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# Double dissociated effects of the functional TNF-α -308G/A polymorphism on processes of cognitive control

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ABSTRACT

Neuroimmunological factors may modulate brain functions and are important to understand the molecular basis of cognition. The tumor necrosis factor alpha (TNF-α) is known to induce neurodegenerative changes in the basal ganglia, but the cognitive effects of these changes are not understood. Since the basal ganglia are neurobiologically heterogeneous, different cognitive functions mediated by basal ganglia-prefrontal loops (response inhibition and error processing) may not necessarily be uniformly affected. Response inhibition and error processing functions were examined using event-related potentials (ERPs) and subjects ($N = 71$) were genotyped for the functional TNF-α -308G→A polymorphism. We show a double-dissociated effect of the functional TNF-α -308G→A polymorphism on response inhibition and error processing. While response inhibition functions were more effective in the AA/AG genotype group, error monitoring functions are adversely affected in this genotype group. In the GG genotype group, the pattern of results was vice versa. The results refine the view of the effects of TNF-α on cognitive functions.



## 1. Introduction

Functional basal ganglia-prefrontal loops mediate several important executive functions related to the monitoring of actions (e.g. Chudasama & Robbins, 2006), like response inhibition and error processing. It has been suggested that neuroimmunological factors such as pro-inflammatory cytokines may play a role in mediating functions of basal ganglia-prefrontal loops. For example, the tumor necrosis factor alpha (TNF-α) is a pro-inflammatory cytokine that has been shown to affect dopaminergic processes (e.g. Nakajima et al., 2004; Niwa et al., 2007; Yamada, 2008). Moreover, since TNF-α is assumed to be a key player in the pathogenesis of dopaminergic neurodegeneration (Boka et al., 1994; Sriram & O'Callaghan, 2007; Sriram et al., 2002; Sriram, Miller, & O'Callaghan, 2006; for review: McCoy & Tansey, 2008), this cytokine has been suggested as a pathogenic factor in Parkinson's Disease (PD) (e.g. Sawada, Imamura, & Nagatsu, 2006; Tansey et al., 2008).

Cognitive processes such as response inhibition and error processing have been found to be altered in Parkinson's disease (PD) (e.g. Beste, Willemssen, Saft, & Falkenstein, 2009a, 2010a). It has been shown that these cognitive functions depend on the dopaminergic system and subsequently, both are altered in PD. More specifically, error monitoring functions are compromised in PD (e.g. Beste et al., 2009a; Falkenstein et al., 2001), while response inhibition functions can be rendered more efficiently (Beste et al., 2010a). These patterns of results have been reported due to alteration in function of the direct and indirect basal ganglia pathways in PD (e.g. DeLong & Wichmann, 2007; Kravitz et al., 2010), where the direct pathway becomes less active and the indirect pathway becomes more active (Beste et al., 2010a; Gale, Amirnovin, Williams, Flaherty, & Eskandar, 2008). Such opposite effects of dopamine-dependent basal ganglia dysfunction on error processing and response inhibition have been supported by recently published molecular data showing an opposing influence of the brain-derived-neurotrophic factor (BDNF) on error process-

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ing and response inhibition (Beste, Baune, Domschke, Falkenstein, & Konrad, 2010; Beste et al., 2010e).

Since TNF-α is known to compromise dopaminergic neural transmission in basal ganglia-prefrontal loops (for review: McCoy & Tansey, 2008; Sriram & O'Callaghan, 2007; Sriram et al., 2002, 2006), it can be assumed that this cytokine may also affect response inhibition and error monitoring processes in a divergent or even opposing direction. Similarly to BDNF, it may be hypothesized that TNF-α affects response inhibition and error processing in a dissociated fashion in that response inhibition processes may show enhanced efficacy, while error monitoring processes may be compromised. Error monitoring processes seem to rely upon processing of a temporal-difference error signal (e.g. Schultz, 2007; Holroyd & Coles, 2002) that is carried by phasic dopaminergic responses of the D1-receptor system (e.g. Floresco, West, Ash, Moore, & Grace, 2003; Grace, 1991). However, a relevance of the dopamine D2 system cannot be ruled out. Yet, other theories do not rely upon specific assumptions related to neurotransmitter systems, but conceptualize error processing in terms of post-response conflict processes (e.g. Yeung, Botvinick, & Cohen, 2004). The putative reliance of the D1-receptor system may be of particular relevance for TNF-α related decreases in error monitoring efficacy, since some evidence suggests that especially dopamine D1 receptor activity contributes to the secretion of TNF-α (Besser, Ganor, & Levite, 2005).

