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ASSOCIATIONS BETWEEN THE TUMOR NECROSIS FACTOR ALPHA GENE (-308G→A) AND EVENT-RELATED POTENTIAL INDICES OF ATTENTION AND MENTAL ROTATION

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Abstract—The tumor necrosis factor alpha (TNF-α) is a cytokine that exerts neuroprotective and neurodegenerative effects. While some research suggests enhancing effects of the *TNF-α* gene (TNF-α -308G→A) on cognitive function, further research is needed to clarify the association between the *TNF-α* gene and specific areas of cognitive performance including their neurophysiological correlates. In this study we examine association of the *TNF-α* -308G→A single nucleotide polymorphism (rs1800629) with attention and mental rotation performance in an event-related potential (ERP) study in healthy participants (*n*=67). The results show that carriers of the -308 A allele display elevated attentional processes (i.e. a stronger N1) as compared to the GG genotype group. Mental rotation performance varied across genotypes when demands on mental rotation were high. Here, carriers of the -308 A allele performed better than the GG genotype group. This is paralleled by the neurophysiological data showing genotype-dependent variations in parietal positivities only under the condition of high demands on mental rotation. The finding of enhanced attentional and mental rotation performance in A allele carriers supports recent findings that the A allele of this single nucleotide polymorphism (SNP) enhances cognitive performance on a general measure of cognitive processing speed.

Key words: attention, mental rotation, event-related potentials (ERPs), tumor necrosis factor alpha (TNF-α), cytokines, imaging genetics.

The tumor necrosis factor alpha (TNF-α) is a cytokine that has been shown to exert neuroprotective and neurodegenerative effects (McAfoose and Baune, 2009; Sriram and O'Callaghan, 2007). TNF is known to play an important role in glutamatergic neural transmission (Pickering et al., 2005) and has therefore been postulated to serve essential functions in neural plasticity (e.g. Kaneko et al., 2008) and cognitive processes like learning and memory (McAfoose and Baune, 2009; Baune et al., 2008a).

Examining associations of the TNF-α -308G→A single nucleotide polymorphism (SNP) (rs1800629) (Hajeer and Hutchison, 2001; Wilson et al., 1997) with cognitive performance, a recent study by Baune et al. (2008b) showed that the A allele fastens cognitive processing speed in a visual task, compared to G allele carriers. A potential explanation for this finding is that the *TNF-α* -308G→A SNP denotes a G(TNFα1)→A(TNFα2) single nucleotide exchange may lead to a stronger transcriptional activity of the -308 A allele than the -308 G allele (Wilson et al., 1997), thereby enhancing cognitive performance; however, the results on the transcriptional effects are not entirely conclusive (Baune et al., 2008b).

Another approach to enhance the understanding of possible neuromodulatory effects of genetic variants of TNF-α is the investigation of its relationship with the neurophysiological correlates underlying specific cognitive tasks such as attention and mental rotation, both mediated by occipito-parietal networks. The visual domain was chosen, because the previous work by Baune et al. (2008b) reports data from the visual domain. Furthermore, other evidence suggests that the effects of TNF-α are special for occipital regions in that TNF-α seems to exert neuroprotective effects in these regions (Kaneko et al., 2008), as opposed to usually observed neurodegenerative effects (Sriram and O'Callaghan, 2007).

Mental rotation describes the cognitive process of imagining an object turning around (Shepard and Metzler, 1971). Mental rotation is usually examined using objects (e.g. letters) that are rotated by certain degrees clockwise or counter-clockwise from the vertical upright. This angular displacement allows a parametrical modulation of task difficulty and the demand of processing in working memory. Working memory processes are closely interrelated to attentional processes (e.g. Knudsen, 2007; Awh and Jonides, 2001), as attention permits information to be further stored and processed in working memory. Attentional processes are reflected by the visual N1 event-related potential (ERP)-component (Luck, 1995). The visual N1 may reflect effects of attention on sensory processing (Eimer, 1994; Hillyard et al., 1998), or an integrated process of perception and attention (Wascher and Beste, in press).

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Abbreviations: ERP, event-related potential; RTs, response times; SNP, single nucleotide polymorphism; TNF-α, tumor necrosis factor alpha.

