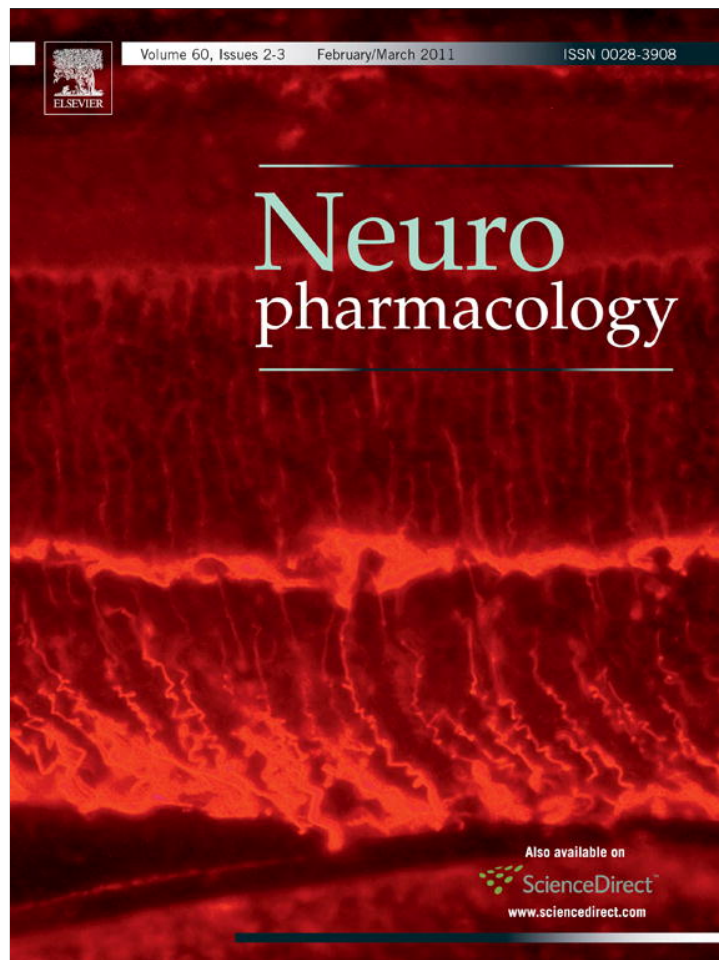


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The functional BDNF Val66Met polymorphism affects functions of pre-attentive visual sensory memory processes

Christian Beste^{a,1,*}, Daniel Schneider^{a,1}, Jörg T. Epplen^b, Larissa Arning^b

^a Institute for Cognitive Neuroscience, Department of Biopsychology, Ruhr-University Bochum, Universitätsstrasse 150, D-44780 Bochum, Germany

^b Department of Human Genetics, Medical Faculty, Ruhr-University Bochum, Germany

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ABSTRACT

The brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, is involved in nerve growth and survival. Especially, a single nucleotide polymorphism (SNP) in the *BDNF* gene, Val66Met, has gained a lot of attention, because of its effect on activity-dependent BDNF secretion and its link to impaired memory processes. We hypothesize that the BDNF Val66Met polymorphism may have modulatory effects on the visual sensory (iconic) memory performance. Two hundred and eleven healthy German students (106 female and 105 male) were included in the data analysis. Since BDNF is also discussed to be involved in the pathogenesis of depression, we additionally tested for possible interactions with depressive mood. The *BDNF* Val66Met polymorphism significantly influenced iconic-memory performance, with the combined Val/Met–Met/Met genotype group revealing less time stability of information stored in iconic memory than the Val/Val group. Furthermore, this stability was positively correlated with depressive mood exclusively in the Val/Val genotype group. Thus, these results show that the BDNF Val66Met polymorphism has an effect on pre-attentive visual sensory memory processes.

