Neurophysiological markers of novelty processing are modulated by COMT and DRD4 genotypes

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ABSTRACT

Humans are faced with the dilemma to maintain a stable cognitive set on the one hand and to be able to redirect and switch attention to novel stimuli of potential importance. The dopaminergic system has been implicated in the balance between these two antagonistic constraints and in particular in novelty processing. Here we studied the impact of two polymorphisms affecting dopaminergic functioning (COMT Val108/158Met and DRD4 SNP −521) on neurophysiological correlates of novelty processing. Recording event-related potentials (ERPs) and oscillatory activity in a modified oddball task that featured infrequent but task-irrelevant novel sounds in addition to frequent standard and rare target tones, we examined participants homozygous for the Met or Val variant of COMT as well as homozygous for the C or T variant of DRD4. We found effects mainly on the P3a component to novel stimuli. A greater P3a amplitude was found for the COMT-ValVal group relative to MetMet. There was a tendency for DRD4-TT participants to show greater P3a amplitude and shorter P3a latency. Finally, DRD4-TT and COMT-ValVal participants showed the greatest increase of theta-power to novel stimuli. By contrast, the P3b component to target stimuli showed little influence of the studied polymorphism. Individual differences in dopaminergic genes explain part of the interindividual variance in the neural correlates of novelty but not target processing.

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Introduction

Humans are faced with the necessity to react to novel, surprising stimuli as these are of potential significance. Such stimuli are processed preferentially by the human brain and are known to capture attention (Öhman, 1979) by eliciting an orienting response and, therefore, are likely to initiate a call for attention. On the other hand, distraction by novel stimuli might interrupt important ongoing activity, such as the processing of an attentionally demanding task. As a consequence, for optimal behavior, organisms are faced with the dilemma to keep a balance between two antagonistic constraints: the stable maintenance of an attentional set and the flexible switching to novel and potentially important events. As has been pointed out by Goschke (2003), favoring one of the constraints over the other would lead to suboptimal behavior: if a person is not able to shield intentions and goals from interfering novel stimuli, he or she will show dis-

tractibility and impulsivity. On the other hand, if a person is not able to flexibly update a currently active cognitive set and switch to an important stimulus, perseverative behavior and behavioral rigidity will result.

Genetic variability in the dopaminergic system and novelty processing

The present study aimed to pinpoint the role of the dopaminergic system in attentional control and in particular in the processing of novel stimuli. We investigated the impact of two dopaminergic polymorphisms (COMT Val108/158Met and DRD4 SNP −521) on an electrophysiological marker of novelty processing, the auditory P3a component of the event-related brain potential (ERP).

DRD4

The highly polymorphic dopamine D4 receptor (DRD4) gene shows preferential expression in prefrontal cortex (PFC) (Oak et al., 2000), which plays an essential role in regulating the direction of attention and, specifically, in processing novelty (Knight, 1984, 1991). Of particular relevance to the present investigation, polymorphisms of

the DRD4, including the single nucleotide polymorphism located at position −521 in the promoter region (C to T substitution), have been implicated in ADHD (Bellgrove et al., 2005; Faraone et al., 2005), a disorder characterized by increased distractibility. Several studies have also linked this polymorphism to the personality trait novelty seeking and have demonstrated that CC homozygotes have higher novelty seeking scores (Bookman et al., 2002; Eichhammer et al., 2005; Golimbet et al., 2006, 2007; Okuyama et al., 2000; Ronai et al., 2001; but see Mitsuyasu et al., 2001, for an exception). On the molecular level, the T-allele results in 40% reduction of transcriptional efficiency (Okuyama et al., 1999, but see Kereszturi et al., 2006). On the basis of these prior findings, we hypothesized that electrophysiological effects to novel stimuli should be smaller in TT participants compared to CC carriers.

COMT

COMT is an enzyme involved in DA degradation, mostly present in the prefrontal cortex (Chen et al., 2004). A common polymorphism at codon 158/108 (valine/methionine exchange) is associated with a three- to fourfold variation in the enzymatic activity. As a result, persons homozygous for the Val/Val allele have a fourfold higher COMT activity in the prefrontal cortex compared to Met/Met carriers. This leads to lower tonic DA levels and therefore an inhibition of prefrontal functioning. More importantly, several authors have pointed out that different levels of prefrontal dopamine lead (via glutamatergic projections to the striatum and midbrain) to effects on phasic dopamine release in the striatum (Bilder et al., 2004; Meyer-Lindenberg and Weinberger, 2006): Val/Val carriers are thought to have low tonic prefrontal but high phasic subcortical dopaminergic responses, whereas for the Met/Met carriers the opposite is supposed. This is thought to result in increased cognitive stability but decreased flexibility for COMT Met/Met (see also Grace, 1991; Grace et al., 2007). With regard to the stability/flexibility dilemma in the processing of novel stimuli, this would imply a less extensive processing of novel stimuli by Met/Met subjects compare to Val/Val allele. This lead us to hypothesize a greater electrophysiological novelty response in homozygous carriers of the Val allele.

