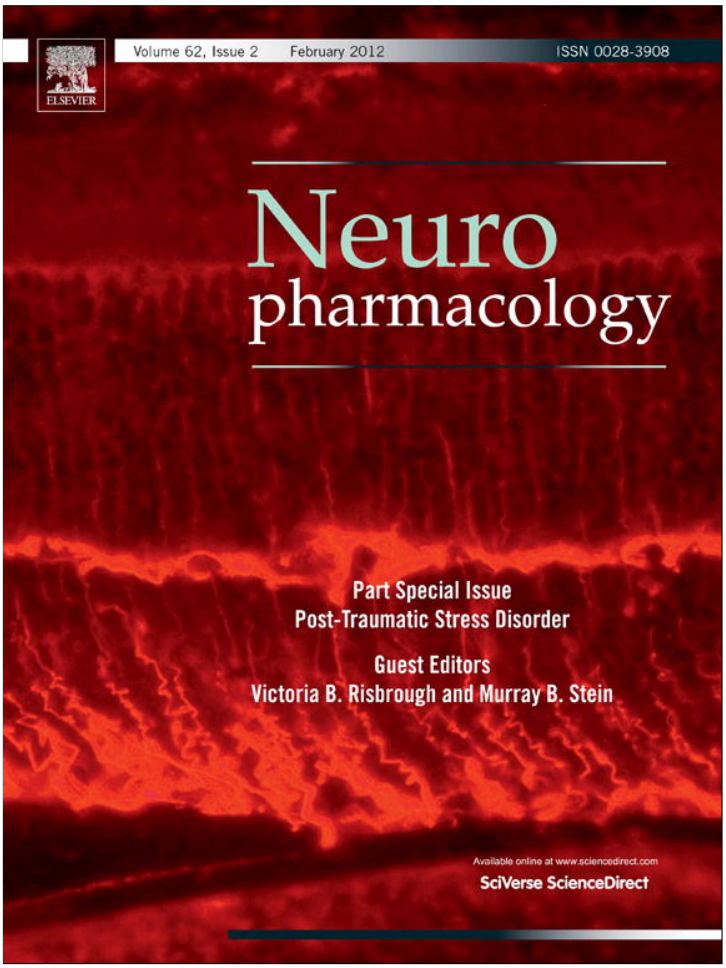

Neuropharmacology 62 (2012) 1028–1033

Contents lists available at SciVerse ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

When control fails: Influence of the prefrontal but not striatal dopaminergic system on behavioural flexibility in a change detection task

Stefanie Schulz [a,*], Larissa Arning [b], Marlies Pinnow [a], Edmund Wascher [c], Jörg T. Epplen [b], Christian Beste [a]

[a] Institute for Cognitive Neuroscience, Biopsychology, Ruhr-University Bochum, Germany
[b] Department for Human Genetics, Faculty of Medicine, Ruhr-University Bochum, Germany
[c] IFADO – Leibniz Research Centre, Dortmund, Germany

ARTICLE INFO

Article history:
Received 13 August 2011
Received in revised form
16 September 2011
Accepted 24 October 2011

Keywords:
Behavioural flexibility
COMT Val158Met
DAT1
Change detection
Attention

ABSTRACT

There is growing interest in understanding the neurobiological foundations of attention. To examine whether attentional processes in a change detection task are modulated by dopamine signalling, we investigated the influence of two polymorphisms, i.e. Val158Met (rs4680) in the catechol-O-methyl transferase (*COMT*) and a variable number of tandem repeats polymorphism (VNTR, rs28363170) in the dopamine transporter (*DAT1*).

The *COMT* Met allele, which results in lower enzyme activity and therefore probably enhanced PFC dopamine signalling, was significantly associated with task-performance and modulated executive control: Homozygous Met/Met allele carriers had difficulties when performing a change detection task, particularly showing the greatest difficulties in case cognitive and behavioural flexibility was necessary and the required reaction was not part of the subject's primary task set. Contrary, no difference between the two genotype groups were evident, when an attentional conflict emerged and attentional control was needed for adequate responding. No association with variation in *DAT1* was observed.

The results indicate a dissociation of the prefrontal and striatal dopamine system for attentional control and behavioural flexibility in a change detection task: While prefrontal dopamine turnover seems to modulate performance, putatively via difficulties in set shifting leading to behavioural inflexibility in COMT Met allele carriers, striatal dopamine turnover seems less important in this regard. With respect to other studies examining mechanisms of attentional functions in different paradigms, the results suggest that behavioural flexibility and attentional control as two executive subprocesses are differentially influenced by genetic polymorphisms within the dopaminergic system.

This article is part of a Special Issue entitled 'Post-Traumatic Stress Disorder'.

1. Introduction

Due to limited cognitive capacities, we are not able to process all stimuli in our surrounding at once. We have to select important stimuli for further processing while suppressing others. Attentional selection might be driven by feature properties of a stimulus (bottom-up driven) (e.g. Theeuwes, 2010; Egeth and Yantis, 1997) or by an individual's intentions while observing a visual scene (top-down).