To investigate the above hypothesized dissociative modulation of error monitoring and response inhibition processes by TNF-α, we combine an event-related potential (ERP) account with a molecular genetic approach. Using ERPs, error processing is reflected by the error negativity (Ne/ERN) (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993) that possibly drives post-error slowing of reaction times (RTs) (Debener et al., 2005). Response inhibition processes are reflected by two distinct ERP components, the Nogo-N2 and the Nogo-P3. The latter is assumed to reflect the evaluation of inhibition (e.g. Roche, Garavan, Foxe, & O'Mara, 2005; Schmajuk, Liotti, Busse, & Woldorff, 2006), while the first is seen as to reflect pre-motor inhibition or conflict (Beste et al., 2009a; Beste, Dziobek, Hielscher, Willemssen, Falkenstein, 2009b; Falkenstein, Hoormann, & Hohnsbein, 1999; Nieuwenhuis, Yeung, van den Wildenberg, & Ridderinkhof, 2003).

We investigated a particular SNP of the *TNF-α* gene, the -308G→A single nucleotide polymorphism (SNP) (rs1800629), which denotes a G(TNFα1)→A(TNFα2) single nucleotide exchange (Hajeer & Hutchison, 2001; Rainero et al., 2004; Wilson, Symons, McDowell, McDevitt, & Duff, 1997). The -308A allele has been found to confer stronger transcriptional activity than the -308G allele (Wilson et al., 1997). We selected this particular SNP since it has recently been found to be associated with cognitive functions (Baune et al., 2008; Beste, Heil, Domschke, Baune, & Konrad, 2010f).

In summary, we hypothesize that A-allele carriers show a reduced error processing ability, compared to the GG genotype group, which is reflected in a decrease of the Ne/ERN amplitude and in a reduction in the degree of post-error slowing (Rabbitt, 1966). To reflect the opposing effects of TNF-α, we hypothesize that A-allele carriers reveal a reduced rate of false alarms (i.e. better behavioural performance) as part of response inhibition, which is accompanied by an increased Nogo-N2 amplitude. It is assumed that especially the Nogo-N2 (not the Nogo-P3) amplitude is affected as recent studies showed a close relationship between variations in false alarm rate and the Nogo-N2 amplitude (e.g. Beste et al., 2010a, 2010b).

## 2. Materials and methods

### 2.1. Subjects

A sample of 71 genetically unrelated, right-handed, healthy participants of Caucasian descent (country of origin: Germany) were recruited by newspaper announcements. The mean and standard deviation (SD) are given. The mean age of the subjects was 25.1 years (5.6). The sample consisted of 27 males and 44 females. Hardy–Weinberg equilibrium was examined using the program Finetti provided as an online source (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl; Wienker TF and Strom TM). As the AA genotype had an expectedly low frequency (see below), we combined the AA and GA genotype groups to one group. The distribution of TNF-α -308G→A genotypes did not significantly differ from the expected numbers calculated on the basis of observed allele frequencies according to Hardy–Weinberg equilibrium (AA = 2, AG = 29, GG = 40; $p = .198$). The distribution of females and males did not differ across genotype groups (Mann–Whitney-*U* test: $Z = -.241$; $p > .8$; Monte-Carlo significance). Also, age was not different for the genotype groups ($F(1,69) = 0.29$; $p > .6$). Since error monitoring and response inhibition processes are known to be modulated by factors related to depression and anxiety (e.g. Ruchsow et al., 2006; Sehlmeyer et al., 2010), the anxiety sensitivity questionnaire (ASI) (McNally, 2002) and the Beck depression inventory (BDI) were administered. Both, the ASI score (AA/AG: 14.1 ± 8.2; GG: 13.1 ± 10.5) and the BDI (AA/AG: 3.1 ± 2.5 GG: 2.5 ± 2) score did not differ between genotype groups (all *F*'s < 0.6; $p > .3$). All subjects enrolled into the study had no history of any neurological or psychiatric diseases. The study was approved by decision of the ethics committee of the University of Münster. All subjects gave written informed consent before any of the study procedures were commenced.

