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The Met-allele of the BDNF Val66Met polymorphism enhances task switching in elderly

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Abstract

In this study we examined the relevance of the functional brain-derived neurotrophic factor (BDNF) Val66Met polymorphism as a modulator of task-switching performance in healthy elderly by using behavioral and event-related potential (ERP) measures. Task switching was examined in a cue-based and a memory-based paradigm. Val/Val carriers were generally slower, showed enhanced reaction time variability and higher error rates, particularly during memory-based task switching than the Met-allele individuals. On a neurophysiological level these dissociative effects were reflected by variations in the N2 and P3 ERP components. The task switch-related N2 was increased while the P3 was decreased in Met-allele carriers, while the Val/Val genotype group revealed the opposite pattern of results. In cue-based task-switching no behavioral and ERP differences were seen between the genotypes. These data suggest that superior memory-based task-switching performance in elderly Met-allele carriers may emerge due to more efficient response selection processes. The results implicate that under special circumstances the Met-allele renders cognitive processes more efficient than the Val/Val genotype in healthy elderly, corroborating recent findings in young subjects.

Keywords: Aging; BDNF Val66Met polymorphism; Task switching; Response selection; Inhibition; Memory; Event-related potentials; Genetic imaging; N2; P3

1. Introduction

There is strong interindividual variability in cognitive performance in elderly (Hultsch et al., 2002). The question which factors determine these larger interindividual differences is of high importance in aging research. In this respect, the examination of genetic factors in close relation to neurophysiological and cognitive processes may be useful explaining the strong interindividual variability in cognitive performance.

During aging there is a decrease in secretion of the brain-derived neurotrophic factor (BDNF) affecting different cognitive functions (Hayashi et al., 2001; Pang and Lu, 2004). However, molecular genetic studies investigating the relevance of the functional BDNF Val66Met polymorphism (rs6265) for cognitive functions in elderly revealed contradictory results: some results accounted for compromised cognitive functions in Met-allele carriers (Miyajima et al., 2008) while other results accounted for better cognitive functions in Met-allele carriers (Erickson et al., 2008; Matsushita et al., 2005; Ventriglia et al., 2002). The study by Erickson et al. (2008) suggests that at younger ages the Val/Val homozygotes provide some neuronal and cognitive benefits but with increasing age they are associated with cognitive impairment, whereas the Val/Met carriers provide some protection against cognitive declines in older age (Harris et al., 2006).

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Variations in the functional BDNF Val66Met polymorphism modulate functions mediated by basal ganglia-prefrontal loops (e.g., Beste et al., 2010a, 2010c). These loops may be of special interest in elderly, as these are affected by aging processes (e.g., Beste et al., 2009, 2010b; Wild-Wall et al., 2008; Buckner, 2004). However, even though the ability to flexibly switch between different tasks is mediated via basal ganglia-prefrontal loops (Chudasama and Robbins, 2006; Kehagia et al., 2010); most existing studies on task switching in elderly showed impairments in maintenance of task goals, but not disturbed task-set switching performance (switch costs) in older versus younger participants (e.g., Kramer et al., 1999; Kray, 2006; Kray and Lindenberger, 2000; West and Travers, 2008). There are different theoretical accounts of switch costs, i.e., longer processing times when participants switched between cognitive tasks rather than repeating the same task. Switch costs may represent an additional active reconfiguration process (Monsell, 2003; Rogers and Monsell, 1995). This dynamic reconfiguration process may involve shifting attention between perceptual and conceptual elements, retrieving goals and condition-action rules from working memory or activation of relevant task sets and inhibition of irrelevant task sets (Kiesel et al., 2010; Monsell, 2003). An alternative account explained switch costs in terms of interference from the previous trial (task-set inertia) (Allport and Wylie, 2000; Allport et al., 1994).

As outlined above, aging selectively impairs some of the functions involved in task switching: whereas differentiating and updating of internal control settings seems to decline with decreasing age, small age-related changes were found for the task-set interference (e.g., Cepeda et al., 2001). However, age related impairments are often undetected when tasks are too easy, or performance declines are compensated by strategies. These strategies of elderly to compensate switch costs can be overcome by enhancing working memory load by means of memory-based task switching (Kray, 2006). As BDNF plays a pivotal role in working memory processes (Matsushita et al., 2005; Ventriglia et al., 2002), a task-switching paradigm in which working-memory load is varied seems well-suited to examine the relevance of the BDNF Val66Met polymorphism for cognitive control processes in elderly.

In the last decade processes underlying switch costs has been often related to event-related potentials (ERPs). Behavioral switch costs seem to be closely related to a frontocentrally distributed ERP component, the N2 reflecting the resolution of conflict (or task-set inertia) between simultaneously active stimulus-response mappings during response selection (Gajewski et al., 2010a). Besides the N2, task switching is related to a smaller P3b likely reflecting increased working memory load or stronger involvement of cognitive resources during implementation of a switching task-set (Barceló et al., 2000; Gajewski et al., 2010b; Gehring et al., 2003; Jost et al., 2008; Karayanidis et al., 2003; Kieffaber and Hetrick, 2005; Lorist et al., 2000; Poulsen et al., 2005). Thus, an efficient processing of a switching task would include an increased N2 and decreased P3 in the target-locked ERPs compared with the nonswitch trials.

With respect to findings suggesting superior cognitive performance in elderly Met-allele than Val-Val-allele carriers (Erickson et al., 2008), we expect better switching performance (i.e., lower switch costs and lower variability) in the Met-than the Val/Val group. The difference in switching costs between the genotypes should be particularly evident under high working memory load, i.e., when switching is memory based compared with a cue-based condition. Due to the relation of the N2 to overt performance (e.g., Beste et al., 2008; Gajewski et al., 2008, 2010a; Hohnsbein et al., 1998) we hypothesize an enhanced and/or faster N2 in Met allele carriers is related to lower switching costs in memory-based task switching. As the smaller P3b seems to go hand in hand with an increased N2, the reduction of the P3b in switch, compared with nonswitch trials is also stronger in Met-allele than in Val/Val genotype carriers.

2. Methods

2.1. Participants

One hundred thirty-one healthy volunteers aged from 65 to 88 (mean = 70.5, SD = 4.5) participated in the study. Eighty-one (61.8%) of them were female. Eleven participants were left- or ambidexter. They had normal or corrected-to-normal vision and gave informed consent for participation. All participants received a payment for their participation. The sample consisted of 79 subjects carrying the Val/Val genotype, 47 carrying the Val/Met genotype and 5 subjects carrying the Met/Met genotype group. The distribution of genotypes in the sample did not differ from Hardy-Weinberg equilibrium ($p = 0.537$), as determined using the program Finetti provided as an online source (ihg.gsf.de/cgi-bin/hw/hwa1.pl; T.F. Wienker and T.M. Strom). As to the expected low frequency of the Met/Met genotype group, the Val/Met and Met/Met genotype group were combined to 1 group (i.e., Val/Met-Met/Met genotype group). With respect to the frequencies reported in HapMap data for European populations, one would expect approximately 88 Val/Val genotypes, approximately 37 Val/Met genotypes, and approximately 4 Met/Met genotypes. The frequency of genotypes is therefore well in line with the frequency one would expect on HapMap data.