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The visual N1 is an exogenous potential that is modulated by attentional processes modifying the magnitude of neural responses to incoming information (e.g. Hillyard et al., 1999). The N1 is generated in extrastriate occipito–parietal and ventral occipital temporal cortical areas (Masaki et al., 2000; Gomez-Gonzalez et al., 1994), which is of special relevance with respect to modulatory influences of TNF-α on visual processes.

Once an object representation has been set up in parietal networks (e.g. Gottlieb, 2007) mental rotation processes can operate on this representation (Beste et al., 2010b). In ERPs, this process (i.e. mental rotation) is reflected at parietal electrodes 300 until 700 ms after stimulus presentation (e.g. Beste et al., 2010a; Heil and Rolke, 2002; Johnson et al., 2002). The amplitude at this time epoch reflects the amount of mental rotation performed (Heil, 2002). The late positivity becomes relatively more negative with increasing angular displacements from the upright (Wijers et al., 1989) and this (relative) negativity is understood as a direct correlate of the mental rotation process itself (Heil, 2002).

In our study, we investigate the association of *TNF*-α -308G→A with neurophysiological correlates underlying specific cognitive processes namely attention and mental rotation, mediated by occipito–parietal networks. Assuming that the *TNF*-α -308 A allele enhances cognitive functions as compared to G allele carriers (Baune et al., 2008b), we hypothesize that the A allele shows stronger visual N1 anplitudes, compared to the G allele. These elevated attentional processes may in turn lead to similar increases in mental rotation performance (i.e. reduced response times and error rates). Furthermore, we hypothesize that the assumed increased behavioural performance in the TNF-α -308 AA and AG genotype groups is paralleled by a more negative parietal neurophysiological component between 300 and 700 ms after stimulus presentation in A allele carriers as compared to the GG genotype group.

EXPERIMENTAL PROCEDURES

Participants

A sample of 67 genetically unrelated healthy participants of Caucasian descent were recruited by newspaper announcements. The mean age of the participants was 25.5 years (±4.9). The age did not differ between genotype groups. The sample consisted of 27 males and 40 females. As the AA genotype had an expectedly low frequency (see below), we combined the AA and the AG genotype groups to one group for further analyses. Sexes did not differ across genotype groups (H-Test: chi^2=.389; df=1; P>.5). Similar the IQ of the participants was not different between the genotype groups (F(1,65)=0.5; P>.6). The descriptive data is given in Table 1.

Participants had no history of neurological or psychiatric diseases, as assessed by means of psychiatric screening. 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). The distribution of *TNF*-α -308G→A genotypes did not significantly differ from the Hardy–Weinberg equilibrium (AA=2, AG=30, GG=35; P=.202). The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the University of Münster. All procedures were carried out with the adequate understanding and written consent of the participants.

Table 1. Demographic data of the subjects. The mean and standard deviation are given

	AA/AG	GG
N	32	35
Age	24.9 (4.4)	26.1 (5.59)
Sex	11 females:21 males	16 females:19 males
IQ	113 (12.5)	108 (11)

Genotyping

Genotyping of *TNF*-α -308G→A (rs1800629) SNP located on chromosome 6p21.3 (position 31651010 5′ to the gene (possibly promoter/enhancer region)) was carried out on the basis of blood samples 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.

Task

In each trial, one of the letters F, P, R, and L was presented in their normal or mirror-image version at either 30°, 90°, or 150° clockwise or counter-clockwise from the vertical upright on a computer screen. The letters had a height of 3.2 cm, subtending 2.28° of visual angle. Each trial began with the presentation of a fixation point in the center of the computer monitor. One second later, a letter was presented in the center of the screen and remained visible until a button press response. Depending on whether the letter was normal or mirror-reversed, participants pressed a response panel with their left or right hand. To indicate, whether the response was correct or not, the letter was replaced by a "+" or "−" for 500 ms. Participants were instructed to respond as fast as possible, but accuracy was stressed in the instruction. The inter-trial-interval (ITI) varied randomly between 1 and 3 s. Overall, 384 experimental trials were commenced and divided into eight blocks of 48 trials each. The 384 resulted from the combination of orientation, version and letter, because each combination occurred eight times. Before recording, participants were familiarized with the task.

