

# 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. © 2014 The Authors. Published by Elsevier Ltd. on behalf of IBRO. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/3.0/>).

**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.

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

**Table 1.** Demographic, psychometric and behavioral information

	Met carriers N = 18	Val/Val carriers N = 17	Statistic
Gender (%)	8 females (44%)	10 females (59%)	n.s
Age (mean $\pm$ SD)	32.7 $\pm$ 13.1	29.7 $\pm$ 8.5	n.s
Years of education	15.5 $\pm$ 2.7	15.7 $\pm$ 2.4	n.s
Left-handed	1	1	
STAI-T (mean $\pm$ SD)	32.2 $\pm$ 8.6	34.8 $\pm$ 7.3	n.s
ADS-Scale (mean $\pm$ SD)	5.2 $\pm$ 4.0	4.8 $\pm$ 4.1	n.s
BFI-neuroticism (mean $\pm$ SD)	9.7 $\pm$ 3.2	10.7 $\pm$ 2.7	n.s
PSS (mean $\pm$ SD)	30.8 $\pm$ 6.3	33.1 $\pm$ 9.1	n.s
BIS anxiety (mean $\pm$ SD)	10.9 $\pm$ 3.5	11.1 $\pm$ 2.7	n.s
BIS frustration (mean $\pm$ SD)	11.5 $\pm$ 5.8	10.8 $\pm$ 2.9	n.s
BAS drive (mean $\pm$ SD)	17.2 $\pm$ 2.0	17.4 $\pm$ 1.7	n.s
BAS gratification (mean $\pm$ SD)	17.6 $\pm$ 2.3	17.7 $\pm$ 1.9	n.s
% SA gains (mean $\pm$ SD)	59.5 $\pm$ 5.4	60.0 $\pm$ 6.3	n.s
% EA gains (mean $\pm$ SD)	58.2 $\pm$ 8.3	59.8 $\pm$ 6.2	n.s
% Miss (mean $\pm$ SD)	1.0 $\pm$ 1.6	0.5 $\pm$ 0.7	n.s
RT correct (mean $\pm$ SD)	487.9 $\pm$ 90.6	523.4 $\pm$ 156.9	n.s
RT incorrect (mean $\pm$ SD)	524.4 $\pm$ 87.6	551.0 $\pm$ 165.7	n.s
RT post-SA losses (mean $\pm$ SD)	513.6 $\pm$ 11.7	533.1 $\pm$ 161.2	n.s
RT post-SA gains (mean $\pm$ SD)	497.8 $\pm$ 89.5	528.7 $\pm$ 172.1	n.s
RT post-EA losses (mean $\pm$ SD)	489.1 $\pm$ 87.6	517.8 $\pm$ 154.3	n.s
RT post-EA gains (mean $\pm$ SD)	490.8 $\pm$ 91.6	517.5 $\pm$ 157.7	n.s

STAI-T, Spielberger Trait Anxiety Inventory; ADS, General Depression Scale; BFI-Neuroticism, Short version of the Big Five Inventory-Neuroticism score; PSS, Perceived Stress Scale; BIS, Behavioral Inhibition System; BAS, Behavioral Approach System; SA, self-attributed; EA, externally-attributed; RT, reaction time (ms); n.s, not significant.

predict, which ball would cross the finish line first and to indicate the decision by a left or right button press, using the left or right hand, respectively. Only after the response was made, subjects were instructed whether their response was relevant or irrelevant to the upcoming feedback. Specifically, subjects were told that on each trial they would gain or lose 50 cents indicated by a “+50” or “−50” feedback. At random 50% of the trials feedback was performance-dependent (SA). The other 50% of trials feedback was dependent on chance, being randomly selected by the computer (EA). 750 ms after the response, the words “You” and “Coin” and an arrow pointing toward either word was presented to indicate whether the upcoming feedback depended on the subject’s performance or not. Finally, feedback about winning (+50) or losing (−50) was presented. The next trial started after  $2000 \pm 500$  ms, which provided some jittering between trials. If the subject failed to respond, the arrow pointed toward the word “You” followed by the feedback “Missed”. To keep uncertainty about performance high during the functional magnetic resonance imaging (fMRI) paradigm, task difficulty was adapted for each participant such that none of the participants had an error rate lower than 30%. The average error rate was around 40%. Prior to the task, difficulty levels were individually determined based on a training session of 100 trials performed during the anatomical scans, during which subjects received only a performance feedback (correct: smiley face, incorrect: unhappy face). Participants were unaware that the difficulty of the task was manipulated; they were told to do their best at winning and were paid based on performance plus a modest compensation for participating in the study. Three *Met* and one *Val/Val* carrier performed a shorter version of

the task of 100 trials, all other subjects completed 130 trials. The chance of monetary gain for EA and SA feedback was around 60% and similar across genotypes (Table 1).

