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DRD4 and DAT1 Polymorphisms Modulate Human Gamma Band Responses

Tamer Demiralp[1,2], Christoph S. Herrmann[2], M. Emin Erdal[3], Tolgay Ergenoglu[4], Yasemin H. Keskin[1], Mehmet Ergen[1] and Hüseyin Beydagi[4]

[1]Department of Physiology, Istanbul Faculty of Medicine, Istanbul University, Turkey, [2]Department of Biological Psychology, Otto-von-Guericke University Magdeburg, Germany, [3]Department of Medical Biology and Genetics, Medical Faculty, Mersin University, Turkey and [4]Department of Physiology, Medical Faculty, Mersin University, Turkey

Gamma oscillations (30–80 Hz) have been demonstrated to be important for perceptual and cognitive processes. Animal and in vitro studies have revealed possible underlying generation mechanisms of the gamma rhythm. However, little is known about the neurochemical modulation of these oscillations during human cognition. Schizophrenia and Attention Deficit Hyperactivity Disorder, which lead to failure of attentional modulation and working memory, introduce significant changes in gamma responses and have significant associations with genetic polymorphisms of dopamine receptor D4 (DRD4), dopamine transporter (DAT), and catechol-*O*-methyltransferase (COMT). Therefore, the presence of direct relations between these polymorphisms and gamma oscillations was investigated in human subjects using an auditory target detection paradigm. The 7-repeat isoform of the DRD4 polymorphism that produces a subsensitive variant of the D4 receptor enhanced the auditory evoked and induced gamma responses to both standard and target stimuli. The 10/10 genotype of the DAT1 polymorphism, which reduces DAT expression and hence yields an increase in extracellular dopamine, specifically enhanced evoked gamma responses to target stimuli. The COMT polymorphism did not significantly change gamma responses. It seems plausible to assume that the modulation pattern of the evoked gamma response by DRD4 polymorphism relates to reduced inhibition via the D4 receptor, whereas the DAT1 effect is related to the target detection mechanism probably mediated by the D1 receptor.

Keywords: ADHD, COMT, dopamine, gamma band response, schizophrenia

Introduction

Electrophysiological recordings in different species indicate that gamma oscillations (30–70 Hz) in the brain are associated with a variety of fundamental perceptual and cognitive processes (Freeman 1975; Gray and others 1989; Pantev and others 1991; Basar-Eroglu and others 1996; Demiralp and others 1996; Karakas and Basar 1998; Basar, Basar-Eroglu, and others 2001; Basar, Schürmann, and others 2001; Engel and others 2001). Possible generation mechanisms such as intrinsic oscillatory membrane properties of chattering cells (Gray and McCormick 1996), thalamocortical resonant loops (Llinas and Ribary 1993), and the interaction of the glutamatergic pyramidal cells and γ-aminobutyric acidergic (GABAergic) inhibitory interneurons (Traub and others 1999) have been proposed for gamma oscillations. Additionally, Schutt and Basar (1992) showed that dopamine enhanced evoked gamma oscillations in the visceral ganglia of the helix pomatia. Even though cognitive tasks like attention and working memory, which are known to depend upon the level of dopamine (Müller and others 1998; Durstewitz, Kelc, and Güntürkün 1999; Durstewitz and others 2000), modulate both evoked (Tiitinen and others 1993; Herrmann and Mecklinger 2001; Herrmann, Lenz, and others 2004) and induced gamma oscillations (Tallon-Baudry and others 1997; Gruber and others 1999; Fries and others 2001; Gruber and Muller 2005), little is known about the neurochemical basis of such modulation of gamma band responses (GBRs) during cognitive processes (Ahveninen and others 2000).

Associations of certain cognitive disorders with changes of the gamma oscillations as well as with genetic polymorphisms of specific neurotransmission components open a new path for such investigation. Significant changes in the gamma responses have been observed in schizophrenia and Attention Deficit Hyperactivity Disorder (ADHD), which accompany a dysfunction of attentional modulation and working memory deficits. With an auditory target detection paradigm, higher amplitudes of evoked gamma oscillations and stronger phase locking to the stimulus were observed in ADHD children compared with normal children (Yordanova and others 2001). For schizophrenic patients, a reduction of their evoked gamma responses has been demonstrated repeatedly (Clementz and others 1997; Haig and others 2000; Spencer and others 2003; Gallinat and others 2004). An increase of gamma activity in spontaneous electroencephalogram (EEG) during hallucinations seemed to be in contradiction to these findings (Baldeweg and others 1998). However, a recent study showed that negative symptoms are correlated with a reduction of gamma synchrony, whereas for predominantly positive symptoms gamma synchrony increases significantly compared with a healthy group (Lee and others 2003).

Both disorders also have significant associations with 3 genetic polymorphisms concerning the dopamine system, which is critical for cognitive functions such as executive cognition and working memory (Sawaguchi and Goldman-Rakic 1994; Durstewitz, Kelc, and Güntürkün 1999; Durstewitz, Kroner, and Güntürkün 1999; Durstewitz and others 2000). Polymorphisms of the dopamine receptor D4 (DRD4) gene, dopamine transporter (DAT1) gene, and catechol-*O*-methyltransferase (COMT) gene showed significant associations with schizophrenia (COMT: Eisenberg and others 1999; Herken and Erdal 2001) and ADHD (DRD4: Oak and others 2000; Faraone and others 2001, DAT1: Cook and others 1995; Gill and others 1997).

Investigation of the electrophysiological correlates of genetic polymorphisms of specific components of neurotransmitter systems has important advantages compared with classical neuropharmacological studies on cognition (Porjesz and others 2002). First, human experiments are necessary for observing specific cognitive effects, which limits the neuropharmacological research to substances that are certified for medical use. Second, although the specificity increases with every new

generation of drugs, they still act on various sites making it difficult to obtain a final conclusion on the neurochemical mechanisms. Additionally, drug responsiveness is variable in the population as a consequence of genotype. While the application of a drug must be considered a state variable, the polymorphisms represent trait variables of human subjects. Therefore, studies of genetic polymorphisms may yield more precise and specific results on the neurochemical modulation of brain electrical activity.

We tried to test the hypothesis that DRD4, DAT1, and COMT polymorphisms modulate evoked gamma activity in an auditory target detection paradigm. This hypothesis was based on 2 findings: on the one hand, auditory evoked gamma activity was shown to be modulated by a dopamine antagonist (Ahveninen and others 2000) and on the other hand, these polymorphisms have been related to psychiatric diseases such as schizophrenia and ADHD which at the same time yielded changes in auditory evoked gamma activity.

Since Tiitinen and others (1993) demonstrated that auditory stimuli evoke gamma oscillations that are enhanced by attention and Ahveninen and others (2000) reported that these evoked gamma oscillations to attended but not to ignored auditory stimuli were suppressed by the dopamine D1/D2 receptor antagonist haloperidol, we focused on "evoked" gamma activity. To test the specificity of the effects of the dopamine system on evoked gamma oscillations, broadband event-related potentials (ERPs) and evoked oscillations in lower frequency range were also included in our analyses. Additionally, considering that the generation of both evoked and induced gamma oscillations might share common mechanisms—although with different temporal dynamics—we included induced gamma oscillations in our analyses.

In order to avoid confounds due to pathological conditions or medication, the study has been carried out on a homogeneous group of 50 healthy volunteers in a narrow range of age (21.5 ± 1.64 years), with the same education level (2-year medical students), handedness (right), and gender (male). The classical auditory target detection paradigm in which evoked gamma oscillations are known to be enhanced in response to targets (Yordanova and others 1997; Debener and others 2003) was employed for this investigation.

Methods

Subjects

Fifty right-handed, healthy, male, 2-year medicine students aged 21.5 ± 1.64 years were investigated. All experiments were performed in accordance with the guidelines of the local ethics committee, and written informed consent about experimental processes was acquired from all of the subjects.

