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COMT genotype predicts BOLD signal and noise characteristics in prefrontal circuits

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Objective: **Prefrontal dopamine (DA) is catabolized by the COMT (catechol-*O*-methyltransferase) enzyme. Literature suggests that the Val/Met single nucleotide polymorphism (SNP) in the COMT gene predicts executive cognition in humans with Val carriers showing poorer performance due to less available synaptic DA. Recent fMRI studies are thought to agree with these studies having demonstrated prefrontal hyperactivation during *n*-back and attention-requiring tasks. This was interpreted as "less efficient" processing due to impaired signal-to-noise ratio (SNR) of neuronal activity. However, electrophysiological studies of neuronal SNR in primates and humans imply that prefrontal cortex should show a diminished prefrontal BOLD response in Val carriers. In the present study, we addressed the question of whether the prefrontal SNR of the BOLD response is decreased in Val carriers using a visual oddball task and an approach to analysis of fMRI data that maximizes noise characterization.**

Methods: **We investigated $N=17$ homozygous Met carriers compared with $N=24$ Val carriers matched for age, sex, education, IQ, reaction time (variability) and head motion. Event-related fMRI was conducted presenting 160 visual stimuli (40 targets, checkerboard reversal). Subjects had to respond as quickly as possible to targets by button press. In the fMRI GLM $[y(t)=\beta^*x(t)+c+e(t)]$ analysis, voxel-by-voxel 'activation' $[y(t)]$ as well as residual noise variance $[e(t)=\sigma^2]$ were calculated using a conservative full-width half maximum (FWHM=6 mm).**

Results: **As compared to Val carriers, we observed a stronger and more extended BOLD responses in homozygous Met carriers in left supplementary motor area (SMA) extending to ACC and dorsolateral prefrontal cortex. Vice versa, increased levels of noise were seen in Val carriers surrounding the peak activation maximum.**

Discussion: **In line with our expectations from prior electrophysiological studies, we observed a diminished BOLD response and increased noise in Val carriers. This suggests that the DA stabilizes cortical microcircuits by sharpening the signal and suppressing surrounding noise.**

Keywords: Dopamine; COMT; Prefrontal; Attention; fMRI

Introduction

In 2001, Egan et al. reported that a single nucleotide polymorphism (Val$^{108/158}$Met) in the catchol-*O*-methyltransferase (COMT) gene predicts executive cognition and the efficiency of prefrontal function in humans as assayed with functional magnetic resonance imaging (fMRI) during a working memory task. Since this initial report, several neuropsychological, electrophysiological and functional neuroimaging studies have been published which essentially confirmed and extended the original findings (Bilder et al., 2002; Malhotra et al., 2002; Mattay et al., 2003; Gallinat et al., 2003; Enoch et al., 2003; Goldberg et al., 2003; Diamond et al., 2004; Rosa et al., 2004; Foltynie et al., 2004; Bertolino et al., 2004; Weickert et al., 2004; Bearden et al., 2004; Blasi et al., 2004; Meyer-Lindenberg et al., 2005; De Frias et al., 2005; Bruder et al., 2005; Galderisi et al., 2005; Baker et al., 2005; Winterer et al., 2006). In line with these results are studies of COMT knockout mice (Gogos et al., 1998) as well as pharmacological investigations with COMT inhibitors showing specific prefrontal effects on dopamine (DA) levels (Turnbridge et al., 2004) and improved cognitive performance both in rats (Khromova et al., 1997; Liljequist et al., 1997) and in humans (Gasparini et al., 1997; Apud et al., in press). The particular scientific meaning of this work is that the COMT Val$^{108/158}$Met single nucleotide polymorphism (SNP) possibly contributes to the risk for schizo-

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phrenia illness (Glatt et al., 2003; Harrison and Weinberger, 2005; Williams et al., 2005) and that it is the first SNP, which has been consistently associated with human prefrontal function (Weinberger et al., 2001; Winterer and Goldman, 2003). In addition, this work is contributing to our knowledge about the neuromodulatory action of DA on prefrontal brain function, which is important because there is still a lack of clear understanding of the basic principles of actions of DA in the prefrontal cortex (Seamans and Yang, 2003).

The COMT gene codes for the dopamine DA catabolizing enzyme COMT and contains a functional and common variation in its coding sequence, i.e., a substitution of valine (Val) by methionine (Met) in the peptide sequence, which is caused by a transition of guanine to adenine at codon 158 (Lotta et al., 1995; Lachman et al., 1996). This single amino acid substitution affects the temperature lability of the enzyme; at body temperature, the Met allele has less than half of the enzyme activity as compared to the Val allele (Lotta et al., 1995; Lachman et al., 1996; Weinshilboum et al., 1999; Chen et al., 2004). These data suggest that individuals with Val alleles would have relatively greater inactivation of prefrontal DA and therefore less effective prefrontal DA signaling which in turn provides an explanation for its impact on cognition since DA agonists are well known to affect physiologic correlates of human frontal-lobe-related cognitive function (Mattay et al., 1996).