Change detection tasks can be used to investigate the interplay between bottom-up and top-down attentional processes, if both kinds of stimuli are presented at once (e.g. Simons and Rensink, 2005). Under certain circumstances, a perceptual conflict between these two sources of information may occur (Wascher and Beste, 2010): It has been suggested that perceptual competition occurs, if two stimuli change concurrently, whereas only one of them is designated as target (Sussman et al., 2003; Wascher and Beste, 2010). Even if the non-target stimulus comprises a very salient feature change as e.g. an orientation change, this feature specific change detection can be counteracted by top-down processes which are in favour of the non salient feature change of the target stimuli, particularly, if the distractor is not part of the primary task set (see also Folk and Remington, 1999; Knudsen, 2007; Maunsell and Treue, 2006; Simons and Rensink, 2005). In broader terms, this top-down control belongs to the executive processes, which consists of several higher order cognitive functions. Two of these are cognitive, respectively behavioural

* Corresponding author. Department of Biopsychology, Institute for Cognitive Neuroscience, Faculty of Psychology, Ruhr-University Bochum, GAFO 05/621, Universitätsstr. 150, D-44780 Bochum, Germany. Tel.: +49 234 32 24032; fax: +49 234 32 14377.
E-mail address: Stefanie.Schulz-2@rub.de (S. Schulz).

0028-3908/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuropharm.2011.10.012

flexibility and attentional top-down control (e.g. Miller and Cohen, 2001).

In our change detection paradigm, behavioural flexibility and attentional control are required for good task-performance. Subjects had to detect a luminance change of a laterally presented bar.

This change could occur alone, or was accompanied by an orientation change at the same location. In those two conditions, change detection is hardly demanding. In 25% of the trials however, the luminance change occurred simultaneously with a more salient orientation change at the opposite location (CONflict trials). Consequently, conflicting information has to be suppressed, which requires high levels of top-down control. In another 25% of the trials only an orientation change occurred with no luminance change in the scene (ORIentation change). Under this condition, subjects were required to disregard the primary task to localize the luminance change and to press a third button to indicate the appearance of an orientation change. By means of this experimental setup, attentional control (CONflict condition) and behavioural flexibility (ORIentation change), as two central executive top-down control functions, can be dissociated.

Several lines of research in health and disease suggest that cognitive control is regulated by the dopaminergic system (e.g. Arnsten and Pliszka, 2011; Van Schouwenburg et al., 2010). Despite a large body of research, to date no task has investigated, how the dopaminergic system modulates top-down control in case of emerging perceptual conflict between stimuli of different saliency levels. Aim of this study was thus to examine whether individual differences related to the *COMT* and *DAT1* polymorphisms influence the performance of subjects in a change detection task, in which high and low salient stimuli compete against each other for detection, perceptual processing and response.

Availability of dopamine (DA) is regulated by two important proteins, the catechol-O-methyl transferase (COMT) and the DA transporter (DAT1). COMT is responsible for the degradation of the catecholamines dopamine and norepinephrine and plays a central role in regulating prefrontal dopamine levels (Dickinson and Elvevåg, 2009; Meyer-Lindenberg and Weinberger, 2006). Studies examining variation in the *COMT* gene have largely focused on a functional single nucleotide polymorphism (SNP) in exon 4 that leads to an amino acid substitution of valine (Val) by methionine (Met) at amino acid position 158 (Val158Met, rs4680). This polymorphism has been shown to substantially affect *COMT* enzyme activity, with the Val allele being associated with greater *COMT* enzyme activity leading to lower synaptic DA levels than the Met allele (Chen et al., 2004; Weinshilboum et al., 1999). It has been demonstrated, that Met allele carriers show enhanced cognitive stability compared to Val allele carriers, who in turn reveal comparably low cognitive stability, but high flexibility (for reviews see: Cools, 2006; Savitz et al., 2006). This assumption has been underlined in several studies with different paradigms (e.g. Egan et al., 2001; Goldberg et al., 2003). Blasi et al. (2005) postulated comparatively enhanced attentional control in subjects homozygous for the Met allele. Furthermore, the Met allele was associated with low performance in a reversal learning task, in which cognitive flexibility was necessary. Along these lines, higher switch costs in a task switching paradigm were evident in Met carriers (Colzato et al., 2010a).

DAT1 regulates the DA reuptake in the synaptic cleft in the striatum (e.g. Uhl, 2003). The mostly studied genetic polymorphism of the *DAT1* (*SLC6A3*) gene is a 40 base pair (bp) variable number of tandem repeats polymorphism (VNTR) in the 3′ untranslated region (rs28363170), (Giros et al., 1992; Mitchell et al., 2000; Vandenberg et al., 1992). The most common alleles are the 9- and 10-repeat alleles, with the 10-repeat allele showing increased gene expression, greater overall DAT activity and corresponding increase in DA reuptake as compared to the 9-repeat allele (Brookes et al., 2007; Mill et al., 2002). Colzato et al. (2010b) showed, that 9-repeat allele carriers displayed enhanced cognitive flexibility in an "Inhibition of return" paradigm which was evident in a more pronounced IOR effect at short SOAs. This result is in line with studies by Cools (2008), Cools and D'Esposito (2011) and Garcia-Garcia et al. (2010), suggesting that higher DA levels in the striatum facilitate cognitive flexibility.

Based on the findings mentioned above, we hypothesize that dopaminergic polymorphisms modulate executive functions, i.e. behavioural flexibility as well as attentional control similarly: Higher dopamine levels in the PFC of *COMT* Met allele carriers should lead to excessive top-down control together with diminished behavioural flexibility. This should be reflected by higher error rates, if flexible responding to the seldom occurring orientation change is necessary, especially because the orientation change is not part of the subject's task set in 75% of their demanded reactions. In contrast to this, these subjects are supposed to perform better than Val allele carriers in the conflict condition, in which attentional control and fixation on their certain task set is important. In summary, Met allele carriers should show enhanced attentional control at the expense of cognitive and behavioural flexibility.

