Brain structural alterations, genetic risk variants and the onset of psychosis

Inauguraldissertation
zur
Erlangung der Würde eines Dr. sc. med.
vorgelegt der
Medizinischen Fakultät
der Universität Basel

von

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aus Basel, Basel-Stadt

Basel, 2016

Genehmigt von der Medizinischen Fakultät
auf Antrag von

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Basel, den 30.11.15

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Acknowledgments

To start with, I like to thank my supervisor, Prof. Stefan Borgwardt. I am grateful for the possibility to work in the neuroimaging field and I appreciated our pleasant discussions and that I could pursue my own ideas.
Many thanks go to my second advisor, Prof. Andreas Papassotiropoulos, for the opportunity to perform the genetic analysis in his lab and I appreciated the fruitful discussions. Moreover, it was great fun to work with his team.
Of course I thank the whole Neuropsychiatry and Brain Imaging group for their invaluable help, whenever needed. I am particularly thankful for the guidance by Renata Smieskova and André Schmidt especially during the beginning.
Dear Su, thank a lot for proofreading.
Big thanks go to of my mum, my dad, my sister, my parents-in-law and my whole family who unremittingly supported me, especially after the birth of my son, and believed in me throughout this thesis and beyond. I feel very honoured to have you in my life.
And last, but with all my heart I deeply thank my husband and my son for all their love, support and critics; that means the world to me.

Abstract

One of the central motivations behind research of the at-risk mental state is to prevent or delay potential transition to psychosis and further progression to schizophrenia, by studying the early signs and symptoms without potential confounding effects of disease progression and medication. And although the pathophysiological mechanism is still poorly understood, it is known that there is a large genetic heritability where a combination of different genetic variants sets a predisposition. Therefore, the identification of markers that characterise all states of the disease, namely schizophrenia, first-episode of psychosis and the at-risk mental state, are a main goal. A very robust marker is hippocampal volume reduction in schizophrenia, first-episode of psychosis and the at-risk mental state.

In this thesis, I will present research for a deeper characterisation of the hippocampus in schizophrenia, first-episode of psychosis and the at-risk mental state and the association to genetic risk variants. First, we we found no association of the brain-derived neurotrophic factor rs6265 polymorphism with the hippocampal volumes neither in the original analysis of large cohort of young healthy individuals nor a meta-analysis with 5298 healthy subjects in total. Moreover, we detected differences between the applied hippocampal measuring techniques, i.e. manual or automated segmentation. Second, a meta-analysis of the same association but in 18 independent neuropsychiatric patient cohorts including schizophrenia revealed again no association. Also, we showed similar hippocampal reductions for Val/Val homozygote and Met-carrier patients compared to healthy controls. Third, group-related comparison of subcortical volumes revealed hippocampal and thalamic reductions in at-risk mental state individuals compared to healthy controls. Moreover, we found comparable medium effect sizes for both structures assessed with two different statistical methods. Fourth, in a cohort of at-risk mental state individuals and first-episode of psychosis patients we found a negative association between the hippocampal volumes and a polygenic schizophrenia-related risk score. Furthermore, a higher polygenic schizophrenia-related risk score was significantly associated with a higher probability of an individual being assigned to the first-episode of psychosis group compared to the total at-risk mental state group.

These studies aid a better understanding of hippocampal volume reduction and genetic variants associated with schizophrenia, first-episode of psychosis and the at-risk mental state.

Abbreviations

ARMS: At-risk mental state
BDNF: Brain-derived neurotrophic factor
FEP: First-episode psychosis
GWAS: Genome-wide association study
HC: Healthy controls
Met: Methionine
MRI: Magnetic resonance imaging
PFC: Prefrontal cortex
PSRS: Polygenic schizophrenia-related risk score
SNPs: Single nucleotide polymorphisms
Val: Valine

1. Introduction

1.1 Schizophrenia: Epidemiology, clinical symptoms and aetiology

Schizophrenia can be a severe mental disorder affecting around 1% of the population worldwide (Lopez and Murray, 1998), while affective- and non-affective psychoses account for even 6.3% of global disease burden ("WHO | Global burden of disease," 2004). Disease onset is generally in adolescence or early adulthood, although early- as well as late-onset schizophrenic forms are known. The risk for male and female is comparable, but the average age of onset is 3-4 years later for females (Murray and Van Os, 1998) and males tend to be more impaired by negative symptoms with poorer social functioning and worse outcome (Fusar-Poli et al., 2012b; Rietschel et al., 2015).

Schizophrenia has a broad range of clinical symptoms, which overlap with other neuropsychiatric disorders. The symptoms are classified into positive and negative symptoms according to *DSM-5* and *ICD-10*. Positive symptoms comprise paranoia, delusion, hallucination, suspiciousness and conceptual disorganization, while negative symptoms include blunted effect, emotional and social withdrawal, disorganized speech and apathy. The disease can be additionally characterized by cognitive deficits. The symptoms are highly heterogeneous between patients, though positive symptoms generally appear in an episodic form whereas negative symptoms are more persistent over time (Mueser and McGurk, 2004).

Twin and family studies reported a strong genetic component of schizophrenia. Twin studies revealed a heritability of up to 80% (Cannon TD et al., 1998; Cardno AG et al., 1999; Farmer et al., 1987; Sullivan et al., 2003), whereas environmental variance accounted for 11% (Sullivan et al., 2003). Moreover, first degree relatives have a higher lifetime prevalence of 6-46% compared to the general population and second degree relatives have still a 2-4% higher risk for developing schizophrenia (Agerbo et al., 2015; Kendler et al., 1993, 1985; Lichtenstein et al., 2009). This high percentage of heritability points towards a complex polygenic disorder of non-mendelian inheritance rather than a single causal genetic factor (McGue et al., 1983). Besides genetic predisposition, several lines of evidence also suggest environmental trigger-factors increase the risk for schizophrenia. Possible environmental stressors are obstetric complications, place of birth, migration, stressful life events and cannabis consumption (Cannon et al., 2002; van Os et al., 2010). The observed clinical symptoms, the onset timepoint, the high genetic predisposition and the involvement

of environmental factors resulted in two different concepts for schizophrenia origin. The first is the neurodegenerative concept from the early days of Kraepelin (Kraepelin and Robertson, 1919) and the second is the neurodevelopmental concept proposed first by Weinberger and also Murray (Murray and Lewis, 1987; Weinberger, 1987). Although this is still a matter of debate, both take into account that critical neuronal circuits are under plastic rearrangement especially before adulthood and that impairments in these circuits, e.g. altered synaptic plasticity, might be a cause of a long-lasting disturbance. Examining the underlying neurobiology of schizophrenia without confounding effects such as medication, disease progression or hospitalization, early clinical detection and intervention assesses the stages before the onset of schizophrenia, the first-episode of psychosis (FEP) and the at-risk mental state (ARMS).

1.2 First-episode psychosis and at-risk mental state

FEP patients experience psychotic symptoms for the first time. They fulfil the criteria for acute psychotic disorder according to *ICD-10* or *DSM-5* but not for schizophrenia and meet the operational criteria according to Breitborde et al. (Breitborde et al., 2009; Kahn and Sommer, 2015). The most common treatments for FEP patients are psychological therapy (e.g. cognitive behavioural therapy) and pharmacological treatment (mainly antipsychotics and antidepressants). While all antipsychotics essentially interact with the dopamine receptor (Seeman, 2001), positive symptoms are thereby improved, but they have a limited impact on negative symptoms (Fusar-Poli et al., 2015; Leucht et al., 2009) and cognitive deficits (Keefe et al., 2007). Moreover, around 30% of patients are treatment-resistant to antipsychotics (Meltzer, 1997).

The ARMS is described on the diagnostic level by early signs and symptoms that precede the characteristics of an acute FEP (Fusar-Poli P et al., 2013). In more detail, the ARMS is characterized by attenuated psychotic symptoms and a decline in social and occupational functioning, corresponding to the criteria by Yung et al. (Riecher-Rössler et al., 2009, 2007; Yung et al., 2005). In comparison to genetic high-risk individuals these clinical high-risk individuals already have subtle symptoms and might not have relatives with schizophrenia. The ARMS might lead to an enhanced risk for psychiatric diseases, especially for schizophrenia. Around 30% of the heterogeneous ARMS group undergo transition to psychosis in the first two years and develop a FEP (Fusar-Poli et al., 2012a), and some of them continue to develop

schizophrenia (Fusar-Poli et al., 2013). In contrast, the long-term outcome of ARMS individuals that do not develop psychosis is not clear. Most of them may continue in the ARMS while few will remit spontaneously (Brandizzi et al., 2015; Simon et al., 2013; Ziermans et al., 2011). A central motivation of high-risk research is to prevent or delay transition to psychosis by early intervention (Clark et al., 2015; van der Gaag et al., 2013). However, solely on clinical symptoms it is not possible to identify those ARMS individuals with subsequent transition to psychosis. Therefore, the identification of risk markers such as structural and functional brain alterations, neurocognitive, environmental and genetic markers might help to identify the ARMS individuals who undergo subsequent transition to psychosis.

1.3 Endophenotype concept in schizophrenia: Neuroimaging

The endophenotype approach was created to unravel the genetic architecture of psychiatric diseases by using easier measurable characteristics that have a closer relationship to the biological processes than diagnostic criteria (Flint and Munafò, 2007; Gottesman and Shields, 1973; Preston and Weinberger, 2005). The definition of Gottesman and Gould (Gottesman and Gould, 2003) states that the biological marker is associated with the heritable disease, is present also when the disease is not (primarily state-independent), co-segregates with the psychiatric illness and can also be observed at a higher rate in healthy siblings of patients than in the population. An appealing endophenotype is that of neuroimaging, with which the effect of candidate risk genes can be observed in fewer patients using structural and/or functional magnetic resonance imaging (MRI) findings compared to clinical symptoms (Meyer-Lindenberg and Weinberger, 2006; Rose and Donohoe, 2013).

The identification of brain structural alterations revealed several reproducible results for ARMS and FEP in comparison to healthy controls (HC). Namely, FEP patients and even ARMS individuals show similar grey matter volume reduction of medial frontal gyrus, anterior cingulate, superior temporal gyrus, insula and medial temporal lobe compared to HC (Fusar-Poli et al., 2011; Radua et al., 2012; Shepherd et al., 2012; Steen et al., 2006; Vita et al., 2012, 2006).

A very robust marker of schizophrenia, FEP and the ARMS is volumetric hippocampal reduction (Adriano et al., 2012; Fusar-Poli et al., 2012c, 2011; Haijma et al., 2013; Shepherd et al., 2012; Steen et al., 2006; Vita et al., 2006; Wright et al., 2000). However, results are inconsistent on the differences in hippocampal volume between first-episode of psychosis (FEP) patients and ARMS individuals, regardless

of future transition to psychosis (Fusar-Poli et al., 2014, 2012c; Smieskova et al., 2010). Additionally, moderate genetic heritability of the hippocampal volumes was shown in large extended families affected with schizophrenia (Roalf et al., 2015), making it an acceptable endophenotype.

The hippocampus is of special interest as it is involved in cognitive functioning (Wixted and Squire, 2011) which is impaired in schizophrenia and already to some extent in the ARMS (Bora and Murray, 2014; Fusar-Poli et al., 2012b; Mesholam-Gately et al., 2009; Savla et al., 2013). Therefore, hippocampal activation during working memory processing are widely conducted in ARMS individuals, FEP and schizophrenia patients revealing neurofunctional alterations (Fusar-Poli et al., 2007; Henseler et al., 2009; Kraguljac et al., 2013; Radua et al., 2012; Yan et al., 2015).

In addition, the memory network, including the hippocampus and the prefrontal cortex (Smith and Jonides, 1999), is of interest, but until now not many studies conducted functional or structural connectivity analyses in schizophrenia (Benetti et al., 2009; Ellison-Wright and Bullmore, 2009; Harms et al., 2013; Henseler et al., 2010; Meyer-Lindenberg et al., 2005; Samartzis et al., 2014; Wolf et al., 2009). However, already in 1995 Friton and Frith proposed the disconnectivity hypothesis of schizophrenia with altered connections between temporal and prefrontal cortices (Friston and Frith, 1995).

1.4 Single nucleotide polymorphisms and polygenic schizophrenia-related risk score

The high heritability suggests a strong genetic element in the development of schizophrenia with a multifactorial polygenic model as mode of transmission (McGue et al., 1983). This is suggestive of many thousands of common genetic variants with weak effect that in combination with specific individual environmental factors can induce psychosis (International Schizophrenia Consortium et al., 2009; Lee et al., 2012). Rare genetic variants exist that are highly penetrant and associated with a high risk for schizophrenia, like the 22q11.2 deletion syndrome (Bassett and Chow, 1999) but they are not frequent in the common population. The common genetic marker, single nucleotide polymorphisms (SNPs), is a single base pair substitution, occurring about every 300 base pairs in the genome with a minor allele frequency of more than 1% in the common population. Although individual effects of SNP on the genetic risk for schizophrenia was found to be small, it was estimated that 23% of variation in susceptibility to schizophrenia is captured by SNPs with a substantial proportion of

this variation attributed to common causal variants (Lee et al., 2012; Ripke et al., 2013).

At first, SNPs within chromosomal regions identified though linkage studies or within genes of causal biological reasoning, such as target sites of antipsychotic medication, were further investigated in association studies, to assess an overrepresentation of one allele in patients that might indicate a risk for the disease (McGuffin et al., 2003). Multiple susceptibility loci that co-segregate with the disease were repeatedly investigated leaving contradictory findings (Allen et al., 2008) where most of the early candidates disappeared again (Crow, 2011). But through genome-wide association studies (GWAS) the examination of hundreds of thousands of SNPs was made possible (International Schizophrenia Consortium et al., 2009; O'Donovan et al., 2008; Psychosis Endophenotypes International Consortium et al., 2014; Rietschel et al., 2012; Ripke et al., 2013; Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Shi et al., 2009). This allows the hypothesis-free identification of risk variants covering the entire genome and the utilization of large sample sizes achieved by international collaboration and the formation of consortia. The newest and largest of these GWAS, investigating putative risk variants in nearly 37'000 schizophrenia patients and more than 113'000 HC, identified 108 schizophrenia-associated genetic loci, explaining up to 3.4% of the phenotypic variance in case-control studies (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

1.5 Imaging genetics

1.5.1 Candidate single nucleotide polymorphisms

The association of identified neuroimaging markers with causal or newly identified genetic variants, i.e. imaging genetics, generated a long list of candidate SNPs associated to schizophrenia. However, studies exploring the association of only one single or few SNPs with brain structures or function in schizophrenia and FEP patients, ARMS individuals and HC mostly generated few replication studies which in turn produced contradictory results (e.g. Review by(Meyer-Lindenberg, 2010; Rasetti and Weinberger, 2011; van Haren et al., 2008)).

The association most investigated in HC and across neuropsychiatric disorders is that of the brain-derived neurotrophic factor (BDNF) rs6265 polymorphism and the

hippocampal volumes. BDNF is highly expressed in the hippocampus where it plays an important role in adult neurogenesis and is thought to be involved in learning- and memory-dependent processes (Cunha et al., 2010). The SNP results in a substitution of valine (Val) to methionine (Met) at codon 66 of the BDNF gene and leads to improper BDNF sorting through the activity-dependent secretion pathway (Chen et al., 2004; Egan et al., 2003).
In order to summarize and further evaluate such putative associations meta-analyses are a very important tool (Munafò and Flint, 2004).

