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Daniella J Furman
University of California, San Francisco

Ioannis Pappas
University of California, Berkeley

Robert L White 3rd
Washington University School of Medicine in St. Louis

Andrew S Kayser
University of California, San Francisco

Mark D'Esposito
University of California, Berkeley

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Enhancing dopamine tone modulates global and local cortical perfusion as a function of COMT val158met genotype

Daniella J. Furman[a,b,†,*], Ioannis Pappas[b,c,†,*], Robert L. White III[d], Andrew S. Kayser[a,b,c,‡], Mark D'Esposito[b,c,‡]

[a] Department of Neurology, University of California, San Francisco, CA, United States
[b] Helen Wills Neuroscience Institute, University of California, Berkeley, CA, United States
[c] Division of Neurology, VA Northern California Health Care System, United States
[d] Department of Neurology, Washington University School of Medicine, St. Louis, MO, United States

A B S T R A C T

The cognitive effects of pharmacologically enhancing cortical dopamine (DA) tone are variable across healthy human adults. It has been postulated that individual differences in drug responses are linked to baseline cortical DA activity according to an inverted-U-shaped function. To better understand the effect of divergent starting points along this curve on DA drug responses, researchers have leveraged a common polymorphism (rs4680) in the gene encoding the enzyme catechol-O-methyltransferase (COMT) that gives rise to greater (Met allele) or lesser (Val allele) extracellular levels of cortical DA. Here we examined the extent to which changes in resting cortical perfusion following the administration of two mechanistically-distinct dopaminergic drugs vary by COMT genotype, and thereby track predictions of the inverted-U model. Using arterial spin labeling (ASL) and a double-blind, within-subject design, perfusion was measured in 75 healthy, genotyped participants once each after administration of tolcapone (a COMT inhibitor), bromocriptine (a DA D2/3 agonist), and placebo. COMT genotype and drug interacted such that COMT Val homozygotes exhibited increased prefusion in response to both drugs, whereas Met homozygotes did not. Additionally, tolcapone-related perfusion changes in the right inferior frontal gyrus correlated with altered performance on a task of executive function. No comparable effects were found for a genetic polymorphism (rs1800497) affecting striatal DA system function. Together, these results indicate that both the directionality and magnitude of drug-induced perfusion change provide meaningful information about individual differences in response to enhanced cortical DA tone.

1. Introduction

Cortical dopamine (DA) is known to modulate higher-order cognition, but baseline DA system function has emerged as a potentially critical mediator of dopaminergic drug effects on human cognition, behavior, and neuronal function (Cools and D'Esposito, 2011). Based on the view that DA influences cognitive and neuronal processes according to an inverted-U-shaped function, a prominent hypothesis is that augmenting DA tone will optimize neuronal dynamics and improve components of cognition in individuals with lower dopaminergic activity but will degrade function in those with higher baseline activity (Arnsten et al., 2015; Durstewitz and Seamans, 2008). As a proxy for baseline DA in humans, researchers have leveraged a functional polymorphism in the gene encoding catechol-O-methyltransferase (rs4680 or COMT Val158Met; Lachman et al., 1996), an enzyme that catabolizes cortical DA (Käenmäki et al., 2010). Relative to the COMT Met variant, the Val allele promotes increased enzymatic activity (Chen et al., 2004), yielding reduced accumulation of released DA. This genotypic difference has been used as the basis for predicting and interpreting divergent biophysiological and cognitive effects of dopaminergic drugs such as tolcapone (Apud et al., 2007; Barkus et al., 2016; Farrell et al., 2012), a COMT inhibitor that increases accumulation of released DA in the frontal cortex (Tunbridge et al., 2004).

Nevertheless, COMT-based evidence for the full inverted-U model has been mixed, including reports of only cognitive facilitation by tolcapone in Val homozygotes (Giakoumaki et al., 2008), only deleterious effects in Met homozygotes (Furman et al., 2020), both facilitation in Val and worsening in Met homozygotes (Apud et al., 2007; Farrell et al., 2012), or no modulation of drug effect by COMT genotype (Cameron et al., 2018). Such variability limits our ability to understand and predict dopaminergic modulation: absence of a predicted effect can be due to dosage issues, poor sensitivity of the utilized task to DA effects, true absence of a DA effect on the construct of interest, or a non-U-shaped (Floresco, 2013) relationship between DA and the target cognitive component. Thus, to better characterize differential effects of DA on brain function and cognition, it is desirable to quantify physiological responses to drugs independently of cognitive paradigms.

Arterial spin labeling (ASL) has emerged as a non-invasive, economical, and reliable (Chen et al., 2011) magnetic resonance imaging (MRI) technique for measuring brain perfusion by assessing cerebral blood flow (CBF). Unlike in blood-oxygen-level-dependent (BOLD)

* Corresponding authors.
E-mail addresses: Daniella.Furman@ucsf.edu (D.J. Furman), ioannis@berkeley.edu (I. Pappas).
† DJF and IP contributed equally to this work.
‡ ASK and MD contributed equally to this work.