### 2.2. Genotyping

Genotyping of TNF-α -308G→A (rs1800629) located on chromosome 6p21.3 (position 31651010 5′ to the gene (possibly promoter/enhancer region)) 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 100%. Genotypes were determined by investigators blinded for the study.

### 2.3. Experimental paradigm

To examine error processing and response inhibition processes we applied a modified flanker task (Kopp, Rist, & Mattler, 1996). Vertically arranged visual stimuli were presented. The target-stimulus (arrowhead or circle) was presented in the centre with the arrowhead pointing to the left or right. The central stimuli were flanked by two vertically adjacent arrowheads which pointed in the same (compatible) or opposite (incompatible) direction as the target. In case of target stimuli (arrowheads pointing to the left or right) participants were required to press a response button with their left or right thumb. A circle as central stimulus indicates a Nogo trial, where the subject is required to inhibit the response. The flankers preceded the target by 100 ms to maximize premature responding to the flankers (Beste, Saft, Andrich, Gold, & Falkenstein, 2008c), which would result in errors especially in the incompatible and the Nogo condition. The target (arrowheads or circles) was displayed for 300 ms. The response-stimulus interval was 1600 ms. Flankers and target were switched off simultaneously. Time pressure was administered by asking the subjects to respond within 600 ms. In trials with reaction times exceeding this deadline a feedback stimulus (1000 Hz, 60 dB SPL) was given 1200 ms after the response; this stimulus had to be avoided by the subjects. Four blocks of 105 stimuli each were presented in this task. Compatible (60%) and incompatible stimuli (20%) and Nogo stimuli (circle) (20%) were presented randomly.

### 2.4. EEG recording 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 and re-referenced to linked mastoids. 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, Coles, & Donchin, 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 amplitude threshold of ±80 μV, and visually by rejecting all trials contaminated by technical artifacts.

Regarding error processing functions, the Ne was quantified in amplitude and latency at electrodes Fz and FCz using a pre-response baseline −200 until 0 (i.e. time point of response). The Nc (i.e. post-response negativity occurring on correct trials) was quantified similarly. Ne and Nc were defined as the most negative peak within 50–120 ms after response. Ne and Nc were only quantified in incompatible trials where arrowheads were presented as targets because this condition yielded the highest error rate. Regarding response inhibiton the N2 and the P3 were quantified for amplitude and latency in both Nogo- and Go-trials. The N2 was measured at electrodes Fz and FCz, the P3 at electrodes FCz and Pz. These electrodes were chosen, because of the scalp topography (N2) and because the P3 on Go-trials is usually largest at electrode Pz, whereas on Nogo-trials, the P3 is largest at frontal leads (i.e. FCz). The N2 was defined as the most negative peak occurring 200–300 ms after

target stimulus onset, the P3 as the most positive peak occurring 350–500 ms after stimulus onset. Amplitudes were measured against a pre-stimulus baseline of −200 to zero (i.e. time point of target stimulus presentation).

### 2.5. Statistical analyses

Behavioural and neurophysiological data were analyzed using (repeated measures) analyses of variance (ANOVAs). ERPs denoting error processing functions, were analyzed using the within-subject factors "electrode" and "correctness (error/correct)" and the between-subject factor "genotype group". ERPs denoting response inhibition were analyzed using "electrode" and "Go/Nogo" as within-subject factors and the between-subject factor "genotype group". All variables subjected to analyses of variance were normal distributed as indicated by Kolmogorov–Smirnow tests (all $z$'s < 1.01; $p > .2$). In all analyses, Greenhouse-Geisser corrections were applied when appropriate. Post hoc tests were Bonferroni-corrected, when necessary. For all analyses the means and standard error of mean (±SEM) are provided.