1.5.2 Polygenic schizophrenia-related risk score

Although single SNP analyses illustrate the potential benefit of imaging genetics, they have to be treated with caution since the analysis of one single SNP neglects the multifactorial nature of schizophrenia. Therefore, it can only account for a very small amount of genetic risk for susceptibility to the disorder. However, the accumulation of the estimated cumulative genomic risk for schizophrenia can be incorporated into a polygenic schizophrenia-related risk score (PSRS). The PSRS can overcome the small risk related to an individual SNP by explaining a slightly larger genetic predisposition for schizophrenia using the predictive power of GWAS analyses.
Studies applying the PSRS approach showed a significantly negative association with total brain volume (Terwisscha van Scheltinga et al., 2013) and especially white matter volume (Oertel-Knöchel et al., 2015; Terwisscha van Scheltinga et al., 2013) in different cohorts of schizophrenia patients, their relatives and/or HC. Unfortunately, another study failed to replicate these findings in an independent cohort of HC (Papiol et al., 2014). Moreover, a PSRS of 41 SNPs was positively associated with dorsolateral prefrontal cortex inefficiency during a working memory task in schizophrenia patients and HC (Walton et al., 2013). The same research group could replicate their findings with a larger set of nominally significant SNPs and in a bigger cohort of schizophrenia patients and HC (Walton et al., 2014). However, none of them investigated the association of a PSRS with brain volume in ARMS individuals and/or FEP patients. And although a GWAS analysis identified single SNPs linked to hippocampal volume in HC (Hibar et al., 2015), no study to date investigated the association of a PSRS with volumetric differences of this region.

2 Aim and own contribution

The aim of this doctoral thesis was to identify genetic and neuroimaging markers that might indicate a predisposition for vulnerability to psychosis. The schizophrenia-associated candidate variants might have a measurable impact on brain regions known to differ in ARMS individuals and FEP patients. Therefore, we wanted to investigate the neurobiology of vulnerability to psychosis by the association of specific genetic variants with structural MRI measures implicated in the susceptibility for schizophrenia.

The role of the most investigated endophenotype in schizophrenia, FEP and ARMS – hippocampal volume reduction in the developing disorder in association with genetic markers – was chosen to obtain a better understanding of the genetic risk for schizophrenia especially for ARMS individuals and FEP patients.

First, in collaboration with the research groups of Prof. Andreas Papassotiropulos and Prof. Dominique De Quervain, we investigated the association of BDNF rs6265 polymorphism and hippocampal volume in their large HC sample. Furthermore, I performed a meta-analysis including these new data and 27 original publications to elaborate the basis of this aspect in health.

Second, I performed a meta-analysis of this association in 1695 neuropsychiatric patients with either schizophrenia, bipolar disorder, major depressive disorder or anxiety disorder.

Third, I analyzed differences of subcortical volumes, including the hippocampus, between ARMS and HC in a cohort from Basel and Zurich.

Fourth, I applied the PSRS approach in association with hippocampal volume, on our cohort of ARMS individuals and FEP patients.

The following four publications report the findings of this thesis:

Harrisberger F*, Spalek K*, Smieskova R, Schmidt A, Coynel D, Milnik A, Fastenrath M, Freytag V, Gschwind L, Walter A, Vogel T, Bendfeldt K, de Quervain DJ-F, Papassotiropoulos A, Borgwardt S, 2014. The association of the BDNF Val66Met polymorphism and the hippocampal volumes in healthy humans: A joint meta-analysis of published and new data. Neurosci. Biobehav. Rev. 42, 267–278. doi:10.1016/j.neubiorev.2014.03.011

Harrisberger F, Smieskova R, Schmidt A, Lenz C, Walter A, Wittfeld K, Grabe HJ, Lang UE, Fusar-Poli P, Borgwardt S, 2015. BDNF Val66Met polymorphism and hippocampal volume in neuropsychiatric disorders: A systematic review and meta-analysis. Neurosci. Biobehav. Rev. doi:10.1016/j.neubiorev.2015.04.017

Harrisberger F, Buechler R, Smieskova R, Schmidt A, Lenz C, Bendfeldt K, Simon A, Richer-Rössler A, Lang U E, Heekeren K, Borgwardt S. Volumetric subcortical alterations in individuals at high-risk for psychosis: A multi-center study. (in preparation)

Harrisberger F, Smieskova R, Vogler C, Egli T, Schmidt A, Lenz C, Simon A, Richer-Rössler A, Papassotiropoulos A, Borgwardt S. Impact of polygenic schizophrenia-related risk and hippocampal volumes on the onset of psychosis. (submitted)

* These authors contributed equally to this work.

3 Results

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

By
Harrisberger F*, Spalek K*, Smieskova R, Schmidt A, Coynel D, Milnik A, Fastenrath M, Freytag V, Gschwind L, Walter A, Vogel T, Bendfeldt K, de Quervain DJ-F, Papassotiropoulos A, Borgwardt S

Published in Neurosci. Biobehav. Rev. 42, 267–278. 2014
doi:10.1016/j.neubiorev.2014.03.011

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Neuroscience and Biobehavioral Reviews 42 (2014) 267–278

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

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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ARTICLE INFO

Article history:
Received 21 November 2013
Received in revised form 17 February 2014
Accepted 16 March 2014

Keywords:
BDNF Val66Met
rs6265
Brain-derived neurotrophic factor
BDNF
MRI
Hippocampus
sMRI
Structural

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.

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http://dx.doi.org/10.1016/j.neubiorev.2014.03.011

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 (θ = 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

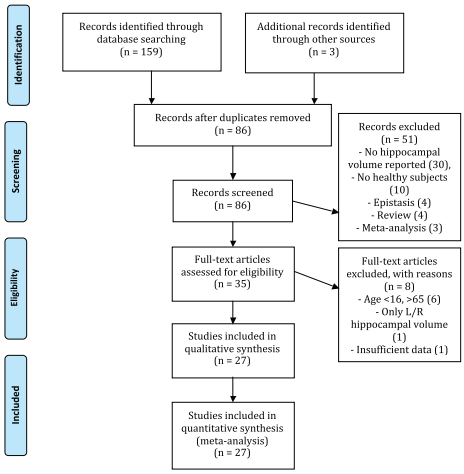

Fig. 1. Flow chart of the search strategy and included studies for meta-analysis.

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

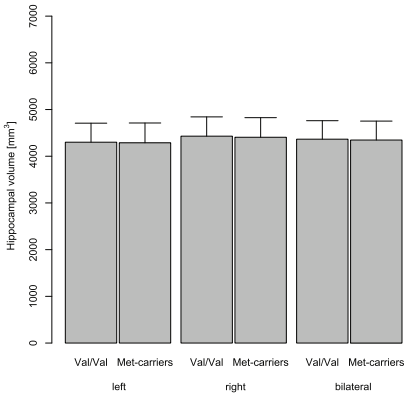

Fig. 2. Barplot showing left, right and mean bilateral hippocampal volumes [mm^3] ± standard deviation of our original data. Neither the left, right nor mean bilateral hippocampus showed a significant difference between 230 Met-carriers and 413 Val/Val homozygotes.

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(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(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.

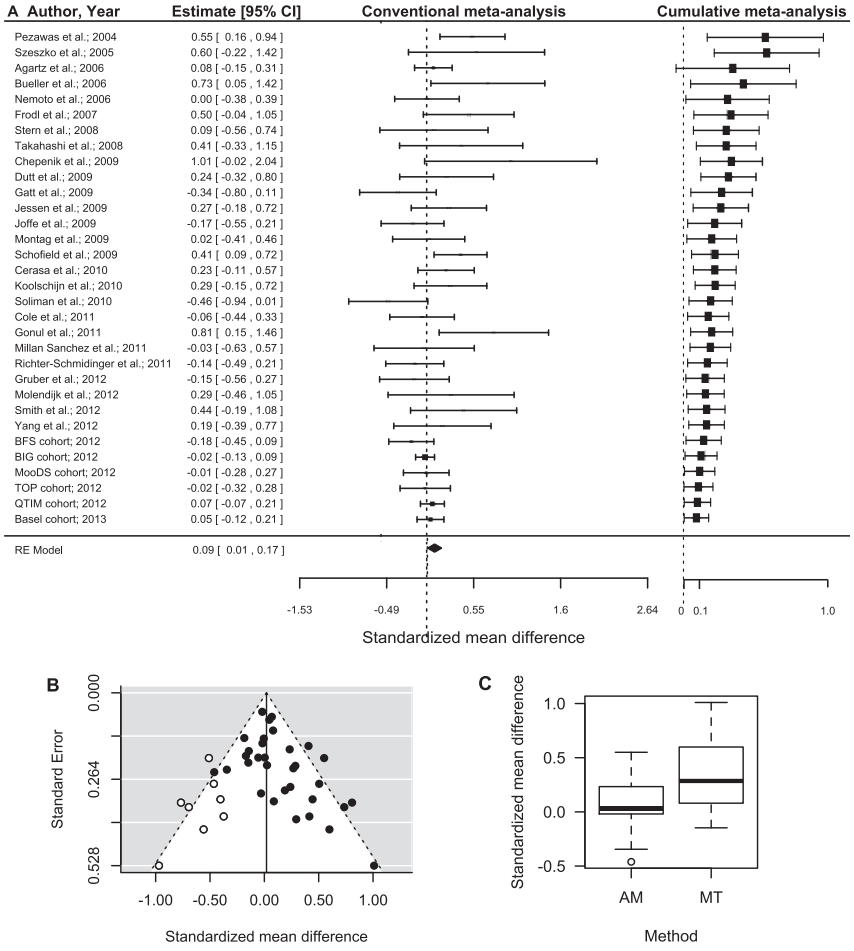

Fig. 3. (A) Forest plots of random-effects meta-analysis assessing hippocampal volumes with structural MRI and the BDNF SNP rs6265. Positive effect sizes indicate larger hippocampi in the Val allele subjects than with the Met allele subjects. The forest plot of a cumulative meta-analysis shows the change 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

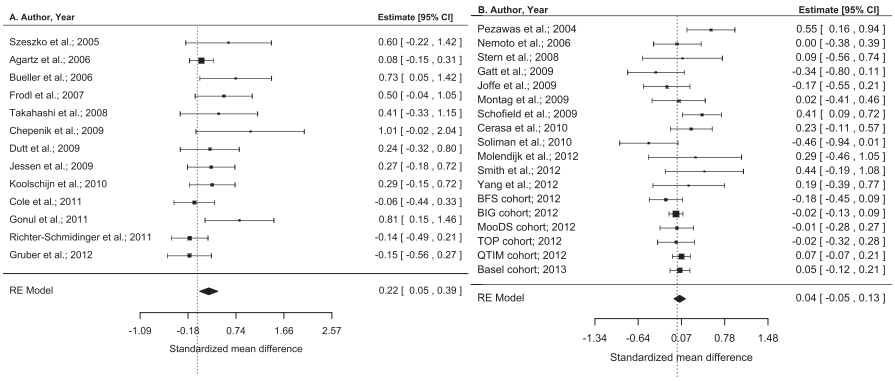

Fig. 4. Forest plots of BDNF SNP rs6265 of structural MRI studies assessing potential publication bias arising from the applied hippocampus analysis technique. (A) Manual traced hippocampus; (B) Hippocampus volumes evaluated by automatic measurement; positive effect sizes indicate larger hippocampi in 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).

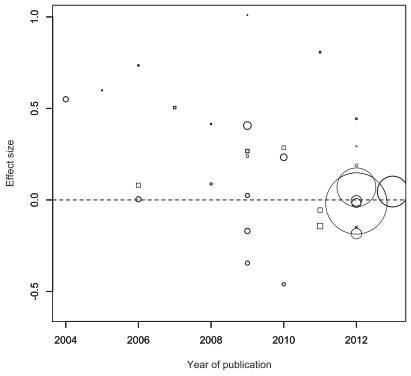

Fig. 5. Scatter plot showing the relation between effect size and year of publication for the association of the hippocampal volume and BDNF SNP rs6265. The size of the shapes indicates the sample size of each study. Squares represent the studies that traced the hippocampus manually; circles represent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

Acknowledgments

Special thanks go to Dr. Ole Andreassen, Dr. Alejandro Arias Vasquez, Dr. Antonio Cerasa, Dr. Narelle Hansell, Dr. Neeltje van Haren, Dr. Unn Kristin Haukvik, Dr. Andrew McIntosh, Dr. Manuel Mattheisen, Dr. Christian Montag, Prof. Markus Nöthen, Dr. Koji Matsuo, Marc Molendijk, Dr. Kiyotaka Nemoto, Dr. Martina Papmayer and Xuejuan Yang who provided additional information and volumetric data.

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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Supplementary Methods

Sample quality control with Bayesian clustering algorithm

Within each center, the Bayesian Clustering Algorithm[31] was applied on genome-wide summary statistics to identify and exclude atypical samples. Considering a combination of two summary statistics, the algorithm infers each sample's posterior probability to belong to the outliers class. A first outlier assessment was based on genome-wide call rate and heterozygosis rates, for which extreme values may be indicative of genotyping bias. A second assessment, aiming at identifying subjects with unusual ancestry according to the majority of the samples, was performed by projection of the samples genotypic data on the two first components inferred from a PCA applied on Hapmap African, European and Asian populations. Samples were also checked for consistency between genotypic inferred and self-reported gender.

Investigation of main effect of age or sex and interaction effect of sex and rs6265 genotype groups on hippocampal volumes

Additionally, we specified univariate ANOVA for each variable of interest using sum of square type III. Hippocampal volumes, as the (quantitative) dependent variable, were corrected separately for ICV, differences due to software and gradient updates and either sex or age by using the z-transformed residuals of a linear regression. Independent variables were age as quantitative variable, sex and rs6265 genotype groups as factors and the interaction term of sex and rs6265 genotype group.

