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BDNF Val66Met polymorphism and goal-directed behavior in healthy elderly — evidence from auditory distraction

Stephan Getzmann [a,*], Patrick D. Gajewski [a], Jan G. Hengstler [a], Michael Falkenstein [a], Christian Beste [b]

[a] Leibniz Research Centre for Working Environment and Human Factors at the Technical University of Dortmund (IfADo), Germany
[b] Institute for Cognitive Neuroscience, Biopsychology, Ruhr-University Bochum, Germany

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ABSTRACT

Aging affects the ability to focus attention on a given task and to ignore distractors. These functions subserve response control processes for which fronto-striatal networks have been shown to play an important role. Within these networks, the brain-derived-neurotrophic-factor (BDNF), which is known to underlie aging effects, plays a pivotal role. We investigated how cognitive subprocesses constituting a cycle of distraction, orientation and refocusing of attention are affected by the functional BDNF Val66Met polymorphism using event-related potentials (ERPs) in 122 healthy elderly. Using an auditory distraction paradigm we found that the Val/Val genotype confers a disadvantage to its carriers. This disadvantage was partly compensated by intensified attentional shifting mechanisms. It could be based on response selection processes being more vulnerable against interference from distractors in this genotype group. Processes reflecting transient sensory memory processes, or the re-orientation of attention were not affected by the BDNF Val66Met polymorphism, suggesting a higher importance of BDNF for mechanisms related to response control, than stimulus processing. The results add on recent literature showing that the Met allele confers some benefit to its carriers. We suggest an account for unifying different results of BDNF Val66Met association studies in executive functions, based on the role of BDNF in fronto-striatal circuits.

Introduction

To achieve efficient and smoothly unfolding of behavioral control, attentional and action selection processes have to be orchestrated (Duncan, 2006; Redgrave et al., 1999). Infrequent unpredictable events are automatically detected and may trigger an orienting response that may lead to a deterioration of performance in the primary task at hand (e.g. Horváth et al., 2009; Ruzzoli et al., 2012; Schröger, 1997). This interplay of goal-directed and orientation-related cognitive processes has been described within a three stage model (e.g. Polich and Criado, 2006; Escera et al., 2000; Schröger and Wolff, 1998): Here, the first stage filters task-relevant information and automatically detects task-irrelevant information, which violates sensory regularities in sensory memory buffers. These irregularities lead to involuntary attention shifts at the second stage, which may be subsequently compensated by mechanisms in the third stage (Horváth et al., 2009).

The interplay of involuntary attention shifts and top–down attentional control subserving action selection mechanisms has been shown to be sensitive towards age-related processes (Cooper et al., 2006; Horváth et al., 2009; Ruzzoli et al., 2012), resulting in an increased susceptibility to distracting stimuli in old age. In aging, fronto-striatal circuits have been shown to be compromised (e.g. Buckner, 2004). In particular, it has been shown that basal ganglia gray matter volume declines in aging (Gunning-Dixon et al., 1998; Raz et al., 2003) and especially so in the caudate head (Koikkalainen et al., 2007). This may partly be due to the fact that secretion of the brain-derived-neurotrophic-factor (BDNF), which is necessary for the structural integrity of the basal ganglia (Han et al., 2010), is decreased in aging (Hayashi et al., 2001; Pang and Lu, 2004). In fronto-striatal circuits, BDNF further modulates the efficacy of glutamatergic cortico-striatal neural transmission (Foltynie et al., 2009; Han et al., 2010; Kleim et al., 2006; Mattson, 2008).

These mechanisms have been found to be crucial for the interplay of attentional shifts and top–down attentional control (Beste et al., 2011; Beste et al., 2012) and especially so in an auditory distraction paradigm (Schröger and Wolff, 1998) in which infrequent deviant pitches distracted attention necessary to solve a primary task, i.e., judging the length of tones (Beste et al., 2008). The striatum appears to play a pivotal role, as it has been shown to contain auditory sensory neurons (Nagy et al., 2005), to be involved in sound discrimination (Kropotov et al., 2000; Saft et al., 2008), and to be especially important for the prediction of upcoming auditory events (Grahn and Rowe, 2012) and context (Geiser et al., 2012). These properties play an important role in the above mentioned paradigm (Schröger and Wolff, 1998). As far as

* Corresponding author at: Leibniz Research Centre for Working Environment and Human Factors, Ardeystraße 67, D-44139 Dortmund, Germany. Fax: +49 231 1084 401.
E-mail address: stephan.getzmann@rub.de (S. Getzmann).

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BDNF plays a major role in striatal integrity in aging, which has been shown to be important in auditory perception, attentional shifts and top–down attentional control, BDNF may be a crucial modulator of interindividual differences in the processes.

In-vivo access to neurobiological factors modulating cognitive processes can be achieved by means of candidate gene association studies (van Thriel et al., 2012). For BDNF, the functional BDNF Val66Met polymorphism (Chen et al., 2004; Egan et al., 2003) has widely been studied for various cognitive processes (e.g. Gatt et al., 2007; Schofield et al., 2009; review: Dincheva et al., 2012). However, the association pattern is not conclusive (review: Mandelman and Grigorenko, 2012), partly because of pleiotrophic effects (e.g. Beste et al., 2010a, 2010b; Kennedy et al., 2009; Thomason et al., 2009). In the elderly, previous results indicated compromised cognitive functions in Met-allele carriers (Miyajima et al., 2008). On the other hand, there is evidence for better cognitive functions in Met-allele carriers (Erickson et al., 2008; Gajewski et al., 2011; Matsushita et al., 2005; Ventriglia et al., 2002). The contradictory effects observed in the Met-allele carriers may be explained by different age-related manifestations of this genotype (Lindenberger et al., 2008), or by the variability of BDNF isoforms and the diversity of transcripts in different brain areas (Mandelman and Grigorenko, 2012). To approach a more unique picture of associations between BDNF Val66Met and cognitive functions Mandelman and Grigorenko (2012) suggested that "cognitive phenotypes should be grouped on the basis of their similarities in the brain activation pathways that underlie these phenotypes (p. 131)". To approach this goal it is necessary to accumulate further data on the effects of BDNF Val66Met effects on cognitive processes that have already been shown to be modulated by circumscribed mechanisms, e.g. fronto-striatal circuits. In this regard the experimental paradigm used should be sensitive to mechanisms modulating fronto-striatal circuits.