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signal imaging, which indirectly infers neural activity-related changes based on the ratio of oxygenated to deoxygenated blood, in ASL scans protons in arterial blood are magnetically "tagged" as they flow into the brain. Acting as an endogenous contrast, these tagged protons subsequently perfuse brain tissue, enabling the quantification of regional CBF in meaningful units, even in the absence of explicit activity (Liu and Brown, 2007). Thus, ASL provides a tool for gauging absolute blood flow in the resting brain and constitutes a promising avenue for assaying dopaminergic and other drug effects (Detre et al., 2012). Indeed, D2 receptor-modulating drugs influence blood flow in the midbrain and striatum (Hawkins et al., 2018; Michels et al., 2016), where D2 receptors are most abundantly expressed, and administration of a D1 agonist has been shown to increase prefrontal cortex (PFC) perfusion in schizophrenia (Mu et al., 2007). Less is known about the influence of cortical DA tone on perfusion in healthy humans. One recent report identified an effect of COMT genotype on PFC perfusion following placebo, but not tolcapone, administration (Martens et al., 2021). However, the use of a between-subjects pharmacological design likely decreased sensitivity to drug effects, as baseline perfusion itself varies considerably between participants independent of putative DA effects (Viviani et al., 2009).

Here, we implemented a within-subject, placebo-controlled design to examine the impact of tolcapone and bromocriptine, a DA D2/3 receptor agonist, on cortical perfusion in healthy, young COMT Met and Val homozygotes. Based on the hypothesis that participants with high vs. low cortical DA tone will exhibit opposing responses to enhanced DA activity, we predicted that tolcapone-related changes in cortical perfusion would distinguish genotype groups and covary with a previously-reported cognitive effect of tolcapone in the same sample of participants (Furman et al., 2020). In contrast, we hypothesized that bromocriptine would modulate cortical CBF in the two groups to a lesser extent, given the relative sparsity of D2 receptors in the cortex. Together, we hope to demonstrate that CBF can serve as a quantitative, task-independent measure of drug-elicited change in cortical DA tone in healthy humans.

2. Methods and materials

2.1. Participants

Healthy, young participants were recruited for genetic sampling from the University of California, Berkeley community and surrounding area as part of a larger study of dopaminergic drug effects on brain function and behavior (see Supplementary Materials for full inclusion criteria). Saliva samples were obtained using Oragene collection kits with stabilizing liquid (DNA Genotek, Ottawa, ON, Canada) and genotyping was performed using polymerase chain reaction-based TaqMan technology (Applied Biosystems, Foster City, CA). Individuals who were homozygous for the COMT Val or Met allele were invited to participate in the remainder of the study. To determine whether genotypic effects on drug-elicited CBF changes are specific to COMT genotype, or instead, whether polymorphisms influencing other aspects of DA system function could similarly modulate drug effects, our analyses additionally included Taq1A (rs1800497) genotype, associated with individual differences in striatal DA system function (Gluskin and Mickey, 2016; Laakso et al., 2005). Taq1A genotypes were binned according to the presence ("A1+") or absence ("A1-") of the minor A1+ allele. All participants gave written informed consent in accordance with the Committee for the Protection of Human Subjects at the University of California, San Francisco and University of California, Berkeley, and were compensated for their participation.

2.2. Experimental overview

Eligible participants were scheduled for three pharmacological study sessions to be completed on different days. During each of the three sessions, participants received a single oral dose of bromocriptine (1.25 mg), tolcapone (200 mg), or placebo in identical, compounded capsules. Drug doses were selected on the basis of their demonstrated ability to elicit changes in cognitive performance (e.g., Cameron et al., 2018; Farrell et al., 2012; Gibbs and D'Esposito, 2005). ASL scans were performed approximately 110 min after drug/placebo administration, within the window of maximal plasma concentration for both drugs (Jorga et al., 1998; Kvernmo et al., 2006). The order of drug administration was double-blinded and counterbalanced across participants. Participants were unable to accurately guess whether they had received drug or placebo during a given session, and rates of "drug" vs. "placebo" guesses did not differ significantly across the three sessions ($\chi^2[2]=2.18$, $p=0.34$, excluding 3 omitted session responses).

2.3. Structural images acquisition and preprocessing

T1-weighted magnetization prepared rapid gradient-echo (MPRAGE) scans [repetition time (TR) = 2300 ms; echo time (TE) = 2.98 ms; flip angle (FA) = 9°; bandwidth = 238 Hz/Pixel; matrix = 240 × 256; field-of-view (FOV) = 256 cm; sagittal plane; voxel size = 1mm^3; 160 slices] were acquired using a Siemens 3T Trio Tim scanner at UC Berkeley's Brain Imaging Center. A 12-channel coil was used to provide reliable signal to noise ratio in subcortical regions (Kaza et al., 2011) and to enhance participant comfort across the three days of MRI scans. The Advanced Normalization Tools (ANTs; Avants et al., 2011) longitudinal thickness pipeline (Tustison et al., 2018) was used to obtain high quality brain and tissue images for all subjects and sessions. For each subject, a single subject template (SST) was constructed from the three MPRAGE scans and then segmented into tissue components and brain. In turn, SST tissue and brain masks were used as priors to perform brain extraction and tissue segmentation for each individual session's native space image. Diffeomorphic transformations were also obtained, allowing non-linear registration between the SST and each session's structural data.