Table S1 Categories scored in the quality assessment

Category	0	1	2
1. Funding - role in analysis and interpretation of data	company producing studied drug or missing	could have	none
2. Sample size	< 20	20 - 29	30 +
3. Clear inclusion criteria for participants	not reported	partly reported	reported
4. Reported allele distribution	not reported	.	reported
5. Ethnicity assessed	not reported	.	reported
6. If mixed ethnicity: Discussing problems	not included	included	.
7. IQ/educational level available	not reported	.	reported
8. Inter-and intrarater reliability	not reported	.	reported
9. Hardy-Weinberg equilibrium reported	not reported	matched sample	reported
10. Sample in Hardy-Weinberg equilibrium	not reported/ not enough data to calculate	matched sample	reported
11. Sufficient descriptive data (age, gender, genotyping method, magnetic field strength of scanner)	not all reported	Of larger sample	reported

max 22. high (80-100%) >18, moderate-high (60-79%): 14-17, moderate (40-59%): 9-13, moderate-low (20-39%): 5-8, low (0-19%) <4

Table S2 Quality assessment and rating of the published studies

Author, Year	1	2	3	4	5	6	7	8	9	10	11	Sum of the score & category	
Agartz et al., 2006	0	2	2	2	2	2	0	2	0	2	2	16	moderate-high
Bueller et al., 2006	1	2	2	2	2	0	2	0	2	2	2	17	moderate-high
Cerasa et al., 2010	0	2	2	2	2	2	2	0	2	2	2	18	high
Chepenik et al., 2009	1	0	1	2	2	2	0	2	0	2	2	14	moderate-high
Cole et al., 2011	2	2	2	2	0	0	2	2	2	2	2	18	high
Dutt et al., 2009	2	2	2	0	2	2	0	0	2	2	2	16	moderate-high
Frodl et al., 2007	0	2	2	2	0	0	0	2	2	2	2	14	moderate-high
Gatt et al., 2009	1	2	0	0	2	2	2	2	2	2	2	17	moderate-high
Gonul et al., 2011	2	2	1	0	0	0	0	2	2	2	2	13	moderate
Gruber et al., 2012	0	2	2	2	2	2	2	2	2	2	1	19	high
Jessen et al., 2009	0	2	2	0	0	0	0	2	0	0	2	8	moderate-low
Joffe et al., 2009	1	2	2	2	2	2	0	2	2	2	1	18	high
Koolschijn et al., 2010	0	2	1	2	2	2	0	2	2	2	2	17	moderate-high
Millan Sanchez et al., 2011	2	2	1	0	2	2	2	2	0	0	1	14	moderate-high
Molendijk et al., 2012	2	2	1	2	0	0	2	2	2	2	1	16	moderate-high
Montag et al., 2009	2	2	2	2	2	2	0	2	2	2	2	20	high
Nemoto et al., 2006	1	2	2	2	2	2	2	2	2	2	2	21	high
Pezawas et al., 2004	0	2	2	0	2	2	2	2	0	0	2	14	moderate-high
Richter-Schmidinger et al., 2011	0	2	2	2	2	2	2	2	0	2	2	18	high
Schofield et al., 2009	0	2	2	2	0	0	2	2	2	2	2	16	moderate-high
Smith et al., 2012	2	2	2	0	0	0	0	2	2	2	2	14	moderate-high
Soliman et al., 2010	0	2	2	2	2	2	0	0	0	2	2	14	moderate-high
Stern et al., 2008	2	2	2	2	2	2	2	0	0	2	2	18	high
Szeszko et al., 2005	1	1	2	2	2	2	2	2	2	2	2	20	high
Takahashi et al., 2008	2	1	2	2	2	2	0	2	2	2	2	19	high
Yang et al., 2012	2	2	2	2	2	2	2	0	2	2	2	20	high
Stein et al., 2012	2	2	2	2	2	2	0	0	2	2	2	18	high

Table S3 Main effect of age and sex as well as interaction effect of sex and rs6265 genotype on hippocampal volumes

Variables	left hippocampus volume		right hippocampus volume		bilateral hippocampal volumes	
	$F_{(df)}$	p-values	$F_{(df)}$	p-values	$F_{(df)}$	p-values
age	$1.32_{(1,640)}$	0.200	$1.29_{(1,640)}$	0.257	$1.64_{(1,640)}$	0.201
sex	$0.87_{(1,640)}$	0.352	$0.01_{(1,640)}$	0.943	$0.209_{(1,640)}$	0.648
sex x rs6265 genotype groups	$0.74_{(1,639)}$	0.390	$0.46_{(1,639)}$	0.496	$0.67_{(1,639)}$	0.415

Table S4 Overview of the results form the performed meta-analyses

			All samples (k = 32, n = 5298)	Manually segmented hippocampi (k = 13, n = 829)	Automatically segmented hippocampi (k = 18, n = 4426)
Hedge's g			0.09	0.22	0.04
Standard error			0.04	0.09	0.05
Lower confidence interval			0.01	0.05	-0.05
Upper confidence interval			0.17	0.39	0.13
Z-value			2.08	2.51	0.89
p-value of Z			0.0376*	0.0121*	0.3751
Heterogeneity I^2			38.24	38.12	37.87
Heterogeneity Q (df)			50.20 (31)	19.39 (12)	27.36 (17)
p-value of Q			0.02*	0.08	0.05
p-value of Egger's			0.0075*	0.0012*	0.5894
Meta-regression analyses	Publication year	b-value	-0.38	-0.42	-0.18
		F-value (df)	5.01 (30)	2.32 (11)	0.52 (16)
		p-value	0.03*	0.16	0.48
	Age of probands	b-value	-0.08	-0.33	0.01
		F-value (df)	0.18 (30)	1.37 (11)	0.002 (16)
		p-value	0.67	0.27	0.97
	Gender ratio	b-value	0.13	0.26	0.07
		F-value (df)	0.48 (30)	0.80 (11)	0.08 (16)
		p-value	0.49	0.39	0.78
	Ethnicity	b-value	0.26	0.53	0.25
		F-value (df)	1.83 (25)	2.74 (7)	1.03 (16)
		p-value	0.19	0.14	0.33
	Val/Met ratio	b-value	0.14	0.29	-0.02
		F-value (df)	0.48 (24)	0.80 (9)	0.01 (13)
		p-value	0.5	0.4	0.94
	Sample size	b-value	-0.23	-0.72	-0.1
		F-value (df)	1.71 (30)	12.07 (11)	0.15 (16)
		p-value	0.2	0.01*	0.7
	Quality rating	b-value	-0.32	-0.35	-0.17
		F-value (df)	2.74 (24)	1.51 (11)	0.32 (11)
		p-value	0.11	0.25	0.58
	Hippocampal volume normalized to ICV	b-value	-0.01	0.22	0.03
		F-value (df)	0.002 (30)	0.54 (11)	0.01 (16)
		p-value	0.96	0.48	0.91
	Magnetic field strength	b-value	-0.22	-0.07	-0.1
		F-value (df)	1.49 (28)	0.06 (11)	0.14 (15)
		p-value	0.23	0.82	0.71
	Hippocampal measuring technique	b-value	0.43	-	-
		F-value (df)	6.55 (29)	-	-
		p-value	0.02*	-	-

Abbreviations: k, number of included studies; n, number of included individuals; *, significant results; df, degrees of freedom

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

By
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Published in Neurosci. Biobehav. Rev. 2015
doi:10.1016/j.neubiorev.2015.04.017

Neuroscience and Biobehavioral Reviews 55 (2015) 107–118

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

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

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ARTICLE INFO

Article history:
Received 6 December 2014
Received in revised form 15 April 2015
Accepted 25 April 2015
Available online 5 May 2015

Keywords:
BDNF Val66Met
rs6265
Brain-derived neurotrophic factor
BDNF
MRI
Structural
Hippocampus
Neuropsychiatric patients
Depression
Anxiety disorders
Bipolar disorder
Schizophrenia
Meta-analysis

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.

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http://dx.doi.org/10.1016/j.neubiorev.2015.04.017

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 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).

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., 2004, 2006; Ninan et al., 2010; 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 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.

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 Fig. 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

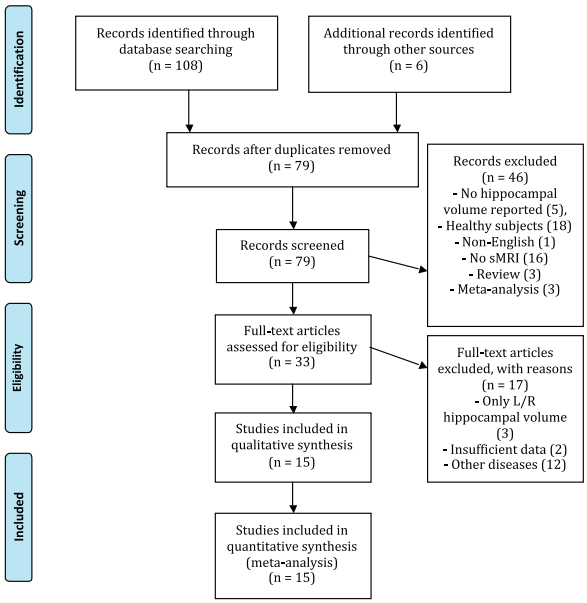

Fig. 1. Flow chart of the search strategy and studies included in the meta-analysis.

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.

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 Higgins and Green (2011) ("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 Table 1).

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 (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). 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.

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 Fig. 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 Fig. 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).

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 Fig. 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 ($\beta = -0.53$, $F(1,16) = 6.34$, $p = 0.02$, Fig. 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 Fig. 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 Fig. 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 either left ($g = 0.09$, 95%CI = [−0.02–0.19], $p = 0.12$, $k = 14$, $n = 1541$, see Supplementary Fig. 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 Fig. 2C and Table 2). Data from two studies were not available and could not be included (Agartz et al., 2006; Gruber et al., 2012).

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 Fig. 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 Fig. 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 ($p < 0.0001$) (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 Fig. 2D–G and Table 2).

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

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

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

	Meta-analyses						Heterogeneity		
	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
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
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
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
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
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
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*
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*
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*
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
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
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

	Publ. bias	Trim&fill	Meta-regression analyses: *p*-values							
	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)	0.03	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)	0.98	0	0.40	0.69	0.80	0.51	0.98	0.80	0.27	0.84
MDD only (*k* = 8, *n* = 903)	0.75	0	0.37	0.94	na	0.27	0.84	0.41	0.54	0.98
L Hippocampus (*k* = 14, *n* = 1541)	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)	0.60	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)	0.10	0	0.43	na	na	0.26	0.11	0.93	0.36	0.30
Patient vs. HC Val L (*k* = 13, *n* = 2265)	0.002	0	0.27	na	na	0.49	0.02*	0.43	0.76	0.03
Patient vs. HC Val R (*k* = 13, *n* = 2265)	0.96	0	0.45	na	na	0.48	0.50	0.83	0.56	0.56
Patient vs. HC Met (*k* = 13, *n* = 1255)	0.13	2	0.44	na	na	0.25	0.36	0.21	0.57	0.05
Patient vs. HC Met L (*k* = 13, *n* = 1255)	0.07	2	0.20	na	na	0.42	0.24	0.47	0.39	0.04*
Patient vs. HC Met R (*k* = 13, *n* = 1255)	0.47	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.

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,

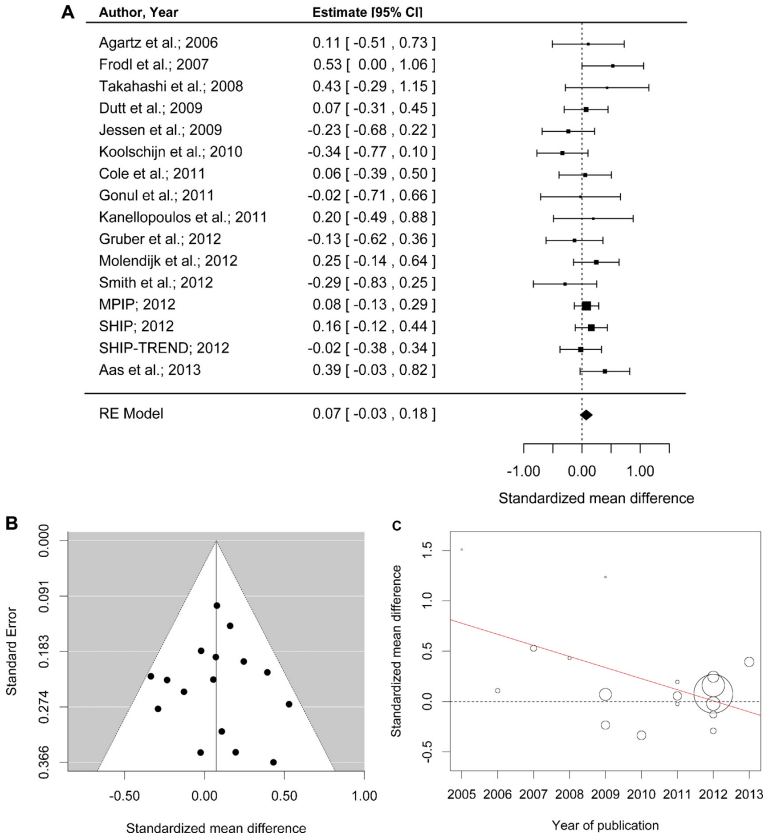

Fig. 2. (A) Forest plot of random effects meta-analysis investigating the association between hippocampal volumes and the BDNF SNP rs6265. Positive effect sizes indicate larger hippocampi for Val allele neuropsychiatric patients than Met allele neuropsychiatric patients. Dashed lines indicate zero line. 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.

hippocampal volume loss was similar for the two investigated genotypes in neuropsychiatric patients relative to healthy controls.

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 × 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

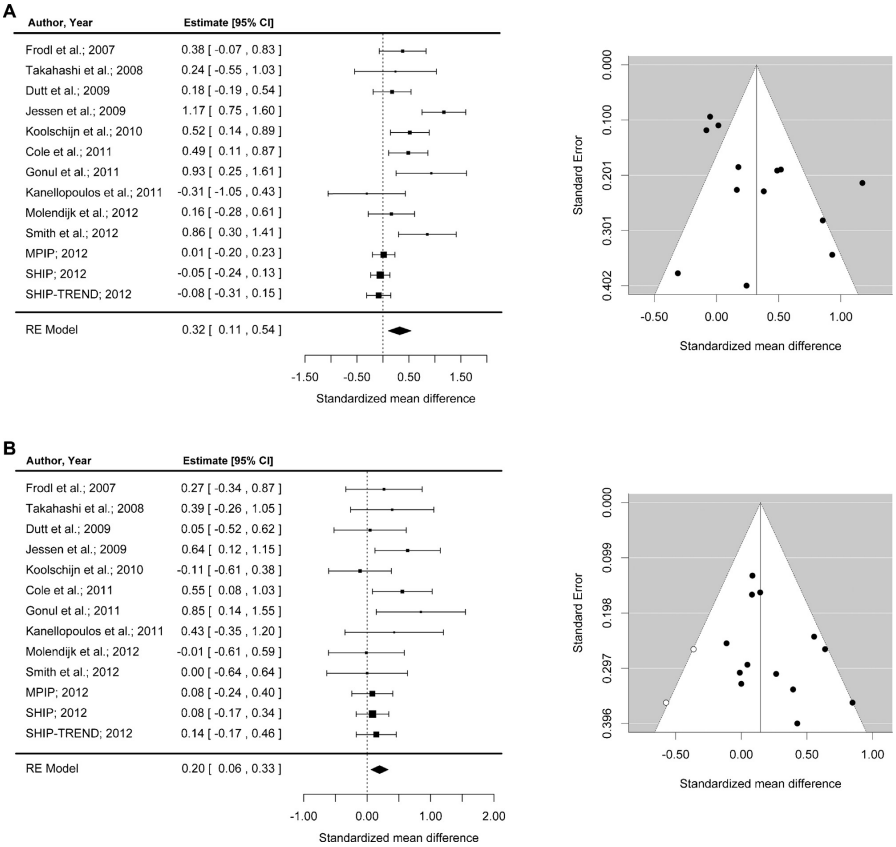

Fig. 3. (A) Forest plot of random-effects meta-analyses investigating the association between hippocampal volumes and the BDNF SNP rs6265 in Val/Val homozygote patients and healthy controls. Positive effect sizes indicate larger hippocampi for healthy control subjects than neuropsychiatric patients. 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.

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 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. First, 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. Second, 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. Third, 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. Fourth, 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. Fifth, 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. 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.

Acknowledgments

Special thanks go to Dr. Philipp Saemann, Dr. Elisabeth Binder, Dr. Michael Czisch, Dr. Neeltje van Haren and Dr. Marc Molendijk who provided additional information and volumetric data. This study was supported by the University of Basel.