Electrophysiological Recordings

EEG was recorded in an electrically shielded, sound attenuated, and dimly illuminated room, using 16 Ag–AgCl electrodes at Oz, O1, O2, Pz, P3, P4, Cz, C3, C4, T3, T4, Fz, F3, F4, Fp1, Fp2 (10–20 system) referenced to linked earlobes. For monitoring both horizontal and vertical eye movements, bipolar electro-oculogram (EOG) was recorded with 2 electrodes placed at the outer cantus and supraorbitally to the right eye. Electromyographic activity was recorded to detect subject's motor responses by using 2 electrodes placed on metacarpal region of the right index finger. EEG was amplified between 0.1 Hz and 100 Hz, and 500-ms prestimulus and 1000-ms poststimulus periods were digitized using a 16-bit analog/digital converter (National Instruments, Austin, Texas) with a sampling rate of 256 Hz.

Cognitive Paradigm

A classical auditory target detection paradigm was employed. Target tones (1500 Hz) and standard tones (1000 Hz) were binaurally presented by headphones at 75 dB sound pressure level with 50 ms duration. Total number of trials was 300 and target probability was 20%. The tones were presented in a random series once every 2 s.

Analysis of ERPs and Oscillations

An automatic artifact rejection procedure based on an amplitude threshold of ±50 μV and a manual artifact elimination stage based on EOG channel were applied. After rejection of the artifacts, the numbers of trials were balanced by randomly picking the number of standard trials equal to the number of target trials for each subject. The P50, N100, and P300 waves of the averaged ERPs were identified as the positive peak within the 30–60 ms, negative peak within the 80–120 ms, and the positive peak within the 250- to 400-ms time windows, respectively. Peak amplitudes were measured relative to the mean amplitude of the 200-ms period preceding the stimulus presentation, and peak latencies were assessed as the time from the stimulus onset to maximum peak amplitudes.

For the analysis of event-related oscillations, the data were transformed to the time-frequency plane using a wavelet transform as explained below. The average of the transforms of both standard and target trials was used to choose the individual center frequencies of the evoked delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–29 Hz), and gamma oscillations (30–70 Hz). The time courses at these individual frequencies were used for the quantification of the evoked and induced oscillations. Inspection of the time courses of each of these oscillatory components in each single subject showed that temporal peaks were present within the 50- to 500-ms time window for the delta, 50- to 400-ms time window for the theta, 30- to 250-ms time window for the alpha and beta, and 30- to 150-ms time window for the gamma oscillations. Therefore, as a robust measure, mean amplitudes of the oscillations within these time windows were measured relative to a prestimulus baseline and submitted to statistical analysis. Measurements were carried out separately for standard and target potentials.

In order to test whether the induced gamma oscillations occurring in a later time window were modulated by the dopaminergic polymorphisms, we also analyzed the induced gamma activity by averaging the magnitudes of the single-trial time-frequency transforms in order to obtain the total amplitude of gamma oscillations that includes the oscillations not phase locked to the triggering event.

The Wavelet Transform

To compute a wavelet transform, the original signal was convolved with a wavelet function (Herrmann and others 1999, 2005). In the case of the Morlet wavelet used here, it was calculated according to the formula

$$\Psi(t) = e^{j\omega t} \cdot e^{-t^2/2},$$

where ω is 2π times the frequency of the unshifted and uncompressed mother wavelet.

Mathematically convolving wavelets with signals produces a new signal (the convolution) that can be interpreted as the similarity of the wavelet to the signal. These wavelets can be compressed by a scaling factor a and shifted in time by a parameter b. Convolving the signal and the shifted and dilated wavelet leads to a new signal

$$s_a(b) = A \int \bar{\Psi}\left(\frac{t-b}{a}\right) \cdot x(t)\, dt,$$

where $\bar{\Psi}$ is the conjugate of the complex wavelet and $x(t)$ is the original signal. These new signals $s_a(b)$ were computed for different scaling factors a and were displayed on a time-frequency plane where the color represents the amplitude of $s_a(b)$ (Fig. 3).

To represent phase-locked (evoked) activity, the wavelet transform was computed on the average of the single trials, that is, the ERP. This is denoted by the formula Wavelet Transform of Average (WTAvg).

Because the wavelet transform returns complex numbers, the absolute values were calculated

$$\mathrm{WTAvg} = \left| A_\Psi \int \Psi^* \left(\frac{t-b}{a} \right) \cdot \frac{1}{n} \sum_{i=1}^{n} \mathrm{eeg}_i(t)\, \mathrm{d}t \right|.$$

This time-frequency representation contains only that part of the activity that is phase locked to stimulus onset. To compute the activity that is not phase locked to stimulus onset (and is therefore canceled out in the average), the total activity (sum of evoked and induced activity) can be computed. To calculate the sum of all activity at one frequency, the absolute values of the wavelet transforms of the single trials are averaged, which means that each single trial is at first transformed and the absolute values are averaged subsequently

$$\mathrm{AvgWT} = \frac{1}{N} \sum_{i=1}^{N} \left| A_\Psi \int \Psi^* \left(\frac{t-b}{a} \right) \cdot \mathrm{eeg}_i(t)\, \mathrm{d}t \right|.$$

The corresponding time-frequency (TF) representation (sum) contains all activity of one frequency that occurred after stimulus onset, no matter whether it was phase locked to the stimulus or not.

After calculating the time-frequency transform, the frequency-specific baseline activity in a prestimulus period can be subtracted to yield values that indicate amplitude changes relative to baseline. When wavelet convolutions are computed, the convolution peaks at the same latency as the respective frequency component in the raw data, although the peak width will be smeared. Therefore, the baseline should be chosen to precede the stimulation by half the width of the wavelet to avoid the temporal smearing of poststimulus activity into the interval directly preceding the stimulus. Therefore, for the gamma range (30–80 Hz) analyzed with a Morlet wavelet with 6 cycles (1000/30 ms × 6 = 200 ms), we used the time interval between –200 and –100 ms before the stimulus to compute the baseline values.

Genotyping

ERP recording session was followed by venous blood sample collection into ethylenediaminetetraacetic acid containing tubes for genotype identification. DNA was extracted from peripheral blood leukocytes by salting out procedure (Miller and others 1988). The polymerase chain reaction (PCR) –based genotyping of the polymorphisms were carried out according to the following procedures.

Dopamine Receptor D4

The DRD4 gene is located on chromosome 11p15 (http://www.ncbi.nlm.nih.gov/LocusLink/LocRpt.cgi?l=1815). Association studies have evaluated a 48-bp variable number of tandem repeats (VNTR) polymorphism in exon III. The most common isoform of the DRD4 contains 4 repeats, whereas less common isoforms contain 2, 6, and 7 repeats. 7-repeat isoform has been shown to be less responsive to dopamine stimulation (Asghari and others 1995). A formal meta-analysis (Faraone and others 2001) based on 7 case control studies and 14 family-based studies concluded that a statistically significant association between ADHD and the 7-repeat allele of DRD4 existed. The association of D4 receptors with schizophrenia, ADHD, and other mental disorders has been reviewed by Oak and others (2000).

The primers employed were 5′-GCGACTACGTGGTCTACTCG-3′ (forward) and 5′-AGGACCCTCATGGCCTTG-3′ (reversed). PCR was performed with GC-Rich PCR System (Roche Molecular Biochemicals, Indianapolis, Indiana) in a 25-μl volume containing 50 ng DNA, 0.2 mM deoxynucleoside triphosphate (dNTPs), 20 pmol each primer, and 1.5 mM $MgCl_2$. DNA was denatured at 97 °C for 1 min and subjected to 35 cycles of 20 s denaturation at 96.5 °C, 1 min annealing at 57 °C, and 1 min extension at 72 °C, final extension 7 min at 72 °C. The genotyping of the DRD4 exon III 48-bp VNTR polymorphism was determined by fragment separation at 100 V for 30–45 min on a 2.5% agarose gel containing 0.5 μg/ml ethidium bromide.

