2013; Rybakowski et al., 2005; Tsai et al., 2003; Xu et al., 2010; Zai et al., 2012; Zou et al., 2010).

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The single nucleotide polymorphism (SNP) Val66Met, also known as G189A or rs6265, represents substitution of a valine (Val) by a methionine (Met) at codon 66. This substitution in the pro-region of BDNF modifies sorting of the protein and its availability in the synaptic cleft. Met/Met transgenic mice exhibit less activity-dependent BDNF, with smaller hippocampal volumes, decreased complexity of the dendritic arbor of hippocampal neurons (Chen et al., 2006; Ninan et al., 2010; Chen et al., 2004; Egan et al., 2003) and impaired synaptic plasticity, as indicated by a decrease in NMDA receptor-dependent long-term depression and long-term potentiation (Ninan et al., 2010). Several studies have demonstrated an association between rs6265 polymorphism and neuropsychiatric disorders (e.g. Chen et al., 2008; Gratacòs et al., 2007; Lohoff et al., 2005; Sklar et al., 2002), although just as many have found no effect (e.g. Frustaci et al., 2008; González-Castro et al., 2014; Kanazawa et al., 2007; Verhagen et al., 2008). However, these association studies may indicate that the Met allele is protective for bipolar disorder, but is a risk allele for depression and schizophrenia. More specifically, several studies have investigated the effect of this BDNF polymorphism on brain volumes of patients with depression, bipolar disorder or schizophrenia (Aas et al., 2013; Agartz et al., 2006; Chepenik et al., 2009; Cole et al., 2011; Dutt et al., 2009; Frodl et al., 2007; Gonul et al., 2011; Gruber et al., 2012; Ho et al., 2006, 2007; Jessen et al., 2009; Kanellopoulos et al., 2011; Koolschijn et al., 2010; Molendijk et al., 2014; Smith et al., 2012; Stein et al., 2012; Szeszko et al., 2005; Takahashi et al., 2008). Many of these studies have focussed on the hippocampus, where BDNF has been shown to play a role in normal learning and memory (Baj et al., 2013; Cunha et al., 2010) and learning- and memory-dependent deficits in neuropsychiatric disorders (Baig et al., 2010; Egan et al., 2003; Lau et al., 2010; Molendijk et al., 2012b; Ninan, 2014) may be associated with declines in hippocampal volume. Two previous meta-analyses have investigated the association of BDNF rs6265 and hippocampal volumes using MRI techniques in a neuropsychiatric patient sample (Kambeitz et al., 2012; Molendijk et al., 2012a). Both studies reported smaller hippocampal volumes for

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Met-carriers than for Val/Val homozygotes, but the differences were non-significant. This is in line with our recently published meta-analysis of healthy individuals that did not indicate a significant association between the SNP and hippocampal volumes (Harrisberger et al., 2014). In contrast, studies of the effect of the BDNF val66met in major depressive disorder and psychosis found that the status of Met-carrier and exposure to childhood trauma have an interactive effect on hippocampus volume (Aas et al., 2013; Carballedo et al., 2013).

The available meta-analyses addressing hippocampal volumes in neuropsychiatric patients genotyped for SNP rs6265 included relatively small samples and yielded inconclusive results (Kambeitz et al., 2012; Molendijk et al., 2012a). To overcome this lack of knowledge and to reconcile inconsistencies across individual studies, we present here the first robust quantitative meta-analysis of BDNF rs6265 effects on hippocampal volumes in different neuropsychiatric disorders. In the present meta-analysis of a total of 1695 individuals, we sought to explore a putative association between hippocampal volumes and the BDNF polymorphism in neuropsychiatric disorders, such as major depressive disorder, bipolar disorder, anxiety disorders or schizophrenia. Furthermore, we investigated whether the Met allele can be designated as a “risk” or as a “protective” allele in relation to the hippocampus volume. We therefore examined for the first time the risk that patients had smaller hippocampal volumes than healthy controls, both for Val/Val homozygote individuals and for Met carriers.

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2. Materials and Methods

We followed the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guidelines (Moher et al., 2010).

2.1. Literature search strategy and selection of studies

The electronic databases PubMed and Embase were searched, with consideration of all publications with the following search terms: "BDNF Val66Met" AND "MRI" and "rs6265" AND "MRI" published until the end of May 2014. In addition, the reference lists of the included articles were reviewed. This resulted in 79 publications, from which the abstracts were screened (more information is presented in figure 1). In this meta-analysis, we included studies addressing the relation between hippocampal volumes and the SNP rs6265 in neuropsychiatric patients using the following inclusion criteria: (a) published in a peer-reviewed journal, (b) reporting a relation between the SNP rs6265 and structural magnetic resonance imaging (sMRI), and (c) showing hippocampal data. A total of 15 publications met these criteria and, in addition, data from three independent cohorts were obtained. Altogether a total of 18 datasets were included in this meta-analysis. Criteria for exclusion were as follows: non-neuropsychiatric brain disorder (multiple sclerosis ;Dinacci et al., 2011; Liguori et al., 2009; Ramasamy et al., 2011; Weinstock-Guttman et al., 2007; Zivadinov et al., 2007), Alzheimer's disease (Honea et al., 2013; Lim et al., 2014; Voineskos et al., 2011), reversible cerebral vasoconstriction syndrome (Chen et al., 2011), alcohol-dependence (Mon et al., 2013), premenstrual dysphoric disorder (Comasco et al., 2014), obesity (Marqués-Iturria et al., 2014)), no clearly defined patient group, overlapping datasets, and only left or right hippocampal volumes reported. The authors were contacted when essential information was missing for the calculation of effect sizes.

