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Effects of Dopaminergic Drugs on Cognitive Control Processes Vary by Genotype

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Abstract

■ Dopamine (DA) has been implicated in modulating multiple cognitive control processes, including the robust maintenance of task sets and memoranda in the face of distractors (cognitive stability) and, conversely, the ability to switch task sets or update the contents of working memory when it is advantageous to do so (cognitive flexibility). In humans, the limited specificity of available pharmacological probes has posed a challenge for understanding the mechanisms by which DA, acting on multiple receptor families across the PFC and striatum, differentially influences these cognitive processes. Using a within-subject, placebo-controlled design, we contrasted the impact of two mechanistically distinct DA drugs, tolcapone (an inhibitor of catechol-*O*-methyltransferase [COMT], a catecholamine inactivator) and bromocriptine (a DA agonist with preferential affinity for the D2 receptor), on the maintenance and switching of task rules. Given previous work demonstrating that drug effects on behavior are dependent on baseline DA tone, participants were stratified according to genetic polymorphisms associated with cortical (COMT Val158Met) and striatal (Taq1A) DA system function. Our results were partially consistent with an inverted-U-shaped relationship between tolcapone and robust rule maintenance (interaction with COMT genotype) and between bromocriptine and cued rule switching (interaction with Taq1A genotype). However, when task instructions were ambiguous, a third relationship emerged to explain drug effects on spontaneous task switching (interaction of COMT genotype and bromocriptine). Together, this pattern of results suggests that the effects of DA drugs vary not only as a function of the DA system component upon which they act but also on subtle differences in task demands and context. ■

INTRODUCTION

To thrive in a dynamic environment, an organism must have the capacity to rapidly switch goal-directed strategies when internal demands or external contexts render the current one suboptimal. Concurrently, while a strategy or task set remains relatively optimal, its neural representation should be protected from decay or distraction. These facets of cognitive control—cognitive flexibility and cognitive stability, respectively—have been linked to the actions of the neuromodulator dopamine (DA; Ott & Nieder, 2019; Cools & D'Esposito, 2011). However, disentangling the specific effects of DA modulation on cognitive processes has been difficult because DA acts on two different G-protein-coupled receptor classes, the D1-like (D1/D5 subtypes) and D2-like (D2/D3/D4 subtypes) families, that are expressed to varying degrees throughout subcortical nuclei and layers of the cortex and that exert opposing influences on membrane excitability and cyclic adenosine monophosphate pathways. Models of DA neuromodulation have taken advantage of these opposing effects, positing that actions of D1 and D2 receptors in the PFC and striatum can effectively regulate the opposing demands of cognitive stability and flexibility (e.g., Klanker, Feenstra, & Denys, 2013; Durstewitz & Seamans, 2008).

Rodent and nonhuman primate research has demonstrated an important role for PFC DA signaling in the stabilization of items in working memory (Brozoski, Brown, Rosvold, & Goldman, 1979), as well as in the maintenance of more abstract representations, such as attentional sets or task rules (e.g., Ellwood et al., 2017; Ott, Jacob, & Nieder, 2014; Crofts et al., 2001). Early work found that depletion of DA in the nonhuman primate PFC impairs the ability to develop an attentional set (Crofts et al., 2001) and increases susceptibility to distraction (Roberts et al., 1994). At optimal levels of DA, the D1 receptor is thought to promote robust maintenance in working memory by enhancing the excitatory *N*-methyl-D-aspartate (NMDA) receptor currents that facilitate recurrent excitation in PFC pyramidal cells and to reduce noise from neighboring cell populations representing competing or irrelevant stimulus (or task) features by modulating interneuron gamma-aminobutyric acid (GABA) receptor and hyperpolarization-activated cyclic nucleotide-gated channel currents; these actions are thought to enhance the signal-to-noise ratio of maintained

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neural representations (Arnsten, Wang, & Paspalas, 2015). Importantly, the effect of D1 receptor activation on neuronal signal-to-noise ratio appears to follow an inverted-U-shaped pattern in nonhuman primates and rodents, such that DA levels that are either too low or too high impair working memory performance (Vijayraghavan, Wang, Birnbaum, Williams, & Arnsten, 2007; Zahrt, Taylor, Mathew, & Arnsten, 1997; Sawaguchi & Goldman-Rakic, 1994).

