Neuroscience 166 (2010) 178–184

PARADOXICAL ASSOCIATION OF THE BRAIN-DERIVED-NEUROTROPHIC-FACTOR val66met GENOTYPE WITH RESPONSE INHIBITION

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Abstract—Response inhibition is a basic executive function which is dysfunctional in various basal ganglia diseases. The brain-derived-neurotrophic-factor (BDNF) plays an important pathophysiological role in these diseases. In the current study we examined the functional relevance of the BDNF val66met polymorphism for response inhibition processes in 57 healthy human subjects using event-related potentials (ERPs), i.e. the Nogo-N2 and Nogo-P3, which likely reflect different aspects of inhibition. Our results support the premotor inhibition theory of the Nogo-N2. We show that the BDNF val66met polymorphism selectively modulates the Nogo-N2. Response inhibition was better in the val/met–met/met group, since this group committed fewer false alarms, and their Nogo-N2 was larger, compared to the val/val group. This is the first study showing that met alleles of the BDNF val66met polymorphism confer an advantage for a specific cognitive function. We propose a neuronal model how this advantage gets manifest on a neuronal level.

Key words: response inhibition, event-related potentials (ERPs), Nogo-N2, Nogo-P3, basal ganglia, BDNF val66met.

The basal ganglia are involved in a considerable number of cognitive functions (Chudasama and Robbins, 2006), ranging from learning and rehearsing visual-motor associations (Bédard and Sanes, 2009) to response inhibition (Li et al., 2008). Response inhibition functions are important cognitive functions, and their neurophysiological correlates can be measured using event-related potentials (ERPs) (Falkenstein et al., 1999; Roche et al., 2005; Fallgatter et al., 2004; Band and van Boxtel, 1999; Nieuwenhuis et al., 2003). Response inhibition subprocesses are reflected by two distinct fronto-central ERP-components, namely Nogo-N2 and Nogo-P3. While the Nogo-N2 is suggested to reflect inhibition or revision of a motor plan/program before the actual motor process (Falkenstein et al., 1999) or response conflict (Nieuwenhuis et al., 2003), the Nogo-P3 is supposed to be related to motor inhibition (e.g. Zordan et al., 2008; Bruin et al., 2001). More specifically, and because of its long latency, the Nogo-P3 has been suggested to reflect the evaluation of a successful inhibition rather the inhibition process itself (Beste et al., 2008; Schmajuk et al., 2006; Roche et al., 2005; Fallgatter et al., 2004; Band and van Boxtel, 1999).

Altered response inhibition and ERP measures have been reported in both Parkinson's (Beste et al., 2009; Bokura et al., 2005) and Huntington's disease (Beste et al., 2008), illnesses with known effects on medium spiny neurons of the basal ganglia (Stephens et al., 2005; Obeso et al., 2008; Taverna et al., 2008; Solis et al., 2007; Cepeda et al., 2003), and on neurons projecting to the basal ganglia from the substantia nigra (Yohrling et al., 2003). In Huntington's disease, the nuclear effects of huntingtin are associated with dysregulation of dopaminergic signaling (Cummings et al., 2006; Johnson et al., 2006; Tang et al., 2007), and decreases in brain-derived neurotrophic factor (BDNF) (Zuccato et al., 2003; Gauthier et al., 2004). BDNF has been shown to be an important regulator of gene expression in medium spiny neurons (Saylor et al., 2006; Saylor and McGinty, 2008), of reduced dopamine release after methamphetamine (Narita et al., 2003), and of normal expression of the dopamine D3 receptor in the basal ganglia (Guillin et al., 2001). Altogether, these findings raise a question regarding whether or not BDNF genotype might have an effect on cognitive functions such as response inhibition.

In humans, genotype distribution of a single nucleotide polymorphism in the BDNF gene at codon 66 (val66met) reveals the methionine allele to be present in approximately 30% of the US population (Shimizu et al., 2004). To date, studies of the BDNF val66met polymorphism in humans have focused predominantly on memory functions, along with short-term plasticity/learning, and addiction/reward processing. The first two areas of research (memory and plasticity/learning) constitute the largest areas of study (e.g., Egan et al., 2003; Hariri et al., 2003; Goldberg and Weinberger, 2004; Goldberg et al., 2008; Kleim et al., 2006; McHughen et al., (in press)), and appear to be consistent in associating the met allele with diminished function. However, to be evolutionary sustained it seems necessary that met alleles of the BDNF val66met polymorphism confer an advantage (Tettamanti et al., 2010). A recent study of reward function and BDNF indirectly sug-

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Abbreviations: BDNF, brain-derived-neurotrophic-factor; ERPs, event-related potentials; SBE, single base extension.

