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Dopaminergic Modulation of Cognitive Preparation for Overt Reading: Evidence from the Study of Genetic Polymorphisms

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Abstract

Choosing and implementing the rules for contextually adequate behavior depends on frontostriatal interactions. Observations in Parkinson’s disease and pharmacological manipulations of dopamine transmission suggest that these corticobasal loops are modulated by dopamine. To determine, therefore, the physiological contributions of dopamine to task-rule–related processing, we performed a cue–target fMRI reading paradigm in 71 healthy participants and investigated the effects of COMT Val158Met, DAT1 VNTR 9/10, and DRD2/ANKK1 polymorphisms. The DRD2/ANKK1 polymorphism did not affect results. IntermediateprefrontaldopamineconcentrationsinCOMTVal158Metheterozygotesfacilitatedpreparatoryinteractionsbetweenthesemialprefrontalcortexandtheleftstriatumduringpreparationforovertreading. Tounderstandthis, this is the first report of an inverted U-shaped curve modulation of cognition-related brain activity by prefrontal dopamine levels. In contrast, a lineareffectofCOMTVal158MetandDAT1VNTR9/10polymorphismsonpreparatoryactivityintheleftinferiorfrontalgyrustointedtoanegativeinteractionbetweentoniclateralprefrontalandphasicsubcorticaldopamine. TheCOMTVal158Metpolymorphismaffectedalsofeedforwardandfeedbackprocessinginthesensorimotorspeechsystem. Ourresultssuggestthatdopaminemodulatescorticobasalinteractionsonbothislandsubcorticallevelbutdifferentlydependingonthespecificcognitivessubprocessesinvolved.

Key words: COMT Val158Met, DAT1 VNTR 9/10, fMRI, inverted U-shaped curved cortical–subcortical interactions, speech production

Introduction

Cognition involves corticosubcortical loops that are modulated by 3 major dopaminergic pathways: the nigrostriatal, mesocortical, and mesolimbic dopaminergic systems (Lindvall and Bjorklund 1978; Moore and Bloom 1978; Cools 2008). The involvement of the nigrostriatal system in cognition is obvious in Parkinson’s disease in which the negative effects of subcortical dopamine depletion on cognitive function precede neocortical pathology (Dubois and Pillon 1996; Monchi et al. 2007; Arnold et al. 2014). The mesolimbic system consists of dopaminergic fibers arising in the ventral tegmental area (VTA) and projecting to limbic regions. It has been associated with dopaminergic modulation of reward and goal-directed behavior (Schultz et al. 1992). Dopaminergic neuromodulation is anatomically not restricted to the basal ganglia. The mesocortical dopaminergic system provides a large part of the neocortex with dopaminergic...
innervation (Hosp, Hertler, et al. 2011; Hosp, Pekanovic, et al. 2011) and plays a major role in decision-making, motor, executive, and attentional control (Floresco and Magyar 2006; Cools 2008). The primary target of mesocortical dopaminergic projections, at least in rodents (Thierry et al. 1973; Berger et al. 1976), is the prefrontal cortex (PFC), which has been intensively studied with regard to dopaminergic modulation of neocortical functions (Chudassama and Robbins 2004; Seemans and Yang 2004). Thus, dopamine modulates neural processes associated with cognitive functions in both the basal ganglia and the PFC (Arnsten 1997; Seemans and Yang 2004; Colzato et al. 2010; van Schouwenburg et al. 2010).

Along these lines, evidence has been provided that dopaminergic neuromodulation in man is physiologically influenced by genetic functional polymorphisms that code, respectively, for neuromodulator degrading enzymes, transporters, or receptors. Behaviorally relevant frequent functional polymorphisms have been described for the catechol-O-methyltransferase (COMT) gene that codes for the dopamine degrading COMT enzyme, and that is primarily translated in the PFC (Fig. 1; Matsumoto, Weickert, Akil, et al. 2003; Matsumoto, Weickert, Beltaifa, et al. 2003; Chen et al. 2004). In the PFC, COMT is the main clearance mechanism for dopamine (Karoum et al. 1994; Gogos et al. 1998; Reuter et al. 2004). In the PFC, COMT met/met individuals degrade extrasynaptic dopamine to a lesser extent and consequently have higher dopamine availability in the PFC compared with COMT val/val subjects. The codominance of the alleles implies that heterozygous met/val individuals have intermediate prefrontal dopamine levels (Lotta et al. 1995; Fig. 1).

An influential framework suggests that the relationship between prefrontal dopamine levels and cognition (especially working memory performance) follows an inverted U-shaped curve (Williams and Goldman-Rakic 1995; Arnsten 1998; Goldman-Rakic et al. 2000; Castner et al. 2000; Williams-Gray et al. 2007). This suggests that COMT Val158Met homozygosity could be associated with suboptimal cognitive performance compared with COMT met/val heterozygotes. To our knowledge, the inverted U-shaped relationship that has been observed between behavioral parameters and genotype has not been documented for brain activity, suggesting more complex interactions on the neural level. In this fMRI study, we systematically explore whether brain activity related to executive control—specifically task preparation for overt reading—follows the proposed inverted U-shaped curve, which we studied as a function of the COMT Val158Met polymorphism.

Also basal ganglia contribute to higher cognitive processes (Mink 1996; Frank 2005), where subcortical dopamine is secreted phasically via burst firing (Grace 1991; Floresco et al. 2003). Importantly, subcortical dopamine availability and transmission are influenced by genetic polymorphisms in genes coding for the dopamine transporter DAT1 (Ciliax et al. 1995; Sesack et al. 1998; Lewis et al. 2001; Dreher et al. 2009). These polymorphisms act on dopamine availability both intra- and extrasynaptically (COMT Val158Met and DAT1 VNTR 9/10) or directly on synaptic dopamine signaling (DRD2/ANKK1), and could explain interindividual physiological variations in cognitive processes, such as working memory and attention (Reuter et al. 2005).

Three different genotypes of the COMT Val158Met polymorphism exist: Individuals can be homozygous (met/met or val/val) or heterozygous (met/val; Lotta et al. 1995). The distribution of COMT met/met: met/val : val/val in the mixed European population is 27 : 48 : 16 (Palmatier et al. 1999).

Given that the COMT met protein is relatively thermolabile at body temperature, its enzymatic activity is about 25–75% lower compared with the COMT val protein, which is fully active at body temperature (Lotta et al. 1995; Lachman et al. 1996). Thus, COMT met/met individuals degrade extrasynaptic dopamine to a lesser extent and consequently have higher dopamine availability in the PFC compared with COMT val/val subjects. The codominance of the alleles implies that heterozygous met/val individuals have intermediate prefrontal dopamine levels (Lotta et al. 1995; Fig. 1).

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The DRD2/ANKK1 Taq1a SNP (rs1800497) has previously been described as important for working memory processes (Stelzel et al. 2009; Nymberg et al. 2014; Soderqvist et al. 2014). The presence of at least one A1 allele (A1+) has been associated with reduced dopamine D2 receptor density in the human striatum compared with A2 allele subjects (A1−) (Fig. 1; Thompson et al. 1997; Pohjalainen et al. 1998; Jönsson et al. 1999; Ritchie and Noble 2003).

Cortical and subcortical processes involved in cognition do not act in isolation. They rather form functional corticobasal loops, which suggests corticobasal functional interactions. Given the fact that prefrontal dopamine is released tonically

Figure 1. Simplified illustration of polymorphism effects (COMT Val158Met, DAT1 VNTR 9/10, and DRD2/ANKK1) on dopaminergic neuromodulation and cognition. Circles illustrate tonic dopamine effects, and triangles phasic dopamine transmission. DA, dopamine.
from mesocortical axon boutons (Servan-Schreiber et al. 1990; Yacubian et al. 2007), whereas subcortical dopamine is secreted primarily via phasic burst firing (Grace 1991; Floresco et al. 2003), a second influential framework for the modulation of cognitive processes by dopamine has been suggested, that is, the dual-state tonic–phasic dopamine hypothesis which has been related to cognitive flexibility and stability (Bilder et al. 2004). Within this framework, the relationship between prefrontal tonic and subcortical phasic dopamine levels is characterized by an antagonistic relationship. The PFC is thought to tonically inhibit phasic dopamine signals in the midbrain and striatum and vice versa (Carr and Sesack 2000; Bilder et al. 2004). Thus, dopamine effects in the striatum and PFC may be inversely related when studied with respect to cognition. High prefrontal tonic dopamine levels have been associated with cognitive stability, while high subcortical phasic dopamine burst firing has been related to cognitive flexibility (Kolachana et al. 1995; Bilder et al. 2004; Cools and Robbins 2004; Cools et al. 2008). Cognitive flexibility is defined as the ability to change, adapt, update, and/or shift cognitive behavior in response to environmental or performance changes. Therefore, it has been associated with transient brain activation states mainly subcortically (Marklund et al. 2009; Cools and D’Esposito 2011). In contrast, cognitive stability relates to sustained activity of neural networks in the PFC and is required for the maintenance of a given task rule (Colzato et al. 2010; Cools and D’Esposito 2011). Thus, individuals with stronger subcortical dopamine signaling (DAT1 9-repeat individuals and DRD2 A1− subjects) may perform better in tasks requiring cognitive flexibility. However, relatively weaker subcortical dopamine signaling (as in DAT1 10-repeat subjects and DRD2 A1+ individuals) is linked with improved performance in tasks that involve cognitive stability at the expense of decreased efficiency in adjusting and updating newly learned task rules (Fig. 1; Jochem et al. 2009). This inverse relationship between prefrontal tonic and subcortical phasic dopamine signaling manifests in a mirror image for prefrontal COMT Val158Met polymorphism effects. Lower prefrontal tonic dopamine concentrations in COMT Val/met subjects may be advantageous for cognitive flexibility, whereas higher prefrontal tonic dopamine levels in COMT met/met individuals have been associated with better cognitive stability (Fig. 1; Colzato et al. 2010; de Frias et al. 2010).