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Figure 1 about here

2.2. Data extraction

We extracted the following variables: First author, publication year, number of independent samples per study. For each independent sample, we extracted sample size of genotype subgroups, ethnicity, gender, mean age, Hardy-Weinberg equilibrium (HWE; calculated, when not reported), genotyping method, structural MRI measurement technique, direction of effect, field strength of MR scanner, disorder itself, duration of disorder, age of onset of disorder and medication (antipsychotics, antidepressants), whether the hippocampal volumes were normalised to intracranial volume (ICV) or not and finally, mean hippocampal volumes and standard deviation per genotype or corresponding t-statistic, F-statistic and p-values. One single effect size per sample was included in this meta-analysis, in order to sustain statistical independence.

2.3. Quality assessment

The Newcastle-Ottawa Scale (NOS) (Wells et al., 2014) was adapted to assess the quality of each study as recommended by the Cochrane collaboration ("Cochrane Handbook for Systematic Reviews of Interventions"). 0 or 1 point was awarded for each of the eight criteria, giving a total score of high (above 80% of the maximal sum of points), moderately high (60-79%), moderate (40-59%), moderately low (20-39%), or low (below 19%). The mean quality was moderately high at 76% (for more details see supplementary tables 1).

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2.4. Meta-analytic procedure

Quantitative meta-analysis was performed using R 3.0.2 statistical software (R Core Team, 2012). The extracted data were converted to Hedge's g effect sizes, which provides an unbiased standardised mean difference and — in contrast to Cohen's d — incorporates a correction for small sample sizes (Lipsey and Wilson, 2000). Hedge's g was calculated from mean hippocampal volumes, standard deviations and sample sizes; where these data were not available, the t-statistic, F-statistic or p-values together with the corresponding sample sizes were used. Random effects model were employed with the DerSimonian-Laird estimator, using the metafor package 1.9.2 in R (DerSimonian and Laird, 1986; Wolfgang Viechtbauer, 2010). The random effects model shows more flexibility with respect to variable effect size in different studies and study populations (Cooper et al., 2009), as it incorporates the between-study variance τ^2. With high between-study heterogeneity, the random effects model is the model of choice, rather than the fixed-effects model (Ioannidis et al., 2007).

Cochran's Q test was used to evaluate statistical significance of between-study heterogeneity and the magnitude of heterogeneity was assessed by I^2 (I^2>50%: high) (Higgins and Thompson, 2002). We investigated potential publication bias by funnel plot asymmetry and Egger's regression test (Egger et al., 1997). In the presence of a bias, the "trim-and-fill" method was performed (Duval and Tweedie, 2000). Power analysis was performed using G*Power (Faul et al., 2007). For sensitivity analysis, the potential influence of each individual study was examined by excluding each study in turn (Viechtbauer and Cheung, 2010). Moreover, meta-regression analyses were carried out to assess the impact of possible moderating factors such as publication year, age of participants, gender ratio, ethnicity, Val/Met ratio, sample size, quality rating, magnetic field strength, type of disorder (major depressive disorder, bipolar disorder, anxiety disorders and schizophrenia) and applied hippocampal measuring techniques. All but two studies used a dominant allele approach

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(Agartz et al., 2006; Gruber et al., 2012). Nevertheless, these were treated equivalently in this analysis. Data from healthy individuals is available in Harrisberger et al, 2014 (Harrisberger et al., 2014). Finally, effect sizes were compared to assess whether Val/Val homozygotes or Met-carriers with a neuropsychiatric disorder might have a greater risk of hippocampal loss.

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3. Results

3.1. Description of studies

All included studies were published between 2005 and 2013. A total of 1695 subjects from 18 independent datasets were selected for this random effects meta-analysis (mean age ± SD: 43.13 ± 11.13 years, 56% females) (Aas et al., 2013; Agartz et al., 2006; Chepenik et al., 2009; Cole et al., 2011; Dutt et al., 2009; Frodl et al., 2007; Gonul et al., 2011; Gruber et al., 2012; Jessen et al., 2009; Kanellopoulos et al., 2011; Koolschijn et al., 2010; Molendijk et al., 2012b; Smith et al., 2012; Szeszko et al., 2005; Takahashi et al., 2008). The meta-analysis of structural MRI hippocampal volumes comprised 661 Met-carriers and 1034 Val/Val homozygotes. Ethnicity was reported in 14 samples, of which 11 were of Caucasian origin, one a Japanese sample and two of mixed ethnicity. The Hardy-Weinberg equilibrium did not deviate in 17 datasets, whereas this parameter could not be calculated from one dataset, due to insufficient data. The assessment of the BDNF rs6265 genotype frequency showed similar results for all disorders (Supplementary Figure 1A). A comparison of the mean hippocampal volumes in Val/Val homozygotes and Met-carriers for each disorder separately resulted in non-significant volumetric alterations between the genotypes of each disorder (Supplementary Figure 1B). Details of the included studies are presented in table 1. Quality analysis showed that most of the included studies were rated as being of high or moderately high quality (22% and 50%, respectively, supplementary Table 1).