Dopamine Transporter 1

Reuptake of dopamine into presynaptic neurons by means of the DAT is believed to be the primary mechanism for termination of dopaminergic neurotransmission. The DAT1 gene maps to chromosome 5p15.3 (http://www.ncbi.nlm.nih.gov/projects/LocusLink/LocRpt.cgi?l=6531) and carries a 40-bp VNTR polymorphism in the 3′-untranslated region (3′-UTR) (Sano and others 1993). Because this VNTR is not in the coding region of the DAT gene, it may affect the translational efficiency and thus the amount of protein expressed. Indeed, subjects homozygous for the 10-repeat allele (10/10) show significantly lower DAT binding than carriers of the 9-repeat allele (Jacobsen and others 2000; Miller and Madras 2002). Cook and others (1995) and Gill and others (1997) found a significant association between the DAT1 gene and ADHD.

The primers employed were 5′-TGTGGTGTAGGGAACGGCCTGAG-3′ (forward) and 5′-CTTCCTGGAGGTCACGGCTCAAGG-3′ (reversed). PCR was performed with an automated Thermal Cycler (Techne Flexigene, Cambridge, UK) in a 25-μl reaction volume with 50 ng DNA, 0.2 mM dNTPs, 20 pmol of each primer, 1.5 mM $MgCl_2$, 1× PCR buffer with $(NH4)_2SO_4$ (MBI Fermentas, Vilnius, Lithuania) and 1.25 U Taq polymerase (MBI Fermentas). PCR conditions were 2 min for initial denaturation at 95 °C; 35 cycles at 95 °C for 30 s for denaturation, 45 s at 66 °C for annealing, and 1 min at 72 °C for extension, followed by 7 min at 72 °C for final extension. The PCR products were resolved at 120 V for 45 min on a 2.5% agarose gel containing 0.5 μg/ml ethidium bromide.

Catechol-O-methyltransferase

COMT is an enzyme involved in the breakdown of dopamine. A G → A transition at position 1947 in COMT gene on 22q11 (http://www.ncbi.nlm.nih.gov/projects/LocusLink/LocRpt.cgi?l=1312) results in a 3- to 4-fold difference in COMT activity (Lachman and others 1996). A valine at codon 108/158 results in the heat-stable, high-activity COMT variant (H), whereas a methionine at this position results in the heat-labile, low-activity variant (L), which has been reported to be involved in schizophrenia (Herken and Erdal 2001) and ADHD (Eisenberg and others 1999).

The primer sequences were 5′- GGAGCTGGGGGCCTACTGTG-3′ (forward) and 5′- GGCCCTTTTTCCAGGTCTGACA-3′ (reversed). PCR was performed with an automated Thermal Cycler (Techne Flexigene, Cambridge, UK) in a 25-μl volume with 50 ng DNA, 0.2 mM dNTPs, 20 pmol of each primer, 1 mM $MgCl_2$, 1× PCR buffer with $(NH_4)_2SO_4$, 0.2% (w/v) bovine serum albumin, and 1 U Taq polymerase (MBI Fermentas). PCR conditions were 3 min for initial denaturation at 94 °C; 35 cycles at 94 °C for 1 min for denaturation, 1 min at 60 °C for annealing, and 1 min at 72 °C for extension, followed by 7 min at 72 °C for final extension. The resulting PCR products were subjected to restriction digestion for 3 h at 37 °C using 5 U Nla III (BioLabs Inc., Hitchin, UK). The digest products were resolved at 100 V for 20–30 min on a 4% NuSieve 3:1 Agarose (FMC BioProducts, Rockland, ME) containing 0.5 μg/ml ethidium bromide. The COMT-HH genotype was represented by 114, 36, and 35 bp fragments; COMT-LL by 96, 35, 36, and 18 bp fragments; and COMT-HL by 114, 96, 36, 35, and 18 bp fragments.

A 100-bp marker (100-bp DNA Ladder, MBI Fermentas) was used as a size standard for each gel lane. The gel was visualized under UV light using a gel electrophoresis visualizing system (Vilber Lourmat, Marne La Vallée, France). Genotyping was based upon independent scoring by 2 reviewers who were unaware of case/control status.

Statistics

The differences of the amplitudes and latencies of the P50, N100, and P300 waves and the amplitude differences of evoked and induced oscillations between groups with different genotypes were tested by repeated measures analysis of variance (ANOVA) designs. Here, the genotype served as the independent variable, that is, genotype was the between-subjects factor (genotype: 2 levels—7 repeat vs. others for DRD4, homozygous 10/10 vs. others for DAT1, and homozygous H/H vs. others for COMT). For all variables except the P300 amplitude and latency, stimulus type (2 levels: standard vs. target), anteroposterior topography (3 levels: frontal, central, parietal), and lateral topography (3 levels: left, midline, right) were within-subject factors. The P300 amplitude and latency were measured only in target trials; hence, the factor stimulus type was not defined for these tests. Greenhouse–Geisser correction procedure was applied to the degrees of freedom for the repeated measures factors, with only the corrected probability values reported.

In order to double-check the results related with the evoked gamma response, we conducted an additional analysis, where we sorted subjects according to phenotype and investigated the genotype. This excludes the possibility of confounding variables to obscure the ANOVA results. The subjects were divided into 2 groups of 24 subjects each by the median of the evoked gamma amplitudes (low- vs. high-gamma responses), and the homogeneity of the distribution of the genotypes between the low and high-gamma groups were tested by Chi-square test.

Results

Because 2 of the 50 subjects had a high number of trials containing artifacts, they were excluded from further analyses. For the remaining 48 subjects, mean number of trials without artifacts was 51 for target and 198 for standard stimuli. The numbers of targets and standards were matched for further analysis.

Mean numbers of missed targets and reaction times for each group are reported in Tables 1 and 2. The ERPs include only the trials with correctly identified standard and target stimuli. Statistical analyses revealed no significant difference between both genotypes of any polymorphism.

Each of the DRD4, DAT1, and COMT polymorphisms were divided into 2 subgroups according to the associations of the genotypes with cognitive disorders. The groups are named in such a way, that "genotype 2" always corresponds to the genetic group that shows association with cognitive disorders.

The frequencies of the DRD4 exon III 48-bp repeat allele in all 96 alleles of the 48 subjects were 0.11 for 2-repeat, 0.02 for 3-repeat, 0.74 for 4-repeat, 0.01 for 6-repeat, and 0.11 for 7-repeat alleles. Because earlier reports on this polymorphism showed mainly associations between the presence of the 7-repeat allele and ADHD (Faraone and others 2001), the subjects were divided into 2 groups according to the presence of the 7-repeat allele. The 7-repeat allele was absent in 38 subjects (genotype 1) and present in one homozygous (7/7) subject (i.e., 2 out of the 96 alleles) and 9 heterozygous (7/X) subjects (i.e., 9 out of 96 alleles), yielding a total of 11 alleles (0.11 × 96) for genotype 2.

The frequencies of the DAT1 VNTR polymorphism were 0.02 for the 8-repeat allele, 0.29 for the 9-repeat allele, and 0.69 for the 10-repeat allele. Because earlier studies showed that subjects homozygous for the 10-repeat allele showed significantly lower DAT binding than carriers of the 9-repeat allele (Jacobsen and others 2000), the subjects were divided into 2 subgroups: the homozygous 10/10 group (genotype 2) and the remaining subjects (genotype 1). The number of homozygous 10/10 subjects was 23 out of 48.

For the COMT polymorphism, the frequencies of the homozygous high-activity variant (H/H), the homozygous low-activity variant (L/L), and the heterozygous genotype (H/L) were 0.31, 0.11, and 0.58, respectively. Because earlier studies showed that the presence of the L allele was associated with ADHD (Eisenberg and others 1999) and the severity of clinical signs in schizophrenia (Herken and Erdal 2001), the statistical analyses were carried out after dividing the subjects into 2 groups, as genotypes containing an L allele (H/L and L/L, genotype 2) and homozygous high-activity genotype (H/H, genotype 1). The number of the subjects with an L allele was 33.