### Image acquisition

Images were acquired on a Philips Achieva TX 3T whole-body MR unit equipped with an eight-channel head coil. Functional time series were acquired with a sensitivity-encoded single-shot echo-planar sequence (echo time = 35 ms,  $80 \times 80$  voxel matrix, interpolated to  $128 \times 128$ , voxel size:  $2.75 \times 2.75 \times 4$  mm<sup>3</sup>, SENSE acceleration factor  $R = 2.0$ ). Thirty-six contiguous axial slices were placed along the anterior-posterior commissure plane covering the entire brain and acquired in ascending order (repetition time = 2000 ms). The first four acquisitions were discarded due to T1 saturation effects. T1-weighted high-resolution images were also acquired for each participant.

### Data analysis

Demographic, psychometric, and behavioral data were analyzed with unpaired *t*-tests and gender with the Chi-squared test using StatView 5.0.1 (SAS Institute, Inc., Cary, NC, USA) with the significance level of 0.05 (two-tailed). Mean reaction time (RT) differences for correct and incorrect trials were analyzed with repeated-measures analyses of variance (RM-ANOVA) with reaction time for incorrect and correct trials as within-subject factors, and genotypes (*Met* and *Val/Val*) as independent factors.

In order to correctly attribute gains/losses on each trial, participants must attend to and discriminate the two

attribution conditions: SA versus EA. It is important to know whether genotypes differed in this basic capacity to discriminate. We therefore compared the two genotypes on 'post-SA slowing', a behavioral measure of discrimination. Post-SA feedback slowing refers to longer RT in trials following a SA feedback relative to EA feedback, and is found in healthy subjects (Späti et al., 2014). We made this genotype comparison via RM-ANOVA.

Image processing was carried out using MATLAB R2012a (The Mathworks, Natick, MA, USA) and Statistical Parametric Mapping (SPM8; Wellcome Department of Imaging Neuroscience, London, UK; <http://www.fil.ion.ucl.ac.uk>). The preprocessing is described in detail in Späti et al. (2014). In brief, functional images preprocessing included motion correction, coregistration to a standard template, alignment to the first volume for each subject, spatial normalization to the Montreal Neurological Institute (MNI) template, and smoothing using a Gaussian-kernel filter with a full-width-at-half-maximum of 8-mm. Statistical analysis was performed by modeling the different conditions convolved with a hemodynamic response function and its temporal derivative as explanatory variables within the context of the general linear model on a voxel-by-voxel basis.

The  $2 \times 2$  factorial design independently manipulated the agency and valence of feedback. Several regressors were modeled as events, including the four feedback conditions (SA losses, EA losses, SA gains, EA gains), the regressors of no interest [the missed feedback, the

motor response (button press), and the realignment parameters [see also (Späti et al., 2014)]. The other sub-components of the trial (fixation, ball motion, attribution assignment) were not explicitly modeled with separate regressors. Because our mean reaction time for incorrect trials was significantly longer than for correct trials (see Results), we included reaction time as a first-order parametric modulator. Subject-specific analyses provided contrast images which were then submitted to a second-level random effects analysis to examine genotype differences, using two-sample *t*-tests with age and gender as covariates. Unless otherwise specified, clusters of activation were identified with a global height threshold of  $p < 0.001$  uncorrected and *family-wise error* (FWE) corrected for multiple comparison to achieve a statistical threshold of  $p < 0.05$ . Regions were anatomically labeled using the automatic anatomical labeling (aal) from the SPM toolbox and by visual inspection; the mean percent signal change across all the voxels in a functional cluster was calculated using marsbar. A VS mask, defined as two spheres of Ø 14-mm centered in the ventral putamen at coordinates  $x = \pm 20$ ,  $y = 12$ ,  $z = -14$  according to our previous findings (Späti et al., 2014), was created using wfu-pickatlas. Coordinates are reported in MNI space.

### Model-based prediction error analysis

We also considered an augmented model with four additional predictors. Specifically, for each cell of the agency by valence factorial design, we included a