Concerning the effects of DAT1 we hypothesize that 9-repeat carriers would have difficulties in cognitive and behavioural flexibility due to lower striatal DA levels as compared to 10-repeat carriers.

2. Material and methods

2.1. Participants

The sample consisted of 261 young adults (118 males/143 females) of Caucasian descent, with a mean age of 23.93 years (23.93 ± .17, range: 17–31 years), who participated in the study for course credit or financial compensation. 232 subjects where right handed and 29 left handed as measured with the Edinburgh Handedness Inventory (Oldfield, 1971). All subjects reported no history of any neurological or psychiatric disorder and had normal or corrected to normal vision. The study was approved by the local ethics committee and written informed consent was obtained from all subjects.

2.2. Stimuli and experimental procedure

Subjects had to perform a change detection task, similar to the one described by Wascher and Beste (2010) (Fig. 1).

Two vertically or horizontally oriented bars were presented on a 100 Hz CRT-monitor positioned left and right of a fixation cross. The bars could either be brighter or darker than the background (30 cd/m^2) with a Fechner-contrast of ±.2. Luminance and orientation in the first frame were randomly chosen in any possible combination. Each trial comprised the presentation of two frames with two bars each in rapid succession. The first frame was shown for 200 ms followed by a 50 ms gap in which only the fixation cross was visible. After the gap a second frame was presented for 200 ms. Between these two frames the luminance and orientation of one bar or of both bars could change. With this task design four conditions are possible: The luminance (LUM), or orientation (ORI) of one bar could differ between the two frames, the luminance and orientation of one bar (LOU) could be altered, or the luminance and orientation change occurred at different spatial positions, i.e. the orientation changed left and the luminance changed right of the fixation cross. The latter condition is called conflict condition (CON). This condition is especially attentional demanding, since the detection of the relevant luminance change of one bar is distracted by the irrelevant orientation change of the other bar. Subjects had to indicate with a button press, whether the luminance between the two frames changed on the right or on the left of the fixation cross (two buttons on a response pad) or if there was only an orientation change without alteration of luminance (one button in the middle between the two others). Task difficulty was further varied by the length-to-width ratios of the bars and thus the saliency of the orientation change (1:2.41 = strong transient, 1:1.35 = weak transient). The experiment consisted of 768 trials presented in random order, with 96 trials for each condition (four change conditions with two saliency levels). The inter-trial interval was jittered between 2000 and 2500 ms.

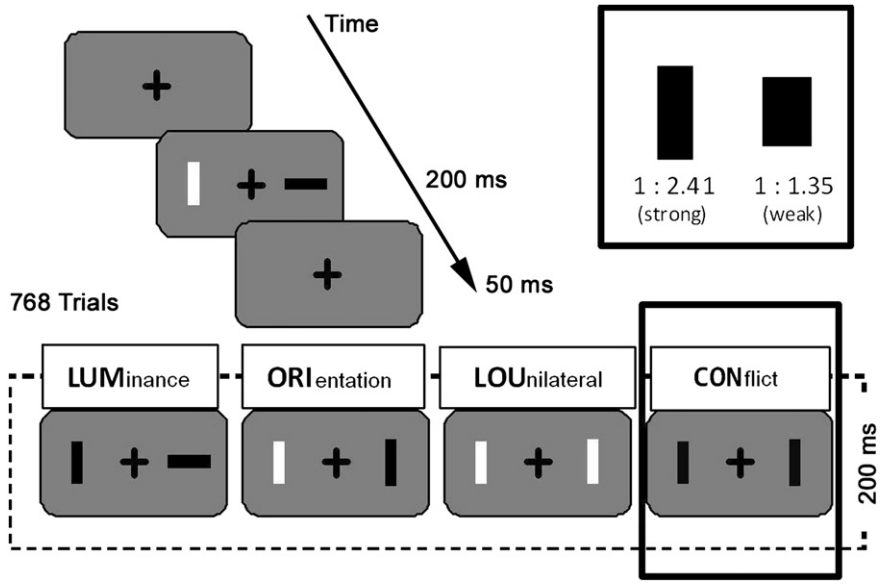

Fig. 1. Change detection task. Schematic overview of the stimulus setup and experimental procedure. Subjects had to detect a luminance change of one of two bars in a fast sequence of frames. The luminance change of one bar could either occur alone (LUM) or was accompanied by an orientation change of the same bar (LOU) or by an orientation change of the bar on the other side of the fixation cross (CON). In 25% of all trials only orientation changed without luminance change (ORI). Difficulty of the task was varied by manipulating the length-to-width rations of the bars.

2.3. Genotyping

DNA was isolated from saliva using QIAamp DNA mini Kit (50) (Qiagen GmbH, Hilden, Germany) according to the protocol supplied by the manufacturer. Whole-genome amplification was performed using GenomiPhi DNA Amplification Kit from Amersham Biosciences. The *COMT* Val158Met, rs4680, polymorphism was genotyped using polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP). PCR amplification was performed using 5′-TGTAAAAC-GACGGCCAGTGCTCATCACCATCGAGATCAAC-3′ and 5′-TGCCCACAGCCGGC-3′ as the tailed forward and reverse primer, respectively. PCR products were digested with the restriction enzyme NlaIII and visualised on 2% agarose gels stained with ethidium bromide.