While there is consistent evidence that the COMT Val$^{108/158}$Met SNP impacts on frontal-lobe-related cognitive function, the precise physiological mechanism by which this is achieved is not clear. Based on electrophysiological studies during attention-requiring and working memory tasks with DA agonists in non-human primates (Sawaguchi et al., 1986, 1990; Williams and Goldman-Rakic, 1995) as well as functional imaging studies of small animals with dopaminergic drugs (Chen et al., 1997), one would expect that Val carriers with less available synaptic DA would show a diminished signal-to-noise ratio (SNR) of prefrontal activity during working memory or attention-requiring tasks. In fact, when discussing their data on the effects of the COMT gene variation on prefrontal function, the authors of the abovementioned imaging studies frequently emphasize that their findings may point to a lower neuronal SNR in Val carriers. However, this interpretation is not easily reconciled with their data. This is because all previously conducted functional magnetic resonance imaging (fMRI) studies found the opposite in Val carriers, i.e., an enhanced BOLD (blood-oxygenation-level-dependent) signal in dorsolateral prefrontal and anterior cingulate cortex either during a working memory task (Egan et al., 2001; Mattay et al., 2003; Bertolino et al., 2004) or during an attentional control task (Blasi et al., 2004). In both experimental conditions, a parametric task design was chosen, that is, the level of task difficulty was systematically varied whereby the observed COMT genotype effect on the prefrontal BOLD response increased with cognitive load consistent with recent neuropsychological studies showing a linear increase of COMT genotype effect on working memory performance or attention as a function of task difficulty (Goldberg et al., 2003; Blasi et al., 2004). When interpreting their results, the authors generally point out that the observation of an enhanced BOLD response in Val carriers may reflect a compensatory, “less efficient” task-related brain response resulting from a diminished neuronal SNR, more or less explicitly referring to the frequently reported observations that more difficult tasks are associated with increased brain activation (Grasby et al., 1994) while task practice is correlated with decreased brain activation (Buckner et al., 1998). This interpretation is also considered to be consistent with evidence that patients with Parkinson's disease show less efficient cortical processing during working memory tasks when they are DA depleted than when they are DA repleted (Mattay et al., 2002; Cools et al., 2002).

This interpretation, however, does not take into account recent comparative studies of the BOLD signal and intracortical electrophysiological recordings as conducted, for instance, by Logothetis et al. (2001). Their findings rather suggest a positive correlation between neuronal SNR and BOLD response. On the other hand, it is also conceivable that the maximal BOLD response in the peak voxels may be greater in Met carriers while in Val carriers the BOLD response is spatially more extended. Given these difficulties when interpreting COMT genotype effects on the BOLD response, scalp-recorded electrophysiological studies in humans, although spatially less accurate, might be helpful for interpretation since they provide a direct measure of neuronal activity. So far, resting EEG (electroencephalogram) and event-related potentials studies reported findings that are more in line with the expectation from animal data of a DA-induced enhancement of neuronal SNR (s.a.). Enoch et al. (2003) reported that Val carriers are characterized by an increase of background noise (alpha-power) in resting EEG. Furthermore, Baker et al. (2005) found that Val carriers have a lower prefrontal signal amplitude of the mismatch negativity event-related potential. In contrast, Gallinat et al. (2003) found that Val carriers show a higher frontal P300 signal amplitude. It has been argued, however, that the frontal P300 characteristically shows a very low amplitude and that the finding of an enhanced frontal P300 amplitude in Val carriers could reflect that event-related electrophysiological noise, i.e., event-related response variability, is increased (Winterer et al., 2003, 2004). In fact, a follow-up event-related P300 potential study in an independent sample, which directly addressed the question of whether prefrontal electrophysiological noise is increased in Val carriers, found that this is the case (Winterer et al., 2006). Together, these electrophysiological studies indicate that Val carriers show apparently higher electrophysiological noise levels while the signal amplitude is decreased, i.e., the SNR is reduced—a finding which was recently further substantiated by Stefanis et al. (2005) who found that reaction variability during an attention-requiring Continuous Performance Task is increased in Val carriers. In light of these electrophysiological and behavioral findings, the question arises whether the previously conducted fMRI studies of an increased task-related BOLD signal in Val carriers reflected increased noise primarily in the spatiotemporal domain. In other words, while Met carriers may show a focused BOLD response in a circumscribed area, Val carriers would be characterized by a spatially extended “noisy” BOLD response pattern. This interpretation of the data gains some support from earlier PET (positron emission tomography) studies, which tested the effect of DA agonists on cerebral blood flow (Weinberger et al., 1988; Daniel et al., 1989, 1991; Mattay et al., 1996). In these studies, the authors interpreted their data as reflecting a sharpening of the signal, i.e., increase SNR. Unfortunately, these earlier studies did not quantify this possible effect of DA agonists but merely conveyed their subjective impression.

In the present study, we addressed the question of whether the prefrontal SNR of the BOLD response is decreased in Val carriers using a visual oddball task and an approach to analysis of fMRI data that maximizes noise characterization (Winterer et al., in press; Musso et al., 2006). In previous work, we have shown that prefrontal activation with maximum activation in the supplemen-

tary motor cortex (SMA) during comparable task conditions is related to 'motivation' respectively 'task engagement' and 'selective attention' (Winterer et al., 2001, 2002, in press; Mulert et al., 2001; Gallinat et al., 2002; Musso et al., 2006). Analyses of fMRI indices were done separately for the region of the peak BOLD response in SMA as well as for the surrounding medial frontal lobe (MFL).

Methods

Subjects

$N=44$ unrelated healthy Caucasian (European) subjects (20 males, age: 22.7±1.7 years, all right-handed) were investigated with fMRI and genotyped for COMT Val/Met. Participants were only included if there was no evidence of a medical or neurological condition that could interfere with the purpose of the study or if there was a history for any psychiatric DSM-IV axis I or axis II disorder including current or recent drug or alcohol abuse as assessed by a Structured Clinical Interview (First et al., 1995), a formal medical and neurological examination including urine toxicology for illegal drug abuse screening, routine blood and urine investigation and a clinical EEG session. Written informed consent was obtained from all study participants. The study was approved by the Ethics Committee of the Johannes Gutenberg-University.