These effects of dopaminergic neuromodulation have been studied intensively using working memory paradigms. However, it is so far unclear whether other prefrontal computations are also modulated by dopamine and, if so, in which way. Another important prefrontal function is the implementation of contextually adequate behavioral rules (Dosenbach et al. 2006; Sakai and Passingham 2006). The implementation and maintenance of so-called task-sets can be studied by using cue–target paradigms in which cues inform participants about the task rule to be applied to a subsequently presented target stimulus. This requires flexible switching from the former rule to a new one, but also entails the maintenance of the task-set during the preparation and execution period of each trial. The set-up and maintenance of these task rules have been associated with a core network consisting of bilateral mesial prefrontal and anterior insular cortices (Dosenbach et al. 2006), while more dorsolateral parts of the PFC (DLPFC) have been associated with contextual control (Koechlin et al. 2003). All these regions are innervated by the mesocortical dopaminergic system, but cognitive preparation for a given task could also be affected by subcortical dopaminergic systems through modulation of frontobasal loops. We previously studied cognitive preparation for articulation and observed that it involved both the PFC and basal ganglia together with a preactivation of the cortical speech networks (Kell et al. 2011).

Importantly, frontobasal loops involved in cognitive preparation for overt reading are impaired early in Parkinson’s disease patients, before cortical involvement becomes manifest and overt speech symptoms develop (Arnold et al. 2014). Corticobasal interactions during overt speaking have recently been related to nigrostriatal dopaminergic signaling (Simonyan, Herscovitch, et al. 2013). These findings suggest that cognitive preparation for speaking is at least modulated by the nigrostriatal dopaminergic system. They do not, however, provide an answer whether dopamine effects in the PFC also contribute to setting up and implementing task-sets.

To target effects related to the generation and implementation of speech production task-sets, we investigated cognitive preparation for overt versus covert reading. The execution phase of overt versus covert trials of a sentence reading paradigm was studied to delineate effects of the aforementioned polymorphisms in the dopaminergic system on sensorimotor processes underlying articulation itself. By investigating effective connectivity in addition to brain activity, we target corticobasal loops hypothesizing that they can be affected by subcortical (nigrostriatal) or cortical (mesocortical) dopamine effects. To test whether the studied polymorphisms also affect mesolimbic processing, we included a condition in which participants were asked to pronounce the emotionally neutral sentences happily, which requires emotion induction besides additional sensorimotor processing and executive control compared with neutral intonation (Pichon and Kell 2013). All dependent variables were tested for effects that could confirm the dual-state tonic–phasic model (Bilder et al. 2004) and/or the proposed model of an inverted U-shaped curve (Williams and Goldman-Rakic 1995; Meyer-Lindenberg et al. 2005). We found gene-activation and gene-connectivity effects for the COMT Val158Met and DAT1 VNTR 9/10, but not for the DRD2/ANKK1 polymorphism, although in different parts of the PFC. While linear effects of COMT Val158Met and DAT1 VNTR 9/10 polymorphisms related to the tonic–phasic model were found in the left inferior frontal gyrus (IFG), the COMT Val158Met polymorphism modulated preparatory mesial PFC (mPFC) activity and frontostriatal effective connectivity in such a way that it followed an inverted U-shaped curve. To our knowledge, this is the first report demonstrating such a relationship between genes controlling dopaminergic signaling and corticobasal interactions.

Our results suggest that polymorphisms affecting dopaminergic signaling determine the degree of mesial prefrontal engagement in cognitive preparation differently from the way they affect the left IFG. Thus, different cognitive subprocesses appear to be differently modulated by dopamine.

**Materials and Methods**

**Participants**

Seventy-one healthy male participants [mean age 27.6 years, standard error of the mean (SEM) = 0.5 years, average laterality quotient of 71.5 as measured by the Edinburgh handedness preference inventory (Oldfield 1971)] were recruited via advertisements and via the German Red Cross Blood Service in Frankfurt (see Supplementary Table 1 and Table 1). Each participant was a native German speaker, gave written informed consent according to the guidelines of the local research ethics committee (Goethe University, Frankfurt, Germany), and was paid for participation.
Participants were excluded if they reported visual, hearing, reading impairments, as well as other cognitive, neurological, psychiatric/affective, or speech/language disorders. General fMRI exclusion criteria were pace-makers, other implanted metal parts, or claustrophobia.

Primarily, the estrogen metabolism but also other female gonadal hormones have been shown to influence dopamine availability (Becker and Cha 1989; Xiao and Becker 1994; Pasqualini et al. 1995; Becker 2008) via modulation of striatal DAT1 (Alyea et al. 2008) or prefrontal COMT activity (Jacobs and D’Esposito 2011). The fact that estrogen is modulating dopamine activity was only observed in females but not in males (McDermott et al. 2011). The fact that estrogen is modulating dopamine activity was only observed in females but not in males (McDermott et al. 2011). The fact that estrogen is modulating dopamine activity was only observed in females but not in males (McDermott et al. 2011).

**Genetic Analyses**

Genetic analyses of the acquired blood samples, taken from the participants, were performed according to standard protocols (see Supplementary Methods). As in earlier studies (Yacubian et al. 2007; Garcia-Garcia et al. 2010), participants genotyped as 10/10 repeat were assigned to the DAT1 VNTR 10-repeat carrier group, and those individuals with DAT1 9/9 or 9/10 repeats were both included in the DAT1 9-repeat group (Table 1). Homozygous A1/A1 individuals are known to be very rare in the Caucasian population (Noble 2000). Participants with at least one A1 allele of the DRD2/ANKK1 polymorphism (A1/A1 and A1/A2) therefore formed the A1+ group, carriers of the A2/A2 allele constituted the A1− group (Ritchie and Noble 2003). The sample of recruited participants reflected the distribution of genetic polymorphisms in the Caucasian population (Table 1; Doucette-Stamm et al. 1995; Kang et al. 1999; Palmatier et al. 1999; Noble 2000; Ritchie and Noble 2003).

**Behavioral Data Acquisition and Analysis**

**Reading Task**

Before fMRI scanning, all participants performed a reading task in which semi-grammatic neutral declarative German sentences with similar syntactic structure (e.g. “Grüne Marken kleben vorne auf dem Umschlag,” translated: “Green stamps are stuck to the front of the envelope”) were presented visually on a computer screen using the Presentation software (Neurobehavioral Systems, Albany, CA, USA). Before the presentation of each sentence, a written word was presented, which indicated how the following sentence had to be read: either covertly or overtly with neutral or overtly with happy intonation. The instruction delays, corresponding to the time between visual presentation of the cue and the sentence, varied between 0.33, 0.67, and 1.00 s. We measured speech reaction times (defined by the duration between visual onset of the sentence as indicated by an auditory trigger and speech intensity exceeding 20 dB) and error rates. In the beginning, all subjects had trouble reading a neutral sentence happily. We thus trained them outside the scanner to make sure that all subjects were later able to speak with convincing affective prosody during fMRI scanning (Pichon and Kell 2013). We audio-recorded the speech samples of the reading task with a standard microphone in Adobe Audition (San Jose, CA, USA) and stored them for further analysis. Error rates and reaction times during reading with neutral or happy intonation as dependent variables were tested in mixed models (SPSS, Inc., Chicago, IL, USA) for task- dependent group differences and did not reveal any significant effects at P < 0.05. The factorial analysis focused on effects of task (overt reading with neutral or happy intonation), instruction delay (0.33, 0.67, and 1.00 s), and group (genetic subgroups of each polymorphism or gene–gene interaction).