Brain correlates of novelty and the dopaminergic system

For the present study, novelty was operationally defined as a stimulus that differs profoundly from its immediate context, i.e., a complex environmental sound appearing in a sequence of pure tones. With regard to the neurophysiological correlates of novelty processing and the orientation of attention, the recording of event-related brain potentials has revealed a specific component, the auditory P3a for novel stimuli (for reviews, see Escera et al., 2000; Friedman et al., 2001). The P3a response peaks between 250 and 350 ms and has been regarded as an index of novelty processing and/or attention switching. The main generators of the auditory P3a reside in the frontal cortex with additional contributions from auditory cortex (Alho et al., 1998; Knight and Scabini, 1998). Whereas the link of the P3a to novelty processing is solid, several studies have demonstrated the P3a to novel stimuli and the positivity seen for non-novel distracter stimuli are the same (Demiralp et al., 2001; Polich and Comerchero, 2003; Simons et al., 2001; Sawaki and Katayama, 2008). Polich (2003) has suggested that a new stimulus initially engages early focal attention that underlies the generation of the P3a, whereas the subsequent memory comparisons with a target template give rise to a subsequent P3b component which has a more parietal distribution.

There have been very few studies investigating the effects of dopaminergic gene polymorphisms on ERP correlates of novelty processing. Strobel et al. (2004) observed an interactive influence of eyeblink rate (EBR), presumably reflecting tonic dopaminergic activity, and DRD4 exon III polymorphism on the P3a. In another study from the same group, Dreisbach et al. (2005) found an interaction between the EBR and the DRD4 exon III polymorphism. A positive association between EBR and flexibility was only observed in participants with the DRD4 4/7-genotype. Birkas et al. (2006) asked whether DRD4 polymorphisms (exon III repeat and the −521 C/T polymorphisms) affect early (associated with the detection) or rather late (associated with attention redirection) ERP indices of auditory novelty processing in healthy 6-year-old children. Whereas early ERP outcomes related to the detection of novel stimuli were not affected by the polymorphisms, two late negativities (LN1 and LN2) that were interpreted as reflecting reorientation after distraction or additional processing of new information did show an influence of polymorphisms. Specifically, children carrying the T.7 haplotype had significantly smaller LN1 and LN2 amplitudes and also significantly enhanced behavioral resistance to distraction. In the present study, we investigated the combined impact of the two polymorphisms mentioned above (COMT Val108/158Met and DRD4 SNP −521) on neurophysiological correlates of novelty processing (P3a and oscillatory activity) in healthy young adults.

Materials and methods

All procedures were approved by the local ethical institutional review board (IRB00003099).

Participants

The genotyping was performed in a sample of 656 students from the University of Barcelona (491 women; age range from 18 to 56 years, mean = 21.7 years, SD = 3.5 years). From this sample, we recruited 48 participants (31 women; age range = 18–35 years) based on their homozygosity for both DRD4 −521 and COMT polymorphisms for the ERP session (see Supplemental materials for genotyping procedure details). Participants were randomly selected from those fulfilling the criterion of being homozygous and were included in the study if they agreed to participate in several electrophysiological studies. All were right-handed, free of neurological and psychiatric disorders (self-report), and of European ancestry, except for one Peruvian-Spanish man. They were paid for their participation and gave written informed consent. We included only participants who were homozygous for both polymorphisms, yielding a 2 × 2 factorial design with the four groups TT-ValVal, TT-MetMet, CC-ValVal, and CC-MetMet. One TT-MetMet subject and one TT-ValVal subject were excluded because of a genotyping error. One CC-ValVal subject was excluded from the study because she selected correctly a very low number of targets (15%). The final set included 11 participants in the TT-MetMet, TT-ValVal, and CC-ValVal groups and 12 in the CC-MetMet. Demographic data of all the groups are summarized in Table 1.

Paradigm

We used a modified auditory oddball task in which subjects were instructed to respond to an infrequent target tone (1620 Hz, 60-ms duration, 5-ms rise/fall times, 60 dB SPL) that occurred with a $P = 0.1$ in a stream of standard tones (1500 Hz, 60-ms duration, 5-ms rise/fall times, 60 dB SPL) that occurred with a probability of $P = 0.8$. In addition, irrelevant natural novel sounds, such as the barking of a dog or the honking of a car, were delivered with $P = 0.1$ (duration of novel sounds between 120 and 410 ms, 60 dB SPL). Subjects were instructed to ignore standard and novel tones and to respond as quickly and accurately as possible with their right index finger to target tones.

ERPs

The electroencephalogram (EEG) was recorded from 29 tin electrodes mounted in an elastic cap (electrode positions: Fp1/2,

Table 1
Demographic, behavioral, and EEG data.

	CC-MetMet	CC-ValVal	TT-MetMet	TT-ValVal
N	12	11	11	11
Sex (F/M)	7/5	7/4	7/4	9/2
Age (mean, years)	20.7	21.5	24.5	22.1
RT (target)	526.9	558.7	572.7	553.6
% Misses	8.9	6.0	7.5	5.3
No. false alarms	8.9	8.3	8.5	7.0
% Artifact rejections	13.1	8.2	12.9	13.7

N is the number of subjects in each group. RT refers to mean reaction time of target responses in milliseconds. % misses refers to percentage of non-answered trials of all target trials. No. false alarms is the total number of responses in non-target trials. % artifact rejection means the average percentage of rejected EEG epochs due to artifacts.