2.4. ASL data acquisition and preprocessing

Perfusion data were acquired using a pseudo-continuous ASL (PCASL) sequence. Interleaved images with and without labeling (tagged/control images) were acquired for 5.3 min (80 vols) using a gradient-echo echo-planar imaging sequence (TR/TE = 4000/11 ms; flip angle = 90°; bandwidth = 2604 Hz/pixel; FOV = 22 cm; image size 64 × 64 × 20 voxels; voxel size = 3.44 × 3.44 × 5 mm; 1 mm gap; labeling duration = 1480 ms; post-labeling delay = 1500 ms). CBF maps were obtained using FSL's oxford_asl (Chappell et al., 2009), motion corrected using FSL's MCFLIRT, and quantified in standard physiological units (ml blood/100 mg tissue/min) using a standard kinetic model (Alsop et al., 2015), with labeling efficiency set to α=0.85 and longitudinal relaxation time of the blood set to T1_*b*=1600 ms. A mean control image was obtained by averaging all control images in the motion-corrected data. This image was used for calibration, as no designated calibration image was obtained during data acquisition. Results were unchanged when the first control image was used for calibration. CBF maps were co-registered to anatomical T1-weighted images to derive an estimate of average cortical gray matter (GM) perfusion. To facilitate voxel-wise comparison across sessions and participants, CBF maps were co-registered to participants' first session co-registered map, and then transformed to MNI-152 space with the ANTs command *antsRegistationSyNQuick.sh* (an initial rigid, affine transformation followed by a diffeomorphic transformation) and spatially smoothed (8 mm FWHM).

2.5. Cognitive task

To determine whether alterations in cognition covaried with changes in resting cortical perfusion, we used performance metrics found to exhibit drug-by-genotype effects in this sample of participants (Armbruster et al., 2012; Furman et al., 2020; see Supplementary Figure 1). Participants were required to respond to digits that appeared

on a black background every 2000 ms. On most trials (N=810 per session), participants made either odd/even or low/high decisions about a single digit appearing above a central fixation cross ("ongoing task"). Every 3–6 trials, two digits appeared on the screen simultaneously. The relative brightness of the digits varied and encoded a task cue. When the upper digit was brighter (N=60 per session), participants were instructed to ignore the lower digit and continue to perform the ongoing task with their index fingers ("distractor trials"). When the lower digit was brighter (N=60 per session), participants were signaled to switch attention to the lower digit and apply the alternate task rule with their middle fingers ("switch trials"). For the remaining trials (N=60 per session), the difference in brightness between the digits was reduced. As participants were only trained to respond to the brighter of the two digits, this trial type assessed participants' bias toward switching under ambiguous conditions (Armbruster et al., 2012). The cognitive task was completed immediately before ASL scanning. Data cleaning procedures are described in Furman et al. (2020).

Processes facilitating cognitive stability are thought to preferentially engage cortical/frontal regions, whereas those supporting flexibility depend on interactions with the basal ganglia (e.g., Cools and D'Esposito, 2011). Thus, to most directly test the link between drug-related cortical perfusion changes and cognitive performance, we focused primarily on distractor cost, computed as the difference in response time (in ms) between distractor trials and ongoing task trials. We previously reported a detrimental impact of tolcapone on such distractor resistance in Met, but not Val, homozygotes in this group of participants (Furman et al., 2020). However, as frontal cortex interacts with the basal ganglia (and striatal dopamine system) to affect cognitive flexibility (e.g., Stelzel et al., 2010), we additionally report correlations between drug-related changes in cortical perfusion and switch-related metrics to provide a more comprehensive picture of effects: switch cost was computed as the difference in response time (in ms) between switch trials and ongoing task trials, and spontaneous switch rate was computed as the proportion of accurate ambiguous trials that were treated by the participant as switch trials (as evidenced by their use of middle fingers).

2.6. Statistical analysis

A linear regression model was used to examine genotypic differences on baseline (i.e., placebo) cortical GM perfusion, with COMT genotype, Taq1A genotype, sex, and age as predictors. A separate linear mixed effects model was used to investigate genotypic influence on drug-related CBF change following the administration of bromocriptine or tolcapone. The CBF difference between drug and placebo sessions was entered as the dependent variable, and fixed effect predictors included drug (tolcapone or bromocriptine), COMT genotype, Taq1A genotype, sex, age, as well as the interactions of both genotypes with drug. Interactions with age or sex did not improve the model fit, so these terms were excluded. Participant intercept was included as a random effect. Mixed effect statistics were implemented with the "lme4" (Bates et al., 2015) and "afex" (Singmann et al., 2018) libraries in R (R Core Team, 2017). Degrees of freedom were approximated using the Satterthwaite method, and estimated marginal means ("emm") were obtained with the "emmeans" package (Lenth, 2018).

To examine regional changes in CBF, equivalent models were implemented voxel-wise. Specifically, an initial linear model including COMT genotype, Taq1A genotype, sex, and age was implemented with AFNI's 3dttest++ function to determine genotypic differences in baseline (i.e., placebo) CBF. A second linear mixed effect model was used to probe genotypic effects on CBF drug responses. To this end, voxel-wise drug difference maps were constructed for each participant by subtracting placebo from tolcapone and bromocriptine CBF maps and analyzed with AFNI's 3dLME tool, with subject entered as a random effect and age and sex included as covariates. Statistical significance of resulting clusters was determined using AFNI's 3dClustSim with a Gaussian plus mono-exponential spatial autocorrelation function and parameters estimated by 3dFWHMx. Simulated null results (N=10,000) were generated with residuals within a whole-brain mask that was limited to voxels present in at least 75% of participants. With voxel-wise p=0.001, clusters were determined to require k=23 and k=33 adjacent (first-nearest neighbor) voxels to achieve corrected α=0.05 for the baseline/placebo and drug difference analyses, respectively.