Figure 1 displays the superimposed grand averages of standard and target ERPs for each pair of genotypes of each polymorphism at Cz. The amplitudes of the P300 were slightly higher for the 7-repeat allele of the DRD4 polymorphism as compared with the non–7-repeat allele group ($F_{1,46}$ = 1.06; not significant [NS]) and slightly lower for the group with L allele of the COMT polymorphism as compared with the group with the H/H genotype ($F_{1,46}$) = 0.63; NS). However, neither these differences nor any other differences of P50, N100, or P300 amplitudes or latencies were significantly different between the 2 groups of genotypes for any polymorphism.

The focus of this study was to investigate the effects of the dopaminergic system on the evoked GBR. Figure 2 shows the grand average of the frontocentral ERPs to standard and target stimuli high-pass filtered at 25 Hz. A clear transient oscillation of 3 cycles in this frequency range can be observed within the first 20–130 ms of the ERPs as previously shown by a number of electroencephalographic and magneoencephalographic studies in the auditory modality (Pantev and others 1991; Tiitinen and others 1993; Yordanova and others 1997; Jääskeläinen and others 1999; Ahveninen and others 2000, 2002; Debener and others 2003; Senkowski and others 2005). Because the wavelet transform has a compact support in time and enables a better quantification of the amplitudes of such transient oscillatory wave packets, further analyses have been carried out using the time-frequency transform of the signal.

In order to test whether any effect of the dopaminergic polymorphisms on the GBR are specific to this frequency range or rather part of a wideband modulation of the evoked activity, signal components in lower frequency ranges of the time-frequency transforms were also included in the analyses. The time-frequency transforms of the averaged ERPs revealed that the maxima of all frequency components except the delta response were located in frontal midline electrodes. Therefore, we display the grand averages of the time-frequency transforms of all standard + target trials in Figure 3 for electrode Fz. Due to the different amplitude scales of gamma and lower frequency activity, the gamma frequency range (*A*) and lower frequency range (*B*) of the time-frequency transforms are presented separately in Figure 3.

In order to test the effects of stimulus type and topographical distribution on the evoked oscillations, an ANOVA design with the within-subject factors "stimulus type" (standard vs. target), "anteroposterior topography" (frontal, central, parietal), and "lateral topography" (left, midline, right) was applied to the amplitudes of each frequency range. The amplitudes of the auditory evoked gamma and delta responses to target stimuli

Table 1
Mean number of missed targets of each genotype of DRD4, DAT, and COMT polymorphisms were compared using *t*-test

Genotype	DRD4	DAT	COMT
1	2.3*t* ± 2.4	2.5 ± 2.5	2.5 ± 2.9
2	2.0 ± 1.9	1.9 ± 2.5	2.1 ± 1.9
p	NS	NS	NS

Note: No significant differences were found between the 2 genotypes of any polymorphism.

Table 2
Mean reaction times of each genotype of DRD4, DAT, and COMT polymorphisms were compared using *t*-test

Genotype	DRD4	DAT	COMT
1	424.69 ± 103.55	403.69 ± 101.33	432.03 ± 136.16
2	379.50 ± 75.03	427.86 ± 97.73	407.66 ± 78.64
p	NS	NS	NS

Note: No significant differences were found between the 2 genotypes of any polymorphism.

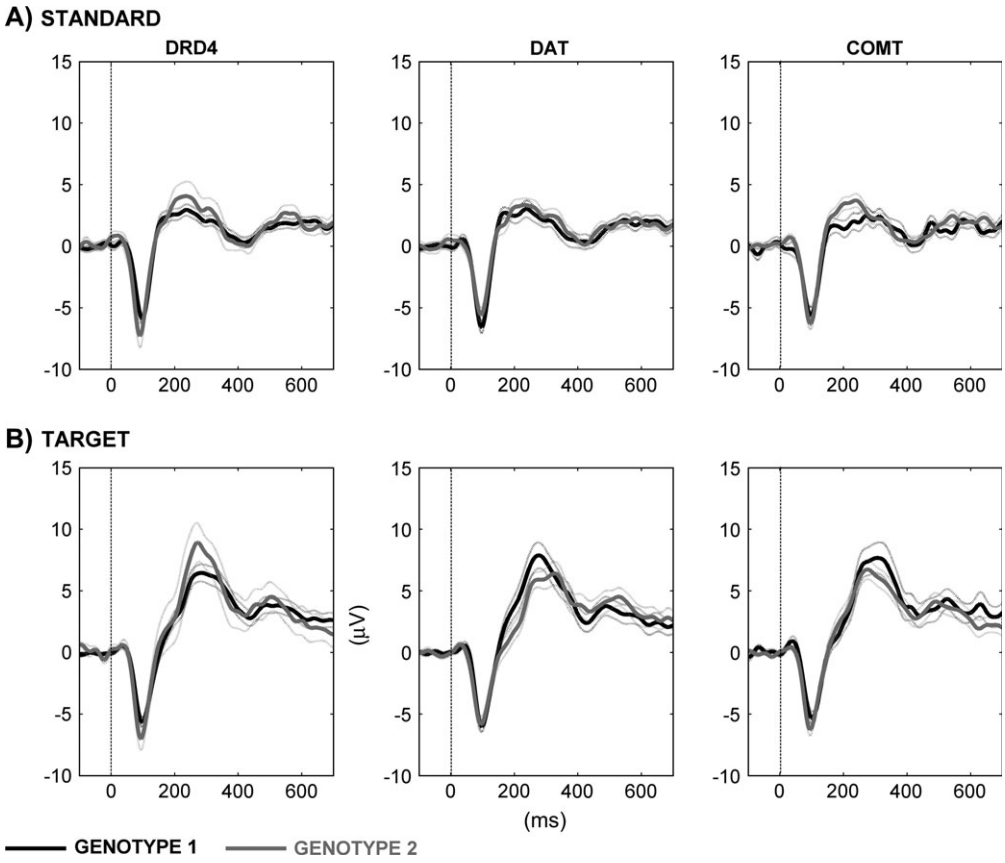

Figure 1. Grand averages of the ERPs to (*A*) standard and (*B*) target stimuli at electrode Cz. The ERPs obtained from each of the 2 genotypic groups of DRD4, DAT, and COMT polymorphisms are superimposed (solid lines). The standard error of the mean is shown by dashed lines. None of the P50, N100, and P300 amplitude and latencies were significantly different between the genotypes.

were significantly larger than those to standards (stimulus type: $F_{1,47} = 4.85$; $P < 0.05$ and $F_{1,47} = 8.81$; $P < 0.01$, respectively), whereas no significant main effect of stimulus type was observed for other oscillations. All frequency components except the delta response showed a significant anteroposterior distribution due to frontal maxima ([For sake of simplicity, we report the minimal *F*-values and maximal *P*-values of all comparisons] all $F_{2,94} > 6.33$; all $P < 0.01$), whereas the maximum of the evoked delta response was in the central region ($F_{2,94} = 3.7$; $P < 0.05$). A significant lateral distribution effect was observed for all frequency components due to maximum amplitudes on the midline electrodes (all $F_{2,94} > 3.14$; all $P < 0.05$).

The effects of genetic polymorphisms on the evoked oscillations were tested with an ANOVA design with the between-subjects factor genotype and within-subjects factors stimulus type (standard vs. target), anteroposterior topography (frontal, central, parietal), and lateral topography (left, midline, right). The DRD4 exon III polymorphism yielded a significant difference only for the gamma range, with larger amplitudes for the 7-repeat allele group (genotype 2) as compared with the group without a 7-repeat allele (genotype 1) ($F_{1,46} = 10.66$ $P < 0.01$). This gamma effect did not show any significant interaction with the stimulus type or topography (Figs 4 and 5). There were neither significant DRD4 main effects nor DRD4 × stimulus type interactions for any of the other frequency components.