F3/4, C3/4, P3/4, O1/2, F7/8, T3/4, T5/6, FC1/2, FC5/6, CP1/2, CP5/6, PO1/2, Fz, Cz, Pz) with reference electrodes placed on the right and left mastoids. All scalp electrodes were recorded with an average reference and offline re-referenced against the algebraic mean of the activity at the two mastoid electrodes. Electrode impedances were kept below 5 kΩ. Vertical eye movements and blinks were monitored by an electrode placed below the right eye. EEG and EOG were recorded continuously and digitized with a sampling rate of 250 Hz (band-pass filtered from 0.01 to 70 Hz). Stimulus-locked averages were obtained for the different conditions (−100 to 1000 ms), with a baseline located in the 100 ms preceding the stimulus. Epochs exceeding ±100 μV in EOG or EEG were removed from further analysis.

We performed two complementary statistical analyses. First, we computed the mean amplitude 100 ms around the grand average peak of the studied component (i.e., P3a or P3b) and we computed a repeated measures ANOVA with the between-subject factors COMT (MetMet vs. ValVal) and DRD4 (TT vs. CC) and the within-subject factors electrode position. For all statistical effects involving more than one degree of freedom in the numerator, the Greenhouse–Geisser correction was applied to correct for possible violations of the sphericity assumption. The corrected probabilities together with the corresponding ε-values are reported. Second, in order to avoid problems due to the different individual latencies of the studied P3 components, we computed for each subject the peak amplitude and latency of the studied component in the electrode that presented greater amplitude (Cz for P3a and Pz for P3b). We then computed an ANOVA of individual peak amplitudes and latencies with the genetic groups as between-subject factors.

To study time-frequency behavior of the electrical activity elicited by the different conditions, single-trial data (−2000 ms before to 2000 ms after the stimulus) were convoluted using a complex Morlet wavelet:

$$w(t, f_0) = \left(2\pi\sigma_t^2\right)^{-1/2} e^{\frac{-t^2}{2\sigma_t^2}} e^{2i\pi f_0 t}$$

The relation f_0/σ_f (where $\sigma_f = 1/(2\pi\sigma_t)$) was set to 6.7 (Tallon-Baudry et al., 1997). Changes in time varying energy (square of the convolution between wavelet and signal) in the studied frequencies (from 1 to 40 Hz; linear increase) with respect to baseline were computed for each trial and averaged for each subject before performing a grand average. Mean increase/decrease values in power were obtained for the different conditions. Given the different window width of the wavelet transform in the different frequencies, time ranges around power peaks were adapted to the frequency range studied. Time-frequency power mean statistical differences were assessed by means of repeated measures ANOVA, as stated above with the ERPs analysis.

Results

Behavioral results

Table 1 summarizes the behavioral results. Mean reaction time to the target stimulus was 552 ± 66 ms. We found no significant effect on the reaction time as a function of genotype ($F(1,42)<2$, $P>0.1$ for DRD4 and COMT main effects and interactions). Percentage of missed targets was 8.9 ± 13. There were no significant differences between genetic groups ($F(1,42)<1.1$, $P>0.3$).

Event-related potentials

The percentage of EEG epochs that were rejected due to artifacts were 12% (± 9), with no difference among the groups (main effects and interaction of COMT and DRD4: $F(1,41)<1.1$; *n.s.*). In Fig. 1, ERPs associated to the standard, target, and novel stimuli are illustrated. A P3b component is present in the target waveforms, whereas a more frontocentrally distributed P3a is seen for the novel stimuli.

In order to isolate the neural correlates of target and novelty processing, difference waveforms were obtained by subtracting ERPs to standard stimuli from ERPs to target and novel stimuli.

Fig. 2A illustrates that the difference between novel and standard conditions showed a positive peak around 300 ms after stimulus onset with a maximum amplitude at the Cz electrode. Fig. 3A shows the mean amplitude measure between 250 and 350 ms for the midline electrodes (Fz, Cz, Pz). Statistically (ANOVA with COMT, DRD4, and midline electrodes as factors), we found a significant COMT main effect ($F(1,41)=5.3$, $P<0.05$; see Supplementary Table 1), reflecting a greater amplitude in the ValVal group, and a marginal DRD4 effect ($F(1,41)=3.3$, $P<0.1$; see Supplementary Table 1), indicating a tendency for an increased P3a component for the TT subjects. Neither a COMT×DRD4 interaction ($F(1,41)=0.3$, *n.s.*) nor significant interactions between electrodes and groups studied ($F(2,82)<1.2$, *n.s.*; see Supplementary Table 1) were found.

The analysis of the P3a peak latency at the Cz electrode revealed a marginal DRD4 effect ($F(1,42)=2.9$, $P<0.1$; see Table 2) with a tendency of the TT group to present a shorter latency. The analysis of the individual novel minus standard peak amplitude at Cz showed a significant effect of the COMT polymorphism ($F(1,42)=8.4$, $P<0.01$) showing a greater P3a amplitude for the ValVal group compared to the MetMet (see Table 2). In addition, we found a marginal DRD4 effect ($F(1,42)=3.6$, $P<0.1$), suggesting a tendency for an increased P3a component for the TT subjects.