**Table 2.** Brain activity associated with BDNF Val66Met polymorphism on the valence  $\times$  attribution interaction

Cluster (voxels)	<i>T</i> (peak)	<i>p</i> Cluster-level	Region	<i>x</i>	<i>y</i>	<i>z</i>	Hem
<b>(SA gains vs EA gains) &gt; (SA losses vs EA losses)</b>							
<i>Met</i>							
251	8.23	< 0.003	Caudate	14	14	−10	R
			Putamen	22	14	−14	R
1082	7.34	< 0.001	Paracentral lobule	10	−42	70	R
			Paracentral lobule	20	−36	46	R
			Precuneus	−14	−44	72	L
149	5.85	< 0.03	Inferior occipital G	−48	−68	−10	L
			Inferior occipital G	−52	−74	−4	L
			Cerebellum	−46	−58	−20	L
<i>Val/Val</i>							
139	6.07	< 0.04	Middle frontal G	26	14	52	R
125	5.94	< 0.05	Angular G	−48	−66	28	L
			Middle occipital G	−38	−76	26	L
228	5.70	< 0.004	Angular G	44	−60	24	R
			Angular G	40	−52	22	R
<i>Met</i> > <i>Val/Val</i>							
None							
<i>Val/Val</i> > <i>Met</i>							
None							
<b>(SA losses vs EA losses) &gt; (SA gains vs EA gains)</b>							
<i>Met</i>							
None							
<i>Val/Val</i>							
None							
<i>Met</i> > <i>Val/Val</i>							
305	5.66	< 0.003	Precentral G	40	6	38	R
<i>Val/Val</i> > <i>Met</i>							
None							

G, gyrus; Hem, hemisphere; L, left; R, right.



parametric modulator which coded trial by trial prediction errors. To do this, we first used Rescorla–Wagner to separately model the prediction error to SA and EA outcomes, respectively denoted  $s$  and  $e$  trials. These two learners had the same form, i.e.

$$\eta_{t+1}^s = \eta_t^s + \alpha(x - \eta_t^s)$$

$$\eta_{t+1}^e = \eta_t^e + \alpha(x - \eta_t^e)$$

where for example  $\eta_t^s$  is the expected value on the SA trial  $t$  and  $x$  is the outcome of that trial. This outcome is compared with expectation via  $(x - \eta_t^s)$ , i.e. the prediction error. This prediction error ( $\eta_t^s$ ) updates value expectations for the next SA trial,  $t + 1$ .  $\alpha$  is an unknown learning rate, which we fixed to 0.1 and 0.3 in different simulations. In this way, the prediction error on every trial could be categorized as either SA/EA and either positive/negative, perfectly reflecting the factorial structure of our main  $2 \times 2$  factorial analysis (see previous section). As mentioned above, this correspondence permitted us to simply include the four prediction error types as parametric modulators for each of the corresponding factorial event types. After convolving with hemodynamic response function, we treated these parametric modulators as covariates and repeated the analyses discussed above.

## DNA analysis

After the imaging session, participants were given the Oragene DNA OG-500 self-collection kit for DNA sampling. Genomic DNA was extracted from saliva samples following the manufacturer's instructions (DNA Genotek Inc., Ontario, Canada). Genotyping was done with Pyrosequencing on a PyroMark™ID System (Qiagen, Hilden, Germany). Primers for BDNF SNP rs6265 were: 5'-CCA TGG GAC TCT GGA GAG CG-3' (forward, 5'-biotinylated), 5'-TGA CTA CTG AGC ATC ACC CTG GAC-3' (reverse), 5'-CCA ACA GCT CTT CTA TCA-3' (sequencing primer). Genotype frequencies (*Val/Val* 49%, *Val/Met* 40%, and *Met/Met* 11%) were consistent with those reported previously in Caucasian populations (Shimizu et al., 2004; Beste et al., 2011). The Hardy–Weinberg equilibrium was examined using an online source [<http://www.oege.org/software/hwemr-calc.shtml>]; (Rodriguez et al., 2009)]. None of the genotype frequencies violated Hardy–Weinberg equilibrium ( $\chi^2 = 0.18$ ;  $p > 0.05$ ). Individuals who were homozygous for the *Met* allele ( $n = 4$ ) were merged with heterozygous individuals ( $n = 14$ ) into a group of *Met* carriers and compared to homozygous *Val* carriers ( $n = 17$ ).

## RESULTS

### Demographic and behavioral data

Subject demographic and psychometric characteristics grouped by *BDNF Val66Met* genotype are presented in Table 1. Our *Met* and homozygous *Val* samples did not differ in average age, years of education, other psychometric scores (ADS, STAI-T, BIS/BAS, BFI) or measures related to task's performance (% SA gain, % EA gain, % missed trials, mean reaction time for incorrect and correct trials). None of the subjects had a

particularly high level of depressive or anxiety symptoms (ADS < 17 and STAI-T < 49).

As reported previously (Ullsperger and von Cramon, 2003; Späti et al., 2014), mean reaction time for incorrect trials was significantly longer than for correct trials across genotype: reaction time (mean  $\pm$  SD) incorrect trials:  $537 \pm 130$  ms, correct trials:  $505 \pm 127$  ms,  $F(1,33) = 18.3$ ,  $p < 0.002$ ; no effect of genotype ( $p > 0.5$ ). Moreover, mean RT (ms) on trials following SA feedback was longer compared to trials following EA feedback ( $F(1,33) = 5.2$ ,  $p < 0.03$ ; RT post-SA feedback:  $517.9 \pm 134.7$ ; RT post-EA feedback:  $503.4 \pm 124.3$ ). Importantly, no significant effect of genotype ( $p > 0.5$ ), or valence ( $p > 0.5$ ) or genotype  $\times$  valence ( $p > 0.7$ ), genotype  $\times$  attribution ( $p > 0.8$ ) or genotype  $\times$  valence  $\times$  attribution ( $p > 0.5$ ) interactions was found. Thus genotypes were behaviorally indistinguishable.