Genotyping of the *DAT1* VNTR, rs28363170, was performed on the Beckman Coulter CEQ8000 8-capillary system using 'Fragment Analysis Module' software (Beckman Coulter, Inc., Fullerton, USA). The genotypes were confirmed by sequence analysis. Oligonucleotides were designed using Primer Express 2.0 Software (Applied Biosystems). Further details of methodology and primer sequences are available upon request.

2.4. Statistical analysis

Error rates and reaction times (RTs) were analyzed using repeated-measures analyses of variance (ANOVAs). Responses which occurred after 1500 ms after the onset of the second frame were categorized as misses. Response times are defined as the interval between the onset of the second frame and the button press. Error categories comprised misses and choice errors (e.g. the subject indicated a luminance change when only an orientation change occurred). The repeated-measures ANOVAs included "distractor saliency (high *vs*. low)" and "condition (LUM, ORI, LOU, CON)" as within-subject factors and "genotype group" as the between subject factor (*COMT* or *DAT1* genotypes). As it is known that the COMT polymorphism has a co-dominant mode of action (Spielman and Weinshilboum, 1981), we considered each genotype group separately. The same was applied for *DAT1* genotypes. Where necessary, significances where Greenhouse Geisser corrected. Post-hoc tests were adjusted by Bonferroni correction, when required. The significance level was $<.05$ for all statistical tests. Numbers of correct responses are given in percentage values. Mean (M) and standard error (SEM) are given (M ± SEM). All analyses were computed with Predictive Analytics Software (PASW) 18.0.

3. Results

Genotyping the *COMT* Val158Met polymorphism in this study revealed that 62 probands were homozygous for Val/Val, 117 were heterozygous (Val/Met) and 82 were homozygous for Met/Met. The allelic distribution of the *DAT1* VNTR polymorphism revealed 17 homozygous 9-repeat/9-repeat carriers, 84 heterozygous 9-repeat/10-repeat carriers and 143 homozygous 10-repeat/10-repeat carriers. Genotyping of the *DAT1* polymorphism was not possible for 17 subjects. Genotype distribution of the two polymorphisms did not differ from Hardy–Weinberg equilibrium (all $p > .11$).

Regarding the Val158Met polymorphism, following results were obtained. Correct response rates varied significantly across the four change conditions ($F_{(3,774)} = 338.70$, $p < .001$, $\eta^2 = .57$) and were highest in the ORI condition (87.49 ± .84) followed by LOU (79.63 ± .75), LUM (76.09 ± .82) and CON (62.11 ± .94). Furthermore, the main effect type of orientation change transient ($F_{(1,258)} = 60.96$, $p < .001$, $\eta^2 = .19$) yielded significance. No significant main effect was observed for the type of genetic polymorphism ($F_{(2,258)} = 1.06$, $p > .34$, $\eta^2 = .01$). The number of correct responses decreased with saliency increase of the orientation change (strong *vs*. weak transient) from 75.11 (±.69) to 77.11 (±.68). Overall conditions, subjects homozygous for the Met allele accomplished fewer correct responses (75,00 ± 1.17) than subjects heterozygous (Val/Met, 76.45 ± .98) or homozygous for the Val allele (77.54 ± 1.34).

The effects of genotype and change condition were involved in a two-way interaction ($F_{(6,774)} = 3.19$, $p < .01$, $\eta^2 = .02$) (Fig. 2A). As shown by a post-hoc test ANOVA, the two-way interaction between change condition and genotype was caused by the Val158Met polymorphism group performance differences in the ORI condition with the Met/Met carriers (83.20 ± 1.45) giving less correct responses than the Val/Met (88.31 ± 8.21) and Val/Val carriers (90.97 ± 1.66) ($F(2,258) = 6.81$, $p < .002$, $\eta^2 = .05$). No difference was found between the Val/Met and Val/Val carrier subjects in the ORI condition ($p > .58$) and no three-way interaction between type of transient, genotype and change condition was evident ($F_{(6,945)} = 1.26$, $p > .27$, $\eta^2 = .01$).

A more detailed analysis of the errors in the ORI condition revealed that in average 12% (22.57 ± 1.53) were choice errors and .83% (1.59 ± .21) were misses. The three genotype groups did not differ in the absolute frequency of misses (($F_{(2,258)} = .51$, $p > .60$, $\eta^2 = .004$)), but in the absolute frequency of choice errors in the ORI condition. The Val/Val (15.39 ± 3.07) and Val/Met (20.80 ± 2.23)

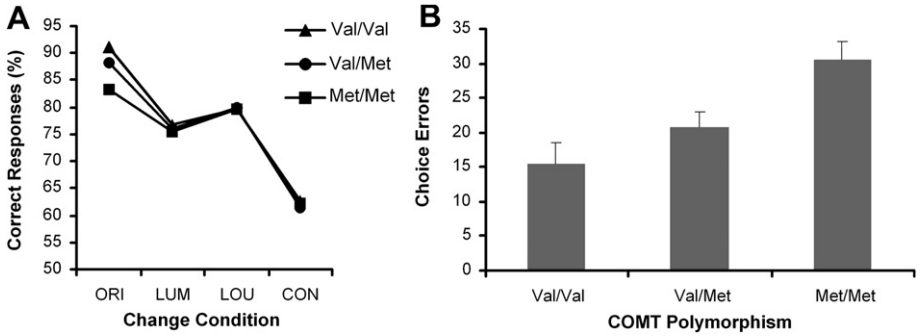

Fig. 2. Performance in the change detection task. A) Correct responses (%) in the four conditions of the change detection task depending on the *COMT* Val158Met polymorphism. B) Mean error rates for choice errors in the ORI condition with respect to COMT genotype; error bars depict the standard error.

genotype subjects made significantly less choice errors than the Met/Met subjects (30.52 ± 2.67) ($F_{(2,258)} = 7.50$, $p < .002$, $\eta^2 = .06$), whereas the Val/Val carriers did not differ from subjects heterozygous for the Val/Met polymorphism ($F_{(1,177)} = 3.22$, $p > .07$, $\eta^2 = .02$). Regarding both types of errors, no differences between the three genotype groups were observable in the other conditions LUM, LOU and CON (all p's $> .84$) (Fig. 2B).