3. Results

3.1. Participants

Our initial sample included eighty-two participants. Seven participants were excluded for having incomplete sets of useable imaging data (N=6) or behavioral data (N=1). Our final sample of 75 participants belonged to the following COMT/Taq1A genotype groups: Met/A1+ (N=17, 8 female, age (mean±sd) = 20.8±2.4 years); Val/A1+ (N=20, 14 female, 21±1.7 years); Met/A1- (N=19, 15 female, 21.8±3.6 years); Val/A1- (N=19, 11 female, 21.3±2.3 years).

3.2. Global cortical gray matter perfusion

Consistent with previous work (e.g. Parkes et al., 2004), average GM perfusion during the placebo session was higher in females than males (emm: 33.3 vs 28.1; β=5.27, t=3.99, p=0.0002), and decreased with years of age (β=−0.71, t=−2.84, p=0.006). There were no significant effects of COMT (Met vs Val: β=−0.21, t=−0.16, p=0.87) or Taq1A (A1- vs A1+: β=−1.17, t=−0.93, p=0.36) genotype.

The mixed model of drug-related change in GM CBF revealed no main effects of drug type (tolcapone-placebo vs bromocriptine-placebo: β=−0.98, t=−1.64, p=0.10), Taq1A genotype (A1- vs A1+: β=−0.71, t=−0.77, p=0.44), age (β=0.06, t=0.35, p=0.73), or sex (female vs male: β=−0.5, t=−0.53, p=0.60). However, COMT genotype significantly influenced drug effects on GM CBF (Met vs Val: β=−2.47, t=−2.71, p=0.008), such that Met homozygotes exhibited numerically decreased CBF (emm±se = −0.75±0.67) whereas Val homozygotes exhibited increased CBF (+1.715±0.645) following DA drug administration (Fig. 1). Notably, drug type (i.e., tolcapone vs bromocriptine) did not interact with either Taq1A (β=−0.27, t=−0.23, p=0.82) or COMT (β=−0.93, t=−0.78, p=0.44) genotype, suggesting that the observed effect of COMT genotype on drug-related change in CBF did not vary as a function of which drug was administered. To confirm the presence of the genotype effect within each drug condition, we performed post hoc comparisons between COMT groups and found a significant difference in CBF following tolcapone administration (Met vs Val: −1.47 vs 1.46, t=−2.7, p=0.008) and a trend-level difference following bromocriptine administration (Met vs Val: −0.035 vs 1.97, t=−1.8, p=0.07). The difference in the effects of tolcapone and bromocriptine on GM CBF in Met homozygotes did not reach statistical significance (t=1.68, p=0.097).

3.3. Local gray matter perfusion

Examining voxel-wise CBF data collected on placebo, we found no suprathreshold clusters that differentiated COMT genotype groups or Taq1A genotype groups. However, drug-related change in CBF could be significantly differentiated by COMT genotype within two adjacent clusters of voxels along the right inferior frontal gyrus (IFG) and a cluster spanning parts of putative right frontal eye fields and premotor cortex (FEF/PMC; see Table 1 & Fig. 2). Mirroring the result with global GM perfusion, Taq1A genotype groups did not exhibit varying drug responses in any region, nor did COMT or Taq1A genotype interact with drug type to significantly bias CBF change in any region.

3.4. Perfusion-behavior correlations

Next, we examined the relationship between drug-related change in CBF and distractor cost (Δdistractor cost) derived from the cognitive