Here, we examined goal-directed behavior and its interplay with attention-related cognitive processes in an auditory distraction paradigm that has been shown to be at least partly reliant on fronto-striatal circuits (Beste et al., 2008; Beste et al., 2011; Beste et al., 2012), and we expected that goal-directed behavior is more efficient in Met-allele carriers, than in Val/Val genotype carriers. To disentangle the different cognitive subprocesses involved in the cycle of distraction, orientation, and refocusing of attention described within a three stage model, we analyzed event-related potentials (ERPs). While the early ERP components (P1 and N1) generally reflect transient stimulus detection in the auditory system (Näätänen and Picton, 1987), processes of deviance detection in sensory memory, as the first stage of the three stage model are reflected by the mismatch negativity (MMN) (e.g. Näätänen and Picton, 1987; Sussman et al., 2003), which has been shown to decline with aging (e.g. Cooper et al., 2006; Czigler et al., 1992; Ruzzoli et al., 2012). Similarly, attentional shifting processes occurring in the second stage, which are reflected by the frontal P3 (P3a) (e.g. Beste et al., 2008; Escera et al., 2000; Schröger, 1996), have been shown to decline with aging (Fjell and Walhovd, 2004; Mager et al., 2005). On the other hand, there is also evidence suggesting the P3a to be a correlate of allocation of attentional processing resources (Polich, 2007), and as an adjustment of mental resources (Getzmann and Falkenstein, 2011). Processes related to the recovery from distraction (i.e. third stage processes) are reflected by the re-orienting negativity (RON) (e.g. Schröger et al., 2000), and have also been found to decline with aging (e.g. Mager et al., 2005). The combination of analysis of ERPs elicited in the auditory distraction paradigm and the three-stage model thus provides a theoretical basis for investigation of the different cognitive subprocesses involved in the distraction–orientation–refocusing cycle: Specifically, differences between Met-allele and Val/Val genotype carriers in the early components (i.e., P1, N1, MMN) would suggest that differences in performance are based on differences in early auditory processing or initial deviance detection; in contrast, differences in P3a or RON would suggest deficits to be based on differences in attentional orienting or re-orienting attentional shifting.

Methods

Participants

A total of 122 healthy volunteers, all of Caucasian descent (mean age 70.4 years; range 65–88 years; 46 female; 111 right-handed), took part in the study. All subjects reported normal hearing and were able to distinguish the tone pitches of the frequent and deviant stimuli employed in the auditory distraction task. The scope of the study was explained to the subjects, and they gave written informed consent before any study protocol was commenced. They received a payment for their participation. The sample consisted of 74 subjects carrying the Val/Val genotype, 44 carrying the Val/Met genotype and 4 subjects carrying the Met/Met genotype group. The distribution of genotypes in the sample did not differ from the Hardy–Weinberg equilibrium ($p = 0.39$, as determined by the program Finetti provided as an online source ihg.gsf.de/cgi-bin/hw/hwa1.pl; T.F. Wienker and T.M. Strom). As in a previous study (Gajewski et al., 2011), the Val/Met and Met/Met genotype group were combined into one group (i.e., Val/Met-Met/Met genotype group). The two subgroups (Val/Val genotype and Val/Met-Met/Met genotype) did not differ significantly regarding gender distribution, age, and a number of neuropsychological and psychiatric parameters (Table 1). The study conformed to the Code of Ethics of the World Medical Association (Declaration of Helsinki) and was approved by the local Ethical Committee of the Leibniz association.

Genotyping

Isolation of genomic DNA of leukocytes was performed according to standard procedures. Analysis of the [A/G] substitution (rs6265) of BDNF on chromosome 11p14 and differentiation between the homozygous (A/A), homozygous (G/G) and the heterozygous (A/G) form of the sequence: CATCATTGGCTGACACTTTCGAACAC[A/G]TG ATAGAAGAGCTGTTGGATGAGGA was detected via TaqMan_Assay (e.g., Golka et al., 2009). Briefly, 5–8 mL of venous blood was taken into a 9 mL tube (Sarstedt, Nümbrecht, Germany) from the cubital vein with EDTA as the anticoagulant and was frozen at −20 °C. DNA was isolated using a QIAamp DNA Blood Maxi Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol (Arand et al., 1996). DNA concentrations were determined using a NanoDrop ND-1000 UV/visspectrophotometer (PEQLAB Biotechnologie, GmbH, Erlangen, Germany). Genotyping was performed on an ABI7500 Sequence Detection System with the use of TaqMan® assays (Applied Biosystems, Darmstadt, Germany). A final reaction volume of 15 μL was used per well of a 96-well plate. The reaction mix for amplification was prepared by mixing 7.5 μL TaqMan Universal PCR Master Mix (Applied Biosystems, Foster City, CA, USA) and 0.75 μL working stock of SNP Genotyping Assay (Applied Biosystems) per sample. To this reaction mixture 1 μL DNA solution (with a total of 10 ng DNA) and 5.75 μL distilled water were added to achieve a final volume of 15 μL. Amplification was performed using a protocol with 40 cycles, 15 s at 92 °C (denature), 1 min at 60 °C (anneal/extend). An initial hold with 10 min at 95 °C was applied. Analysis of data was performed according to the manufacturer's instructions (Applied Biosystems 7300/7500/7500, fast real-time PCR System Allelic Discrimination Getting Started Guide).