Although D1-selective agonists are not yet available for experimental use in healthy humans, to examine the impact of PFC DA levels on cognitive stability researchers have capitalized on a common single-nucleotide polymorphism (SNP) in the gene encoding catechol-*O*-methyltransferase (COMT; Lachman et al., 1996), a principal catabolizer of PFC DA (Käenmäki et al., 2010). Relative to the COMT Val variant, the Met allele is associated with a considerable decrease in enzymatic activity (Syvänen, Tilgmann, Rinne, & Ulmanen, 1997). The resultant accumulation of extracellular DA diffuses from the synapse where it is hypothesized to preferentially stimulate extrasynaptic D1 receptors over intrasynaptic D2 receptors (Bilder, Volavka, Lachman, & Grace, 2004; Winterer & Weinberger, 2004). Consistent with a D1 receptor mechanism underlying cognitive stability, Met allele carriers are reported to outperform their Val allele counterparts on tasks that primarily probe the maintenance of memoranda in working memory (e.g., delayed memory for simple stimuli; Berryhill, Wiener, Stephens, Lohoff, & Coslett, 2013) and those that require stabilization of information among other processes (e.g., *n*-back; Farrell, Tunbridge, Braeutigam, & Harrison, 2012; see also Savitz, Solms, & Ramesar, 2006) but to perform worse on tests that predominantly assess cognitive flexibility (e.g., Cameron, Wallace, Al-Zughoul, Kayser, & D'Esposito, 2018; Colzato, Waszak, Nieuwenhulis, Posthuma, & Hommel, 2010). Pharmacological studies using the brain-penetrant COMT inhibitor tolcapone further support the inverted-U-shaped model of PFC DA: The benefits (or costs) of tolcapone administration on cognitive stability measures depend on COMT genotype in both healthy human participants (for a review, see Schacht, 2016) and transgenic mice (Barkus et al., 2016), such that low-DA Val allele carriers typically exhibit improved, whereas high-DA Met allele carriers exhibit diminished, performance on tasks of cognitive stability following treatment.

D2 receptor expression in the human PFC is considerably lower than that of the D1 receptor (Hurd, Suzuki, & Sedvall, 2001) and its role in modulating cognitive control is less clear (Vijayraghavan, Major, & Everling, 2017). In their influential dual-state neural attractor model, Durstewitz and Seamans (2008) propose opposing actions of D1 and D2 receptor stimulation based on their relative receptor affinities. Specifically, they argue that, at moderate DA levels, the PFC enters a D1-dominant state characterized by stable representations separated by high-energy barriers, whereas when DA levels are low or high, the PFC transitions to a D2-dominant state in which shallow and unstable representations are separated by low-energy barriers and therefore susceptible to distraction and spontaneous switching. However, empirical studies of D2 receptor function have yielded conflicting results (Vijayraghavan, Major, & Everling, 2016; Ott et al., 2014). For example, in contrast to the opponent actions predicted by the dual-state model, several studies report that D2 receptor stimulation in nonhuman primate PFC predominantly influenced the perisaccadic period of an oculomotor working memory task, pointing to a more circumscribed role for the receptor in the gating of response signals to the BG, thalamus, or other motor effector regions (Vijayraghavan et al., 2016; Wang, Vijayraghavan, & Goldman-Rakic, 2004). Other data, however, suggest that D2 receptor stimulation may influence PFC rule coding and maintenance, in part through mechanisms that complement those of D1 receptor stimulation (Ott et al., 2014). Although methodological variability may in part explain these divergent results, another possibility is that the effects of D2 receptor stimulation on cognitive control processes are mediated by individual differences in DA system function (or proxies for them). Indeed, pharmacological studies in humans have reported differential effects of D2 family drugs on task-elicited PFC activation (Cools, Sheridan, Jacobs, & D'Esposito, 2007) and tasks associated with frontal lobe function (Kimberg, D'Esposito, & Farah, 1997) as a function of individual differences in trait impulsivity and reading span, respectively.