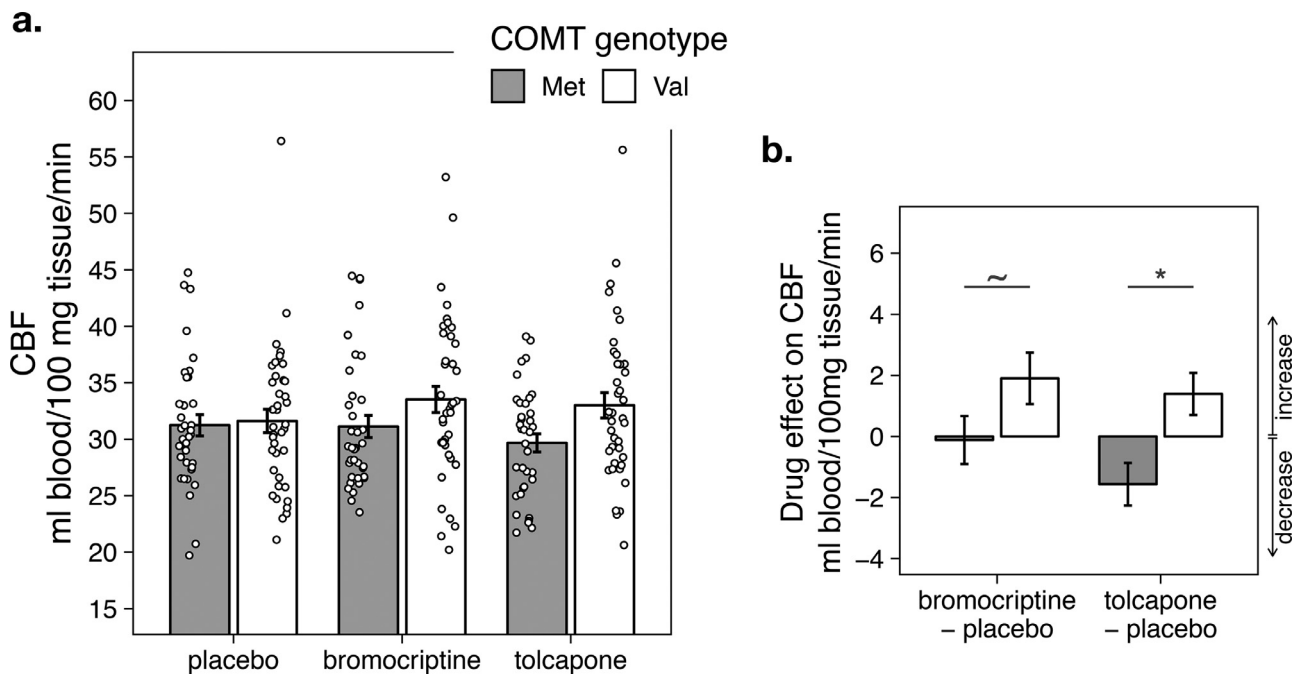

Fig. 1. Global gray matter perfusion by condition, and drug-related change, in COMT Met (gray) and Val (white) homozygotes. (a) COMT genotype groups did not differ in CBF on placebo but (b) showed divergent responses to drug administration. Error bars represent ±1 standard error of the mean. $^{*}p < 0.05$; $^{\sim}p < 0.1$; CBF = cerebral blood flow.

Table 1
Regions exhibiting COMT genotype-dependent change in cerebral blood flow (CBF) following administration of bromocriptine or tolcapone.

Cluster region	Center of mass (MNI)			Peak voxel (MNI)			Peak F-value	k
	X	Y	Z	X	Y	Z		
R. frontal eye fields (FEF), premotor cortex (PMC)	34	0	55	36	8	54	20.5	51
R. inferior frontal gyrus (IFG)	43	16	15	50	18	18	16.1	45
R. inferior frontal gyrus (IFG)	40	35	5	40	32	6	16.9	35

task. In our paradigm, distractor cost tracks the degree to which the simultaneous appearance of a salient but currently-irrelevant stimulus increases the time required to complete the ongoing task. Thus, this metric can be interpreted as the extent to which participants can robustly maintain task representations in the face of competing information (i.e., distractors), a cognitive process thought to be affected by PFC dopamine (Cools and D'Esposito, 2011). We previously reported a detrimental impact of tolcapone on such distractor resistance in Met, but not Val, homozygotes in this group of participants (Furman et al., 2020), consistent with an interpretation of cortical DA "overdose."

Mean CBF change across the two IFG clusters inversely correlated with tolcapone-related Δdistractor cost across the group (Spearman's rho=−0.29, p=0.01; Fig. 3) and within COMT Met homozygotes (rho=−0.4, p=0.02), such that poorer performance (higher distractor cost) accompanied reductions in perfusion. A significant association was not observed for any other genotypic subgroup (COMT Val: rho=−0.03; Taq1A A1+: rho=−0.30; A1-: rho=−0.25; all ps>0.1). Considered separately, the more caudal IFG cluster (group: rho=−0.31, p=0.006; Met only: rho=−0.33, p=0.05) best tracked behavioral change across the group whereas the more rostral IFG cluster (group: rho=−0.22, p=0.06; Met only: rho=−0.44, p=0.008) best tracked behavioral change within Met homozygotes. In contrast to regional CBF, tolcapone-related change in global GM CBF was unrelated to Δdistractor cost across the group (rho=−0.06, p=0.62), within COMT genotype groups (Met: rho=−0.05, p=0.78; Val: rho=0.07, p=0.66) or within Taq1A genotype groups (A1+: rho=−0.12, p=0.48; A1-: rho=0.03, p=0.85). Mean tolcapone-elicited change in CBF in the FEF/PMC cluster was likewise uncorrelated with Δdistractor cost (group: rho=−0.09; COMT Met: rho=−0.06; Val: rho=0.07; Taq1A A1+: rho=0.07; A1-: rho=−0.22; all ps>0.1).

Following bromocriptine treatment, Δdistractor cost did not correlate with changes in CBF across right IFG clusters (group: rho=−0.07; Met: rho=0.06; Val: rho=−0.09; Taq1A A1+: rho=−0.09; A1-: rho=0.003; all ps>0.5), in FEF/PMC (group: rho=0.02; Met: rho=0.15; Val: rho=0.02; Taq1A A1+: rho=0.14; A1-: rho=−0.06; all ps>0.3), or across cortical gray matter (group: rho=−0.05, p=0.65; Met: rho=0.03; Val: rho=−0.07; Taq1A A1+: rho=−0.25; A1-: rho=0.12; all ps>0.1).

To determine whether the observed relationship between cortical perfusion change and behavioral change was specific to distractor resistance, we also examined covariation of drug effects between CBF and two cognitive flexibility metrics: switch cost (Δswitch cost) and spontaneous switch rate (Δswitch rate). These metrics assess, respectively, the speed with which participants flexibility shift task representations in response to an explicit cue, and the tendency to switch tasks even in the absence of an explicit cue. There were no significant correlations between drug-related change in CBF and either task metric (see Supplementary Materials for details).