Stimuli, task, and procedure

The paradigm is similar to that of Schröger and Wolff (1998). The auditory stimuli were sine waves composed of base frequencies of either 500 Hz, 1000 Hz, or 2000 Hz. The stimuli were generated digitally using CoolEdit 2000 (Syntrillium Software Co., Phoenix, AZ, USA), and were presented binaurally using stereo headphones (AKG, K271 Studio) at the intensity of 70 dB(A). The auditory stimuli were short (200 ms) and long (400 ms) tones (both including 5 ms rise and

Table 1
Sample characteristics and results of the neuropsychological assessment for the Val/Val and Val/Met-Met/Met genotype groups.

	Val/Val	Val/Met-Met/Met	*F* (*df*)	*p*
Number	n = 74	n = 48		
Age	70.8 (4.4)	69.6 (4.0)	$F(1, 121) = 2.1$	ns
MMSE	28.4 (1.9)	28.6 (1.6)	$F(1, 121) < 1$	ns
BDI	4.9 (3.5)	4.8 (3.7)	$F(1, 121) < 1$	ns
NEO-FFI[a]				
Neuroticism	1.4 (0.5)	1.5 (0.5)	$F(1, 120) < 1$	ns
Extraversion	2.1 (.05)	2.0 (0.5)	$F(1, 120) = 1.6$	ns
Openness to experience	2.1 (0.5)	2.1 (0.5)	$F(1, 120) < 1$	ns
Agreeableness	2.3 (0.6)	2.1 (0.6)	$F(1, 120) = 2.1$	ns
Conscientiousness	2.6 (0.6)	2.6 (0.6)	$F(1, 120) < 1$	ns
D2				
Total number of symbols	380 (87.5)	406 (80.3)	$F(1, 120) = 2.8$	ns
Number omitted symbols	21 (17.2)	22 (22.4)	$F(1, 120) < 1$	ns
Number confused symbols	4.7 (7.4)	5.4 (7.5)	$F(1, 120) < 1$	ns
Digit-symbol-test				
Total number of symbols	44.7 (10.6)	44.2 (10.1)	$F(1, 120) < 1$	ns
Number correct	44.6 (10.9)	44.2 (10.0)	$F(1, 120) < 1$	ns
Stroop				
Word reading	14.1 (2.3)	14.7 (3.8)	$F(1, 120) = 1.5$	ns
Color naming	21.5 (3.5)	22.4 (6.2)	$F(1, 120) = 1.0$	ns
Interference list	43.1 (7.8)	45.5 (14.4)	$F(1, 120) = 1.4$	ns
Digit-span				
Forward	3.5 (0.9)	4.2 (3.9)	$F(1, 120) = 2.3$	ns
Backward	2.7 (0.7)	3.0 (0.9)	$F(1, 120) = 1.9$	ns
Word-fluency	31.0 (3.3)	31.5 (2.7)	$F(1, 120) < 1$	ns
MWT-B (multiple choice word test)				
Number total	83.0 (20.0)	84.9 (17.3)	$F(1, 120) < 1$	ns
IQ	116.5 (12.1)	117.3 (11.9)	$F(1, 120) < 1$	ns
CVLT				
Total score trials 1 to 5	37.3 (9.9)	38.0 (7.9)	$F(1, 120) < 1$	ns
Delayed recognition	12.5 (2.2)	13.0 (1.8)	$F(1, 120) = 2.2$	ns
Rey-Figure (ROCF)				
Reproduction	33.6 (2.9)	33.3 (3.3)	$F(1, 120) < 1$	ns
Delayed recall	15.7 (5.6)	16.3 (5.9)	$F(1, 120) < 1$	ns
Mental rotation				
Total number	6.8 (2.8)	7.0 (3.2)	$F(1, 120) < 1$	ns
Number correct	5.5 (2.9)	5.9 (3.2)	$F(1, 120) < 1$	ns
TMT[a]				
TMT-A	36.5 (12.7)	38.6 (11.2)	$F(1, 111) < 1$	ns
TMT-B	101.0 (41.5)	93.4 (36.0)	$F(1, 111) < 1$	ns
CFQ[a]				
Total score	29.2 (11.1)	28 (10.6)	$F(1, 120) < 1$	ns

Significance level was set at $p < 0.05$.
Key: BDI, Beck Depression Inventory; CFQ, Cognitive Failures Questionnaire; CVLT, California Verbal Learning Test; D2, Test of Attention; MMSE, Mini Mental State Examination; MWT-B, test of premorbid intelligence; NEO-FFI, "Big Five" personality factors questionnaire; ROCF, Rey–Osterrieth Complex Figure Test; TMT, Trail Making Test.
[a] Reduced number of participants.

5 ms fall times) presented with equal probability. 80% of these long and short tones were frequent standard stimuli (1000 Hz), and 20% were rare deviant stimuli (either 500 Hz or 2000 Hz, each 10%). The sequence of standard and deviant stimuli was pseudo-randomized. During testing, the participants sat on a comfortable chair in a dimly lit and quiet room. Employing a two-alternative forced-choice duration discrimination task, the participants had to determine the duration of the tones. They had to press one response button for short and another for long tones irrespective of the pitch of the tone. The response buttons were held in the subject's hands. The duration-hand contingency was counterbalanced between participants. Participants were instructed to respond in a fast but accurate manner. To avoid EEG alpha-activity and wandering eye-movements during the recordings, participants were instructed to keep their eyes open and to focus on a visual fixation point presented at a monitor placed in front of them. The participants were given a written instruction that explained the task, and the instruction was also explained by the experimenter before starting the test. No feedback was given to the participants at any time during the experiment.

At the beginning of the session, the participants carried out a short training until the task was familiar. Then, all participants completed two test blocks interrupted by a rest break. A test block consisted of 120 trials (48 short and 48 long standard tones and 12 short and 12 long deviant tones). The stimulus onset asynchrony was 1400 ms. The timing of the stimuli and the recording of the participants responses were controlled by custom-written software. Reaction times (RTs) were measured by a high-resolution timer interface connected with the external response buttons.