**Table 1 Genetically defined groups**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean age (SEM)</th>
<th>Mean handedness</th>
<th>COMT Val158Met</th>
<th>DAT1 VNTR</th>
<th>DRD2/ANKK1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mm : mv : vv</td>
<td>9/10 : 9</td>
<td>A1+ : A1−</td>
</tr>
<tr>
<td>COMT met/met</td>
<td>26</td>
<td>27.9 (0.9)</td>
<td>70.5</td>
<td>—</td>
<td>13 : 13</td>
<td>10 : 16</td>
</tr>
<tr>
<td>COMT met/val</td>
<td>26</td>
<td>26.6 (0.6)</td>
<td>73.5</td>
<td>—</td>
<td>13 : 13</td>
<td>8 : 18</td>
</tr>
<tr>
<td>COMT val/met</td>
<td>19</td>
<td>28.3 (1.4)</td>
<td>70.4</td>
<td>—</td>
<td>6 : 13</td>
<td>6 : 13</td>
</tr>
<tr>
<td>DAT1 9-repeat</td>
<td>39</td>
<td>27.7 (0.7)</td>
<td>70.9</td>
<td>13 : 13 : 13</td>
<td>—</td>
<td>15 : 24</td>
</tr>
<tr>
<td>DAT1 10-repeat</td>
<td>32</td>
<td>27.4 (0.9)</td>
<td>72.3</td>
<td>13 : 13 : 6</td>
<td>—</td>
<td>9 : 23</td>
</tr>
<tr>
<td>DRD2 A1+</td>
<td>24</td>
<td>27.7 (1.0)</td>
<td>79.1</td>
<td>10 : 8 : 6</td>
<td>9 : 15</td>
<td>—</td>
</tr>
<tr>
<td>DRD2 A1−</td>
<td>47</td>
<td>27.5 (0.7)</td>
<td>67.7</td>
<td>16 : 18.13</td>
<td>23 : 24</td>
<td>—</td>
</tr>
<tr>
<td>COMT met/met and DAT1 9-repeat</td>
<td>13</td>
<td>27.5 (1.1)</td>
<td>65.7</td>
<td>—</td>
<td>—</td>
<td>5 : 8</td>
</tr>
<tr>
<td>COMT met/met and DAT1 10-repeat</td>
<td>13</td>
<td>28.4 (1.5)</td>
<td>75.2</td>
<td>—</td>
<td>—</td>
<td>5 : 8</td>
</tr>
<tr>
<td>COMT met/val and DAT1 9-repeat</td>
<td>13</td>
<td>26.5 (0.9)</td>
<td>74.9</td>
<td>—</td>
<td>—</td>
<td>5 : 8</td>
</tr>
<tr>
<td>COMT met/val and DAT1 10-repeat</td>
<td>13</td>
<td>26.8 (0.8)</td>
<td>72.0</td>
<td>—</td>
<td>—</td>
<td>3 : 10</td>
</tr>
<tr>
<td>COMT val/val and DAT1 9-repeat</td>
<td>13</td>
<td>29.1 (1.5)</td>
<td>72.2</td>
<td>—</td>
<td>—</td>
<td>5 : 8</td>
</tr>
<tr>
<td>COMT val/val and DAT1 10-repeat</td>
<td>6</td>
<td>26.7 (2.9)</td>
<td>66.3</td>
<td>—</td>
<td>—</td>
<td>1 : 5</td>
</tr>
<tr>
<td>COMT met/met and DRD2 A1+</td>
<td>10</td>
<td>27.2 (1.6)</td>
<td>74.7</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>COMT met/met and DRD2 A1−</td>
<td>16</td>
<td>28.4 (1.2)</td>
<td>67.8</td>
<td>—</td>
<td>8 : 8</td>
<td>—</td>
</tr>
<tr>
<td>COMT met/val and DRD2 A1+</td>
<td>8</td>
<td>27.3 (1.5)</td>
<td>78.1</td>
<td>—</td>
<td>3 : 5</td>
<td>—</td>
</tr>
<tr>
<td>COMT met/val and DRD2 A1−</td>
<td>18</td>
<td>26.4 (0.5)</td>
<td>71.4</td>
<td>—</td>
<td>10 : 8</td>
<td>—</td>
</tr>
<tr>
<td>COMT val/val and DRD2 A1+</td>
<td>6</td>
<td>29.3 (2.3)</td>
<td>87.8</td>
<td>—</td>
<td>1 : 5</td>
<td>—</td>
</tr>
<tr>
<td>COMT val/val and DRD2 A1−</td>
<td>13</td>
<td>27.9 (1.8)</td>
<td>62.3</td>
<td>—</td>
<td>5 : 8</td>
<td>—</td>
</tr>
<tr>
<td>DAT1 9-repeat and DRD2 A1+</td>
<td>15</td>
<td>27.2 (1.2)</td>
<td>78.6</td>
<td>5 : 5 : 5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>DAT1 9-repeat and DRD2 A1−</td>
<td>24</td>
<td>28.0 (0.9)</td>
<td>66.2</td>
<td>8 : 8 : 8</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>DAT1 10-repeat and DRD2 A1+</td>
<td>9</td>
<td>28.7 (1.7)</td>
<td>80.0</td>
<td>5 : 3 : 1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>DAT1 10-repeat and DRD2 A1−</td>
<td>23</td>
<td>26.9 (1.0)</td>
<td>69.2</td>
<td>8 : 10 : 5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>All participants</td>
<td>71</td>
<td>27.6 (0.5)</td>
<td>71.5</td>
<td>26 : 26 : 19</td>
<td>32 : 39</td>
<td>24 : 47</td>
</tr>
</tbody>
</table>

N, number of participants; mm, met/met; mv, met/val; vv, val/val; 10, 10-repeat; 9, 9-repeat; SEM, standard error of the mean.
Functional Imaging Data Acquisition and Analysis

fMRI Data Acquisition

Two sessions of a gradient-echo T$_1$-weighted transverse echo-planar image (EPI) sequence (separated by a minute of rest) were run on a 3 T magnetic resonance scanner (Siemens Trio, Erlangen, Germany). Each of these EPI sequences consisted of 456 volumes and every volume included 33 axial slices with a repetition time (TR) of 2000 ms, echo time (TE) of 30 ms, flip angle of 90°, isotropic voxel size of 3 × 3 × 3 mm$^3$, distance factor of 25%, and slice thickness of 3 mm. The sequence has been optimized to allow for 3 s of ongoing speech production (Freibisch et al. 2003). High-resolution T$_1$-weighted anatomical scans [144 sagittal slices, 1 slab, TR 2250 ms, inversion time (TI) 900 ms, TE 2.6 ms, flip angle 9°, voxel size 1 × 1 × 1 mm$^3$, distance factor 50%] were acquired to detect potential brain lesions for exclusion of subjects.

All subjects lay supine and obtained headphones for scanner noise protection and for acoustic cue delivery. Foam cushions were used to immobilize the participants’ heads.

fMRI Experimental Procedure

Written sentences were projected using the Presentation software (Neurobehavioral Systems, Albany, CA, USA) onto a screen that participants watched via a coil-mounted mirror. Each session comprised 3 randomized presentations of 25 semantically neutral declarative German sentences with similar syntactic structure (e.g. “Große Kerzen erleuchten hell den Raum,” translated: “Large candles illuminate the room brightly”; every sentence was presented in each condition) that were presented for 3 s each. A randomized auditory cue indicated how the following sentence had to be read [either covertly (without orofacial movement and neutral internal intonation) or overtly with neutral or with happy intonation] 2–4 s before sentence presentation. During this time interval between cue and target, which we termed “cognitive preparation phase,” participants could prepare task rules for subsequent optimal task performance. Specific linguistic or motor processing was not yet possible, given that the auditory cues did not contain any information about the following sentence. The subsequent execution phase thus contained stimulus-related linguistic and, for the overt conditions, motor processing (Fig. 2). The jittered instruction delay between auditory cue and visual sentence presentation temporally de-correlated variance explained by the 2 trial phases to allow for further analyses in SPM8 (Kell et al. 2011; Pichon and Kell 2013; Arnold et al. 2014). About 46% shared variance entered the error term and reflect late phases of task-set maintenance. The preparation regressors thus capture the set-up and early phases of task-set maintenance. The intertrial interval varied between 2 and 10 s (mean 6 s). Despite randomization of the cues, the same trial was repeated in 30% of cases.