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doi:10.1016/j.neuroscience.2009.12.022

gested a domain where a functional advantage might be observed with the BDNF val66met polymorphism, namely in the control of reward/aversion circuitry function and key-press behavior (Gasic et al., 2009). A direct measure of cognitive control, such as response inhibition, has not, to date, been studied with imaging genetics.

However, as stated above BDNF is especially important for dopaminergic neuron functioning in basal ganglia structures, such as the substantia nigra (Oo et al., 2009; Andressoo and Saarma, 2008) which becomes evident in studies in Parkinson's disease (e.g. Nagatsu and Sawada, 2007; Fumagalli et al., 2006). If met alleles are associated with diminished cognitive functions, it may be hypothesized that the Nogo-N2 is decreased and response inhibition performance is adversely affected. However, we observed a contrary effect with decreased nigrostriatal activity leading to an enhanced Nogo-N2 with elevated response inhibition performance (Beste et al., 2009, in press). Furthermore, the evolutionary motivation for conserving the met-allele across generations is still unclear. Therefore we postulate that the general view associating the met allele with diminished cognitive functions needs to be challenged.

EXPERIMENTAL PROCEDURES

Subjects

A sample of 57 genetically unrelated, healthy subjects of Caucasian descent was recruited by newspaper announcements. Genotyping of the BDNF val66met polymorphism (see below) showed that 31 subjects carried the val/val genotype, 19 carried the Val/Met genotype and seven carried the met/met genotype. The Hardy-Weinberg equilibrium was examined using the program Finetti provided as an online source (http://ihg.gsf.de/http://cgi-bin/hw/hwa1.pl; Wienker TF and Strom TM). The distribution of BDNF val66met genotypes did not significantly differ from the expected numbers calculated on the basis of observed allele frequencies according to Hardy–Weinberg equilibrium ($P=0.193$). As the met/met genotype had an expectedly low frequency, we combined the val/met and met/met genotype groups to one group.

The mean and standard deviation are provided to describe demographical data. The sample consisted of 17 males and 40 females with mean age of 25.4 ($\pm$4.9) years. Sexes were equally distributed across genotype groups (Kruskal–Wallis-Test (H-Test): $chi^2=0.02$; $df=1$; $P>0.8$). The Beck depression inventory (BDI) (Beck et al., 1961) score was 4.6 ($\pm$3.2) and did not differ between the groups ($F(1,55)=0.5$; $P>0.4$). Similarly, the anxiety sensitivity index (ASI mean/SD: 13.1$\pm$4.5) (Reiss et al., 1986) did not differ between the genotype groups ($F(1,55)=0.8$; $P>0.3$). All participants were right handers and their educational background ranged between 13 and 20 years.

Volunteers were paid eight Euros per hour as compensation. The study was approved by the ethics committee of the University of Münster. All subjects gave written informed consent before any of the study procedures were commenced.

Genotyping

Genotyping of the genetic variants of BDNF val66met SNP rs6265 (position: chr11:27,636,492) was carried out following published protocols applying the multiplex genotyping assay iPLEX™ for use with the MassARRAY platform (Oeth et al., 2007), yielding a genotyping completion rate of 98.2%. Genotypes were determined by investigators blinded for the study. In more detail, genotyping of the BDNF functional SNP rs6265 (val66met) was performed as part of a larger genotyping project using the iPLEX panel. Assay was performed on Sequenom MassArray® platform (Sequenom, San Diego, CA, USA). The assay consists of an initial locus-specific PCR reaction, followed by single base extension (SBE) using mass-modified dideoxynucleotide terminators of an oligonucleotide primer which anneals immediately upstream of the polymorphic site of interest. In the following step, a chip-based matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry is employed to identify the SNP alleles based on distinct mass of the extended primer. Primer sequences rs6265BB-1 ACGTTGGATGCATCATTGGCTGACACTTTC and rs6265BB-2 ACGTTGGATGTTTTCTTCATTGGGCCGAAC used for first PCR amplification and rs6265BB-EXT cagCCAACAG-CTCTTCTATCA for SBE step were designed using Assay Design 3.0.0 software (iPLEX). PCR amplification and SBE assays were carried out following published protocols (Oeth et al., 2007). Random selection of 10% samples was re-genotyped and based on the results we estimated the error rate less than 1%.