Fifty-eight participants of the Val/Val genotype (age mean = 70.8, SD = 4.7; Mini Mental State Examination [MMSE] = 28.3), were female (73.4%, $\chi^2 = 17.3$, $p < .0001$) and 23 of the combined Val/Met and Met/Met genotype group (age mean = 70.2, SD = 4.3; MMSE = 28.7), were female (44.2%, $\chi^2 = 0.7$, $p = 0.4$). The subgroups did not significantly differ regarding a number of neuropsychological and psychiatric parameters (Table 1).

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	$n = 79$	$n = 52$		
Age	70.8 (4.7)	70.2 (4.3)	$F(1,129) = 1.3$	0.255
MMSE	28.3 (1.9)	28.8 (1.4)	$F(1,129) = 2.6$	0.135
BDI	5.3 (4.0)	5.2 (4.4)	$F(1,129) = 2.6$	0.936
NEO-FFI[a]				
Neuroticism	1.4 (0.6)	1.5 (0.5)	$F(1,121) = 0.7$	0.390
Extraversion	2.1 (.05)	2.0 (0.5)	$F(1,121) = 1.2$	0.267
Openess to experience	2.1 (0.5)	2.1 (0.5)	$F(1,121) = 0$	0.882
Agreeableness	2.3 (0.6)	2.1 (0.6)	$F(1,121) = 1.8$	0.172
Conscientiousness	2.6 (0.6)	2.6 (0.6)	$F(1,121) = 0.1$	0.783
D2				
Total number of symbols	380 (87.5)	408 (77.6)	$F(1,129) = 3.3$	0.072
Number omitted symbols	21 (16.9)	21 (22.0)	$F(1,129) = 0$	0.867
Number confused symbols	4.8 (7.6)	5.2 (7.2)	$F(1,129) = 0.1$	0.750
Digit-symbol-test				
Total number of symbols	44.7 (10.7)	44.2 (9.7)	$F(1,129) = 0.1$	0.780
Number correct	44.6 (11.0)	44.2 (9.7)	$F(1,129) = 0.1$	0.792
Stroop				
Word reading	14.1 (2.3)	14.7 (3.8)	$F(1,129) = 1.4$	0.237
Color naming	21.6 (3.6)	22.3 (6.0)	$F(1,129) = 0.7$	0.398
Interference list	43.7 (8.3)	45.1 (14.1)	$F(1,129) = 0.5$	0.476
Digit span				
Forward	3.5 (1.0)	4.2 (3.8)	$F(1,129) = 2.3$	0.127
Backward	2.7 (0.8)	3.0 (0.9)	$F(1,129) = 3.0$	0.082
Word fluency	31.0 (3.2)	31.5 (2.7)	$F(1,129) = 0.4$	0.571
MWT-B (multiple-choice word test)				
Number total	82.7 (19.8)	85.0 (17.3)	$F(1,129) = 0.4$	0.504
IQ	116.3 (12.1)	117.2 (11.7)	$F(1,129) = 0.2$	0.652
CVLT				
Total score trials 1 to 5	37.3 (9.9)	38.2 (8.4)	$F(1,129) = 0.3$	0.599
Delayed recognition	12.5 (2.2)	13.1 (1.8)	$F(1,129) = 2.3$	0.132
Rey-figure (ROCF)				
Reproduction	33.6 (2.9)	33.2 (3.2)	$F(1,129) = 0.2$	0.669
Delayed recall	15.6 (5.6)	16.2 (5.8)	$F(1,129) = 0.4$	0.546
Mental rotation				
Total number	6.7 (2.8)	6.8 (3.2)	$F(1,129) = 0$	0.814
Number correct	5.4 (2.8)	5.7 (3.2)	$F(1,129) = 2$	0.613
TMT[a]				
TMT-A	37.4 (11.8)	37.4 (12.8)	$F(1,112) = 0$	0.978
TMT-B	95.7 (33.3)	102.5 (46.7)	$F(1,112) = 0.8$	0.371
CFQ[a]				
Total score	29.2 (11.1)	28 (10.6)	$F(1,119) = 0.3$	0.537

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 Examinaion; 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 particpants.

2.2. Genotyping

Isolation of genomic DNA of leukocytes was performed according to standard procedures (Lehmann et al., 2010). 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]TGATAGAAGAGCTGTTGGATGAGGA 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/vis-spectrophotometer (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

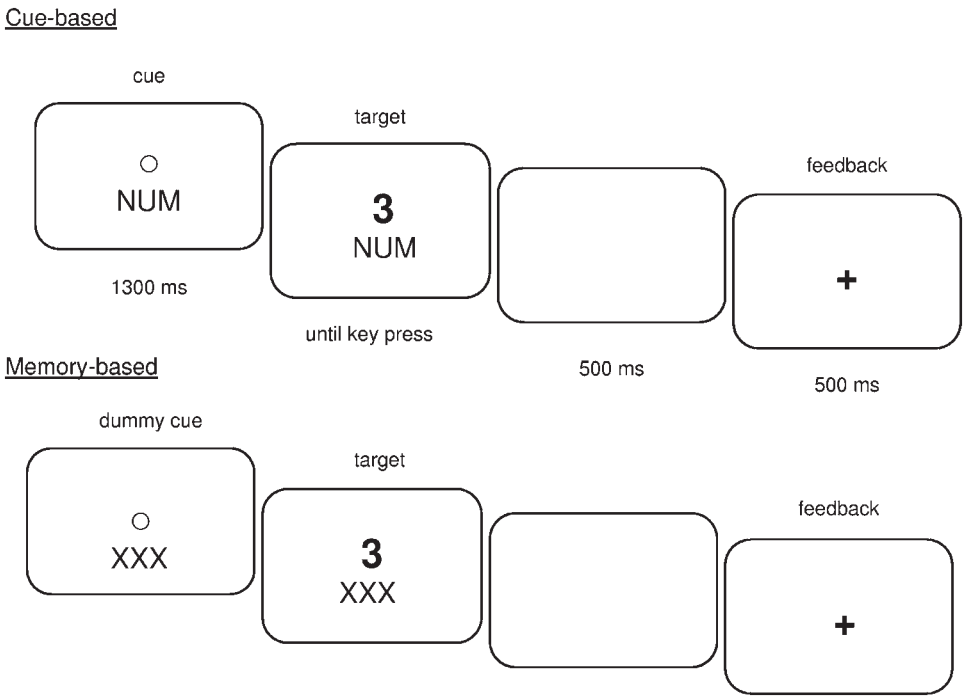

Fig. 1. Schematic illustration of a trial in the cue- and memory-based conditions.