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.2015.04.017

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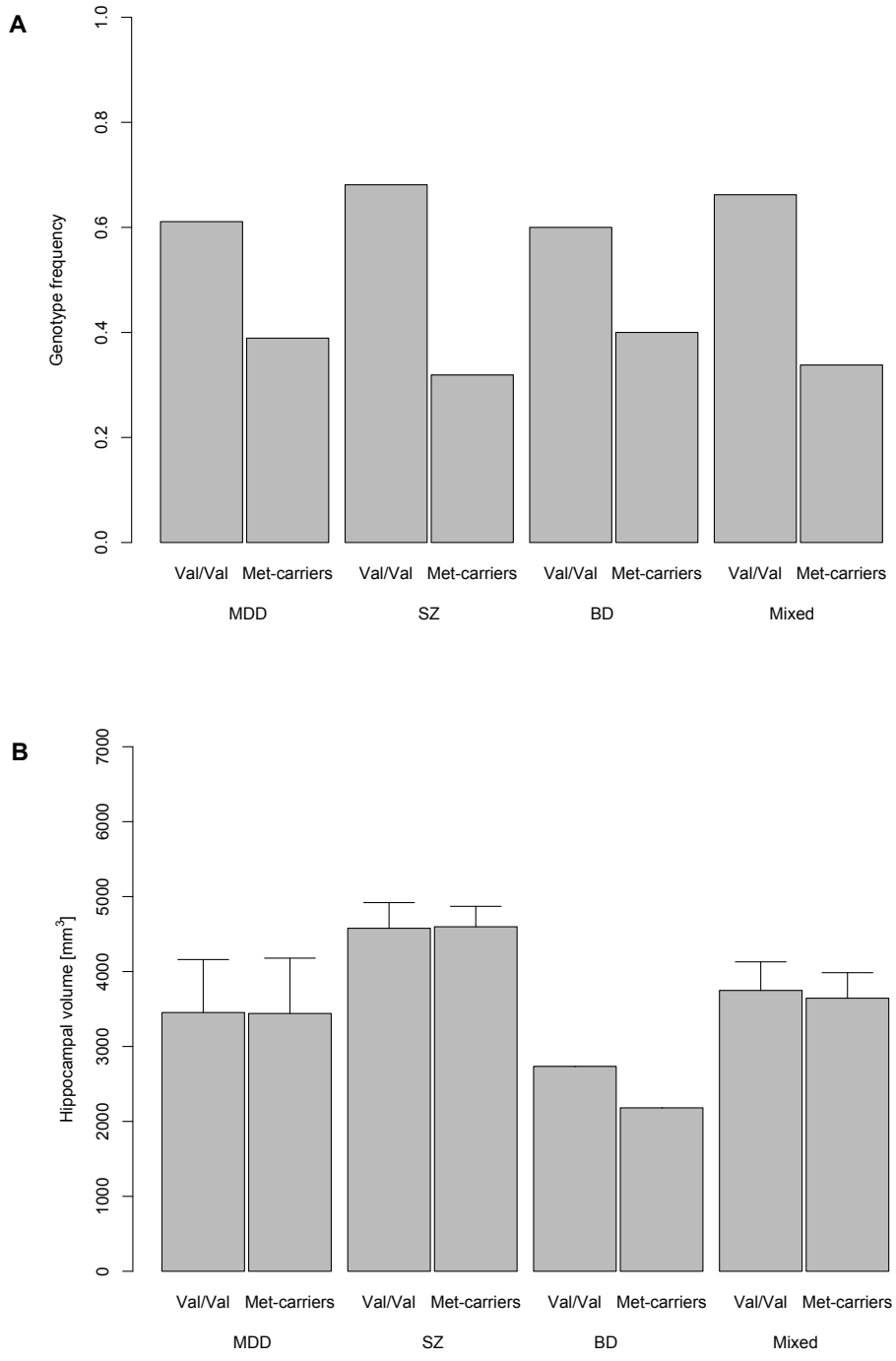
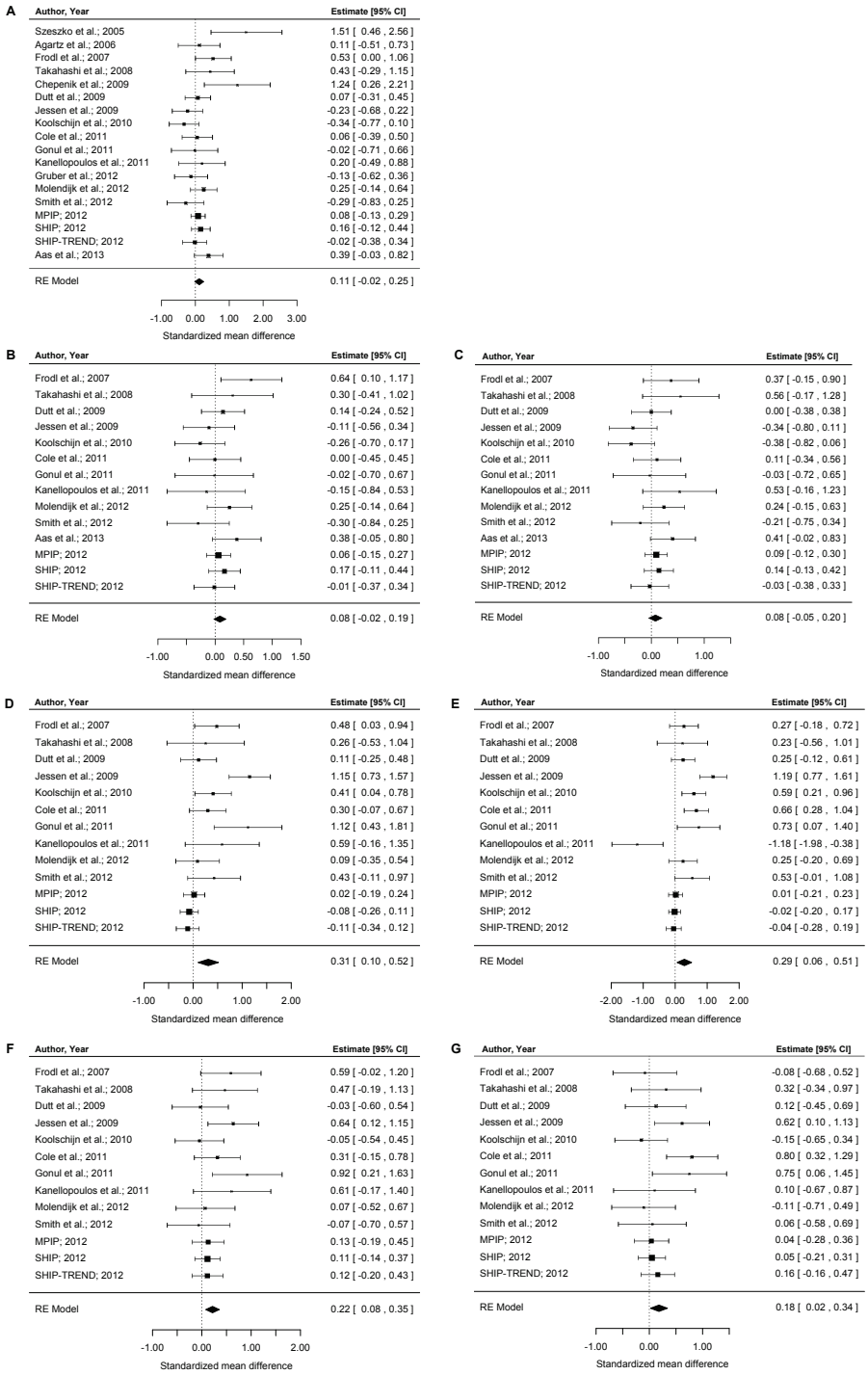
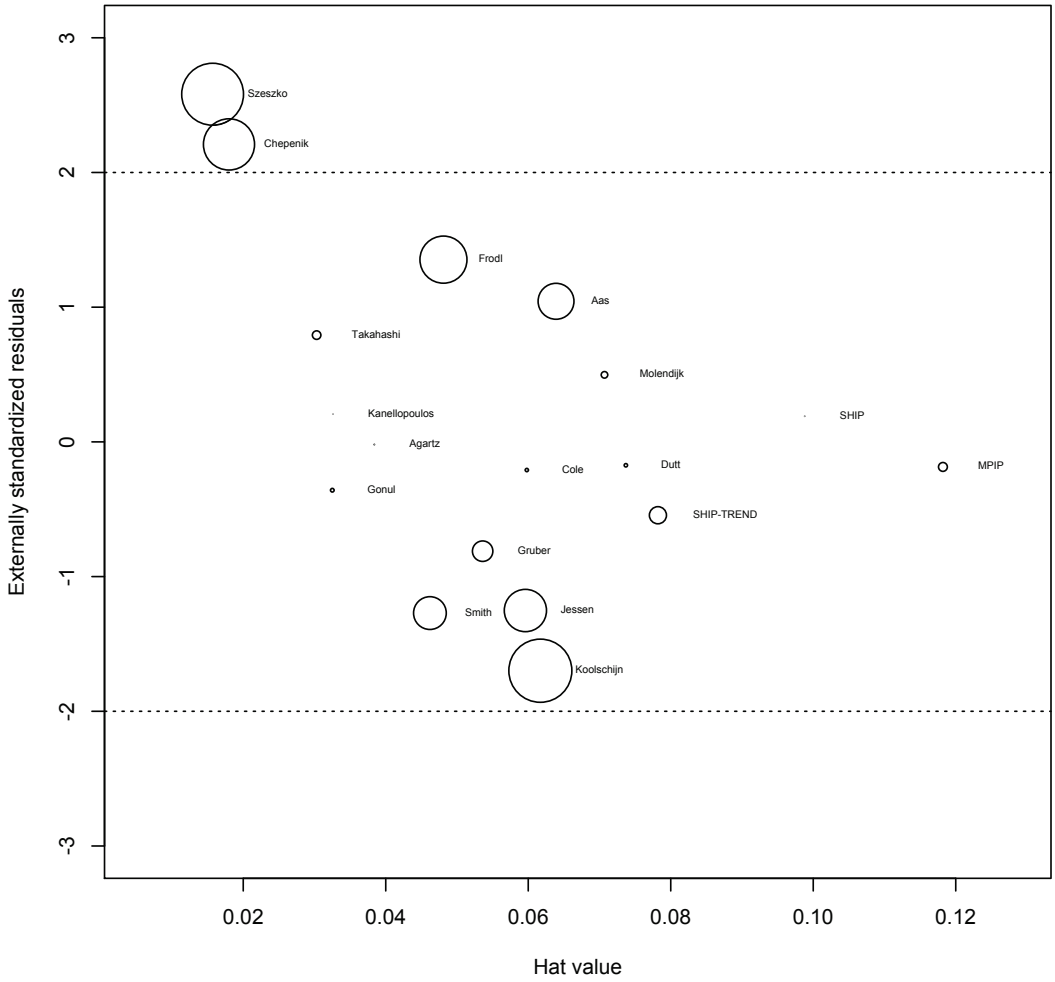


Supplementary Figure 1. Barplots showing disorder specific information of A. mean bilateral hippocampal volumes [mm^3] ± standard deviation of all studies reporting these values. The hippocampal volumes did not differ significantly between the BDNF rs6265 genotypes of each disorder. We explicitly avoided the comparison among the disorders due to only few or even a single published study per disorder and also negative results of the meta-regression in the overall meta-analysis. B. the BDNF rs6265 genotype frequency. All disorders had similar genotype frequencies. BD, Bipolar Disorder; MDD, Major Depressive Disorder; SZ, Schizophrenia;



Supplementary Figure 2. Forest plot of random effects meta-analyses investigating the difference between: A. hippocampal volumes and the BDNF SNP rs6265 of all studies. B. left hippocampal volume and the BDNF SNP rs6265. C. right hippocampal volume and the BDNF SNP rs6265. D. left hippocampal volume and Val/Val homozygote patients versus healthy controls. E. right hippocampal volume and Val/Val homozygote patients versus healthy controls. F. left hippocampal volume and Met-carrier patients versus healthy controls. G. right hippocampal volume and Met-carrier patients versus healthy controls.



Supplementary Figure 3. B. Sensitivity parameters: Hat value plotted against externally standardised residuals.

Supplementary Table 1: Quality analysis of each study according to NOS criteria

Source	Independent validation of cases (1)	Cases representative of population (2)	Cases and controls from same population	Statement that controls have no history of outcome	Comparability (matching or adjusting for one variable)	Comparability (matching or adjusting for two or more variables)	Ascertain exposure through records or structured interviews	Same method to ascertain exposure in cases & controls
Aas et al.	✱	✱	✱	✱			✱♦	✱
Agartz et al.	✱	✱	✱	✱			✱	✱
Chepinek et al.	✱	✱	✱	✱			✱	✱
Cole et al.	✱	✱	✱				✱	✱
Dutt et al.	✱	✱	✱				✱	✱
Frodl et al.	✱	✱	✱	✱	✱	✱	✱	✱
Gonul et al.	✱	✱	✱				✱	✱
Gruber et al.	✱	✱	✱	✱			✱	✱
Jessen et al.	✱	✱	✱	✱			✱	✱
Kanellopulos et al.	✱	✱	✱	✱				✱
Koolschijn et al.	✱	✱	✱	✱	✱	✱		✱
Molendijk et al.	✱	✱	✱				✱♦	✱
Smith et al.	✱	✱	✱	✱	✱	✱	✱♦	✱
Szeszko et al.	✱	✱	✱	✱			✱	✱
Takahashi et al.	✱	✱	✱	✱	✱	✱	✱	✱
MPIP	✱	✱	✱	✱			✱	✱
SHIP	✱	✱	✱	✱			✱	✱
SHIP_TREND	✱	✱	✱	✱			✱	✱

Abbreviations: ♦: Not possible to rate because of different measuring technique.

3.3 Volumetric subcortical alterations in individuals at high-risk for psychosis: A multi-center study

By

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In preparation

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Abstract

Volumetric hippocampal reductions are a hallmark of schizophrenia and already of the clinical high-risk state. A recent study automatically segmented subcortical volumes and showed the involvement of several subcortical volumes in schizophrenia. We sought to investigate the role of these subcortical volumes assessed by automatic segmentation in a multi-center cohort of clinical high-risk individuals.

Clinical high-risk individuals and healthy controls underwent structural MRI measurements and thereafter the bilateral volume of seven subcortical brain regions were automatically segmented, namely the hippocampus, the thalamus, the caudate, the putamen, the pallidum, the amygdala and the accumbens. We then used a linear mixed-effects model and prospective meta-analysis to assess group-related volumetric differences.

We report reduced hippocampal and thalamic volume in clinical high-risk individuals compared to healthy controls. Moreover, we found comparable medium effect sizes for group-related comparison of the hippocampus and the thalamus using two different methods. These findings demonstrate that some of the subcortical volumes are already altered in the high-risk state. This might suggest that these volumes can be used as a very early marker in the prediction of psychosis.

Keywords: Hippocampus, Thalamus, Structural, MRI, At-risk mental state, Ultra-high risk, Psychosis

Introduction

Structural brain alterations assessed with magnetic resonance imaging (MRI) are commonly reported in schizophrenia patients. The most replicated findings are an increase of ventricle size and reduction of hippocampal volumes [1]. Furthermore, hippocampal volumetric alterations are already present in subjects at high clinical risk for psychosis [2,3]. These alterations are therefore present before the onset of psychosis and can be studied in clinical high-risk (CHR) individuals with minimal confounding effects of medication and disease progression. The high-risk state is of special interest, as only around 30% of these individuals will develop psychosis [4–6] and the identification of these individuals and early intervention might thus prevent or delay transition to psychosis from the CHR state [7,8].

A recent publication with more than 2000 schizophrenia patients and around 2500 healthy controls (HC) assessed the subcortical volumes with automated segmentation methods [9]. They showed in schizophrenia patients that the hippocampus, the thalamus, the amygdala and the accumbens were smaller and the pallidum larger compared to healthy controls. Smaller hippocampal and larger pallidum volumes were already shown by a multi-scanner study applying automated subcortical segmentation [10]. Both studies applied a prospective meta-analysis procedure, while the latter compared it to a univariate mixed model regression analysis. They found that the effect sizes of the multisite sample were 13% smaller compared to the prospective meta-analysis, a result that indicates between-site variance due to the different magnetic resonance imaging (MRI) scanners. Additionally, automated segmentation of the subcortical volumes (i.e. hippocampus, thalamus, caudate, putamen, pallidum, amygdala and accumbens) allows the fast and robust

segmentation with comparable accuracy, sensitivity and reproducibility compared to the gold standard of manual segmentation [11–14].