Go/Nogo task

We used a simple Go/Nogo-Task, in which two stimuli "press" (Go-stimulus) and "stop" (Nogo-stimulus) were presented for 300 ms on a PC-Monitor. The response-stimulus interval was fixed at 1600 ms. In trials with response times exceeding the deadline of 1200 ms a feedback stimulus (1000 Hz, 60 dB SPL) was given. This stimulus had to be avoided by the subjects. Two blocks of 100 stimuli each were presented in this task. Of these 70% were Go-stimuli and 30% were Nogo-stimuli. The subjects had to react with the thumb to "Go-stimuli" and to refrain from responding on "Nogo-stimuli." The response button had to be operated either with the right or left hand thumb. Fifty percent of the subjects studied used their right thumbs, and the other 50% their left, based on random assignment.

Data processing and analysis

During the task the EEG was recorded from 24 Ag-AgCl electrodes (Fpz, Fp1, Fp2, Fz, F3, F4, F7, F8, FCz, FC3, FC4, FC5, FC6, C3, C4, C7, C8, Pz, P3, P4, P7, P8, Oz, O1, O2, left mastoid − M1, right mastoid − M2) against a reference electrode located at Cz at a sampling rate of 500 Hz applying a filter bandwidth 0–80 Hz to the EEG. Electrode impedances were kept below 5 kΩ. EEG was filtered off-line from 0.5 to 16 Hz. Eye movements were monitored and recorded by means of two lateral and four vertical EOG electrodes. These EOG electrodes were used to correct trials for ocular artifact by means of the Gratton-Coles-Algorithm (Gratton et al., 1983). Results of the ocular correction procedure were visually inspected to be sure that the regression method did not distort frontal channels. Artifact rejection procedures were applied twice: automatically, with an amplitude threshold of $\pm$80 μV, and visually by rejecting all trials contaminated by technical artifacts. Before quantifying ERPs, the data was re-referenced to linked mastoids.

The N2 and P3 amplitudes in Go- and Nogo-trials were evaluated in correct trials only. The baseline was set at 200 ms pre-stimulus until stimulus presentation. The N2 was defined as the most negative peak occurring 200 till 300 ms after stimulus onset. The P3 was measured relative to the baseline. The P3 was defined as the most positive peak occurring 350–500 ms after stimulus onset. Amplitudes and peak latencies were measured for each subject separately. As stated above, met/met had an expectedly low frequency. Hence, we combined the val/met and met/met genotype groups to one group. The neurophysiological data of the N2 and P3 were analyzed in two separate repeated measures ANOVAs. The N2 data were analyzed using the factors "electrode" (Fz, FCz, Cz) and "Go/Nogo" as within-subject factors and "BDNF val66met genotype" as between subject factor. For the

P3-data the electrodes FCz and Pz were analyzed with the same design. Greenhouse-Geisser corrections were applied when appropriate. Post hoc tests were corrected using Bonferroni-correction.

RESULTS

Behavioural data

Three measures were collected: reaction times (RTs) on Go-trials, error rates on Go-trials, and error rates on Nogo-trials (i.e., false alarms). For each, mean and standard error of the mean are provided. Across subjects, the RT was 279.5 (3.13). A univariate ANOVA revealed that the genotype groups did not differ in their RTs ($F(1,55)=1.01$; $P>0.3$). The mean rate of false alarms was 6.54 (0.36). A univariate ANOVA revealed that the genotype groups differed with respect to their rate of false alarms ($F(1,55)=72.20$; $P<0.001$). It is shown that false alarm rates were higher in the val/val genotype group (8.4±0.32) as compared to the combined val/met–met/met genotype group (4.3±0.35). Error rates on Go trials did not differ between the groups ($F(1,55)=1.01$; $P>0.3$).