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 seconds at 92 °C (denature), 1 minute at 60 °C (anneal/extend). An initial hold with 10 minutes 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).

2.3. Stimuli and tasks

Stimuli consisted of the digits 1–9, excluding the number 5. The digits were presented in white on a black computer screen 3 mm above the white fixation point (10-mm diameter). Each digit was presented in small (7 × 10 mm) and in large (12 × 18 mm) size on the computer screen. A cue (16 × 32 mm) indicating the relevant task was presented 3 mm below the fixation point. The cue "NUM" (German "Numerisch", numeric) indicated a numerical task (greater or less than 5), "GER" (German "Geradzahligkeit", parity) the parity task (odd vs. even), "SCH" (German "Schrift", font) the font-size task (small vs. large). In the memory-based condition (see below) 3 letters × were presented instead of the informative cue. Responses consisted of pressing 1 of 2 buttons which were mounted in a response box. The buttons should be pressed with the index fingers. The stimulus-response mapping of the 3 tasks was overlapping, that is responses according to 'smaller than five,' 'even,' and 'small size' were assigned to the left key and 'larger than five,' 'odd,' and 'large size' to the right key. This assignment was counterbalanced across participants.

2.4. Design and procedure

A schematic example of a trial is shown in Fig. 1.

A trial started with a presentation of the fixation point. A cue stimulus was presented for 1300 ms which remained visible when the digit was presented. A response had to be given within 2500 ms after target-onset. 500 ms after the response a feedback was displayed for 500 ms. In case of a correct response a plus sign, after a wrong response a minus sign was displayed. After that the next cue was shown. The response-cue interval (RCI) was set to 1000 ms and included the response-feedback delay and the feedback. There were 2 types of mixed blocks: (1) In the cue-based block the participants had to switch or repeat the task rules according to a cue that randomly changed during task performance with 4 consecutive trials as the maximal trial number that was repeated; (2) In the memory-based block the participants were instructed to switch the rule after every 3 trials in the following order "NUM-NUM-NUM-GER-GER-GER-SCH-SCH-SCH," etc., while "XXX" instead of a cue was presented, i.e., participants had to keep the trial sequence in mind. When 3 consecutive errors were made or no response within the 2500-ms interval was given, cues were consecutively presented for the next 3 trials helping the participants to find the track.

Before each block, the participants performed 3 practice blocks with 16 trials for each task rule, followed by the

cue-based block (124 trials) and the memory-based block (126 trials). Each block included an equal number of stimuli (i.e., digits) as well as responses (i.e., left, right). The frequency of task switch in the cue-based block amounted to 50%. The frequency of task switch in the memory-based block amounted to 33.3% of trials. The participants were given a written instruction that explained the task. The instruction encouraged quick and accurate responses.

2.5. ERP recordings

Electroencephalography (EEG) was recorded continuously from 32 scalp electrodes according to the extended 10−20 system (Jasper, 1958) and mounted on an elastic cap. The montage included 8 midline sites and 12 sites on each hemisphere and 2 mastiod electrodes (M1 and M2). The EEG was rereferenced offline to linked mastoids. The horizontal and vertical electrooculogram (EOG) was recorded bipolarly from electrodes at both eyes. Eye movement artifacts were corrected using the correction algorithm of Gratton et al. (1983). Electrode impedance was kept below 10 kΩ. The amplifier bandpass was 0.01–140 Hz. EEG and EOG were sampled continuously with a rate of 2048 Hz. Offline, the EEG was downscaled to a sampling rate of 1000 Hz and cut in stimulus-locked epochs by using the software Vision Analyzer (Brain Products, Munich, Germany). Epochs in which the amplitude exceeded ± 150 μV were rejected. The ERPs were filtered digitally offline with a 17-Hz low and 0.05-Hz high pass.

2.6. Data Analysis

The first trial of each test block, trials with responses faster than 100 ms or slower than 2500 ms, as well as error trials, were excluded from the reaction time (RT) analysis. Mean RTs, standard deviation of the mean RTs and error rates were subjected to an analysis of variance (ANOVA) design including 2 within-subject factors, "block type" (cue-based vs. memory based), "task-set transition" (nonswitch vs. switch), and the between-subject factor "BDNF genotype" (Val/Val vs. combined Val/Met-Met/Met) group. Group differences were assessed using one-way ANOVA with Bonferroni corrected post hoc testing. The ERP analysis was restricted to the midline electrodes (Fz, FCz, Cz, and Pz) as the Contingent Negative Variation (CNV), N2, and P3 are usually maximum at the midline.

Peak amplitudes and latencies of transient components were measured at their local maximal or minimal amplitudes in predefined time windows: the N2 was measured as the most negative peak at FCz and Cz in the time range 200–400 ms after the target, the P3b was measured as the most positive peak at Pz in the time range 300–600 ms after target onset. These post target ERPs were measured relative to 100 ms pretarget baseline. The CNV was measured as the mean amplitude in the time range −300 to 0 ms prior to target onset at FCz and Cz.

Similar to the RT and error rate analyses, the ERP—amplitudes and latencies were subjected to a 2-way ANOVA with repeated measures with the inner-subject factors "type of block" and "task-set transition" and the between subject factor "BDNF genotype." To test specific effects or interactions, additional one-way ANOVAs with post hoc tests using Bonferroni correction for multiple comparisons were employed. The relationship between behavioral and electrophysiological parameters was assessed by correlation analysis using the Pearson correlation coefficient (2-tailed).

For each measure mean and standard error of the mean are provided (M ± SEM).

3. Results

3.1. Behavioral data

Mean reaction times (RTs) and error rates (ERs) for nonswitch and switch trials from cue-based and memory-based mixed blocks are presented in Fig. 2.

For the analysis of response times, error trials (10.2% and 9.0%) and outliers (5.8% and 4.8%) for cue- and memory-based block, respectively, were discarded.