## 3. Results

### 3.1. Behavioural data

#### 3.1.1. Response inhibition

The mean rate of false alarms was 4.7 ± 0.4. The rate of false alarms was lower for the AA/AG genotype group (3.6 ± 0.3) that for the GG genotype group (5.7 ± 0.3) ($F(1,69) = 17.48$; $p < .001$). Reaction times in these false response trials were not different between the groups ($F(1,69) = 0.41$; $p > .6$).

#### 3.1.2. Error processing

Reaction times (RTs) were faster on error trials (330 ± 10) than on correct trials (404 ± 10) ($F(1,52) = 193.73$; $p < .001$), which is a typical findings in these kind of reaction time tasks. This effect was not different for the genotype groups (AA/AG vs. GG) ($F(1,69) = 0.41$; $p > .6$), the groups did also not differ in their average RT ($F(1,69) = 0.33$; $p > .6$). To calculate this post-error slowing (Rabbitt, 1966), the mean reaction time of correct responses in succession and those after an error ("sequence") were subjected to a repeated measures ANOVA. A robust slowing effect was obtained ($F(1,69) = 100.69$; $p < .001$) (mean difference: 22 ± 2 ms), that was different for the genotype groups ($F(1,69) = 9.73$; $p = .001$). Post hoc tests showed that the post-error slowing was larger for the GG genotype group (31 ± 3) than for the AA/AG genotype group (17 ± 4) ($F(1,52) = 9.73$; $p = .001$). Error rates were higher in the incompatible (7.9 ± 0.4), compared to the compatible condition (2.2 ± 0.3) ($F(1,69) = 249.32$; $p < .001$). While the compatibility effect was not different for the genotype groups ($F(1,69) = 0.48$; $p > .5$), error rates (across compatible and incompatible trials) were generally lower in the AA/AG genotype group (4.5 ± 0.3) than in the GG genotype group (6.3 ± 0.4) (main effect error rate: $F(1,69) = 10.11$; $p < .001$).

### 3.2. Neurophysiological data

#### 3.2.1. Response inhibition

Stimulus-locked ERPs on Go and Nogo Trials are given in Fig. 1.