Another two-way interaction was present between type of transient and change condition ($F_{(3,774)} = 51.49$, $p < .001$, $\eta^2 = .17$). Bonferroni-corrected pair-wise comparisons revealed that correct response rates were significantly higher in the weak change transient conditions compared to the strong change transient conditions for ORI (weak: 88.0700 ± .81, strong: 86.60 ± .88) ($T_{(260)} = -4{,}35$, $p < .001$) and CON (weak: 64.64 ± .88, strong: 59.32 ± .98) ($T_{(260)} = 10.98$, $p < .001$), but not for LUM (weak: 75.75 ± .82, strong: 76.30 ± .80) ($T_{(260)} = -1.68$, $p = .10$) and LOU (weak: 79.48 ± .72, strong: 79.87 ± .77) ($T_{(260)} = -1.05$, $p = .30$).

No main effects or interactions were found for genotype with respect to reaction times (all p's $> .28$). Thus, no speed-accuracy trade off occurred.

The same analyses as for the *COMT* polymorphism were conducted for the *DAT1* polymorphism. These analyses did not reveal any significant results for genotype (all p's $> .14$).

Due to our sample size, it was not possible to account for gene–gene interactions or additive effects (refer Table 1 for cross table of genotype frequencies).

4. Discussion

This study investigated how performance in a change detection task is modulated by *COMT* Val158Met and *DAT1* genetic polymorphisms, which affect cognitive and behavioural flexibility as well as attentional control as important executive subprocesses.

In line with Wascher and Beste (2010), performance declined when strong, compared to weak change transients were used. The ability to detect luminance changes was especially compromised in the CON condition where a perceptual conflict emerges between change of luminance on the one side and orientation change on the other side. Under such conditions, the detection efficiency of the luminance change as the target stimuli depends on the saliency of the competing stimuli (orientation change) (Wascher and Beste, 2010). Compared to subjects homozygous for the *COMT* 158 Val allele and heterozygous Val/Met carriers, subjects homozygous for the Met allele made more errors in the ORI condition, where no luminance change occurred and an orientation change had to be detected. The higher error rate in the group of Met/Met subjects was due to a higher number of choice errors and not to a higher frequency of misses. No significant differences between the three genotype groups were found in the CON condition and generally no associations were obtained for the *DAT1* VNTR polymorphism.

The finding that the *COMT* Val158Met polymorphism influences performance in a change detection task provides further support for an important role of DA in executive processes. Several studies showed, that the dorsolateral prefrontal cortex (DLPFC) and the parietal cortex are important for these goal-directed control processes (e.g. Botvinick et al., 1999; Carter et al., 2000; Casey et al., 2000; Desimone and Duncan, 1995; Durston et al., 2003).

Since DA levels in the PFC are higher in Met/Met homozygous individuals compared to Val/Val homozygous subjects (Bilder et al., 2004; Cools, 2006), it can be assumed that these individuals might show difficulties in responding, when switching from one task set to another is required in a certain task (Arnsten and Pliszka, 2011; Cools and Robbins, 2004; Goldman-Rakic, 1992). This behavioural inflexibility causes difficulties in Met allele carriers to respond correctly upon orientation changes in the ORI condition, in which flexible behavioural adjustment to a new task set is essential for good performance. In the ORI condition, subjects have to tune their response set in terms of responding to the rarely occurring orientation change (25%) instead of responding to the more often appearing luminance change (75%). Based on our data, it can be concluded that Met/Met carriers are not able to flexibly adjust their response set, if this is required by a sudden change in the task set. Moreover, the behavioural inflexibility deficit in the Met/Met subject group can be explained on the basis of an action selection deficit due to cognitive and, as a result of this, behavioural flexibility.

The reason why especially Met/Met genotype carriers reveal these deficits can be inferred from the inverted "*U*" shaped curve model describing the relationship between the DA concentration and cognitive control (e.g. Cools and D'Esposito, 2011; Mattay et al., 2003; Seamans and Yang, 2004; Vijayaraghavan et al., 2007). According to this model, deviance from an optimal DA level (i.e. a too low or a too high DA level) compromises cognition. Several studies dealing with the influence of the *COMT* polymorphism revealed that the high activity Val allele is associated with decreased cognitive stability in PFC attention networks, but with enhanced updating ability for new information (Bilder et al., 2004; Winterer and Weinberger, 2004). Opposed to this, the Met allele is

Table 1
Distribution of the genetic polymorphisms.