### Imaging data

Here we report the interaction and main effects, both between and within genotype. In parallel analyses, we use a small-volume correction for VS then whole-brain correction. In Table 3, we report the whole-brain analysis of the simple effects (the simple contrasts SA–EA losses, SA–EA gains, SA gains–losses, EA gains–losses).

**Valence  $\times$  attribution interaction.** Within-genotype. Within-genotype, whole-brain corrected effects for the contrast (SA gains–EA gains)–(SA losses–EA losses) are reported in Table 2. *Met* carriers showed three significant clusters in the right caudate/putamen, the bilateral paracentral lobule/precuneus and the left inferior occipital cortex, whereas *Val/Val* carriers showed significant activation in the right middle frontal gyrus, the left angular/occipital gyri and the right angular gyrus. No significant cluster was found for the other tail of this whole-brain analysis, i.e. the contrast (SA losses–EA losses)–(SA gains–EA gains).

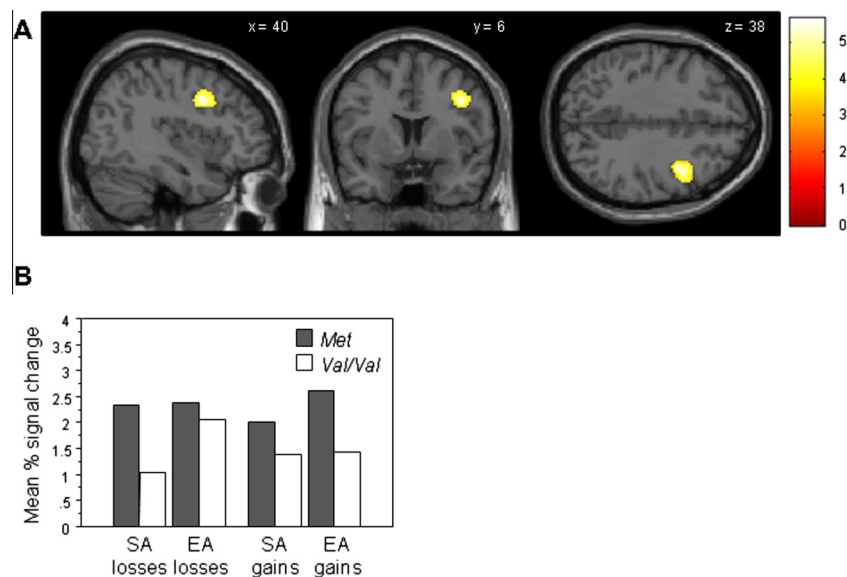
**Between-genotype. Whole brain:** There was no genotype difference for the interaction (SA gains–EA gains)–(SA losses–EA losses) at the whole-brain level. In contrast, the converse interaction contrast (SA losses–EA losses)–(SA gains–EA gains) showed a genotype effect in the right precentral gyrus ( $p = 0.002_{\text{FWE\_corrected}}$  Fig. 1A, Table 2) near the inferior frontal sulcus, a region referred as the inferior frontal junction [IFJ; (Derrfuss et al., 2004, 2012)]. Mean percent signal change for the right IFJ is reported in Fig. 1B.

To interpret significant interactions, we also tested simple effects. A simple effect – i.e. a contrast between just two conditions of a factorial design – can be tested in SPM just like any other factorial effect (i.e. main or interaction effect). Examination of the simple effects showed that this interaction was driven by *Met* carriers having a greater contrast (SA losses–EA losses) as compared to *Val/Val* subjects (right IFJ:  $p < 0.05_{\text{FWE\_corrected}}$ , Table 3).