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1. Introduction

Sensations from our environment are initially registered by modality-specific, sensory memory systems (buffers) that provide an initial copy of external stimulation to human sense organs before any other cognitive operation is made on this input (Lu et al., 2005). Important or relevant information is then selected by attentional mechanisms and further processed. In the auditory domain it has been shown that sensory memory processes likely rely upon glutamatergic neural transmission and especially N-methyl-D-aspartate (NMDA) receptors (Beste et al., 2008; Javitt et al., 1996; Kreitschmann-Andermahr et al., 2001; Umbricht et al., 2002; for review: Kujala et al., 2007; Näätänen et al., 2007). In particular it has been shown that blocking NMDA-receptors induces a decline in auditory sensory memory performance (Javitt et al., 1996; Kreitschmann-Andermahr et al., 2001; Umbricht et al., 2002). Besides the glutamatergic system, also the cholinergic system has been suggested to be important for sensory memory (Woolf, 1996). The administration of scopolamine, a cholinergic antagonist, for example seems to impair rapid information

processing (Wesnes and Warburton, 1984) and lesions of the basal forebrain seem to impair processing of briefly presented stimuli (Stoehr et al., 1997). Also patients suffering from Alzheimer's disease reveal deficits in sensory memory (Engeland et al., 2002), which again underlines the relevance of the cholinergic system for these cognitive processes. However, both of these systems (the glutamatergic and the cholinergic) are strongly modulated by neurotrophic factors. Glutamatergic neural transmission via NMDA-receptors has been shown to be modulated by the brain-derived neurotrophic factor (BDNF) (Carvalho et al., 2008). BDNF seems to increase the expression of several NMDA-receptor subunits (Caldeira et al., 2007; Margottil and Domenici, 2003) and influences the activity and biophysical properties of the receptor (Carvalho et al., 2008). With respect to cholinergic processing, different neurotrophins like nerve growth factor (NGF), neurotrophin-3 (NT-3) and also BDNF have been shown to increase the production of cholinergic enzymes in cholinergic cells (Friedman et al., 1993; Nonner et al., 1996; Takei et al., 1997).

These lines of evidence suggest that BDNF may modulate sensory memory processes. Therefore, we genotyped the functional BDNF Val66Met polymorphism (rs6265) and examined associations of this functional single nucleotide polymorphism (SNP) with visual sensory (iconic) memory performance. The Met isoform is associated with activity-dependent secretion of BDNF in neurons and neurosecretory cells (Chen et al., 2005, 2006, 2004; Egan et al.,

* Corresponding author. Tel.: +49 234 322 4323; fax: +49 234 321 4377.

E-mail address: christian.beste@rub.de (C. Beste).

¹ C. Beste and D. Schneider contributed equally.

2003). Compared to the Met isoform, the more frequent Val isoform is associated with higher activity of the BDNF system (Rybakowski, 2008). These characteristics are consistent with functional deficits associated with the BDNF Met isoform concerning impairment of cognitive abilities (Beste et al., 2010a, 2010b; Chen et al., 2004). It is therefore likely that Met allele carriers reveal a compromised iconic-memory performance, when compared to Val allele carriers. However, since BDNF seems to be involved in the pathophysiology of depression (Aydemir et al., 2005; Chen et al., 2001; Gervasoni et al., 2005; Gonul et al., 2005; Karege et al., 2005, 2002) it is necessary to control for these modulatory effects, even though the BDNF Val66Met polymorphism has not consistently be shown to be associated with depressive mood (Duncan et al., 2009; Gatt et al., 2008; Gratacos et al., 2007; Groves, 2007).

2. Materials and methods

2.1. Participants

211 physically and mentally healthy, genetically unrelated German students (106 female and 105 male) participated in this study. Participants were recruited with flyers at the Ruhr-University of Bochum (Germany) and were rewarded for participation with a payment of 20€ and 2 credit points. Participants stated no history of neurological or psychiatric diseases as assessed by means of a screening questionnaire. The mean age was 24.21 (range 19–30, SD = 3.01) and mean duration of education was 13.89 years (range 10–16 yrs, SD = 1.5). The mean alcohol consumption was 2.19 units (SD = 2.61) per week. As analyzed in ANOVAs, BDNF genotype groups did not significantly differ in age, education and alcohol consumption (all *p*'s > .5). The Beck Depression Inventory (BDI) was chosen to indicate depressive mood changes. The BDI is a 21-item self-rating scale to follow individuals' depressive mood changes and to estimate the severity of depression (Richter et al., 1998). The mean BDI score was 3.6 (range 0–18, SD = 1.2). All participants were naive to the hypotheses. The study was conducted and approved by the ethics committee of the medical faculty of the Ruhr-University Bochum (Germany). All procedures were carried out with adequate understanding and written consent of the participants.