Through the interconnection with cortical and other subcortical areas, the subcortical structures are involved in a variety of tasks. e.g. learning and memory [15], emotional or motivational processing [16]. Aspects of these neuronal brain circuits are at least in part impaired in schizophrenia and already the high-risk state [17,18]. Moreover, moderate to high heritability of subcortical volumes showed large extended families affected with schizophrenia [19].

To date there has been no investigations of all these subcortical volumes in one analysis in the clinical high-risk state for psychosis. Therefore we thought to elaborate all subcortical volumes automatically segmented with FSL-FMRIB 's Integrated Registration and Segmentation Tool [20] in CHR individuals and healthy controls (HC) in a combined cohort of from Basel and Zurich. The linear mixed-model approach account for scanner effects but group comparison requires similar effect sizes per site, which reduced the sample sizes drastically. Therefore, we additionally performed a prospective meta-analysis with 91 CHR individuals and 64 HC. Based on previous meta-analyses [2,3], we hypothesized to find smaller hippocampal volume in CHR individuals compared to HC.

Material and Methods

Participants

For this structural MRI analysis individuals with a prodromal psychosis and healthy controls were recruited in two individual centres: In Basel as part of the early detection of psychosis research program, FePsy, at the Psychiatry Outpatient Department, Psychiatric University Clinics Basel [6,21] and in Zurich as part of a prospective study on the early recognition of psychosis [22] within the Zurich Program for Sustainable Development of Mental Health Services (ZInEP), conducted at the Psychiatric University Hospital, University of Zurich.

For details of the recruiting process and clinical assessment as well as inclusion and exclusion criteria, see Smieskova et al. [23] and Theodoridou et al. [22].

Briefly, a total of N=94 CHR and N=64 healthy controls from Basel and Zurich were recruited (Table 1). 7 CHR individuals received already at the time of scanning antipsychotic-medication and 15 received antidepressants. In addition, a subgroup was selected to have equal numbers of CHR individuals and HC per scanner. This resulted in N=45 CHR individuals and N=43 HC (Table 2). All individuals of the smaller sample were antipsychotic-naïve at the time of scanning whereas 15 of the CHR were receiving antidepressants.

All participants provided written informed consent, and the studies had research ethics committee permission.

MRI acquisition

Basel: All anatomical scans were performed on a 3 T scanner (Siemens Magnetom Verio, Siemens Healthcare, Erlangen, Germany). For structural images, a 3D T1-

weighted MPRAGE sequence was used with the following parameters: an inversion time of 1,000 ms (θ =8 degrees), TR = 2 s, TE = 3.37 ms, FOV = 25.6 cm, acquisition matrix = 256 x 256 x 176, resulting in 176 contiguous sagittal slices with 1x1x1 mm^3 isotropic spatial resolution. All scans were screened by an experienced neuroradiologist for radiological abnormalities.

Zurich: Structural MRI data were acquired on a Philips Achieva TX 3-T whole-body MR unit, using an 8-channel head coil. Three-dimensional T1-weighted images of the whole brain were acquired (FFE pulse sequence, TR = 8.3 ms, TE = 3.8 ms, flip-angle 8 degree, FOV 240x240 mm^2, voxel size 1x1x1 mm^3 (reconstructed: 0.94x0.94x1 mm^3), 160 contiguous slices). An experienced neuroradiologist screened all structural MRI images to check for organic abnormalities.

Image processing

Volumetric segmentation of subcortical structures were estimated on T1-weighted MPRAGE images using FMRIB 's Integrated Registration and Segmentation Tool 5.0.4 (FSL-FIRST) [20]. All seven structures (accumbens, amygdala, caudate, hippocampus, pallidum, putamen, thalamus) were obtained for both hemispheres. To account for non-gaussian volume distribution, the cube root of all volumes was calculated. Then, the volumes were normalised with the cube root of the intracranial volume (ICV) and mean-centered for each site separately, to correct for different intensities measured between sites. After an outliers control (mean ± 3.5 SD), these pre-processed volumetric data were included in the further analyses.

Statistical Analysis

The R 3.0.2 software (R Core Team, 2012) [24] and the packages lme4 [25] and lmerTest [26] were used for statistical, group-related analysis. We employed a linear mixed-effects (LME) model to assess the relationship between group affiliation and each subcortical volume with left and right volumes combined in one model as separate input. As fixed effects, diagnosis and site information with interaction terms were entered, as well as age and gender. As random effect, intercepts for subject and hemispheric information were included. Visual inspection of residual plots did not reveal a deviation from homoscedasticity or normality. The significance threshold was set to $p < 0.0071$ to correct for multiple comparison (two-tailed).

Prospective meta-analysis

Data were entered into an electronic database and quantitative meta-analysis was performed using the R 3.0.2 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 [27]. Hedge's g values above 0.5 correspond to medium effect sizes. Hedge's g was calculated using data of mean hippocampal volumes, standard deviations and sample sizes. A positive value of the effect size reflected larger volumes for HC than for CHR individuals. We employed a random-effects model with the DerSimonian-Laird estimator using the metafor package [28]. Cochran's Q test was used to evaluate statistical significance of between-study heterogeneity.

Statistical analysis of clinical and socio-demographic data

One-way ANOVAs and chi-square tests were used to test the distribution between diagnosis group and age, sex, handedness, years of education, IQ, positive symptoms cluster, negative symptoms cluster, each single item of these clusters, GAF, scanner and ICV. Basel and Zurich have used different scales for measuring psychotic symptoms. We combined several items of the BPRS with the PANSS outcomes into a positive (BPRS9, BPRS10, BPRS11, BPRS15 and PANSS P2, PANSS P3, PANSS P6, PANSS G9) and a negative (BPRS16, BPRS17, BPRS18 and PANSS N1, PANSS N2, PANSS G7) symptom cluster according to Lyne et al. [29]. These statistical analyses were performed with R 3.0.2 software (R Core Team, 2012). Values are presented as mean ± SD (see table 1). In addition, associations between subcortical volumes and clinical symptoms (positive and negative symptom clusters and global functioning) were examined by Pearson correlation analysis.

Results

Clinical and demographic characteristics

There were no significant differences among our groups with respect to gender ($p = 0.20$), handedness ($p = 0.99$) and site ($p = 0.58$). There were significant between-group differences in age ($p = 0.02$), education ($p < 0.0001$), IQ ($p = 0.04$), positive ($p < 0.0001$) and negative symptom cluster ($p < 0.0001$) and global functioning (GAF) ($p < 0.0001$) (Table 2).

In the larger cohort there were no significant differences with respect to gender ($p = 0.14$), handedness ($p = 0.68$) and IQ ($p = 0.08$). There were significant between-group differences in age ($p = 0.03$), education ($p = 0.0002$), positive ($p < 0.0001$) and negative symptom cluster ($p < 0.0001$) and global functioning (GAF) ($p < 0.0001$) and site ($p < 0.0001$) (Table 1). Among the high-risk individuals no significant correlation was detected between any of the significant subcortical volumes and psychopathological measures.

Table 1, Table 2 here

Subcortical volume differences

Significant group effects were detected for the volumes of the hippocampus ($F = 11.13$, $p = 0.001$, Table 3 and $g = -0.68$, $se = 0.22$, $Z = -3.11$ $p = 0.002$, 95%CI = [-0.25 – -1.12]) and the thalamus ($F = 7.74$, $p = 0.0066$, Table 3 and $g = -0.67$, $se = 0.22$, $Z = -3.04$, $p = 0.002$, 95%CI = [-0.23 – -1.1]). High-risk individuals showed significant smaller volumes compared to HC. These results are multiple comparison corrected by passing the conservative Bonferroni-corrected threshold of $p < 0.0071$

(two-tailed). Moreover, there were significant effects of gender on hippocampal volumes. In addition, we performed a meta-analysis of the regions with significant group differences (i.e. hippocampus and thalamus) within a larger cohort (n=158; including the above individuals). These meta-analyses showed again smaller volumes for CHR compared to HC for both regions (Hippocampus: g = -0.52, se = 0.18, Z = -2.89, p = 0.004, 95%CI = [-0.88 – -0.17], Q(df = 2) = 0.23, p = 0.89; Thalamus: g = -0.64, se = 0.18, Z = -3.49, p = 0.0005, 95%CI = [-0.99 – -0.28], Q(df = 2) = 0.10, p = 0.95, Figure 1).

Table 3, Figure 2 here

Discussion

We analysed volumetric subcortical differences between antipsychotic-naïve individuals at clinical high risk for psychosis and healthy controls. We found significant smaller volumes of the hippocampus and the thalamus in CHR individuals compared to HC. And no between-group difference was observed between the volumes of the caudate, putamen, pallidum, amygdala and accumbens. The further comparison of the significant different volumes determined by LME models with results from prospective meta-analyses within a larger cohort revealed comparable medium effect sizes for the thalamus. However, the results for the hippocampal volumes differed slightly, though both detected medium effect sizes.

In line with a recent study of subcortical volumes in schizophrenia patients and the current meta-analyses in CHR populations [2,3], we could replicate smaller hippocampal volumes for CHR individuals compared to HC. Moreover, we could increase the findings of an influence of thalamic volumes in the CHR state. Then, structural thalamic reduction were recently shown in a CHR cohort [30], as well as in schizophrenia [31] and especially in antipsychotic-naïve patients [1]. As both applied methods revealed significant differences in volume between CHR individuals and HC, we might speculate that the inclusion of 7 antipsychotic-treated individuals in the larger cohort, did not have a influential effect on these results. It was speculated that these two structures and their interconnection might be involved in a mechanism for the sudden onset of schizophrenia [32], which definitively needs further investigation.

In our analysis the different image acquisition modalities (generally higher image intensities measured in Zurich) lead to differences in the segmentation of the subcortical volumes. Therefore, we preprocessed the data for each site separately

before group-related comparison although this reduced the sample size drastically. In addition, we performed a prospective meta-analyses, as proposed by the ENIGMA consortium [9,10,33], which is an elegant way for group-related comparison from different sites. However, we must account that a meta-analysis with only three included studies is not very powerful. Nevertheless, we obtained similar results with the meta-analytic approach and the LME model.

Future research should also investigate the association of common genetic variants on subcortical brain volumes in CHR populations, as it was shown that genetic components can influence the volumes of the subcortical structures in healthy humans [34–36].

Altogether, we found smaller hippocampal and thalamic volumes in CHR individuals compared to HC individuals with two different comparison methods. These findings demonstrate that some of the subcortical volumes are already altered in the high-risk state. Moreover, we found comparable medium effect sizes for both structures assessed with both methods. This might suggest that these volumes and the interrelated neuronal network can be used as a very early marker in the prediction of psychosis.

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Table 1: Demographics and clinical characteristics for meta-analysis				
Characteristics	Ultra high risk (n=94)	Healthy controls (n=64)	Statistics	
Gender M/F (%male)	59/32 (%)	33/31 (%)	χ^2=2.22	p=0.14
Mean age in years (SD)	23.70 (5.11)	25.50 (4.76)	t=2.24	p=0.03*
Handedness r/l (%left)	84/7 (%)	57/7 (%)	χ^2=0.17	p=0.68
Years of education (SD)	12.90 (3.00)	14.89 (2.97)	t=3.87	p=0.00023
IQ (SD)	108 (15.31)	112 (14.38)	t=1.76	p=0.08
Negative cluster (SD)	6.54 (3.17)	3.00 (0)	t=-10.62	p<0.0001*
Positive cluster (SD)	9.02 (3.52)	4.00 (0)	t=-13.53	p<0.0001*
GAF (SD)	61.05 (14.83)	88.08 (4.15)	t=15.19	p<0.0001*
Scanner ZH1/ZH2/BS	16/15/60	5/35/24	χ^2=25.25	p<0.0001*
Antidepressants no/yes	59/32 (%)	64/0	χ^2=26.25	p<0.0001*
Antipsychotics no/yes	87/7	64/0	χ^2=3.53	p=0.06
Abbreviations: F: Female; l:left; M:Male; r:right				

Table 2: Demographics and clinical characteristics for linear mixed-effects model				
Characteristics	Ultra high risk (n=45)	Healthy controls (n=43)	Statistics	
Gender M/F (%male)	29/16 (64%)	21/22 (51%)	χ^2=1.59	p=0.20
Mean age in years (SD)	23.55 (5.28)	26.16 (4.74)	t=2.42	p=0.02*
Handedness r/l (%left)	41/4 (9%)	39/3 (7%)	χ^2=0.09	p=0.99
Years of education (SD)	12.27 (2.92)	15.31 (2.91)	t=4.71	p<0.0001*
IQ (SD)	108 (15.58)	115 (14.43)	t=2.06	p=0.04*
Negative cluster (SD)	6.86 (2.86)	3.00 (0)	t=-8.97	p<0.0001*
Positive cluster (SD)	9.07 (3.19)	4.00 (0)	t=-10.55	p<0.0001*
GAF (SD)	58.20 (11.80)	88.17 (4.22)	t=15.24	p<0.0001*
Scanner ZH1/ZH2/BS	8/11/26	5/14/24	χ^2=1.09	p=0.58
Antidepressants no/yes	30/15 (33%)	43/0	χ^2=15.00	p=0.0001*
Abbreviations: F: Female; l:left; M:Male; r:right				

Table 3: Results of linear mixed-model analysis

Variable (nd.f., dd.f)	Hippocampus		Thalamus		Caudate		Putamen		Pallidum		Amygdala		Accumbens	
	F	p-value	F	p-value	F	p-value	F	p-value	F	p-value	F	p-value	F	p-value
Diagnosis (1, 186)	11.13	0.001*	7.74	0.0066*	4.96	0.03*	4.00	0.05	3.79	0.05	0.07	0.79	4.76	0.03*
Hemisphere (1, 186)	0.33	0.57	0.04	0.84	0.02	0.89	0.12	0.73	0.01	0.92	0.13	0.72	0.32	0.57
Site (2, 186)	0.39	0.68	0.62	0.54	2.52	0.09	0.40	0.67	0.12	0.88	0.38	0.68	0.23	0.80
Diagnosis x Hemisphere (1, 186)	0.76	0.38	0.00	0.95	0.00	0.97	0.06	0.81	1.88	0.17	0.37	0.54	4.89	0.03
Diagnosis x Site (2, 186)	1.46	0.24	0.04	0.96	2.04	0.14	3.88	0.02*	0.37	0.69	2.06	0.13	0.48	0.62
Diagnosis x Site x Hemisphere (2, 186)	0.82	0.45	1.52	0.22	4.05	0.02	3.86	0.02	2.31	0.11	0.05	0.95	1.36	0.26
Sex (1, 186)	11.58	0.001*	0.02	0.89	2.35	0.13	0.73	0.39	0.15	0.70	1.38	0.24	0.13	0.72
Age (1, 186)	1.62	0.21	0.28	0.60	11.71	0.001*	3.07	0.08	0.79	0.38	1.63	0.21	0.90	0.35
Comparison to null-model (χ^2 and p)	14.01	0.03*	12.96	0.04*	14.69	0.02*	18.65	0.005*	9.23	0.16	5.57	0.47	9.82	0.13

Abbreviations: nd.f.: Nominator degrees of freedom; dd.f.: Denominator degrees of freedom; corrected for multiple-comparison

