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BDNF *VAL66MET* POLYMORPHISM INFLUENCE ON STRIATAL BLOOD-LEVEL-DEPENDENT RESPONSE TO MONETARY FEEDBACK DEPENDS ON VALENCE AND AGENCY

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Abstract—Animal work implicates the brain-derived neurotrophic factor (BDNF) in function of the ventral striatum (VS), a region known for its role in processing valenced feedback. Recent evidence in humans shows that BDNF *Val66Met* polymorphism modulates VS activity in anticipation of monetary feedback. However, it remains unclear whether the polymorphism impacts the processing of self-attributed feedback differently from feedback attributed to an external agent. In this study, we emphasize the importance of the feedback attribution because agency is central to computational accounts of the striatum and cognitive accounts of valence processing. We used functional magnetic resonance imaging and a task, in which financial gains/losses are either attributable to performance (self-attributed, SA) or chance (externally-attributed, EA) to ask whether BDNF *Val66Met* polymorphism predicts VS activity. We found that BDNF *Val66Met* polymorphism influenced how feedback valence and agency information were combined in the VS and in the right inferior frontal junction (IFJ). Specifically, *Met* carriers' VS response to valenced feedback depended on agency information, while *Val/Val* carriers' VS response did not. This context-specific modulation of valence effectively amplified VS responses to SA losses in *Met* carriers. The IFJ response to SA losses also differentiated *Val/Val* from *Met* carriers. These results may point to a reduced allocation of attention and altered motivational salience to SA losses in *Val/Val* compared to *Met* carriers. Implications for major depressive disorder are discussed.

Key words: Brain-derived neurotrophic factor gene, *Val66Met*, feedback processing, inferior frontal junction, ventral striatum, functional magnetic resonance imaging.

INTRODUCTION

The brain-derived neurotrophic factor (BDNF) is a prevalent growth factor in the central nervous system, which is important for synaptic plasticity and neuronal survival throughout life (Poo, 2001). One common functional variant of the BDNF gene is the single-nucleotide polymorphism rs 6265, which results in a valine to methionine substitution at codon 66 (*Val66Met*) of the precursor protein pro-BDNF. This single-nucleotide polymorphism alters intracellular trafficking and secretion of the mature BDNF: Carriers of the *Met* allele show reduced activity-dependent secretion of BDNF compared to *Val/Val* homozygotes (Egan et al., 2003; Chen et al., 2004).

BDNF *Val66Met* polymorphism predicts cognitive performance as well as brain structure in healthy subjects (Chen et al., 2008; Dincheva et al., 2012), but these genotype differences have a complex profile. Compared to *Val/Val* subjects, *Met* carriers show poorer performance in hippocampal-dependent memory tasks (Egan et al., 2003; Hariri et al., 2003; Schofield et al., 2009) and reduced hippocampal gray matter volume (Pezawas et al., 2004; Bueller et al., 2006; Frodl et al., 2007), but improved response inhibition and interference resolution (Beste et al., 2010a; Gajewski et al., 2012). These findings appear to tie *Met* carriers' deficits to fronto-hippocampal function (Schofield et al., 2009),

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Abbreviations: ADS, General Depression Scale; BAS, Behavioral Activation System; BDNF, Brain-derived neurotrophic factor; BFI, Big-Five inventory; BIS, Behavioral Inhibition System; BOLD, blood-level-dependent; EA, externally-attributed; FWE, family-wise error; IFJ, inferior frontal junction; MDD, major depressive disorder; MNI, Montreal Neurological Institute; PSS, Perceived Stress Scale; RM-ANOVA, repeated-measures analyses of variance; RT, reaction time; SA, self-attributed; STAI, State-Trait Anxiety Inventory; VS, ventral striatum.

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whereas *Val/Val* carriers' deficits may rather reflect fronto-striatal function (Beste et al., 2010a; Gajewski et al., 2012; Getzmann et al., 2013). Animal studies also point to a dissociation of BDNF's effect on different neural circuits depending on direction and location of manipulations: Increasing BDNF in the hippocampus promotes hippocampal-dependent learning (Peters et al., 2010), whereas decreasing BDNF in the ventral tegmental area promotes reward sensitivity and presumably reward learning (Koo et al., 2012). Moreover, depressive-like behaviors induced by chronic exposure to stressors are related to lower BDNF levels in the hippocampus, but higher BDNF levels in the ventral tegmental area and the nucleus accumbens [(Berton et al., 2006; Krishnan et al., 2007); see also (Yu and Chen, 2011)].

