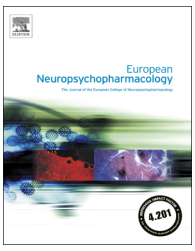
European Neuropsychopharmacology (2014) 24, 930–938



www.elsevier.com/locate/euroneuro

Impact of variation in the BDNF gene on social stress sensitivity and the buffering impact of positive emotions: Replication and extension of a gene-environment interaction

Mark van Winkel[a,h,*], Frenk Peeters[a], Ruud van Winkel[a,b], Gunter Kenis[a], Dina Collip[a], Nicole Geschwind[c], Nele Jacobs[a,d], Catherine Derom[e], Evert Thiery[f], Jim van Os[a,g], Inez Myin-Germeys[a], Marieke Wichers[a]

[a]*Department of Psychiatry and Neuropsychology, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht University, PO Box 616 (DRT 10), Maastricht 6200 MD, The Netherlands*
[b]*University Psychiatric Centre, Catholic University Leuven, Kortenberg, Belgium*
[c]*Clinical Psychological Science, Maastricht University, The Netherlands*
[d]*Faculty of Psychology, Open University of the Netherlands, Heerlen, the Netherlands*
[e]*Centre of Human Genetics, University Hospitals Leuven, Department of Human Genetics, KU Leuven, Belgium*
[f]*Dept of Neurology, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium*
[g]*King's College London, King's Health Partners, Department of Psychosis Studies, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK*
[h]*Riagg Maastricht, Parallelweg 45-47, 6221 BD, Maastricht, the Netherlands*

Received 8 May 2013; received in revised form 15 January 2014; accepted 12 February 2014

KEYWORDS
BDNF genotype;
Gene-environment interaction;
Stress sensitivity;
Experience sampling method (ESM);
Positive emotions;
Major depressive disorder (MDD)

Abstract
A previous study reported that social stress sensitivity is moderated by the brain-derived-neurotrophic-factor^{Val66Met} (BDNF rs6265) genotype. Additionally, positive emotions partially neutralize this moderating effect. The current study aimed to: (i) replicate in a new independent sample of subjects with residual depressive symptoms the moderating effect of BDNF^{Val66Met} genotype on social stress sensitivity, (ii) replicate the neutralizing impact of positive emotions, (iii) extend these analyses to other variations in the BDNF gene in the new independent sample and the original sample of non-depressed individuals.
Previous findings were replicated in an experience sampling method (ESM) study. Negative Affect (NA) responses to social stress were stronger in "Val/Met" carriers of BDNF^{Val66Met}

*Corresponding author at: Department of Psychiatry and Neuropsychology, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht University, PO Box 616 (DRT 10), Maastricht 6200 MD, The Netherlands. Tel.: +31 433299699.
E-mail address: mark.vanwinkel@maastrichtuniversity.nl (M. van Winkel).

http://dx.doi.org/10.1016/j.euroneuro.2014.02.005
0924-977X

compared to "Val/Val" carriers. Positive emotions neutralized the moderating effect of $BDNF^{Val66Met}$ genotype on social stress sensitivity in a dose-response fashion. Finally, two of four additional BDNF SNPs (rs11030101, rs2049046) showed similar moderating effects on social stress-sensitivity across both samples. The neutralizing effect of positive emotions on the moderating effects of these two additional SNPs was found in one sample.
In conclusion, ESM has important advantages in gene-environment (GxE) research and may attribute to more consistent findings in future GxE research. This study shows how the impact of BDNF genetic variation on depressive symptoms may be explained by its impact on subtle daily life responses to social stress. Further, it shows that the generation of positive affect (PA) can buffer social stress sensitivity and partially undo the genetic susceptibility.