**Table 3.** BOLD response associated with BDNF *Val66Met* polymorphism on the simple effects of valence and attribution

Cluster (voxels)	T (peak)	p Cluster-level	Region	x	y	z	Hem
<b>SA gains–EA gains</b>							
<i>Met</i> > <i>Val/Val</i>							
404	5.42	< 0.001 <sub>FWE-corrected</sub>	Precuneus	16	–44	56	R
			Paracentral lobule	18	–36	52	R
			Precuneus	–2	–52	56	L
231	4.64	< 0.01 <sub>FWE-corrected</sub>	Supramarginal G	–64	–28	20	L
			Supramarginal G	–52	–36	32	L
			Superior Temporal G	–48	–40	18	L
<i>Val/Val</i> > <i>Met</i>							
None							
<b>SA losses–EA losses</b>							
<i>Met</i> > <i>Val/Val</i>							
174	4.66	< 0.05 <sub>FWE-corrected</sub>	Middle frontal G	38	14	36	R
			Precentral G	44	8	38	R
			Middle frontal G	50	14	44	R
<i>Met</i> > <i>Val/Val</i>							
None							
<b>SA gains–SA losses</b>							
<i>Met</i> > <i>Val/Val</i>							
None							
<i>Val/Val</i> > <i>Met</i>							
None							
<b>EA gains–EA losses</b>							
<i>Met</i> > <i>Val/Val</i>							
None							
<i>Val/Val</i> > <i>Met</i>							
434	6.06	< 0.001 <sub>FWE-corrected</sub>	Superior parietal	–22	–50	54	L
			Paracentral lobule	18	–36	50	R
			Precuneus	16	–46	52	R

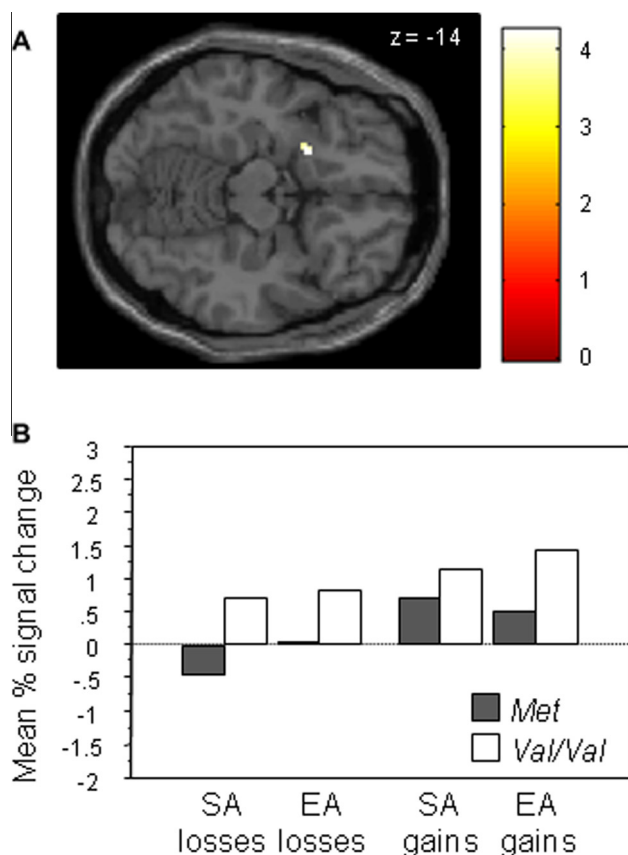
FWE, family-wise error; G, gyrus; Hem, hemisphere; L, left; R, right.

**Fig. 1.** Whole-brain analysis of BDNF *Val66Met* polymorphism effect on the attribution (SA/EA)  $\times$  valence (gains/losses) interaction. (A) We found a genotype effect in the right inferior frontal junction. (B) Mean percent signal change in the right inferior frontal junction for self-attributed (SA) and externally-attributed (EA) losses and gains in *Val/Val* carriers (white) and *Met* carriers (gray).

**Small volume:** A small-volume corrected VS analysis showed a genotype difference for the interaction contrast (SA gains–EA gains)–(SA losses–EA losses) in left ventral putamen ( $p = 0.009_{\text{FWE\_corrected}}$  corresponding to a cluster of 28 voxels,  $t = 4.25$ ,  $x = -22$ ,  $y = 10$ ,  $z = -14$ ; Fig. 2A). This significant three-way interaction is depicted in Fig. 2B, in terms of mean percent signal change. The other tail of this interaction effect, i.e. (SA losses–EA losses)–(SA gains–EA gains), was not significant anywhere within the mask.

Examination of the simple effects showed that this interaction was driven by *Met* carriers showing a greater contrast (SA gains–SA losses) as compared to *Val/Val* subjects (in the left and right ventral putamen (left putamen:  $p < 0.02_{\text{FWE\_corrected}}$  corresponding to a cluster of 19 voxels,  $t = 3.89$ ,  $x = -24$ ,  $y = 8$ ,  $z = -14$ ; right putamen:  $p < 0.03_{\text{FWE\_corrected}}$  corresponding to a cluster of 10 voxels,  $t = 3.80$ ,  $x = 26$ ,  $y = 10$ ,  $z = -16$ ). No significant effects were found for the contrasts (EA gains–EA losses), (SA gains–EA gains) and (SA losses–EA losses).