Behavioral task

Subjects were required to perform a visual oddball task adapted to an 'event-related' fMRI design with presentation of 160 visual stimuli (40 targets, 120 non-targets, checkerboard reversal, that is, target stimuli were reversed black–white checkerboards). Stimuli were presented by means of a back-projection system onto a translucent screen using the 'Presentation' software package (Neurobehavioral Systems Inc.®). Subjects were instructed to respond as quickly and accurate as possible to each stimulus by pressing with either the left or the right thumb either the left button (non-target) or the right button (target) of a button box held with both hands. Stimuli were presented with a duration of 500 ms in counter-balanced and pseudorandomized order at 'jittered' inter-stimulus intervals (ISIs) of 6000±500 ms between stimulus onsets. The relatively short and pseudorandomized ISIs were chosen because a similar stochastic task design was successfully used in previous fMRI studies (Winterer et al., 2002; Musso et al., 2006). Motor responses (latencies, errors and missing button presses) were recorded through a fiber optic response box. The total duration of the task was 960 s.

MRI scanning

Imaging was performed with a 1.5 T Siemens Sonata® scanner with an 8-channel head coil. In order to avoid head movements, the head of each subject was tightly fixated during the scanning procedure using cushions. To facilitate localization and co-registration of functional data, structural scans were acquired using T1-weighted MRI sequences (magnetization prepared rapid gradient echo (MP-RAGE)): TR/TE=2860/3.93 ms, flip angle=15°, 176 slices, slice thickness=1 mm, matrix: 176*256*256. While subjects performed the visual oddball task, event-related functional magnetic resonance imaging (fMRI) data (TR/TE=3000 ms/60 ms, flip angle=90°, field of view (FOV)=192*192 mm^2, matrix=64*64, 25 axial slices, voxel dimensions 3.0*3.0*5.5 mm^3) were collected (in total: $N=320$ TRs). Stimulus presentation was triggered continuously by slice acquisition of functional images. The imaging experiment was previously validated in a subset of the present sample to measure attentional network function (Musso et al., 2006).

Image analysis

fMRI analysis was performed with FSL (FMRIB's Software Library, http://www.fmrib.ox.ac.uk/fsl). The first three volumes (TRs) were excluded from further analysis. Visual inspection of motion correction estimates confirmed that no participant's head moved >1.0 mm from one volume acquisition to the next. The following pre-statistics processing was applied: employing different modules of FSL software package, we conducted motion correction using MCFLIRT (Jenkinson et al., 2002), non-brain removal using BET (Smith, 2002), spatial smoothing using a Gaussian kernel of FWHM=6 mm, mean-based intensity normalization of all volumes by the same factor and highpass temporal filtering (Gaussian-weighted LSF straight line fitting, with sigma=9.0 s). General linear model (GLM) time-series statistical analysis of individual data sets was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction. Registration of functional images to high-resolution structural images was carried out using FLIRT (Jenkinson et al., 2002; Forman et al., 1995). For further analysis of the functional data, we used one explanatory variable (i.e., visual target stimulus) convolved with a Double-Gamma hemodynamic response function, that is, the target-related BOLD response was compared to baseline. The Double-Gamma function is a mixture of two Gamma functions—a standard positive function and a small delayed, inverted Gamma to model the late undershoot. In the GLM $[y(t)=\beta^* x(t)+c+e(t)]$ analysis, cluster-corrected ($Z>2.3$) voxel-by-voxel 'activation' $[y(t)]$ and the residual noise variance $[e(t)=\sigma^2]$ of the BOLD target responses were calculated for each individual and then subjected to a group-level mixed effect analysis which was conducted with FLAME (FMRIB's Local Analysis of Mixed Effects) (Behrens et al., 2003) with spatial normalization to Talairach space and applying a cluster significance thresholded of $Z>2.3$ (Worsley et al., 1992; Friston et al., 1994; Forman et al., 1995). For visual display of the Talairach-transformed group results, Z-maps of the functional data were imported to AFNI (Analysis of Functional Neural Images software; http://www.afni.nimh.nih.gov/afni/afni) and cortical surface maps were created with SUMA (Surface Mapping AFNI).

In addition, we conducted volume-of-interest (VOI) analyses. These analyses were based on a region-of-interest identified in previous electromagnetic source analyses and fMRI studies (Winterer et al., 2001, 2002, in press; Mulert et al., 2001; Musso et al., 2006), which encompasses the MFL with maximum activation in the SMA and includes the adjacent dorsal anterior cingulate cortex (ACC). Two different strategies of VOI analysis were adopted: (1) for VOI analyses of the BOLD response and residual error variance (noise), we draw a bihemispheric VOI along the anatomical borders of the MFL including the adjacent ACC (Fig. 1) as previously described (Winterer et al., in press). This strategy was chosen in order to detect residual error variance (noise) surrounding the area of the maximum task-related BOLD response ("extended" VOI).