Audio-recordings of the acoustic data were assessed with an MRI-compatible microphone (mr confon) and a scanner background noise was filtered out with Adobe Audition to control for behavior inside the scanner.

fMRI Image Processing

All data were preprocessed and statistically analyzed with the standard parameters of SPM8 (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/spm/): First, functional EPI images were spatially realigned using a rigid body spatial transformation (Friston et al. 1994). Then, images were spatially normalized to the standard EPI template of the Montreal Neurological Institute (MNI; Friston et al. 1995). Normalized images were resampled to an isotropic voxel size of 2 mm and smoothed with an isotropic 8-mm full-width at half-maximum Gaussian kernel.

fMRI Whole-Brain Activity

The standard general linear model (GLM) for time series as implemented in SPM8 was used to analyze individual event-related BOLD responses. We created a linear model with 7 regressors for each session. Three regressors modeled the preparation phase (preparation for covert reading, preparation for overt reading with neutral intonation, and preparation for overt reading with happy intonation). Another 3 regressors modeled the corresponding execution phases (covert, neutral, and happy reading). In addition, one regressor for transient cue-related activations for auditory cue presentation and the described 6 movement regressors (realignment parameters as conditions of no interest) were included in the matrix. We identified condition-specific activations of interest separately for preparation and execution of the 3 tasks by convolving the regressors of interest with a canonical hemodynamic response function (HRF). We corrected the data for serial autocorrelations (AR1) and globally normalized them (Kell et al. 2009, 2011; Pichon and Kell 2013; Arnold et al. 2014), such that negative BOLD responses observed in our fMRI data do not necessarily reflect deactivations but rather have to be interpreted as reduced activity compared with the global mean.

Effects of Polymorphisms on Brain Activity

We tested whether and how dopaminergic polymorphisms affected brain activity in the different trial phases and conditions by entering the individual voxel-wise condition- and phase-specific whole-brain beta maps into a between-group three-way ANOVA in SPM8. The design matrix for brain activity included the following 5 factors: subject (71 levels), COMT Val158Met (3 levels: val/val, met/val, and met/met), DAT1 VNTR 9/10 (2 levels: 9- and 10-repeat), DRD2/ANKK1 (2 levels: A1+ and A1–), and condition (7 levels: preparation for covert, neutral and happy reading, execution of covert, neutral and happy reading, auditory cue).

We assessed the main effects of COMT Val158Met, DAT1 VNTR 9/10, DRD2/ANKK1, the interaction terms (COMT × DAT1, COMT × DRD2, or DAT1 × DRD2), the interactions of each polymorphism with the conditions, and the gene–condition interactions. Statistical thresholds were set to $P < 0.05$, “family-wise error” (FWE) corrected. The search spaces for genetic effects were restricted to brain regions that showed an effect of condition. To do so, we created a mask of task-related activations by

Figure 2. Study design. During fMRI scanning, subjects performed a cue–target reading paradigm. An auditory cue indicated 2–4 s prior to each sentence presentation how to read the upcoming sentence. Covert with neutral internal intonation, overt with neutral intonation, or overt with happy intonation. Thus, all trials could be dissociated into a cognitive preparation phase for set-up of task-relevant networks and an execution phase for speech processing. We compared overt reading with neutral intonation vs. covert reading for the preparation (shown in green) and execution phase (illustrated in red), as well as overt reading with happy vs. neutral intonation for the preparation (blue) and execution phase (yellow).
contrasting the highest hierarchical condition (overt reading with happy intonation) against the lowest hierarchical condition (covert reading), separately for the preparation and execution phases, on the individual first level. The resulting contrast maps were subjected to one sample \( t \)-tests separately for preparation and execution and for each studied group, thresholded at \( P < 0.05 \), FWE-corrected. Resulting supra-threshold group activations were summed linearly using SPM8’s imcalc function, resulting in one activation mask (see Supplementary Fig. 1). This approach was selected to keep brain regions inside the mask that activated differently for the separately genetic groups.

To examine which conditions drove the main effects, we extracted individual condition-specific beta values from the main effect clusters and illustrate them in Figure 7. For the main effect of DAT1, the conditions and phases of interest (preparation and execution of neutral or happy vs. covert reading) were compared in two-sample \( t \)-tests. For the main effects of COMT, mixed models were used for post hoc testing. A value of \( P < 0.05 \) was set as significance threshold.

We additionally tested for effects confirming or refuting the inverted U-shaped curve hypothesis only for the COMT Val158Met polymorphism, because it is the only one for which such curves have been reported on the behavioral level and at least three different genotypes are needed to perform such analyses. To focus on modulatory effects of task-sets related with overt articulation, covert reading was used as cognitive baseline. \( T \)-contrasts were performed on all conditions in which we assessed whether the COMT Val158Met polymorphism modulated brain activity in such a way that the distribution over COMT genotypes followed a U-shaped or inverted U-shaped curve (Fig. 3A,B).

![U-shaped and inverted U-shaped curve models](image)

**Figure 3.** Hypothesized relationship between dopamine concentration and brain activity. (A and B) How the COMTVal158Met genotype related to the prefrontal dopamine concentration (\( x \)-axis) may modulate brain activity (\( y \)-axis) in such a way that the distribution over COMT Val158Met genotypes follows an inverted U-shaped curve (A) or a U-shaped curve (B). To test whether the DAT1 VNTR 9/10 or DRD2/ANKK1 polymorphism interacts with the COMT Val158Met polymorphism regarding the U-shaped or inverted U-shaped distribution, DAT1 VNTR 9/10 and DRD2/ANKK1 subgroups are sorted differently (exchanging the position of 9- and 10-repeat or A1+ and A1- individuals on the proposed curves; exemplarily shown for the COMT × DAT1 interaction). The interaction variant 1 (C and D) tests upon the global dopamine concentration in the brain, suggesting an additive subcortical and prefrontal dopamine effect. For the interaction variant 2 (E and F), genetic subgroups are sorted according to the cortical dopamine concentrations, considering a negative interaction between subcortical phasic and prefrontal tonic dopamine. We do not wish to imply drastic effects of the COMT Val158Met polymorphism on brain activity, but rather assume that all 3 genotypes are located closely to the vertex of the U-shaped curve.
separately for each condition of interest (preparation for overt reading with neutral intonation > covert reading, execution of overt reading with neutral intonation > covert reading, preparation for happy > neutral overt reading, execution of happy > neutral overt reading). The first 2 contrasts thus revealed effects related to overt articulation, while the latter pointed to effects associated with increased affective prosodic demands. At the second level, these analyses were implemented as independent two-sample t-tests, in which homozygote groups (val/val and met/met) were compared against heterozygotes (met/val). The conditions of interest were weighted differently for each genotype to detect brain regions in which activity followed an inverted U-shaped curve (val/val = −1, met/val = +2, and met/met = −1), while the cognitive baseline was weighted inversely (val/val = +1, met/val = −2, and met/met = +1; Fig. 3A). To test for activity that followed a U-shaped curve, the values were multiplied by −1 (Fig. 3B). Given previous knowledge and specific hypotheses (see Introduction), we apply a lower statistical threshold of P < 0.001, uncorrected for multiple comparisons within the activation mask at P < 0.05, FWE-corrected (see above). To visualize the gene-activation interactions, we extracted the individual beta values of those brain regions in which brain activity was modulated in such a way that the distribution over COMT Val158Met genotypes followed a U-shaped or inverted U-shaped curve and plotted them as a function of genotype.

We additionally checked whether there were gene–gene interactions affecting the U-shaped or inverted U-shaped curve (Fig. 3A,B), in particular, if the DAT1 VNTR 9/10 or DRD2/ANKK1 polymorphisms interacted with the COMT Val158Met polymorphism. An interaction has to be assumed if the inverted U-shaped curves or U-shaped curves as defined by the COMT Val158Met polymorphism are affected by re-sorting subgroups defined as a function of DAT1/COMT or DRD2/COMT genotypes. In case of a lack of gene–gene interactions, re-sorting subgroups should not alter the shape of the (inverted) U-shaped curves (Fig. 3A,B) and reveal relationships depicted in Figure 3C–F. Interaction effects of COMT × DAT1 or COMT × DRD2 would instead result in an (inverted) U-shaped curve profile only in one possible arrangement but not in the other (variant 1: Fig. 3C,D, or variant 2: Fig. 3E,F). Both variants are theoretically plausible: The interaction variant 1 (Fig. 3C,D) assumes that both cortical and subcortical dopamine affect the measured brain activity in the same way. Given that a negative interaction between prefrontal and subcortical dopamine levels has been proposed (Fig. 1; Karrenman and Moghaddam 1996; Bilder et al. 2004), genetic subgroups could also be sorted accordingly (Fig. 3E,F). For DAT1, we tested for interaction effects with the COMT Val158Met polymorphism by exchanging the position of 9-repeat and 10-repeat and for DRD2 by exchanging the position of A1+ and A1− groups on the proposed curves. To test the inverted U-shaped curve for interaction effects of DAT1, the conditions of interest were thus weighted either vv1010 = −1, vv99 = 0, mv1010 = +1, mv99 = +1, mm1010 = 0, mm99 = −1 (variant 1), or vv99 = −1, vv1010 = 0, mv99 = +1, mv1010 = +1, mm99 = 0, mm1010 = −1 (variant 2). Cognitive baseline conditions were multiplied by −1. The interaction effects between DAT1 and the U-shaped curve were tested accordingly. To test the inverted U-shaped curve for interaction effects of DRD2, the conditions of interest were weighted either vvA1+ = −1, vvA1− = 0, mvA1+ = +1, mvA1− = +1, mmA1+ = 0, mmA1− = −1 (variant 1), or vvA1− = −1, vvA1+ = 0, mvA1− = +1, mvA1+ = +1, mmA1− = 0, mmA1+ = −1 (variant 2). Baseline conditions were multiplied by −1. The interaction effects between DRD2 and the U-shaped curve were also tested accordingly. All tests were thresholded at P < 0.001, uncorrected for multiple comparisons within the activation mask at P < 0.05, FWE-corrected (see above).