Fig. 2B shows that target minus standard difference wave showed the N2b and P3b components. The P3b was quantified by a mean amplitude measure between 450 and 550 ms, as can be seen in Fig. 3B. Statistically (ANOVA with COMT, DRD4, midline electrodes), neither significant differences between groups ($F(1,41)<1$, *n.s.*) nor interactions between group and electrode position ($F(2,82)<1.3$, *n.s.*; see Supplementary Table 1) were found. There were also no group differences for the individual P3b amplitude at the Pz electrode where the P3b is maximal ($F(1,42)<0.3$, *n.s.* for COMT, DRD4, and COMT×DRD4 interaction; see Table 2). A significant DRD4×COMT interaction was found for the P3b latency ($F(1,42)=6.3$, $P<0.05$), indicating a reduced latency for the P3b component in the AA-ValVal (see Table 2).

Time-frequency data

The time-frequency data for the different stimulus classes are shown in Fig. 4. Standard trials were characterized by an increase in the theta range (100–300 ms, 4–8 Hz), while novel trials were characterized by an increase of power between 200 and 500 ms in the theta range (4–8 Hz) and an increase of power between 100 and 200 ms in the low beta (12–15 Hz) frequency band. To parallel the ERP analysis, Fig. 5 shows the power difference between the novel and the
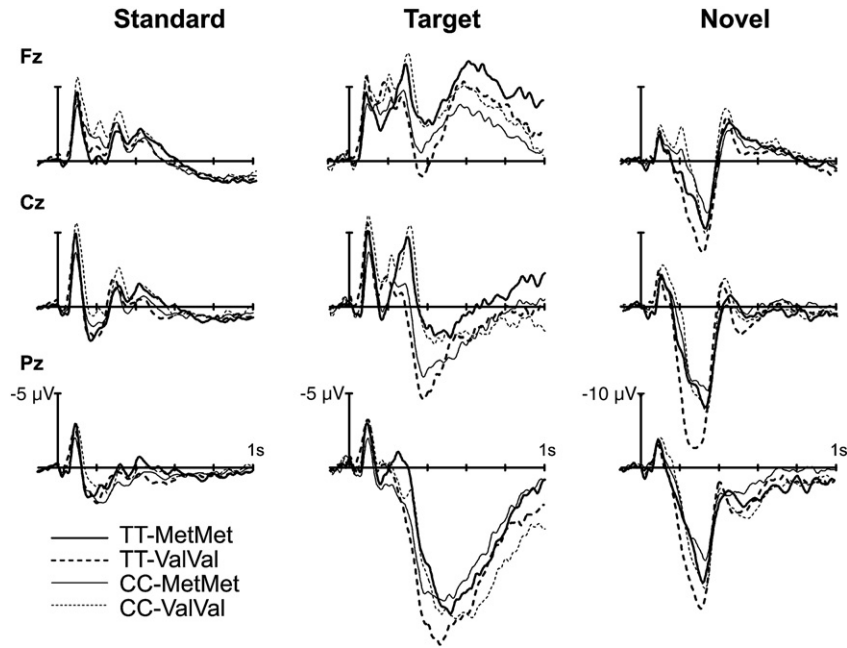
Fig. 1. ERP associated to the standard (left), target (medium), and novel tone (right) for the four groups at Fz (top), Cz (medium), and Pz (bottom). Thick line: TT; thin line: CC; solid line: MetMet; dashed line: ValVal.

standard stimuli. The analysis carried out on these difference data were between 4 and 8 Hz (theta), and 200–500 ms at the three midline electrodes yielded a significant COMT effect ($F(1,42) = 6.5$, $P < 0.05$), reflecting the greater power in the ValVal participants. Moreover, a significant electrode $\times$ DRD4 ($F(2,84) = 3.7$, $\varepsilon = 0.68$,

$P < 0.05$) and electrode $\times$ COMT $\times$ DRD4 interaction ($F(2,84) = 4.9$, $\varepsilon = 0.68$, $P < 0.05$) indicated the greater power of the TT-ValVal group compared to the other groups (see Fig. 5).