		Val/Val	Val/Met	Met/Met	
DAT1	9/9	3	7	7	17
	9/10	24	33	27	84
	10/10	30	71	42	143
		57	111	76	244

associated with increased cognitive stability and therefore impairs an individual's cognitive and behavioural flexibility (e.g. Colzato et al., 2010a,b; Goldberg et al., 2003; Nolan et al., 2004; Savitz et al., 2006). The finding that no effect of the *DAT1* VNTR polymorphism was evident regarding the performance in our change detection paradigm possibly suggests that the striatal part of the basal ganglia-prefrontal loop (Chudasama and Robbins, 2006), operating via D2 receptors is not important for performance in change detection. Instead, the observed results are presumably due to the D1 receptor mediated mechanisms in the PFC. Based on its distribution in the human brain, the D1 receptor is specifically important for the stabilization of activity patterns in the PFC neural networks and DA action on this receptor type is modulated in particular by *COMT* activity (see e.g. Palner et al., 2010; Weinberger et al., 2001). Additionally, DA stabilizes goal representations or rather intentions and response sets in the PFC (Durstewitz et al., 1999).

Yet, contrary to our predictions, no modulatory effect of *COMT* Val158Met genotypes on performance was evident in the conflict condition in our change detection task. The behavioural data revealed no interaction between genotype and strength of change transient and no difference between the three *COMT* genotype groups concerning the performance in the conflict condition. The change transient has been varied to modulate visual perceptual processes in order to scale the degree of perceptual competition in the conflict condition (Wascher and Beste, 2010). Thus, the conflict condition can be taken as a measurement of attentional control (e.g. Beste et al., 2011; Sänger and Wascher, 2011; Wascher and Beste, 2010). The fact that the *COMT* genotype did not modulate these two processes, argues for an influence of this genetic polymorphism on behavioural flexibility in terms of action selection. Along this line, our results can also be further interpretated in terms of response inhibition processes. Subjects carrying at least one Val allele were better than Met/Met carriers at withholding their response to the very salient luminance change for the benefit of correctly responding to the orientation change. This is especially noteworthy because responding to the luminance change is part of the subject's task set in most of the trials. In this context, Krämer et al. (2007) found that subjects homozygous for the Val allele displayed amplified neurophysiological processes reflecting behavioural inhibition. Moreover, Congdon et al. (2009) investigated the influence of the *COMT* polymorphism on the performance in a stop signal task by using fMRI and concluded that an optimal range of dopamine is necessary for efficient behavioural inhibition processes.

Specific modulation of distinct prefrontal cognitive processes via monoaminergic systems were also found in other studies in the past (e.g. Robbins and Roberts, 2007). However, it may be argued that possible effects of COMT and DAT1 genotypes on attentional control processes are too small to be detectable in the current sample. Yet, even this is the case, this would still suggest that the effect of COMT genotype is stronger for processes related to behavioural flexibility, compared to attentional control. With respect to the latter, Beste et al. (2011) showed that performance in the conflict condition is altered by LTP and LTD-like perceptual learning and processes related to glutamatergic neural transmission (Dinse et al., 2003; Seitz and Dinse, 2007). It is therefore conceivable that genetic polymorphisms related to the glutamatergic system may show stronger association with performance in conditions of perceptual conflict.

In summary, our results provide evidence that dopamine plays an essential role in the modulation of behavioural flexibility in a change detection task. The results strongly suggest that, in the context of change detection, this modulation is crucially dependent on prefrontal dopaminergic structures. Our results reveal that no *COMT* Val158Met genotype differences exist regarding the detection of target stimuli changes (luminance change). But Met allele carriers tended to respond inflexibly in terms of choice errors even without occurring changes in the relevant stimulus dimension (orientation change), if the required reaction was only part of the subject's task set in 25% of all trials. Furthermore it was evident, that not all kinds of executive processes are modulated in the same way by the *COMT* polymorphism. The results add to the evidence that altered dopamine signalling induced by variation in *COMT* influences executive processes in a very specific manner.

Acknowledgements

This work was funded by the Rektorat Program of Ruhr-University Bochum to C.B.

References

Arnsten, A.F.T., Pliszka, S.R., 2011. Catecholamine influences on prefrontal cortical function: relevance to treatment of attention deficit/hyperactivity disorder and related disorders. Pharmacol. Biochem. Behav. doi:10.1016/j.pbb.2011.01.020.

Beste, C., Wascher, E., Güntürkün, O., Dinse, H., 2011. Improvement and impairment of visually guided behavior through LTP- and LTD-like exposure-based visual learning. Curr. Biol. 21 (10), 876–882.

Bilder, R., Volavka, K., Lachman, H., Grace, A., 2004. The catechol-methyltransferase polymorphism: relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. Neuropsychopharmacology 29 (11), 1943–1961.

Blasi, G., Mattay, V.S., Bertolino, A., Elvevåg, B., Callicott, J.H., Das, S., Kolachna, B.S., Egan, M.F., Goldberg, T.E., Weinberger, D.R., 2005. Effect of Catechol-*O*-Methyltransferase *val*^{158}*met* genotype on attentional control. J. Neurosci. 25 (20), 5038–5045.

Botvinick, M., Nystrom, L.E., Fissell, K., Carter, C.S., Cohen, J.D., 1999. Conflict monitoring versus selection-for-action in anterior cingulate cortex. Nature 402, 179–181.

Brookes, K.J., Neale, B.M., Sugden, K., Khan, N., Asherson, P., D'Souza, U.M., 2007. Relationship between VNTR polymorphisms of the human dopamine transporter gene and expression in post-mortem midbrain tissue. Am. J. Med. Genet. B 144B, 1070–1078.