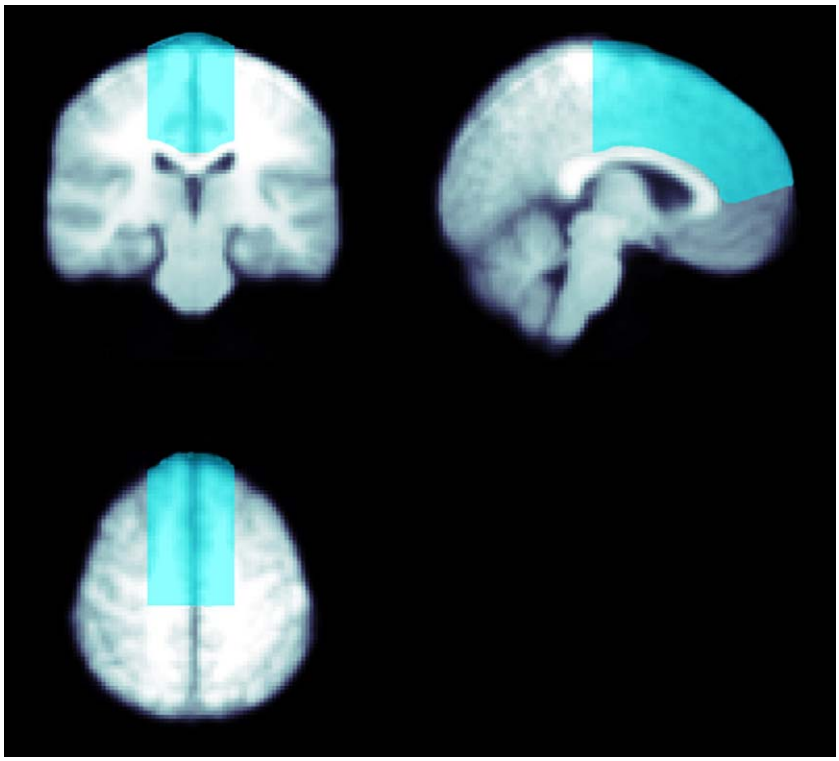

Fig. 1. Volume-of-interest (VOI) of the bilateral medial frontal lobe (MFL) and adjacent anterior cingulate cortex (ACC) ("extended" VOI).

Within the resulting (bihemispheric) VOIs, cluster-corrected 'activated' voxels (thresholded at $Z>2.3$) were counted and the residual error variance (σ^2) was quantified for each subject. (2) In addition, we quantified the task-related peak BOLD response and residual error variance in the SMA, that is, a mask was created based on the peak response of the overall group average (Fig. 2) and transformed back to individual brains ("peak" activation VOI).

Genotyping

DNA was obtained from venous blood using standard techniques. Polymerase chain reactions (PCRs) were performed with primers flanking the COMT Val^{158}Met site (forward: 5′ACT GTG GCT ACT CAG TGT G 3′, reverse: 5″ CCT TTT TCC AGG TCT GAC AA 3′). The single nucleotide polymorphism (rs4680) was genotyped using a template-directed dideoxy dye-terminator incorporation assay with fluorescent detection based upon BigDye terminator reagents (Applied Biosystems®, Weiterstadt, Germany). Analyses were performed using a Megabace 1000 automatic sequencer (Amersham Biosciences®, Freiburg, Germany).

Statistics

For between-group comparisons of genotypes, heterozygous and homozygous Val carriers were combined to one group in order to obtain a sufficiently large group for statistical analyses and then compared with homozygous Met carriers. Between-genotype group comparisons of experimental (behavioral oddball data) and demographic variables were conducted with 2-tailed Student's t tests or chi-square tests as appropriate. Between-genotype group comparisons of fMRI VOI measures (dependent variables) were performed with an ANOVA model with genotype as factor to allow for the inclusion of covariates.

Results

Experimental and subject parameters

Task and subject parameters are provided in Table 1. Genotype distribution with a relatively high prevalence of Met carriers in our sample of European Caucasians is in accordance with a previous independent investigation conducted in Germany (Gallinat et al., 2003). The only significant between-genotype group difference was found for age, which, however, was minimal. Genotype had no statistically impact on behavioral performance. Even so, Met carriers showed numerically faster and less variable reaction times as well as less absolute head movements in the scanner differences that may have become statistically significant with a larger sample size. Also, Met carriers had a numerically longer duration of education.

Imaging data

Task-related effects on BOLD response

Fig. 2 provides an overview of GLM voxel-by-voxel group-level target-related BOLD signal changes. As expected from previous work using similar or the same task conditions (Winterer et al., 2002, in press; Musso et al., 2006), significant BOLD responses were found bilaterally in the MFL with a maximum in the left-hemispheric SMA extending into the dorsal ACC, dorsolateral prefrontal and parietal cortex.