Data recording

The continuous EEG (amplifier bandpass 0.01–140 Hz) was sampled at 2048 Hz using 32 Ag/AgCl electrodes mounted on an elastic cap according to the extended 10–20 system. The montage included 8 midline sites and 12 sites on each hemisphere. Horizontal and vertical eye positions were recorded by EOG using 4 electrodes positioned around both eyes. The ground electrode was placed on the center of the forehead, just above the nasion. Two additional electrodes were placed on the left and right mastoids (M1 and M2). Electrode impedance was kept below 10 kΩ. The raw data were offline downscaled to a sampling rate of 1000 Hz, band-pass filtered (cut-off frequencies 0.05 and 17 Hz), re-referenced to linked mastoids, and segmented into 1300-ms stimulus-locked epochs covering the period from −100 to 1200 ms relative to tone onset, using the Brain Vision Analyzer software (Version 1.05; Brain Products, Munich, Germany). The data were corrected for ocular artifacts using the Gratton and Coles procedure (Gratton et al., 1983). Individual epochs exceeding a maximum–minimum difference of 300 μV were excluded from further analysis (automatic artifact rejection as implemented in the BrainVision Analyzer software). The remaining epochs were baseline corrected with reference to a 100-ms prestimulus window. Finally, the epochs were averaged for each participant, separately for standard and deviant tones. To improve the signal-to-noise ratio of the EEG signal, trials with short and long tones were pooled, and averaged across the two test blocks.

Data analysis

RT was defined as the time between the offset of the 200-ms tone and the push of a response button. Individual RTs of less than 100 ms and more than 1200 ms, as well as error trials were excluded from further analysis. Rates of correct responses and mean RTs were subjected to an analysis of variance (ANOVA) design with the within-subject factor Stimulus (standard vs. deviant tone) and the between-subject factor BDNF genotype (Val/Val vs. combined Val/Met-Met/Met) group. Group differences were assessed using one-way ANOVAs with Bonferroni-corrected post-hoc testing.

The ERP analysis was restricted to midline electrodes (Fz, FCz, Cz, and Pz) chosen to be commensurate with previous knowledge of the topographical scalp distribution of specific ERPs (for review, Barrett et al., 1987; Friedman et al., 1993; Lovrich et al., 1988; Näätänen and Picton, 1987; Polich, 1986, 2007; Smith et al., 1980), indicating that the P1 and N1 typically peak over fronto-central areas (FCz), the P3a over frontal areas (Fz), and the P3b over parietal areas (Pz) of the scalp. Peak amplitudes and latencies of these components were defined as their local maximum positivity or negativity within a particular latency window (P1 at FCz: 0–100 ms; N1 at FCz: 50–150 ms, P3a at Fz: 225–400 ms; P3b at Pz: 400–700 ms after tone onset). The amplitudes and latencies of these components were subjected to ANOVAs with the within-subject factor Stimulus (standard vs. deviant tone) and the between-subject factor Genotype (Val/Val vs. combined Val/Met-Met/Met group). To analyze the deviance-related MMN and RON components, difference waves were calculated

(deviant minus standard), and peak amplitudes and latencies were defined as the most negative peaks at Fz in the time range 100–200 ms (MMN) and 400–700 ms (RON) after tone onset. The amplitudes and latencies of MMN and RON were subjected to one-way ANOVAs with the between-subject factor BDNF genotype (Val/Val vs. combined Val/Met-Met/Met group). To test specific effects or interactions, additional one-way ANOVAs with Bonferroni-corrected post-hoc tests were employed, and only the corrected probability values are reported.

Results

Behavioral data

The BDNF genotype subgroups differed significantly in performance: The combined Val/Met-Met/Met group produced overall more correct responses than the Val/Val group, according to a main effect of Genotype (85.5% vs. 77.2%; $F[1,120]=7.16$; $p<0.01$; $\eta^2=0.056$; Fig. 1A). Moreover, there was a significant interaction of Stimulus and Genotype ($F[1,120]=8.98$; $p<0.005$; $\eta^2=0.070$), resulting from the fact that the rate of correct responses of the Val/Val group was especially reduced with the deviant tones, relative to the combined Val/Met-Met/Met group, whereas both subgroups did marginally differ in their rate of correct responses with the standard tones. This was confirmed by additional ANOVAs, separately for deviant and standard tones, revealing a significant main effect of Genotype with the deviant tones ($F[1,120]=11.00$; $p<0.005$; $\eta^2=0.084$), but not standard tones ($F[1,120]=3.20$; $p>0.05$; $\eta^2=0.026$). There was no main effect of Genotype on RTs ($F[1,120]=2.17$; $p>0.05$; $\eta^2=0.018$), and no interaction of Genotype and Stimulus ($F[1,120]=0.58$; $p>0.05$; $\eta^2=0.005$), but a main effect of Stimulus ($F[1,120]=121.22$; $p<0.001$; $\eta^2=0.503$) indicated that RTs were longer with deviant than standard tones (Fig. 1B). In sum, the behavioral data indicated that the performance of the Val/Val genotype in duration discrimination is impaired when the stimuli were rare deviant tones, relative to the performance of the combined Val/Met-Met/Met genotype.

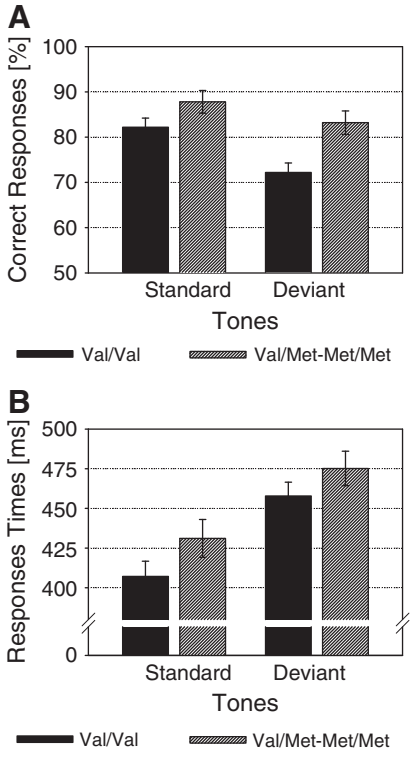

Fig. 1. Rates of correct responses (A) and response times (B) for the brain-derived neurotrophic factor (BDNF) Val/Val and Val/Met-Met/Met groups, shown separately for the frequent standard tones (stan) and the rare deviant tones (dev). Error bars indicate standard errors across participants (Val/Val: $N=74$; Val/Met-Met/Met: $N=48$).

