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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