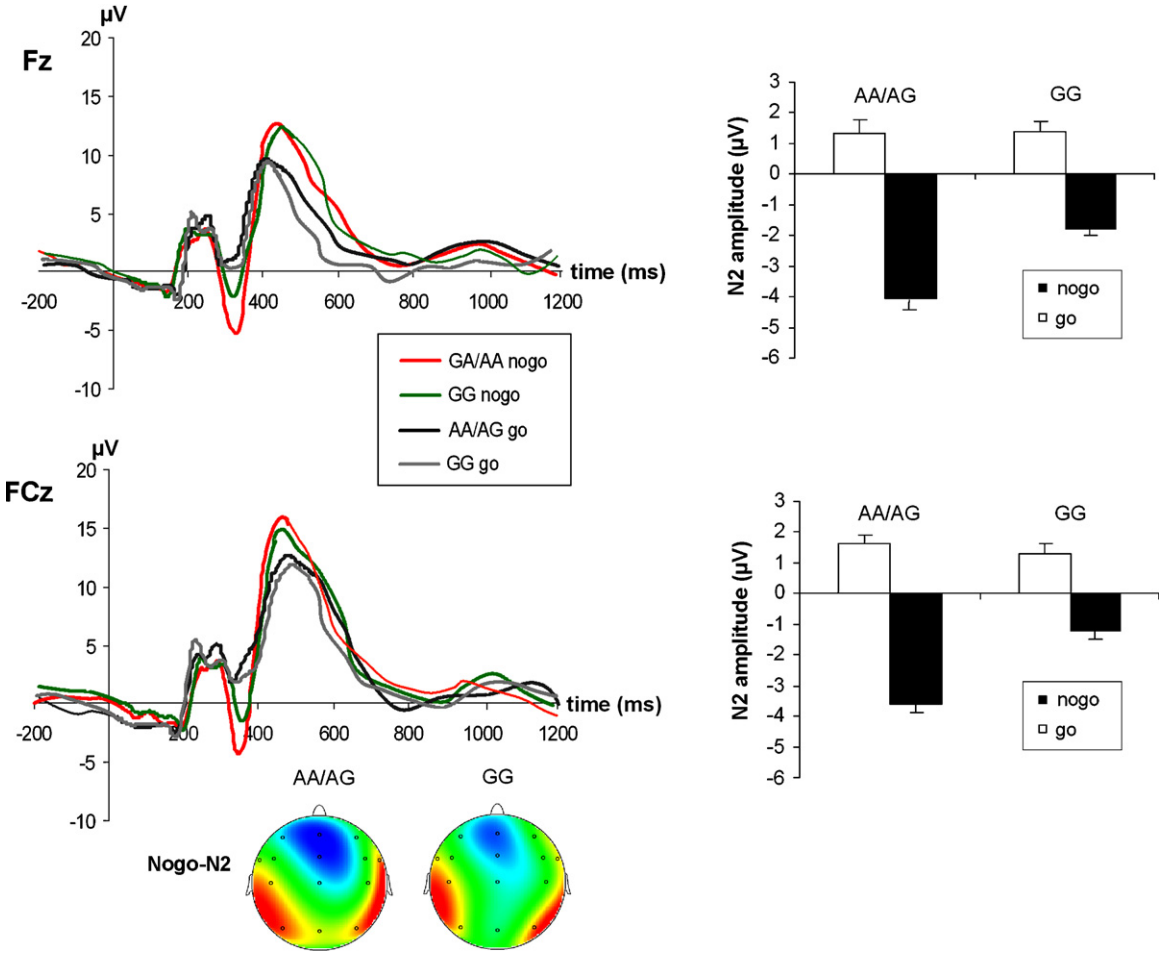


**Fig. 1.** Left panel: Stimulus-locked potentials (locked on the target) on Go and Nogo trials at electrode Fz and FCz enclosed with the maps are given. Time point 0 denotes the point of stimulus presentation. Right panel: The mean amplitudes on Go and Nogo trials are given, separated for the TNF-α -308G→A genotype groups and electrode sites. Error bars denote the standard error of the mean (SEM).