EEG recording and analysis

The EEG was recorded from 32 EEG electrodes (Ag/AgCl) (Fpz, Fp1, Fp2, Fz, F3, F4, F7, F8, FCz, FC3, FC4, FC5, FC6, Cz, C3, C4, C7, C8, Pz, P3, P4, P7, P8, Oz, O1, O2, M1, M2), two lateral and four vertical EOG electrodes with a sampling rate of 500 Hz. Cz was used as primary reference. The filter bandwidth was set from DC to 80 Hz. Impedances were kept below 5 kΩ. The EEG was digitally filtered using a 0.10 Hz high-pass and 20 Hz low-pass filter. From the EEG recordings, stimulus-locked ERPs were computed based on correct responses only. The epochs began 200 ms before and ended 700 ms after stimulus presentation. Eye movement artifacts were corrected with the Gratton-Coles-Algorithm using the EOG data (Gratton et al., 1983) within these epochs as implemented in the BrainVision Analyzer. Following this, a baseline correction (−200–0 ms) was conducted and artifacts were rejected using an amplitude criterion of ±80 μV. Finally, data were re-referenced to linked mastoids. We calculated ERPs by averaging single trials with correct responses separately for participants, electrodes and experimental conditions.

The N1 was quantified at electrodes P7 and P8, since these electrodes revealed the maximum of this potential, as denoted by the maps. The N1 was defined as the most negative peak after

stimulus onset occurring between 100 and 220 ms. To analyze ERPs reflecting the process of mental rotation, the average amplitude of the epoch 300–700 ms after letter presentation (Jansen-Osmann and Heil, 2007; Heil and Rolke, 2002) was quantified. In accordance with the literature, ERPs were quantified at electrodes P3, Pz and P4. For the mental rotation data a linear detrending procedure was applied for each single epoch before any baseline correction procedure was conducted. This was done to normalize the data. Analyses based on un-detrended original data produced qualitatively identical results. Both, the N1 and the parietal positivity reflecting mental rotation were analyzed against a pre-stimulus baseline from −200 ms till stimulus presentation.

Statistical analysis

Behavioural and neurophysiological data were analyzed using analyses of variance (ANOVAs). Before conducting the ANOVA, each variable was tested for deviation from normal distribution using Kolmogorov-Smirnov Tests. These tests revealed that each variable was normally distributed (all z's<0.8; $P>.3$). For statistical analyses, amplitudes were subjected to a repeated measure ANOVA with the within-subject factors "electrode" and "angular displacement" and the between-subject factor "genotype group". Since "parity" (normal vs. mirror-reversed) had no effect on ERPs (see also: Heil, 2002), data are presented averaged across this factor. For the behavioural data, error rates and response times (RTs) were analyzed using a repeated measures ANOVA using the identical within and between-subject factors. If necessary, Greenhouse-Geisser corrections were applied and each post-hoc test was Bonferroni-corrected. To control for possible effects of age and intelligence, we performed additional ANCOVAs using scores of these factors as covariates to control for these effects. To control for the effects of sex, we included this factor as an additional between-subject factor to the analysis.

RESULTS

Behavioural data

The means and standard errors are given for descriptive statistics. Response times (RTs) differed as a function of angular displacement ($F(2,130)=111.89$; $P<.001$; $\eta^2=.63$). Response times were shortest for 30 degrees angular displacement (610±13) and increased for 90 (674±15) and 150 degrees displacement (777±14) ($P<.001$). However, this effect was different for the genotype groups, as indicated by the interaction term "angular displacement x genotype" ($F(2,130)=10.69$; $P<.001$; $\eta^2=.14$) (refer Fig. 1A).

Post-hoc tests revealed that the genotype groups did not differ in their response times in the condition of 30 and 90 degrees angular displacement (F's<0.06; $P>.7$), but in the condition of 150 degrees angular displacement ($F(1,65)=8.99$; $P=004$; $\eta^2=.12$). In this condition, the AA/AG genotype group revealed faster RTs (735±20) than the GG genotype group (819±19). There was no main effect "genotype group" ($F(1,65)=0.9$; $P>.3$; $\eta^2=.01$).