In contrast to the PFC, the striatum is characterized by dense expression of DA D2 receptors (Hurd et al., 2001). The dorsal striatum receives topographically organized PFC inputs and propagates information along two parallel pathways through the BG circuitry—the putative "direct" and "indirect" pathways—that ultimately excite or inhibit, respectively, thalamic projections back to the cortical regions of origin. Release of DA into the striatum from brainstem dopaminergic neurons differentially modulates aspects of cell membrane excitability within these two pathways (Nicola, Surmeier, & Malenka, 2000), facilitating the "direct" pathway by binding to D1 receptors and inhibiting the "indirect" pathway by binding to inhibitory D2 receptors, the net effect of which is thought to bias the system toward cognitive flexibility, that is, the activating or updating of behavioral and cognitive representations (Frank & O'Reilly, 2006). Striatal DA has been repeatedly associated with cognitive flexibility in rodents, primates, and humans (Klanker et al., 2013). For example, intrastriatal administration of haloperidol, a D2 receptor antagonist, reduces behavioral flexibility in rats (Cools, 1980) and cats (Jaspers, Schwarz, Sontag, & Cools, 1984). Similarly, humans with Parkinson disease, associated with profound loss of DA-producing neurons in the substantia nigra, exhibit impairments in cognitive flexibility that are remediated by dopaminergic medication (Costa et al., 2014; Cools, Barker, Sahakian, & Robbins, 2001, 2003). Strikingly, the degree to which DA improves cognitive flexibility in Parkinson's disease correlates with enhanced striatal activation during

task-switching (Aarts et al., 2014). Furthermore, in healthy human adults, performance on tasks of cognitive flexibility vary with nigrostriatal DA synthesis capacity (Berry, Shah, & Jagust, 2018) and genetic polymorphisms affecting aspects of DA signaling in the striatum, such as the ANKK1/Taq1a SNP (Taq1A; Stelzel, Basten, Montag, Reuter, & Fiebach, 2010). Located 10 kB downstream of the DRD2 gene (Neville, Johnstone, & Walton, 2004), the minor A1+ allele of Taq1A is associated with reduced D2 receptor density (Gluskin & Mickey, 2016) but enhanced DA synthesis (Laakso et al., 2005), and its carriers have been found to outperform A1− homozygotes on measures of task switching (Stelzel et al., 2010).

As in the PFC, pharmacological modulation of striatal DA does not uniformly improve cognitive flexibility. Indeed, whereas studies of healthy adults frequently report no main cognitive benefit of bromocriptine, a DA agonist with strong affinity for D2 receptors (Cameron et al., 2018; Stelzel, Fiebach, Cools, Tafazoli, & D'Esposito, 2013; van Schouwenburg et al., 2013; van Holstein et al., 2011; Cools et al., 2007), significant effects emerge when samples are stratified according to putative proxies for striatal DA system function, such as DAT1 genotype (van Holstein et al., 2011), working memory span (van Holstein et al., 2011), or trait impulsivity (Cools et al., 2007). In these studies, bromocriptine typically enhances flexibility only in individuals posited to have relatively low baseline striatal DA neurotransmission, suggesting that, as in the PFC, there is a restricted range of striatal DA stimulation within which cognitive flexibility is optimized.