2.2. Genotyping

DNA was isolated from saliva using QIAamp DNA mini Kit (50) (Qiagen GmbH, Hilden, Germany) according to the protocol supplied by the manufacturer. Whole-genome amplification was performed using GenomiPhi DNA Amplification Kit (Amersham Biosciences). SNPs were genotyped using polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) analysis. Oligonucleotides were designed using Primer Express 2.0 Software (Applied Biosystems). PCR amplification of the *BDNF* 198-G > A (rs6265) polymorphism (Val66Met) was performed using 5'-CAAACATCCGAGGACAAGGTG-3' and 5'-GCTGCCGTTACCCACTCACT-3' as the forward and reverse primer, respectively. PCR products were digested with the restriction enzyme Tail and visualised on 2% agarose gels stained with ethidium bromide. We examined the difference of the allelic effect of the minor allele vs. the common allele using different allelic combinations corresponding to a dominant or recessive genetic effect of the rarer allele or dose-response relationships, respectively.

2.3. Partial-report task

The experimental paradigm is illustrated in Fig. 1. The task was similar to that used by Lu et al. (2005). Visual stimuli were presented on CFT-monitor (100 Hz) in a darkened room. The distance between the observer and the Monitor was approx. 52 cm. In each trial eight letters appeared simultaneously on the (105 ms presentation time). Each letter (spanning 1.3 × 1.3 visual angle) presented on the screen was randomly chosen from a set containing "D", "F", "J", "K" and shown in uppercase with .1 degree-wide strokes. The letters were arranged on a circle (radius 3.5° visual angle) around a fixation point. Each partial-report trial began with a fixation cross. After 400 ms the circular stimulus array was presented for 105 ms. Eight target-cue asynchronies (SOAs) were used. The cues occurred from 0, 11, 32, 74, 221, 516 or 1105 ms after the offset of the circular display with corresponding SOAs of 0, 116, 137, 179, 326, 621 or 1210 ms. The cues (arrow) were oriented in a way that a cue pointed towards a specific point on the circle, where the letters had previously been presented. In all SOA conditions the cue stayed at the monitor until the response. The subjects were asked to indicate via button presses on the corresponding letters on a computer keyboard ("D", "F", "J", "K"), which letter had been on the position the cue is currently directed to. The experiment was divided into 9 blocks of 50 trials each, with each SOA occurring equally frequent within all 9 blocks. On average each SOA was presented 65 times across the whole experiment. The first block was considered as training and hence omitted from data analysis (i.e. 8 blocks were

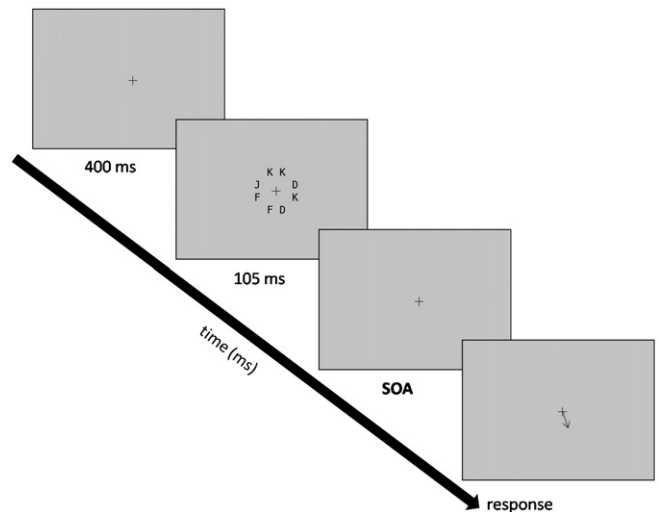


Fig. 1. Schematic illustration of the experimental paradigm to measure iconic-memory performance. At the beginning of each trial the central fixation cross is presented for 400 ms and followed by a 105 ms lasting presentation of the eight random "D", "F", "J", "K" letters. With a certain target-cue onset asynchrony (SOA) an arrow is shown pointing towards the letter to be reported (correct response here: "D").