Effective Connectivity Analyses (Psychophysiological Interactions)

We additionally studied whether the observed group effects in activity related to changes in modulation of effective connectivity of these brain regions. Psychophysiological interactions (PPIs; Friston et al. 1997) estimate correlations between the temporal series of a given region with the rest of the brain and test whether these correlations are modulated by a psychological variable (in our case overt reading with neutral intonation > covert reading or overt reading with happy intonation > covert reading, separately for preparation and execution), independent of task-related activity changes. Thus, these analyses tested whether the modulation of the effective connectivity between the selected seeds and the rest of the brain induced by overt reading (either with neutral or happy intonation) changed as a function of genetic polymorphisms. First, we tested the effective connectivity of 5 brain regions that showed a COMT Val158Met-dependent U-shaped or inverted U-shaped curve distribution in brain activity during the neutral speech task, namely the mesial frontopolar cortex (BA10) (8, 54, 6), anterior cingulate cortex (ACC; 2, 40, 6), middle cingulate cortex (MCC; 2, 14, 30), mPFC (BA10; 2, 34, 50), and left dorsal striatum (caudate nucleus, CN; −6, 10, 12). Individual seeds were single voxels representing the individual local maxima of activation in a sphere with 5 mm radius centered around the peak of the group activation coordinate (see above). For each seed region and for each task phase, separate PPIs were estimated by extracting the time courses of the first eigenvariate. The time series were corrected for amplitude changes induced by conditions of interest such that the connectivity analyses were performed only on the residuals of the individual models. The deconvolved time series were multiplied with values reflecting whether the condition of interest was ongoing or not. This produced a PPI regressor that again was convolved with the canonical HRF before regressing it voxel-wise over the entire brain.

For each individual participant, we assessed a PPI design matrix for every seed region. Each model included the estimated PPI regressor (see above), the physiological variable, the psychological factor, and 6 realignment parameters. We studied 4 PPIs per regions of interest (ROI) given that we were interested in modulation of functional connectivity by overt reading with neutral intonation > covert reading and overt reading with happy intonation > covert reading (for affective prosody generation), each separately for preparation and execution (Arnold et al. 2014).

PPI maps of the seed regions were entered into separate ANOVAs for genetic connectivity pattern differences including the following 5 factors: subject (71 levels), COMT Val158Met (3 levels: val/val, met/val, and met/met), DAT1 VNTR 9/10 (2 levels: 9- and 10-repeat), DRD2/ANKK1 (2 levels: A1+ and A1−), and condition (4 levels: preparation for overt reading with neutral intonation > covert reading, preparation for overt reading with happy intonation > covert reading, execution of overt reading with neutral intonation > covert reading and execution of overt reading with happy intonation > covert reading). These ANOVAs additionally allowed studying the effects of affective prosody generation on connectivity patterns (preparation for and execution of overt reading with happy > neutral intonation). We also tested whether the effective connectivity of those seed regions whose activity followed a U-shaped or inverted U-shaped curve as a function of the COMT Val158Met genotype (BA10, ACC, MCC, mPFC, and left CN) showed the same profile. We additionally tested for interactions between DAT1 and DRD2 and the inverted U-shaped and U-shaped curves (interaction variants
1 and 2: Weighting the subcortical DAT1 or DRD2 influence differently in effective connectivity of the aforementioned seed regions. We report results of these PPI analyses at $P < 0.05$, FWE-corrected for multiple comparisons in the same 5-mm spheres, which already had served as search volumes for the individual maxima of the studied ROIs (small volume correction, SVC).

We additionally tested whether effective connectivity of brain regions, showing a main effect of COMT Val158Met or DAT1 VNTR 9/10-repeat on the degree of activation, was also modulated by these polymorphisms. Effective connectivity of the left ventral IFG (vIFG, $−52, 12, 4$) and left middle temporal gyrus (MTG, $−62, −32, −2$) was tested for a main effect of COMT Val158Met and effective connectivity of the left dorsal IFG (dIFG, $−56, 8, 18$) for effects of the DAT1 VNTR 9/10 polymorphism. The results of the PPI analyses were thresholded at $P < 0.05$, FWE-corrected for multiple comparisons within the search mask (see above).

To examine which COMT Val158Met genotype drove the main effects, we extracted individual genotype-specific beta values from the main effect clusters and illustrate them in Figure 8. Mixed models were used for post hoc testing. A value of $P < 0.05$ was set as significance threshold.

**Correlation Between Individual Brain Activity and Effective Connectivity**

Given the observed inverted frontostriatal effects of the COMT Val158Met polymorphism, we explored whether there were individual inverse relationships between preparatory prefrontal activity/frontostriatal effective connectivity and striatal activity during execution. We thus correlated the condition- and task-specific individual beta values of brain activity in ACC (which followed an inverted U-shaped curve as a function of the COMT Val158Met genotype, see Results section) and CN (which followed a U-shaped curve as a function of the COMT Val158Met genotype, see Results section) during preparation and execution. We also correlated the individual beta values of the effective connectivity between ACC and left CN during preparation (which followed an inverted U-shaped curve as a function of the COMT Val158Met genotype, see Results section) and CN (which followed a U-shaped curve as a function of the COMT Val158Met genotype, see Results section) during execution. For each correlation, the condition- and brain region-specific mean beta values of all 71 subjects were entered into a Pearson correlation analysis in SPSS (SPSS, Inc., Chicago, IL, USA). Correlations, thresholded at $P < 0.05$, are illustrated in scatter diagrams with their corresponding trend lines.

We used the probability maps from the SPM8 anatomy toolbox (Eickhoff et al. 2005) and the stereotactic atlas of the human brain, named Talairach Daemon (Talairach and Tournox 1988; Lancaster et al. 2000), to identify Brodmann areas corresponding to the MNI coordinates of activation. MRicron was used for displaying the fMRI results (Rorden and Brett 2000).

**Results**

This study investigated the neural differences in brain activity and effective connectivity underlying cognitive preparation for and execution of neutral and happy overt reading induced by genetic polymorphisms of the dopaminergic system. We discuss our results in the context of two influential hypothetical models regarding dopaminergic modulation of cognition.

**Behavioral Results**

Genetically defined groups did not differ in terms of speech reaction times or error rates during cued overt reading (neutral and happy intonation) even at short instruction delays (see Supplementary Tables 2 and 3A, B). No other overt behavioral differences were observed between genetically defined groups.

**fMRI Results**

We did not observe any significant DRD2/ANKK1 effect either in isolation or in an interaction with the other two polymorphisms on brain activity or effective connectivity. Thus, we elaborate on effects of COMT Val158Met and DAT1 VNTR 9/10 polymorphisms and their interactions.

**Cognitive Preparation for and Execution of Overt Reading Is Modulated by the COMT Val158Met Polymorphism**

Despite similar overt behavior, we observed that elements of the preparatory network related to task-set generation for overt reading with neutral intonation (relative to covert reading, see Supplementary Fig. 1) were modulated by the COMT Val158Met polymorphism in such a way that the profile corresponded to an inverted U-shaped curve: Preparatory activity in the mesial frontopolar cortex (BA10), mPFC (BA8), ACC, MCC, presupplementary motor area (pre-SMA), right DLPFC, and IFG was higher in heterozygotes (met/val) compared with both homozygous groups (met/met and val/val). Fig. 4, left upper images, green; Table 2; Fig. 5A, B; and see Supplementary Table 4). We did not observe a COMT × DAT1 interaction (Table 2; see Supplementary Fig. 2A–D and Table 4) in cognitive preparatory activity.