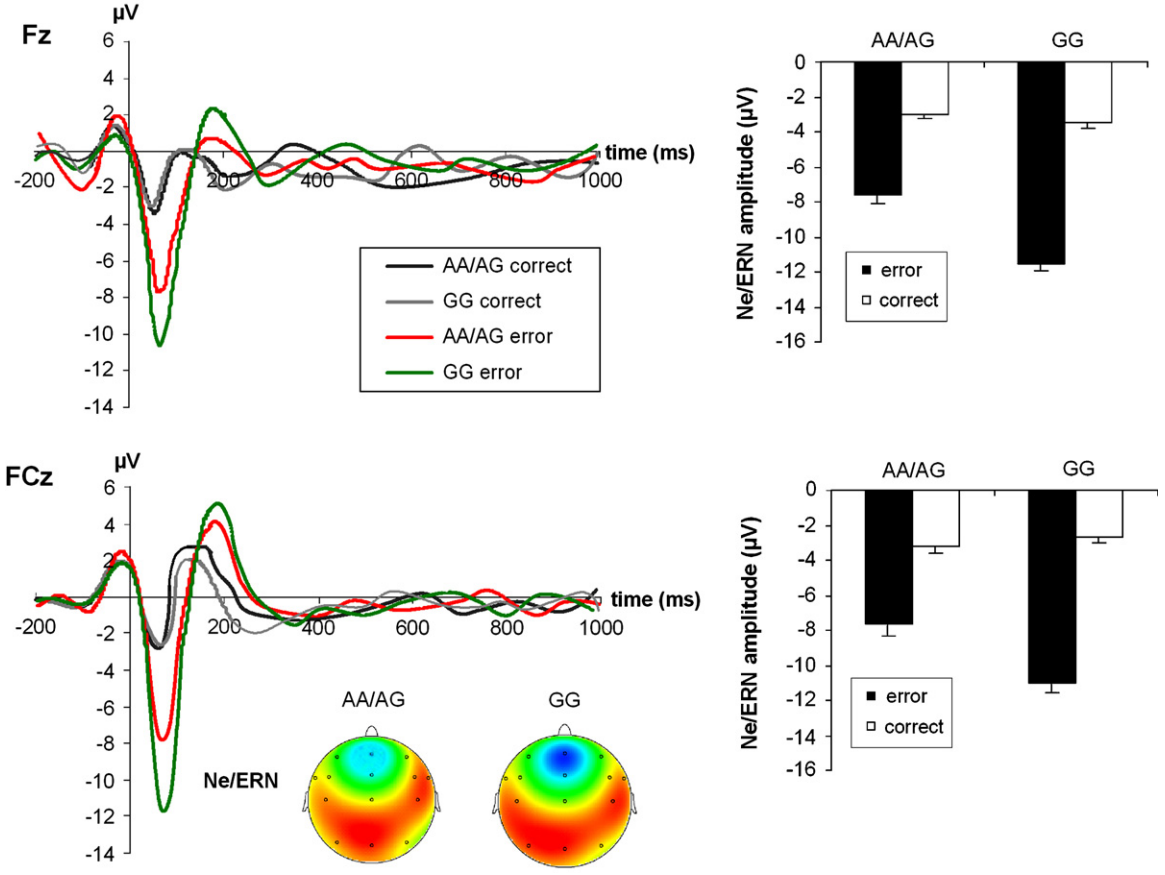


**Fig. 2.** Left panel: Response-locked potentials on correct and error trials at electrode Fz and FCz enclosed with the maps are given. Time point 0 denotes the time point of button press. Right panel: The mean amplitudes on correct and error trials are given, separated for the TNF-α -308G→A genotype groups and electrode sites. Error bars denote the standard error of the mean (SEM).

*N2-effects*: The repeated measures ANOVA showed that potentials were larger at Fz (−1.3 ± 0.2), compared to FCz (−0.2 ± 0.3) ($F(1,69) = 59.24$; $p < .001$). Potentials were more negative on Nogo (−2.9 ± 0.3) than on Go trials (1.4 ± 0.2) ($F(1,52) = 304.22$; $p < .001$) and stronger for the AA/AG (−1.3 ± 0.3), compared to the GG genotype group (−0.3 ± 0.2) ($F(1,69) = 18.50$; $p < .001$). However, both factors "Go/Nogo" and "group" interacted with each other ($F(1,69) = 10.66$; $p = .002$). Subsequent univariate ANOVAs showed that the genotype groups did not differ on Go trials ($F(1,69) = 0.1$; $p > .7$), but on Nogo trials ($F(1,69) = 25.83$; $p < .001$). Here, the AA/AG genotype group revealed a stronger Nogo-N2 (−3.8 ± 0.2) than the GG genotype group (−1.8 ± 0.3). All other main or interaction effects were not significant (all $F$'s < 0.8; $p > .5$). There were no latency effects (all $F$'s < 0.6; $p > .5$). As with the analysis or error related processes, the BDI and ASI scores were used as additional covariates in the above ANOVAs. Also here the pattern of results did not change (all $F$'s < 0.9; $p > .5$) when considered as covariates showing that also the N2 results are unbiased due to these factors

*P3-effects*: Here, the repeated measures ANOVA revealed a main effect "Go/Nogo" ($F(1,69) = 88.07$; $p < .001$) with the potentials being larger for Nogo (13.5 ± 0.3), than for Go trials (11.7 ± 0.2). There was also an interaction "Go/Nogo x electrode" ($F(1,69) = 102.56$; $p < .001$). This interaction is due to the expected reversed pattern of Go/Nogo effects at these electrodes. Potentials at electrode FCz were larger for the Nogo (15.9 ± 0.4), compared to the Go trials (9.4 ± 0.3) ($F(1,69) = 79.61$; $p < .001$), while at electrode Pz potentials were larger for Go (14.9 ± 0.3), than for Nogo-trials (10.6 ± 0.4) ($F(1,69) = 41.62$; $p < .001$). There were no main or interaction effects with "group" (all $F$'s < 0.9; $p > .4$)

There were not latency effects (all $F$'s < 0.8; $p > .4$). As with the Nogo-N2, using the BDI and ASI score as covariate did not change the pattern of results (all $F$'s < 1; $p > .3$), showing that the P3-data is unbiased due to these factors.

