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BDNF Val66Met and reward-related brain function in adolescents: Role for early alcohol consumption

F. Nees [a,*], S.H. Witt [b], R. Dinu-Biringer [a,c], A. Lourdusamy [d,e], J. Tzschoppe [a], S. Vollstädt-Klein [f], S. Millenet [g], C. Bach [g], L. Poustka [g], T. Banaschewski [g], G.J. Barker [d], A.L.W. Bokde [h], U. Bromberg [i], C. Büchel [i], P.J. Conrod [d,j], J. Frank [b], V. Frouin [k], J. Gallinat [l], H. Garavan [m,n,o], P. Gowland [p], A. Heinz [l], B. Ittermann [q], K. Mann [f], J.-L. Martinot [r,s], T. Paus [t,u], Z. Pausova [v], T.W. Robbins [w], M.N. Smolka [x], M. Rietschel [b], G. Schumann [d,e], H. Flor [a], the IMAGEN consortium

[a] Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany
[b] Division of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany
[c] Department of Clinical Psychology and Psychotherapy, Ruprecht-Karls University Heidelberg, Heidelberg, Germany
[d] Institute of Psychiatry, King's College London, United Kingdom
[e] MRC Social, Genetic and Developmental Psychiatry (SGDP) Centre, London, United Kingdom
[f] Department of Addictive Behaviour and Addiction Medicine, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany
[g] Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany
[h] Institute of Neuroscience and Discipline of Psychiatry, School of Medicine, Trinity College Dublin, Dublin, Ireland
[i] NeuroImage Nord, Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Germany
[j] Department of Psychiatry, Universite de Montreal, CHU Ste Justine Hospital, Canada
[k] Neurospin, Commissariat à l'Energie Atomique et aux Energies Alternatives, Paris, France
[l] Department of Psychiatry and Psychotherapy, Campus Charité Mitte, Charité – Universitätsmedizin Berlin, Berlin, Germany
[m] Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland
[n] Department of Psychiatry, University of Vermont, USA
[o] Department of Psychology, University of Vermont, USA
[p] School of Physics and Astronomy, University of Nottingham, United Kingdom
[q] Physikalisch-Technische Bundesanstalt, Berlin, Germany
[r] INSERM CEA Unit 1000 "Imaging & Psychiatry", Institut National de la Santé et de la Recherche Médicale, University Paris Sud, Orsay, France
[s] AP-HP Department of Adolescent Psychopathology and Medicine, Maison de Solenn, University Paris Descartes, Paris, France
[t] Rotman Research Institute, University of Toronto, Toronto, Canada
[u] Montreal Neurological Institute, McGill University, QC, Canada
[v] The Hospital for Sick Children, Department of Physiology and Nutritional Sciences, University of Toronto, Toronto, Canada
[w] Behavioural and Clinical Neurosciences Institute, Department of Experimental Psychology, University of Cambridge, United Kingdom
[x] Department of Psychiatry and Psychotherapy, Neuroimaging Center, Technische Universitaet Dresden, Dresden, Germany

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ABSTRACT

Changes in reward processing have been identified as one important pathogenetic mechanism in alcohol addiction. The nonsynonymous single nucleotide polymorphism in the brain-derived neurotrophic factor (BDNF) gene (rs6265/Val66Met) modulates the central nervous system activity of neurotransmitters involved in reward processing such as serotonin, dopamine, and glutamate. It was identified as crucial for alcohol consumption in healthy adults and, in rats, specifically related to the function in the striatum, a region that is commonly involved in reward processing. However, studies in humans on the association of BDNF Val66Met and reward-related brain functions and its role for alcohol consumption, a significant predictor of later alcohol addiction, are missing. Based on an intermediate phenotype approach, we assessed the early orientation toward alcohol and alcohol consumption in 530 healthy adolescents that underwent a monetary incentive delay task during functional magnetic resonance imaging. We found a significantly lower response in the putamen to reward anticipation in adolescent Met carriers with high versus low levels of

* Corresponding author. Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, J 5, D-68159, Mannheim, Germany. Tel.: +49 621 1703 6306; fax: +49 621 1703 6305.

E-mail address: frauke.nees@zi-mannheim.de (F. Nees).

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alcohol consumption. During reward feedback, Met carriers with low putamen reactivity were significantly more likely to orient toward alcohol and to drink alcohol 2 years later. This study indicates a possible effect of BDNF Val66Met on alcohol addiction-related phenotypes in adolescence.

Introduction

The brain-derived neurotrophic factor (BDNF) is a secreted protein encoded by the BDNF gene, which acts on cortical neurons. It is involved in the survival of existing neurons, (e.g., striatal neurons), and the differentiation and growth of new neurons and synapses (Maisonpierre et al., 1990; McAllister, Katz, & Lo, 1996; Tuszynski & Gage, 1994), and affects several neurotransmitter systems such as glutamate (Carvalho, Caldeira, Santos, & Duarte, 2008), serotonin (Mössner et al., 2000), or dopamine (Guillin et al., 2001). The BDNF gene on chromosome 11p13 encodes the most abundant neurotrophin in the brain. The placement of Met over Val in the coding exon at position 66 disrupts activity-dependent BDNF secretion and leads to less efficient intracellular trafficking (Egan et al., 2003).