4. Discussion

The aim of the current study was to investigate genotypic differences in the effect of tolcapone, an inhibitor of the catecholamine-degrading enzyme COMT, and bromocriptine, a DA D2/3 receptor agonist, on cortical perfusion as measured with ASL. We found that changes in

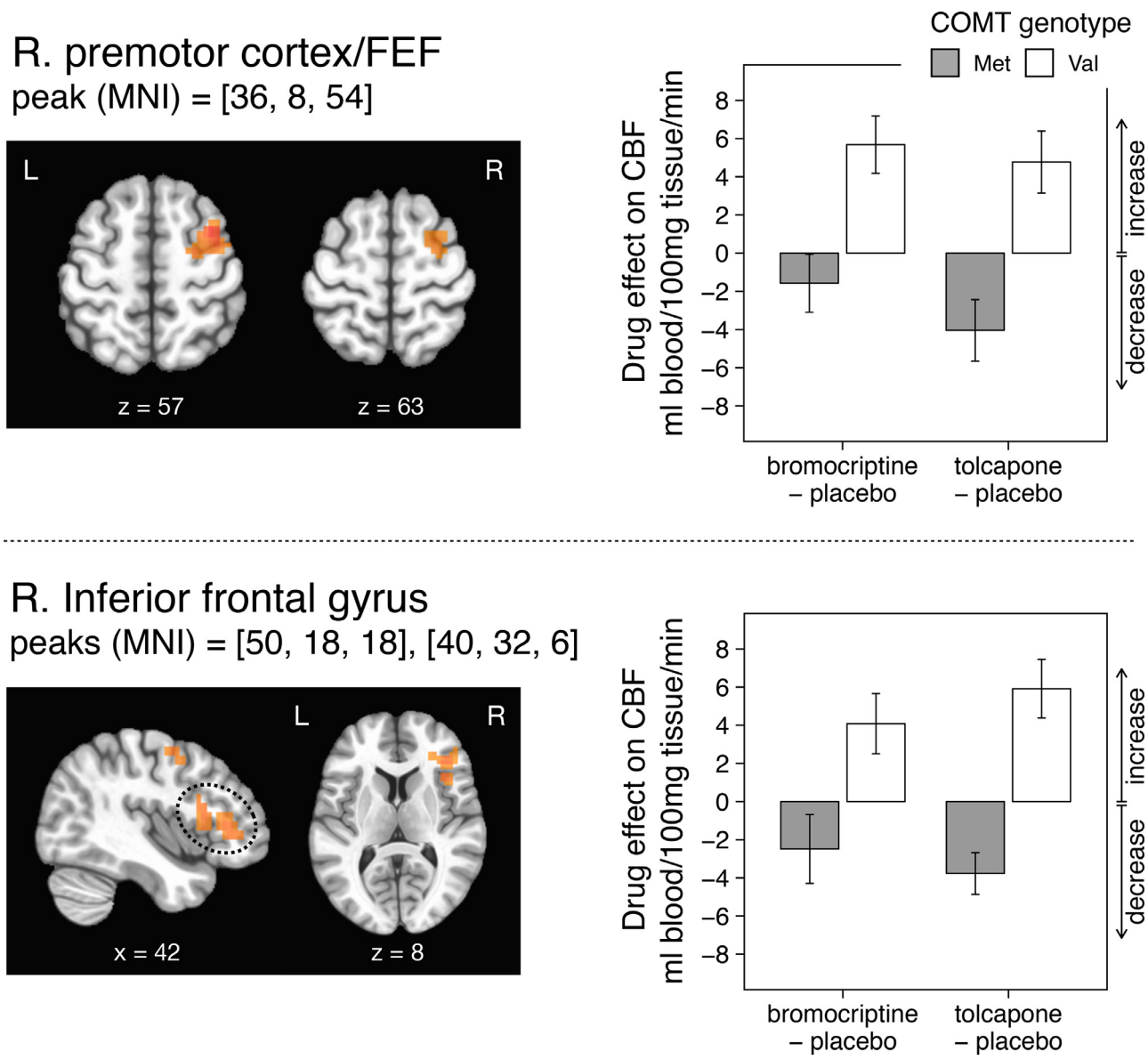

Fig. 2. Interaction of COMT genotype and drug (tolcapone/bromocriptine vs. placebo) on CBF in right frontal eye fields and premotor cortex (top panel) and right inferior frontal gyrus (bottom panel). Bar plots depict average effect across significant cluster voxels separately for each region, genotype group, and drug contrast; error bars represent ±1 standard error of the mean. FEF = frontal eye fields, CBF = cerebral blood flow.

CBF following acute administration of either drug significantly differentiated COMT Met and Val homozygotes, such that global GM perfusion tended to increase in Val/Val participants, but to decrease in Met homozygotes. This interaction is consistent with the overarching predictions of the inverted-U model: augmentation of dopaminergic signaling triggers opposing consequences on the basis of differences in baseline function. Mirroring the observed drug effect on global perfusion, voxel-wise analysis identified a genotypic influence on CBF change in right IFG and right FEF/PMC, such that tolcapone and bromocriptine tended to increase perfusion in Val participants, but to reduce or insignificantly affect perfusion in Met participants. In no case was Taq1A genotype found to moderate the impact of study drugs on cortical perfusion. Together, this pattern of results highlights the baseline dependence of mechanistically-distinct DA drug effects on cortical perfusion. It also adds weight to the proposal that ASL is an appropriate methodology for determining both the directionality and magnitude of dopaminergic drug effects on the brain independent of task-based metrics.