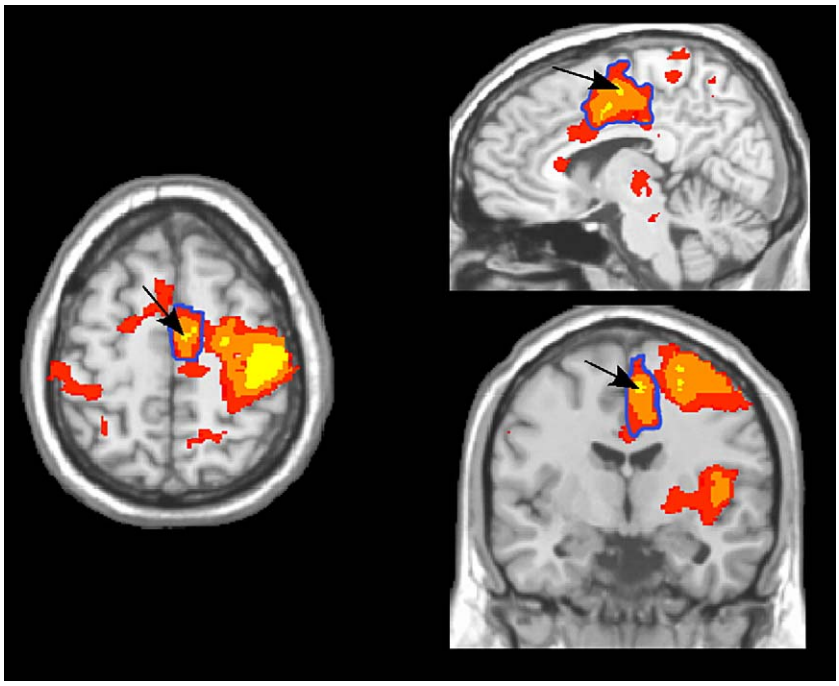

Fig. 2. Averaged event-related BOLD response (all subjects) [AFNI-View] during visual oddball task (checkerboard reversal) in the area of interest (Omnibus statistical threshold: $Z=2.3$, $P<0.01$, cluster-corrected, 2-sided; Talairach-transformed, FWHM=6 mm). The encircled area is the region of maximum response and was used as a mask for a VOI analysis of the peak BOLD response ("peak" activation VOI). The maximum BOLD response is seen in the SMA ($Z=5.5$; $P<0.00001$; $x=6$ mm, $y=8$ mm, $z=51$ mm). For further details, see the Results section.

Effect of COMT genotype on BOLD response (voxel-by-voxel analysis)

Fig. 3 provides an overview on the effect of COMT genotype on the event-related BOLD response. It becomes apparent that Val carriers show a stronger and less extended BOLD response than homozygous Met carriers (for quantitative analysis, see VOI analyses, below). An overview on the residual error variance (noise) pattern is given in Fig. 4. In Val carriers, more noise was observed over a wide area of the cortical surface than do homozygous Met carriers.

Table 1
Experimental and subject parameters by genotype group

	Met/Met ($N=17$)	Val/Met ($N=14$)+ Val/Val ($N=10$)	P
Age (years)	23.6±1.7	22.2±1.4	0.005
Sex (m/f)	7/10	11/13	0.767
Smoking (yes/no)	6/11	7/17	0.678
Education (years)	14.9±3.1	13.5±3.0	0.172
Reaction time (ms)	510.7±48.4	533.5±61.2	0.209
Reaction time variability (ms)	87.9±16.9	97.5±30.1	0.241
Reaction errors (%)	0.9±0.6	0.9±1.0	0.840
Head movement (mm, absolute)	0.25±0.19	0.39±0.29	0.105
Head movement (mm, relative)	0.06±0.05	0.06±0.04	0.851
VOI size (n of voxels, mask)	537.8±43.2	552.9±62.8	0.409
VOI size (n of voxels, anatomical)	3720.3±275.6	3790.6±468.2	0.594

Difference significance obtained with 2-tailed Student's t test except for sex and smoking status (χ^2).

Effect of COMT genotype on BOLD response (extended anatomical VOI)

Comparing Val carriers with homozygous Met carriers in the "extended" anatomical VOI, a significantly stronger BOLD response ($F=7.0$; $df=38$; $P=0.0115$) was found in the latter group (Fig. 5). At the same time, the residual error (noise) of the BOLD response was found to be significantly higher ($F=4.7$; $df=38$; $P=0.0360$) in Val carriers (Fig. 6). The difference of the BOLD response hardly changed when covarying either for age ($F=7.3$; $df=1$, 37; $P=0.0102$), education ($F=6.3$; $df=1$, 37; $P=0.0171$), reaction time ($F=5.9$; $df=1$, 37; $P=0.0197$), reaction time variability ($F=6.2$; $df=1$, 37; $P=0.0177$) or absolute head movement ($F=6.0$; $df=1$, 37; $P=0.0187$). The obtained BOLD response also was comparable bilaterally (left: $F=5.9$; $df=1$, 38; $P=0.0204$; right: $F=5.5$; $df=1$, 38; $P=0.0240$). No linear genotype–dose effect was observed, i.e., homozygous Val carriers were found to activate the medial prefrontal cortex about as much as heterozygous Val/Met subjects (mean n of voxels: 23.6±29.0 vs. 20.0±33.9). This is consistent with our previous electrophysiological investigation using similar oddball task conditions (Gallinat et al., 2003).

Effect of COMT genotype on BOLD response (peak activation VOI)

Similar to the finding in the "extended" anatomical VOI (s.a.), homozygous Met carriers showed an about twice as strong BOLD response in the VOI of the "peak" activation, i.e., n of significantly activated voxels (Met/Met: 58.3±75.1 vs. Val/Met+Val/Val: 21.4±31.5; $F=4.8$; $df=38$; $P=0.0352$) in the ANOVA model. However, when comparing residual error (noise) in the peak