In conclusion, the AA/AG genotype group displayed a higher level of response inhibition performance than the GG genotype group, as reflected in the Nogo-N2 as well as in the false alarm rate.

### 3.2.2. Error processing

The response-related potentials on error (Ne) and corrects trials (Nc) are given in Fig. 2.

The repeated measures ANOVA showed that average amplitudes (across conditions) were larger at electrode Fz (−6.9 ± 0.2), compared to FCz (−5.7 ± 0.3) ($F(1,69) = 21.50$; $p < .001$). Potentials were generally much larger on error trials (Ne: −9.7 ± 0.4) than on correct trials (Nc: −2.9 ± 0.2) ($F(1,69) = 223.65$; $p < .001$). The main effect group was significant ($F(1,69) = 6.57$; $p < .013$) with the AA/AG group showing lower amplitudes (−5.6 ± 0.4) than the GG genotype group (−7.1 ± 0.5). However, this effect was modulated by response correctness as indicated by the interaction "correctness x group" ($F(1,52) = 14.14$; $p < .001$). Calculating univariate ANOVAs across groups using correct and error trials separately, the groups did not differ in their amplitude on correct trials (i.e. Nc) ($F(1,69) = .02$; $p > .9$), but in their amplitude on error trials (i.e. Ne) ($F(1,69) = 11.46$; $p < .001$). The Ne was larger for the GG (−11.3 ± 0.6), compared to the AA/AG genotype group

(−8.1 ± 0.4). All other main or interaction effects were not significant (all $F$'s < 1.6; $p$ > .2).

Concerning the latencies, only the main effect "correctness" was significant ($F(1,69) = 170.93$; $p < .001$) showing that the peak-latency was larger for error (76 ± 2), compared to correct trials (49 ± 3). Using the ASI and BDI score as additional covariates in the above ANOVAs did not change the pattern of results (all $F$'s < 1.0; $p$ > .4), showing that the results are unbiased due to these factors.

In conclusion, the AA/AG genotype group displayed a lower level of error monitoring, than the GG genotype group, as reflected in the Ne as well as in post-error slowing. This contrast with the enhanced response inhibition functions (see above).

### 3.3. Cross-validation procedure

All analyses were cross-validated in order to test the validity of the results by randomly dividing participants of each genotype group into two subgroups (two halves). The two subgroups built by randomly dividing participants constituted the cross-validation factor. This factor was used as additional between-subject factor in the ANOVAs (see: Beste, Baune, Domschke, Falkenstein, & Konrad, 2010d). Performing these ANOVAs using this cross-validation factor, no significant main effect or interaction with this validation factor was found (all $F$'s < 1.1; $p$ > .4), suggesting that the pattern of results remained the same, even when genotype groups are splitted (i.e. the cross-validation factor is introduced), underlining the validity of results.

## 4. Discussion

The results of the present study suggest a double dissociation between cognitive functions related to error monitoring and response inhibition and the AA/AG and the GG genotypes of the TNF-α -308G→A polymorphism. Carriers of at least one of the more active -308A alleles showed higher performance levels of response inhibition (i.e. lower rate of false alarms), but reduced error processing functions (i.e. less post-error slowing), while the reverse pattern applied to the GG genotype group. These behavioural manifestations were paralleled by a corresponding pattern of dissociated effects in the Nogo-N2 and the Ne/ERN. The results obtained are unbiased with respect to mood and affective status of the participants. Since error monitoring and response inhibition are cognitive tasks probably mediated via distinct basal-ganglia prefrontal interactions due to their neocortical target areas in the orbitofrontal cortex (OFC) (e.g. Schoenbaum, Roesch, et al., 2009) and anterior cingulate cortex (ACC) (e.g. Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004), the TNF-α -308G→A polymorphism seems to affect functioning in these loops in a different manner. The results obtained in this study have been validated by means of cross-validation procedure.