Table 1 about here

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3.2. Meta-analysis of neuropsychiatric patients

The random effects meta-analysis of all datasets (k=18, n=1695) showed no evidence for a significant association between hippocampal volumes and the BDNF SNP rs6265 (g=0.11, 95%CI=[-0.02 - 0.25], p=0.11, see supplementary Figure 2A and Table 2). The visual inspection of the funnel plot and the Egger's regression test (p=0.03) revealed a potential publication bias. In order to account for this bias, the trim-and-fill procedure suggested one missing study on the left side of the funnel plot, leading to a smaller effect size (g=0.09, 95%CI=[-0.06 – 0.25], p=0.22), (Table 2). Evidence of moderate between-study heterogeneity was detected (I^2=38.29%, Q(df=17)=27.55, p=0.05), while a meta-regression analyses indicated that this can probably be explained, in part, by the year of publication (β=-0.53, F(1,16)=6.34, p=0.02, Figure 2C, Table 2). The other tested confounders, age of participants, gender ratio, ethnicity, Val/Met ratio, sample size, quality rating, magnetic field strength, type of disorder (major depressive disorder, bipolar disorder, anxiety disorders or schizophrenia) and applied hippocampal measuring techniques did not significantly influence the meta-analytic result (Table 2). Power analysis suggested that 1665 Val/Val homozygote and 1065 Met-carriers (2730 patients in total) would be necessary to achieve a power of 80% at α-level of 0.05 (two-sided). Sensitivity analysis indicated that two studies (Chepenik et al., 2009; Szeszko et al., 2005) with standardised residuals larger than ± 1.96 might be potential outliers (Supplementary Figure 3). Removal of these two studies might reduce the amount of heterogeneity and increase the precision of the effect size.

After excluding these two studies (k=16, n=1656), the mixed-effect model showed an even smaller and non-significant effect size (g=0.07, 95%CI=[-0.03 - 0.22], p=0.16, see Figure 2A and Table 2), but with a non-significant Egger's regression test (p=0.98) and no significant between-study heterogeneity (I^2=0.75%, Q(df=15)=15.11, p=0.44). The investigation of the lateral differences revealed the same magnitude of effect as in the latter meta-analysis, using

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either left (g=0.09, 95%CI=[-0.02 – 0.19], p=0.12, k=14, n=1541, see supplementary Figure 2B and Table 2) or right hippocampal volumes (g=0.08, 95%CI=[-0.05 – 0.20], p=0.22, k=14, n=1541, see supplementary Figure 2C and Table 2). Data from two studies were not available and could not be included (Agartz et al., 2006; Gruber et al., 2012).

Figure 2 about here

3.3. Meta-analysis of patients versus healthy controls with the same allele

Furthermore, we investigated the difference in magnitude between patients and healthy controls of the same genotype, using the recessive model of the BDNF Val allele. For this analysis, one study was excluded from further analysis due to the lack of a healthy control sample (Aas et al., 2013) and two studies could not be further included because of missing data (Agartz et al., 2006; Gruber et al., 2012). The meta-analysis of Val/Val homozygous individuals (k=13, n=2265) revealed that Val/Val homozygous neuropsychiatric patients had smaller hippocampal volumes than Val/Val homozygous healthy controls (g=0.32, 95%CI=[0.11 - 0.54], p=0.004, see Figure 3A and Table 2). The meta-analysis of Met-carriers (k=13, n=1255) indicated that Met-carrier neuropsychiatric patients had smaller hippocampal volumes than did Met-carrier healthy controls (g=0.20, 95%CI=[0.06 - 0.33], p=0.004, see Figure 3B and Table 2). As expected, the effect was in the direction of smaller hippocampal volumes for patients than for healthy controls for both alleles. However, the effect sizes were not significantly different for these two comparisons (F(1,24)=0.36, p=0.55)). Visual inspection of the funnel plot as well as the Egger's regression test (p=0.10, P=0.13) indicated no potential bias. No moderator was detected as a potential source of heterogeneity, although the between-study heterogeneity for the Val/Val meta-analysis was high and significant

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($p<0.0001$) (Table 2). Separate inspection of left and right hippocampal volumes for Val/Val homozygotes and Met-carriers revealed comparable effect-sizes to the combined meta-analysis (see supplementary Figure 2D-G and Table 2).

Table 2 about here

Figure 3 about here

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4. Discussion

This meta-analysis addressed the relation between hippocampal volumes and the BDNF rs6265 genotype in a neuropsychiatric patient cohort. Furthermore, we investigated differences in hippocampal volumes between patients and controls of the same genotype. The first meta-analysis did not support an association between hippocampal volumes and the BDNF rs6265 genotype in neuropsychiatric patients, either for the left, or for the right, or for the bilateral hippocampus. This finding is of the same magnitude as found in previous meta-analyses of patients (Kambeitz et al., 2012; Molendijk et al., 2012a). The present finding in patients, as well as the negative finding in a recently published meta-analysis in healthy individuals (Harrisberger et al., 2014), might suggest that structural hippocampal differences are not primarily dependent on the BDNF polymorphism in humans.