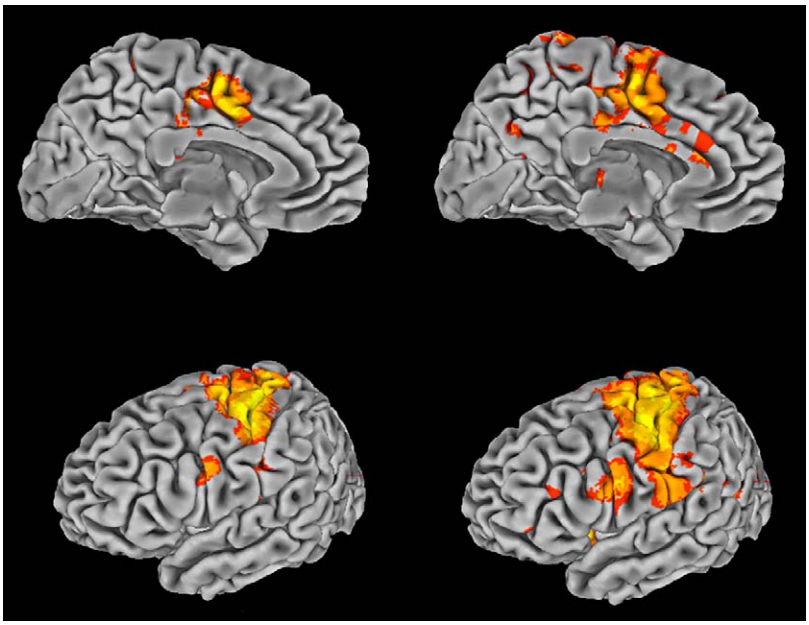

Fig. 3. Surface map [SUMA] of event-related BOLD response in Val carriers (left) and homozygous Met carriers (right). A stronger and more extended BOLD response is seen in homozygous Met carriers in the area of the SMA with extension into the ACC, dorsolateral prefrontal cortex and parietal cortex (Omnibus statistical threshold: $Z=2.3$, $P<0.01$, cluster-corrected, 2-sided; Talairach-transformed, FWHM=6 mm).

activation area between genotype groups, the difference was no longer statistical significant (Met/Met: 5387.2±2598.4 vs. Val/Met+Val/Val: 7066.6±5298.4; $F=1.4$; $df=38$; $P=0.2464$). Again, no major changes were seen for the peak BOLD response when covarying for age ($F=6.1$; $df=1, 37$; $P=0.01885$), education ($F=4.2$; $df=1, 37$; $P=0.0471$), reaction time ($F=4.5$; $df=1, 37$; $P=0.0410$), reaction time variability ($F=4.7$; $df=1, 37$; $P=0.0370$) or absolute head movement ($F=4.5$; $df=1, 37$; $P=0.0413$). As opposed to the analysis in the extended anatomical VOI, the peak BOLD response showed, however, a bilateral difference (left: $F=4.6$; $df=1, 38$; $P=0.0377$; right: $F=1.7$; $df=1, 38$; $P=0.1963$).

Regression analysis

In an additionally conducted regression analysis, a significant correlation ($R=0.37$; $P=0.0188$) was found between reaction time variability (but not reaction time) and residual error variance (anatomical VOI) as previously observed in a similar way in an independent sample (Winterer et al., in press). No statistically

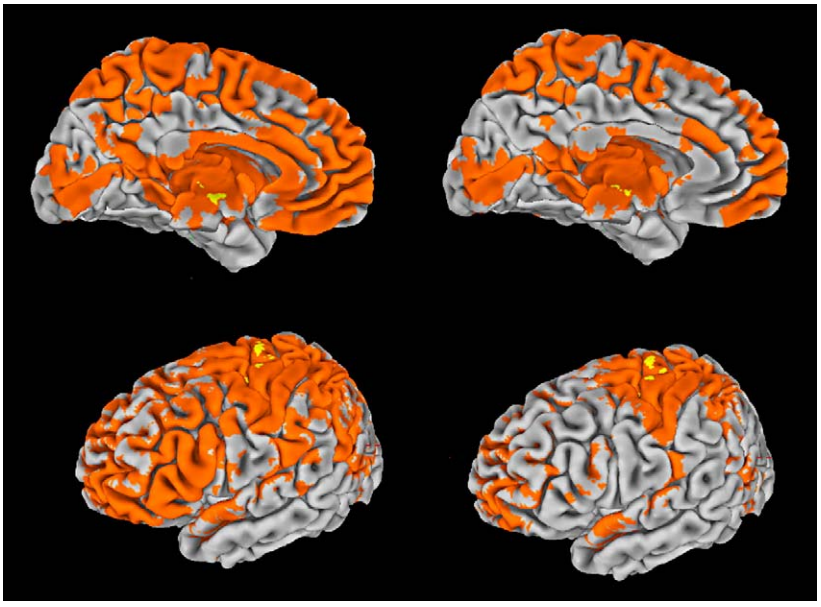

Fig. 4. Surface map [SUMA] of event-related BOLD response noise, i.e., residual error variance (σ^2) in Val carriers (left) and homozygous Met carriers (right). Less noise is seen in homozygous Met carriers in the area of the SMA with extension into the ACC, dorsolateral prefrontal cortex and parietal cortex (Omnibus statistical threshold: $Z=2.3$, $P<0.01$, cluster-corrected, 2-sided; Talairach-transformed, FWHM=6 mm).