analyzed). The whole procedure lasted approx. 20 min. To estimate the time course of iconic memory, the following exponential-decay function (Gegenfurtner and Sperling, 1993; Lu et al., 2005) was fitted onto the data (frequency of correct responses) of each participant:

$$D'(SOA) = a_0 + a_1 e^{-SOA/\tau}$$

This fitting was performed using the MATLAB Curve-fitting Toolbox applying the Levenberg–Marquart algorithm for the estimation of the three variables *a*₀, *a*₁ and *τ* (tau). Each experimental block was fitted separately. In the function, *a*₁ is the fast-decaying sensitivity that reflects the initial visual availability of stimulus information, *τ* is the time constant of the fast-decay sensitivity that represents the duration of iconic memory, and *a*₀ is the sensitivity at long delays that reflects the amount of information transferred into short-term memory without the benefit of cuing (Gegenfurtner and Sperling, 1993; Lu et al., 2005).

2.4. Statistical analyses

Behavioural indices of task performance as well as computed parameters of exponential-decay function were analyzed using single- or repeated analyses of variance (ANOVAs). All variables subjected to analyses of variance were normal distributed as indicated by Kolmogorov–Smirnow tests (all *z*'s < .3; *p* > .4). In all analyses, Greenhouse–Geisser corrections were applied whenever appropriate.

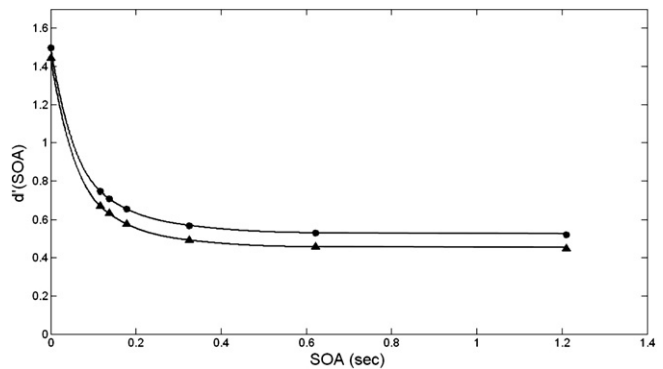


Fig. 2. Exponential-decay functions in dependence of BDNF isoforms. An exponential-decay function was employed to fit the relationship between *d'* values as functions of target-cue asynchronies (SOAs) for the two BDNF isoform groups (Val/Val vs. Val/Met–Met/Met). The curves represent the mean fit of the exponential-decay function for the two groups. The line connecting triangles denotes the Val/Met–Met/Met group, the line with circles represents the Val/Val group.

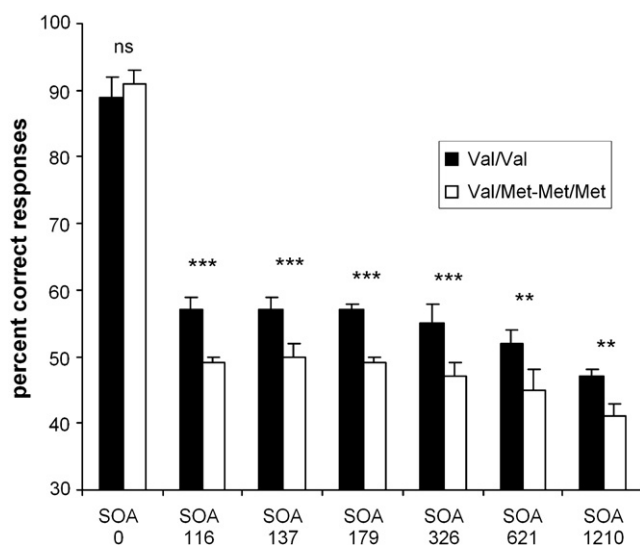


Fig. 3. Percentage of correct responses at each SOA time point. Means (\pm SEM) of the percentage of correct responses are shown at each SOA as given for the Val/Val encoding genotype and the combined Val/Met–Met/Met encoding genotype groups.