Such functional dissociations may obscure our understanding of the human BDNF *Val66Met* polymorphism both in healthy subjects and patients with neuropsychiatric disorders, including major depressive disorder (MDD) (Autry and Monteggia, 2012). Hippocampal structure and function in healthy *Met* carriers resemble that of depressed patients (Hariri et al., 2003; Gatt et al., 2007, 2008). Additionally, exposure to early-life stress, a known contributing factor to MDD, has been shown to predict higher syndromal depression through loss of hippocampus and prefrontal gray matter in *Met* carriers (Gatt et al., 2009). These findings strongly suggest that the *Met* allele may increase vulnerability to MDD by affecting hippocampal-related functions. The association between the *Met* allele and MDD (Hwang et al., 2006), however, has not been consistently replicated (Verhagen et al., 2010; Lee et al., 2014). Furthermore, there are reasons to expect increased vulnerability among *Val/Val* carriers: Trait anxiety and neuroticism are risk factors for MDD that are reportedly higher in *Val/Val* rather than *Met* carriers (Sen et al., 2003; Lang et al., 2005; Hunnerkopf et al., 2007; Frustaci et al., 2008). Given the apparent inconsistencies detailed above, it seems plausible that BDNF *Val66Met* polymorphism may impact risk for MDD through different, allele-specific, neurocognitive systems (Gatt et al., 2009; Gottfredson et al., 2014).

The ventral striatum (VS) plays a key role in the processing of valenced outcomes [e.g.(Ullsperger and von Cramon, 2003; Studer et al., 2012)] and altered VS response to feedback has been widely reported in MDD (Eshel and Roiser, 2010). Recent evidence shows that BDNF *Val66Met* polymorphism modulates activity in the VS and the ventral tegmental area in anticipation of monetary losses (Pecina et al., 2014). Moreover, the polymorphism has been shown to influence brain activity in response to errors (Beste et al., 2010b), as well as to the passive presentation of pleasant and aversive stimuli (Montag et al., 2008; Gasic et al., 2009). However, it remains unclear whether the polymorphism impacts responses to self-attributed feedback differently from externally-attributed feedback. Because agency is central to computational accounts of the striatum (Dayan and Niv, 2008) and of cognitive accounts of valence processing (Weiner, 2010), we investigated whether genotype predicted the magnitude of the blood-level-dependent (BOLD) responses to financial gains and losses arising either by chance (externally-attributed outcomes, EA) or due to subjects' performance (self-attributed outcomes, SA) (Späti et al., 2014). We had three hypotheses. First, we hypothesized that BDNF *Val66Met* polymorphism influences striatal encoding of causal information about rewards and punishments. More specifically, we hypothesized that information about valence and causal attribution would be combined differentially between genotypes. Second, we hypothesized that these differences may reduce to genotype-specific striatal prediction errors. Third, because individual differences in reward sensitivity (measured by the Behavioral Activation Scale) have been found to shape behavioral responses to incentive stimuli (Pickering and Gray, 2001), as well as VS responses to such stimuli (Beaver et al., 2006; Simon et al., 2010), we expected individual reward sensitivity to predict VS responses to financial feedback.

EXPERIMENTAL PROCEDURES

Participants

Thirty-five unrelated healthy Caucasians without any reported psychiatric, neurologic or medical illness (as confirmed by a Structured Clinical Interview for Axis I Disorders) between the age of 20 and 59 years were included in the study. As reported below, individuals who were homozygous for the *Met* allele were merged with the heterozygous individuals into a group of *Met* carriers ($n = 18$) and compared to homozygous *Val* carriers ($n = 17$). Groups were matched for age, gender, years of education, psychometric measures and task's performance (see Table 1).

The study was approved by the University of Zurich's Institutional Review Board, and all subjects gave written informed consent.

Psychometric measures

All participants completed the German version of the Action Regulating Emotion Systems scale [ARES, (Hartig and Moosbrugger, 2003)], which provides Behavioral Inhibition System (BIS) and Behavioral Activation System (BAS) scores reflecting, respectively, punishment and reward sensitivity. BIS and BAS are composed of two subscores: Anxiety/frustration and drive/gratification, respectively. In addition, participants completed the short version of the Big-Five inventory [BFI, (Rammstedt and John, 2005)], which provided five personality measures, including neuroticism, extraversion, openness, conscientiousness and agreeableness; the General Depression Scale [ADS, Allgemeine Depressionsskala (Hautzinger and Bailer, 1993)]; the State-Trait Anxiety Inventory [STAI, (Laux et al., 1981)] and the Perceived Stress Scale (PSS, (Cohen et al., 1983)].

Motion prediction task

The motion prediction task has been previously described in detail (Späti et al., 2014). In brief, each trial started with two balls moving, at different speeds and from different starting positions, toward a finish line. The task was to