ERP data

Grand average ERP-waveforms for standard and deviant tones at Fz, FCz, Cz, and Pz averaged across test blocks are shown in Fig. 2A for each of the two 2 BDNF genotype groups. The difference waveforms (deviant minus standard tones) are shown in Fig. 2B.

P1

The P1 peaked at 39 ms after tone onset over fronto-central brain areas. There were no main effects of Genotype or Stimulus, and no interaction of Genotype and Stimulus, neither on P1 amplitudes, nor P1 latencies (all $p>0.05$).

N1

The N1 amplitude reached its maximum over fronto-central brain areas. It was larger with deviant than standard tones (−5.2 μV vs. −4.5 μV; $F[1,120]=22.70$; $p<0.001$; $\eta^2=0.159$). Also, the N1 peaked later with the deviant than standard tones (97 ms vs. 94 ms; $F[1,120]=20.92$; $p<0.001$; $\eta^2=0.148$). However, there were no main effects of Genotype or Stimulus, and no interaction of Genotype and Stimulus, neither on amplitudes, nor latencies (all $p>0.05$).

MMN

The MMN peaked at 139 ms over frontal brain areas. The MMN appeared to be more pronounced in the combined Val/Met-Met/Met group than in the Val/Val group (−2.6 μV vs. −2.3 μV), but the difference was not statistically significant ($F[1,120]=0.48$; $p>0.05$; $\eta^2=0.004$). Neither did the genotype groups differ in MMN latency ($p>0.05$).

P3a

The frontal P3a was more pronounced with the deviant than standard tones (6.5 μV vs. 2.8 μV) and, more important, it was greater in the Val/Val group than in the combined Val/Met-Met/Met group (5.1 μV vs. 4.2 μV; Fig. 3A). Accordingly, the ANOVA indicated significant main effects of Stimulus ($F[1,120]=228.80$; $p<0.001$; $\eta^2=0.656$) and Genotype ($F[1,120]=4.28$; $p<0.05$; $\eta^2=0.034$), but no interaction of Stimulus and Genotype ($F[1,120]=1.83$; $p>0.05$; $\eta^2=0.015$). There were no main effects of Genotype or Stimulus, and no interaction of Genotype and Stimulus on P3a latencies (all $p>0.05$). In sum, irrespective of tones presented, the Val/Val group had a larger P3a than the combined Val/Met-Met/Met group.

P3b

There were significant main effects of Stimulus on amplitude and latency of the parietal P3b, resulting from the P3b being larger (5.9 μV vs. 4.3 μV; $F[1,120]=62.41$; $p<0.001$; $\eta^2=0.342$) and earlier (568 ms vs. 609 ms; $F[1,120]=39.41$; $p<0.001$; $\eta^2=0.247$) with the deviant than standard tones. In addition, the ANOVA revealed a main effect of Genotype ($F[1,120]=4.89$; $p<0.05$; $\eta^2=0.039$), indicating larger P3b amplitudes in the Val/Val group than in the combined Val/Met-Met/Met group (5.6 μV vs. 4.6 μV; Fig. 3B). A significant interaction of Genotype and Stimulus ($F[1,120]=4.41$; $p<0.05$; $\eta^2=0.035$) resulted from the fact that, relative to the combined Val/Met-Met/Met group, the P3b amplitude of the Val/Val group was especially increased with the deviant tones. Additional one-way ANOVAs thus indicated a main effect of Genotype on P3b amplitude only with the deviant tones ($F[1,120]=6.56$; $p<0.05$; $\eta^2=0.052$), whereas both subgroups did not differ significantly with the standard tones ($F[1,120]=1.56$; $p>0.05$; $\eta^2=0.013$).

Likewise, the ANOVA indicated a main effect of Genotype on P3b latency ($F[1,120]=6.02$; $p<0.05$; $\eta^2=0.048$), with latencies being shorter in the Val/Val group than in the combined Val/Met-Met/Met