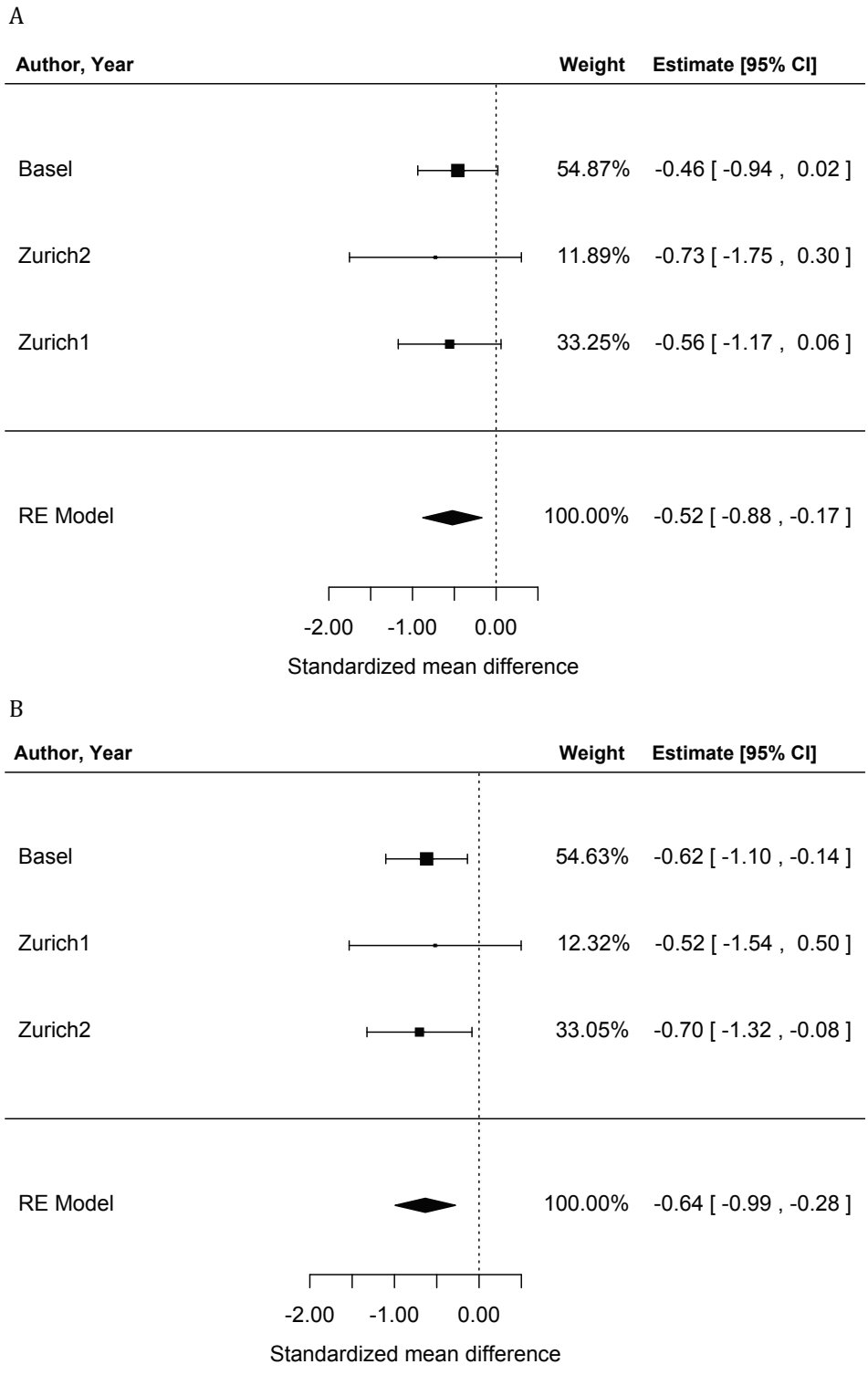

Figure 1: Forest plot of prospective, random effects meta-analyses investigating the difference between: A. hippocampal volumes and group affiliation rs6265 of all studies. B. thalamic volumes and group affiliation. Negative values represent smaller volumes for CHR compared to HC.

3.4 Impact of polygenic schizophrenia-related risk and hippocampal volumes on the onset of psychosis

By

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Submitted

Impact of polygenic schizophrenia-related risk and hippocampal volumes on the onset of psychosis

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Word count of main body: 2995 words

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Conflict of interest disclosure:
The authors declare no potential conflict of interest.

Abstract

Importance

Alterations in hippocampal volume are a known marker for first-episode psychosis as well as for the clinical high-risk states. The polygenic schizophrenia-related risk score, derived from a large case-control study, indicates the polygenic predisposition for schizophrenia in our clinical sample.

Objectives

To investigate whether the association between hippocampal volumes and the onset of psychosis is modulated by a polygenic schizophrenia-related risk score.

Design

Linear and logistic regression of the polygenic schizophrenia-related risk score and hippocampal volume data in individuals with an at-risk mental state for psychosis and first-episode psychosis patients.

Setting

Participants were recruited through the specialised service for the early detection of psychosis at the Department of Psychiatry, University of Basel, Basel, Switzerland.

Participants

Thirty-eight individuals with an at-risk mental state (mean [SD] age, 23.83 [4.31] years) and twenty-seven first-episode psychosis patients (mean [SD] age, 28.33 [7.91] years).

Main Outcome and Measures

Automatic segmentation of hippocampal volumes derived from T_1-weighted magnetic resonance images, using FSL software and an odds-ratio weighted

polygenic schizophrenia-related risk score, based on the publicly available top single nucleotide polymorphisms from the Psychiatric Genomics Consortium GWAS.

Results

We observed a negative association between the polygenic schizophrenia-related risk score and hippocampal volumes ($R^2 = 0.11$, $p = 0.01$, 95%CI = [-0.54 – -0.10]) across first-episode psychosis patients and at-risk mental state individuals. Moreover, a higher polygenic schizophrenia-related risk score was significantly associated with a higher probability of an individual being assigned to the first-episode psychosis group relative to the at-risk mental state group ($\beta = 0.64$, $p = 0.03$, 95%CI = [0.08 – 1.29]).

Conclusion and Relevance

A subset of schizophrenia risk variants is negatively associated with hippocampal volumes and higher values of this polygenic schizophrenia-related risk score are significantly associated with first-episode psychosis compared to the at-risk mental state. These findings imply that FEP patients have a higher genetic risk for schizophrenia than the total cohort of ARMS individuals. The identification of associations between genetic risk variants and structural brain alterations will increase our understanding of the neurobiology underlying the transition to psychosis.

Keywords: Hippocampus, Hippocampal Volumes, Structural, MRI, At-Risk Mental State, Ultra-high risk, First-Episode Psychosis, Psychosis, Schizophrenia

Schizophrenia can be a severe mental disorder, affecting around one percent of the population [1]. Although the pathophysiological mechanisms underlying schizophrenia are still poorly understood, it is known that genetic factors and combinations thereof (i.e. single nucleotide polymorphisms, copy-number variations or mutations) are involved in disease aetiology, as is indicated by the substantial heritability estimates for schizophrenia [2]. And whether an individual will make the transition to psychosis from the clinical high-risk state also presumably depends on the presence of different environmental trigger-factors. Around 30% of clinical at-risk mental state (ARMS) individuals will make a transition to psychosis within the subsequent two years [3–5]. Finding markers that further characterise these ARMS individuals is a main goal of psychiatric research, as early treatment of this group is thought to prevent or delay the onset of a first episode of psychosis [6,7]. Several markers besides clinical characteristics describe prodromal psychosis, for example, structural and functional brain alterations or cognitive functioning. Even in the ARMS, neuroimaging observations revealed reductions in the grey matter of the medial temporal lobe, including the hippocampus [8–12], as well as neurofunctional aberrations within the hippocampus [13] and deficits in verbal fluency and memory functioning [14]. However, results are inconsistent on the differences in hippocampal volume between first-episode of psychosis (FEP) patients and ARMS individuals, regardless of future transition to psychosis [8,9,15]. Moreover, hippocampal volumes were shown to be highly heritable in twin studies of healthy individuals [16,17], but twin studies where one of the twins was affected by schizophrenia also revealed substantial modulation of hippocampal volumes by environmental factors [18–21]. In addition, moderate genetic

heritability of the hippocampal volumes was shown in large extended families affected with schizophrenia [22].

Although individual effects of single nucleotide polymorphisms (SNPs) on the genetic risk for schizophrenia were found to be small, it was estimated that 23% of variation in liability to schizophrenia is captured by SNPs with a substantial proportion of this variation attributed to common causal variants [23,24]. The largest genome-wide association study (GWAS), performed by the Psychiatric Genomic Consortium (PGC), identified 108 schizophrenia-associated loci [25], which explained up to 3.4% of the phenotypic variance in case-control studies. In general, the combination of GWAS-significant risk SNPs, the polygenic schizophrenia-related risk score (PSRS), describes the estimated cumulative genomic risk for schizophrenia.

Only a few studies have reported associations between a PSRS and brain volumes. All of these studies investigated the above mentioned association in different cohorts of schizophrenia patients, their relatives and/or healthy controls [26–28]. They found association of a PSRS with total brain volume [26], especially with white matter volume [26,27]. Unfortunately, these results could not be replicated in another independent sample [28]. However, none of these studies investigated the association of a PSRS with brain volume in ARMS individuals and FEP patients. Moreover, a GWAS identified single SNPs linked to hippocampal volume in healthy controls [16], but no study to date has investigated the association of a PSRS with volumetric differences in this region.

On the basis of findings supporting a role for hippocampal alterations in FEP and even in the ARMS [8–12], we aimed to explore the association between the PSRS,

hippocampal volume and the onset of psychosis. The identification of associations between genetic risk variants and structural alterations will increase our understanding of the neurobiology underlying psychosis, as well as the transition to psychosis. Linking the PSRS to structural alterations in the brain will be helpful in elucidating the neurobiology underlying psychosis and may also increase our understanding of the factors contributing to the transition to psychosis in ARMS individuals. We hypothesised that a higher PSRS is associated with both smaller hippocampal volumes and the probability of being FEP.

Methods

Participants and clinical assessment

Individuals included in this study were recruited via the early detection of psychosis research program at the Psychiatry Outpatient Department, Psychiatric University Clinics Basel [5,29] and were either ARMS individuals or FEP patients. All individuals were assessed by the Basel Screening Instrument for Psychosis (BSIP) [30], the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Negative Symptoms (SANS) and the Global Assessment of Functioning (GAF), at the time of the MRI scan. We additionally obtained information on current and previous psychotropic medication, nicotine, and illegal drug consumption using a semi-structured interview adapted from the Early Psychosis Prevention and Intervention Centre Drug and Alcohol Assessment Schedule (eppic.org.au).

ARMS was defined in accordance with the criteria by Yung and resulted in the inclusion of N = 43 ARMS individuals in the study [31]. Thus, inclusion required one or more of the following: (a) ‘‘attenuated’’ psychotic symptoms, (b) brief limited intermittent psychotic symptoms, or (c) a first- or second-degree relative with a psychotic disorder plus at least two indicators of a clinical change, according to the BSIP [29,32]. Inclusion because of criterion (a) required a change in mental state at least several times a week and for more than 1 week (a score of 2 or 3 on the BPRS hallucination item or 3 or 4 on BPRS items for unusual thought content or suspiciousness). Inclusion due to (b) required BPRS scores of ≥ 4 on the hallucination item or ≥ 5 on the unusual thought content, suspiciousness, or conceptual

disorganisation items, with each symptom lasting less than 1 week before resolving spontaneously. None of the included subjects fulfilled criterion (c). All individuals were antipsychotic-naïve at the time of scanning whereas 18 of the ARMS individuals were receiving antidepressants.

The FEP patients (N = 36) met the operational criteria according to Breitborde et al. [33] and they fulfilled criteria for acute psychotic disorder according to *ICD-10* or *DSM-V* but not for schizophrenia. Inclusion required scores of ≥ 4 on the hallucination item or ≥ 5 on the unusual thought content, suspiciousness or conceptual disorganisation items of the BPRS. The symptoms had to have occurred at least several times a week and persisted for more than 1 week. 14 of our FEP patients were antipsychotic-naïve, 3 were antipsychotic-free and 10 were receiving antipsychotic medication at the time of scanning (three quetiapine, three risperidone, two olanzapine, one clozapine, one aripiprazole). In the antipsychotic-free group antipsychotic medication (two risperidone, one aripiprazole) has been stopped 4, 19 and 24 months previously. Antipsychotic dose was converted into chlorpromazine (CPZ) equivalents using the supplementary table 'Antipsychotic dose conversion' by Ho et al. [34]. The mean chlorpromazine equivalents (standard deviation) were 227.39 (202.90). Of all FEP patients, 3 received only antidepressants alone and 4 were on a combined treatment with antidepressants and antipsychotics.

The following exclusion criteria were applied for both groups: history of previous psychotic disorder, psychotic symptomatology secondary to an 'organic' disorder, psychotic symptoms associated with an affective psychosis or a borderline personality disorder, substance abuse according to *International Statistical*

Classification of Diseases, 10th Revision (ICD-10) research criteria, head trauma, neurological illness, serious medical or surgical illness, being younger than 18 years, inadequate knowledge of the German language, and IQ less than 70 as measured by the Mehrfachwahl Wortschatz [Multiple Choice Vocabulary] Test Form B (MWT-B). All participants provided written informed consent, and the studies had permission from the ethics committee.

MRI acquisition

All anatomical scans were performed on a 3T magnetic resonance imaging (MRI) scanner (Siemens Magnetom Verio, Siemens Healthcare, Erlangen, Germany) using a 12-channel phased-array radio frequency head coil. For structural images, a 3D T_1-weighted magnetisation prepared rapid gradient echo (MPRAGE) sequence was used with the following parameters: an inversion time of 1,000 ms, flip angle = 8 degrees, TR = 2 s, TE = 3.37 ms, FOV = 25.6 cm, acquisition matrix = 256 x 256 x 176, resulting in 176 contiguous sagittal slices with 1x1x1 mm^3 isotropic spatial resolution. All scans were screened for gross radiological abnormalities by an experienced neuroradiologist.

Genotyping and Imputation

DNA was extracted from whole blood samples using the QIAamp® DNA Blood Maxi kit according to standard procedures (Qiagen Inc., Chatsworth, CA). DNA samples were further processed on the Affymetrix® Genome-Wide Human SNP Array 6.0. in one centralised microarray facility as described in the Genome-Wide Human SNP

Nsp/Sty 6.0. User Guide (Affymetrix, Santa Clara, CA, USA). 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, leading to a total of 921 523 genotyped SNPs per sample. Appropriate SNP QC filtering was applied in PLINK 1.9 software [35,36], where the gender check in PLINK led to the exclusion of 3 individuals.

Population stratification was assessed using principal component analysis implemented in the EIGENSTRAT software [37] to detect genotypic outliers (with default parameters: >6 standard deviations on any of the top ten principal components (PC) in five iterations) and correct for potential population substructure by analysing all array-based pruned, autosomal SNPs. Eight individuals were identified as outliers and therefore excluded from further analyses.

Imputation was performed with IMPUTE2 [38], which aligns SNPs between haplotype and genotype databases on the basis of base-pair position, using the 1000 Genomes Project (www.1000genomes.org) as reference panel. Inclusion and subsequent analysis of an imputed SNP was set to proper info > 0.9.

PSRS calculation

PSRS were calculated, following the suggestions by Wray et al. [39], by taking LD pruned loci identified by the Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC) in a GWAS of 36 989 schizophrenia patients and 113

075 healthy controls [25] (http://www.med. unc.edu/pgc/downloads). A total of 87 SNPs that could be mapped to one of the top SNPs of the 108 loci associated with schizophrenia and survived quality control was used to calculate the PSRS. (Included: 18 SNPs represented on the Affymetrix 6.0 Genotyping Array and 69 imputed SNPs. Excluded: 7 SNPs could not be imputed, 3 SNPs on allosome, 11 Insertion/Deletion variants, 20 variants in physically dependent genomic regions.) In summary, the number of risk alleles per person was weighted for each SNP by the logarithm of its odds ratio as reported in the PGC SZ dataset [25] and summed across SNPs [40] using the PLINK 1.9 software [35,36]. The PSRS was then corrected for the first twenty genotypic PCs and the number of SNPs used to calculate the PSRS by using the z-transformed residuals of a linear regression.