Despite mounting evidence in the animal literature for region-, receptor-, and task-specific effects of DA on cognitive stability and flexibility (Ott & Nieder, 2019), few human studies to date have directly compared the differential impact of mechanistically variable DA manipulations on discrete aspects of cognitive control. The ability to target selective components of the brain's DA system is quite limited in human subjects, as most available drugs bind with variable affinity to multiple receptor types and act diffusely across all brain tissue expressing these receptors. To overcome this limitation, several strategies have been used, such as the co-administration of selective agonists and antagonist to isolate effects attributable to specific receptors (e.g., van Holstein et al., 2011; Frank & O'Reilly, 2006) and the use of multiple drugs with only partially overlapping mechanisms of action to identify shared and nonshared effects on behavior (e.g., Cameron et al., 2018; Bestmann, Ruge, Rothwell, & Galea, 2015; Bloemendaal et al., 2015; Dodds et al., 2008; Müller, von Cramon, & Pollmann, 1998). Building on the latter strategy, we used a within-subject, placebo-controlled design to contrast the effects of tolcapone (a COMT enzyme inhibitor) and bromocriptine (a DA receptor agonist with highest affinity for the D2 receptor) on task maintenance and switching. In addition to modulating the DA system through distinct physiological mechanisms, the net influence of these drugs is likely to be differentially distributed across brain regions and receptor types. Although COMT influences the degradation of DA to varying degrees throughout regions of the brain, including the striatum and hippocampus (Laatikainen, Sharp, Harrison, & Tunbridge, 2013), relatively low levels of DA transporter (DAT) expression in the PFC makes this region more reliant on COMT for extracellular DA clearance. Thus, tolcapone is expected to exert its effect to a greater extent in cortex than in striatum (Yavich, Forsberg, Karayiorgou, Gogos, & Männistö, 2007; Matsumoto et al., 2003). By contrast, bromocriptine's actions at D2 receptors are expected to occur across cortical and subcortical tissues, though the expression of this receptor type is much greater in the striatum than in the PFC (Hall et al., 1994; Camps, Cortés, Gueye, Probst, & Palacios, 1989). To account for differences in drug effect related to baseline variation in DA system function, our participants were stratified according to two SNPs (COMT and Taq1A) associated with variation in cortical and striatal DA system function, respectively. We hypothesized, based on the evidence reviewed above, that, although tolcapone would improve distractor-resistant task rule maintenance via optimization of D1 stimulation in COMT Val homozygotes (low PFC DA), it may impair such distractor resistance in Met homozygotes (high PFC DA) potentially by shifting the balance of D1/D2 stimulation to a D2 state. In contrast, bromocriptine was hypothesized to facilitate task rule switching more generally and, to a greater extent, in COMT Met (high PFC DA) and Taq1A A1− (low striatal DA) homozygotes by optimizing D2 receptor stimulation in PFC and striatum. Finally, we explored the extent to which drug manipulations exert opposing effects on facets of cognitive control, consistent with the view that dopaminergic modulation, even acting across multiple receptor systems and regions, ultimately serves to bias an organism toward stability or flexibility.

METHODS

Procedure Overview

Individuals meeting advertised inclusion criteria were invited to the Helen Wills Neuroscience Institute at University of California, Berkeley, to provide a saliva sample for genotyping. Following genotyping, individuals who met our genotypic criteria (see below) were invited back to the lab to take part in a health screening and medical history. During this appointment, participants also completed a listening span test (Salthouse & Babcock, 1991) and the Barratt Impulsivity Scale (Patton, Stanford, & Barratt, 1995) to assess working memory capacity and trait impulsivity, respectively. Participants meeting medical criteria were scheduled for three pharmacological study sessions to be completed on different days. The number of days separating subsequent sessions ranged from 2 to 86 (median = 7, mean = 10.2, SD = 9.7). At each of the three sessions, participants were administered a single

dose of bromocriptine, tolcapone, or placebo, after which they performed a cognitive task in an MRI scanner. Neuroimaging results will be described elsewhere. Although session start times varied between 7 a.m. and 4 p.m., efforts were made to keep start times consistent across sessions for each participant. 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 the University of California, Berkeley, and were compensated for their participation.

Participants

Healthy young participants were recruited for genetic sampling from the University of California, Berkeley, community and surrounding area using online and print advertisement. Participants affirmed at the time of genetic sampling that they met initial inclusion criteria: (1) 18–30 years old, (2) right-handed, (3) current weight greater than 100 pounds, (4) able to read and speak English fluently, (5) nondrinker or light drinker (women: <7 alcoholic drinks/week; men: <8 alcoholic drinks/week), (8) no recent history of substance abuse, (9) no history of neurological or psychiatric disorder, (10) not currently using psychoactive medication or street drugs, (11) not pregnant, and (12) no contraindications to MRI (e.g., no claustrophobia, pacemakers, history of seizures, or MRI-incompatible metal in body). Genetically eligible participants underwent a medical screening with an on-site physician or nurse practitioner, as well as a liver function test, to ensure that there were no medical contraindications to tolcapone and bromocriptine use and to verify the absence of neurological and psychiatric history.

Genotyping Overview

Saliva samples were obtained using Oragene collection kits with stabilizing liquid (DNA Genotek). Genotyping of COMT (rs4680) and Taq1A (rs1800497) SNP testing was performed at the UCSF Genomics Core, Vincent J. Coates Genomics Sequencing Laboratory, and Kashi Clinical Laboratories using polymerase chain reaction-based TaqMan technology (Applied Biosystems). Only individuals who were homozygous for either the Val or Met allele of the COMT polymorphism were invited to participate in the remainder of the study. Consistent with previous studies (e.g., Stelzel et al., 2010), Taq1A genotypes were binned according to the presence ("A1+") or absence ("A1−") of any copies of the A1+ minor allele. To enable us to independently investigate the effects of each genotype on drug response, participants were selected based on compound COMT/Taq1A genotype, with roughly equal representation in each of the following groupings: Met/A1+, Val/A1+, Met/A1−, Val/A1−.