Our response inhibition results are in line with the pre-motor inhibition hypothesis of the Nogo-N2 (Falkenstein et al., 1999). This theory states that the Nogo-N2 reflects processes related to the inhibition of a motor program, which are exerted before action onset. The stronger Nogo-N2 in the AA/AG genotype group suggests an enhanced pre-motor inhibition compared to the GG genotype group. Consequently, the AA/AG group also evinced low false alarm rates, indicating an effective response inhibition process. The fact that no systematic effects for the Nogo-P3 were observed shows that Nogo-N2 and Nogo-P3 are subprocesses of response inhibition that are dissociable at the neurobiological level (see also: Beste et al., 2010b; Beste et al., 2010a; Beste et al., 2008a). In line with the results by Beste, Baune, Domschke, Falkenstein, and Konrad (2010c) pre-motor inhibition processes were increased in their efficacy under a condition of likely compromised basal ganglia-prefrontal circuits (i.e. AA/AG genotype of the TNF-α -308G→A polymorphism) (e.g. Sriram et al., 2006). According to Beste et al. (2010a, 2010b), it is conceivable that these mechanisms shift the balance of parallel inhibitory and excitatory loops (e.g. Gale et al., 2008; DeLong & Wichmann, 2007) towards a dominance of inhibition, resulting in an advantage during trials where a predominant response has to be stopped.

Interestingly, the effectiveness of error monitoring processes was decreased in parallel, as indicated by a lower Ne/ERN and a reduced post-error slowing in carriers of at least one of the more active A alleles. This is also likely due to neurotoxic effects of TNF-α on basal ganglia circuits (e.g. McCoy & Tansey, 2008; Sriram et al., 2006). Subsequent to a response error, the mesocortico-limbic system phasically decreases its activity (Schultz, 2007). By means of this error signal, the anterior cingulate cortex (ACC), which has consistently been shown to be involved in error processing (e.g. Beste et al., 2008b; for rev. Ridderinkhof et al., 2004) and behavioural monitoring processes (e.g. Beste et al., 2007; Bush, Luu, & Posner, 2000; Saft et al., 2008; Wild-Wall, Willemssen, Falkenstein, & Beste, 2008) is trained to recognize the appropriate response (Holroyd & Coles, 2002) with the Ne/ERN being the outcome of this process. The mesencephalic dopaminergic cell groups are the origin of the mesocortico-limbic system. Our observation of a reduced Ne/ERN suggests that the mesocortico-limbic system may be more compromised in the AA/AG genotype. This decrease of the Ne/ERN may in turn lead to an attenuation of subsequent behavioural adjustments (i.e. post-error slowing). In support of this interpretation, such detrimental effects are frequently found in conditions with dysfunctions in basal ganglia-prefrontal interactions (overview: Beste et al., 2009a). The above discussion is centered around the modulating effects of TNF-α on the dopaminergic system. However, TNF-α is known to modulate glutamatergic neural transmission as well (e.g. Balosso et al., 2009; Beattie et al., 2002; Pickering, Cumiskey, & O'Connor, 2005; Wei, Guo, Zou, Ren, & Dubner, 2008) giving raise to the possibility that this neurotransmitter system may have mediated the observed effects. Yet, recent results by our group suggest that NMDA-receptor related neural transmission may affect response inhibition, but not error processing (Beste et al., 2010d), making a "glutamatergic explanation" of the divergent results less likely. A limitation of the current study is that only a single SNP from the *TNF-α* gene was investigated. However, the selected SNP had previously shown to be functionally relevant. Furthermore, the relatively limited sample size may be regarded as a weakness of the study. Yet, the cross-validation analysis suggests validity of the results. Future studies may incorporate other SNPs of the *TNF-α* gene or other functionally relevant cytokines for the dopaminergic system in order to evaluate further the potential interaction between the dopaminergic system and inflammatory cytokines such as TNF-α that may underlie the modulation of response inhibition and error processing.

In summary, we examined associations between the TNF-α -308G→A SNP (rs1800629) and response inhibition and error processing. The results extent the relevance of the TNF-α -308G→A SNP (rs1800629) as a modulator of cognitive functions. Carriers of the A allele demonstrated better response inhibition, but worse error monitoring processes as compared to G allele carriers. The pattern of results suggests that even though TNF-α compromises basal ganglia dopaminergic neural transmission, the functional effect of this modulation on cognitive processes seems to be dissociated.

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