3.1.1. Reaction times

Comparison of switch and nonswitch trials across the cue- and memory-based block yielded a main effect of "block" ($F(1,129) = 41.3$, $p < 0.0001$, $\eta^2 = 0.243$), suggesting longer RTs in the memory than the cue-based block (1257 ± 43.0 vs. 1045 ± 21.5 ms) and a main effect of "task-set transition" ($F(1,129) = 126.2$, $p < 0.0001$, $\eta^2 = 0.495$), indicating huge switch costs, i.e., longer RTs in switch than in nonswitch trials (1253 ± 35.4 vs. 1048 ± 43.0 ms). The significant interaction "block" by "task-set transition" ($F(1,129) = 21.1$, $p < 0.0001$, $\eta^2 = 0.141$) indicates higher switch costs in the memory than the cue-based block (280 ± 31.8 vs. 130 ± 11.0 ms). None of these factors were modulated by the between subject factor "BDNF genotype." However, the BDNF genotype subgroups differed regarding the general RT level ($F(1,129) = 5.6$, $p < 0.05$, $\eta^2 = 0.042$) which was higher in the Val/Val group than the in the combined Val/Met-Met/Met group (1221 ± 37.4 vs. 1080 ± 46.2 ms).

3.1.2. RT variability

In order to assess the variability between the conditions and subgroups, we conducted an analysis of standard deviations (SDs) of the mean RTs as dependent variable. As expected the SDs were higher in switch than nonswitch trials (436 ± 7.2 vs. 386 ± 7.5 ms, $F(1,129) = 82.9$, $p < 0.0001$, $\eta^2 = 0.391$) and significantly higher in the cue-based than the memory-based block (423 ± 8.3 vs. 399 ± 7.4 ms; $F(1,129) = 9.7$, $p < 0.005$, $\eta^2 = 0.070$). Finally, the SDs differed generally between the BDNF genotypes: the Val/Val group showed higher variability in RTs than the

combined Val/Met-Met/Met group (427 ± 8.6 vs. 396 ± 10.6 ms; $F(1,129) = 5.2$, $p < 0.05$, $\eta^2 = 0.039$).

3.1.3. Error rates

More errors were committed by the Val/Val than the Val/Met-Met/Met group (12.7 ± 0.9% vs. 9.5% ± 1.1%; $F(1,129) = 4.2$, $p < 0.05$, $\eta^2 = 0.031$). Participants made more erroneous responses in task switch than nonswitch trials (12.4 ± 0.9% vs. 9.6% ± 0.7%; $F(1,129) = 24.4$, $p < 0.0001$, $\eta^2 = 0.159$). This effect was strongly influenced by the type of block ($F(1,129) = 37.2$, $p < 0.0001$, $\eta^2 = 0.224$), suggesting higher switch costs in accuracy in the memory-based than the cue-based block (5.9 ± 0.9% vs. 0.3% ± 0.5%). Importantly, this interaction was modulated by the "BDNF genotype" ($F(1,129) = 5.7$, $p < 0.05$, $\eta^2 = 0.042$). In order to resolve this interaction, 2 ANOVAs were conducted for the cue- and memory-based block separately. For the cue-based block, neither the main effect of "task-set transition" nor the interaction with "BDNF genotype" was found (both F's < 1). However, significant differences between switch und nonswitch trials were found in the memory based block (13.9 ± 1.3% vs. 8.0% ± 0.8%; $F(1,129) = 39.3$, $p < 0.0001$, $\eta^2 = 0.234$) which was modulated by the BDNF genotype, resulting in an interaction "task-set transition" × "BDNF genotype" ($F(1,129) = 4.5$, $p < 0.05$, $\eta^2 = 0.033$). This interaction was due to higher error rates in switch relative to nonswitch trials in BDNF Val/Val (17.2 ± 1.6 vs. 9.2 ± 1.0%) than in the combined Val/Met-Met/Met group (10.7 ± 2.0% vs. 6.7 ± 1.3%). After computing local switch costs by subtracting task repetition from task switch trials, a univariate ANOVA revealed higher switch costs for the Val/Val than Val/Met-Met/Met groups (7.9 ± 11.8% vs. 3.9 ± 8.6%, $p < 0.05$).

In summary, reaction times were enhanced and more variable in the Val/Val than the Met genotype while the switch costs in reaction time did not differ across the groups. As to accuracy, the Val/Val carriers showed also generally higher error rates but also higher switch costs in accuracy than the Val/Met-Met/Met group in the memory-based block.

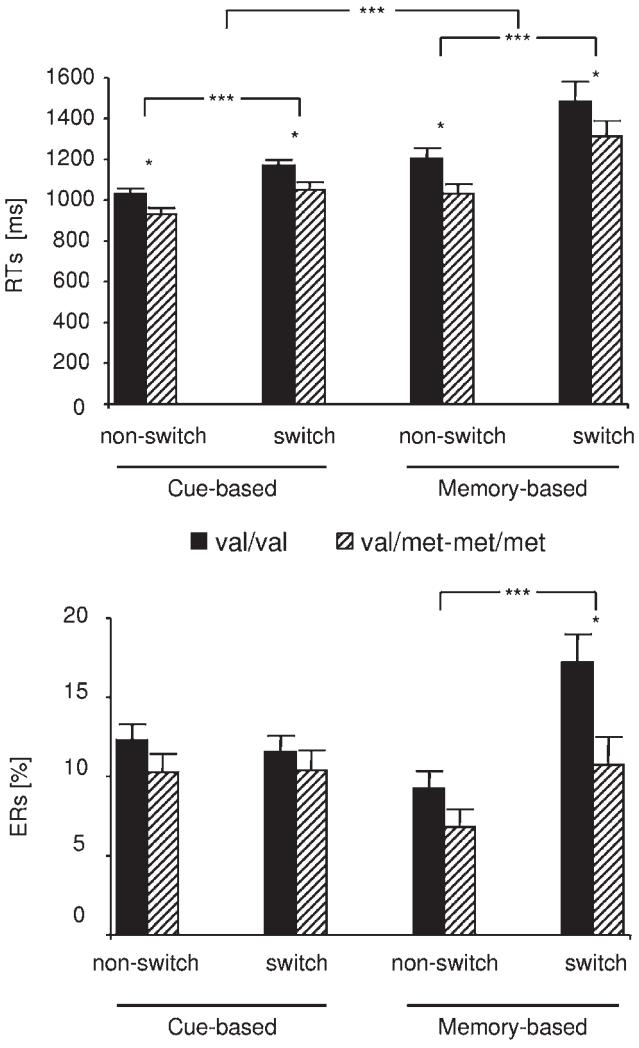

Fig. 2. Mean reaction times (top) and error rates (bottom) with standard errors as a function of nonswitch and task switch conditions in the cue-based and memory-based blocks for the brain-derived neurotrophic factor (BDNF) Val/Val and Val/Met-Met/Met groups. The number of asterisks indicates the alpha-level: * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

3.2. ERP data

Grand average ERP-waveforms for the cue- and memory-based blocks at Fz, FCz, Cz, and Pz for each of the 2 BDNF genotype groups are shown in Figs. 3 and 4. The mean amplitudes for all conditions and groups are plotted in Fig. 5.