Post-hoc tests were Bonferroni-corrected, wherever necessary. The mean and standard errors of the mean (SEM) are given.

3. Results

3.1. Genotyping

The genotype distribution of the Val66Met polymorphism in our German healthy cohort comprised 119 Val/Val homozygotes (56%), 82 Val/Met heterozygotes (39%) and 10 Met/Met homozygous subjects (5%). These allele frequencies are consistent with those reported previously for individuals of Caucasian descent (Li et al., 2009). The distribution of genotypes did not differ from the frequencies expected from Hardy–Weinberg equilibrium.

3.2. Partial report

The average exponential-decay function in the partial-report procedure is plotted in Fig. 2 for the two BDNF groups (Val/Val vs. combined Val/Met–Met/Met). From the SOA at 116 ms onwards, the overall exponential-decay functions of the Val/Val homozygotes exceed the values of Met carriers, thus demonstrating better

performance of Val/Val homozygous subjects in the partial-report task.

Next, with respect to the BDNF Val66Met polymorphism the percentage of correct responses was analyzed via repeated measures ANOVA using the factors “block” and “SOA” as within-subject factors and “genotype group” as between-subject factor. The performance augmented across blocks (main effect “block”, $F(7,1463) = 22.33$; $p < .001$; $\eta = .097$), thus indicating a practice effect. Yet, this effect was not different for the genotype groups, as indicated by the non-significant interaction “block \times genotype” ($F(7,1463) = .9$; $p > .3$; $\eta = .009$). As expected, the main effect “SOA” was significant ($F(6,1254) = 946.61$; $p < .001$; $\eta = .819$). Performance dropped remarkably from SOA 0 to SOA 116 ($p < .001$), remained stable for SOAs 116, 137 and 179 ($p > .2$) and then decreased further with increasing SOAs ($p < .01$). Fig. 3 shows the percentage of correct responses at each SOA time point.

The effect of “SOA” was different for the genotype groups, as indicated by the interaction “SOA \times genotype” ($F(6,1254) = 15.54$; $p < .001$; $\eta = .069$). This interaction was due to the fact that the genotype groups did not differ in their performance at SOA 0 ($p > .8$), but on all other SOA ($p < .01$, Fig. 3). All other main or interaction effects were not significant (all F s $< .99$; $p > .4$; $\eta = .005$). In the conditions with SOA > 0 , the frequency of correct responses is correlated with τ , the time constant of the fast-decay sensitivity that represents the duration of iconic memory (all $.388 \leq r \leq .533$; $p < .001$). In the condition SOA 0, no correlation is evident ($r = -.09$; $p > .36$). Thus, the lack of genotype differences in SOA 0 driving the above described interaction, provides additional information beyond τ .

Fig. 4 shows the mean values of the different parameters of the exponential-decay function (a_0 , a_1 and τ) in the BDNF isoform groups (Val/Val vs. Val/Met–Met/Met). A repeated measures ANOVA using the factor “block” as within-subject factor and “genotype group” as between-subject factor revealed a main effect “genotype group” in which τ was elevated in the Val/Val homozygous individuals ($.73 \pm .03$) as compared to the combined Val/Met–Met/Met group ($.21 \pm .04$, Fig. 3, $F(1,209) = 92.20$; $p < .001$; $\eta = .306$). Yet, τ was not different for the blocks ($F(7,1463) = .64$; $p > .7$; $\eta = .003$), and there was no interaction “block \times genotype group” ($F(7,1463) = .54$; $p > .8$; $\eta = .003$). ANOVAs on parameters a_0 (sensitivity at long delays that reflects the amount of information transferred into short-term memory without the benefit of cuing of the exponential-decay function) and a_1 (the fast-decaying sensitivity that reflects the initial visual availability of stimulus information) revealed no significant effects (all F s $< .37$; $p > .5$; $\eta < .003$).