DAT1 VNTR polymorphism did not yield any significant main effect in any of the evoked frequency components. However, there was a significant genotype × stimulus type interaction

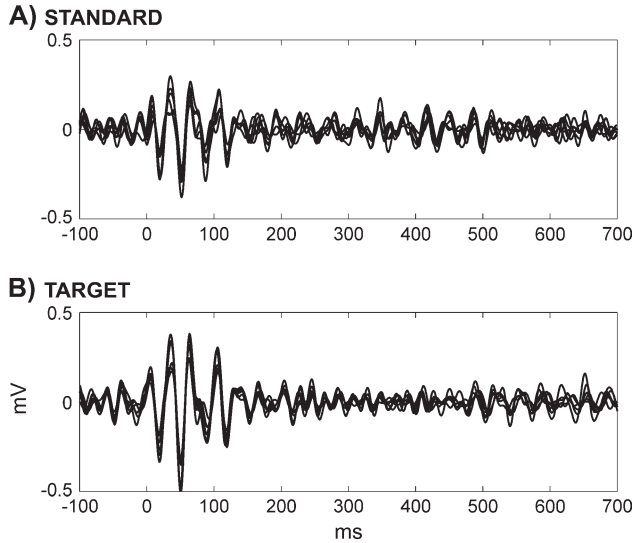

Figure 2. The grand averaged ERPs to (*A*) standard and (*B*) target stimuli high-pass filtered at 25 Hz. The potentials from the frontocentral leads (F3, Fz, F4, C3, Cz, C4), where the auditory evoked GBR reaches a maximum, are superimposed. A clear transient evoked GBR with 3 cycles can be observed within the first 120 ms of the ERPs.

only for the evoked gamma response ($F_{1,46} = 4.33$; $P < 0.05$). In the group with the homozygous 10/10 genotype (genotype 2), the target gamma response was significantly higher than in the subjects with 9/10 or 9/9 genotype (genotype 1) ($F_{1,46} = 4.62$;

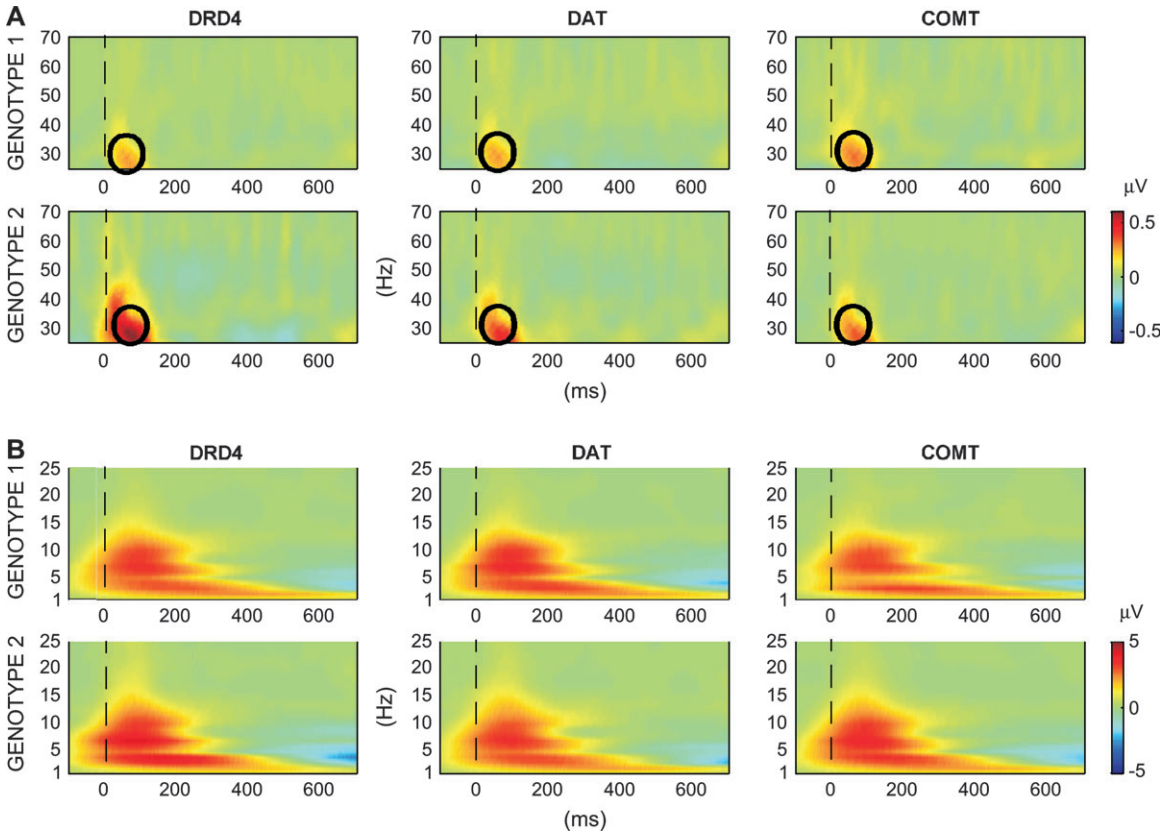

Figure 3. Time-frequency transforms of the evoked activity phase locked to the auditory stimulus in the frontal midline electrode (Fz) for genotypes 1 and 2 averaged across targets and standards. Due to the different amplitude scales of gamma and lower frequency activity, the gamma frequency range (*A*) and lower frequency range (*B*) are presented separately. The 7-repeat allele group of the DRD4 polymorphism (genotype 2) and the homozygous 10/10 genotype of the DAT1 polymorphism (genotype 2) show enhanced evoked gamma oscillations (see circles), whereas no difference is obvious in the evoked gamma activity for the COMT polymorphism. In the lower frequency bands, no clear difference could be observed for any of the polymorphisms.

$P < 0.05$). However, no significant difference was observed for the evoked gamma response to standard stimuli. There were no significant topographical differences between the 2 genotypes, such that the maximum gamma response was in the frontal region for both groups (Fig. 5).

There was no main effect of the COMT polymorphism on any of the evoked oscillatory components. The only significant genotype × stimulus type interaction for COMT was obtained for the evoked gamma response. However, post hoc analyses did not show any significant differences of the evoked gamma responses to standard or target stimuli between the homozygous high-activity (H/H) group (genotype 1) and the group with at least one L allele (genotype 2).

The DRD4 effect observed for the evoked gamma oscillations occurred in the same manner also for the induced gamma oscillations in the later time window between 100 and 350 ms (cf., Fig. 6). The DRD4 7-repeat allele group revealed significantly larger induced gamma oscillations compared with the non–7-repeat allele group ($F_{1,46} = 8.02$; $P < 0.01$). This effect did not show a significant interaction with stimulus type, which means that the same increase in induced gamma amplitudes was obtained for both standard and target responses. The DAT1 effect on the evoked gamma oscillations to target stimuli, however, was not present for the induced gamma oscillations. COMT polymorphism revealed no significant difference in the induced gamma response as in the evoked gamma response.

In order to double-check our main results related with the evoked gamma response, the analyses were repeated in the inverse direction. The subjects were divided into 2 groups according to their evoked gamma amplitudes: if it exceeded the median gamma amplitude, they were considered high-gamma subjects and otherwise low-gamma subjects. For each polymorphism, these 2 groups were tested for a homogeneous distribution of the 2 genotypes by a Chi-square test (Fig. 7).

The results of these analyses fully support the ANOVA results reported above. In case of the DRD4, the low-gamma group for both the standard and target stimuli contained only 2 subjects with the 7-repeat allele, whereas the high-gamma group contained 8 subjects with 7-repeat allele. Accordingly, 22 subjects with low-amplitude gamma and 16 subjects with high-amplitude gamma responses were belonging to the non–7-repeat allele group. The significance of this nonuniform distribution was tested against the expected equal distribution of 10 7-repeat subjects (5/5) and 38 non–7-repeat subjects (19/19) into low- and high-gamma groups by a Chi-square test. The results were significant for both standards and targets ($P < 0.05$).