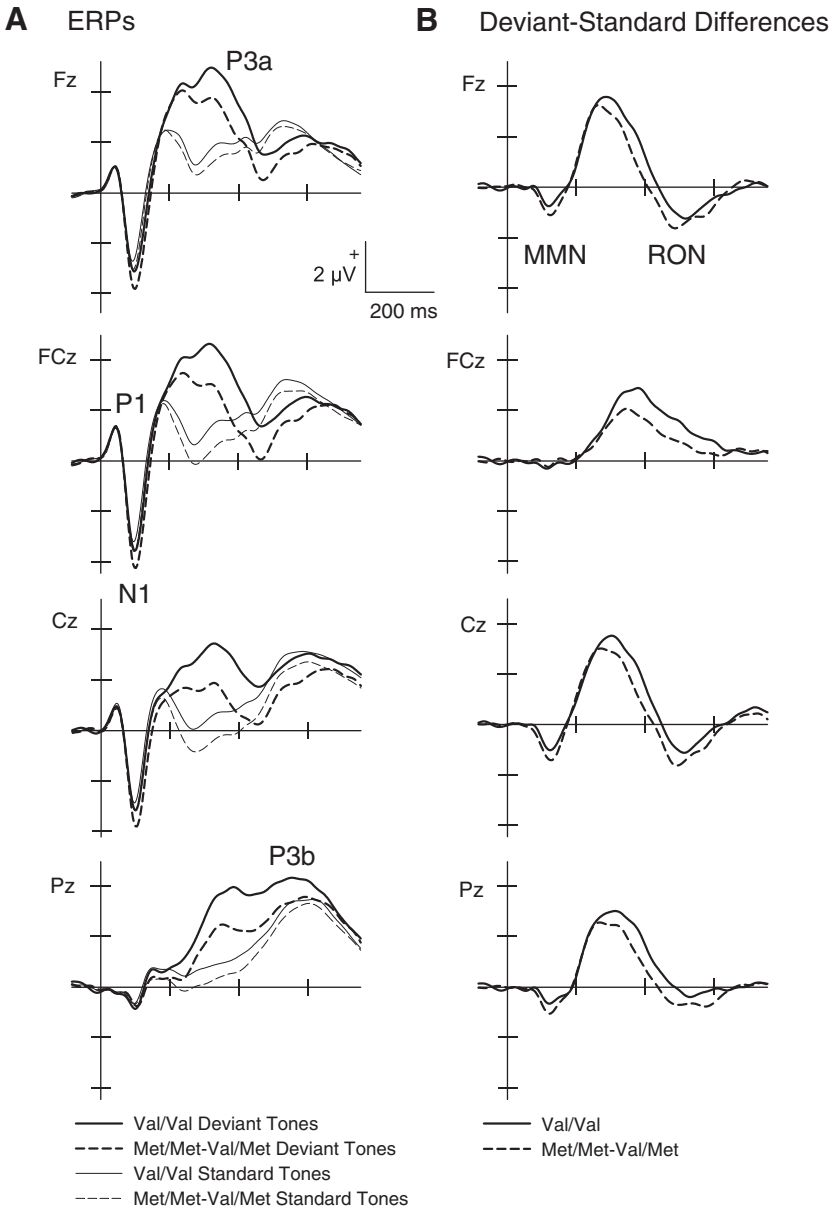

Fig. 2. (A) Grand average ERPs of the frequent standard tones and the rare deviant tones and (B) difference waves (deviant minus standard tones) at Fz, FCz, Cz, and Pz, shown for the brain-derived neurotrophic factor (BDNF) Val/Val and Val/Met-Met/Met groups. The vertical lines reflect the onset of the tone stimulus. ERP components (P1, N1, P3a, P3b, MMN, and RON) are marked at the waveform of maximal amplitude.

group (577 ms vs. 600 ms). There was also an interaction of Genotype and Stimulus ($F[1,120]=4.06$; $p<0.05$; $\eta^2=0.033$), with latency differences between subgroups being more pronounced with the deviant than standard tones. Accordingly, one-way ANOVAs indicated a significant main effect of Genotype with the deviant tones ($F[1,120]=8.24$; $p<0.01$; $\eta^2=0.064$), but not with standard tones ($F[1,120]=3.27$; $p>0.05$; $\eta^2=0.008$). In sum, relative to the combined Val/Met-Met/Met group, the Val/Val group had a greater and earlier P3b with the deviant tones, whereas differences between the two groups were marginal with the standard tones.

RON

The RON peaked at 546 ms over frontal brain areas. There were no main effects of Genotype on RON amplitudes or latencies (all $p>0.05$).

Correlational analysis behavioral and ERP data

To relate the main ERP findings to behavioral performance, correlations between P3a and P3b amplitudes to deviant and standard tones on the one hand, and the rates of correct responses (averaged across deviant and standard tones) on the other hand were separately computed for the two genotype groups. As shown in Fig. 4A, there was a significant correlation of P3a amplitude to standard tones and rate of correct responses in the Val/Val group ($r=0.33$; $p=0.004$), but not in the combined Val/Met-Met/Met group ($r=-0.06$; $p>0.05$). The correlation coefficients of the two genotype groups differed significantly (Fisher's $Z=2.11$, two-tailed $p<0.05$). No such correlation was found between the P3a amplitude to deviant tones and rate of correct responses, neither in the Val/Val group ($r=-0.02$), nor in the combined Val/Met-Met/Met group ($r=0.12$; both $p>0.05$). Thus, when processing the standard tones, superior performance of the Val/Val group came along with stronger activation of frontal brain areas, whereas performance of the combined Val/Met-Met/Met group was not related to frontal activation.

Regarding P3b, there was a significant correlation between P3b amplitude to standard tones and rate of correct responses in the Val/Val group ($r=0.25$; $p=0.032$), and a marginal correlation in

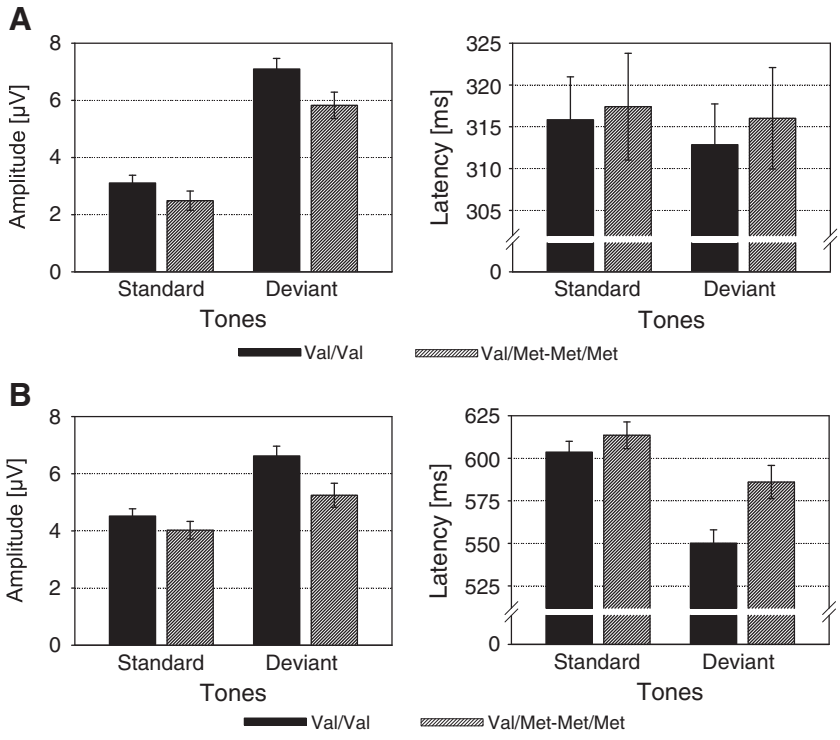

Fig. 3. Mean amplitudes (left) and latencies (right) of the P3a at Fz (A) and P3b at Pz (B) for the frequent standard tones and the rare deviant tones for the brain-derived neurotrophic factor (BDNF) Val/Val and Val/Met-Met/Met groups. Error bars indicate standard errors across participants (Val/Val: $N=74$; Val/Met-Met/Met: $N=48$).

the combined Val/Met-Met/Met group ($r=0.27$; $p=0.065$), whereas no correlations occurred between P3b amplitudes to deviant stimuli and rate of correct response, neither in the Val/Val group ($r=-0.07$), nor in the combined Val/Met-Met/Met group ($r=0.13$; both $p>0.05$). Thus, irrespective of the genotype group, higher performance was associated with a more pronounced P3b to the standard tones (Fig. 4B).

