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

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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.

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.,

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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 TaiI 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 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:

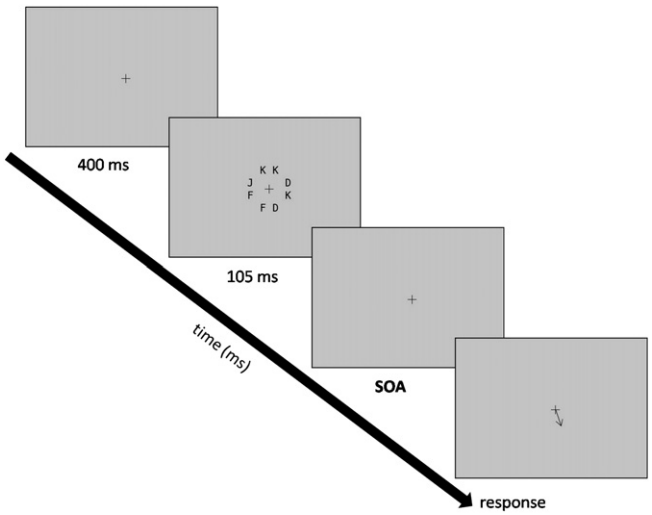

Fig. 1. Schematic illustration of the experimental paradigm to measure iconic-memory performance. At the beginning of each trial the central fixation cross is presented for 400 ms and followed by a 105 ms lasting presentation of the eight random "D", "F", "J", "K" letters. With a certain target-cue onset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

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

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.

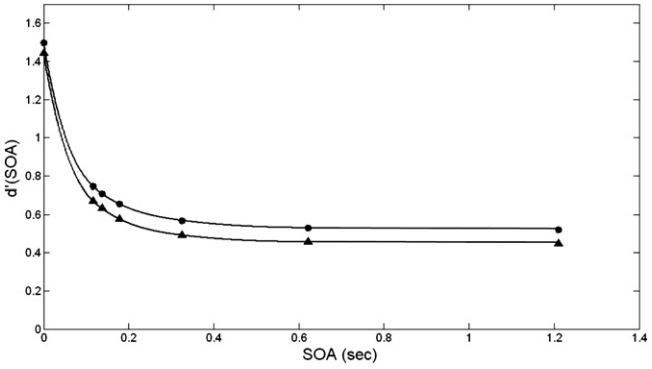

Fig. 2. Exponential-decay functions in dependence of BDNF isoforms. An exponential-decay function was employed to fit the relationship between d' values as functions of target-cue asynchronies (SOAs) for the two BDNF isoform groups (Val/Val *vs.* Val/Met–Met/Met). The curves represent the mean fit of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