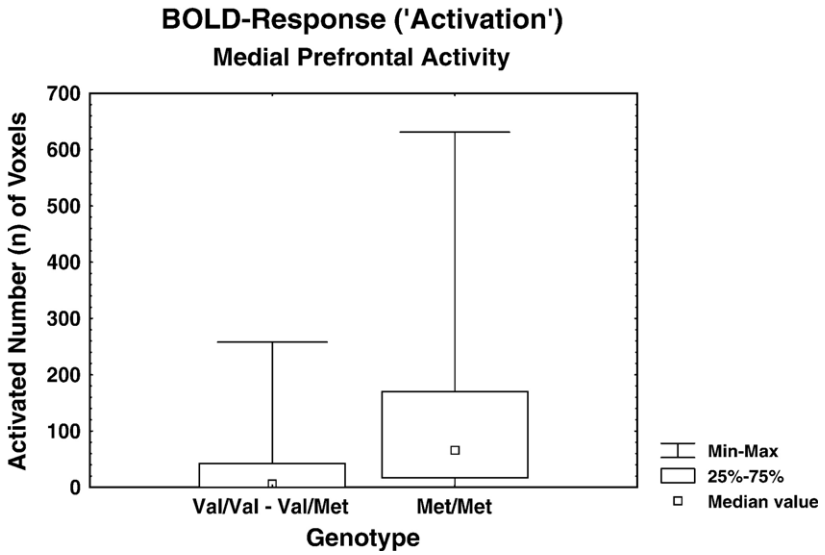

Fig. 5. Volume-of-interest (VOI) analysis of the anatomical "extended" VOI (MFL) comparing the event-related BOLD response (n of activated voxels, $Z=2.3$, $P<0.01$, cluster-corrected, 2-sided; FWHM=6 mm, untransformed) of Val carriers (left) with Met carriers (right).

significant correlations were seen between reaction time and BOLD response.

Discussion

Earlier electrophysiological studies in non-human primates have shown that the modulatory role of DA on neuronal activity critically determines the SNR of neuronal firing in prefrontal cortex (Sawaguchi et al., 1986, 1990; Williams and Goldman-Rakic, 1995). Using COMT genotype as a probe, Winterer et al. (2006) demonstrated this DA effect in humans by means of scalp-recorded electrophysiological recordings, that is, a higher prefrontal level of event-related electromagnetic response variability was observed. The present investigation is the first neuroimaging study which provides direct and quantifiable evidence that COMT Met genotype – and by extension DA– impacts on prefrontal brain physiology by enhancing the SNR of the task-related BOLD response. In essence, it could be demonstrated in this study that the DA effect on brain function may not only depend on the overall level of "activation" (i.e., GLM BOLD response) in distinct prefrontal brain regions but rather that DA also is reducing signal variability (noise) of prefrontal brain responses. This DA effect of noise reduction appears to be particularly strong in the area surrounding the peak activation rather than in the peak area itself. Thus, while noise was not significantly different in the peak activation area between genotype groups, the difference was significant in the extended area (anatomical VOI). It needs to be taken into account at this

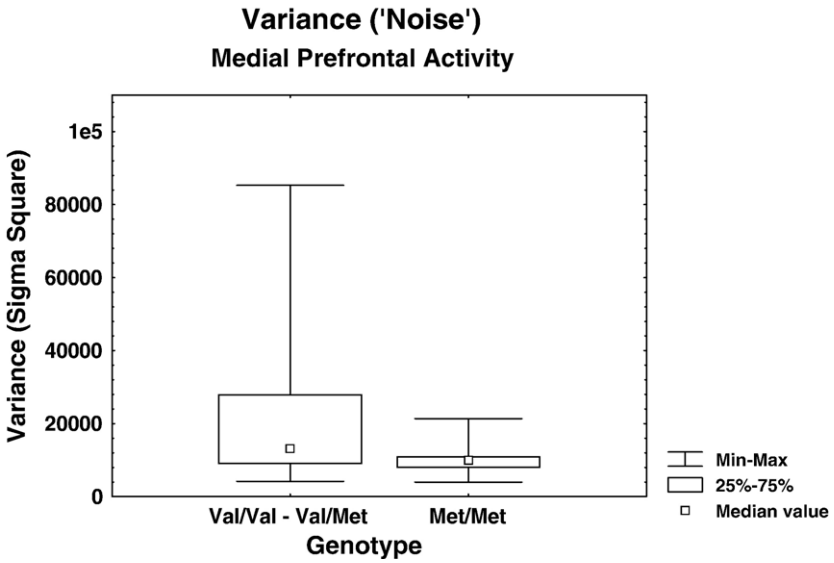

Fig. 6. Volume-of-interest (VOI) analysis of the anatomical "extended" VOI (MFL) comparing the event-related BOLD response noise (residual error variance σ^2, $Z=2.3$, $P<0.01$, cluster-corrected, 2-sided; FWHM=6 mm, untransformed) of Val carriers (left) with Met carriers (right).

point, however, that the time resolution of electrophysiological measures is three orders of magnitude higher than in fMRI investigations, which provides a higher sensitivity with regard to the detection of brain response latency jittering. Vice versa, spatial resolution of fMRI is higher so that both methodological approaches can be considered complementary. In fact, while our previous electrophysiological investigation (Winterer et al., 2006) emphasized variability of brain responses in the time domain as a function of COMT genotype, the present fMRI investigation shows brain response variability being also affected in the spatial domain, i.e., in the surrounding area of the peak response. Taken together, the fMRI findings as well as electromagnetic brain responses (Winterer et al., 2006) and observations of behavioral performance (Stefanis et al., 2005) together suggest that DA ultimately stabilizes prefrontal cortex function both in the spatial domain (surrounding inhibition of spontaneous activity) and in the time domain (stimulus phase-locking of brain responses) and that these two effects ultimately may lead to a stabilization of prefrontal-cortex-related cognitive operations.