In further meta-analyses, we investigated the relative hippocampal loss of Val/Val homozygous neuropsychiatric patients versus healthy controls and also Met-carrier patients versus healthy controls. These meta-analyses revealed a significant association of the left, the right and the bilateral hippocampal volumes with the rs6265 polymorphism. It was confirmed that neuropsychiatric patients had smaller hippocampal volumes than healthy controls, regardless of the genotype. This finding corresponds with other studies in major neuropsychiatric disorders that found smaller hippocampal volumes in patients (e.g. review (Geuze et al., 2005)). In this study, however, we were interested in whether there is a difference in magnitude between the genotypes. We found that the reductions in hippocampal volume in neuropsychiatric patients relative to healthy controls did not depend on the specific genotype, which suggests that other factors drive the reductions in hippocampal volume in patients.

Neuropsychiatric patients appeared to have similar hippocampal volumes, irrespective of their BDNF rs6265 genotype. Moreover, hippocampal volume loss was similar for the two investigated genotypes in neuropsychiatric patients relative to healthy controls.

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This might suggest that the rs6265 SNP is not inherently involved in the loss of hippocampal volume in neuropsychiatric patients and that the Met allele might not be a possible risk allele (A/Met) for depression and schizophrenia or a protective allele for bipolar disorder. Further investigation is needed on how this polymorphism can affect any reduction in secreted BDNF and what this means for cellular processing. As reported by several studies, a promising direction for future work might be the field of gene-environment (G x E) interaction and also psychopharmacological interventions. For example, most previous studies investigating interactions between the BDNF rs6265 and stressful life events, trauma or childhood abuse indicated smaller hippocampal volumes in Met-carriers with adversity (Aas et al., 2013; Carballedo et al., 2013; Frodl et al., 2014; Gatt et al., 2009; Gerritsen et al., 2012; Joffe et al., 2009; Molendijk et al., 2012b; Rabl et al., 2014). Along this line, the hippocampal – hypothalamus-pituitary-adrenocortical pathway and the medial PFC- hippocampal-amygdala pathway may be necessary in the regulation of stress (Ninan, 2014; Rosas-Vidal et al., 2014). Thus hippocampal volume loss and also impairment of cognitive functions might be associated with decreased BDNF availability in these pathways, where Val/Val and Met-carriers differ in coping with stress, thereby exacerbating symptom severity. Unfortunately, however, we could not evaluate such aspects in our meta-analysis, as most studies did not report environmental factors.

Furthermore, preliminary results indicate that the BDNF level is elevated by neuropsychiatric medication and most studies showed that the treatment response to lithium, citalopram, escitalopram or fluoxetine (antidepressants in general) was more efficient for BDNF Met-carriers (Choi et al., 2006; Dmitrzak-Weglarz et al., 2008; El-Hage et al., 2014; Rybakowski et al., 2005; Tsai et al., 2003; Zou et al., 2010), whereas Val/Val homozygotes responded better to clozapine, olanzapine, risperidone and quetiapine (Grande et al., 2014; Hong et al., 2003; Perkovic et al., 2014; Xu et al., 2010; Zai et al., 2012). This opens up a whole new field of personalised medicine/patient treatment. The opposing effects of BDNF expression in the

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hippocampus during stress and neuropsychiatric medication should be further investigated. Another important issue is whether and how the balance between pro-BDNF and mature BDNF is affected by the rs6265 polymorphism, bearing in mind that pro-BDNF promotes cell apoptosis and long-term depression while mature BDNF supports cell survival and long-term potentiation (Barde, 1989; Lee et al., 2001; Park and Poo, 2013) at hippocampal synapses. Some limitations need to be considered. Firstly, the heterogeneity detected in the meta-analysis may have come from other moderators, such as medication, duration of illness or drug use, which were unfortunately not available for most studies. Moreover, the p-values of the meta-analysis were not adjusted for multiple comparison. Secondly, a major limitation of this meta-analysis is that most original studies were underpowered and this tends to reduce the power of the meta-analysis. For this reason, the absence of an association between the BDNF rs6265 genotype and hippocampal volume must be confirmed by meta-analyses including additional replication studies, preferably with large datasets. . Thirdly, most of the included studies conducted their research on individuals of Caucasian origin where the Met/Met variant is normally very rare (Petryshen et al., 2010) and no comparison with heterozygote individuals is possible. The only study with an Asian sample (Takahashi et al., 2008), and thus with a larger proportion of Met/Met homozygotes, did not look into this issue. Fourthly, it could not be evaluated how the known ethnic differences (Petryshen et al., 2010; Shimizu et al., 2004) would affect the result, as most studies were conducted in Caucasian samples. Fifthly, the difference between the investigated disorders in the reported risk allele might imply different outcomes for the individual disorders. To investigate this issue, more studies would be needed for each of these disorders. Finally, differences in hippocampal sub-regions between rs6265 genotypes might shed light on the involvement of impaired anatomical connectivity in the brain. If a sub-region of the hippocampus is altered in volume, the interrelated cortical and subcortical brain regions, such as the prefrontal cortex or amygdala (Ninan, 2014; Rosas-Vidal et al., 2014) , should also be included in further investigations to assess possible impairments in the network.

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The present meta-analysis does not support the existence of BDNF-dependent volume differences in the hippocampus of neuropsychiatric patients. The significant association between hippocampal volumes and the rs6265 SNP for neuropsychiatric patients versus healthy controls confirms previous results and does not support the risk hypothesis of the Met-allele.