**Valence main effect.** Within-genotype. **Whole Brain:** For the contrast Gains–Losses, *Val/Val* carriers



**Fig. 2.** Small-volume corrected analysis of BDNF *Val66Met* polymorphism effect on the attribution (SA/EA)  $\times$  valence (gains/losses) interaction in the ventral striatum. (A) We found a genotype effect in the left ventral putamen. (B) Mean percent signal change in the left ventral putamen for self-attributed (SA) and externally-attributed (EA) losses and gains in *Val/Val* carriers (white) and *Met* carriers (gray).

showed significant bilateral VS (caudate/putamen) activation and numerous significant regions in the occipital/calcarine gyri, supplementary motor area/superior frontal cortex, parahippocampal gyrus, superior parietal cortex. Analogous activations were found in *Met* carriers. For the contrast Losses–Gains, activation in the medial superior frontal cortex was found in *Val/Val* subjects and in the left inferior frontal cortex pars orbitalis and triangularis in *Met* Carriers. There was no evidence for the contrast Losses–Gains in either genotype.

**Between-genotype.** No statistical genotype difference was found at the whole-brain level or with the small-volume corrected analysis.

**Agency main effect.** Within-genotype. **Whole brain:** For the contrast SA–EA feedback, *Val/Val* carriers showed a significant activation in the left caudate, *Met* carrier activations were in the dorsal anterior cingulate cortex and the midbrain extending into the thalamus. For the contrast EA–SA feedback, *Val/Val* carriers that showed numerous bilateral activations were found in the superior and middle frontal cortex, the postcentral gyrus/superior parietal lobule and posterior cingulate cortex, the angular gyrus, the right middle and inferior temporal cortex temporal pole and parahippocampal areas and the left cerebellum consistent with previous results (Späti et al., 2014). Analogous activations were found in *Met* carriers.

**Between-genotype.** No statistical genotype difference was found at the whole-brain level or with the small-volume corrected analysis.

### Model-based prediction error

The genotype  $\times$  valence  $\times$  attribution interaction effects described above remain significant when the prediction error for the four feedback conditions were included as covariates. This indicated that they could not be accounted for by these prediction error covariates. We observed no significant effect of genotype on the condition-specific scaling of prediction errors themselves. Thus all interesting variance appears to have been captured by a qualitative comparison of our factorial conditions.

### Correlation between BOLD response and BAS-drive scores

Simple regression analysis of mean percent signal change in the ventral putamen (reported in Fig. 2B) on BAS scores were performed for each genotype separately. No significant correlation was found.

However, *Val/Val* carriers showed a positive correlation between BAS scores and % signal change in right IFJ (reported in Fig. 1B) for all four feedback conditions separately (SA losses:  $r^2 = 0.39$ ,  $p < 0.008$ , EA losses:  $r^2 = 0.37$ ,  $p < 0.001$ , SA gains:  $r^2 = 0.30$ ,  $p < 0.03$ ; EA gains:  $r^2 = 0.39$ ,  $p < 0.008$ ). These correlations were driven by the BAS Drive sub-score (SA losses:  $r^2 = 0.55$ ,  $p < 0.0008$ , EA losses:  $r^2 = 0.56$ ,  $p < 0.0006$ , SA gains:

$r^2 = 0.44$ ,  $p < 0.004$ ; EA gains:  $r^2 = 0.57$ ,  $p < 0.0006$ ). For illustration, the scatter plot between mean percent signal change for SA losses and BAS Drive in *Val/Val* and *Met* carriers is reported in Fig. 3. No significant correlation was found in *Met* carriers. The stronger correlation with the BAS-Drive is consistent with the definition of the BAS sub-scores: BAS-Drive ‘measures an individual’s general tendency to actively pursue reward’ in the immediate environment, whereas BAS-gratification ‘reflects the inclination to seek out new rewarding experiences’ (Beaver et al., 2006).

## DISCUSSION

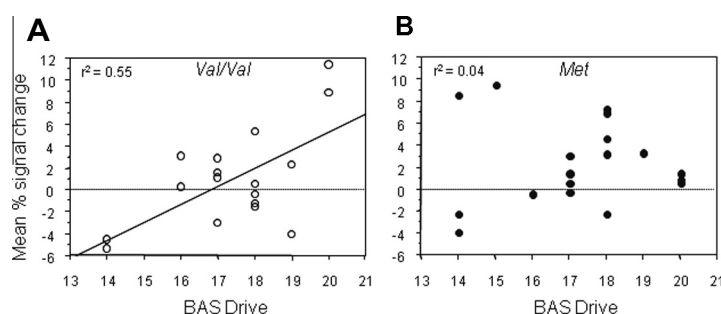
Our study is the first to examine the effect of BDNF polymorphism on human VS responses to feedback valence and attribution. We showed that BDNF *Val66Met* polymorphism predicts VS responses to financial feedback. Specifically, we found that *Met* carriers’ VS response reflected a significant valence  $\times$  agency interaction while *Val/Val* carriers’ VS response was relatively independent of agency (hence a significant genotype  $\times$  valence  $\times$  agency interaction). Closer examination revealed a genotype difference strongest for the simple contrast SA gain–SA losses. Our whole-brain analysis showed another genotype  $\times$  valence  $\times$  agency interaction effect in the right IFJ. Here *Val/Val* carriers showed a lower IFJ response, leading to a genotype difference for the simple contrast SA–EA losses. Interestingly, greater IFJ response in *Val/Val* carriers was associated with higher motivation (BAS-Drive scores). This pattern of results may arise from reduced attention allocation/motivational salience during the processing of SA losses in *Val/Val* compared to *Met* carriers.