Drugs

During each session, participants received a single oral dose of bromocriptine (1.25 mg), tolcapone (200 mg), or placebo. These doses were selected based on their demonstrated efficacy in eliciting changes in cognitive performance (e.g., Cameron et al., 2018; Bloemendaal et al., 2015; Farrell et al., 2012; Gibbs & D'Esposito, 2005). Bromocriptine reaches peak plasma concentrations between 0.5 and 3.5 hr (mean time to peak = 1.7 hr) after administration and has an elimination half-life of 3–7 hr (Kvernmo, Härtter, & Burger, 2006; Price, Debono, Parkes, Marsden, & Rosenthaler, 1978). Tolcapone reaches peak plasma concentration, on average, 1.8 hr after oral administration and has an elimination half-life of about 2 hr (Jorga, Fotteler, Heizmann, & Zürcher, 1998). To increase the probability that participants were near peak plasma drug concentrations during task performance on both of the drug days, participants began the task approximately 75 min after drug/placebo administration. The order of drug administration was under a double blind and counterbalanced across participants (and within genotype groups). Participants reported side effects (e.g., "drowsy," "fatigued") using visual analogue scales at the beginning of each session ("baseline"), before task performance, and immediately following task performance. Given concerns that drug-related changes in drowsiness or fatigue may influence task performance, we computed changes in "drowsy" and "fatigued" scores from baseline to prescan ("prescan scores") and from baseline to postscan ("postscan scores") for each of the three sessions and included these variables in control iterations of relevant statistical models.

At the conclusion of each session, participants were asked to guess whether they had received a placebo or drug on that day. As a group, participants demonstrated no better than chance-level accuracy in their guesses, and rates of "drug" vs. "placebo" guesses did not differ significantly across the three sessions, $\chi^2(2) = 3.2, p = .2$ (excludes four omitted responses). Following placebo, 56% of participants believed they had been given one of the dopaminergic drugs, whereas 51% and 42% believed this to be the case following bromocriptine and tolcapone administration, respectively.

Cognitive Paradigm

We adapted the task-switching paradigm developed by Armbruster, Ueltzhöffer, Basten, and Fiebach (2012; see Figure 1). On each trial, participants were required to respond quickly to digits between 1 and 9 (excluding 5) that appeared in different shades of gray against a black background. On 82% of trials, a single digit appeared above a central fixation cross at a constant, medium gray value (i.e., 127). For these "ongoing task" trials, participants performed an operation on the digit and responded by pressing the index finger of either their left