During actual neutral speech production (overt > covert reading), the left dorsal striatum of COMT val/val and met/met homozygotes activated less than the dorsal striatum of heterozygotes. This resulted in a U-shaped curve, a mirror image of what we observed in the mPFC during cognitive preparation (Fig. 4, right upper image, red; Table 3; Fig. 5E; and see Supplementary Table 5). The DAT1 VNTR 9/10 polymorphism did not interact with the U-shaped curve, nor was any other COMT × DAT1 interaction observed (Table 3; see Supplementary Fig. 2E,F and Table 5). The COMT val/met heterozygotes who activated the mesial prefrontal areas most strongly during cognitive preparation (Fig. 4; left upper images, green; Table 2; Fig. 5A, B; and see Supplementary Table 4) also showed stronger preparatory effective connectivity between mesial prefrontal cortices (BA10, BA8, ACC, and MCC) and the left dorsal striatum compared with both COMT homozygous groups (Fig. 4, lower images, green; Table 4; inverted U-shaped curve in Fig. 5C, D; and see Supplementary Table 6).

The individual preparatory activity in the ACC during neutral speech (overt > covert reading) correlated inversely with the activity in the left dorsal striatum during task execution (Pearson correlation $r = −0.4$, $R^2 = 0.15$, $P < 0.001$, Fig. 5F). This was mediated by a positive correlation between preparatory ACC and preparatory striatal activity ($r = 0.5$, $R^2 = 0.24$, $P < 0.001$) and a negative correlation between striatal activity in preparation and execution ($r = −0.5$, $R^2 = 0.25$, $P < 0.001$). This frontostriatal relationship based on a negative correlation between the preparatory effective connectivity between the ACC and dorsal striatum ($x$-axis) and the activity in the left dorsal striatum during task execution ($y$-axis) (Pearson correlation $r = −0.5$, $R^2 = 0.24$, $P < 0.001$, Fig. 5G).

For generation of affective prosody (both preparation for and execution of overt reading with happy compared with overt reading with neutral intonation), we did not observe any further brain activity that was modulated by the COMT Val158Met polymorphism in such a way that the profile corresponded either to an inverted U-shaped curve or a U-shaped curve.
Figure 4. Brain activity and effective connectivity that followed an inverted U-shaped curve (green during preparation) or U-shaped curve (red during execution) as a function of the COMT Val158Met polymorphism. Brain activity during preparation for neutral speech (overt > covert) is shown in green and during execution of overt reading with neutral intonation > covert reading in red. Preparatory effective connectivity for neutral speech is marked by green lines and the target regions are shown in the lower parts of the image in green. A (+) denotes that the COMT Val158Met polymorphism affects activity and effective connectivity in the same direction. All group differences in brain activity were significant at $P < 0.001$ uncorrected within the mask of the task-relevant network at $P < 0.05$, FWE-corrected for multiple comparisons. All results for effective connectivity were significant at $P < 0.05$, FWE-corrected after SVC.

Table 2 Brain regions in which activity follows an inverted U-shaped curve as a function of the COMT Val158Met polymorphism ($P < 0.001$, uncorrected, inclusive mask of $P < 0.05$ FWE-corrected)

<table>
<thead>
<tr>
<th>L/R</th>
<th>Anatomical region</th>
<th>BA</th>
<th>MNI coordinates ($x$, $y$, $z$)</th>
<th>T-value</th>
<th>$P$-value (uncorrected)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preparation for overt neutral &gt; covert reading</td>
<td>Inverted U-shaped curve activation depending on the COMT Val158Met polymorphism</td>
<td>Mesial frontopolar cortex</td>
<td>10</td>
<td>$-6, 52, 10$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ACC</td>
<td>32</td>
<td>2, 40, 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MCC</td>
<td>24</td>
<td>2, 14, 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mPFC</td>
<td>8</td>
<td>2, 34, 50</td>
</tr>
<tr>
<td>R</td>
<td>Dorsolateral PFC</td>
<td>9</td>
<td>48, 10, 36</td>
<td>3.66</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td></td>
<td>IFG</td>
<td>44</td>
<td>58, 14, 14</td>
<td>3.89</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td></td>
<td>Inverted U-shaped curve activation depending on the COMT × DAT1 interaction (variant 1)</td>
<td>Mesial frontopolar cortex</td>
<td>10</td>
<td>$-4, 52, 10$</td>
<td>3.16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ACC</td>
<td>32</td>
<td>0, 46, 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MCC</td>
<td>24</td>
<td>0, 20, 24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mesial prefrontal cortex</td>
<td>8</td>
<td>0, 34, 46</td>
</tr>
<tr>
<td>R</td>
<td>Dorsolateral PFC</td>
<td>9</td>
<td>46, 26, 32</td>
<td>3.25</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>IFG</td>
<td>44, 45</td>
<td>52, 26, 6</td>
<td>3.72</td>
<td>$&lt;0.001$</td>
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<tr>
<td></td>
<td>Inverted U-shaped curve activation depending on the COMT × DAT1 interaction (variant 2)</td>
<td>Mesial frontopolar cortex</td>
<td>10</td>
<td>2, 52, 10</td>
<td>3.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ACC</td>
<td>32</td>
<td>4, 46, 8</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>24</td>
<td>6, 12, 32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mPFC</td>
<td>8</td>
<td>$-2, 34, 50$</td>
</tr>
<tr>
<td>R</td>
<td>Dorsolateral PFC</td>
<td>9</td>
<td>44, 22, 36</td>
<td>3.93</td>
<td>$&lt;0.001$</td>
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<tr>
<td></td>
<td>IFG</td>
<td>44, 45</td>
<td>50, 38, 8</td>
<td>4.01</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td></td>
<td>Execution of overt neutral &gt; covert reading</td>
<td>Inverted U-shaped curve activation depending on the COMT Val158Met polymorphism</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inverted U-shaped curve activation depending on the COMT × DAT1 interaction (variant 1)</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inverted U-shaped curve activation depending on the COMT × DAT1 interaction (variant 2)</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Main Effect of the DAT1 VNTR 9/10 Polymorphism**

A main effect of DAT1 VNTR 9/10 on task-related brain activity was found in the dorsal part of the left IFG (dIFG) (Fig. 6, left upper image, blue; Table 5). Post hoc t-testing revealed that this main effect resulted from group differences during cognitive task preparation, mainly for generation of affective prosody (overt reading with happy intonation > covert reading): DAT1 10-repeat subjects with lower levels of subcortical phasic dopamine preactivated the left dIFG more strongly than 9-repeat individuals ($P = 0.001$; Fig. 7A and see Supplementary Table 7).

**Main Effect of the COMT Val158Met Polymorphism**

We observed a main effect of the COMT Val158Met polymorphism in the left vIFG (Fig. 6, right upper image, blue; Table 5) and in the left MTG (Fig. 6, right upper image, yellow; Table 5). Post hoc t-tests in the left vIFG revealed that the main effect of COMT Val158Met was driven by cognitive task preparation for affective prosody (overt reading with happy intonation > covert reading; $P = 0.016$; Fig. 7B and see Supplementary Table 7). During cognitive preparation for overt reading with happy intonation, participants with higher prefrontal dopamine levels (COMT
met/met individuals) showed increased activity in the left vIFG compared with those with lower (met/val individuals) or lowest (val/val individuals) prefrontal dopamine concentrations (Fig. 7B and see Supplementary Table 7). In the left MTG, post hoc analyses revealed that COMT val/val subjects with the lowest dopamine levels exhibited the highest BOLD responses especially during execution of happy reading (relative to covert reading), compared with COMT met/met and met/val individuals ($P = 0.037$; Fig. 7C and see Supplementary Table 7). Note that these effects are linear and do not follow an inverted U-shaped curve.

### Table 3 Brain regions in which activity follows a U-shaped curve as a function of the COMT Val158Met polymorphism ($P < 0.001$, uncorrected, inclusive mask of $P < 0.05$ FWE-corrected)

<table>
<thead>
<tr>
<th>L/R</th>
<th>Anatomical region</th>
<th>BA</th>
<th>MNI coordinates ($x$, $y$, $z$)</th>
<th>T-value</th>
<th>$P$-value (uncorrected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparation for overt neutral &gt; covert reading</td>
<td>U-shaped curve activation depending on the COMT Val158Met polymorphism</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>U-shaped curve activation depending on the COMT × DAT1 interaction (variant 1)</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>U-shaped curve activation depending on the COMT × DAT1 interaction (variant 2)</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Execution of overt neutral &gt; covert reading</td>
<td>U-shaped curve activation depending on the COMT Val158Met polymorphism</td>
<td>L CN</td>
<td>$-6$, $10$, $12$</td>
<td>3.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>U-shaped curve activation depending on the COMT × DAT1 interaction (variant 1)</td>
<td>L CN</td>
<td>$-6$, $10$, $12$</td>
<td>3.53</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>U-shaped curve activation depending on the COMT × DAT1 interaction (variant 2)</td>
<td>L CN</td>
<td>$-4$, $10$, $10$</td>
<td>2.86</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

*Subthreshold.