Analyzing the reaction times (RTs) using a similar ANOVA as for the percentage of correct responses exclusively revealed a main

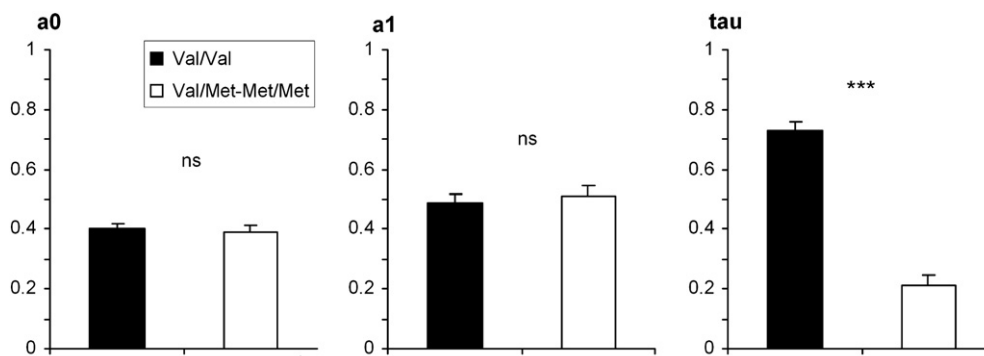


Fig. 4. Parameters of the exponential-decay function for the BDNF isoform groups. Mean values of the different parameters of the exponential-decay function (a_0 , a_1 and τ) are given (\pm SEM) for the BDNF isoform groups (Val/Val vs. Val/Met–Met/Met).

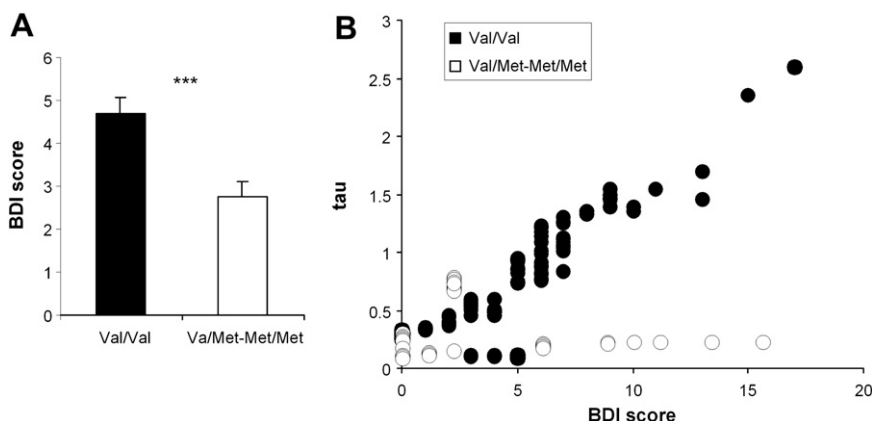


Fig. 5. Associations of BDNF isoform groups with the BDI score. (A) Overall differences in the BDI mean score (±SEM) in the two BDNF isoform groups (Val/Val vs. Val/Met–Met/Met) (B) Plot of estimated iconic-memory lifetime (τ) vs. BDI score in the two BDNF isoform groups.

effect “SOA” denoting that RTs increase with increasing SOAs ($F(7,1463) = 159.39; p < .001; \eta = .433$). No main or interaction effect with “genotype group” was evident here (all F s $< .59; p > .6; \eta = .004$).

Additionally, we examined the association between the BDNF Val66Met polymorphism and BDI-scores. These analyses revealed that there were differences in depressive mood with regard to the BDNF genotypes. Individuals carrying at least one Met encoding allele (Val/Met–Met/Met group) showed significantly lower mean BDI-scores as compared to Val/Val carriers ($F(1,209) = 17.94; p < .001; \eta = .079$, Fig. 5A).

Furthermore, we evaluated whether the significant association between the BDNF Val66Met and depression score also influences the aforementioned pattern of results. Because τ differentiated most between the genotype groups, this parameter was further investigated in relation to the BDI score within each BDNF group. These analyses revealed a positive linear correlation between BDI-scores and τ in the Val/Val homozygous individuals ($r = .880; p < .001; R^2 = .64$), while no correlation was evident in the combined Val/Met–Met/Met group ($r = -.014; p < .449; R^2 = .0001$). The results are plotted in Fig. 5B.