The pattern observed for error rates was similar to that of the RTs. Error rates were lowest for 30 degrees angular displacement (4.3±0.5) and increased for 90 (5.3±0.5) and 150 degrees displacement (14.5±0.8) ($F(2,130)=163.23$; $P<.001$; $\eta^2=.71$); each condition differed from each other ($P<.021$). There was a main effect "genotype group" ($F(1,65)=5.20$; $P=.026$; $\eta^2=.07$), indicating that error rates were generally lower in the AA/AG genotype group (6.8±0.7), compared to the GG genotype group (9.2±0.7). Yet, the interaction "angular displacement x genotype" indicates that this effect was differently strong for varying degrees of angular displacement ($F(2,130)=34.73$; $P<.001$; $\eta^2=.34$). Similar to RTs genotype groups did not differ in their response times in the condition of 30 and 90 degrees angular displacement (F's<0.4; $P>.5$), but in the condition of 150 degrees angular displacement ($F(1,65)=27.86$; $P<001$; $\eta^2=.30$) (refer Fig. 1B). The AA/AG genotype group revealed better performance (i.e. a lower error rate) (10.3±1.5) than the GG genotype group (18.7±1.1). Since this effect paralled the one with RTs, a speed-accuracy trade-off can safely be excluded. Using sex as additional between-subject factor did not change the pattern of results (all F' s related to "sex" <0.3; $P>.6$). Similar, analyses of covariance (ANCOVAs) using "age" and "IQ" as covariates did not change the pattern of results (all F's<0.5; $P>.4$).

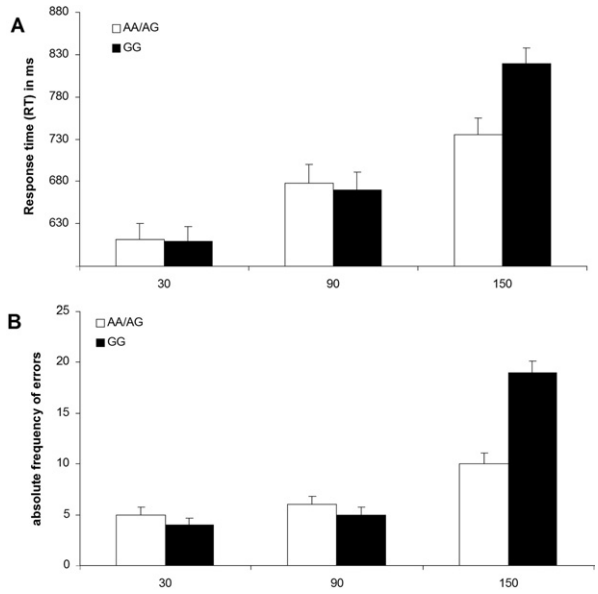

Fig. 1. (A) Response times (RTs) in ms for the *TNF-α* -308 AA/AG and GG genotype groups separated for the different degrees of angular displacement (30°, 90° and 150°). (B) The absolute frequency of error responses for the AA/AG and GG genotype groups separated for the different degrees of angular displacement (30°, 90° and 150°).

Neurophysiological data

Attention. The N1 is given in Fig. 2.

The ANOVA revealed that the N1 was stronger at electrode P7 (−10.5±0.2), compared to P8 (−9.1±0.2) ($F(1,65)=85.70$; $P<.001$; $\eta^2=.569$). Moreover, the main effect "angular displacement" ($F(2,130)=38.16$; $P<.001$; $\eta^2=.370$) showed that the N1 amplitude increased with increasing degrees of angular displacement (30°: −8.7±0.2; 90°: −10.1±0.2; 150°: −10.7±0.2). The main effect "genotype group" ($F(1,65)=56.62$; $P<.001$; $\eta^2=.466$) indicated that the AA/AG genotype group revealed a stronger N1 (−11.1±0.2) than the GG genotype group (−8.5±0.2). All other interaction effects were not significant (all F's<1.5; $P>.2$). Similar to the behavioural data, neither