To test for allele dose effects, we performed an analysis using each genotype separately. These analyses were performed using non-parametric tests, because of the small sample size of the met/met genotype group. The mean of the Nogo-N2 (across electrodes Fz and FCz) was 8.41 in the val/val genotype group, 4.89 in the val/met genotype group and 2.71 in the met/met genotype group. A median test with all three genotype groups revealed genotype differences in the Nogo-N2 ($chi^2=33.67$; $df=2$; $P<0.001$, Monte-Carlo significance). Subsequent Mann–Whitney-*U*-tests revealed that the val/met genotype group differed from the val/val ($Z=-3.33$; $P<0.001$, Monte-Carlo significance) and met/met genotype group ($Z=-4.11$; $P<0.001$, Monte-Carlo significance). The met/met genotype group also differed from the val/val genotype group ($Z=-4.11$; $P<0.001$, Monte-Carlo significance). The results suggest an allele dose effect of the BDNF val66met polymorphism for response inhibition processes.

Neurophysiological data

N2 data. Stimulus-locked ERPs on Go and Nogo stimuli are given in Fig. 1.

The analysis of the N2 revealed a main effect of electrode location ($F(1,55)=66.91$; $P<0.001$), with the N2 being stronger at electrode Fz (−0.95±0.15), compared to FCz (0.32±0.1). There was a two-way interaction "electrode×Go/Nogo×group" ($F(1,55)=9.47$; $P=0.017$). This interaction was subsequently analyzed calculating a repeated measures ANOVA using the factors Go/Nogo and group for each electrode separately. While for both electrodes the interaction "Go/Nogo×group" was significant (Fz: $F(1,55)=38.90$; $P<0.001$; FCz: $F(1,55)=31.21$; $P<0.001$), the effect size was larger at electrode Fz ($\eta=0.414$), than at FCz ($\eta=0.362$), leading to this significant interaction. Using separate univariate ANOVAs for