Image processing

Subcortical structures were segmented from T_1-weighted MPRAGE images with FMRIB 's Integrated Registration and Segmentation Tool 5.0.4. (FSL-FIRST) [41]. Raw volumes for the left and right hippocampus were extracted and separately corrected for intracranial volume (ICV), age, gender antidepressant intake and CPZ equivalents by using the z-transformed residuals of a linear regression. After a separate outlier control for both hippocampal sides (mean ± 3.5 SD), which resulting in the exclusion of 3 individuals, the mean hippocampal volume was calculated.

Statistical Analysis

The R 3.0.2 software [42] with the packages stats was used for statistical, group-related analysis. Chi-square tests or t-tests were used to test the distribution between diagnosis group and age, sex, handedness, years of education, IQ, BPRS, SANS, GAF, antipsychotics, antidepressants, cannabis consumption and smoking. Values are presented as mean ± SD (see table 1). In addition, associations between clinical symptoms and PSRS or hippocampal volumes were examined with Pearson correlation. The relationship between PSRS (corrected for the first twenty genotypic PCs and the number of SNPs used to calculate the PSRS) and the bilateral hippocampal volumes (corrected for ICV, age, gender antidepressant intake and CPZ equivalents) was assessed by Pearson's correlation. We then fitted a logistic regression using the generalised linear model function in R with diagnosis status as binary dependent variable and the corrected bilateral hippocampal volumes and the corrected PSRS score as independent variables.

Results

Clinical and demographic characteristics

There were no significant differences among the investigated groups with respect to gender ($p = 0.83$), handedness ($p = 0.11$), years of education ($p = 0.96$) MWT-B ($p = 0.74$), SANS ($p = 0.27$) and number of individuals treated with antidepressants ($p = 0.14$). There were significant between-group differences in age ($p = 0.01$), BPRS ($p = 0.001$), GAF ($p = 0.009$) and the number of patients treated with antipsychotics ($p < 0.001$) (Table 1). None of the clinical characteristics was associated with the PSRS or the hippocampal volumes at the time of MR scanning.

Table 1 here

Association between diagnosis, PSRS and hippocampal volume

Pearson's correlation analysis revealed a significant relationship between the PSRS and hippocampal volumes ($R^2 = 0.11$, $p = 0.01$, 95%CI = [-0.54 – -0.10]) in our total sample and the subgroup of ARMS individuals ($R^2 = 0.14$, $p = 0.02$, 95%CI = [-0.62 – -0.06], Figure 1) and FEP patients separately ($R^2 = 0.14$, $p = 0.05$, 95%CI = [-0.66 – 0.005], Figure 1). To further analyse this association in the total sample, we performed a logistic regression analysis. A significant main effect of the PSRS on the log odds of an individual being assigned to the FEP state was observed ($\beta = 0.64$, $p = 0.03$, 95%CI = [0.08 – 1.29], Table2, Figure 2). In addition, neither a main effect of the hippocampal volumes ($\beta = 0.59$, $p = 0.11$, 95%CI = [-0.11 – 1.36], Table2) nor an interaction effect of PSRS and hippocampal volumes ($\beta = -0.14$, $p = 0.70$, 95%CI = [-0.88 – 0.60], Table2) on the log odds was detected. Therefore, a higher PSRS score is

associated with a higher likelihood that an individual would be assigned to the group of FEP individuals than to the group of ARMS individuals.

Figure 1, Figure 2 and Table 2 here

Discussion

To our knowledge, this is the first study to analyse the association between a polygenic schizophrenia-related risk score, hippocampal volumes and the onset of psychosis. We found a negative association between the hippocampal volumes and the PSRS across ARMS individuals and FEP patients, derived from the top hits within genome-wide significant loci identified by the large GWAS analysis from the Psychiatric Genomics Consortium [25]. Moreover, a higher PSRS was significantly associated with a higher probability of being assigned to the FEP group than to the ARMS group.

We demonstrate that reduced hippocampal volumes were associated with higher PSRS in the total sample of ARMS individuals and FEP patients as well as for each group separately. This association might suggest that schizophrenia-related SNPs are directly linked to smaller hippocampi. However, such a direct link cannot be inferred from our results, because other factors like stressful life events [43] or neuropsychiatric medication [44,45] have been shown to modulate the volumes of the hippocampus. It should be further noted that volumetric alterations in the hippocampus have been linked to psychotic symptoms and cognitive deficits of schizophrenia [46], a core function of the hippocampus, and ARMS individuals already show some deficits in verbal fluency and memory functioning [5,14].

We also observed that a higher PSRS was associated with a higher likelihood of an individual being assigned to the FEP group than to the ARMS group. This finding might reflect the fact that only around 30% of ARMS individuals are correctly predicted to develop psychosis [4,5] and thus might not have a high PSRS. Therefore, further studies should analyse whether the PSRS could be used to further characterise

those ARMS individuals who will develop psychosis and whether ARMS individuals with a higher PSRS are more likely to develop psychosis. Due to the limited number of ARMS individuals with later transition to psychosis, we could not investigate whether this PSRS might be a vulnerability trait for transition. Nevertheless, we observed that four of our six ARMS individuals who (until now) have developed psychosis had a PSRS above the median of the total sample. Therefore, further longitudinal studies should examine whether a combination of clinical, genetic, environmental, neuroimaging and neurocognitive markers can improve the prediction rate for transition to psychosis.

The absence of a significant association between hippocampal volumes and being in either the ARMS or FEP groups supports several findings of similar volumes [8,9,15]. Furthermore, it has been reported that the volumes of the hippocampus were negatively associated with negative symptoms in ARMS individuals and schizophrenia patients [47–50] and that the hippocampal-prefrontal pathway was linked to negative symptoms and cognitive deficits in schizophrenia [51]. Therefore, it might be speculated that the similar levels of negative symptoms in FEP patients and ARMS individuals might partially underlie the absence of volumetric hippocampal differences. However, future functional and structural connectivity studies should further examine the hippocampus and the interrelated cortical and subcortical regions, including the dorsolateral prefrontal cortex, to assess possible impairments in neuronal networks in schizophrenia.

There are some limitations to bear in mind concerning the results of this study. First, the sample size is relatively small. However, the groups are homogeneous with regard to genetic background and clinical characteristics related to disease status and

prognosis [52]. This makes confounding effects of disease duration or antipsychotic medication unlikely. In addition, polygenic risk scores derived from large GWAS generate robust estimators [53] which can be used in small samples. Second, the PSRS explains only a small amount of variance in liability to schizophrenia and cannot be considered as a classifier between ARMS individuals and FEP patients. Thus, prediction of actual transition to psychosis is not possible, but this aspect will be further investigated when we have obtained enough follow-up data.

In summary, this is the first study to evaluate a negative association between a PSRS and hippocampal volumes in ARMS individuals and FEP patients. Our findings suggest that the combination of a subset of schizophrenia risk variants is related to hippocampal volume and that higher values of this genome-wide significant PSRS (but not hippocampal volume or the interaction effect) are associated to FEP status than to the ARMS. These findings imply that FEP patients have a higher genetic risk for schizophrenia than the total cohort of ARMS individuals and encourage further studies on the use of RSPS as an additional marker in the prediction of psychosis from the prodromal state.

Acknowledgments

We thank out radiographer, Tanja Haas, from Basel University Hospital for performing the magnetic resonance measurements and the FePsy (Frueherkennung von Psychosen) Study Group for the recruitment and management of the study participants. Finally, we thank all participants for taking part in our study.

Fabienne Harrisberger had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Acquisition, analysis or interpretation of data: Harrisberger, Smieskowa, Vogler, Egli, Simon, Riecher-Rössler, Borgwardt.

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Study supervision: Papassotiropoulos, Riecher-Rössler and Borgwardt.

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Table 1: Demographics and clinical characteristics

Characteristics	ARMS (n=38)	FEP (n=27)	Statistics	
Gender M/F (%M)	26/12 (32%)	20/7 (26%)	χ^2=0.05	p=0.83
Mean age in years (SD)	23.83 (4.31)	28.33 (7.91)	t=-2.68	p=0.01*
Handedness r/l (%l)	35/3 (8%)	20/7 (26%)	χ^2=2.68	p=0.11
Years of education (SD)	13.72 (2.59)	13.76 (3.15)	t=-0.05	p=0.96
MWT-B (SD)	110.73 (13.85)	109.23 (17.88)	t=0.33	p=0.74
BPRS (SD)	37.16 (7.28)	50.33(15.49)	t=-3.90	p=0.001*
SANS (SD)	19.55 (15.31)	24.14 (15.15)	t=-1.13	p=0.27
GAF (SD)	70.11 (12.35)	59.59 (17.07)	t=2.73	p=0.009*
AP n/y (%y)	38/0 (0%)	17/10 (37%)	χ^2=13.91	p<0.001*
AD n/y (%y)	20/18 (47%)	20/7 (26%)	χ^2=2.23	p=0.14

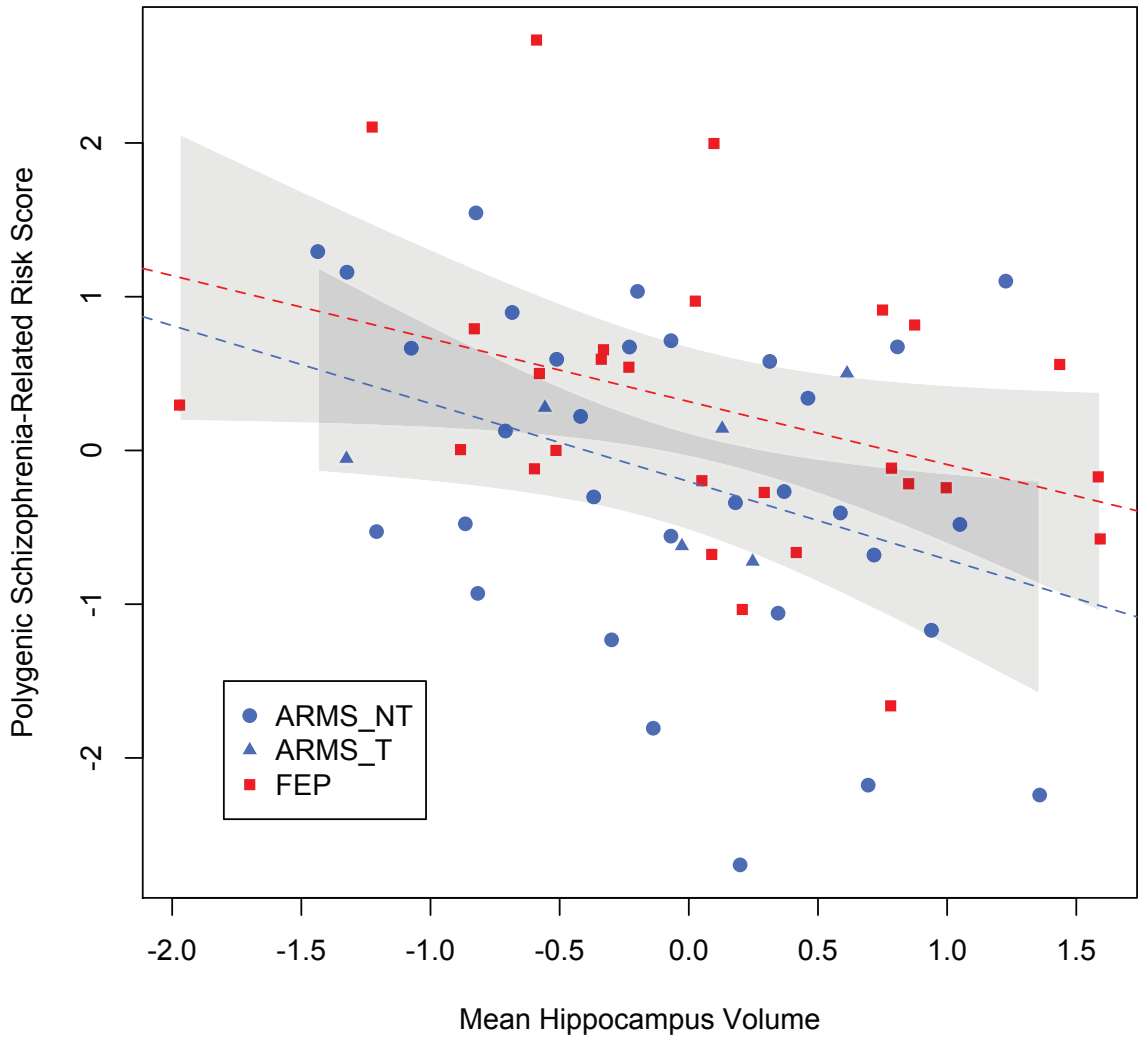
Abbreviations: AD: Antidepressants; AP: Antipsychotics; ARMS: At-risk Mental State Individuals; BPRS: Brief Psychiatric Rating Scale; Cig: Cigarettes; F: Female; FEP: First-Episode Psychosis Patients; GAF: Global Assessment of Functioning; M: Male; MWT-B: Mehrfachwahl Wortschatz Test [Multiple Choice Vocabulary] Form B; SANS: Scale for the Assessment of Negative Symptoms; SD: Standard Deviation;

Table 2: Results of Pearson correlation and logistic regression analyses

Pearson correlation: ARMS and FEP						
Variable	R^2	r	t-value	p-value	95% CI lower	95% CI upper
ARMS and FEP	0.11	-0.34	-2.82	0.01	-0.54	-0.10
ARMS only	0.14	-0.37	-2.39	0.02	-0.62	-0.06
FEP only	0.14	-0.38	-2.03	0.05	-0.66	0.005
Logistic regression: ARMS and FEP						
Variable	Coefficients	Standard Error	Z-value	p-value	95% CI lower	95% CI upper
PSRS	0.64	0.30	2.11	0.03	0.08	1.29
Hippocampal volumes	0.59	0.37	1.60	0.11	-0.11	1.36
PSRS x Hippocampal volumes	-0.14	0.37	-0.39	0.70	-0.88	0.60
Intercept	-0.43	0.29	-1.48	0.14	-1.01	0.13
Nagelkerke-R^2=0.1; *c*-statistic: 64.4%; Comparison to null-model: $\chi^2 = 5.88$ p = 0.12						