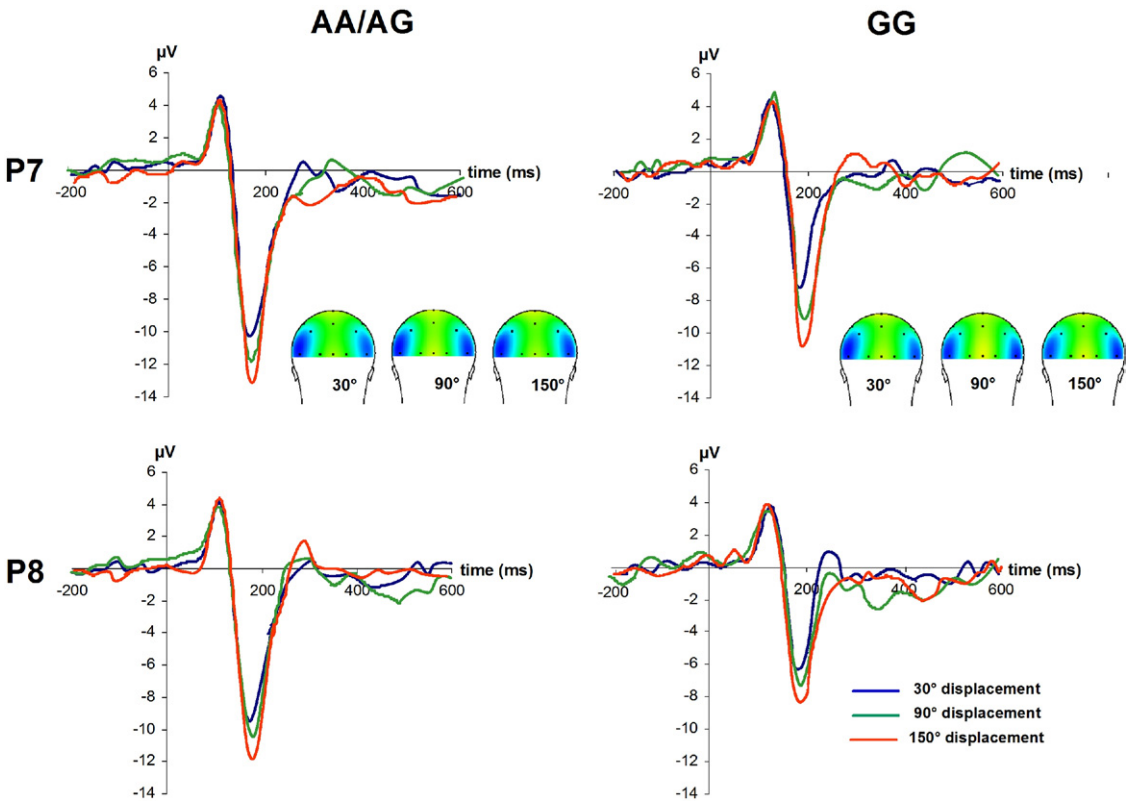

Fig. 2. Stimulus-locked event-related potentials denoting the N1-component at electrodes P7 and P8 for the different rotation angles. The top row denotes potentials for electrode P7, the bottom row for electrode P8. The left column denotes the potentials for the AA/AG genotype group, the right row for the GG genotype group. As can clearly be seen in the Figure the N1 potentials were clearly decreased in the GG, as compared to the AA/AG genotype group. Time point 0 denotes the time point of stimulus presentation. The maps given for each genotype group and degree of angular displacement separately, denote a clear N1-topography. Positivity is plotted upwards. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

"sex" nor "age" and "IQ" affected the pattern of results (all F's$<$0.6; $P>$.4).

Mental rotation. Event-related potentials during mental rotation are given in Fig. 3.

The repeated measures ANOVA across the de-trended data showed a main effect "electrode" (F(2,130)=31.22; $P<$.001; η^2=.359) in that amplitudes were highest at electrode Pz (6.9±0.4), compared to P3 (5.1±0.2) and P4 (5±0.4) ($P<$.001). The main effect "angular displacement" was also significant (F(2,130)=40.44; $P<$.001; η^2=.411). As expected, amplitudes were most positive in the condition with 30 degree rotation angle (6.5±0.3) and decreased with 90 (6.1±0.4) and decreased further with 150 degrees (4.4±0.2) angular displacement ($P<$.010). The effect of angular displacement was different for the genotype groups as indicated by the interaction term "angular displacement x genotype group" (F(2,130)=13.44; $P<$.001; η^2=.191). Subsequent univariate ANOVAs for each degree of angular displacement revealed that the genotypes did not differ in the condition with 30 and 90 degrees angular displacement (all F's$<$1; $P>$.3), but in the condition with 150 degrees angular displacement (F(1,65)=6.33; P=.003; η^2=.122). Under this condition, the combined AA/AG genotype group showed a smaller positivity or a larger (relative) negativity (4.1±0.4) than the GG genotype group (5.1±0.4). All other interaction effects were not significant (all $F's<$0.8; $P>$.4). Also here, "sex", "age" and "IQ" did not affect the pattern of results (all F's$<$0.4; $P>$.5). In previous study of our group saccadic activity during mental rotation processes was different and the main dissociating factor between the genotype groups (Beste et al., 2010b). A similar analysis of the EOG-data in the current study did not reveal any genotype differences (all F's$<$0.5; $P>$.5). Additionally it was tested, whether parity of stimuli (normal or mirror-image version of the stimuli) affected the results obtained. Analyzing this we obtained no effects of parity (all F's$<$0.4; $P>$.4).