### Table 4 Brain regions in which effective connectivity follows an inverted U-shaped or U-shaped curve as a function of the COMT Val158Met polymorphism ($P < 0.05$ FWE-corrected after SVC)

<table>
<thead>
<tr>
<th>L/R</th>
<th>Anatomical region</th>
<th>BA</th>
<th>MNI coordinates ($x$, $y$, $z$)</th>
<th>T-value</th>
<th>$P$-value (SVC corrected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparation for neutral overt &gt; covert reading</td>
<td>Inverted U-shaped curve effective connectivity depending on the COMT Val158Met polymorphism</td>
<td>ACC</td>
<td></td>
<td>3.49</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L CN</td>
<td>$-6$, $18$, $0$</td>
<td>3.49</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mesial frontopolar cortex 10</td>
<td>8, $54, 6$</td>
<td>3.49</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ACC 32</td>
<td>6, $48, 2$</td>
<td>3.26</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MCC 24</td>
<td>2, $26, 30$</td>
<td>2.89</td>
<td>0.020</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mPFC 8</td>
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<td>0.001</td>
</tr>
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<tr>
<td>Execution of neutral overt &gt; covert reading</td>
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<td></td>
<td>3.49</td>
<td>0.001</td>
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<td>U-shaped curve effective connectivity depending on the COMT Val158Met polymorphism</td>
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</tbody>
</table>

Note: Seed regions are left-justified and target regions tabulated.

### Main Effect of COMT Val158Met and DAT1 VNTR 9/10 on Speech Network Effective Connectivity

The DAT1 VNTR 9/10 polymorphism had no significant effect on effective connectivity of the left dIFG. However, effective connectivity between the left vIFG and bilateral primary articulatory motor cortices was modulated by the COMT Val158Met polymorphism (Fig. 6, left and middle lower images, blue lines; Table 5): Participants with the lowest activity in the left vIFG during cognitive preparation (COMT val/met and met/met individuals) showed enhanced effective connectivity between the vIFG and the bilateral articulatory motor cortices, compared with COMT met/met and met/met subjects independent of trial phase ($P < 0.001$; Fig. 8A,B; see Supplementary Table 8). In more posterior parts of the speech network, the COMT Val158Met polymorphism modulated effective connectivity between the left MTG, left articulatory motor cortex (M1), and left posterior planum temporale (area Spt) both during preparation and execution compared with COMT met/met and met/met individuals (post hoc t-test: $P < 0.001$; Fig. 8C,D; see Supplementary Table 8).

### Discussion

This study investigated effects of genetic polymorphisms in dopaminergic systems on brain activity and effective
connectivity related to the implementation of appropriate rules for behavior, in our case overt reading. Effects of genetic polymorphisms on behavior are in general subtle, but could potentially be discovered by cognitive testing (Williams-Gray et al. 2007). The polymorphisms under investigation did not significantly affect processing speed or accuracy during overt reading. One could be tempted to conclude that dopamine does not affect the preparation for or execution of overt reading in our sample of 71 participants. Note that behavioral genetics studies often require larger sample sizes to discover significant polymorphism effects on behavior. While we cannot exclude that such results could be obtained in large cohorts, imaging genetics studies offer the opportunity to study covert variables like different cognitive strategies on a mesoscopic level (O’Reilly et al. 2013). This suggests that reaction time and accuracy are valid, but not comprehensive measures of cognition. The observed significant differences in brain activity and frontobasal connectivity between genetically defined groups suggest that dopamine modulates preparatory cognitive processes for overt reading without evident effects on behavioral measures in this experimental setting. This lack of behavioral effects may indeed be explained by different cognitive strategies or different neural recruitment that leads to similar behavior despite different genetic background (see below).

The Inverted U-Shaped Curve: Intermediate Prefrontal Dopamine Levels Strengthen Frontostriatal Interactions During Task-Set Implementation

Participants characterized by different genotypes of the COMT Val158Met polymorphism differed in their preparatory activity in the PFC and activity during task execution in the dorsal...
Prefrontal preparatory activity was modulated by the COMT Val158Met polymorphism in such a way that activity followed the proposed inverted U-shaped curve (Williams and Goldman-Rakic 1995; Goldman-Rakic et al. 2000; Mattay et al. 2000; Meyer-Lindenberg et al. 2005; Williams-Gray et al. 2007). The increased prefrontal preparatory activity in met/val heterozygotes was accompanied by stronger preparatory effective connectivity between the mPFC and the left dorsal striatum compared with met/met and val/val homozygotes. Consequently, frontostriatal preparatory effective connectivity also followed an inverted U-shaped curve when plotted as a function of the COMT Val158Met polymorphism. During subsequent task execution, modulation of left dorsal striatum activity showed a mirror image of what was observed in the PFC during cognitive preparation. Left CN activity followed a U-shaped curve when plotted over COMT Val158Met genotypes. This could be a direct consequence of the degree of involvement of the functional loop between mPFC and striatum during cognitive task preparation: If processing in the task-relevant frontostriatal loops was enhanced already during task preparation, the need for dorsal striatal processing during subsequent task execution is reduced (as seen in met/val heterozygotes of the COMT Val158Met polymorphism). On the contrary, less engagement of preparatory corticobasal loops in met/met and val/val homozygotes may be balanced during task execution by increased subcortical activation to generate similar overt behavior. This interpretation is supported by the strong negative correlation of individual values of preparatory prefrontal activity, but also of frontobasal preparatory effective connectivity with activity in the dorsal striatum during task execution. Note that group differences in brain activity can often be interpreted in two opposite directions. For example, the increased mesial preparatory activity in COMT heterozygotes could also be interpreted as increased effort on the basis of inefficient rather than efficient preparation. We are confident that this is not the case because the effects during cognitive preparation are counterbalanced during task execution, which should not occur if additional effort...
simply compensated for inefficient processing already during task preparation.

Coding of task rules requires functional interactions between the PFC and the striatum that are dependent on physiological dopamine levels. Frontostriatal loops are affected by dopamine depletion both in healthy volunteers (Nagano-Saito et al. 2008) and in Parkinson’s patients (Monchi et al. 2004, 2007; Arnold et al. 2014). Our results suggest that the COMT Val158Met genotype modulates prefrontostriatal loops involved in coding of task rules in such a way that intermediate physiological prefrontal dopamine concentrations allow for stronger preparatory corticobasal interactions compared with both low and high prefrontal dopamine concentrations. Because cognitive preparation in the studied cue–target paradigm involved both cognitive flexibility for occasional task switching and maintenance of task rules and the mPFC is engaged in both processes (Dosenbach et al. 2006; Stuss and Alexander 2007; Koneiher et al. 2009), intermediate prefrontal dopamine levels (Colzato et al. 2010; de Frias et al. 2010) allowed for more efficient contributions of the mPFC as evidenced by the negative correlation between preparatory mesial prefrontostriatal interactions and striatal activity during task execution. Given that the COMT enzyme is mainly expressed in the PFC (Chen et al. 2004) but relatively scarcely in subcortical task execution. Given that the COMT enzyme is mainly expressed in the PFC (Chen et al. 2004) but relatively scarcely in subcortical brain regions (Karoum et al. 1994; Gogos et al. 1998; Matsumoto, Weickert, Akil, et al. 2003; Matsumoto, Weickert, Beltaifa, et al. 2003; Reuter et al. 2009), very likely the observed COMT polymorphism effects are generated within the mPFC rather than subcortically (Fig. 1). This points to the mesocortical system as a relevant anatomical structure for dopaminergic modulation of task-set networks. This view is supported by the lack of a COMT × DAT1 interaction that we would have expected if dopaminergic modulation in the nigrostriatal dopaminergic system played a major role in setting up task-sets. Yet, altered COMT activity in the PFC has been observed to indirectly influence the VTA of the midbrain by mesocortical feedback loops (Akil et al. 2003; Meyer-Lindenberg et al. 2005).

Taken together, our results suggest that genetic polymorphisms affecting the enzymatic activity of COMT in the PFC modulate functional loops between the mPFC and the dorsal striatum that code task rules. In contrast to findings on working memory, the COMT Val158Met polymorphism did not affect behavioral measures of setting up and maintaining task rules related to overt reading. Instead, it influenced the neural dynamics of implementing and coding these in the different trial phases of the studied cue–target paradigm.