Discussion

In the current study we examined the role of the functional BDNF Val66Met polymorphism for functions related to goal-directed behavior that is disrupted by infrequent, unpredictable events using an auditory distraction task (Schröger and Wolff, 1998) in healthy elderly. The behavioral data indicate that infrequent deviant tones lead to a stronger disruption in goal-directed behavior (i.e. decreases the rate of correct responses) in the Val/Val genotype group, compared to Met-allele carriers. No differences were obtained for RTs.

On a neurophysiological level, there was a clear dissociation between cognitive subprocesses being affected by BDNF Val66Met genotype: The P1, N1, MMN and RON did not show interactive effects of stimulus (standard vs. deviant) and genotype group. This suggests that neither the early auditory processing (P1, N1), nor the initial detection of a deviant in sensory memory buffers (MMN) and the re-orienting of attention towards task-relevant properties (RON) are affected by BDNF turnover. Paralleling the behavioral data the increase of the P3b from standard to deviant tones was larger for the Val/Val genotype group, compared to Met-allele carriers. It has been proposed that the P3b reflects maintaining and updating of working memory representations of the stimulus context on the occurrence of the deviant (Donchin and Coles, 1988; Horváth et al., 2009). However, the P3b has also been suggested to reflect the link between stimulus processing and the response (Falkenstein et al., 1994; Polich, 2007; Verleger, 1988), i.e., the P3b has been related to the "decision or integration" processes between stimulus evaluation and responding (Verleger et al., 2005). As a consequence, deviant tones have stronger access to systems mediating the "decision" process and are therefore processed in more depth. Thus, the greater and earlier P3b of the Val/Val genotype group to deviant (but not standard) tones may indicate a more pronounced link between deviant processing and the response selection, leading to a disruption of behavior as evidenced by the behavioral data. These "decision" processes are not only related to neocortical structures. Several theoretical frameworks consider the basal ganglia and especially the striatum as an important neural substrate mediating "decision" processes of response selection (e.g. Bar-Gad et al., 2003; Gurney et al., 2004; Plenz, 2003; Redgrave et al., 1999). In these conceptions, action selection mechanisms are modeled as a feature of striatal medium spiny neurons (MSNs) (Gurney et al., 2004; Plenz, 2003), which integrate information from prefrontal and sensory cortices (Redgrave and Gurney, 2006). The dense network of inhibitory connections between MSNs is assumed to inhibit neighboring neurons, thereby constituting the winner-takes-all (WTA) network (Bar-Gad et al., 2003; Plenz, 2003). This striatal winner-takes-all network mediates action selection and the chosen action is then conveyed to the output layer of the basal ganglia (Bar-Gad et al., 2003). Entering of the WTA network is mediated via glutamatergic cortico-striatal synapses (Plenz, 2003). This point of intersection has been suggested to play an important role in determining performance in the task examined (c.f. Beste et al., 2008). Compared with the Met allele, the Val allele is associated with higher activity of the BDNF system (Rybakowski, 2008), especially at cortico-striatal synapses BDNF modulates synaptic efficacy (e.g. Foltynie et al., 2009; Kleim et al., 2006). It is therefore possible that neural transmission at the cortico-striatal synapse is rendered more inefficient in Val/Val carriers. This may entail that distracting information has stronger access to the WTA network in Val/Val genotype carriers than in Met-allele carriers and may therefore disrupt goal-directed behavior in the distraction–orientation–refocusing cycle.

However, an alternative explanation is also possible: It has been shown that the above mentioned striatal networks are antagonistically modulated by the direct and the indirect pathways: Decreases in nigro-striatal activity render the direct pathway less active, while the indirect pathway becomes more active (Gale et al., 2008). This leads