The VS has previously been associated with several processes relevant to feedback evaluation, including signaling reward prediction error, incentive motivation, and motivational salience (Haruno and Kawato, 2006; Bromberg-Martin et al., 2010; Berridge, 2012). Fully disentangling the contribution of these different processes is not within the scope of our study. However, our model-based analyses suggest that genotype differences in the valence  $\times$  agency interaction cannot be reduced to genotype differences in reward prediction error. One possibility is that SA trials were more salient than EA trials due to personal responsibility (Zink et al., 2004;

Satterthwaite et al., 2012; Studer et al., 2012), and that salience varied between genotypes. This might be consistent with other reports of higher VS activity in *Met* carriers during anticipation of performance-dependent monetary losses (but not gains) (Pecina et al., 2014). Since neural activity in anticipation of a monetary feedback is considered to reflect appetitive and motivational aspects of reward processing (rather than its hedonic value), these findings suggest that BDNF *Val66Met* polymorphism influences the motivational salience processing of SA losses. As discussed below, this interpretation is also supported by the whole-brain genotype effect found in the right IFJ.

The IFJ is thought to play a major role in top-down modulation of attention and cognitive control (Derrfuss et al., 2005; Corbetta et al., 2008; Kim, 2014). Increased IFJ activity has been reported across various tasks, in which participants needed to shift attention, switch task rules, or filter irrelevant information (Derrfuss et al., 2004, 2005; Kim et al., 2012). Moreover, activity in the IFJ and in the left basal ganglia (including the ventral putamen) during a working memory task has been shown to precede the filtering of irrelevant information and to correlate with working memory capacity (McNab and Klingberg, 2008), indicating that greater IFJ response is associated with better performance. We found that *Val/Val* carriers showed lower IFJ activity across all feedback conditions except EA losses (Fig. 1B). Our observation that *Val/Val* carriers’ IFJ responded more to EA losses than to other types of feedback, invites the speculation (reverse inference) that these EA losses engage more top-down attentional resources in these subjects. It is notable that genotype differences in IFJ were specific to SA losses, mirroring the genotype effect in the ventral putamen. Overall these results may suggest that BDNF *Val66Met* polymorphism modulates attentional processes that influence the perceived motivational salience of SA negative feedback.

Our interpretation of imaging results in VS and IFJ as reduced attention and motivational salience seems reasonable in light of recent findings on the role of motivation in attentional deployment [see (Engelmann et al., 2009; Pessoa and Engelmann, 2010)]. Several lines of evidence indicate that motivation and reward signals are integrated in sensory and cognitive control regions [reviewed by (Pessoa and Engelmann, 2010)]. We found that, across all feedback conditions, greater



**Fig. 3.** Scatterplot showing the correlation between mean% signal change for self-attributed losses in the right inferior frontal junction and BAS Drive scores. (A) *Val/Val* carriers and (B) *Met* carriers.



IFJ activity was associated with higher reward motivation [operationalized via the BAS-Drive scores, (Beaver et al., 2006)] in *Val/Val* carriers. This result is consistent with previous findings showing that incentive value modulates activity in fronto-parietal attentional regions, including the IFJ, and that individual IFJ activity was also predictable from BAS-Drive scores (Engelmann et al., 2009). The frontal lobe receives widespread dopaminergic projections from the midbrain and the VS, regions that potentially mediate individual differences in motivational salience (Bromberg-Martin et al., 2010; Berridge, 2012). This suggests that “dopaminergic neuromodulation may be a key mechanism by which motivation sharpens attention and behavioral performance” (Pessoa and Engelmann, 2010). Recent evidence shows that BDNF *Val66Met* polymorphism influences dopaminergic transmission in the VS (Pecina et al., 2014), and thus potentially also in fronto-striatal circuits. This might provide a mechanism by which the BDNF genotype may influence attentional and motivational processes.