Carter, C.S., Macdonald, A.M., Botvinick, M., Ross, L.L., Stenger, V.A., Noll, D., Cohen, J.D., 2000. Parsing executive processes: strategic vs. evaluative functions of the anterior cingulate cortex. Proc. Natl. Acad. Sci. U.S.A. 97 (4), 1944–1948.

Casey, B.J., Thomas, K.M., Welsh, T.F., Badgaiyan, R.D., Eccard, C.H., Jennings, J.R., Crone, E.A., 2000. Dissociation of response conflict, attentional selection, and expectancy with functional magnetic resonance imaging. Proc. Natl. Acad. Sci. U.S.A. 97 (15), 8728–8733.

Chen, J., Lipska, B.K., Halim, N., Ma, Q.D., Matsumoto, M., Melhem, S., Kolachana, B.S., Hyde, T.M., Herman, M.M., Apud, J., Egan, M.F., Kleinman, J.E., Weinberger, D.R., 2004. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. Am. J. Hum. Genet. 75 (5), 807–821.

Chudasama, Y., Robbins, T.W., 2006. Functions of frontostriatal systems in cognition: comparative neuropsychopharmacological studies in rats, monkeys and humans. Biol. Psychol. 73, 19–38.

Colzato, L.S., Pratt, J., Hommel, B., 2010a. Dopaminergic control of attentional flexibility: inhibition of return is associated with the dopamine transporter gene (DAT1). Front. Hum. Neurosci. 4 (53).

Colzato, L.S., Waszak, F., Niewenhuis, S., Posthuma, D., Hommel, B., 2010b. The flexible mind is associated with the catechol-methytransferase (COMT) Val^{158}-Met polymorphism: evidence for a role of dopamine in the control of task switching. Neuropsychologia 48, 2764–2768.

Congdon, E., Constable, R.T., Lesch, K.P., Canli, T., 2009. Influence of SLC6A3 and COMT variation on neural activation during response inhibition. Biol. Psychol. 81 (3), 144–152.

Cools, R., D'Esposito, M., 2011. Inverted-U-shaped dopamine actions on human working memory and cognitive control. Biol. Psychiatry 69 (12), e113–e125.

Cools, R., Robbins, T.W., 2004. Chemistry of the adaptive mind. Philos. Transact. A Math. Phys. Eng. Sci. 362 (1825), 2871–2888.

Cools, R., 2006. Dopaminergic modulation of cognitive function-Implication for L-Dopa therapy in Parkinson's disease. Neurosci. Biobehav. Rev. 30, 1–34.

Cools, R., 2008. Role of dopamine on the motivational and cognitive control of behaviour. Neuroscientist 14, 381–395.

Desimone, R., Duncan, J., 1995. Neural mechanisms of selective visual attention. Annu. Rev. Neurosci. 18, 193–222.

Dickinson, D., Elvevåg, B., 2009. Genes, cognition and brain through a COMT lens. Neuroscience 164 (1), 72–87.

Dinse, H.R., Ragert, P., Pleger, B., Schwenkreis, P., Tegenthoff, M., 2003. Pharmacological modulation of perceptual learning and associated cortical reorganization. Science 301, 91–94.