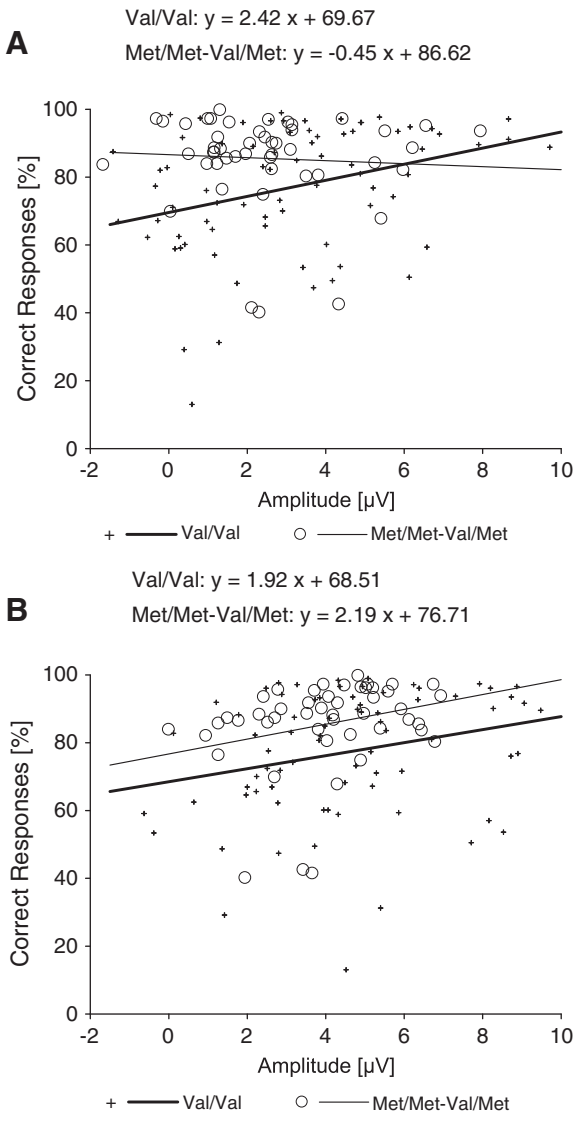

Fig. 4. Pearson correlations of P3a amplitudes to standard tones at Fz (A) and P3b amplitudes to standard tones at Pz (B) against rates of correct responses for each participant, shown separately for the brain-derived neurotrophic factor (BDNF) Val/Val group ($N = 74$) and combined Val/Met-Met/Met group ($N = 48$) with linear regression lines.

to a predominating inhibitory effect (e.g. Gale et al., 2008). Several results suggest that within this basal ganglia network the Met-allele may shift the balance between the direct and indirect pathway towards a predominating inhibitory effect (Beste et al., 2010a, 2010b; Gajewski et al., 2011). Similar effects have also been suggested to emerge as an effect of aging per se (e.g. Beste et al., 2010c; Collier et al., 2007). It may therefore be speculated that the inhibitory tone prevents processing of the deviant stimulus and therefore indirectly 'protects' goal-directed representations against interference. In Val/Val genotype carriers these inhibitory processes are most likely less pronounced. Apparently, the above described possible neuronal mechanisms are not mutually exclusive, but may jointly contribute to the pattern of results.

The neurophysiological data further shows that the frontal P3a was stronger in the Val/Val genotype group, compared to Met-allele carriers, irrespective of the tones presented. Assuming the P3a to reflect additional allocation of attentional processes (e.g. Beste et al., 2008; Escera et al., 2000; Schröger, 1996), it is possible that these enhanced attentional processes reflect compensatory efforts to counteract the intensified processing of deviant tones, as evidenced by the P3b effects. This hypothesis is corroborated by the finding of a significant correlation of the rate of correct responses and the P3a amplitude to *standard* tones in the Val/Val group, but not in the combined Val/Met-Met/Met group. Thus, while a reduced P3b was associated with low performance in both the Val/Val and the combined Val/Met-Met/Met genotype groups (cf. Fig. 4B), differences in P3a within the Val/Val group indicate that high performance in this genotype group was associated with additional engagement of frontal brain areas. This may reflect a compensatory mechanism. Interestingly, no such correlation was found between the rate of correct responses and the P3a amplitude to *deviant* tones, possibly because enhanced attentional effort in the processing of the task-irrelevant stimulus features rather impaired (than improved) processing of the task-relevant stimulus features. This may be true especially for the Val/Val group showing an overall greater P3a than the combined Val/Met-Met/Met group.

The current results add on recent studies providing evidence that BDNF modulates response selection and control processes (Gajewski et al., 2011; Beste et al., 2010a, 2010b) and on studies reporting an advantage of the Met allele in elderly (Erickson et al., 2008; Matsushita et al., 2005; Ventriglia et al., 2002). For the current study we suggest two possible neuronal mechanisms that may underlie the effects observed. These depend on basic properties on fronto-striatal circuit functioning. They are most likely not mutually exclusive, but may reflect complementary mechanisms. The different and divergent explanations put forward in literature to explain the effects of BDNF Val66Met may be due to the fact that previous accounts often lack a close relation to basic cognitive subprocesses that have a straight relation with basic neurophysiological mechanisms. It may be possible to reconcile the different patterns of association and to gain a clearer overall association pattern, even in the light of pleiotrophic effects of BDNF, if 'macroscopic categories' like executive function, cognitive flexibility or memory, are avoided and a more 'brain-based phenotype' is used (Mandelman and Grigorenko, 2012). This phenotype used for the grouping of the effects of the BDNF Val66Met phenotype on a cognitive level should relate to basic neurophysiological mechanisms. Due to the pivotal role of BDNF for fronto-striatal circuit functioning and the role of basal ganglia processes in different 'macroscopic' cognitive domains (e.g. Chudasama and Robbins, 2006), a stronger focus on fronto-striatal circuits and its basic mechanistic properties subserving different cognitive functions may prove useful to simplify the pattern of associations obtained in BDNF Val66Met association studies.

In this regard, it should be noted that the recent meta-analysis of cognitive effects of BDNF did not find consistent results (Mandelman and Grigorenko, 2012). Similarly, genome wide associations studies (GWAS) did not provide conclusive results (Davies, 2011). More genome-wide association studies would be desirable to elucidate the genetic architecture of cognitive aging, but even these studies only detect association not causation. In this regard, animal studies using knock-out mice strains, or other rodent models with specific neurobiological alterations should be used. Currently, the reported results thus provide some evidence for the role of BDNF in subprocesses of goal-directed behavior in healthy elderly, but it will be necessary to accumulate further data of the effects of BDNF on cognitive processes in future research.

In sum, the study shows that the BDNF Val66Met polymorphism specifically affects cognitive subprocesses involved in the distraction–orientation–refocusing cycle, necessary to establish smoothly unfolding of behavioral control. We show that the Val/Val genotype confers a disadvantage to its carriers, possibly because distracting information has better access to fronto-striatal networks and processes determining the selection of actions. However, this process is partly compensated by intensified attentional shifting mechanisms. Processes reflecting transient sensory memory processes, or the re-orientation of attention were not affected by the BDNF Val66Met polymorphism. The results well support the relevance of the functional BDNF Val66Met polymorphism in healthy elderly as a parameter that affects interindividual

variability of cognitive functions. Thus, given the strong inter-individual variability in cognitive performance in the elderly (Hultsch et al., 2002), examining genetic factors in close relation to neurophysiological and cognitive processes appears as a promising approach in neuroscientific aging research.

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