Alcohol addiction is a worldwide health problem with a heritability of 40–60% (Walters, 2002). Previous animal and human studies suggest that BDNF is associated with alcohol consumption (e.g., Jeanblanc, Coune, Botia, & Naassila, 2014; Jeanblanc et al., 2009). However, investigations on this association in adolescence, a risk period where alcohol consumption starts to develop to possibly problematic (ab)use (Chambers, Taylor, & Potenza, 2003), are missing. Early initiation of alcohol drinking, even at very low levels, was shown to be associated with higher risk for the development of alcohol addiction (Behrendt, Wittchen, Höfler, Lieb, & Beesdo, 2009). Studies on the effects of the BDNF gene on alcohol addiction phenotypes have provided, so far, mixed results and also have reported no association (e.g., Nedic et al., 2013). Higher risk for and earlier occurrence of post-treatment relapse was associated with the single nucleotide polymorphism BDNF Val66Met Val/Val genotype (Wojnar et al., 2009), while higher alcohol consumption per week was present in healthy Met allele carriers (Colzato, Van der Does, Kouwenhoven, Elzinga, & Hommel, 2011). On the other hand, a recent study in a large sample of alcohol-addicted patients did not find any significant association of BDNF Val66Met and alcohol addiction (Nedic et al., 2013). These studies reported effects of BDNF on the level of alcohol consumption or clinical alcohol addiction-related symptoms. A mechanism that could mediate such associations may be reward processing. It was not only shown to be associated with the development and maintenance of alcohol addiction, but also identified as critical for risky behavior in adolescence (e.g., Ernst, Pine, & Hardin, 2006). In this context, on a neural level, the striatum (dorsomedial: caudate nucleus; dorsolateral: putamen; ventral/ventromedial: nucleus accumbens) was specifically identified as an important target region (e.g., Delgado, 2007; Ena, de Kerchove d'Exaerde, & Schiffmann, 2011). While the dorsolateral striatum may be associated with the development of habitual alcohol use, the dorsomedial striatum may participate in goal-directed action control, and the ventral striatum may participate in environmental control of drinking alcohol and relapse (e.g., Balleine & O'Doherty, 2010; Chen et al., 2011). An attenuated ventral striatal response to reward anticipation was observed in alcohol-dependent individuals (Bjork, Smith, Chen, & Hommer, 2012). Moreover, sensitivity in the striatum during reward processing was shown to predict adolescents' substance use onset after 1 year (Stice, Yokum, & Burger, 2013). In one study, however, dorsal (caudate and putamen) but not ventral parts of the striatum were shown to be hyperresponsive to monetary reward, in contrast to the often-reported hyporesponsivity as a key risk factor for substance abuse (e.g., Bühler et al., 2010).

BDNF seems to directly affect those brain circuits that are commonly activated during reward processing. Increased BDNF levels within the ventral tegmental area (a region where dopaminergic cell bodies of the mesocorticolimbic dopamine system originate and project to the dorsolateral and ventromedial striatum) induced an opiate dependent-like reward state in rats (Vargas-Perez et al., 2009). Moreover, significantly lower BDNF levels in the nucleus accumbens were found in alcohol-preferring compared to non-preferring rats (Yan, Feng, & Yan, 2005), and BDNF expression in the striatum impaired voluntary alcohol consumption in rats (Bahi & Dreyer, 2013). There was a greater increase in BDNF expression in the dorsolateral striatum than in the dorsomedial striatum, following acute ethanol intake or administration in mice (Jeanblanc et al., 2009). This indicates once more that the investigation of the relationship between the BDNF Val66Met genotype and individual differences in neural responses to reward and the role of orientation toward alcohol and alcohol consumption might be of interest to further understand mechanisms important for alcohol addiction.

Materials and methods

Participants

In the present study, we included a sample of 530 Caucasian healthy adolescents (248 female; partly overlapping with the sample from Nees et al., 2013) who were assessed twice within a period of 2 years, with a mean age of 14.33 years (SD = 0.98, range 14–15 years) at baseline and a mean age of 16.28 years (SD = 0.88, range 16–17 years) at follow-up. The sample was recruited in the European Multicenter Imaging Genetics (IMAGEN) study (Schumann et al., 2010), which included participants from Germany [Hamburg (n = 71), Mannheim (n = 84), Berlin (n = 61), Dresden (n = 42)], Ireland [Dublin (n = 63)], United Kingdom [London (n = 68), Nottingham (n = 70)] and France [Paris (n = 71)]. The study was approved by the local ethics committees and adhered to the Declaration of Helsinki. Exclusion criteria were: any mental disorder as defined by the Development and Well-Being Assessment (DAWBA; Goodman, Ford, Richards, Gatward, & Meltzer, 2000), substance-use disorder, but not drug use alone, serious medical conditions, or previous head trauma with unconsciousness and contraindications for magnetic resonance imaging (MRI) exams. Ethnicity was determined using a genetic screening interview that included information on the country of origin and ethnicity of the parents and the grandparents of the adolescents. After a complete description of the study to the participants and their legal guardians, written informed consent was obtained from both.

Assessment of patterns of alcohol consumption

We assessed the level of orientation toward alcohol and of alcohol consumption by the Alcohol Use Disorders Identification Test (AUDIT; Saunders, Aasland, Babor, de la Fuente, & Grant, 1993)