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The relevance of the functional 5-HT1A receptor polymorphism for attention and working memory processes during mental rotation of characters

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ABSTRACT

Numerous lines of research indicate that attentional processes, working memory and saccadic processes are highly interrelated. In the current study, we examine the relation between these processes with respect to their cognitive-neurophysiological and neurobiological background by means of event-related potentials (ERPs) in a sample of $N = 72$ healthy probands characterized for the functional serotonin receptor 1 A (5-HT1A) C(−1019)G polymorphism.

The results support a close interrelation between working memory, attentional and saccadic processes. Yet, these processes are differentially modulated by the 5-HT1A C(−1019)G polymorphism. The 5-HT1A C(−1019)G polymorphism primarily affects attentional processing, whereas processes related to the mental rotation of an object are independent of 5-HT1A genetic variation. It is shown that an increasing number of −1019 G alleles leads to a differential reduction of the N1 above the left and right hemisphere and hence bottom-up attentional processing. In the way increasing numbers of −1019 G alleles lead to a reduction of attentional processes, saccadic activity increases as a similar function of the number of −1019 G alleles. This increase in activity occurs parallel in time to the process of mental rotation. It is hypothesized that decreased attentional processes, dependent on different 5-HT1A C(−1019)G genotypes, may cause parietal networks to increase saccadic activity in order to perform mental rotation.

1. Introduction

There is increasing evidence that attentional processes, working memory processes and eye-movement processes are closely interrelated (for review Theeuwes et al., 2009). Attention and eye-movement processes may subserve working memory processes, but may also be actively modulated by working memory processes (Knudsen, 2007). A number of studies have shown that saccades influence spatial working memory functions (e.g. Belopolsky & Theeuwes, 2009; Hutton, 2008; Johnson et al., 2002; for review Knudsen, 2007). This relation seems even more plausible considering that the initiation of voluntary eye-movements, similar to spatial working memory functions, partly rely on the parietal cortex (Goldberg, Bisley, Powell, & Gottlieb, 2006; Leigh & Zee, 1999). However, not only working memory and eye-movements may be interrelated, but also attentional processes are closely linked to working memory and saccadic processes (Theeuwes et al., 2009). Attentional shifts can precede eye-movements (Schmidt, Vogel, Woodman, & Luck, 2002) and areas known to be important for attentional processes, like the occipital cortex (e.g. Luck, 1995; Masaki, Takasawa, & Yamazaki, 2000), are known to influence brain areas important for voluntary eye-movements. Attention may be a vehicle by which information is stored in working memory (e.g. Knudsen, 2007; Schmidt et al., 2002). This is supported by various studies showing that working memory performance crucially depends on attentional functions (for review Awh & Jonides, 2001; Awh, Vogel, & Oh, 2006; Theeuwes et al., 2009).

Despite the amount of evidence suggesting a close interaction between these three processes (attention, working memory, eye-movements), the neurobiological processes underlying this relation are so far poorly understood. In the current study, we assess these three processes by means of a mental rotation paradigm while recording event-related potentials (ERPs) as their neurobiological substrate. The serotonergic 1 A receptor system is examined using the functional serotonin 1 A receptor polymorphism (5-HT1A C(−1019)G) (Huang et al., 2004). The 5-HT1A receptor polymorphism influences serotonergic neurotransmission (Albert and

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Lemonde, 2004). More precisely, the presence of a −1019 G allele is accompanied by a de-repression of 5-HT1A autoreceptor expression by disrupting an inhibitory transcription factor-binding site. This leads to a reduced serotonergic neurotransmission (Lemonde et al., 2004). Thus, the degree of serotonergic neurotransmission is different for the three different 5-HT1A genotype groups (CC, CG and GG), making these genotype groups suitable to study the impact of serotonergic neurotransmission on cognitive functions. The serotonin 1 A receptor system is of special interest as incoming visual stimulation induces serotonergic activation within the occipital cortex (e.g. Pum, Huston, De Souza Silva, & Müller, 2008) and stimulation of the 5-HT1A receptor enhances attentional processes (Winstanley, Dalley, Theobald, & Robbins, 2003; Boulougoris & Tsaltas, 2008). Mental rotation processes themselves have been suggested to be widely decoupled from serotonergic neural transmission (for review Mendelsohn, Riedel, & Sambeth, 2009). Similarly, it has been demonstrated that pharmacological modulations of the 5-HT1A receptor system do not affect saccades (Reilly, Lencer, Bishop, Keedy, & Sweeny, 2008). Thus, the examination of the functional serotonin 1 A receptor polymorphism (5-HT1A C(−1019)G) is suitable to further explore the interrelation of attentional, occulomotor and working memory processes as one can specifically examine the influence of modulations in attentional processes on subsequent occulomotor and mental rotation (working memory) processes.