DISCUSSION

In the current study, we analyzed possible associations of the *TNF-α* -308G→A SNP (rs1800629) (Hajeer and Hutchison, 2001; Wilson et al., 1997) with attention and mental rotation performance and its neurophysiological correlates in healthy human participants. The results show that visual attentional processing and mental rotation performance were associated with this SNP. Our data showed that the combined AA/AG genotype group was related to a better mental rotation performance, especially at the highest degree of angular displacement (i.e. 150 degrees). Under this condition, the AA/AG genotype group per-

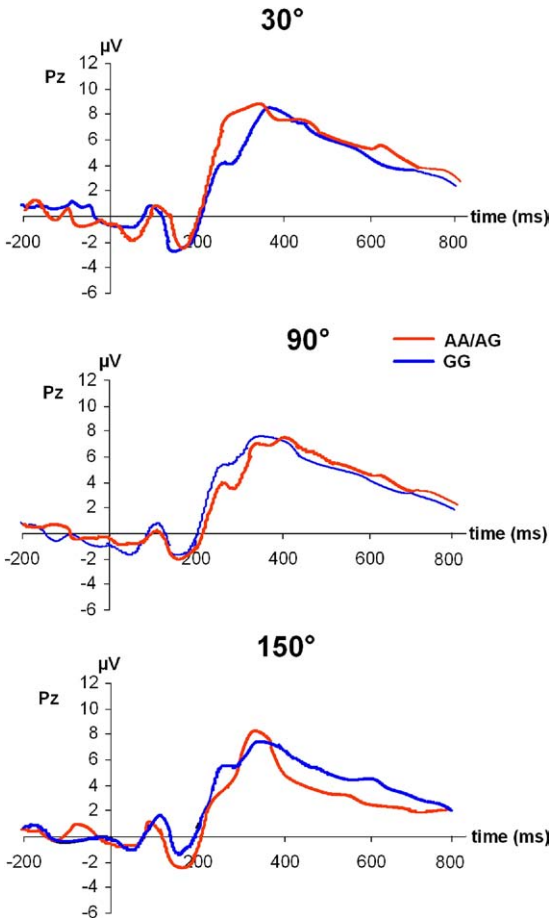

Fig. 3. Stimulus-locked event-related potentials (ERPs) at electrode Pz denoting the process of mental rotation within the time period starting at 350 ms. The plots are separated for each degree of angular displacement (i.e. 30°, 90° and 150° degrees). The different ERP traces in each plot denote *TNF-α* -308 AA/AG and GG genotype groups, respectively. Time point 0 denotes the time point of stimulus presentation. Positivity is plotted upwards. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

formed fewer response errors and also the RTs were faster, compared to the GG genotype group. This behavioural pattern is paralleled by the neurophysiological data, showing differences between the genotype groups only in the condition with 150 degree angular displacement. Here, the parietal amplitude modulation reflecting the processes of mental rotation (Heil, 2002; Wijers et al., 1989) was more negative in the AA/AG genotype group than in the GG genotype group.