We also analyzed the increase in the low beta range in the novel minus standard data (100–200 ms, 12–15 Hz) but found no significant
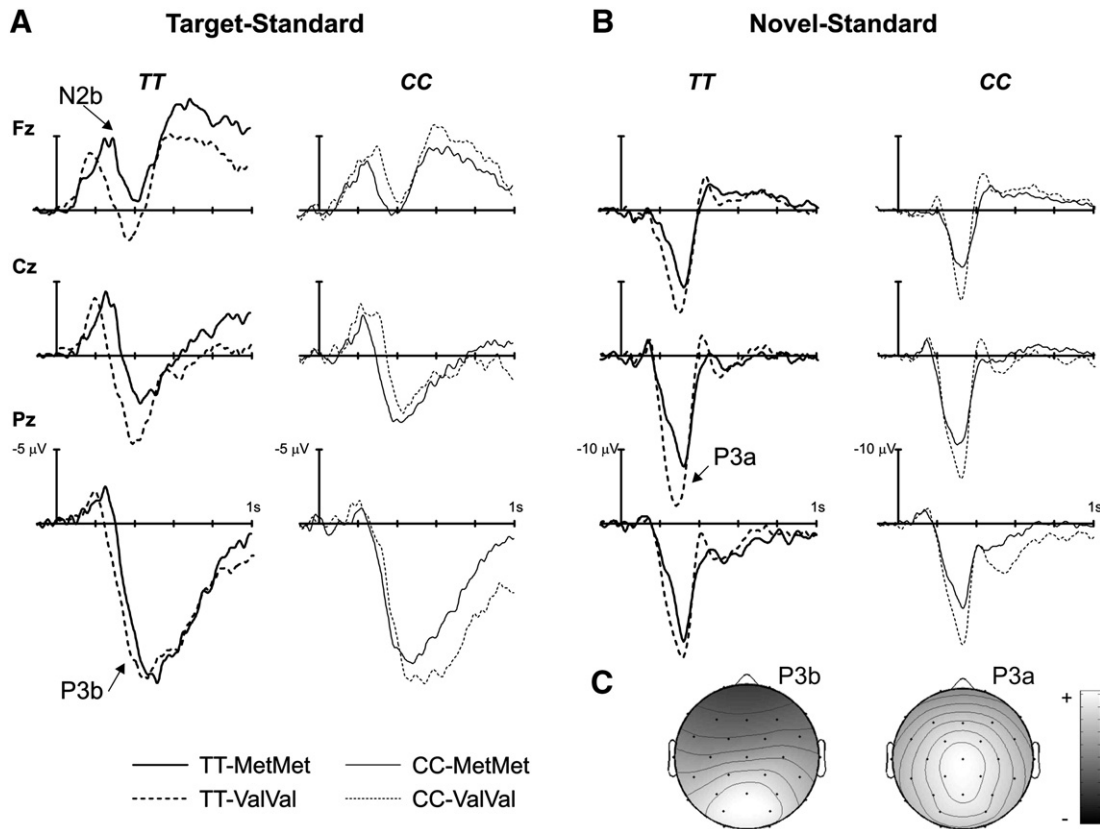

Fig. 2. ERP associated to the target minus standard (A) and novel minus standard (B) conditions for the four groups at Fz (top), Cz (medium), and Pz (bottom). TT: left, thick line; CC: right, thin line; MetMet: solid line; ValVal: dashed line. (C) Voltage distribution of the P3b (left) and P3a (right) ERPs 100 ms around the peak (relative scale, P3b −10/10 μV; P3a −15/15 μV). Note the different distribution of the two components.

A

Target-Standard (450-550 ms)

TT-MetMet CC-MetMet
TT-ValVal CC-ValVal

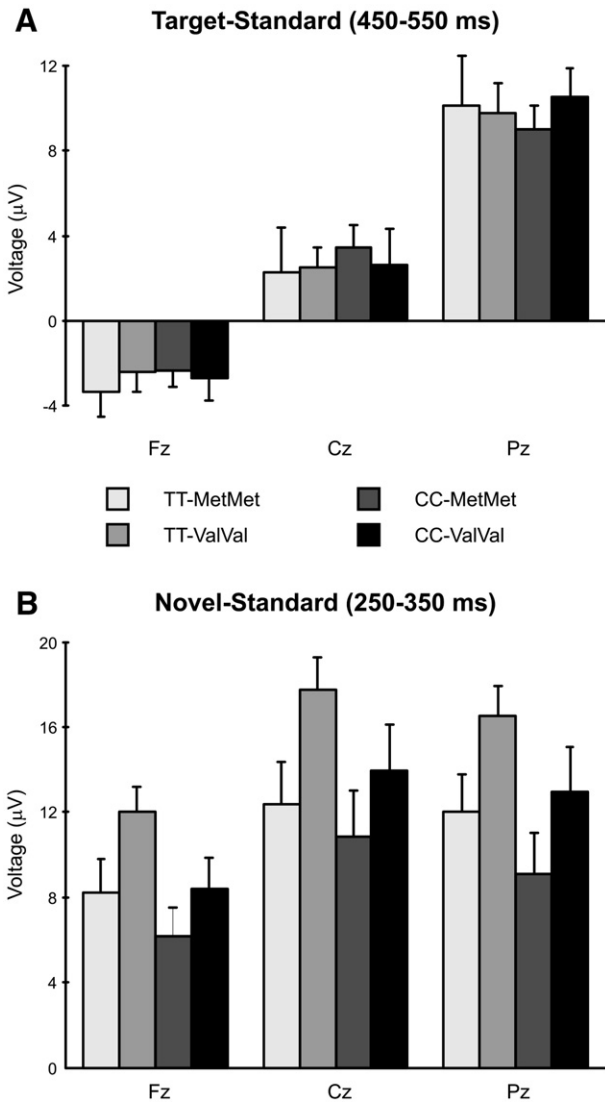**B**

Novel-Standard (250-350 ms)