For the DAT1 polymorphism, 10 of the 23 subjects with 10/10 genotype revealed low-amplitude and 13 high-amplitude gamma responses to standard stimuli. Accordingly, the number of the subjects with other genotypes was 14 in the low-gamma group and 11 in the high-gamma group. This distribution was not significantly different from the expected frequencies. However, if the subjects were divided into low- and high-gamma

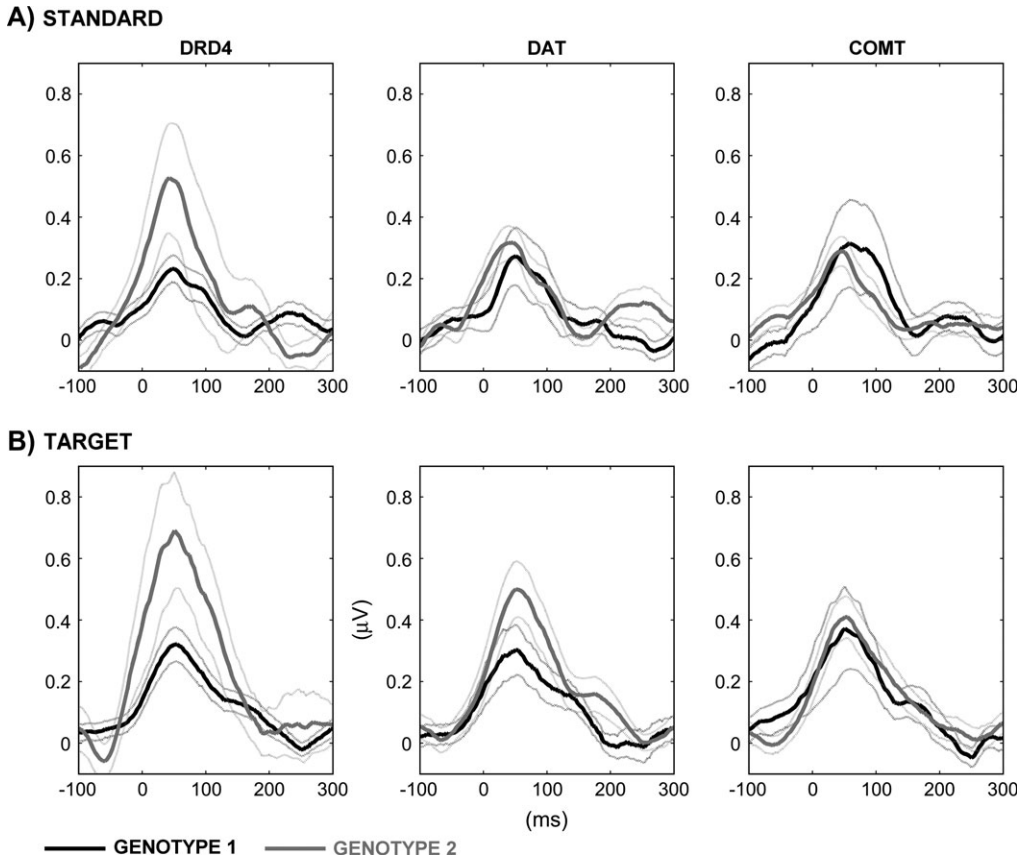

Figure 4. Time courses of evoked gamma activity in response to auditory (*A*), standard, and (*B*) target stimuli in electrode Fz for genotypes 1 and 2 averaged across targets and standards (solid lines). The standard errors are plotted in dashed lines. The analysis of the DRD4 polymorphisms revealed a significant increase of gamma activity for the 7-repeat allele (genotype 2) both for target and standard stimuli. For the DAT polymorphism, only target responses showed a significant difference between genotypes. COMT genotypes revealed no effect on evoked gamma activity.

groups according to gamma amplitudes to target stimuli, the numbers of the 10/10 subjects in the low- and high-gamma groups were 8 versus 15, respectively, whereas 16 of the subjects with other genotypes were in the low and 9 in the high-gamma group. This distribution was significantly different from the expected frequencies of both genotypes in the low- and high-gamma groups ($P < 0.05$).

Discussion

There were no significant effects of the DRD4, DAT1, and COMT polymorphisms on the amplitudes or on the latencies of the ERP waves. A slightly lower P300 amplitude was observed for the group with the L allele of the COMT (Val(108/158)Met) polymorphism as compared with the group with the H/H genotype, which did not reach significance. This amplitude difference showed the same direction as in the study of Gallinat and others (2003), where the authors reported lower frontal P300 amplitudes in homozygous carriers of the L allele, particularly in schizophrenic patients. In that study, the effect also turned out to be nonsignificant within the healthy group. Therefore, our results of a slight decrease of the P300 amplitude in a homogeneous group of healthy subjects carrying the L allele of the COMT polymorphism are in accordance with the results of Gallinat and others (2003). It is conceivable that the significant COMT effect obtained in that study for the group of schizophrenic patients might depend on the dysfunction of additional factors, which affect the monoaminergic system and compensate for the L allele of the COMT polymorphism.

The most important findings of the present study are significant differences in the evoked and induced GBRs for DRD4 and in evoked GBRs for the DAT1 polymorphism. Interestingly, these polymorphisms did not result in any significant differences of amplitudes or latencies of the ERP waves. Neither did they modulate the amplitudes of the evoked oscillations of the lower frequency range. This pattern of results suggests that the effects of the neurotransmission systems on brain electrical responses may occur in specific oscillatory responses that cannot be observed in wideband ERP waveforms. While the ERP reflects the superposition of many event-related oscillations (Basar, Basar-Eroglu, and others 2001), isolation of specific oscillations allows us to observe the effects of the neurotransmitter system more clearly.

Before we discuss the potential mechanism of how genetic polymorphisms might modulate auditory GBR, it is important to clarify the source of this activity. First of all, the auditory evoked GBR is different from the so-called 40-Hz steady-state response (Galambos and others 1981; Picton and others 1987). The latter is evoked by repetitive stimulation at a rate of around 40 Hz—the former is also evoked by single stimuli with randomized interstimulus intervals. Another important differentiation concerns the auditory middle latency responses (MLRs) that typically appear in an auditory ERP in the latency range of roughly 10–60 ms (Kraus and McGee 1995). Auditory MLRs are

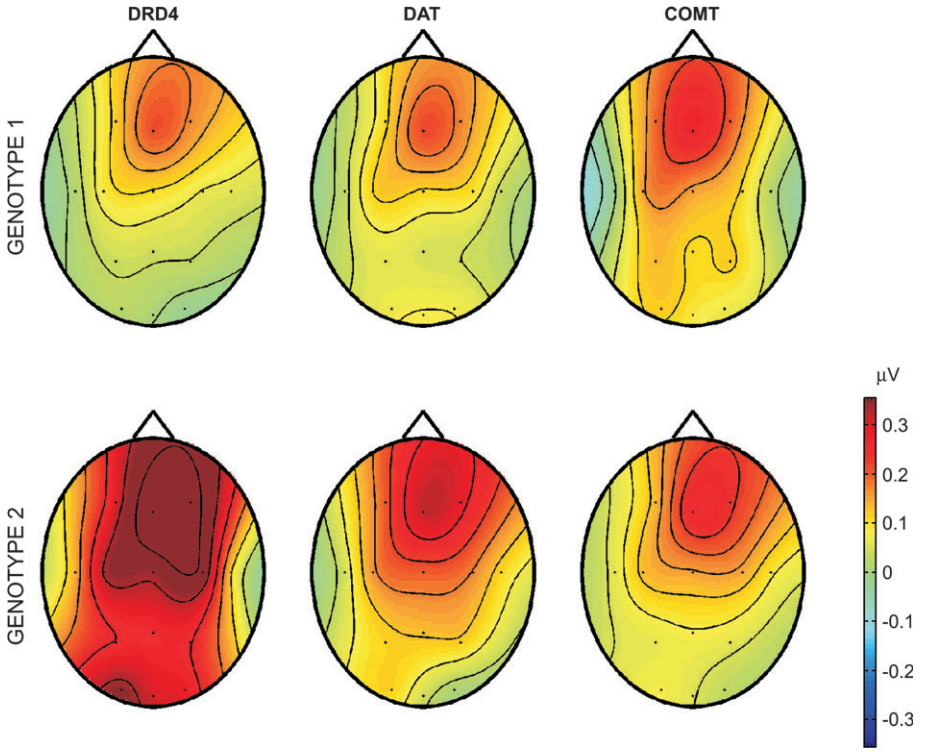

Figure 5. Topographical distribution of the evoked gamma activity in the time interval from 40 to 60 ms for genotypes 1 and 2 averaged across targets and standards. Responses are maximal over frontal electrodes. The increase of gamma oscillations for the 7-repeat allele (genotype 2) of the DRD4 polymorphism and 10/10 genotype (genotype 2) of the DAT polymorphism are also maximal over frontal electrodes.