Attentional ERPs, such as the N1, are assumed to be exogenously driven (bottom-up) sensory components (Luck, 1995), generated in sensory areas in lateral extrastriate cortex (for the visual domain) (Gomez Gonzalez, Clark, Fan, Luck, & Hillyard, 1994) with a contribution of dorsal occipito-parietal and ventral occipital temporal structures (Masaki et al., 2000). In these early stages, attention may act as gain control, modifying the magnitude of neural responses to incoming information (Hillyard, Vogel, & Luck, 1999; Mangun, 1995; Posner & Dehaene, 1994). Modulations of the N1 may therefore not reflect attention per se but its effect on sensory processing (e.g. Eimer, 1994; Hillyard, Teder-Sälejärvi, & Münte, 1998). Recently, Wascher and Beste (in press) discussed sensory processing and attentional selection as integrated phenomena within the biased competition approach of attention (Desimone & Duncan, 1995). Within this framework, attention is conceptualized as an emergent feature of perceptual processing. Consistent with this approach Wascher and Beste (in press) showed that even though the N1 is sensory in its origin, the N1 becomes a correlate of attentional processing. The N1 may hence be reduced with increasing numbers of −1019 G alleles, as these lead to a reduction of serotonergic turnover, which may affect bottom-up attentional processes. Thus, the N1 may be greater in the 5-HT1A CC genotype and decreased in the CG and GG genotype groups.

Studying mental rotation by means of event-related potentials (ERPs; see e.g. Heil & Rolke, 2002; Jansen-Osmann & Heil, 2007; Johnson, McKenzie, & Hamm, 2002), a positivity 300–700 ms after stimulus presentation is observed, located at parietal electrodes. The amplitude of this positivity is a monotonic function of the amount of rotation performed (Heil, 2002). The stimulus-evoked positivity becomes relatively more negative with increasing angular disparities from the upright (Wijers, Otten, Feenstra, Mulder, & Mulder, 1989). Therefore, the decrease of the positivity should be understood as a direct electrophysiological correlate of the mental rotation process itself (Wijers et al., 1989). This idea was validated in a large number of studies, suggesting that the ERP effect observed during mental rotation is indeed highly specific (Heil, 2002). As working memory processes seem to be generally independent of the serotonergic system (Mendelsohn et al., 2009), no modulations may be evident in the potentials as well as behavioural measures of mental rotation performance.

Eye-movements are recorded in the electro-oculogram (EOG) in parallel to the EEG using electrodes located near the eyes (Picton et al., 2000), where saccadic movements are recorded by the horizontal EOG using electrodes placed at the outer canthi of the left and right eye (for review Talsma & Woldorff, 2005).

One may predict that mental rotation performance is impoverished in cases where attentional processes (N1 amplitude) are reduced, e.g. as an effect of reduced efficacy of serotonergic neurotransmission in the presence of the −1019 G allele. However, as eye-movements can subserve working memory functions (Knudsen, 2007) and are closely related to attentional processes, the presence of saccades may reduce the impact of attenuated attentional processes on subsequent cognitive processes, while mental rotation processes may remain unaffected by an attenuation of attentional processing. If eye-movement processes may be supportive for working memory processes, one may expect an increase in EOG activity with concomitant decreases in the N1. Hence, EOG activity may be greater in the 5-HT1A GG genotype group and decreased in the CG and CC genotype group. If eye-movement processes were supportive especially for mental rotation processes, differences in saccadic activity might occur time-locked to processes of mental rotation, i.e. in the interval 300–650 ms after stimulus onset.

2. Materials and methods

2.1. Subjects

A sample of $N = 72$ genetically unrelated subjects of Caucasian descent was recruited by newspaper announcements. The mean age of the subjects was 24.5 years (SD = 4.5). The sample consisted of 22 males and 50 females. The sexes were comparably distributed across the different 5-HT1A C(−1019)G genotype groups as shown by Kruskal–Wallis test (H-Test) ($chi^2 = 0.02$; df = 1; $p > .8$). As the functional 5-HT1A C(−1019)G polymorphism was found to be associated with mood and anxiety disorders (for review Albert & Lemonde, 2004; Drago et al., 2008), we examine the Beck Depression Inventory (BDI) and Anxiety Sensitivity Index (ASI) to account for these factors. The mean BDI score was 3.5 (3.1), indicating a non-depressed population. The BDI score did not differ between genotype groups ($F(2,68) = 1.52$; $p > .2$) (CC: 2.4 ± 2.7; CG: 4.4 ± 3.3; GG: 3.4 ± 3.4). The mean ASI score was 21.1 (12.5). The genotype groups differed from each other with respect to this score ($F(2,68) = 5.84$; $p = .005$). Bonferroni-corrected pair-wise comparisons revealed that the CG genotype group showed a higher ASI score (27.6 ± 10.1) than the other genotype groups (CC: 16.1 ± 10.8; GG: 19.4 ± 13.2). The CC and GG genotype groups did not differ from each other ($p > .7$). The Hardy–Weinberg equilibrium was examined using the program De Finetti provided as an online source (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl; Wienker TF and Strom TM). The distribution of 5-HT1A C(−1019)G genotypes did not significantly differ from the expected numbers calculated on the basis of observed allele frequencies according to Hardy–Weinberg equilibrium (CC = 20, CG = 31, GG = 21; $p = .244$). Volunteers were paid €8 per hour as compensation. The study was approved by the ethics committee of the University of Münster, Germany.