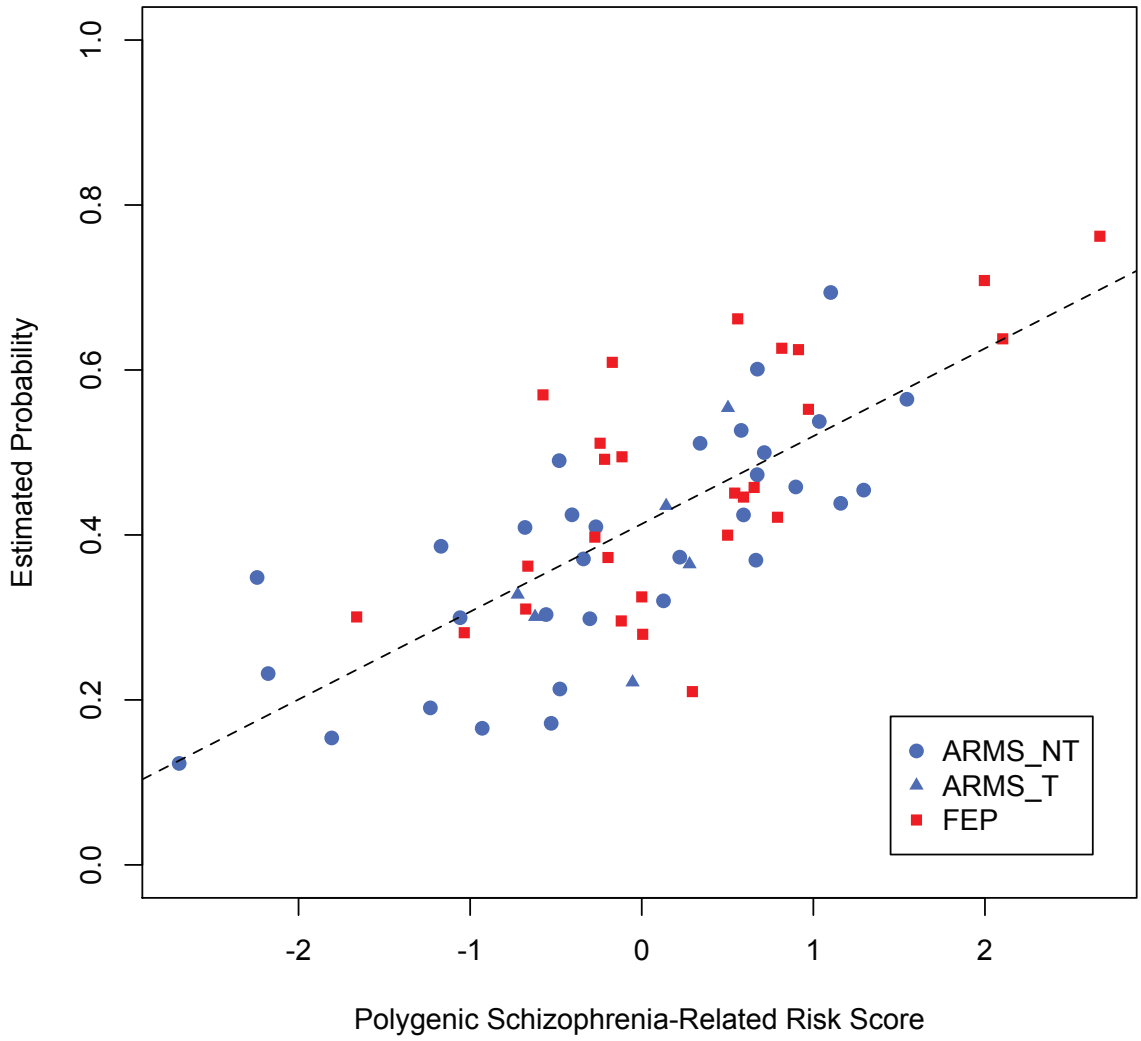
Abbreviations: ARMS: At-Risk Mental State; CI: Confidence Interval; FEP: First-Episode Psychosis; PSRS: Polygenic Schizophrenia-Related Risk Score;

Figure 1. Linear Regression Analyses of Polygenic Schizophrenia-Related Risk Score and Hippocampal Volumes



Standardised residuals of the mean hippocampal volume are adjusted on each side separately for ICV, age, gender antidepressant intake and CPZ equivalents. Standardised residuals of the PSRS are adjusted for the first twenty genotypic PCs and the number of SNPs used to calculate the PSRS. Red dotted line: Regression line with 95% confidence interval of FEP cohort; Blue dotted line: Regression line with 95% confidence interval of ARMS cohort.
ARMS_NT: At-risk mental state individuals without transition to psychosis, ARMS_T: At-risk mental state individuals with subsequent transition to psychosis; CPZ: Chlorpromazine; FEP: First-episode psychosis patients; ICV: Intra-cranial volume; PCs: Principal components.

Figure 2. Plot of Estimated Probability for being FEP versus Polygenic Schizophrenia-Related Risk Score



The standardised residuals of the PSRS are adjusted for the first twenty genotypic PCs and the number of SNPs used to calculate the PSRS are plotted against estimated probability of logistic regression. Black dotted line: Regression line of FEP and ARMS cohort;
ARMS_NT: At-risk mental state individuals without transition to psychosis, ARMS_T: At-risk mental state individuals with subsequent transition to psychosis; FEP: First-episode psychosis patients; PCs: Principal components.

4 Summary

4.1 Discusssion

I investigated throughout this thesis the role of the hippocampal volumes in the developing disorder, especially for FEP patients and ARMS individuals and selected genetic risk markers associated with schizophrenia. Specifically, we analyzed in chapter 3.1 the relation of the BDNF rs6265 polymorphism to the volumes of the hippocampus in healthy individuals, in original data and by meta-analysis to obtain a basis for the potential association. We further examined by meta-analysis whether this association is present in neuropsychiatric patients in chapter 3.2. Moreover, the volumetric subcortical alterations including the hippocampus in ARMS individuals compared to HC were determined in chapter 3.3. And last, the association between a PSRS and the hippocampus in a cohort of ARMS individuals and FEP patients was assessed in chapter 3.4.

Our findings do not support the association between the BDNF rs6265 polymorphism and hippocampal volumes neither in original data of HC, the meta-analysis with HC nor in the meta-analysis with neuropsychiatric patients. In detail, the meta-analysis with HC showed a weak effect that was mainly powered by early studies using manual hippocampal segmentation in combination with small sample sizes. In contrast, the meta-analysis with automated segmentation of the hippocampus revealed no association. Therefore, not only publication year and sample size can influence meta-analytic results but also measuring techniques need to be taken into account. The meta-analysis with neuropsychiatric patients also showed no association between the BDNF rs6265 polymorphism and hippocampal volumes. Moreover, we could replicate smaller hippocampal volume findings for neuropsychiatric patients compared to HC and this reduction is comparable for Val/Val homozygote or Met-carriers, meaning that neither Val or Met is a risk or a protective allele for volumetric hippocampal alterations in neuropsychiatric disorders.

Next, the subcortical volume analysis demonstrated smaller hippocampal and thalamic volumes for ARMS individuals compared to HCs. Moreover, we found comparable medium effect sizes for group-related comparison of the hippocampus and the thalamus using two different methods.

Finally, we could show that a PSRS of GWAS-significant, schizophrenia-associated SNPs was negatively associated with hippocampal volume in ARMS and FEP patients and a higher PSRS was associated with a higher likelihood of an individual being assigned to the group of FEP patients compared to the total ARMS group.

We found further evidence for the role of the hippocampus in health and disease, especially in ARMS individuals and FEP patients. First of all, we could replicate the findings of smaller hippocampal volumes in a cohort of ARMS individuals compared to HC in chapter 3.3. And by meta-analysis we demonstrated smaller hippocampal volumes for neuropsychiatric patients, including schizophrenia in chapter 3.2. These results are in line with many studies of reduced hippocampal volumes in schizophrenia, FEP and the ARMS compared to HC (e.g. meta-analyses by (Adriano et al., 2012; Fusar-Poli et al., 2012c; Haijma et al., 2013; Shepherd et al., 2012; Steen et al., 2006; Vita et al., 2006; Wright et al., 2000)). In contrast, we found no difference in hippocampal volumes between FEP patients and ARMS individual in chapter 3.4. A result that further lines up to the inconsistent literature of hippocampal volumetric differences between FEP patietns and ARMS individuals (Fusar-Poli et al., 2014, 2012c; Smieskova et al., 2010), implying more replication studies. These findings make the hippocampus an excellent marker for schizophrenia, FEP and the ARMS, but maybe not for the transition to psychosis.

Moreover, we further investigated the hippocampus volume in association with genetic variants related to the susceptibility for schizophrenia. Our findings in chapter 3.1 and chapter 3.2 suggest no direct association of BDNF rs6265 polymorphism and hippocampal volumes. This shows the importance and the power of meta-analytic procedures. And also a preliminary analysis with our ARMS and FEP cohort showed no significant association between the BDNF rs6265 polymorphism and hippocampal volumes (results not shown; p=0.08, p=0.16, respectively). However, most gene-environment interaction studies indicate smaller hippocampal volumes for Met-carriers with stressful life events (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., 2012; Rabl et al., 2014). And in addition this BDNF SNP might modulate hippocampal activation during memory paradigms (Cerasa et al., 2010; Dennis et al., 2011; Egan et al., 2003; Hariri et al., 2003; Hashimoto et al., 2008; Kambeitz et al., 2012; Molendijk et al., 2012). Therefore, the role of BDNF in schizophrenia should be further investigated. And in chapter 3.4 we showed for the first time an association of the hippocampal volumes with a PSRS in our cohort of ARMS individuals and FEP patients. Highly speculative, a higher PSRS and lower hippocampal volumes might be associated with severe cognitive impairment, thus worse outcome. In addition, higher values of the PSRS were associated with a higher probability of an individual being assigned to the group of FEP patients compared to the group of ARMS individuals. These findings might suggest that FEP patients have a higher genetic risk for schizophrenia than ARMS individuals, which might reflect the fact,

that only around 30% ARMS individuals are correctly predicted to develop psychosis (Fusar-Poli et al., 2012a; Riecher-Rössler et al., 2009). This encourages the use of the RSPS as an additional marker in the prediction of psychosis from the prodromal state.

4.2 Limitations

Several limitations should be noted along this thesis. All publications from chapter 3.1 to 3.4 measured brain volume changes using neuroimaging methods. Thus, no direct pathophysiological impact, like defects in synaptic transmission or neuronal cell loss, can be inferred. Moreover, the number of participants in the original publications is relatively small. This might result in limited power of the studies and generalizability of the findings. However, the studied group are homogeneous with regard to genetic background and clinical characteristics related to disease status. This makes confounding effects of disease duration or antipsychotic medication unlikely. Next, this PSRS was calculated with most of the 108 schizophrenia-associated SNPs identified by the PGC (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Nevertheless, it is not given that these are the affected genes nor that these SNPs might be the causative SNPs, as the identified association is only directing to the involved loci. Furthermore, the PSRS explains only a small amount of variance in susceptibility to schizophrenia and cannot be considered as a classifier between ARMS individuals and FEP patients. Thus, prediction of actual transition to psychosis is not possible, but this aspect will be further investigated when we have obtained enough follow-up data. In general, the majority of susceptibility to schizophrenia cannot be explained by common genetic variants. Therefore, it is more likely that gene-gene interactions (Mackay, 2014) and corresponding altered biochemical pathways and epigenetic factors (Dempster et al., 2013) might account for the missing heritability. And besides genetic predisposition, neuropsychiatric medication and environmental factors such as stressful life events can modulate gene pathways and neuronal networks.

4.3 Conclusion

Overall, we could show the absence of an association between the volumes of the hippocampus and the BDNF rs6265 polymorphism in HC and in neuropsychiatric patients in chapter 3.1 and chapter 3.2. Moreover, we could replicate the findings of volumetric hippocampal reduction in ARMS individuals compared to HC in chapter 3.3. And for the first time, we could demonstrate a negative association between the

hippocampal volumes and a PSRS in our cohort of ARMS individuals and FEP patients. In addition, we could show that higher values of this PRSR are associated with a higher probability of an individual being assigned to the FEP group compared to the ARMS group, in chapter 3.4.
Altogether, future research should further investigate the early disease states, which might identify markers and improve the knowledge of the underlying neurobiology of psychosis and schizophrenia. And therefore, the hippocampus and its network are the brain region, which should be further investigated. Moreover, replication studies are needed and should be further validated by meta-analytic procedures.

4.4 Outlook

First, as we could show differences in hippocampal volumes in our studies, I suggest further investigation of the interrelated neuronal connections of the hippocampus, especially to the PFC, as the disconnectivity hypothesis by Friston and Frith (Friston and Frith, 1995) proposes. Furthermore, the molecular biology behind this connection should be further evaluated for a better neurobiological understanding of this disorder. Such a potential molecular pathway modulating hippocampal-PFC connectivity might involve aberrant glutamatergic neurotransmission and calcium signaling, both influencing synaptic plasticity, thus cognition (Kandel, 2012; Miyamoto, 2006; Rao and Finkbeiner, 2007). Moreover, whole genome sequencing will allow the application of genetic analysis to large samples, which will increase the identification of schizophrenia candidate variants. And growing collaborations and the formation of consortia are therefore another important factor to increase power in psychiatric research to gain new insight. Together the identification of potentially impaired genetic markers might then also allow the design of new drugs to fitted targets.
Second, a tool for investigation of the diagnostic outcome is machine learning. Supervised learning is the categorization of complex, high dimensional training data and applying the learned classification rules to new data. Several studies could show with automatic pattern classification that structural (Borgwardt et al., 2013; Koutsouleris et al., 2015, 2012, 2009) or functional (Modinos et al., 2013, 2012) neuroimaging markers can classify ARMS individuals and FEP patients from HC. Moreover, machine learning allowed the prediction of transition to psychosis with up to 88% accuracy based solely on structural neuroimaging markers (Borgwardt et al., 2013; Koutsouleris et al., 2015, 2012, 2009). In contrast, only one study used genetic markers in a machine learning approach and reported an accuracy of 68% for the

discrimination of FEP patients from HC at the individual level. However, clinical high-risk individuals could not be separated from FEP patients or HC (Pettersson-Yeo et al., 2013). We are planning to incorporate longitudinal data (demographic, clinical, cognitive, genetic and neuroimaging) into a multivariate machine learning analysis, which might increase the accuracy to separate ARMS individuals with subsequent transition to psychosis from ARMS individuals that do no transition and FEP patients that develop chronic schizophrenia from those with only one episode. This might help to identify relevant biological markers, which might then finally be used for personalised diagnostics applied in clinical psychiatric practice.

Third, this knowledge of new biomarkers can then be further used for better diagnostics across neuropsychiatric disorders. Several studies showed the high genetic similarity of shared risk alleles between neuropsychiatric disorders, especially the genetic relationship between bipolar disorder and schizophrenia (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Cross-Disorder Group of the Psychiatric Genomics Consortium et al., 2013; Ruderfer et al., 2014; Tesli et al., 2014). The high overlapping risk variants of bipolar disorder and schizophrenia in symptomatology stands in favor of the psychosis continuum model. Therefore, it may be necessary to revise psychiatric nosology. One suggestion supporting the idea of a disease continuum in psychiatry was made by the Research Domain Criteria (RDoC) (Cuthbert and Insel, 2013; Insel et al., 2010) initiative. They proposed to classify neuropsychiatric disorders according to dimensions of neurobiology and observable behaviour. In detail these are the positive and negative valence system, the cognitive system, systems for social processes and the arousal/modulatory system. But before a new diagnostic system can be considered, we need a better understanding of the neurobiology underlying neuropsychiatric disorders. For this aim, the transition of ARMS individuals to either schizophrenic or affective psychosis makes the ARMS a potentially useful candidate to study the psychosis continuum as early as possible.

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10/2006 – 06/2009	University of Basel, Basel/Switzerland Bachelor of Science in Biology Major in Molecular Biology
09/2003 – 06/2005	Studies in Physics and Astronomy at Basel University
08/1998 – 06/2003	Matura, Focus Spanish at the Gymnasium Leonhard in Basel

NATIONAL AND INTERNATIONAL CONFERENCES

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02/2014	*Bench to Bedside Symposium 2014*, University of Basel; Visited

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10/2013	*26th European College of Neuropsychopharmacology (ECNP) Congress*, Barcelona, Spain; Poster presentation: The effect of the brain-derived neurotrophic factor Val66Met polymorphism on human hippocampal volume – A meta-analysis
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MEMBERSHIP

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PUBLICATION LIST

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Basel, November 2015