Fig. 3. Mean amplitude value in the midline electrodes (Fz, Cz, Pz) associated to (A) Target minus standard conditions between 450 and 550 ms and (B) novel minus standard conditions between 250 and 350 ms. Error bars correspond to the standard deviation of the mean.
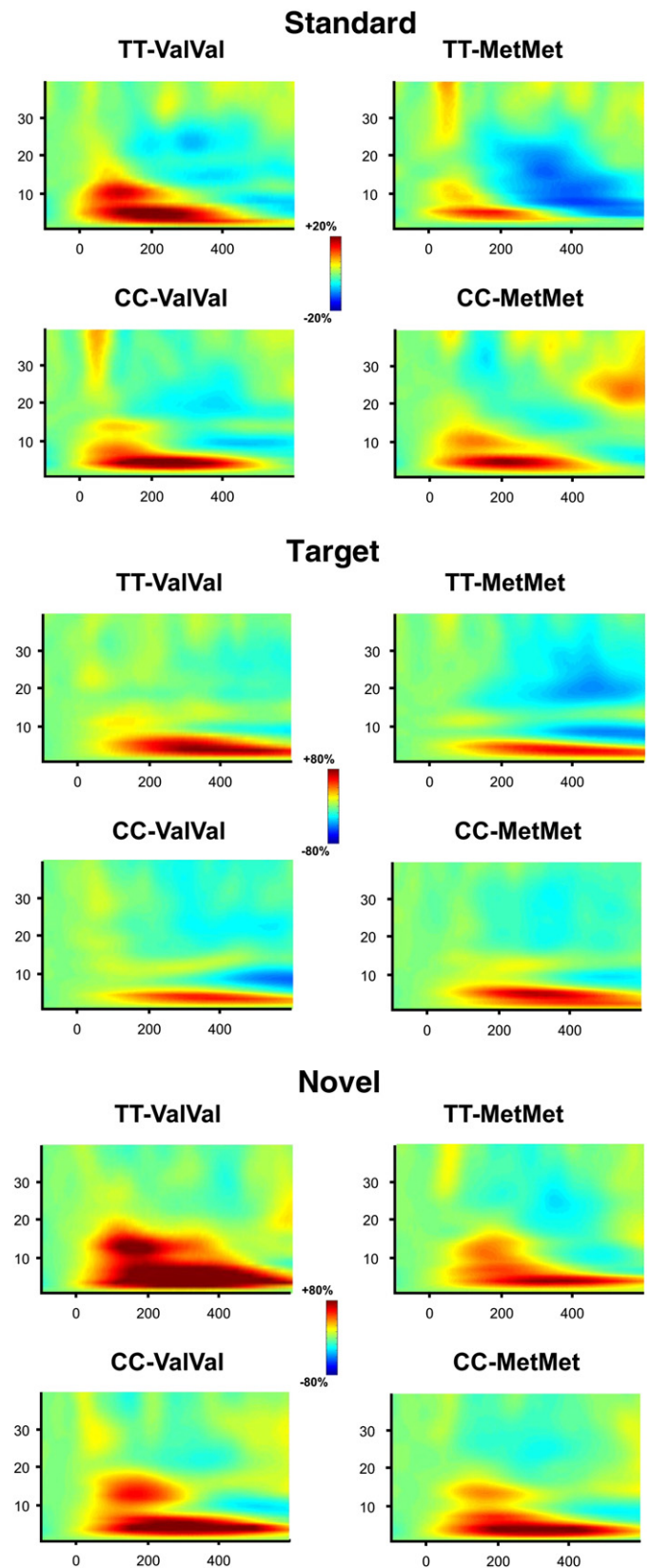

Fig. 4. Changes in power with respect to baseline of (A) standard, (B) target, and (C) novel sounds at Cz. In each condition, the increase/decrease of power is represented from −100 to 600 ms after the presentation of the sound. Top left: TT-ValVal; top right: TT-MetMet; bottom left: CC-ValVal; bottom right: CC-MetMet.

differences for DRD4 and only a marginal effect for COMT ($F(1,42) = 3.8$, $P < 0.1$). Target trials were characterized by a power increase between 200 and 500 ms in the theta range (4–8 Hz, Fig. 4). Analysis of the target minus standard activity (Fig. 5) in the midline electrodes showed a significant DRD4 × COMT interaction in the 200- to 500-ms, 4- to 8-Hz time-frequency range ($F(1,41) = 5.9$, $P < 0.01$), indexing the greater activity of the AA-ValVal group (see Fig. 5) but neither a significant main effect of either polymorphism ($F(1,41) < 1$, n.s.) nor significant interactions with electrode position ($F(2,82) < 0.5$, n.s., see Supplementary Table 2).

Table 2
Latency and amplitude in the difference waveforms.