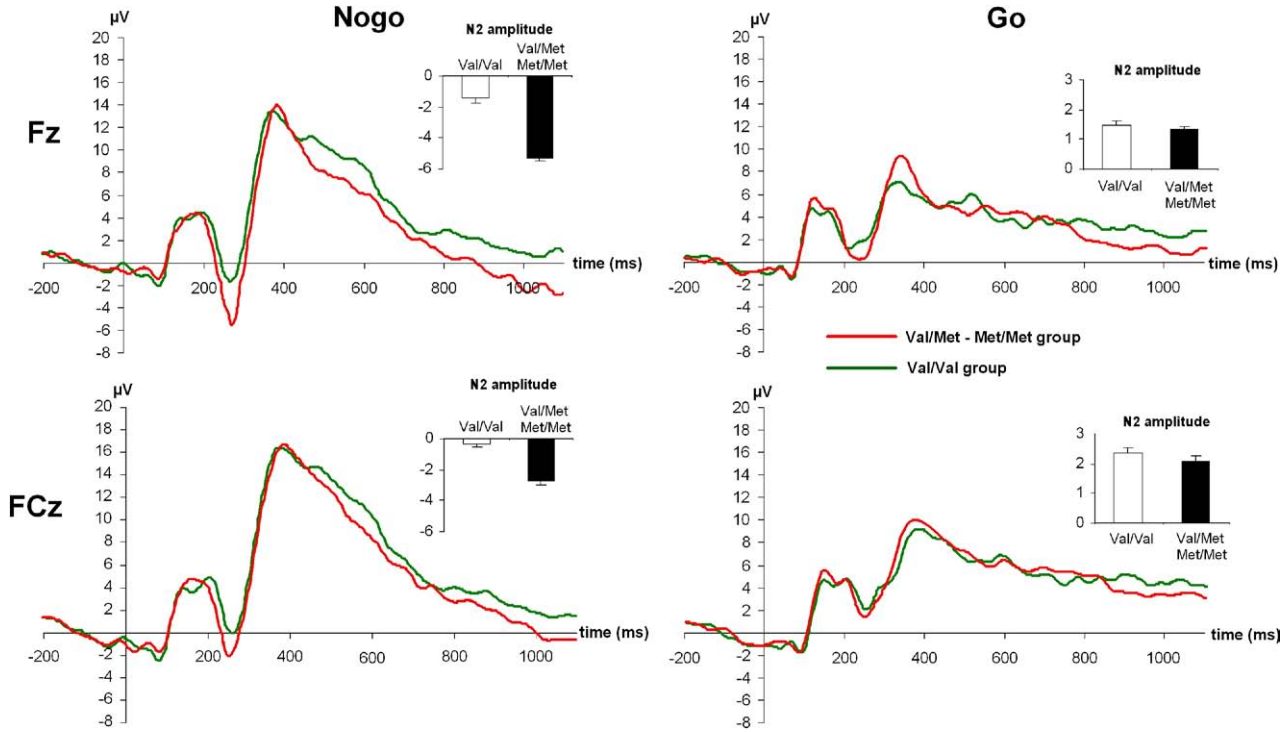

Fig. 1. Stimulus-locked event-related potentials (ERPs) at electrode Fz and FCz, separated for Go and Nogo trials. Red lines indicate the potential for the combined BDNF Val/Met—Met/Met genotype group, green lines indicate potentials for the Val/Val genotype group. Time point 0 denotes the time point of Go or Nogo stimulus presentation. Also bar plots of the Nogo-N2 amplitudes are given for electrodes Fz and FCz. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

electrode Fz (showing largest effects) it is shown that the genotype groups did not differ with respect to their N2 amplitudes on Go-trials ($F(1,55)=0.46$; $P>0.4$), but on Nogo-trials ($F(1,55)=47.61$; $P<0.001$; $\eta=0.464$). The N2 on Nogo-trials was larger for the combined val/met–met/met (-5.25 ± 0.38) genotype group as compared to the val/val genotype group (-1.37 ± 0.38). The strength of this pattern of results is underlined by the fact that a similar result is obtained when using both electrodes (Fz and FCz) for the analysis, which also underlines that the interaction with the factor electrode is weak (interaction "Go/Nogo×group" $F(1,55)=61.23$; $P<0.001$). Again, a group difference was obtained for Nogo-trials ($F(1,55)=82.57$; $P<0.001$) only, but not for Go-trials ($F(1,55)=1.66$; $P=0.2$). The N2 on Nogo-trials was larger for the combined val/met–met/met genotype group (-4.01 ± 0.23), than for the val/val genotype group (-0.87 ± 0.23). Overall, the significant main effect group showed that the N2 was larger for the combined val/met–met/met genotype group (-1.15 ± 0.14) than for the val/val genotpye group (0.52 ± 0.13) ($F(1,55)=72.05$; $P<0.001$). For the latencies, no main or interaction effect was significant (all F′s<0.2; $P>0.6$).

A correlational analysis across the whole sample revealed that the amplitude of the Nogo-N2 was strongly related to the amount of false alarms (refer Fig. 2), i.e. the stronger the Nogo-N2, the lower the frequency of false alarms ($r=0.810$; $R^2=0.65$; $P<0.001$). When repeating this analyses for two genotype groups separately, similar results are obtained (val/val: $r=0.751$; $R^2=0.56$; $P<0.001$; val/met–met/met: $r=0.800$; $R^2=0.64$; $P<0.001$).

Additionally, to test for allele dose effects, an analysis across all three genotypes was performed using non-parametric tests. The mean of the Nogo-N2 (across electrodes Fz and FCz) was −0.81 in the val/val genotype group, −3.40 in the val/met genotype group and −5.67 in the met/met genotype group. A median test with all three genotype groups revealed genotype differences in the Nogo-N2 ($chi^2=39.27$; $df=2$; $P<0.001$, Monte-Carlo significance). Subsequent Mann–Whitney-*U*-tests revealed that the val/met genotype group differed from the val/val ($Z=-5.56$; $P<0.001$, Monte-Carlo significance) and met/met genotype group ($Z=-3.84$; $P<0.001$, Monte-Carlo significance). The met/met genotype group also differed from the val/val genotype group ($Z=-4.08$; $P<0.001$, Monte-Carlo significance). The results suggest an allele dose effect of the BDNF val66met polymorphism for response inhibition processes.

P3 data. Analysing the P3 using the repeated measures ANOVA we found a main effect Go/Nogo ($F(1,55)=15.51$; $P<0.001$), with the P3 being larger on Nogo (13.2 ± 0.29) as compared to Go-trials (12.02 ± 0.29). There was also a significant interaction "electrode×Go/Nogo" ($F(1,55)=88.37$; $P<0.001$). Subsequently, repeated measures ANOVAs were conducted for each condition separately (Go vs. Nogo). It is shown that the P3 on Go-trials was larger at electrode Pz (14.7 ± 0.4) than at electrode FCz (9.17 ± 0.4) ($F(1,56)=77.78$; $P<0.001$). A vice versa pattern was recorded for the P3 on Nogo-trials. Here, the P3 was larger at electrode FCz (15.6 ± 0.5) as compared to electrode Pz (10.8 ± 0.4) ($F(1,56)=55.04$; $P<0.001$). Neither the main effect group nor any interaction with the factor group was significant (all F′s<0.4; $P>0.5$). No latency effects were obtained (all F′s<0.6; $P>0.6$).