3.2.1. N2

The N2 reached its maximum at 334 ms after target onset. No effects regarding the latency were found.

The peak amplitude was more negative at Cz (1.2 ± 0.3 μV) than at Fz (2.0 ± 0.3 μV) or FCz (1.5 ± 0.3 μV), resulting in a main effect of electrode ($F(2,258) = 14.6$, $p < 0.0001$, $\eta^2 = 0.102$). This distribution was not modulated by the "BDNF genotype" factor ($F(2,258) = 1.7$, $p = 0.18$). More important, "task set-transition" interacted with the "BDNF genotype" ($F(1,129) = 5.0$, $p < 0.05$, $\eta^2 = 0.037$). This interaction was marginally influenced by electrode ($F(2,258) = 3.0$, $p = 0.051$, $\eta^2 = 0.023$). In order to resolve these data pattern, we conducted ANOVAs for each electrode separately. For Fz and FCz but not Cz there was a significant interaction between "task-set transition" and "BDNF genotype" ($F(1,129) = 6.9$, $p < 0.01$, $\eta^2 = 0.051$ and $F(1,129) = 4.2$, $p < 0.05$, $\eta^2 = 0.031$), indicating a more negative N2 for the combined Val/Met-Met/Met than the Val/Val subgroup in the task switch than nonswitch trials (1.4 ± 0.5 vs. 2.3 ± 0.4 μV and 2.3 ± 0.4 vs. 2.0 ± 0.3 μV, at Fz and 0.7 ± 0.5 vs. 1.6 ± 0.4 μV and 1.9 ± 0.4 vs. 1.8 ± 0.3 μV, at FCz; see also Fig. 5). In the second step, we analyzed the interaction "task-set transition" and "BDNF genotype" for each block separately at Fz and

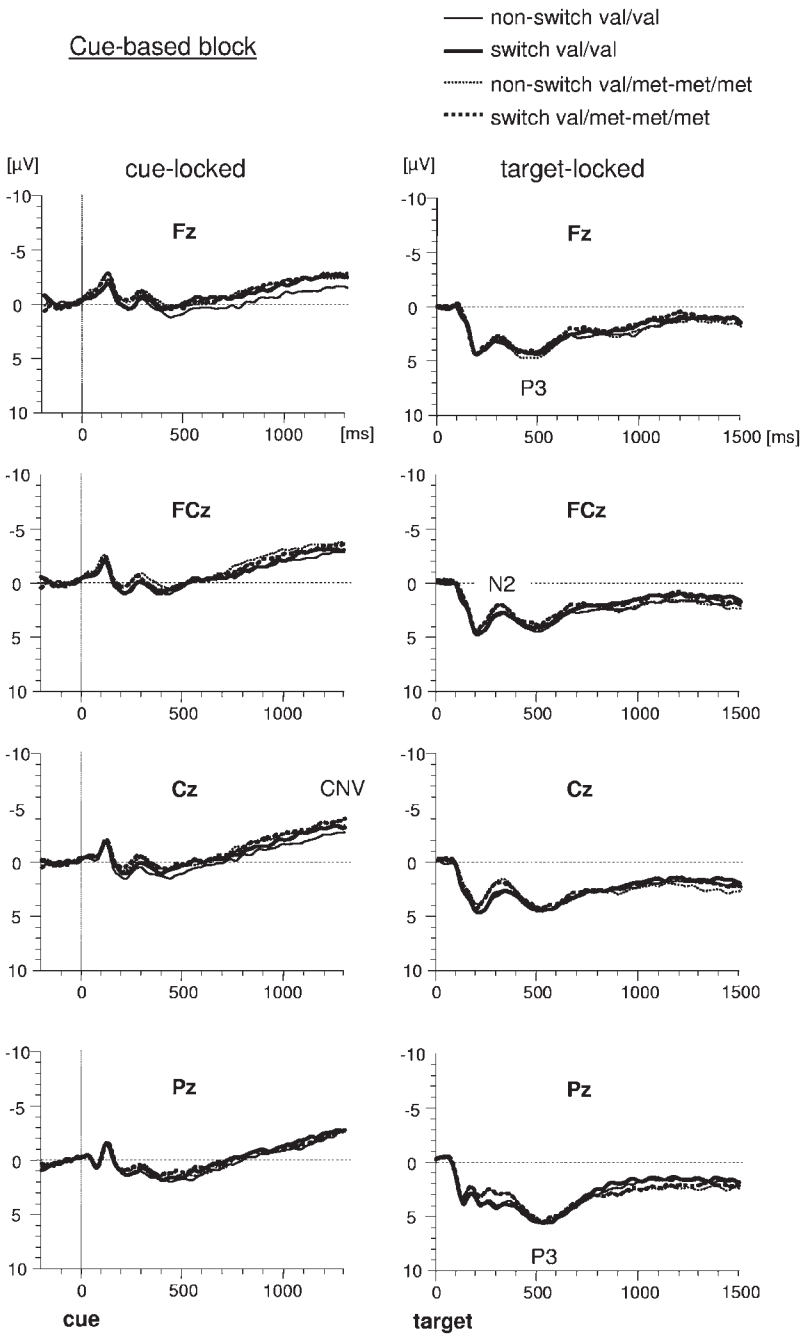

Fig. 3. Grand average event-related potentials ERPs in the cue-based block in the interval preceding target onset (left) and target-locked ERPs (right) at Fz, FCz, Cz, and Pz for nonswitch and switch trials in the brain-derived neurotrophic factor (BDNF) Val/Val and Val/Met-Met/Met groups. The dashed vertical line at the time point 0 ms reflects the onset of the cue stimulus.

FCz: for the cue-based block no main effect of "task-set transition" or interaction with the "BDNF genotype" were found (both F's < 1). In contrast, in the memory-based block the interaction "task-set transition" by "BDNF genotype" was significant for Fz ($F(1,129) = 4.8$, $p < 0.05$, $\eta^2 = 0.036$) and FCz ($F(1,129) = 5.1$, $p < 0.05$, $\eta^2 = 0.038$). Finally, analogous to the computing switch cost in the behavioral data, we subtracted the N2 amplitudes in task-switch from task repetition trials and compared this difference between both BDNF genotype groups in the memory-based block. A one-way ANOVA revealed more negative N2 difference in the combined Val/Met-Met/Met than in the Val/Val group (for Fz: 0.3 ± 0.4 vs. -1.1 ± 0.4 μV; $F(1,129) = 4.9$, $p = 0.029$ and for FCz: 0.2 ± 0.4 vs. -1.0 ± 0.3 μV; $F(1,129) = 5.2$, $p = 0.025$; see also Figs. 4 and 5).