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Appendix A. Supplementary information

- Supplementary figure S1, supplementary figure S2, supplementary figure S3 and supplementary table S1

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Table 1. Overview of included imaging genetics studies

Author	Year	N	Disorder	AP	AD	Age [mean ± SD]	Females / Males	Ethnicity	Met / Met	Val/Met or Met-carriers	Val / Val	HWE	Genotyping method	Norm. to ICV	Magnet field strength	Direction of effect Met-carriers vs. Val/Val	Hippocampal measuring technique
Aas et al. (Aas et al., 2013)	2013	106	SCZ, BD, MDD	+	+	32.7 (10.9)*	54/52	Caucasian	-	30	76	y	Affymetrix Human SNP 6.0	+	1.5T	<	FreeSurfer: ROI
Agartz et al. (Agartz et al., 2006)	2006	49	SCZ	+	+	40.0 (7.3)*	25/71*	Caucasian	3	27	66	y°	Pyrosequencing	+	1.5T	<	Manual tracing
Chepenik et al. (Chepenik et al., 2009)	2009	20	BD	-	+	40 (9)	11/9	Mixed	-	8	12	y°	TaqMan	+	1.5T	<	Manual tracing
Cole et al. (Cole et al., 2011)	2011	79	MDD	-	+	48.8 (8.9)	57/27	Not stated	-	32	47	y	PCR-RFLP or TaqMan	+	1.5T	<	Manual tracing
Dutt et al. (Dutt et al., 2009)	2009	128	Psychosis			36.2 (10.4)	64/82	Caucasian	-	39	89	y	SNuPe technology	-	1.5T	<	Manual tracing
Frodl et al. (Frodl et al., 2007)	2007	60	MDD	-	+	44.2 (11.8)	29/31	Not stated	2	21	37	y	RT-PCR	+	1.5T	<	Manual tracing
Gonul et al. (Gonul et al., 2011)	2011	33	MDD	-	-	33.9 (9.9)	25/5	Not stated	-	18	15	y	RT-PCR	+	1.5T	>	Manual tracing
Gruber et al. (Gruber et al., 2012)	2012	66	BD, SCZ	+	+	38.2 (12.8)*	49/57 *	Caucasian	1	27	38	y	PCR-RFLP	+	1.5T	>	Manual tracing
Jessen et al. (Jessen et al., 2009)	2009	79	MDD			48.2 (12.8)	52/27	Not stated	-	32	47	?	TaqMan	+	1.5T	>	Manual tracing
Kanellopoulos et al. (Kanellopoulos et al. 2011)	2011	33	MDD	-	-	72.3 (6.9)	21/12	Caucasian	-	16	17	y	TaqMan	+	1.5T	<	Manual tracing
Koolschijn et al. (Koolschijn et al., 2010)	2010	87	SCZ	+	-	36.1 (12.8)	16/71	Caucasian	4	28	55	y	Illumina Bead Array	+	1.5T	>	Manual tracing
Molendijk et al. (Molendijk et al., 2012b	2012	114	Anxiety, MDD	-	+	37.4 (10.1)*	100/57*	Caucasian	2	36	76	y°	Single genotyping array	+	3.0T	<	SPM5: VBM: ROI
Smith et al. (Smith et al., 2012)	2012	58	FEP	+	+	20.6 (4.8)	20/38	Mixed	-	20	38	y	TaqMan	+	1.5T	>	FreeSurfer: ROI
Szeszko et al. (Szeszko et al., 2005)	2005	19	FEP	+	-	26.2 (5.8)	5/14	Caucasian	0	7	12	y	TaqMan	+	1.5T	<	Manual tracing
Takahashi et al. (Takahashi et al., 2008)	2008	33	SCZ	+	-	25.6 (4.5)	13/20	Japanese	6	15	12	y	PCR-RFLP	+	1.5T	<	Manual tracing
MPIP	2012	373	MDD	-	+	47.4 (13.8)	213/160	European	18	121	234	y	Illumina 100K - 660K	+	1.5T	<	FSL FIRST: ROI
SHIP	2012	226	MDD, BD, Anxiety	-	+	52.1 (11.1)	159/67	European	7	70	149	y	Affymetrix Human SNP 6.0	+	1.5T	<	FreeSurfer 5.1: ROI
SHIP-TREND	2012	132	MDD	-	+	49.8 (12.0)	98/34	European	4	43	85	y	Illumina Human Omni 2.5M	+	1.5T	>	FreeSurfer 5.1: ROI

Abbreviations: AD, Antidepressants; AP, Antipsychotics; BD, Bipolar Disorder; FEP, First-episode Prychosis; HWE, Hardy-Weinberg equilibrium; ICV, Intracranial volume; Met, Methionine; MDD, Major Depressive Disorder; MPIP, Munich Morphometry Sample of the Max Planck Institute of Psychiatry; ROI, region of interest; SCZ, Schizophrenia; SHIP, Study of Health in Pomerania; SHIP-TREND, Study of Health in Pomerania (independent cohort); Val, Valine; VBM, Voxel-based morphometry;
*, reported of larger sample only; ?, not possible to calculate; °, calculated of raw data

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Table 2. Overview of the results from the performed meta-analyses