It also needs to be acknowledged that the BOLD response in our task is spatially more extended in homozygous Met carriers as opposed to Val carriers. This is different from earlier fMRI studies using working memory tasks (Egan et al., 2001; Mattay et al., 2003). A possible explanation for this discrepancy could be provided by a recent study (Smolka et al., 2005) which indicated that task conditions that are more alerting lead to an extended BOLD response. However, there is also an alternative explanation. An important issue to be discussed in this context is that genotype had no statistically impact on behavioral performance. Most likely this is directly related to the moderate difficulty of task condition in our study because previous investigations, which used parametric task designs, also found no genotype effect on behavior in the low-demand condition (Goldberg et al., 2003; Blasi et al., 2004). However, the next question then would be why a very easy task condition as in our study should induce spatially more extended and stronger BOLD responses in homozygous Met carriers as opposed to Val carriers. The answer to this question could be that the two genotype groups use different information processing strategies to achieve the same behavioral results. For instance, in a previous paper (Musso et al., 2006), we have demonstrated that a more fractionized ("noisier") activation pattern is not necessarily a disadvantage with regard to behavioral performance. In other words, while Met carriers may achieve a certain behavioral performance with a high signal-to-noise ratio of cortical activation, Val carriers may achieve the same results (at least during easy task conditions) by a "noisy" (not stimulus-correlated) activation of even more extended parts of the brain. This explanation may also help to understand why previous fMRI studies (e.g. Egan et al., 2001; Blasi et al., 2004) described a less focused (i.e., more extended) "activation" in Val carriers which, at first glance, appears to be in contradiction with our findings because we found a more extended BOLD response in Met carriers. Given that it is not trivial in fMRI data analysis to precisely differentiate between truly stimulus-correlated BOLD signals and stimulus-uncorrelated "noise" as of the sluggish BOLD response, it is conceivable that what has been reported by those studies in Val carriers as a more extended and less focused "activation" was in fact "noise".

The molecular mechanisms that influence the stability of prefrontal neural network activity are undoubtedly complex (Winterer and Weinberger, 2004). From the now available animal and human data, however, it appears that DA is critically involved in this process, apparently, by shaping the selectivity or SNR of neural activity within cortical microcircuits. DA may function in this way by impacting on the balance of excitatory–inhibitory synaptic interactions, which tend to be dominated by recurrent inhibition (Goldman-Rakic, 1995; Rao et al., 1999). Network simulation studies by Amit and Brunel (1997) and Durstewitz and Seamans (2002) suggest that the local activity of prefrontal excitatory–inhibitory circuits is protected against distractors by dopaminergic mechanisms. How this stabilization and increased SNR of prefrontal networks is exactly achieved on the molecular level is not yet fully understood. However, there is converging evidence that DA impacts glutamatergic activity by enhancing NMDA (*N*-methyl-D-aspartate) and reducing AMPA (alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) receptor postsynaptic currents via D1 receptors in prefrontal pyramidal neurons (Seamans et al., 2001a; Wang and O'Donnell, 2001) and by augmenting a Na^+ current while diminishing an inactivating K^+ current and a dendritic Ca^{2+} current (Yang and Seamans, 1996; Gorelova and Yang, 2000; Maurice et al., 2001). In the computational models of Durstewitz, Seamans and Sejnowski (Durstewitz et al., 1999, 2000; Durstewitz and Seamans, 2002), these dopaminergic effects lead to an input-specific increased firing rate of neurons, thereby increasing inhibitory feedback and thus indirectly reducing activity of the "background" neurons. For the most part, these computational and electrophysiological studies, however, have been conducted in order to model and investigate neuronal activity during the delay period of working memory tasks, and it is not yet clear to what extent comparable mechanisms are also involved during more transient brain responses, e.g. related to selective attention.

DA also appears to affect prefrontal pyramidal neuron activity via input from a direct modulation of GABAergic interneurons (Seamans et al., 2001b). Using whole-cell patch-clamp recordings in vitro and receptor-subtype-specific agonists and antagonists, Seamans et al. (2001b) demonstrated that D2 receptor agonists induce an early and brief decrease in GABA release probability and a reduction of the response to a GABA-A agonist whereas D1 receptor agonists cause a delayed increase of the intrinsic excitability of interneurons. It was concluded from these observations that the early D2-receptor-mediated decrease of inhibition may allow multiple cortical representations of an event to be activated closely in time and even weak representations could pop easily. Conversely, weakly active representations would be subsequently suppressed by D1-receptor-mediated activation and a single or limited number of strongly active representations would become very stable to additional inputs and noise. From these observations, it might be concluded that postsynaptic D2 receptor stimulation is alerting and orienting, but not target discriminating, while D1 receptor stimulation is more critical for response selection, target representation and stability and goal-directed action. Conversely, too much D2 receptor stimulation or a lack of D1-receptor-mediated suppression would be characterized by properties that are reminiscent of neurophysiological, neuropsychological and clinical findings in schizophrenia, i.e., a decreased SNR at the physiological level, poor differentiation of target from background, which could translate into local circuit stimulus overload, and over-alertness and unstable attention to contextually weak internal and external stimuli. It does not seem that far-fetched to speculate that such a state, if prolonged, might ultimately gain the character of poorly vetted sensory and ideational representations, perhaps emerging as hallucinations and paranoia, as well as poor performance on prefrontal-cortex-associated neuropsychological tasks including selective attention, working memory,

planning ability or focused thinking and behavior such as seen in schizophrenia illness. It is therefore an intriguing observation that a poor SNR in prefrontal information processing has also been observed in this illness (Winterer et al., 2000, 2003, in press). Given the prominent role of DA in the pathophysiology of this neuropsychiatric disorder, it was suggested that low prefrontal DA input would tend to favor stimulation of intrasynaptic D2 receptors compared with extrasynaptic D1 receptors resulting in a diminished D1/D2 activation ratio (Winterer and Weinberger, 2004).

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