2.2. Genotyping

Genomic DNA was extracted from a 10 ml EDTA venous blood sample with the Qiagen FlexiGene DNA kit (Qiagen, Hilden, Germany). The 5-HT1A C(−1019)G (rs6295) polymorphism was genotyped by means of a polymerase chain reaction (PCR)-based restriction fragment length polymorphism assay. Primers were designed to amplify a 296-bp DNA fragment containing the forward primer 122-F: 5′-AGTTTTGTTCTTCATTTCGAGAT-3′ and reverse mutagenic primer 122-R: 5′-GAAGAAGACCGAGTGTGTCT***A***C-3′. The mutagenic primer was constructed in order to introduce an artificial polymorphic restriction site. By using a Biometra T-Gradient thermocycler (Whatman, Göttingen, Germany) standard PCR was carried out in a total volume of 20 μl containing 60 ng of genomic DNA, 1× PCR buffer, 8 pmol of each primer, 8 mM dNTPs and 0.4 U of Taq polymerase (5Prime, Hamburg, Germany). After an initial step of denaturation at 94 °C for 5 min, 35 cycles were carried out consisting of 94 °C for 30 s, 54 °C (annealing temperature) for 30 s, 72 °C for 60 s and a final extension step of 10 min at 72 °C. Subsequent digestion overnight for 16 h at 65 °C of an 8 μl sample of the PCR product was accomplished with 3 U of Tail (Fermentas, St. Leon-Rot, Germany) in a total volume of 20 μl resulting in two patterns of fragments consisting of 203 + 57 + 36 bp for the G-allele and 183 + 57 + 36 + 20 bp for the C-allele. Digestion products were visualized by silver staining after separation on a 15% polyacrylamide gel in 1× TBE buffer (Tris-Borate, EDTA) at 220 V for 3 h. Genotypes were determined independently by two investigators.

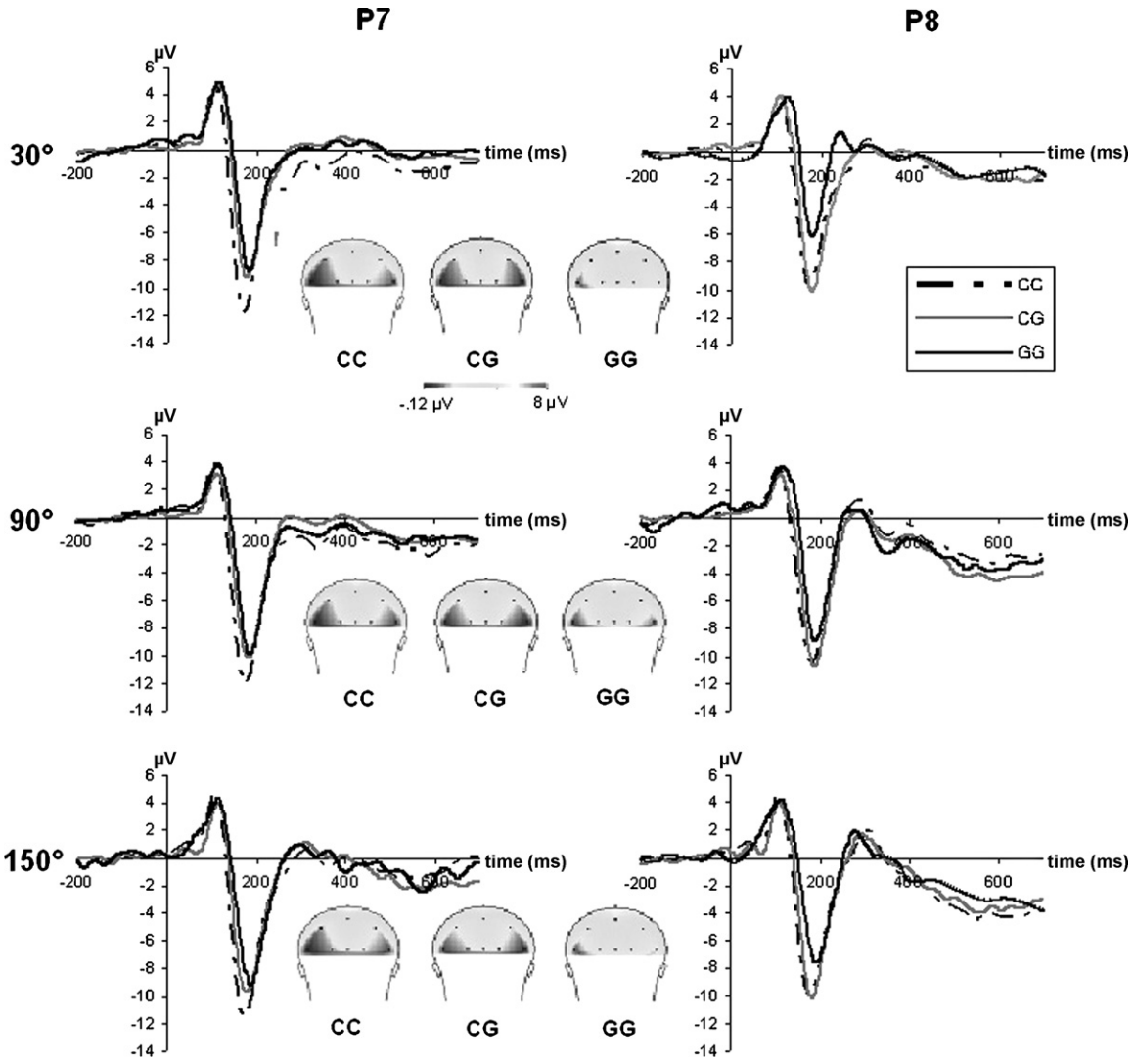

Fig. 1. Stimulus-locked ERPs at the different rotation angle conditions (30°, 90° and 150°), separated for the different 5-HT1A −1019 genotype groups (CC = dashed black; CG = grey; GG = solid black). The ERPs are plotted for the electrode P7 (left column) and P8 (right column) revealing the greater N1. The plots, given for each condition of angular disparity separately, reveal clear N1 topographies. Time point 0 denotes the time point of stimulus presentation.