Against the background of the behavioural data, this suggests that the more negative potential in the AA/AG genotype group is related to more efficient mental rotation processes that lead to elevated performance. The N1 was increased in the AA/AG genotype group, compared to the GG genotype group. The N1 reflects attentional processes (Luck, 1995), or an integrated process of perception and attention (Wascher and Beste, in press). Numerous lines of evidence suggest that TNF-α signalling facilitates glutamatergic neural transmission and increases synaptic strength (e.g. Balosso et al., 2009; Wei et al., 2008; Pickering et al., 2005; Beattie et al., 2002). Especially in visual cortical areas, TNF-α seems to have beneficial effects on neural processes. Kaneko et al. (2008) showed that reductions in TNF-α levels impair processes of neural plasticity that are known to rely on glutamatergic processes. The glutamatergic system is of special importance for attentional processes (Sarter et al., 2003; Turchi and Sarter, 2001). To explain the observed behavioural and ERP-results, it may be hypothesized that increased attentional functions in the AA/AG genotype group relative to the GG genotype group were related to glutamatergic processes modulated by TNF-α levels. As a possible explanation of the reported findings we suggest that enhanced cognition in the AA/AG genotype group occurred due to stimulating effects of TNF-α on the glutamatergic system. Even though TNF-α affects multiple neurotransmitter systems, the glutamatergic system is most likely involved since this neurotransmitter system is highly relevant for attentional processes that may drive performance in mental rotation. However, TNF-α is also well-known to interact with the cholinergic system and especially nicotinic receptors (e.g. Kondo et al., 2010). Nicotinic receptors are supposed to play an important role in the regulation of attentional processes (e.g. Sarter et al., 2006). As far as there is close interaction between TNF-α and nicotinergic receptors, the results observed may also get partly manifest by mechanisms related to the acethylcholinergic system.

As a potential consequence, it could be assumed that the observed increased attentional processes may elevate performance in mental rotation as suggested by the lower rates of errors in the AA/AG genotype groups, compared to the GG genotype group: It is well-known that object representations enter parietal cortical areas and working memory buffers, where these object representations are further processed via attentional processes (e.g. Knudsen, 2007). Based upon this, it may be hypothesized that object representations in parietal areas may be better accessible to processes of mental rotation in the AA/AG genotype group, which lead to a better performance in mental rotation. Yet, as suggested by our data, differences across genotype groups in mental rotation performance and neurophysiological processes reflecting mental rotation were strongest under the most difficult experimental condition (i.e. 150 degrees angular displacement). Following the above suggestion, it is possible that the generally reduced N1 in the GG genotype group leads to less stable neuronal representations of an object in the parietal cortex (Beste et al., 2010b; Knudsen, 2007). However, probably less stable representations in the parietal cortex in the GG genotype group may be sufficient for mental rotation processes of mild to moderate demands (i.e. 30 or 90 degrees angular displacement). Yet, if demands on mental rotation processes increase (i.e. 150 degrees angular displacement), representations provided to parietal networks by attentional processes are no longer sufficient in the GG genotype group. It may be hypothesized that in the AA/AG genotype group the increased attentional processes may provide parietal networks with more stable representations

that allow mental rotation processes operating well even in situations with increased processing demands (i.e. 150 degrees angular displacement). Alternatively, a more direct effect of TNF-α also on parietal areas and mental rotation processes in addition to modulations of attentional processes could represent another mode of action. However, the hypothesis of a rather direct relationship between an enlarged N1 indicating more stable representations and an increased mental rotation-related negativity was not supported since these two electrophysiological measures were not correlated when tested separately for each angular disparity and genotype group. Moreover these ERP indices were also not correlated with performance measures (all $r<.20$, $P>.6$). The relationships between genotype, electrophysiological and behavioural data obviously is much too complex to be identified by simple correlations. Unfortunately, we simply know too little to theoretically guide the formulation of more appropriate multiple regression models.

Future genetic association studies on this topic in healthy and clinical cohorts should incorporate serum levels, such as TNF-α, and may also examine other cytokines in order to gain a more complete understanding of the influence of neuroinflammatory factors on mental rotation and attentional processes and to be more precise about the direction of mechanisms (cause-effect relationship) that may underlie enhanced performance. In the current study none of the above suggested explanations can be safely ruled out and the mechanisms suggested to explain the findings remain largely theoretical.

CONCLUSION

In summary, we examined association between the *TNF-α* -308G→A SNP (rs1800629) and mental rotation performance and attentional processes including their neurophysiological correlates. Carriers of the A allele demonstrated better attentional processes as compared to G allele carriers and also subsequent mental rotation processes were also elevated, specifically when demands on mental rotation processes were increased. The current results support that the *TNF-α* -308 A allele is related to better cognitive performance as previously suggested in the context of other domains of cognitive performance in elderly people (Baune et al., 2008b) and extent the relevance of the *TNF-α* -308G→A SNP (rs1800629) as a modulator for cognitive functions.

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