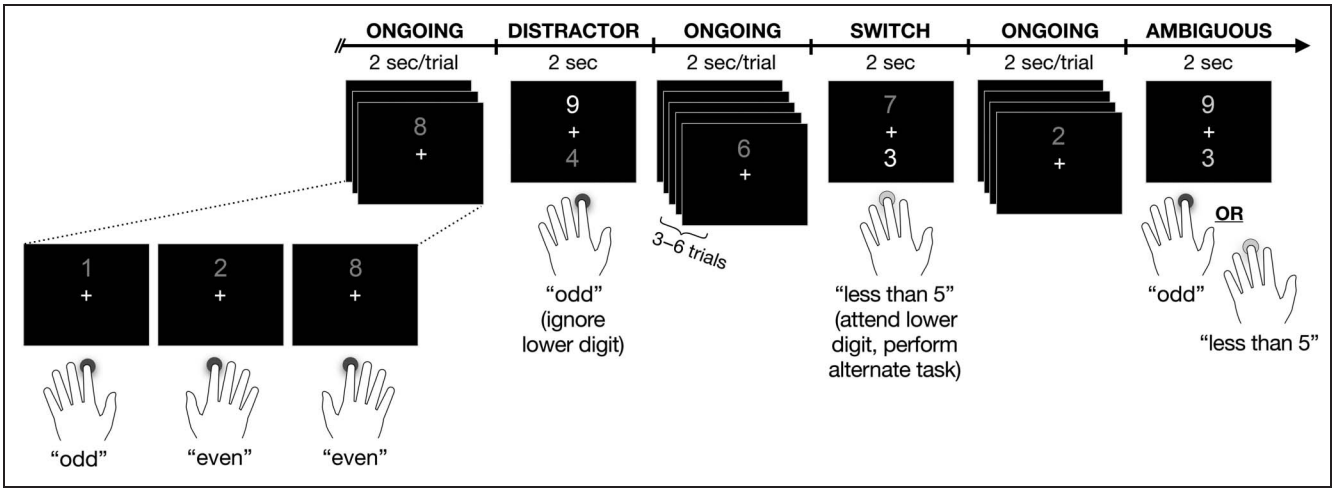

Figure 1. Schematic of task-switching paradigm. Participants applied their dominant task rule (pictured: parity rule) when operating on digits appearing above the central crosshair and the alternate rule (pictured: magnitude rule) when operating on digits appearing below it. When two numbers appeared simultaneously in both locations, participants were instructed to operate on whichever of the upper ("distractor trial") or lower ("switch trial") digits was brightest. Trials on which the difference in brightness between the two digits was reduced ("ambiguous trials") allowed for the examination of spontaneous switch tendency in the absence of explicit cues. Responses to upper and lower digits were made with index and middle fingers, respectively.

or right hand. Participants were trained to make either odd/even or low/high decisions on these ongoing task digits; task assignment ("version") was counterbalanced across individuals within genotype group. On the remaining 18% of trials, two digits appeared on the screen simultaneously, one above and one below the fixation cross. The relative brightness of the upper and lower digits varied and encoded a task cue. When the upper digit was brighter (gray value ranging from 169 to 195; one third of non-ongoing task trials, 6% of total trials), participants were instructed to ignore the lower digit (gray value = [255 − value of upper digit]) and continue to apply the ongoing task rule to the upper digit ("distractor trials"). When the lower digit was brighter (gray value ranging from 169 to 195; one third of non-ongoing task trials, 6% of total trials), participants were signaled to switch attention to the lower digit (gray value = [255 − value of upper digit]) and to apply the alternate task rule to it ("switch trials"). On the final third of these trials (6% of total trials), the difference in brightness between the upper and lower digits was reduced ("ambiguous trials"); for these trials, the gray value of the upper digit remained set at 127 and the value of the lower digit ranged from 117 to 137. As participants were only trained to respond to the brighter of the two digits, this trial type was designed to assess the extent to which participants are prone to switching under ambiguous conditions (Armbruster et al., 2012). In the original paradigm, participants were required to switch hands when they switched tasks; in the current version, we had participants instead switch to responding with the middle fingers of the left and right hand to minimize the biasing of behavior as a function of hemispheric dominance. Participants performed a total of 990 trials distributed across three blocks with brief interposed breaks. Individual switch, distractor, and ambiguous trials were pseudorandomly interspersed among runs of three to six contiguous ongoing task trials. Digits remained on the screen for 900 msec, but responses were registered for the duration of each 2000-msec trial. There were no additional intertrial intervals. Before testing on each of the 3 days, participants underwent task training, the final stage of which required them to respond correctly to at least five of the previous seven switch/distractor trials to proceed to testing. To reduce the extent to which participants developed explicit response strategies, ambiguous trials were only presented during the final stage of training when performance feedback was not provided.

Data Preparation and Analysis

To reduce the inclusion of nonspecific session or drug effects in our analyses, we did not include data from individual task blocks for which ongoing task response rate was lower than 60% or for which accuracy on ongoing, distractor, or switch trials was less than "chance," defined as 50% for ongoing trials and 25% for distracter and switch trials based on the number of potential button presses at play (2 vs. 4) during these trial types. This procedure resulted in the exclusion of 13 total task blocks from eight unique participants (five placebo, six bromocriptine, two tolcapone). We further excluded from analysis the first trial of each block, as well as trials immediately following inaccurate responses and trials immediately following distractor, switch, or ambiguous trials, to reduce possible "contamination" from other cognitive control processes (Armbruster-Genç, Ueltzhöffer, & Fiebach, 2016). Together, these procedures excluded 25.5% of trials. For analysis of RT data, we additionally excluded individual

trials for which RT was greater or less than 3 *SD*s from the subject-level mean for a given trial type and drug, increasing the total number of excluded trials to 26.5%. To better satisfy data normality assumptions associated with linear models, mean RTs were log-transformed, and mean percent error scores were arcsine-square root transformed before analysis.