	CC-MetMet	CC-ValVal	TT-MetMet	TT-ValVal
Amplitude of P3a at Cz (μV)	14.3 ± 7.7	18.3 ± 7.7	16.1 ± 7.2	24.4 ± 5.5
Latency P3a at Cz (ms)	320 ± 52	309 ± 31	303 ± 50	284 ± 27
Amplitude of P3b at Pz (μV)	12.0 ± 3.7	13.3 ± 4.5	12.5 ± 7.8	12.4 ± 4.2
Latency P3b at Pz (ms)	487 ± 79	548 ± 89	515 ± 67	457 ± 78

P3b was measured in the target minus standard condition while P3a was measured in the novel minus standard condition.
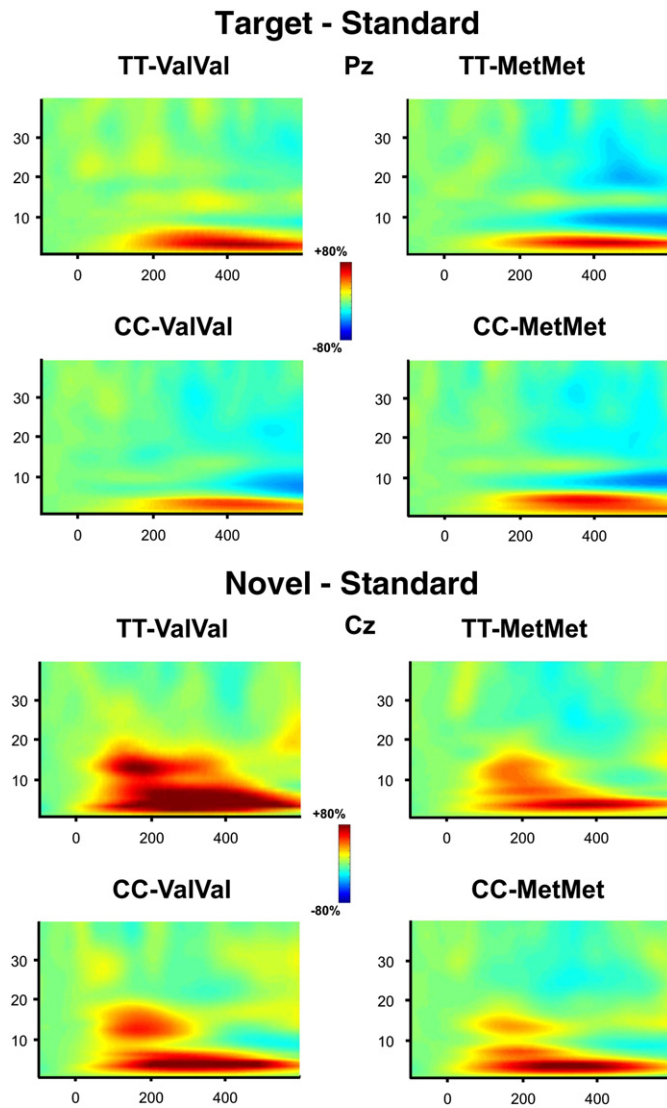
Target - Standard

Pz

Fig. 5. (A) Changes in power with respect to baseline of the target minus standard conditions at Pz. (B) Novel minus standard conditions at Pz. In each condition, the increase/decrease of power is represented from −100 to 600 ms after the presentation of the sound. Top left: TT-ValVal; top right: TT-MetMet; bottom left: CC-ValVal; bottom right: CC-MetMet.

Discussion

The present study demonstrates the impact of two polymorphisms in the dopaminergic system on neurophysiological markers of novelty processing. We have analyzed two groups of subjects homozygous for two dopamine related polymorphisms (COMT Val158Met and DRD4 −521 C/T) allowing a 2×2 factorial design.

Even though findings from twin and family studies regarding the electrophysiological correlates of target and novelty processing have suggested a common genetic background of P3a (novelty) and P3b (target) effects (Frangou et al., 1997; van Beijsterveldt and Boomsma, 1994), our results suggest at least a partial dissociation of the two components with regard to the dopaminergic polymorphisms studied here. For the novel stimuli, a greater P3a amplitude was found for the COMT-ValVal group relative to MetMet participants. Moreover, the TT-ValVal participants showed the greatest increase of theta-power to novel stimuli. We also found a marginal effect of the DRD4 polymorphism on P3a amplitude and latency, reflecting a reduction in the latency and an increase in the amplitude of the P3a for the TT group.

By contrast, the only result for the target stimuli was a slightly earlier peak of the P3b and a greater power in the theta range in the TT-ValVal group compared to the other groups.

P3a to novel stimuli

The P3a component to novel stimuli was sensitive to the studied polymorphisms, as summarized above. The P3a component appears as a response to a task-irrelevant novel tone with a frontocentral maximum and an earlier latency than the P3b and it is thought to reflect the involuntary attention switching towards a change in the environment (Escera et al., 2000). Its main sources are located in the auditory and prefrontal cortex, although other areas such as parietal cortex, anterior cingulate gyrus, parahippocampus/hippocampus, and insula are also involved (Escera et al., 2000; Friedman et al., 2001). Therefore, P3a and P3b components are distinguishable by their different scalp topography, at least partially different generator structure and task sensitivity with the P3a serving as an index for novelty.

Novelty consistently activates the dopaminergic midbrain (Bunzeck et al., 2007; Bunzeck and Düzel, 2006; Schott et al., 2004; Wittmann et al., 2007), which entertains widespread connections to many neocortical and subcortical structures. In light of this involvement of the dopaminergic system, the current results implicating both COMT and DRD4 polymorphisms in the modulation of the novelty response are not surprising. Interestingly, the COMT-ValVal group, which presented a greater P3a amplitude and a higher increase of theta-power activity, is thought to have less tonic dopaminergic activity in the prefrontal cortex. According to the tonic/phasic hypothesis (Bilder et al., 2004; Grace, 1991), this would translate into a greater amplitude of the phasic modulatory dopaminergic signal transmitted from the mesencephalic dopamine system to cortical regions, which in turn might lead to a greater amplitude of the P3a. Hence, the results for the COMT polymorphism are easily accommodated within existing accounts (Bilder et al., 2004; Meyer-Lindenberg et al., 2006).