The degree to which tolcapone reduced perfusion in IFG, both across the entire group of participants and within Met homozygotes, covaried with the deleterious effect of drug on distractor resistance, or the ability to shield ongoing task goals from interference. Often touted for its role in supporting motor and cognitive inhibition (Aron et al., 2004), the IFG has been more broadly implicated in mediating the type of attentional control required for interference resolution and other executive functions (Hampshire et al., 2010). In non-human primates, D1 receptor expression is high in regions of the ventrolateral PFC (Froudist-Walsh et al., 2020) and, in humans, D1 receptor binding potential exhibits an inverted-U-shaped relationship with executive function (i.e., performance on the Wisconsin Card Sorting Test; Takahashi et al., 2008). Further, DA is released bilaterally within human IFG during high-order cognitive performance (N-back task; Aalto et al., 2005), and cognitive training has been found to alter D1 (but not D2) receptor binding in both right IFG and middle frontal gyrus, potentially in response to prolonged increases in DA levels during training (McNab et al., 2009). Interestingly, a recent biophysically-based model (Froudist-Walsh et al.,

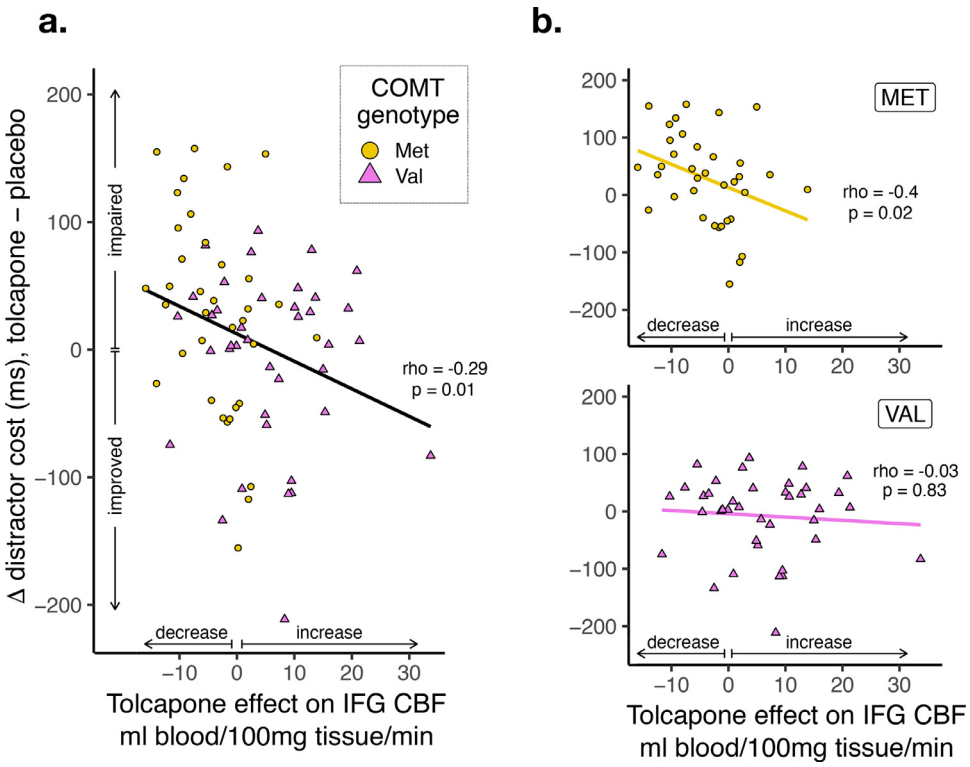

Fig. 3. Tolcapone-induced change in right inferior frontal gyrus perfusion correlates with change in distractor cost across the full sample of participants (a) and in Met homozygotes (b, top), but not in Val homozygotes (b, bottom). Distractor cost reflects the degree to which the appearance of a distracting stimulus slows performance of an ongoing cognitive task. IFG = inferior frontal gyrus, CBF = cerebral blood flow.

2020) accounting for gradients in D1 receptor expression and interareal connections across the primate cortex reproduced the hypothesized inverted-U-shaped relationship between level of D1 receptor stimulation and working memory-related neuronal activity in multiple frontoparietal regions, and most markedly in region 45a, a homologue of human mid-IFG. In concert with our novel finding that gene-by-drug interaction on CBF is robust along the IFG, these studies suggest that the IFG is both an important target of dopaminergic innervation in humans as well as a mediator of the effect of DA, and perhaps particularly of the D1 receptor, on cognition.

Importantly, ASL imaging in the current study was conducted in the absence of explicit task demands. While much of our knowledge about the dose-dependence of DA effects on PFC neuronal and neural network function stems from studies of primates performing cognitive tasks (e.g., see Arnsten et al., 2015), there is some evidence that DA augmentation influences properties of cell firing during off-task periods. In one study, DA had heterogeneous effects across sampled PFC neurons, increasing baseline firing rate in some but decreasing or failing to influence it in others (Jacob et al., 2013). Subsequently, use of selective agonists revealed opposing influences of D1 and D2 receptor stimulation on baseline firing, with the former suppressing and the latter enhancing it, though dosage effects remain to be investigated (Ott et al., 2014). Thus, drug effects on resting CBF may result from changes in neuronal activity and consequent metabolic demand across regions of DA receptor-enriched cortex. Compounding response variability attributable to baseline differences in DA activity, COMT genotype-related differences in DA receptor availability (Silfstein et al., 2008; see also Hirvonen et al., 2010) may alter the ratio of DA receptor types affected by drug administration, thereby yielding different patterns of net excitation. Further, individual differences in baseline DA system function may affect the degree to which D2 agonists, such as bromocriptine, primarily stimulate pre- versus post-synaptic D2 receptors (Horst et al., 2019), and thereby influence the direction of downstream activity, particularly in the striatum. Additional research is needed to explicitly test this hypothesis and to determine whether action at presynaptic D2 receptors *in the cortex* contributes meaningfully to drug response variability.