Higher IFJ activity has previously been related to higher incentive value and better performance during tasks requiring top-down modulation of attention and cognitive control (McNab and Klingberg, 2008; Engelmann et al., 2009). In our study, task difficulty was manipulated and groups were matched for performance, thus we could not assess whether lower IFJ activity in *Val/Val* subjects was related to lower absolute performance. In general, the literature is inconsistent about BDNF *Val66Met* performance deficits: a recent meta-analysis found no clear associations between BDNF *Val66Met* polymorphism and specific cognitive phenotypes (Mandelman and Grigorenko, 2012). As Mandelman and Grigorenko point out, several reasons may contribute to the apparent inconsistencies. These include a failure to group studies by similarities in the brain activation pathways that underlie the cognitive phenotype, rather than behavioral similarities. Furthermore, effects of stratification by demographic characteristics could also be important. For example, a 10-year follow-up study showed a faster decline in task-switching performance in *Val/Val* compared to *Met* carriers (Erickson et al., 2008), suggesting that behavioral deficits in *Val/Val* compared to *Met* carriers may have been more easily detected using IFJ-dependent cognitive tasks and in elderly subjects. This hypothesis is consistent with previous studies in healthy elderly subjects reporting behavioral deficits in *Val/Val* compared to *Met* carriers in cognitive tasks known to engage the IFJ, including the Stroop interference, auditory distraction and task-switching paradigms (Harris et al., 2006; Erickson et al., 2008; Gajewski et al., 2012; Getzmann et al., 2013).

Our genotype effect may suggest a route of vulnerability to MDD. We have recently observed that, compared to healthy controls, unmedicated depressed patients show a VS response modulated by valence but relatively insensitive to agency. This effect was also associated with an increased VS response to SA losses (Späti et al., unpublished observation), similar to our findings in *Val/Val* carriers. This may be relevant because altered striatal responses to performance-dependent monetary losses

have been reported in healthy adolescents at risk for anxiety disorder (Chronis-Tuscano et al., 2009; Helfinstein et al., 2011). Since trait anxiety and neuroticism, known risk factors for MDD, are also reportedly higher in *Val/Val* compared to *Met* carriers (Sen et al., 2003; Lang et al., 2005; Hunnerkopf et al., 2007; Frustaci et al., 2008), these results encourage speculation that altered motivational salience processing of SA losses may represent vulnerability to MDD.

Our study has some limitations. First, our sample size was relatively small. Second, feedback agency in our task required subjects to attend closely to trial-by-trial agency information, which was presented just before feedback. It is possible that genotypes differed in their ability to perform this basic discrimination and/or that differential IFJ activity reflected impaired discrimination. Speaking against this, both genotypes showed behavioral evidence of discrimination, i.e. longer reaction times for trials following a SA feedback compared to an EA feedback. Furthermore, we found no significant genotype difference in BOLD sensitivity to attribution per se (i.e. EA versus SA feedback), and participants did not report difficulty in understanding agency during debriefing. A third limitation of our study is that task difficulty was under experimental control so that we cannot assess whether IFJ is associated with poorer performance. Finally, our task is not optimal for addressing one key distinction in the feedback processing literature. Specifically, it has been proposed that the right IFJ can operate in both ‘proactive’ and ‘reactive’ modes of cognitive control, partly depending on whether subjects are anticipating financial reward or reacting to financial penalty (Locke and Braver, 2008; Braver et al., 2009). While we found no evidence of a genotype effect on the IFJ temporal dynamics across feedback conditions, our task was not designed to investigate proactive and reactive cognitive control processes.

## CONCLUSION

We found that BDNF *Val66Met* polymorphism predicts how feedback valence and agency information are combined in the VS and IFJ. This genotype effect seems to partly reduce to different responses to SA financial losses. Compared to *Met*, *Val/Val* carriers showed a lower IFJ response and an increased VS response to SA losses. Moreover, in *Val/Val* carriers greater IFJ activity was associated with higher BAS-Drive scores. These results may point to a reduced allocation of attentional resources to, and altered motivational salience of SA losses in *Val/Val* compared to *Met* carriers.

## CONFLICT OF INTEREST

None reported.

## CONTRIBUTIONS

SS designed the experiment with the support of JC, MgH and ES. JC and SS analyzed the data. JS, JB and ND conducted the experiments. JC and SS wrote the

manuscript with input from all the other authors. All authors approved the final manuscript.

**Acknowledgments**—The authors would like to thank Prof. Andreas Papassotiropoulos for the genotype analyses and Dr. Philip Stämpfli and Dr. Esther Sydekum for their invaluable assistance in the study procedures. Dr. Justin Chumbley was funded by a grant from FAN of the Zurich University Association (ZUNIV). Dr. Simona Spinelli was funded by the Swiss National Science Foundation (grant PZ00P3\_126363 to S. Spinelli). Dr. Martin Grosse Holtforth and Dr. Nadja Dörig were funded by a grant from the Swiss National Science Foundation (grant PP00P1-123377/1 to M. Grosse Holtforth) and as well as a research grant by the Foundation for Research in Science and the Humanities at the University of Zurich to M. Grosse Holtforth. We acknowledge support by the Clinical Research Priority Program “Molecular Imaging” at the University of Zurich.

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*(Accepted 8 September 2014)*  
*(Available online 16 September 2014)*