With regard to the DRD4 polymorphism, the interpretation is less straightforward. The dopamine D4 receptor is expressed mainly in the prefrontal cortex (including ACC), in the amygdala, and in the hippocampus, making a modulatory impact in these areas very likely (Oak et al., 2000). It has been found that the T-allele results in a 40% reduction of transcriptional efficiency (Okuyama et al., 1999). Moreover, studies with D4 receptor knock-out mice suggest that D4 receptor expression rate leads to compensatory changes in mesencephalic dopamine production, resulting in different tonic dopamine levels in participants homozygous for the T- and C-allele in DRD4 (Rubinstein et al., 1997), which should in turn influence phasic dopamine responses and ultimately the amplitude of the P3a component as found in the present investigation.

Although the main effect found for the P3a is due to the COMT polymorphism, the present results also suggest a combined effect of the ValVal and TT alleles as reflected by the power increase in the theta band associated to P3a. The analysis of power data showed a difference between TT-ValVal and CC-ValVal groups as revealed by the significant electrode×COMT×DRD4 interaction and the corresponding pairwise comparisons for the Pz electrode (see also Fig. 4 for a clear power increase of the TT-ValVal group). Therefore, a combination of less tonic dopaminergic activity in prefrontal regions (attributable to COMT-ValVal, see also Gallinat et al., 2003) and less transcriptional efficiency for the D4 receptor (attributable to DRD4-TT) results in a greater theta-power increase.

P3b and oscillatory activity for target stimuli

The P3b is typically observed for stimuli that need attentive processing and have target status (Polich, 2007). It has a maxi-

mum over the posterior midline scalp. The present study revealed no significant differences with regard to P3b amplitude but a small but significant latency effect in terms of a reduced P3b latency in the TT-ValVal group. This pattern echoes findings of Demiralp et al. (2007) who similarly did not find amplitude effects on P3b amplitude of DRD4 (Exon III), DAT1, and COMT polymorphisms.

The time-frequency data yielded an increased activity in the theta range for the TT-ValVal group compared to the other groups. These results show only a marginal susceptibility of the P3b component to genetic variations in the two dopaminergic genes studied. Indeed, there is evidence suggesting that the P3b amplitude might be driven mainly by widespread norepinephrine input to cortical regions (Nieuwenhuis et al., 2005; but for a null effect of the target P3 with noradrenergic modulation, see Riba et al., 2005) which might explain the lack of effects of the current polymorphisms. According to their hypothesis, phasic activity of the locus caeruleus and the resulting release of NE at axon terminals are critical in generating the P3 response. In fact, experiments in monkeys support the interpretation of a noradren-ergic modulation of the P3 (Pineda et al., 1989). With regard to dopamine, it has been reported that neurochemical lesions of the ventral tegmental area of rats caused a marked reduction of dopamine but did not result in amplitude changes in the rat-equivalent of the P3 (Ehlers et al., 1991). Polich and Criado (2006) have reviewed the available evidence on the involvement of the dopaminergic and noradrenergic systems in the generation of the P3a and P3b responses and concluded that the manipulations or conditions (e.g., Parkinson's disease) involving the dopaminergic system tend to influence the anterior P3a, whereas noradrenergic manipulations result in changes of the parietal P3b component. Thus, the lack of a profound modulation of P3b amplitude to target stimuli by the polymorphisms examined in the current study is in line with existing data.

Alternative approaches

Whereas we found clear differences in genetic effects on the P3a and P3b components, a recent study by Liu et al. (2009) rather pointed to a similar genetic background. In 41 normal participants, they conducted a parallel independent component analysis (ICA) of ERP components in a novelty oddball paradigm and a range of SNPs. Using this ICA method, they found that both target detection (indexed by P3b) and novelty processing (P3a) were associated with a largely shared cluster of genes mainly linked to the adrenergic and dopaminergic pathways. In particular, they found effects of 6 genes coding for the alpha2-adrenergic receptor, tyrosine-hydroxylase, apolipoproteine E, malate dehydrogenase 1, ATP-binding cassette (subfamily B, member 1), and phosphoinositide-3-kinase (PIK3C3). The approach taken by Liu et al. (2009x) seems promising but it has to be pointed out that only a rather small sample was screened, participants were not preselected for homozygosity, and that the results are not easily interpreted with regard to the functional effects of single polymorphism on the cellular level.

Conclusion

In conclusion, the present results show that the brain's novelty response is modulated by two polymorphisms of the dopaminergic system (COMT Val108/158Met and DRD4 SNP −521). Obviously, other polymorphisms in this and other transmitter systems need to be investigated. In light of the hypothesis of a noradrenergic involvement in the generation of the target P3b, noradrenergic genes should be assessed as well.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2010.02.012.

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