It is likely that DA receptor-mediated changes in frontal (i.e., FEF/PMC and IFG) neuronal or ensemble function propagate downstream to influence distributed brain network dynamics. For example, manipulating DA activity in the primate FEF changes the firing rate of sensory neurons in connected posterior cortex (i.e., V4) both during the performance of a visual task and at baseline (Nourdoost and Moore, 2011). Such remote "broadcasting" could help explain the more global effects on resting cortical perfusion found here despite evidence that COMT inhibition does not affect central hemodynamics (e.g., blood pressure; Illi et al., 1994). Indeed, not only do FEF neurons contribute to the tuning of visual cortical neurons, but FEF/PMC and IFG comprise key frontal nodes in the dorsal and ventral attention networks, associated with the deployment of top-down attentional control and the reorientation of attention to unexpected stimuli, respectively (Corbetta and Shulman, 2002). Consistent with large-scale effects, DA depletion alters both fMRI-based signaling dynamics and functional connectivity within a network overlapping the putative ventral attention network (Shafiei et al., 2019).

It is additionally possible that tolcapone and bromocriptine influence perfusion, at least in part, through direct effects on cerebral vasculature. Cerebral vessels express DA receptors (Choi et al., 2006) and are in close proximity to dopaminergic axons in cortical regions characterized by dense dopaminergic innervation, including lateral PFC (Krimer et al., 1998). In cats and primates, DA injection causes dose-dependent constriction of arterioles (Krimer et al., 1998) and reduction in blood flow (von Essen, 1974), likely through actions at adrenergic or serotonergic receptors (Edvinsson et al., 1985). On the other hand, DA agonists produce significant dilation of parietal arterioles (untested in frontal cortex; Edvinsson et al., 1985; McColloch and Harper, 1977), though D1 and D2 receptor-selective drugs exhibit different dose-dependent relationships: whereas D2 receptor agonism elicits a linear, dose-dependent increase in vessel dilation at high concentrations, D1 receptor agonism produces an inverted-U-shaped response, with greatest dilation achieved at mid-range doses and insignificant effects at low or high doses (Edvinsson et al., 1985). From this perspective, the enhanced perfusion found in Val homozygotes following both drug treatments may

reflect greater capacity in these participants for vasodilatory action via both receptor pathways. Nonetheless, the current experiment was not designed to adjudicate among competing physiological explanations of perfusion change; additional, multimodal research is needed to determine the relative contributions of neuronal, neural network, and vascular processes to the observed effects.

A notable aspect of our results is that tolcapone increased CBF in Val homozygotes despite *the absence of performance effects*, facilitative or otherwise. Without an ancillary brain measure of drug effect, our ability to interpret the Met-only pattern of behavioral results hinges on speculation as to whether the null behavioral effect in Val/Val participants is driven by insufficient drug-induced changes in DA activity in this group or, alternatively, by insensitivity of the task (or cognitive process) to dopaminergic modulation at the stimulated levels (Furman et al., 2020). Indeed, these two interpretations are often inextricable: though the sensitivity of a utilized behavioral probe to gradations of DA function is usually unknown, it is frequently the only means of approximating a drug's effect. By providing independent evidence in favor of robust modulation by tolcapone in Val homozygotes, our ASL results help arbitrate among explanations, providing support for the alternative interpretation. Future work is still needed to determine whether greater susceptibility to performance decrement ("overdose") than to enhancement ("optimization") is a feature of cortical dopaminergic modulation of distractor resistance in neurotypical adults or a particularity of our chosen task (and the combination of cognitive processes required for its performance).

We note several limitations of this study. First, our ASL protocol did not include a dedicated calibration scan. While the use of an average control image is not expected to alter the interpretation of our results (Pinto et al., 2020) and the directionality of age and sex effects is consistent with prior work (Parkes et al., 2004), our absolute CBF values may not be directly comparable to studies that use the calibration scan method. Second, due to technical constraints, ASL scanning was conducted within several minutes of the completion of the cognitive task. Thus, it is possible that residual metabolic effects of task performance may have contributed to perfusion estimates. Finally, COMT heterozygotes were excluded to maximize our ability to detect genotypic differences in response to dopaminergic drugs. We are, therefore, unable to determine whether there is a dose-dependent effect of the Met allele on drug-related changes in global or regional CBF. We also do not yet know whether the perfusion-behavior relationship identified here generalizes to the larger population of COMT genotype heterozygotes. Despite these limitations, our results highlight the promise of cerebral perfusion as an efficient and sensitive method for quantifying the effect of dopaminergic drugs on brain function in a manner that is independent of researcher-selected paradigms, an important step toward better characterizing the role of cortical DA in human cognition.

Declaration of Competing Interest

The authors declare no competing financial interests.

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Data and code availability statement

The data that support the findings of this study are available from the senior author (MD), upon reasonable request. The code used for these analyses is publicly available, as detailed in the Methods section.

CRediT authorship contribution statement

DJF: Conceptualization, data acquisition, data analysis, writing (original+final draft). IP: Data analysis, writing (original+final draft). RW: Conceptualization, data acquisition. AK: Conceptualization, Writing (final draft). MD: Conceptualization, Writing (final draft), funding acquisition.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2021.118472.

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