2.3. Materials and procedure

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 counterclockwise 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. Participants pressed the left or right mouse button depending on whether the letter was normal or mirror-reversed. The letter was then replaced by a "+" or "−" for 500 ms indicating the correctness of the response. Participants were instructed to respond as fast as possible, but accuracy was stressed in the instruction. Trials were separated by randomly varying intervals of 1–3 s. Letters were presented in blocks of 48 trials each. Each combination of orientation, version and letter occurred eight times resulting in 384 experimental trials. To familiarize participants with the task, 48 unrecorded practice trials were added. The procedure lasted about 30 min.

2.4. EEG recording and analysis

During the task 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, beginning 200 ms before and ending 700 ms after stimulus presentation. Effects of neural activity, i.e. inversions of polarity stemming from movements of the eyeball (ocular artifacts), were corrected using the Gratton-Coles-Algorithm based on the EOG data (Gratton et al., 1983), followed by a baseline correction (−200 to 0 ms). Remaining artifacts were rejected using an amplitude criterion of ±80 μV followed by re-referencing all data to linked mastoids. Artifact detection was made by algorithm, but subsequently visual inspection was required before discarding the epochs. From the edited set of raw data, we extracted ERPs by averaging single trials with correct responses separately for participants, electrodes and experimental conditions.

For the analysis of ocular activity, a new virtual electrode (EOGL) was calculated based on the data of the two horizontal EOG electrodes. Each of the horizontal electrodes was incorporated to this new electrode to the same extend. In order to obtain a measure for general saccadic ocular activity, we calculated the power of this electrode within the frequency range of 0.1–20 Hz on single trial sweeps. These sweeps were averaged later on. This was done before using ocular electrodes for the correction of the EEG. Hence, EOG was used twice: (i) to estimate ocular activity during mental rotation and (ii) to use these for standard ocular correction of ERP data (Picton et al., 2000).

2.5. Statistical analysis

1. The behavioural data were analyzed in univariate repeated measures ANOVAs with the within-subjects factor "angular displacement" and the between-subjects factor "genotype group".
2. For the analysis of the N1, electrodes P7 and P8 were used, yielding the maximum of this potential (refer maps; Fig. 1). The N1 was defined as the most negative peak after stimulus onset, referenced to a baseline of 200 ms duration pre-stimulus onset. For statistical analysis, amplitudes and latencies were

subjected to a repeated measures ANOVA with the within-subjects factors "electrode" and "angular displacement" and the between-subjects factor "genotype group".

3. For the ERPs during mental rotation, the average amplitude of the epoch 300–700 ms after letter presentation (Heil & Rolke, 2002; Jansen-Osmann & Heil, 2007) was used as dependent variable, referenced to a pre-stimulus baseline of 200 ms duration. In accordance with the literature, ERPs were quantified at electrodes P3, Pz and P4 (e.g. Heil & Rolke, 2002; Jansen-Osmann & Heil, 2007). For statistical analysis, amplitudes were subjected to a repeated measures ANOVA with the within-subjects factors "electrode" and "angular displacement". Between-subjects factor was "genotype group"; i.e. 5-HT1A CC, CG and GG.
4. For the analysis of ocular activity, the mean power of electrode EOGL within the time range of 300–700 ms was subjected to a repeated measures ANOVA with the within-subjects factor "angular displacement" and the between-subjects factor "genotype group".

All ANOVAs were adjusted using Greenhouse–Geisser-Correction, when appropriate, and all post hoc tests were Bonferroni-corrected. In a second step, all these analyses were cross-validated, dividing participants in each allele group randomly into two subgroups. Then, all ANOVAs were repeated using these randomly created subgroups as an additional between-subject factor.

As the 5-HT1A C(−1019)G genotype groups differed in their ASI scores, all the analyses described above were repeated using the ASI scores as covariate in an analysis of covariance (ANCOVA) in order to examine whether the effects are robust or further modulated by this factor.

3. Results

3.1. Behavioural data

Reaction times (RTs) were shortest in the condition of 30° angular displacement (612.38 ± 12.9) and increased with 90° (679.90 ± 16.1) and with 150° (793.80 ± 20.2) ($F(2,136) = 254.43$; $p < .001$; $\eta = .78$). There were no genotype group differences or interactions with this factor (all $Fs < .68$; $p > .6$). Similarly, error rates were lowest in the condition of 30° (4.22 ± 0.4) and increased with 90° (5.89 ± 0.6) and 150° angular displacement (14.82 ± 1.1) ($F(2,136) = 103.98$; $p < .001$; $\eta = .60$), but again no genotype group differences or interactions with this factor were obtained (all $Fs < 1.1$; $p > .3$). The pattern of results is substantiated by the cross-validation analysis, where no effect of the validating factor was found (all $Fs < .7$; $p > .5$). Examining possible further modulatory effects of anxiety sensitivity by extending the above analyses by the ASI score as covariate revealed no significant influence of this covariate (all $Fs < .3$; $p > .9$).

3.2. Neurophysiological data

3.2.1. Attentional processes (N1)

Stimulus-locked grand averages at electrodes P7 and P8 including topographical maps are given in Fig. 1 for each of the genotype groups separately.