Dopaminergic Modulation of Left Inferior Frontal Speech-Related Activity and Connectivity

We observed that both COMT Val158Met and DAT1 VNTR 9/10 polymorphisms modulated left IFG activity linearly especially during cognitive preparation for affective prosody. Thus, the pattern of modulation in the left lateral PFC drastically differed from the inverted U-shaped curve that was observed in the mesial and right lateral PFC. Both the COMT val/val subjects who presumably have low tonic prefrontal dopamine levels and the DAT1 9-repeat individuals who are believed to have high phasic subcortical dopamine levels showed less preparatory activity for affective prosody in the left IFG compared with the other genotypes. Those genetic groups are thought to be cognitively more flexible than the other groups (Fig. 1; Colzato et al. 2010; de Frias et al. 2010; Garcia-Garcia et al. 2010). This points directly to the inverse relationship between prefrontal and subcortical dopamine in the tonic–phasic model of dopaminergic modulation for cognition (Bilder et al. 2004). Given the absence of counterbalancing effects during task execution (see above), higher subcortical dopamine as well as lower cortical dopamine availability in the more flexible subjects presumably reduced the need for additional IFG recruitment during cognitive preparation for reading a neutral sentence happily. The unnatural way of pronouncing a neutral sentence happily may have required higher executive control involving left IFG processing in less flexible participants. This interpretation is congruent with the way dopamine effects on working memory and task switching-related activity in the IFG are generally interpreted and related to cognitive flexibility and stability (Meyer-Lindenberg and Weinberger 2006; Steilzei et al. 2010).

Note that our interpretation of left IFG modulation by dopaminergic polymorphisms is opposite to the aforementioned interpretation of activity modulation in the mesial and right lateral PFC. Our results suggest that separable cognitive subprocesses that engage different PFC regions are modulated differently by dopaminergic signaling. This study proposes that dopaminergic polymorphisms determine the degree of mesial prefrontal engagement in cognitive preparation much differently from the way they affect processing in the left IFG. The different interpretations of the degree of activation in the mesial and left lateral PFC are additionally supported by different effective connectivity profiles of mPFC and left IFG: While additional mesial prefrontal engagement in COMT Val158Met heterozygotes went along with increased effective connectivity of these brain regions, decreased vIFG activation in COMT val/val individuals was associated with enhanced effective connectivity between the left vIFG and the bilateral articulatory motor cortex. Besides its contribution to task-set implementation (Dosenbach et al. 2006), the left IFG is well known to be involved in feedforward control of speech (Guenther 2006) and particularly control of speech melody during generation of affective prosody (Pichon and Kell 2013). Taken together with the peculiar role of COMT in dopamine clearance in the neocortex, the specific modulation of IFG to motor functional connectivity suggests that processes involved in feedforward speech motor control are modulated by mesocortical dopamine.

The observed DAT1 main effect in the left dIFG may have a subcortical origin instead. Given the role of DAT1 in striatal dopamine transmission and the lack of the DAT1 protein in the PFC (Ciliax et al. 1995; Sesack et al. 1998; Lewis et al. 2001; Dreher et al. 2009), we propose that the observed effect of the DAT1 VNTR 9/10 polymorphism in the left dIFG may be an indirect consequence of subcortical phasic dopamine burst firing, although we could not measure it locally. Such short transients may escape BOLD analyses, especially if they occur subcortically, but may nevertheless affect corticobasal loops and thereby modulate cortical activation patterns (Bertolino et al. 2006; Dreher et al. 2009). Because the observed effects occurred primarily during generation of affective prosody, which requires emotional processing besides increased executive and sensorimotor control for an unnatural task (reading neutral sentences happily), the observed cortical differences could also be a consequence of polymorphisms affecting dopamine signaling in the mesolimbic system. Alternatively, the modulation of speech-related dIFG activity by DAT1 could also be an indirect consequence of nigrostriatal effects of the DAT1 polymorphism and thus point more directly to a role of phasic subcortical dopamine in motor control. Such an effect of the nigrostriatal system on motor control is well established. Yet, we did not find any direct evidence in favor of either of these interpretations.

Taken together, low prefrontal dopamine availability and high subcortical dopamine burst firing require the least resources
for cognitive preparation for happy reading in left IFG and allow for most efficient connectivity between the vIFG and the articulatory motor cortex.

The COMT Val158Met Polymorphism Modulates Speech Feedback-Related Activity

The modulation of effective connectivity between the vIFG and the articulatory motor cortex by the COMT Val158Met polymorphism (see above) suggests a modulation of speech-related processing beyond cognitive processes, like working memory or task preparation, that are classically believed to be modulated by dopamine. Indeed, effects of COMT Val158Met polymorphism on brain activity and effective connectivity during overt reading were not restricted to prefrontal cortices: Compared with the other COMT genotypes, COMT val/val individuals activated the left MTG most during overt articulation, especially for production of affective prosody. The MTG is engaged in overt reading with happy compared with neutral intonation, although more strongly in the right hemisphere (Pichon and Kell 2013). This region assists in analyses of auditory feedback parameters that are important for prosody production like speech intensity or modulation of fundamental frequency. Those participants with the strongest MTG activity (COMT val/val subjects) also showed increased functional coupling between the left MTG and left primary motor cortex as well as between the left MTG and the proposed auditory–motor mapping region Spt in the posterior planum temporale (Hickok and Poeppel 2007; Hickok et al. 2011) compared with COMT met/met and met/met individuals. Therefore, a facilitatory role of cortical dopamine on auditory feedback processing can be envisioned. Animal models support this notion by demonstrating a gating role of dopamine on auditory processing. In gerbils, auditory dopamine promotes temporal integration of auditory input by recruiting a positive corticosubcortical feedback loop (Happel et al. 2014). Beside cortical dopamine, also subcortical dopamine may influence auditory feedback processing. Speech-related activity in the auditory cortex has been associated with left nigrostriatal dopamine signaling in healthy subjects (Simonyan, Herscovitch et al. 2013) and is altered in early Parkinson’s patients (Arnold et al. 2014). Parkinson’s patients monitor their auditory feedback less (Ho et al. 2000), which translates into altered cortical activity and connectivity even before the cortex is affected neuropathologically (Arnold et al. 2014). These observations suggest that both cortical and subcortical dopamine gate temporal integration subserving auditory processing. Given that not much is known on dopamine clearance in the temporal lobe, we cannot dissociate whether the MTG effect observed here is mediated by subcortical dopamine or represents a consequence of cortical dopaminergic neuromodulation. Both interpretations appear possible because mesocortical dopaminergic fibers not only innervate the PFC but also other cortical components of the sensorimotor network (Hosp, Hertler, et al. 2011; Hosp, Pekanovic, et al. 2011). Wherever exactly the dopamine effect is generated, our results confirm a physiological role of dopamine in the speech production system (Simonyan, Herscovitch, et al. 2013), as previously suggested on the basis of findings in Parkinson’s disease (Ho et al. 2000; Arnold et al. 2014), stuttering (Wu et al. 1997; Alm 2004), and spasmodic dysphonia (Simonyan, Berman, et al. 2013).

Limitations

We only included young participants in our study. The resource modulation hypothesis of genetic influence suggests that gene effects on cognitive function increase with age and may then be measured at the behavioral level (Kinsbourne and Hicks 1978; Finkel et al. 2005; Lindenberger et al. 2008; Nagel et al. 2008). Older people are thought to function at less than optimal levels of dopaminergic neuromodulation (Nagel et al. 2008). It is thus possible that with age, effects of genetics including the DRD2/ANKK1 Taq1a polymorphism and gene–gene interactions between COMT Val158Met, DAT1 VNTR 9/10, and DRD2/ANKK1 polymorphisms may become apparent.

The relatively small sample size for genetic studies is explained by limitations in scanning time. The lack of polymorphism effects on behavior could possibly be explained by the sample size. Larger cohorts in imaging genetics studies could additionally grant insights into other polymorphisms and/or interactions between them. Finally, using spontaneous prosody instead of instructed artificial prosody may allow better evaluating effects in the mesolimbic system.

Conclusions

Intermediate levels of mesocortical dopaminergic neuromodulation facilitate preparatory interactions between the mPFC and the dorsal striatum during task-set generation for overt speaking. However, cognitive processes that underlie the generation of affective prosody and engage the left IFG show linear effects that relate more directly to a negative interaction between prefrontal tonic and subcortical phasic dopamine.

Thus, intermediate dopamine levels in mesial prefrontostriatal loops ensure a balance between cognitive flexibility and stability in setting up and maintaining task-sets. If additional cognitive flexibility is required, lateral prefrontal cortices are more easily recruited in case genetic polymorphisms favor cortical tonic and subcortical phasic dopamine signaling. Finally, functional COMT Val158Met effects are not restricted to cognitive processes involving prefrontal cortices, but are also observed in the sensorimotor speech system in which dopamine may gate temporal integration of auditory feedback in addition to its well-known effects in motor control.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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Notes

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