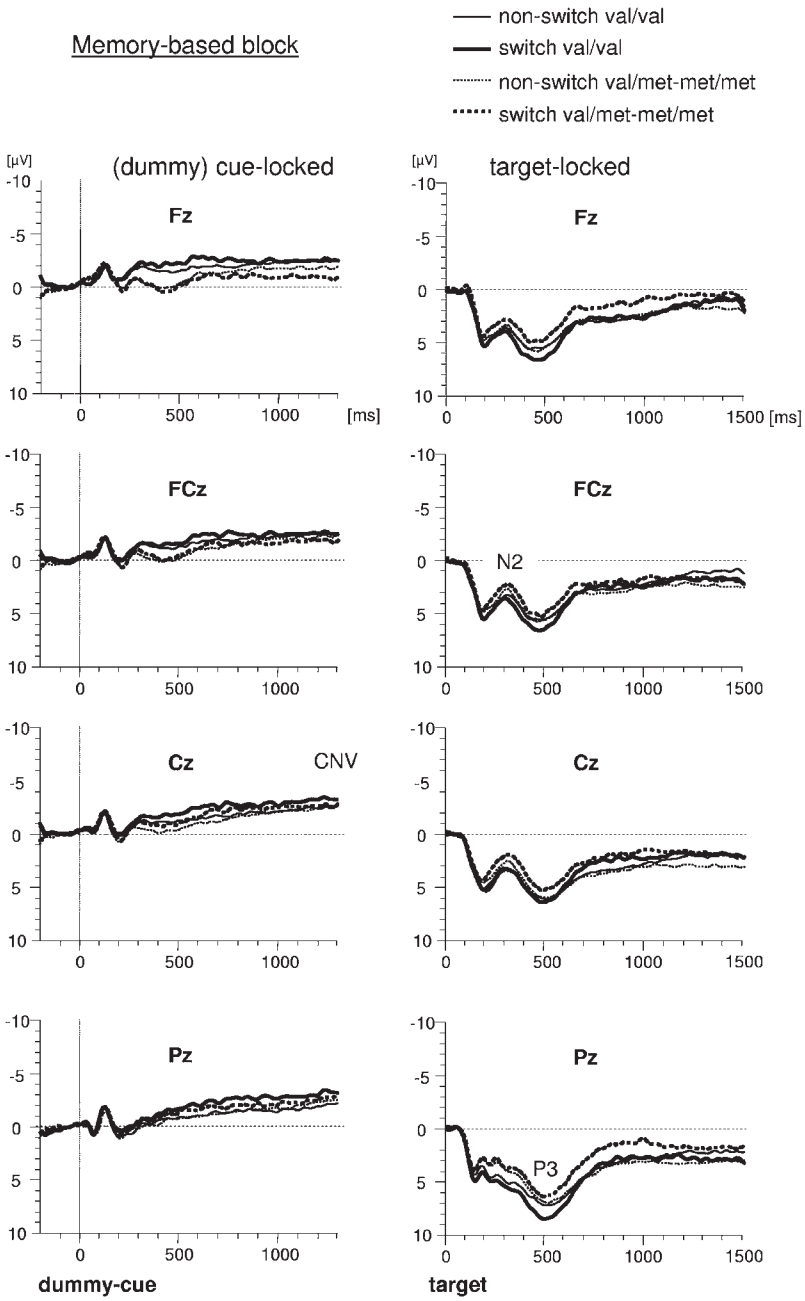

Fig. 4. Grand average event-related potentials ERPs in the memory-based block. Dummy cue (XXX)-locked ERPs (left) and target-locked grand average ERPs (right) at Fz, FCz, Cz, and Pz for nonswitch and switch trials in the brain-derived neurotrophic factor (BDNF) Val/Val and Val/Met-Met/Met groups. The dashed vertical line at the time point 0 ms reflects the onset of the dummy cue stimulus.

In summary, the N2 task-set switching effect was more pronounced in the combined Val/Met-Met/Met than the Val/Val subgroup in the memory-based block, while in the cue-based block no effect of genotype was found.

3.2.2. P3

The latency of the P3 was 470 ms at Fz, and 524 ms at Pz. No P3-latency effects were found.

The P3 amplitude was analyzed as a function of "block type" (cue- vs. memory-based), "task set transition" (switch vs. nonswitch), "electrode" (Fz, Cz, Pz), and "BDNF genotype." The repeated measures ANOVA yielded a main effect "electrode" ($F(2,258) = 12.0, p < 0.0001, \eta^2 = 0.085$), indicating a larger P3 at Pz than Fz, or Cz (7.5 ± 0.3 vs. 6.4 ± 0.3 vs. 6.3 ± 0.3 μV) and "block type" ($F(1,129) = 36.7, p < 0.0001, \eta^2 = 0.222$) which shows a larger P3 in the memory-based than cue-based block (7.7 ± 0.3 vs. 6.0 ± 0.2 μV). No interactions with the factor "electrode" occurred. Whereas the main effect of task-set transition was