DISCUSSION

In the current study in healthy subjects we examined the association between the BDNF val66met polymorphism and subprocesses of response inhibition reflected by distinct ERP-components, namely the Nogo-N2 and Nogo-P3. While RTs on Go-trials were similar between the genotype groups, we observed more false alarms in the val/val genotype groups, compared to the combined val/

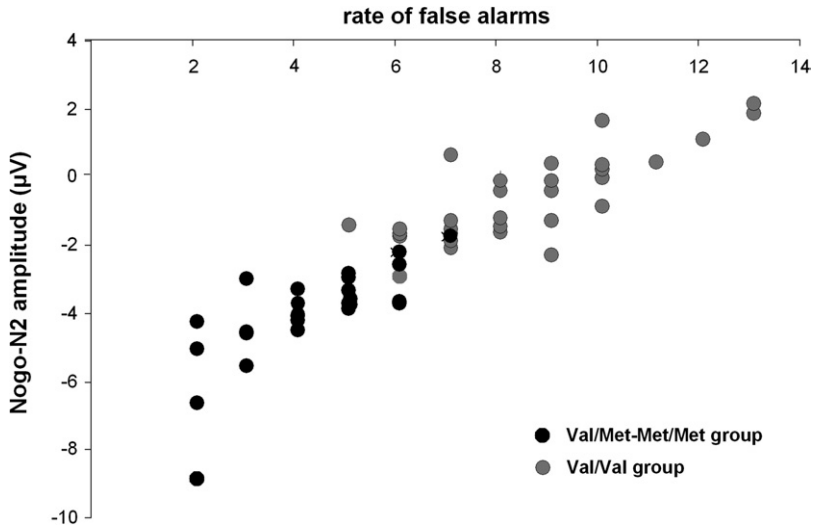

Fig. 2. Scatterplot denoting the correlation between Nogo-N2 amplitude and frequency of false alarms across the whole sample. It is shown that as the Nogo-N2 gets stronger, the frequency of false alarms decreases. Grey circles denote subjects belonging to the BDNF Val/Val genotype group, black circles denote subjects belonging to the combined Val/Met—Met/Met genotype group.

met–met/met genotype group. Error rates on Go-trials did not differ between genotype groups. Genotype effects were obtained for the Nogo-N2 only. The Nogo-N2 was larger in the combined val/met–met/met as compared to the val/val genotype group. Neither the Nogo-P3 nor the Go-N2 or Go-P3 were affected, suggesting that the effects are highly specific. Hence, the results suggest that the val/met–met/met genotype group affected stronger response inhibition processes and better response inhibition performance than the val/val genotype groups.

It has been suggested that the Nogo-N2 reflects pre-motor inhibition processes (Falkenstein et al., 1999), i.e. the suppression or revision of an inappropriate motor program. In line with this hypothesis, decreases in the rate of false alarms are accompanied by a larger Nogo-N2 reflecting stronger pre-motor inhibition processes in Nogo trials. This is substantiated by the finding of a linear correlation between size of the Nogo-N2 and frequency of false alarms, i.e. the stronger the Nogo-N2, the lower the frequency of false alarms (Fig. 2). Assuming instead the conflict detection hypothesis (Nieuwenhuis et al., 2003), a larger Nogo-N2 might also be associated with a smaller false alarm rate, because a better detection of a conflict between pressing and stopping might induce stronger control and hence also a lower false alarm rate (Nieuwenhuis et al., 2003).

The observation in our study that the Nogo-P3 did not differ between the BDNF val66met genotype groups while the frequency of false alarms differed argues against the notion that the Nogo-P3 is related to motor inhibition itself (e.g. Zordan et al., 2008; Bruin et al., 2001). However, it is still compatible with the idea of inhibition evaluation. Even though the BDNF polymorphism modulates inhibition, its evaluation may be unaffected. The results suggest that both components (Nogo-N2 and Nogo-P3) seem to differ with respect to their neurobiological substrates (neurotrophins) modulating these processes. This is in line with a study by Kosslyn and Koenig (1992) who pointed out that processes sharing similar neuronal circuitry often share computational mechanisms. If Nogo-N2 and Nogo-P3 would share common computational functions, one may have expected a modulation of both components by the BDNF val66met polymorphism.