	Meta-analyses						Heterogeneity			Publ. bias	Trim& fill	Meta-regression analyses: p-values							
	Effect size: Hedge's g	Standard error	Lower confidence interval	Upper confidence interval	Z-value	p-value of Z	Heterogeneity I^2	Heterogeneity Q (df)	p-value of Q	p-value of Eggers regression test	Number of missing studies	Publication year	Age of participants	Gender ratio	Ethnicity	Sample size	Quality rating	Type of disorder	Measuring technique
All patient data (k=18, n=1695)	0.11	0.07	-0.02	0.25	1.61	0.11	38.29	27.55 (17)	0.05	0.03	1	0.02	0.51	0.39	0.53	0.28	0.85	0.51	0.45
MA without 2 studies (k=16, n=1656)	0.07	0.05	-0.03	0.18	1.42	0.16	0.75	15.11 (15)	0.44	0.98	0	0.40	0.69	0.80	0.51	0.98	0.80	0.27	0.84
MDD only (k=8, n=903)	0.08	0.07	-0.05	0.22	1.21	0.23	0.00	5.84 (7)	0.56	0.75	0	0.37	0.94	na	0.27	0.84	0.41	0.54	0.98
L Hippocampus (k=14, n=1541)	0.09	0.06	-0.02	0.19	1.54	0.12	3.53	13.48 (13)	0.41	0.85	1	0.26	0.74	0.71	0.79	0.83	0.39	0.15	0.87
R Hippocampus (k=14, n=1541)	0.08	0.06	-0.05	0.20	1.22	0.22	22.97	16.88 (13)	0.21	0.60	1	0.79	0.47	0.72	0.45	0.74	0.80	0.22	0.97
Patient vs. HC Val (k=13, n=2265)	0.32	0.11	0.11	0.54	2.92	0.004	77.37	53.03 (12)	<0.0001	0.10	0	0.43	na	na	0.26	0.11	0.93	0.36	0.30
Patient vs. HC Val L (k=13, n=2265)	0.31	0.11	0.10	0.52	2.92	0.004	75.31	4860 (12)	<0.0001	0.002	0	0.27	na	na	0.49	0.02	0.43	0.76	0.03
Patient vs. HC Val R (k=13, n=2265)	0.29	0.12	0.06	0.51	2.47	0.01	79.60	58.82 (12)	<0.0001	0.96	0	0.45	na	na	0.48	0.50	0.83	0.56	0.56
Patient vs. HC Met (k=13, n=1255)	0.20	0.07	0.06	0.33	2.89	0.004	7.58	12.98 (12)	0.37	0.13	2	0.44	na	na	0.25	0.36	0.21	0.57	0.05
Patient vs. HC Met L (k=13, n=1255)	0.22	0.07	0.08	0.35	3.10	0.002	11.44	13.55 (12)	0.33	0.07	2	0.20	na	na	0.42	0.24	0.47	0.39	0.04
Patient vs. HC Met R (k=13, n=1255)	0.18	0.08	0.02	0.34	2.22	0.03	30.52	17.27 (12)	0.14	0.47	0	0.88	na	na	0.07	0.57	0.16	0.89	0.15

Abbreviation: MDD: major depressive disorder; Met: Methionine; na: not assessed; Val: Valine; *: significant

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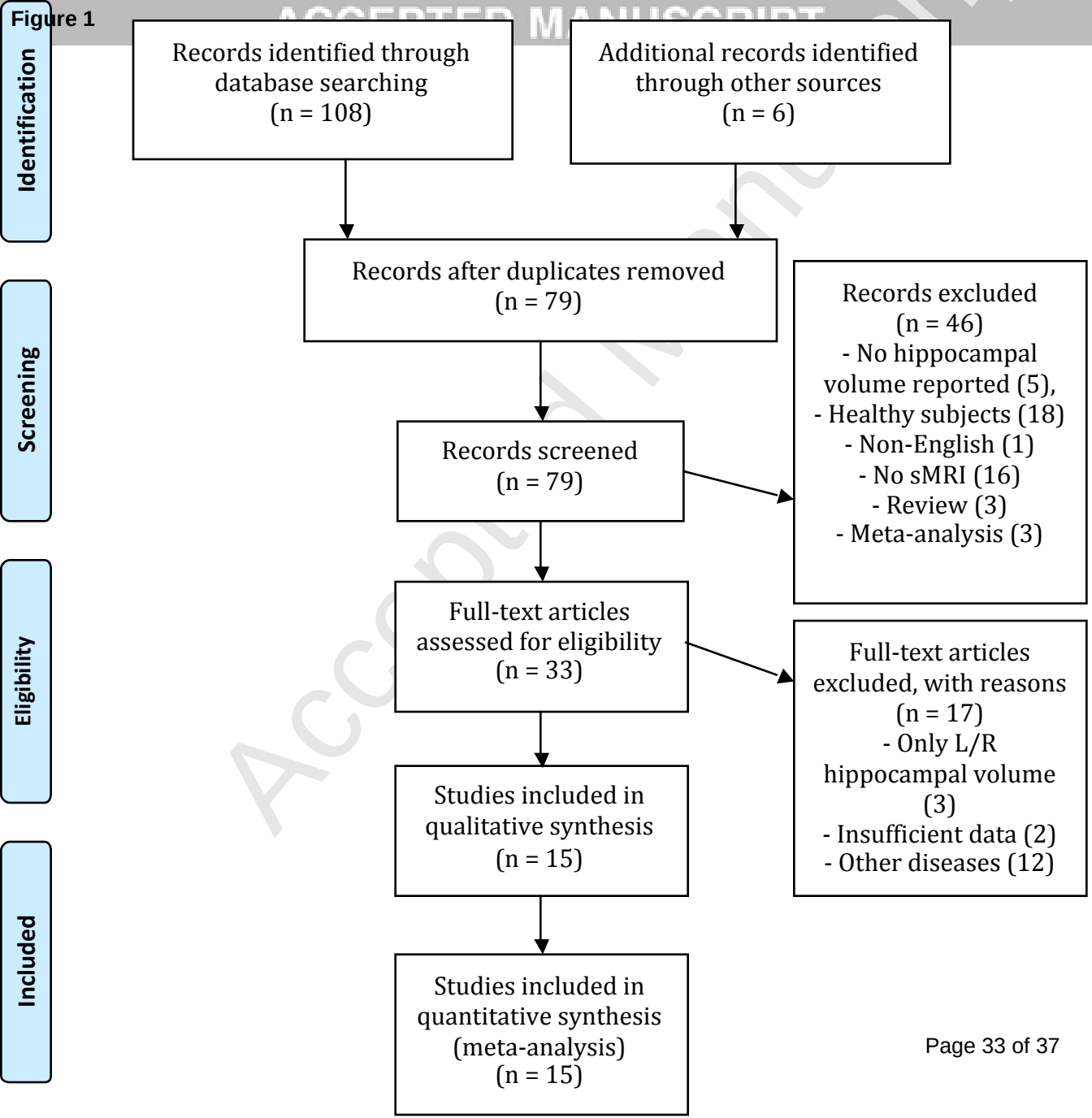
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Figure 1. Flow chart of the search strategy and studies included in the meta-analysis