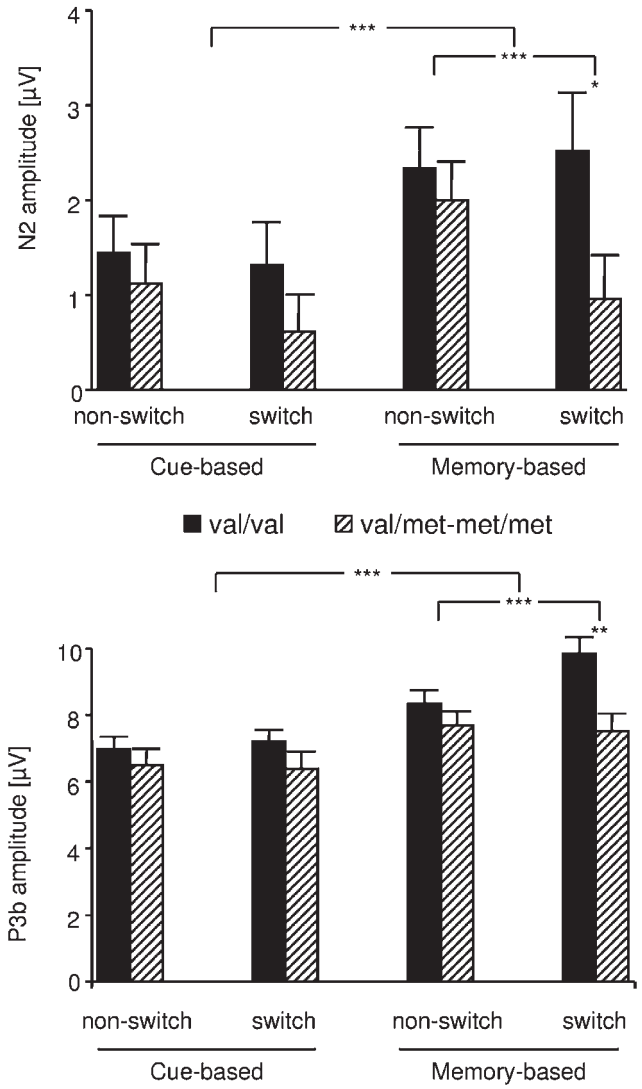

Fig. 5. Mean amplitudes of the N2 at FCz (top) and P3 at Pz (bottom) with standard errors as a function of the nonswitch versus task switch conditions for cue-based and memory-based blocks for the brain-derived neurotrophic factor (BDNF) Val/Val and Val/Met-Met/Met groups. The number of asterisks indicates the alpha-level: * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

not significant ($F(1,129) = 1.2$, $p = 0.27$, $\eta^2 = 0.009$), this factor was modulated by "block type" ($F(1,129) = 4.0$, $p < 0.05$, $\eta^2 = 0.030$) and the "BDNF genotype" ($F(1,129) = 8.4$, $p < 0.005$, $\eta^2 = 0.061$). Importantly, the second order interaction between "BDNF genotype", "block type," and "task-set transition" was significant ($F(1,129) = 7.0$, $p < 0.01$, $\eta^2 = 0.051$). This pattern indicates that the P3 at the midline electrodes differed mainly in the memory-based block by enhancing the P3 in switch relative to nonswitch trials (8.7 ± 0.5 vs. 7.4 ± 0.4 μV) in the Val/Val group, whereas an inverse pattern was observed in the combined Val/Met-Met/Met group (6.7 ± 0.6 vs. 7.1 ± 0.5 μV, for switch and nonswitch trials, respectively, see Fig. 5). No effects were found in the cue-based block.

Analyzing each electrode separately, the crucial interactions "task-set transition" × "BDNF genotype" and "task-set transition × block type × BDNF genotype" occurred at Fz ($F(1,129) = 7.5$, $p < 0.01$, $\eta^2 = 0.055$ and $F(1,129) = 8.1$, $p < 0.005$, $\eta^2 = 0.059$) and Pz ($F(1,129) = 10.2$, $p < 0.005$, $\eta^2 = 0.073$ and $F(1,129) = 4.6$, $p < 0.05$, $\eta^2 = 0.034$) but not at Cz. Analogous to the analysis of the N2 task-set switching effects, we computed the P3 amplitude difference between task switch und task repetition trials and compared it between both BDNF groups. In the cue-based block no effects were found at Fz or Pz (both F's < 1). In the memory-based block however, the task-set switching effect clearly differed between the groups with 1.7 ± 0.5 and −0.7 ± 0.4 μV for Fz ($F(1,129) = 12.1$, $p < 0.001$) and 1.5 ± 0.3 and −0.2 ± 0.3 μV for Pz ($F(1,129) = 14.6$, $p < 0.0001$), see also Fig. 5.

In summary, in the memory-based block the P3 was reduced in switch versus nonswitch trials in the combined Val/Met-Met/Met group, while the P3 was rather enhanced in switch versus nonswitch trials in the Val/Val group. In the cue-based block the groups did not differ with respect to P3 effects.

3.2.3. CNV

To examine if the differences between genotype groups described above were due to differences in preparatory processes prior to target onset, the CNV was examined, too. The ERPs prior to target onset were characterized by a negative slow wave at frontocentral positions which increased in the course of expectation of the forthcoming task (CNV). However, no effects or interactions were found for the CNV. As the last 100 ms of the CNV serves as the baseline for the post-target ERPs, no residual modulation of the posttarget ERPs by to the CNV can be expected.

3.3. Relationship between ERPs and behavioral data

To assess the relationship between ERP-latencies, -amplitudes on the one hand and RTs or error rates on the other, linear regression analyses were conducted.

In the cue-based block, the error rates in switch trials were moderately but significant correlated with the N2-latency at FCz ($r = 0.18$, $p < 0.05$, $\beta = 1.35$). In the memory-based block, however, the N2 latency correlated clearly with the errors rates ($r = 0.31$, $p < 0.0001$, $\beta = 1.97$ and $r = 0.33$, $p < 0.0001$, $\beta = 1.28$, for nonswitch and switch trials, respectively). These correlations remained stable in the Val/Val group ($r = 0.36$, $p < 0.001$, $\beta = 2.33$ and $r = 0.35$, $p < 0.002$, $\beta = 1.36$) but disappeared in the Val/Met-Met/Met group.

Regarding the P3 at Pz, we found negative correlations between P3 amplitude and the error rates in the whole sample in the memory-based block ($r = -0.31$, $p < 0.0001$, $\beta = -0.12$ and $r = -0.20$, $p < 0.05$, $\beta = -0.06$, for nonswitch and switch trials, respectively). Again, these correlations remained significant in the Val/Val subgroup ($r = -0.43$, $p < 0.0001$, $\beta = -0.16$ and $r = -0.30$, $p < 0.01$,

$\beta = -0.06$), but appeared also in switch trials of the memory based block in the combined Val/Met-Met/Met group ($r = -0.34$, $p < 0.05$, $\beta = -0.10$). No further correlations were found.

In summary, increasing error rates are associated with increasing N2 latency and decreasing P3 amplitude, confirming previous results from our group (Hohnsbein et al., 1998).

3.4. Relationship between N2 and P3

As can be seen in Figs. 4 and 5, there is an apparent relationship between the N2 and P3 amplitudes: the more negative the N2 the smaller the P3. In order to investigate this relationship, correlations between N2 and P3 were conducted. This relationship was highly reliable at Cz for non-switch ($r = 0.71$, $p < 0.0001$, $\beta = 0.79$) and switch trials ($r = 0.82$, $p < 0.0001$, $\beta = 0.86$) in the memory based block. For the cue-based block the same was true for non-switch ($r = 0.71$, $p < 0.0001$, $\beta = 0.72$) and switch trials ($r = 0.75$, $p < 0.0001$, $\beta = 0.80$). This suggests a general relationship between N2 and P3.

4. Discussion

In the current study we examined the relevance of variations in the functional BDNF Val66Met genotype for memory-triggered and cue-triggered task switching performance in healthy elderly subjects with special emphasis on the modulation of neurophysiological processes underlie effects of the polymorphism on the behavioral level. To this end, ERPs were analyzed.