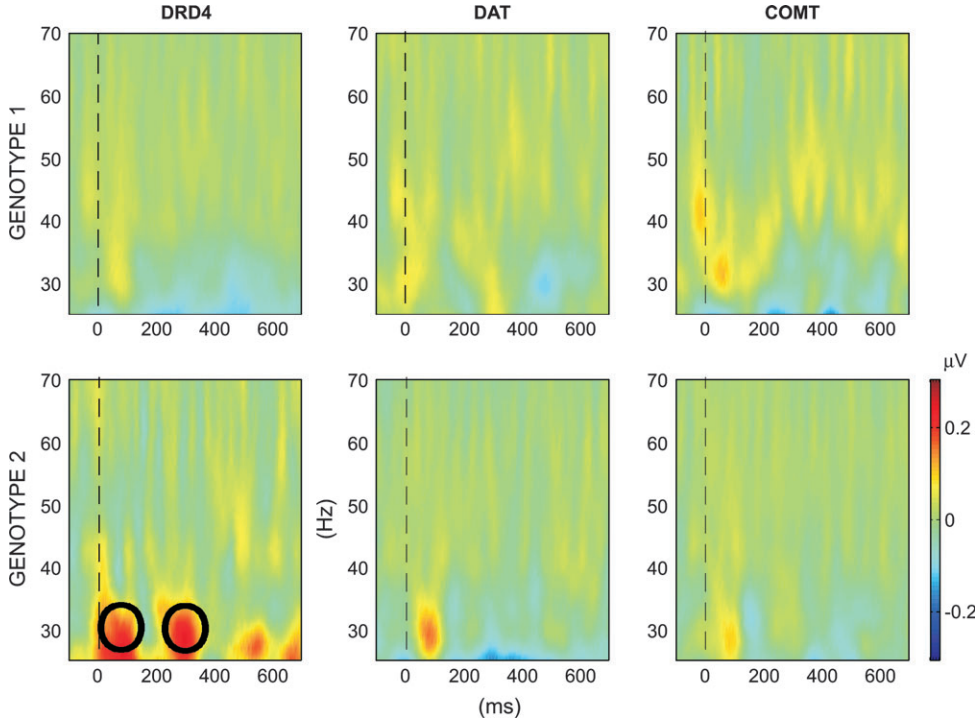

Figure 6. Time-frequency transforms of the total activity in the gamma range in electrode Fz for genotypes 1 and 2 averaged across targets and standards. In addition to the early gamma peak that roughly corresponds to the latency range of the evoked gamma response (left circle), a late induced gamma peak can be observed around 300 ms (right circle) for the 7-repeat allele group of the DRD4 polymorphism (genotype 2), which is absent in the group without 7-repeat allele. In the 2 other polymorphisms, subjects with this late induced gamma peak seem to be equally distributed across both genotype groups, such that it is no more visible in the grand average.

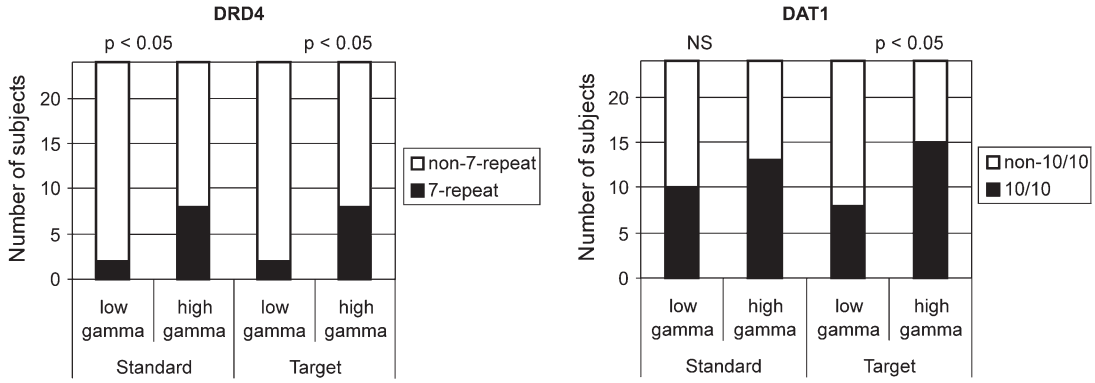

Figure 7. The ANOVA results have been supported by a second line of analysis by dividing the subjects at the median amplitude of the evoked gamma responses into 2 groups with low and high gamma for each of the standard and target conditions. The homogeneity of the distribution of the 2 genotypes of the DRD4 polymorphism (7-repeat allele vs. others) and the DAT1 polymorphism (homozygous 10/10 genotype vs. others) in the low- versus high-gamma groups were tested by using Chi-square test.

a sequence of positive and negative deflections of the ERP—a negative deflection around 18 ms (Na), a positive deflection around 25–30 ms (Pa), and a positivity around 50 ms called Pb, P50, or P1 (Woods and others 1987).

It has been debated for quite some time whether the auditory MLR and evoked GBR are 2 distinct phenomena or just 2 sides of the same coin (e.g., Bertrand and Pantev 1994). One extreme interpretation suggests that the evoked GBR might merely be the frequency representation of MLRs (Müller and others 2001). This notion is based on findings that the MLRs are at least to some extent generated by subcortical generators where each generator is responsible for a different component, and thus, the MLRs do not resemble an oscillation (Hashimoto 1982; Kaseda and others 1991). Because these mid latency ERP components have an interpeak distance of roughly 25 ms, they would show up as 40-Hz activity in a wavelet transform. The other extreme interpretation claims that the MLRs might actually be generated by a 40-Hz oscillation (Basar and others 1987). These authors have demonstrated that prestimulus gamma activity is inversely correlated with poststimulus GBR as well as MLR, indicating that the MLR is strongly related to prestimulus gamma activity which one would not expect for multiple individual brain stem responses. Most probably, however, the activity under question is a superposition of both, MLRs which are at least partly generated cortically (Scherg and Von Cramon 1986; Liegeois-Chauvel and others 1994) and a cortical 40-Hz oscillation (Mäkelä and Hari 1987). Intracranial recordings in auditory cortex show evoked 40-Hz activity around 50 ms after stimulation within a single electrode both in monkeys (Brosch and others 2002) and in humans (Bertrand and others 2001; Edwards and others 2005). While one might still argue that a sequence of subcortical ERP components with 25 ms interpeak distance would show up as evoked 40-Hz activity even in intracranial recordings, a number of modulatory influences on the evoked GBR render this unlikely: Processing of target stimuli significantly enhances auditory evoked gamma activity (Yordanova and others 1997; Debener and others 2003). In addition, we could recently demonstrate a strong attention effect onto the auditory evoked GBR during audiovisual integration (Senkowski and others 2005). Both phenomena represent essentially cortical but not subcortical processes. Furthermore, the modulation of the auditory evoked GBR by agents acting on the GABAergic transmission (Jääskeläinen and others 1999) that is essential in the generation of synchronized gamma oscillations in the cortex and by the blockade of the cholinergic transmission (Ahveninen and others 2002), which modulates sensory processing in the auditory cortex, suggests that the transient auditory evoked GBR which we observed stems from auditory cortex and resembles an oscillation—even though it may be superimposed onto subcortical MLRs. Because intracranial recordings in humans and monkeys find evoked and induced responses in identical locations (Bertrand and others 2001; Brosch and others 2002; Edwards and others 2005), we further assume that the generators of evoked and induced GBRs both reside in auditory cortex but are active at different latencies with different degrees of phase locking to stimulus onset.