Durstewitz, D., Kelc, M., Güntürkün, O., 1999. A neurocomputational theory of the dopaminergic modulation of working memory functions. J. Neurosci. 19 (7), 2807–2822.
Durston, S., Davidson, M.C., Thomas, K.M., Worden, M.S., Tottenham, N., Martinez, A., Watts, R., Ulug, A.M., Casey, B.J., 2003. Parametric manipulation of conflict and response competition using rapid mixed-trial event-related fMRI. Neuroimage 20 (4), 2135–2141.
Egan, M.F., Goldberg, T.E., Kolachana, B.S., Callicott, J.H., Mazzanti, C.M., Straub, R.E., Goldman, D., Weinberger, D.R., 2001. Effect of COMT $Val^{108/158}$ Met genotype on frontal lobe function and risk for schizophrenia. Proc. Natl. Acad. Sci. U.S.A. 98 (12), 6917–6922.
Egeth, H.E., Yantis, S., 1997. Visual attention: control, representation, and time course. Annu. Rev. Psychol. 48, 269–297.
Folk, C.L., Remington, R., 1999. Can new objects override attentional control settings? Percept. Psychophys. 61 (4), 727–739.
Garcia-Garcia, M., Barceló, F., Clemente, I.C., Escera, C., 2010. The role of the dopamine transporter gene DAT1 genotype on the neural correlates of cognitive flexibility. Eur. J. Neurosci. 31 (4), 754–760.
Giros, B., Mestikawy, S., Godinot, N., Zheng, K., Han, H., Yang-Feng, T., Caron, M.G., 1992. Cloning pharmacological characterization, and chromosome assignment of the human dopamine transporter. Mol. Pharmacol. 42, 383–390.
Goldberg, T.E., Egan, M.F., Gscheidle, T., Coppola, R., Weickert, T., Kolachana, B.S., Goldman, D., Weinberger, D.R., 2003. Executive subprocesses in working memory: relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. Arch. Gen. Psychiatry 60 (9), 889–896.
Goldman-Rakic, P., 1992. Dopamine-mediated mechanisms of the prefrontal cortex. Seminars in the Neurosciences 4, 149–159.
Knudsen, E.I., 2007. Fundamental components of attention. Annu. Rev. Neurosci. 27, 611–647.
Krämer, U.M., Cunirella, T., Càmara, E., Marco-Pallarés, J., Cucurell, D., Nager, W., et al., 2007. The impact of Catechol-*O*-Methyltransferase and dopamine D4 receptor genotypes on neurophysiological markers of performance monitoring. J. Neurosci. 27 (51), 14190–14198.
Mattay, V.S., Goldberg, T.E., Fera, F., Hariri, A.R., Tessitore, A., Egan, M.F., Kolachana, B., Callicott, J.H., Weinberger, D.R., 2003. Catechol O-methyltransferase val 158-met and individual variation in the brain response to amphetamine. Proc. Natl. Acad. Sci. U.S.A. 100 (10), 6186–6191.
Maunsell, J.H., Treue, S., 2006. Feature-based attention in visual cortex. Trends Neurosci. 29, 317–322.
Meyer-Lindenberg, A., Weinberger, D.R., 2006. Intermediate phenotypes and genetic mechanisms of psychiatric disorders. Nat. Rev. Neurosci. 7 (10), 818–827.
Mill, J., Asherson, P., Browes, C., D'Souza, U., Craig, I., 2002. Expression of the dopamine transporter gene is regulated by the 3_ UTR VNTR: evidence from brain and lymphocytes using quantitative RT-PCR. Am. J. Med. Genet. 114, 975–979.
Miller, E.K., Cohen, J.D., 2001. An integrative theory of prefrontal cortex function. Annu. Rev. Neurosci. 24, 167–202.
Mitchell, R.J., Howlett, S., Earl, L., White, N.G., McComb, J., Shanfield, M.S., Briceno, I., Papiha, S.S., Osipova, L., Livshits, G., Leonard, W.R., Crawford, M.H., 2000. Distribution of the 3′VNTR polymorphism in the human dopamine transporter gene in world populations. Hum. Biol. 72, 295–304.
Nolan, K.A., Bilder, R.M., Lachman, H.M., Volavka, J., 2004. Catechol O-methyltransferase polymorphism in schizophrenia: different effects of val and met alleles on cognitive stability and flexibility. Am. J. Psychiatry 161 (2), 359–361.
Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edingburgh inventory. Neuropsychologia 9, 97–113.
Palner, M., McCormick, P., Parkes, J., Knudsen, G.M., Wilson, A.A., 2010. Systemic catechol-O-methyl transferase inhibition enables the D1 agonist radiotracer R-[11C]SKF 82957. Nucl. Med. Biol. 37 (7), 837–843.
Robbins, T.W., Roberts, A.C., 2007. Differential regulation of fronto-executive function by monoamines and acetylcholine. Cereb. Cortex 17, 151–160.
Sänger, J., Wascher, E., 2011. The influence of extrinsic motivation on competition – based selection. Behav. Brain Res. 224 (1), 58–64.
Savitz, J., Solms, M., Ramesar, R., 2006. The molecular genetics of cognition: dopamine, COMT and BDNF. Genes Brain Behav. 5, 311–328.
Seamans, J.K., Yang, C.R., 2004. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. Prog. Neurobiol. 74 (1), 1–58.
Seitz, A.R., Dinse, H.R., 2007. A common framework for perceptual learning. Curr. Opin. Neurobiol. 17, 148–153.
Simons, D.J., Rensink, R.A., 2005. Change blindness: past present, and future. Trends Cogn. Sci. 9 (1), 16–20.
Spielman, R.S., Weinshilboum, R.M., 1981. Genetics of red cell COMT activity: analysis of thermal stability and family data. Am. J. Med. Genet. 10, 279–290.
Sussman, E., Winkler, I., Wang, W., 2003. MMN and attention: competition for deviance detection. Psychophysiology 40, 430–435.
Theeuwes, J., 2010. Top-down and bottom-up control of visual selection. Acta Psychol. 135 (2), 77–99.
Uhl, G.R., 2003. Dopamine transporter: basic science and human variation of a key molecule for dopaminergic function, locomotion, and parkinsonism. Mov. Disord. 18 (7), 71–80.
Van Schouwenburg, M., Aarts, E., Cools, R., 2010. Dopaminergic modulation of cognitive control: distinct roles for the prefrontal cortex and basal ganglia. Curr. Pharm. Des. 16, 2026–2032.
Vandenberg, D.J., Persico, A.M., Hawkins, A.L., Griffin, C.A., Li, X., Jabs, E.W., Uhl, G.R., 1992. Human dopamine transporter gene maps to chromosome 5p15.3 and displays a VNTR. Genomics 14, 1104–1106.
Vijayaraghavan, S., Wang, M., Birnbaum, S.G., Williams, G.V., Arnsten, A.F., 2007. Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. Nat. Neurosci. 10 (3), 376–384.
Wascher, E., Beste, C., 2010. Tuning perceptual competition. J. Neurophysiol. 103 (2), 1057–1065.
Weinberger, D.R., Egan, M.F., Bertolino, A., Callicott, J.H., Mattay, V.S., Lipska, B.K., Berman, K.F., Goldberg, T.E., 2001. Prefrontal neurons and the genetics of schizophrenia. Biol. Psychiatry 50 (11), 825–844.
Weinshilboum, R.M., Otterness, D.M., Szumlanski, C.L., 1999. Methylation pharmacogenetics: catechol-O-methyltransferase, thiopurine methyltransferase, and histamine N-methyltransferase. Annu. Rev. Pharmacol. Toxicol. 39, 19–52.
Winterer, G., Weinberger, D.R., 2004. Genes, dopamine and cortical signal-to-noise ratio in schizophrenia. Trends Neurosci. 27 (11), 683–690.