The N1 was larger at electrode P7 (−11.36 ± 0.2) than at P8 (−9.51 ± 0.3) ($F(1,69) = 523.71$; $p < .001$; $\eta = .88$) and also largest for the 150° condition (−11.4 ± 0.2) and continuously decreased in the 90° (−10.4 ± 0.4) and the 30° condition (−9.44 ± 0.3) ($F(2,138) = 401.1$; $p < .001$; $\eta = .85$). The N1 was also greater for the CC (−11.70 ± 0.4) and CG group (−10.56 ± 0.3), differing from the GG group (−9.03 ± 0.4) ($p < .001$) ($F(2,69) = 9.31$; $p < .001$; $\eta = .19$). Interestingly, there was a strong interaction "electrode x genotype group" ($F(2,69) = 130.69$; $p < .001$; $\eta = .82$). This interaction is illustrated in Fig. 2. This interaction was not further affected by the angular displacement of the character ($F(4,138) = 0.85$; $p > .5$).

Fig. 2 reveals a pattern, in which the existence of one −1019 G allele leads to a decrease in N1-amplitude at electrode P7, but not at P8. Homozygosity for the −1019 G allele did not further affect the left-hemispheric N1 (i.e. at electrode P7), but affected the N1 amplitude on the right hemisphere (i.e. at electrode P8). The statistical analysis underlines this. A univariate ANOVA and subsequent post hoc tests of the N1 at electrode P7 revealed that the N1 was largest in the CC genotype group (−12.71 ± 0.5) and comparably smaller in the CG (−10.62 ± 0.4) and GG genotype groups (−10.60 ± 0.4) ($p < .001$) ($F(1,69) = 6.33$; $p = .003$; $\eta = .13$). At electrode P8, the ANOVA and post hoc tests revealed that the GG genotype group (−7.62 ± 0.4) revealed smaller amplitude than the CG (−10.49 ± 0.3) and CC genotype groups (−10.66 ± 0.4) ($p < .001$) ($F(1,69) = 20.74$; $p < .001$; $\eta = .34$). Remaining main or interaction effects were not significant (all $Fs < 1.3$; $p > .2$). Regarding the N1 latencies, no significant effect was obtained (all $Fs < .1$; $p > .2$).

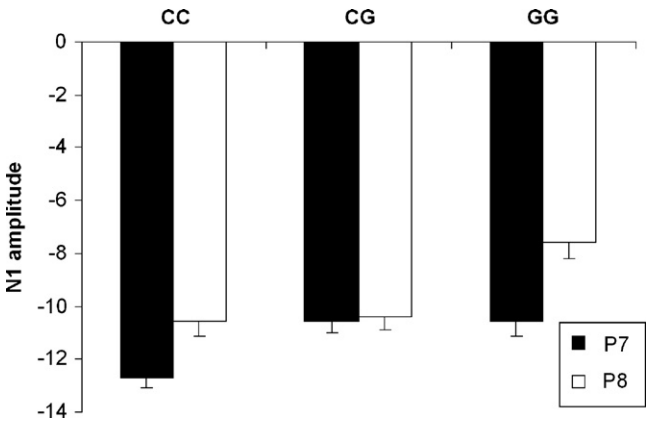

Fig. 2. Amplitudes of the N1 (relative to pre-stimulus baseline) for the different groups at electrodes P7 and P8.

Concerning the cross-validation, the additional between-subject factor "random subgroup" did not interact with any of the other factors (all $Fs < 1.2$; $p > .2$), suggesting that the effects observed are similar for both cross-validated subgroups, underlining the robustness of effects. As with the behavioural data, there was also no modulating effect of the ASI score (all $Fs < .5$; $p > .6$).

3.3. Mental rotation

ERPs during mental rotation across groups and for the different genotype groups are given in Fig. 3 for Pz only, as this electrode revealed stronger mental rotation effects than the other electrodes (P3 and P4).

ERPs during mental rotation were highest at electrode Pz (6.71 ± 0.4) and significantly smaller ($p < .001$) at P3 (4.7 ± 0.3) and P4 (4.6 ± 0.3) ($F(2,138) = 53.17$; $p < .001$; $\eta = .43$). The latter electrodes did not differ from each other ($p > .7$). Amplitudes were also greater in the 30° condition (6.1 ± 0.3) and decreased continuously in the 90° (5.2 ± 0.4) and 150° condition (4.5 ± 0.3) ($ps < .003$) ($F(2,138) = 14.28$; $p < .001$; $\eta = .15$). None of these effects was modulated by the factor "genotype group" (all $Fs < .5$; $p > .6$). Also, no other significant interactions were obtained (all $Fs < 1.2$; $p > .2$). The main effect "genotype group" was also not significant ($F(2,69) = 1.35$; $p > .2$).

This pattern of results again is underlined by the cross-validation procedure. The between-subject factor "random subgroup" did not interact with any of the other factors (all $Fs < 0.7$; $p > .6$). No further modulating effect of the ASI score in all of the above analyses was obtained (all $Fs < .6$; $p > .6$).

3.3.1. Saccadic activity

Fig. 4 denotes the power of ocular activity at the lateral EOG electrode for the whole epoch of mental rotation across polymorphism groups and for each group separately.