Mean RTs from accurate trials and percent error scores were analyzed with separate linear mixed-effects models implemented with the "lme4" (Bates, Mächler, Bolker, & Walker, 2015) and "afex" (Singmann, Bolker, Westfall, & Aust, 2018) libraries in R (version 3.5.1). Models were constructed to test the primary hypothesis that bromocriptine and tolcapone (relative to placebo) administration would differentially influence switch and distractor (relative to ongoing) trial performance and, further, that Taq1A and COMT genotypes might mediate these effects. Additional covariates (i.e., session number and ongoing task version) were included in the model to account for potential confounds at the level of baseline task performance (i.e., ongoing task performance on placebo). Thus, fixed effect predictors included the within-subject variables trial type (treatment-coded: ongoing [reference level], switch, distractor), drug (treatment-coded: placebo [reference level], bromocriptine, tolcapone), and session number (centered on session 1), as well as the between-subject variables ongoing task version (deviation-coded: magnitude, parity), COMT genotype (deviation-coded: Val, Met), and Taq1A genotype (deviation-coded: A1−, A1+). In addition, we included a covariate representing the task block number (within session; centered on Run 1) to determine whether effects of interest varied linearly over the course of the session, potentially due to condition-specific fatigue effects. Our primary terms of interest—interactions between trial type, drug, and genotype—were included separately for each of the two SNPs. Finally, the four-way interactions of trial type, drug, genotype (separately for the two SNPs), and task block number were included to further qualify our interactions of interest. Among these variables, all lower order interactions were included in the model to facilitate interpretability. A maximal random effects structure was used to minimize Type I error (Barr, Levy, Scheepers, & Tily, 2013); thus, random effects included the intercept of subject, as well as the slopes of drug, trial type, and block number within subject. *F* tests were computed for fixed effects using the Satterthwaite method for approximating degrees of freedom. Follow-up z tests contrasting distractor versus ongoing trial estimates ("distractor costs") and switch versus ongoing trial estimates ("switch costs") were corrected for multiple comparisons using the false discovery rate method implemented in the "emmeans" package (Lenth, 2018). For interpretability, we present estimated marginal effects and standard errors that have been back-transformed to the original scale (e.g., milliseconds, % error) in text and figures.

Because errors of commission on switch trials may reflect distinct types of failures of cognitive control, we divided such errors into two categories to better characterize the effects of drug and genotype: (1) switch trials on which participants continued to perform the ongoing task ("failures to switch") and (2) switch trials on which participants switched tasks (as evidenced by use of the middle fingers to respond) but made a response error ("execution error"). "Failures to switch" and "execution error" metrics were computed as the percentage of this type of error out of all (nonomitted) switch trial responses, arcsine-square root transformed to approximate normality, and analyzed with linear mixed-effects models as described above. Because of the relatively small number of exemplars per session, error rates were aggregated across task blocks for these analyses.

Next, we computed the proportion of ambiguous trials (excluding trials with omitted responses) that participants treated as task switches (as evidenced by their use of middle fingers to respond). Here, we report on the analysis restricted to accurate trials, though the pattern of results is unchanged when inaccurate trials are included. In this context, an accurate response reflects the correct response based on the decision to either maintain the ongoing task or to switch tasks, regardless of the relative luminance of the stimuli. This metric was arcsine-square root transformed to approximate normality and analyzed with a linear mixed-effects model. Previous work suggests that DA may influence visual processing (Brandies & Yehuda, 2008); given that the luminance difference between the upper and lower digits varied in magnitude and direction across ambiguous trials, we conducted an additional control analysis to ensure that any drug effects on switching rates were not driven by changes in the ability to perceive these subtle differences in luminance. Accurate trial-wise (n = 11,004) responses (switch, nonswitch) were analyzed using a binomial generalized linear mixed-effects model with fixed effect predictors of drug, session number, ongoing task version, COMT genotype, Taq1A genotype, and luminance difference ($-10 \leq x \leq 10$, where differences are computed relative to the reference gray value of 127, as noted above). For this analysis, the interactions of interest were among the factors drug, genotype, and luminance difference. The maximal random effects structure employed here included the intercept of subject and the slopes of drug, luminance difference, and their interaction within subject. Likelihood ratio tests were used to determine statistical significance. The bromocriptine session for one additional participant (Met/A1−) was excluded from analyses of ambiguous trial behavior due to unusually low performance on this particular trial type (>75% error rate).