The results reveal that variations in the functional BDNF Val66Met polymorphism (e.g., Rybakowski, 2008; Egan et al., 2003) affect task switching performance when switching is governed by working memory processes, but not when it is governed by explicit cues. More particular, the Met-allele was associated with better performance, i.e., generally faster reaction times, lower variability in reaction times, lower error rates and lower switch costs in accuracy in working memory triggered task switching. The effects are unbiased with respect to the affective status of the participants.

The working memory-based task switching block required a simultaneous maintenance of 3 task rules and concomitant monitoring of the task sequence that was not supported by any external information. On a neurophysiological level, Met-allele carriers revealed an increased switch related N2 and decreased P3 effect in these memory-based task switch trials. In the Val/Val genotype group an inverted pattern was found with an attenuated N2 switching and P3 switching effect. Variations in behavioral performance are likely due to N2 and/or P3 related processes and cannot be due to differences in preparatory processes prior to target, because the groups did not differ in the CNV.

A number of neurophysiological studies, obtained an enhanced fronto-central N2 (i.e., more negative N2) in task switch relative to task repetition trials (e.g., Gehring et al., 2003; Jackson et al., 2001, 2004; Karayanidis et al., 2003; Kieffaber and Hetrick, 2005; Nicholson et al., 2005, 2006; Rushworth et al., 2002; Swainson et al., 2003). Recently, we interpreted this N2 as index of resolution of task-set conflict and selection of an appropriate response when a task has to be switched, which increases and delays the N2 (Gajewski et al., 2010a). As the BDNF Met-allele carriers showed enhanced N2 with a concomitant reduction in the rate of erroneous responses, an increased N2 seems to promote performance in working-memory guided task switching by improving response control and selection.

This is in line with response-related account of switch costs, as it has been suggested that the inhibition of an irrelevant (previous) task-set reflects the crucial factor contributing to switch costs (e.g., Allport et al., 1994, 2000; Mayr, 2001; Mayr and Keele, 2000; Schuch and Koch, 2003). A recent study by our groups in young subjects has shown that especially inhibition processes as reflected by the N2 are rendered more efficient in Met-allele carriers, compared with Val/Val genotype carriers (Beste et al., 2010a). From this point of view increases in task switching efficacy in Met-allele carriers, relative to Val/Val genotype carriers may also stem from more efficient inhibition processes.

However, the Met-allele's task-switching advantage was restricted to the memory-based condition. For the working memory domain, Miyajima et al. (2008) accounted for poor memory performance in elderly Met-allele carriers, while others as well as the present data suggest enhanced working memory processes in Met-allele carriers (Erickson et al., 2008; Matsushita et al., 2005; Ventriglia et al., 2002). The current results suggest that stable representation and maintenance of task rules and concomitant monitoring of the task sequence in Met-allele carriers may render response selection processes or the inhibition of the previous task set (N2 effects) more efficient. Within this discussion, it may be argued that variations in BDNF genotype did not affect performance in standard working memory tests (refer: neuropsychological data). However, opposed to these tests the memory-based task-switching paradigm required the maintenance of 3 task rules and task sequence over a long period of time. Demands on working memory may therefore be substantially higher and therefore get critical for performance in our study.

Increased working memory load has been suggested to cause the reduction of the P3b in general (e.g., Kok, 2001) and during task-set switching in particular, reflecting updating, organization, and implementation of the new task-set (Barceló et al., 2000; Gajewski et al., 2010b; Gehring et al., 2003; Goffaux et al., 2006; Karayanidis et al., 2003; Kieffaber and Hetrick, 2005; Kray et al., 2005; Lorist et al., 2000; Nicholson et al., 2005, 2006; Rushworth et al., 2002;

West and Moore, 2005). The P3b reduction in task-switch trials observed in Met-allele carriers, compared with the Val/Val genotype group may stem from the above discussed demands of working memory processes in memory-based task switching. Alternatively, the reduction of P3b amplitude may be explained in terms of the P3 latency jitter as the P3 was also associated with response related process (Falkenstein et al., 1994; Verleger et al., 2005). A cognitively more demanding condition (e.g., task switch) likely produces an enhanced and delayed N2, increasing variability of response selection processes and hence of P3 latency than a cognitively simpler condition (e.g., task repetition), leading to a broader and smaller P3 waveform (Falkenstein et al., 1993). Indeed, this interpretation may account for P3 reductions in switch compared with nonswitch trials as more RT-variability was found in the task switch trials. However, it cannot account for the decreased P3b in Met-allele carriers compared with the Val/Val genotype group because the variability of RTs was lower in the Met-individuals. According to the more general relationship between the N2 and P3 that was confirmed by significant correlations, the P3b reduction may reflect an aftereffect of an efficient and timely selection process that increase the N2 and thereby reduce the variability in the RTs (Gajewski et al., 2008), and reduce error rates (Hohnsbein et al., 1998). It seems that Met-allele carriers are able to complete the decision process faster and more sufficient as reflected in the generally lower reaction times, RT-variability and lower error rates than the Val/Val homozygote. The pattern of data confirmed the finding obtained by Erickson et al. (2008) showing better performance during task switching by shorter RTs in Met- than Val/Val carriers, particularly in advanced age, suggesting more stability and reserve in their cognitive processing. However, Egan et al. (2003) pointed out that BDNF release was less in Met allele in response to activity in animals. Another recent study by Kim et al. (2011) pointed out that in elderly Met allele carriers lower physical activity was related to an increased incidence of dementia. Therefore, it may be important to use reliable markers of physical fitness and/or physical activity in future studies. Furthermore, it would be crucial to learn whether the functions and the corresponding ERPs assessed in this study are modifiable by interventions like cognitive training and which BDNF genotype carriers would benefit more from training.

In summary, the results show that the Met-allele is associated with elevated task-switching performance in elderly subjects. Yet, this advantage was restricted to a condition in which task-switching had to be triggered by working memory processes. This shows that the effects of BDNF Val66Met polymorphism on task-switching in healthy elderly depend on how task-switching is triggered. The results suggest that especially "response selection" or "inhibitory processes" are rendered more efficient in Met-allele carriers of the BDNF Val66Met polymorphism. The results nicely corroborate recent findings suggesting that the Met-allele is associated with superior cognitive performance in healthy elderly and young adults.

Disclosure statement

The authors declare no conflicts of interest.

The study was approved by the local ethics committee of the Leibniz association and is accordance with the declaration of Helsinki. All participants were explained the scope of the study and gave written informed consent before any study protocol was commenced.

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