Power was greater for the 30° condition (164.89 ± 1.3) and decreased continuously in the 90° (146 ± 1.4) and 150° condition (133.64 ± 1.6) ($F(2,138) = 180.33$; $p < .001$; $\eta = .72$). Hence, this data pattern parallels the pattern of ERPs at parietal leads during men-

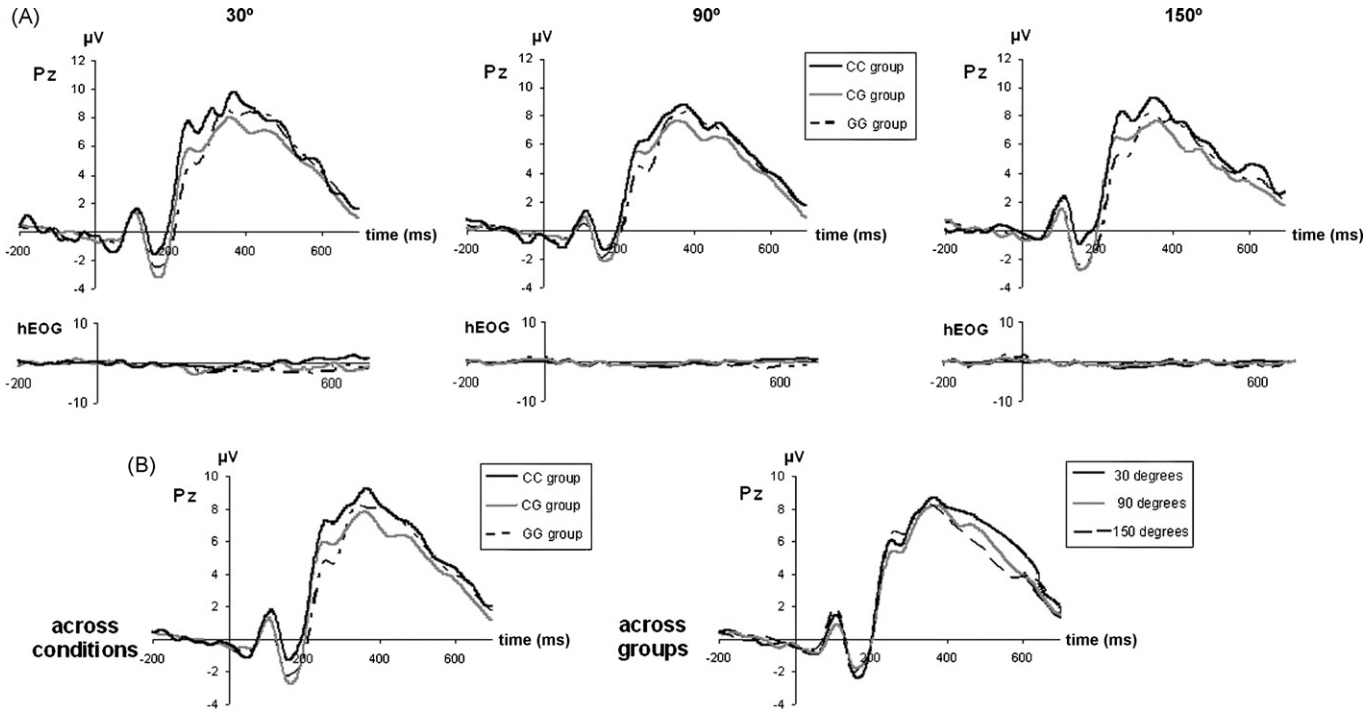

Fig. 3. (A) Stimulus-locked ERPs at electrode Pz, separated for the different rotation angles (30°, 90° and 150°) and 5-HT1A −1019 genotype groups (CC = dashed black; CG = grey; GG = solid black). Below the Pz electrode the horizontal EOG is given for each rotation angle condition and group. (B) On the left, stimulus-locked potentials at electrode Pz are given across conditions of angular disparity, separated for the genotype groups. On the right, stimulus-locked potentials at electrode Pz are given across groups, separated for differing degrees of angular disparity.

tal rotation. Yet, power was also different for the genotype groups ($F(1,69) = 39.37$; $p < .001$; $\eta = .53$). The power was greater in the GG genotype group (162.09 ± 1.8) and smaller in the CG (141.52 ± 1.9) and CC groups (141.85 ± 2.1) ($p < .001$). The latter groups did not differ from each other ($p > .8$). The interaction "angular displacement x genotype group" was not significant ($F(4,138) = 1.3$; $p > .2$).

The pattern of results again was substantiated by the cross-validation analysis, where no effect of the validating factor was found (all Fs < 1.3; $p > .2$). Also here, no further modulating effects of the ASI score in all above analyses was obtained (all Fs < .8; $p > .3$).

4. Discussion

In the current study we examined the relevance of serotonin receptor 1 A (5-HT1A) C(−1019)G polymorphism for the interrelation of attentional, working memory and eye-movement processes by means of ERPs. As it has been suggested that only attention, but not mental rotation and saccadic processes, are modulated by the serotonergic system (Mendelsohn et al., 2009; Pum et al., 2008; Reilly et al., 2008), it was possible to specifically examine the influence of modulations in attentional processes on subsequent occulomotor and mental rotation (working memory) processes. To our best knowledge, this is the first study examining the relation of these three processes in relation to genetic variation, hence examining a specific neurobiological system applying neurophysiological techniques.