The DRD4 and DAT1 modulation of the evoked and induced gamma activity generated in or close to the auditory cortex might be explained by direct dopaminergic innervation of auditory cortex (Atzori and others 2005). However, it is also possible to consider a modulation of the auditory cortex via the prefrontal cortex (PFC) as shown by Knight and others (1999). This modulation can occur as early as within the P30 latency range. This notion seems plausible because PFC is both modulated by midbrain dopaminergic stimulation and critically involved in working memory functions (Fuster 1989), which in turn are necessary for the target detection required in our task.

The associations of the DRD4 and DAT1 polymorphisms with specific pattern of changes in the evoked gamma responses reveal that dopamine modulates gamma oscillations in more than one way. This result may on one side help to understand the complex pattern of changes of evoked gamma oscillations in neuropathological conditions that have been associated with the dopaminergic system (Clementz and others 1997; Haig and others 2000; Yordanova and others 2001; Spencer and others 2003; Gallinat and others 2004) and on the other side shed light on the reactivity of the evoked gamma oscillations to different cognitive variables such as alerting and selective attention in normal subjects (Tiitinen and others 1993; Yordanova and others 1997; Debener and others 2003).

In our study, the DRD4 polymorphism introduced a significant change in the gamma responses. The 7-repeat isoform yielded a significant increase in the auditory evoked and induced gamma responses to both target and standard stimuli. This finding is in line with the gamma and DRD4 results in ADHD. The auditory evoked gamma response in ADHD children was found to be higher in amplitude compared with normal children irrespective of whether they were evoked by the target or the

standard stimuli (Yordanova and others 2001). A meta-analysis of DRD4 polymorphisms showed a significant association between ADHD and the 7-repeat allele of the DRD4 polymorphism (Faraone and others 2001). It has been shown that targets evoke larger gamma oscillations than standard stimuli (Herrmann and Mecklinger 2001; Debener and others 2003). If gamma activity is enhanced unspecifically, as it is the case for the 7-repeat polymorphism of the DRD4 receptor, this could represent a condition in which it becomes hard for subjects to focus to targets because there is hardly any difference in gamma amplitude. This might explain the association of the DRD4 7-repeat allele with the attentional deficits in ADHD.

The D4 receptor can affect potassium channels (Werner and others 1996; Wilke and others 1998) as well as GABAergic chloride channels (Wang and others 2002) thus modulating the excitability of neurons. Generally, dopamine is believed to inhibit activity of pyramidal cells if effective via the D4 receptor because for example, mice with deficient D4 receptors show hyperexcitability (Rubinstein and others 2001). The 7-repeat isoform of the DRD4 gene has been shown to have about half the potency to inhibit cyclic adenosine monophosphate (cAMP) formation compared with the 2- and 4-repeat variants (Asghari and others 1995). Therefore, the increased gamma activity in subjects with the 7-repeat isoform of DRD4 polymorphism might be the result of less inhibition via the D4 receptor.

The main effect of the DAT1 VNTR polymorphism on the evoked gamma response was not significant, but a significant DAT1 × stimulus type interaction was observed. The homozygous 10-repeat allele (10/10) of the DAT1 polymorphism introduced a significant amplitude increase in evoked gamma responses to targets, whereas no significant change was observed in evoked gamma responses to standards or in induced gamma responses. Jacobsen and others (2000) and Miller and Madras (2002) demonstrated that the homozygous 10-repeat allele (10/10) of the DAT1 polymorphism shows significantly lower DAT binding than carriers of the 9-repeat allele, and hence, a higher amount of synaptic dopamine might be expected in subjects with the homozygous 10-repeat allele. The results of Giros and others (1992) revealed that mice lacking the gene encoding the plasma membrane DAT had elevated dopaminergic tone and were hyperactive. This supports the notion that the 10/10 genotype of DAT1, which has been associated with ADHD (Cook and others 1995; Gill and others 1997), leads to increased levels of extracellular dopamine. Accordingly, the increased gamma response to target stimuli in our 10/10 group might be explained by a higher amount of extracellular dopamine in this group.

The differential effect of the DAT1 polymorphism on evoked gamma responses to targets in contrast to the uniform change of both evoked and induced gamma responses to standard and target stimuli by the DRD4 polymorphism raises 2 questions: 1) Why is the effect different from the DRD4 effect if it is due to enhanced levels of synaptic dopamine that would activate also D4 receptors? and 2) Why is the effect specific for targets while the DRD4 polymorphism effects both targets and standards?

In order to answer these questions, we need to make 2 assumptions:

1. The DAT1 effect most probably depends on another dopamine receptor than the D4 type.
2. Some aspect of this other receptor must be specific for targets because increased levels of dopamine would not be.

Because it has been proposed that task-related activity in neurons of PFC during working memory is modulated by dopamine mainly via the D1 receptor (Sawaguchi and Goldman-Rakic 1994; Durstewitz and others 2000; Seamans, Durstewitz, and others 2001; Seamans, Gorelova, and others 2001), it seems plausible to assume that our DAT1 effect was mediated by the D1 receptor. The inefficient variant of DAT1 that yielded the enhanced gamma response to targets probably also resulted in enhanced dopamine levels in extracellular space. It has been demonstrated that such enhanced dopamine levels support working memory function (Fuster 1989; Sawaguchi and Goldman-Rakic 1994). Such working memory functions, which reside in PFC, comprise storage, maintenance, and retrieval of goal-directed representations as well as protections of the former against interference (Durstewitz, Kelc, and Güntürkün 1999; Durstewitz, Kroner, and Güntürkün 1999). Especially, correct retrieval is crucial for target detection. In order to detect a target, subjects have to store a template of the target in working memory before the start of the experiment and then match every perceived stimulus to this template. A number of studies have shown that a positive outcome of this matching process enhances gamma oscillations in human EEG (reviewed by Herrmann, Munk, and Engel 2004). In a sense, target detection is a special case of the delayed matching-to-sample task. It has been demonstrated that matching-to-sample relies more on D1 than on D2 receptors (Müller and others 1998). Thus, these data are in line with our first assumption, and we argue that the special case of target detection, just like the more general case of delayed matching-to-sample, relies more on D1 than D4 receptors.

Studies using functional magnetic resonance imaging have revealed that frontal cortex is only activated for target but not for standard stimuli (Linden and others 1999; Kirino and others 2000; Kruggel and others 2001). In addition, targets usually evoke larger gamma responses than do standard stimuli (Yordanova and others 1997; Herrmann and others 1999; Debener and others 2003). Thus, the PFC, where the effect of the D1 receptors probably occurs, is only activated by targets, which is in line with our second assumption—explaining the selective modulation of target gamma activity by the DAT1 polymorphism.

The absence of any differences between the evoked gamma responses of the subjects with the high and low-activity variants of the COMT gene seems to be contradictory to the results obtained with DAT polymorphism. However, the facts that the uptake by the DAT is the most effective mechanism for the termination of the synaptic action of dopamine in the brain and that the role of COMT remains minimal under normal conditions (Huotari and others 2002) could explain this difference between the DAT and COMT results.

Because the effects introduced by these polymorphisms may be alleviated by compensatory mechanisms such as changes in the release of dopamine, in receptor sensitivities, or other mechanisms of termination of synaptic activity, the results of the present study on healthy subjects cannot be considered to explain the degree of deviations in the functions of the attention networks in ADHD or schizophrenia. However, interindividual differences in the gamma activity in normal subjects, which have been for example correlated with the high switching rate between 2 percepts in a multi-stable perception paradigm (Strüber and others 2000), might depend on genetic variability such as DRD4 and DAT polymorphisms.

In conclusion, our results suggest that the action of dopamine via the D4 receptor inhibits the evoked gamma response non-selectively to all stimuli. However, increased levels of extracellular dopamine, due to an inefficient DAT, selectively enhance target gamma responses and probably reflects the D1-mediated dopaminergic contribution to a prefrontal target detection mechanism.

Notes

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Address correspondence to Prof. Dr Tamer Demiralp, Department of Physiology, Istanbul Medical Faculty, Istanbul University, 34390 Çapa-Istanbul, Turkey. Email: demiralp@istanbul.edu.tr.

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