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Review

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

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ABSTRACT

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

Contents

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1. Introduction

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

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

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

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

2. Material and methods

2.1. Original data of 643 healthy subjects

2.1.1. Participants

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