We observed a strong influence of the 5-HT1A C(−1019)G polymorphism particularly on the N1. The N1 was generally decreased in GG homozygotes as compared to CG and CC genotype groups. Moreover, it was shown that the existence of one −1019 G allele leads to a reduction of the N1 at P7 (left hemisphere), whereas homozygosity for the −1019 G allele does not further modulate the left hemispheric N1 and rather leads to a decrease of the right hemispheric N1 (i.e. at electrode P8). The N1 further decreased with angular displacement. Regarding saccadic activity, the general pattern was similar to ERPs during mental rotation performance, i.e. increasing angular displacements are related to decreases in saccadic activity and parietal ERP amplitudes during mental rotation. Importantly, ERPs during mental rotation at parietal leads seem to be sufficiently corrected for ocular activity, as can be seen in the EOG channel after ocular correction. Yet, saccadic activity was higher for the 5-HT1A −1019 GG genotype group than the other genotype groups (i.e. CG and CC). ERPs during mental rotation only yielded the well-known effects of angular displacement and electrode (e.g. Heil, 2002), but no direct variation of mental rotation processes as a function of the functional 5-HT1A C(−1019)G polymorphism was found. The results are unbiased of the factor "sex" as (i) sexes were equally distributed across the genotype groups and (ii) since mental rotation of characters, which was used here, has repeatedly been shown to be not sensitive to sex (Jansen-Osmann & Heil, 2007). Furthermore, the results are unbiased by mood or anxiety-related states of the participants. All above mentioned effects seem to be very robust, as shown by the cross-validation procedure.

The general decrease in the N1, known to be generated in the occipital cortex (for the visual domain), in the 5-HT1A −1019 GG genotype group as compared to the other genotype groups can be explained by possible influences of the 5-HT1A C(−1019)G polymorphism on occipital serotonergic turnover. As the −1019 G allele has been shown to lead to a reduced serotonergic neurotransmission (Albert & Lemonde, 2004; Lemonde et al., 2004), the usual enhancing properties of the 5-HT1A receptor system on attentional processing may be reduced (Boulougoris & Tsaltas, 2008; Winstanley et al., 2003). Alternatively, occipital activation due to incoming visual stimulation (e.g. Pum et al., 2008) may be reduced, also leading to a reduction of the N1. Yet, the results suggest that the number of −1019 G alleles differentially affects the N1 over the left and right hemisphere. Given that serotonergic turnover is increasingly reduced in CG and GG genotype groups in an allele-dose-fashion, our results can only be explained postulating that