These results are the first showing that the met allele is related to increased cognitive functions. In relation to other results reporting an association of the met allele with diminished memory of learning (Egan et al., 2003; Hariri et al., 2003; Goldberg and Weinberger, 2004; Goldberg et al., 2008; Kleim et al., 2006; McHughen et al., (in press)), the current results suggest a necessity to refine this picture. Met alleles have been associated with a decreased activity-dependent, but not constitutive secretion of BDNF from neurons (Egan et al., 2003; Chen et al., 2004). In conjunction with other results on memory and neural plasticity (e.g. Egan et al., 2003; Hariri et al., 2003; Goldberg and Weinberger, 2004; Goldberg et al., 2008; Kleim et al., 2006; McHughen et al., (in press)) the current results suggest that effects of met alleles vary between brain systems and cognitive functions. This may be of special interest from a genetic point of view, since this result suggests that met alleles of the BDNF val66met polymorphism might confer an advantage (Tettamanti et al., 2010) for a specific cognitive function, i.e. response inhibition.

However, how may this advantage be explained on a neuronal level? In the following short paragraph, a theoretical model is proposed.

As mentioned in the introduction, BDNF is an important modulator of basal ganglia processes (Andressoo and Saarma, 2008; Nagatsu and Sawada, 2007; Fumagalli et al., 2006). It is well-known that basal ganglia circuits are fine-tuned by parallel inhibitory and excitatory loops (DeLong and Wichmann, 2007). As response-inhibition subprocesses are altered in basal ganglia disorders (Beste et al., 2008, 2009; Bokura et al., 2005), the basal ganglia are a likely candidate system where decreases in inhibitory processes may occur under genetic control. Decreases in nigro-striatal activity render the direct pathway less active while the indirect pathway becomes more active (Gale et al., 2008). This may lead to a predominating inhibitory effect (e.g. Gale et al., 2008). Met alleles may displace the balance between the direct and indirect pathway leaving a predominant indirect pathway. Recently, it has been shown that processes reflected by the Nogo-N2 are most likely mediated via the nigrostriatal dopamine system (Beste et al., 2009). Decreases in nigrostriatal system functioning were related to increases in the Nogo-N2 and response inhibition performance. While the pars compacta part of the SN (SNc) mainly projects to the striatum, the SN pars reticulata (SNr) mainly projects to thalamic structures, hence affecting neocortical functioning (Chudasama and Robbins, 2006), which is thus the final common pathway of both the direct and the indirect pathways. The SNr-thalamic connections are likely inhibitory (Humphries et al., 2006). An increase of this inhibitory nigral activity, or the indirect pathway (Gale et al., 2008), most probably leads to even more inhibited thalamic and neocortical circuits (Beste et al., 2009, in press). With respect to neocortical circuits, particularly orbitofrontal areas may be of relevance, as these have been shown to be important for generating the Nogo-N2 and are modulated by BDNF (Lotfipour et al., 2009).

CONCLUSION

In summary, the results show that subprocesses of response inhibition are differentially modulated by the functional BDNF val66met polymorphism. The modulation of inhibitory subprocesses is restricted to pre-motor subprocesses of inhibition, as probably reflected by the Nogo-N2. Interestingly, the val/met–met/met genotype group showed most efficient response inhibition. Therefore, the results refine the view that met alleles are always associated with diminished cognitive functions. Apparently, the effects elicited seem to depend on the specific neuronal system and cognitive function. Our results, for the first time, reveal an evolutionary advantage justifying the conservation of the met allele across generations. On a systems level we propose a model that explains the observed pattern on the

basis of a differentially altered modulation of the direct and indirect pathway within the basal ganglia.

Acknowledgments—This work was supported by a young investigator grant to C.K. by the Interdisciplinary Centre for Clinical Research of the University of Münster, Germany (IZKF FG4), by a grant to K.D. by the Interdisciplinary Centre for Clinical Research of the University of Münster, Germany (Pan3/008/07) and by a grant to C.B. (FoRUM AZ F647-2009), Ruhr-Universität Bochum. We thank both of the unknown reviewers for their helpful and constructive comments.

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(Accepted 7 December 2009)
(Available online 24 December 2009)