1. Introduction

In recent years, the study of gene-environment interactions (GxE) to unravel the pathogenesis of psychiatric disorders like major depressive disorder (MDD) has gained popularity (Caspi and Moffitt, 2006). The Brain-Derived Neurotrophic Factor (BDNF) gene has received much attention in recent GxE MDD research (Kaufman et al., 2006; Chen et al., 2012). The BDNF gene contains a functional polymorphism that results in a change from Valine (Val) in Methionine (Met) ($BDNF^{Val66Met}$ genotype). BDNF is a protein encoded by the BDNF gene and supports survival and growth of neurons. $BDNF^{Val66Met}$ is a common and naturally occurring variation in the BDNF gene and Met-carriers of this polymorphism have decreased secretion of BDNF. A higher number of Met-alleles are associated with a higher susceptibility for MDD and anxiety (Simons et al., 2009; Kalueff et al., 2006). In addition to the $BDNF^{Val66Met}$ genotype, several other Single-Nucleotide Polymorphisms (SNPs) are probably associated with the diagnosis of MDD (Licinio et al., 2009).

Despite the growing interest in GxE interactions consistent replications of findings are rare (Moffitt et al., 2005; Duncan and Keller, 2011). Several explanations for these inconsistencies have been put forward. First, most initial GxE studies included measurements of *distal*, rather than *proximal*, environmental exposures, such as retrospective assessments of stressful events that occurred years ago (Caspi et al., 2003). These measurements may include error due to recall bias and mood-congruency effects at the moment when participants fill out questionnaires. In addition, the large time lag between exposure and the occurrence of variables of interest like a depressive episode allows for considerable noise generated by other factors that may have an impact on outcome. Thus, precision of environmental measurements used in GxE studies deserves more attention. Making use of more proximal, repetitive, and prospective environmental measurements increases precision (Moffitt et al., 2005; Zammit and Owen, 2006).

Second, the lack of consistency relates to the measurement of the outcome variable. Many GxE studies use a (dichotomous) psychiatric diagnosis as outcome variable. The use of these heterogeneous categories, characterized by disputable validity leads to high heterogeneity of outcome variables (Moffitt et al., 2005; Hasler and Northoff, 2011). An alternative strategy to examine etiological mechanisms that are involved in the development of psychiatric disorders is to focus directly on genes impacting on intermediate endophenotypes of psychiatric disorders. One of these putative intermediate endophenotypes in the etiology of MDD is increased stress sensitivity. Stress sensitivity is a dynamic phenotype that involves affective responses to small stressors in the flow of daily life (Csikszentmihalyi and Larson, 1987; Wichers et al., 2007a). A myriad of studies have reported that increased stress sensitivity is a risk factor for the development of psychiatric disorders such as MDD (Drabant et al., 2012; Wichers et al., 2009a) and psychosis (Mueller et al., 2011; Myin-Germeys et al., 2005a).

Third, Plues and Belsky (2012) recently argued that putative risk alleles often operate as 'plasticity' alleles, which is in line with the differential susceptibility hypothesis of Belsky (Belsky et al., 2009). According to Belsky's hypothesis people vary in 'developmental plasticity'. More "plastic or malleable" people are more vulnerable for adverse environmental influences but they may also be more impressionable for factors such as momentary positive affect resulting from positive events in their environment. On the other hand, less malleable people are less affected by environmental exposure. Plues and Belsky conclude that "the failure to explicitly measure and include positive supportive aspects of the environment in $G \times E$ studies may be an important reason why $G \times E$ findings fail to replicate (Pluess and Belsky, 2012, pg. 222)".

The experience sampling method (ESM) (Csikszentmihalyi and Larson, 1987), a self-assessment technique that is used to assess context, thoughts, affect, and symptoms in the flow of daily life, which can be used to investigate GxE in a momentary, prospective and 'real-world' design. Because environmental exposure and experience of stress are measured nearly simultaneously, measurement error due to recall bias and mood-congruency effects is minimized.

Some recent studies applied this methodology in examining the effect of genes on stress-sensitivity as a risk factor for MDD (Wichers et al., 2007a; Wichers et al., 2009a) and psychosis (Van Winkel et al., 2008; Simons et al., 2009; Collip et al., 2011). Only two ESM studies examined the moderating effect of the $BDNF^{Val66Met}$ polymorphism on stress sensitivity, operationalized as emotional responses to minor stressors in daily life (Simons et al., 2009; Wichers et al., 2008b). These studies reported that Met-carriers respond with more negative affect (NA) or paranoia to minor daily life stressors.

Additionally, two studies (Wichers et al., 2008b; Wichers et al., 2007b) showed that the ability to experience positive emotions during daily life stressors neutralized in part the