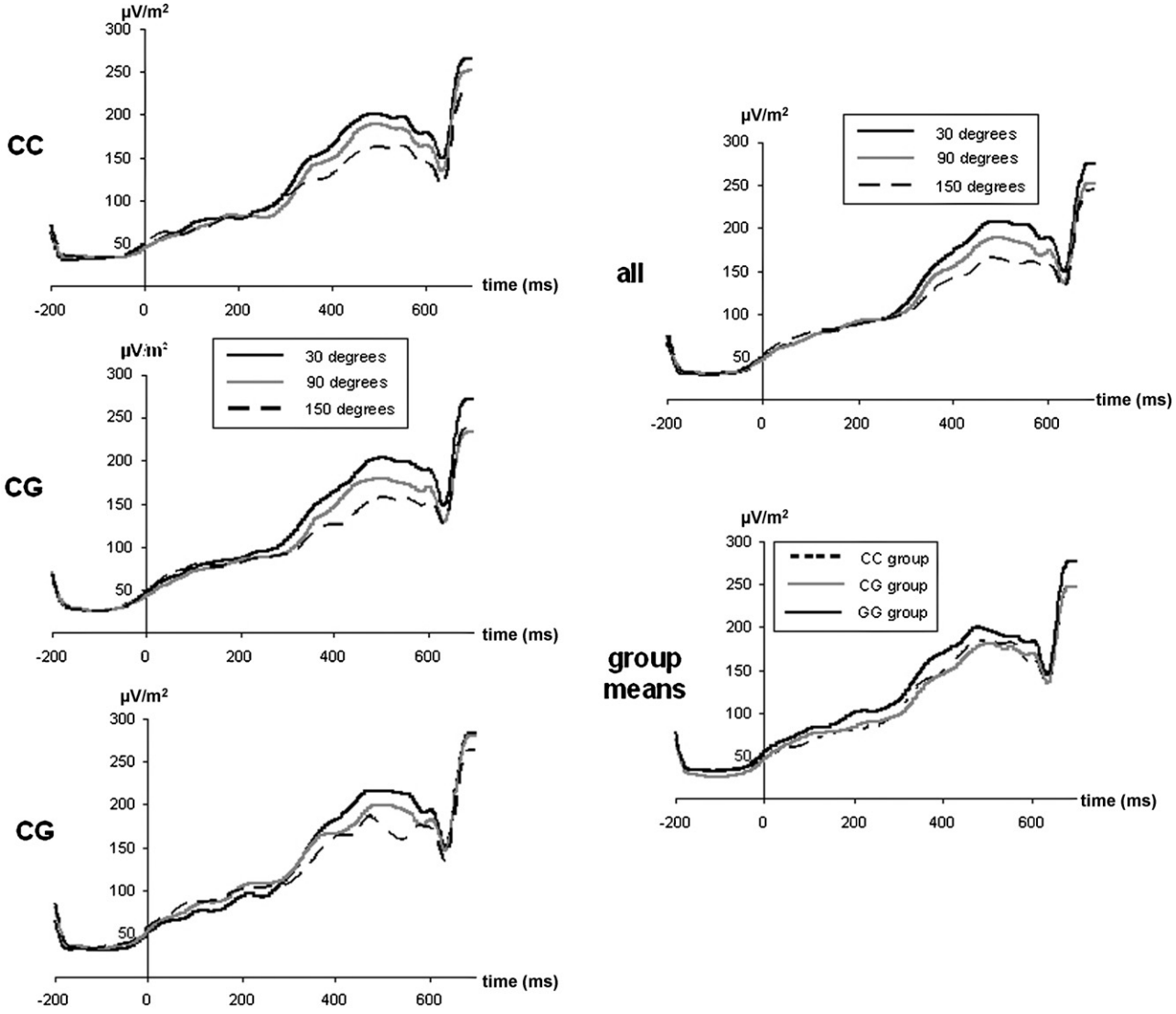

Fig. 4. Plot of saccadic activity, i.e. phase-locked EOG power. The left column depicts saccadic activity separated for the different 5-HT1A −1019 genotype groups and different degrees of angular disparity. On the right (top) saccadic activity is given for the whole sample, only separated for different degrees of angular disparity. Note that saccadic activity begins to fan out between conditions within a time-interval of 300–650 ms after stimulus onset, i.e. is selective for the time period of mental rotation. On the right (bottom) group means of saccadic activity are given collapsed over the conditions of different angular disparity.

the N1 above the left hemisphere (P7) is very sensitive to subtle changes in serotonergic neurotransmission. Contrary, the N1 above the right hemisphere (P8) is less sensitive and thus only changes after stronger decreases in serotonergic neurotransmission. Hence, the results may suggest for a functional asymmetry of the serotonine 1 A receptor system, which has also recently been reported in the language domain (Fink et al., 2009).

Especially the 5-HT1A −1019 GG genotype group showed a decreased N1. Interestingly, modulations in the N1 were without consequences for mental rotation performance, as indicated by a lack of differences between genotype groups in performance or neurophysiological correlates of mental rotation (i.e. parietal positivities) between the genotype groups. As the N1 likely reflects integrated processes of perception and attention (Wascher & Beste, in press), a reduction of these processes probably lead to less stable neuronal representations of an object in the parietal cortex (Knudsen, 2007). The posterior parietal cortex (PPC) is known to be important for object representations (e.g. Gottlieb, 2007; Shomstein & Behrmann, 2006), cognitive maps (Shipp, 2004) and mental rotation of these objects (e.g. Heil, 2002; Jordan, Heinze, Lutz, Kanowski, & Jäncke, 2001; Schöning et al., 2007).

The fact that probably less stable representations in the parietal cortex did not compromise mental rotation performance may suggest a third process preventing the attenuation of performance. From this point of view, the enhanced saccadic activity observed in the 5-HT1A −1019 GG genotype group maybe regarded as doing so. Underlining this interpretation, decreasing rotation angles were generally accompanied with decreases in bottom-up attentional processes (i.e. the N1), but concomitant increases of saccadic activity across genotype groups (see Fig. 4). The notion that saccadic activity is related to the process of mental rotation, or may even support these processes, is further substantiated by the finding that differences in saccadic activity occur time-locked to processes of mental rotation, i.e. in the interval 300–650 ms after stimulus onset (see Fig. 4). It has been shown that pharmacological modulations of the 5-HT1A receptor system do not affect saccades (Reilly et al., 2008). Hence, the increased saccadic activity in the 5-HT1A −1019 GG group relative to the other genotype groups does not likely reflect a direct effect of an altered serotonergic turnover, but may rather reflect an *indirect* effect of effort in working memory and parietal networks to support mental rotation. The finding that no modulation of neuronal processes *directly* related to working

memory functions by the functional 5-HT1A C(−1019)G polymorphism was observed (i.e. modulation of parietal positivities) is in line with studies reporting no influence of acute tryptophan depletion on working memory processes (for review Mendelsohn et al., 2009). The fact that only the 5-HT1A −1019 GG genotype group, but not the other genotype groups revealed increased saccadic activity may suggest that bottom-up attentional processing (N1) has to fall below a certain critical level to necessitate an increase of saccadic activity.

Future studies may use different, sex-sensitive stimulus material in order to disentangle if the observed effects may be different for sex and/or stimulus material. This may be more relevant considering that gonadal steroid hormones affect serotonin 1 A receptor functioning (e.g. Andrade, Nakamuta, Avanzi, & Greaff, 2005; Estrada-Camarena, Loopwez-Rubalcava, & Fernandez-Guasti, 2006) and also modulate mental rotation performance (e.g. Schöning et al., 2007). It may be hypothesized that the lack of genotype-dependent differences during mental rotation observed in our study is due to the insensitivity for sex of the stimulus material used (Jansen-Osmann & Heil, 2007) and that modulating effects of the functional 5-HT1A C(−1019)G polymorphism may be observed using sex-sensitive stimulus material for mental rotation.

In summary, the results provide first evidence for a close interrelation between working memory, attentional and saccadic processes. Yet, these processes are differentially modulated by the functional 5-HT1A C(−1019)G polymorphism. The 5-HT1A C(−1019)G polymorphism primarily affects attentional processing, whereas processes related to the mental rotation of an object seem to be independent of 5-HT1A genetic variation. It is likely that decreased attentional processes cause parietal networks to increase saccadic activity in order to stabilize neural object representations to perform mental rotation.

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