Regression analyses were performed in order to examine the amount of explained variance for the factor “genotype group” and “BDI”. The results are given in Table 1. It is shown that both, the factor “genotype” and the factor “BDI score” additively influenced the time constant of the fast-decay sensitivity that represents the duration of iconic memory (i.e. tau).

4. Discussion

This study examined whether the BDNF Val66Met polymorphism relates to individual differences in the sensory memory (iconic memory) processes examined by means of a partial-report paradigm. The results showed that the Val/Val group revealed a higher time constant of the fast-decay sensitivity, compared to the combined Val/Met–Met/Met group. This suggests that information can be held for longer time in the iconic memory in

individuals of the Val/Val group. This latter group also revealed a concomitant better performance in the partial-report task. This genotype effect was only evident in SOAs from 116 ms to 1210 ms, but not at SOA 0, thus suggesting that BDNF is only relevant when information has to be held in iconic-memory buffers. Moreover, the results revealed that affective scores (depression scores) further modulated these patterns.

The results reveal substantial association of iconic-memory performance with the functional BDNF Val66Met polymorphism, especially the duration of iconic memory as reflected by the τ parameter varies depending on the BDNF genotype. Since BDNF influences glutamatergic synapses (Carvalho et al., 2008), and the Val encoding allele is associated with higher activity of the BDNF system (Rybakowski, 2008), Val/Val homozygous individuals may exhibit either an increase of the NR1, NR2A and NR2B receptor subunits (Caldeira et al., 2007; Margottil and Domenici, 2003) and/or potentiated NMDA-receptor currents (Sandoval et al., 2007). Both factors likely increase NMDA-receptor mediated neural transmission, which may in turn increase iconic-memory performance. Furthermore, BDNF is also able to increase acetylcholine (ACh) release in a concentration-dependent manner in cholinergic neurons (Auld et al., 2001). These results may, therefore, also support the assumption that the cholinergic system is involved in sensory memory processes. The fact that no differentiating effects of the BDNF genotype are evident when letter and cue occur simultaneously (SOA = 0), highlights the crucial role of BDNF in the process of maintaining information in iconic memory and shows that BDNF gets only important when there is delay period in which information has to be held in working memory buffers. Yet, only the duration of iconic memory, but not the sensitivity at long delays reflecting the amount of information transferred into short-term memory (a_0) and the fast-decaying sensitivity reflecting the initial visual availability of stimulus information (a_1) was affected by the BDNF genotypes. This dissociation between parameters shows that BDNF seems to modulate highly circumscribed cognitive sub-processes related to iconic memory.

Yet, this modulation of circumscribed iconic-memory sub-processes by BDNF is further modulated by depressive mood of the subjects. The results indicate that the BDNF Val66Met polymorphism may account for a modest amount of variance in depressive mood as measured by the BDI. These results are consistent with previously reported data that also revealed the Val/Val encoding genotype to be associated with higher scores of the BDI and other personality facets associated with depression in healthy individuals (Duncan et al., 2009; Lang et al., 2005; Sen et al.,

Table 1
Results of the step-wise regression analyses. Delta R2 denotes the differences of explained variance with respect to the simpler model.

Model	R	R2	Delta R2	F	Sig
BDNF genotype group	.553	.306		$F(1,209) = 92.20$	<.001
BDNF genotype group*BDI	.754	.569	.263	$F(1,209) = 137.19$	<.001

2008). This finding is counter-intuitive, as this finding suggests that patients suffering under major depressive disorder may show increased functioning in this circumscribed cognitive process, which would then sharply contrast with deficits in other memory functions in depressive disorders, as frequently reported in literature (e.g. *Gottlib and Joormann, 2010*). To the best of our knowledge, no study has addressed this question.

In order to clarify the interrelations of different neurotransmitter receptor systems and neurotrophic factors which are important for modulations of sensory memory processes future studies should recruit larger cohorts to allow for more comprehensive analyses of different genes and gene–gene interactions that are relevant for sensory memory performance. Additionally, replication in independent and larger cohorts as well as in clinical samples of depression patients is of interest in order to validate the results and to prove the relevance of iconic-memory functions as a putative endophenotype for mood disorders.

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