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Figure 1

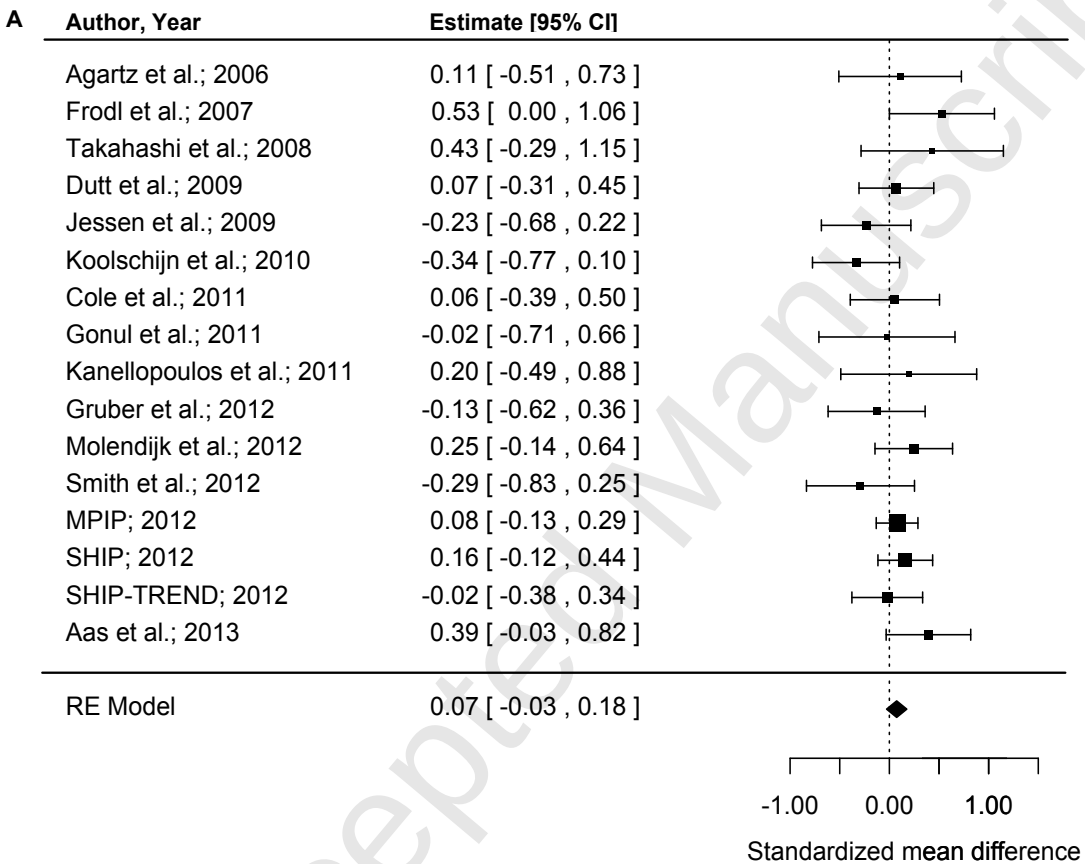


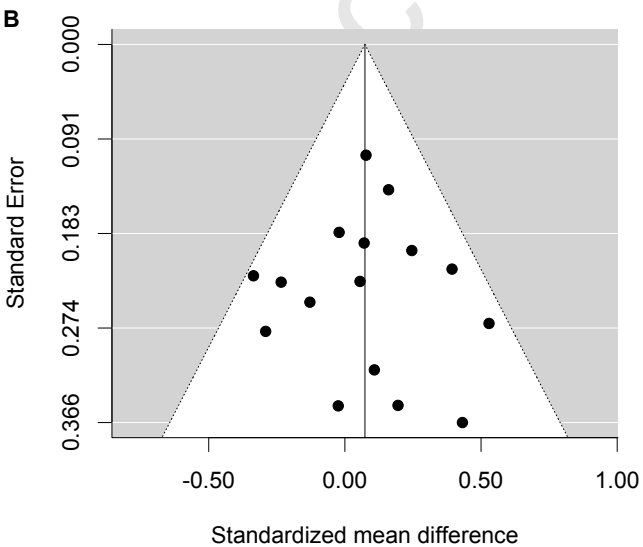
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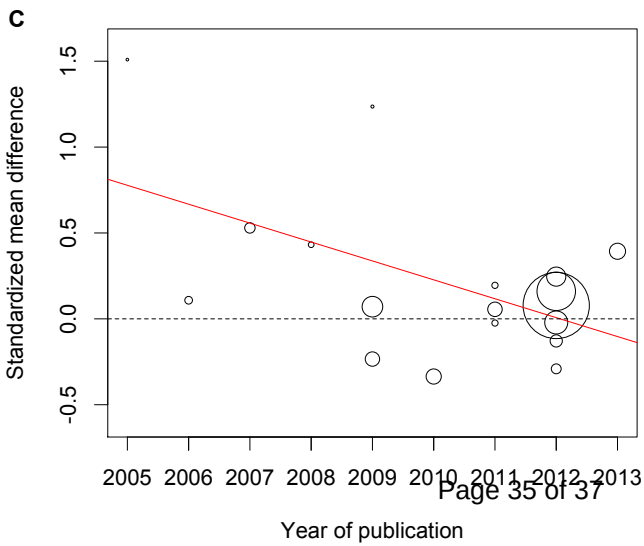
Figure 2. A. Forest plot of random effects meta-analysis investigating the association between hippocampal volumes and the BDNF SNP rs6265. Positive effect sizes indicate larger hippocampi for Val allele neuropsychiatric patients than Met allele neuropsychiatric patients. Dashed lines indicate zero line. Square size proportional to sample size. B. Funnel plot of potential bias where trim and fill procedure revealed no missing studies to correct for potential publication bias. C. Bubble plot of meta-regression analysis reflecting the association between year of publication and effect size. Circle size is proportional to the inverse of the variance, and thus to the precision of each study.

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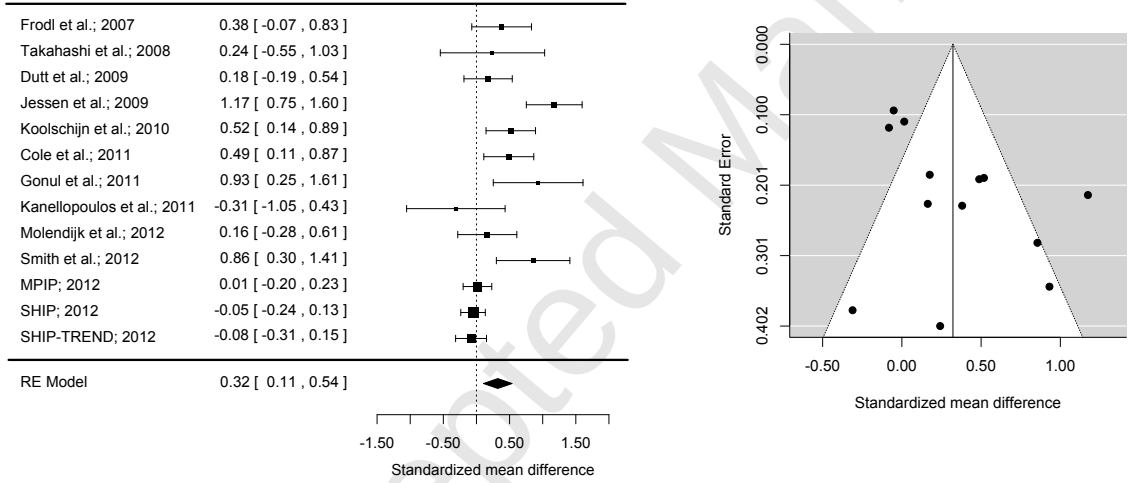
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Figure 3. A. Forest plot of random-effects meta-analyses investigating the association between hippocampal volumes and the BDNF SNP rs6265 in Val/Val homozygote patients and healthy controls. Positive effect sizes indicate larger hippocampi for healthy control subjects than neuropsychiatric patients. Dashed lines indicate zero line. Funnel plot of potential bias where trim and fill procedure revealed no missing studies to correct for potential publication bias.
B. Forest plot of random effects meta-analyses investigating the association between hippocampal volumes and the BDNF SNP rs6265 in Met-carrier patients and healthy controls. Positive effect sizes indicate larger hippocampi for healthy control subjects than patients. Dashed lines indicate zero line. Funnel plot of potential bias where white dots indicate the missing studies to correct for potential publication bias obtained by trim and fill procedure.

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A



B