Finally, in an exploratory set of analyses, we examined the extent to which dopaminergic drugs exert opposing effects on measures of cognitive stability and flexibility. We first computed Spearman's correlations among drug

Table 1. Raw Task Performance by Genotype, Drug, and Trial Type

				Ongoing		*Distractor*		*Switch*			*Ambiguous*
	Genotype	*N*	*Drug*	*RT, msec (SD)*	*% Error (SD)*	*RT, msec (SD)*	*% Error (SD)*	*RT, msec (SD)*	*% Error (SD)*	*% Switch Failures (SD)*	*% Switch Rate (SD)/ % Accurate Only (SD)*
Taq1A	A1+	41	Placebo	574 (109)	6.2 (4.5)	695 (140)	9.2 (7.1)	955 (202)	19.1 (12.1)	4.7 (4.6)	22.5 (18.9)/21.4 (19.0)
		41	Bromocriptine	574 (95)	6.8 (4.6)	709 (135)	11.0 (7.7)	972 (228)	20.1 (12.9)	5.9 (8.0)	25.2 (21.1)/22.9 (20.9)
		41	Tolcapone	568 (80)	7.3 (5.5)	706 (107)	11.0 (6.9)	961 (194)	18.7 (13.2)	4.7 (4.4)	23.6 (20.5)/22.3 (21.2)
	A1−	39	Placebo	568 (100)	5.3 (4.2)	727 (174)	10.0 (6.8)	920 (177)	17.8 (13.6)	5.4 (5.5)	30.0 (22.6)/28.3 (23.9)
		39	Bromocriptine	568 (99)	5.3 (4.3)	730 (155)	9.4 (6.9)	934 (179)	14.3 (11.0)	3.5 (5.1)	28.5 (19.9)/27.0 (20.5)
		39	Tolcapone	575 (100)	5.1 (4.3)	737 (157)	9.3 (5.8)	926 (161)	16.3 (11.7)	4.6 (5.1)	30.1 (20.0)/27.9 (21.1)
COMT	VAL	41	Placebo	560 (119)	5.9 (4.7)	699 (178)	9.0 (6.9)	928 (209)	17.5 (10.7)	5.0 (5.3)	25.1 (19.0)/23.9 (19.5)
		41	Bromocriptine	556 (108)	5.8 (4.4)	696 (165)	9.8 (7.6)	945 (224)	17.4 (12.5)	4.3 (5.1)	21.4 (17.1)/19.3 (15.8)
		41	Tolcapone	556 (105)	5.6 (4.5)	690 (147)	9.4 (6.3)	928 (198)	16.8 (12.2)	4.8 (5.3)	24.2 (19.4)/22.7 (19.8)
	MET	39	Placebo	584 (86)	5.6 (4.0)	723 (134)	10.2 (7.0)	948 (170)	19.6 (14.8)	5.1 (4.8)	27.3 (23.1)/25.6 (23.9)
		39	Bromocriptine	587 (80)	6.3 (4.6)	743 (117)	10.7 (7.1)	963 (186)	17.2 (12.2)	5.1 (8.3)	32.6 (22.4)/30.9 (23.7)
		39	Tolcapone	588 (67)	6.8 (5.6)	754 (111)	11.0 (6.6)	960 (156)	18.3 (12.9)	4.5 (4.1)	29.4 (21.3)/27.5 (22.6)

effects for distractor and switch RT and accuracy (error rate) costs (e.g., Δ distractor RT cost: drug distractor RT cost − placebo distractor RT cost), separately for bromocriptine and tolcapone effects. Given our pattern of results (described below), we used principal components analyses (PCA) to reveal secondary structures in the data. PCA with varimax rotation was conducted separately for bromocriptine- and tolcapone-related changes, with the following metrics: Δ distractor RT cost, Δ distractor accuracy cost, Δ switch RT cost, and Δ switch accuracy cost. Metrics were mean-centered and scaled to unit variance before analysis. To compare the structure of components between the two drug conditions, Procrustes rotation of the tolcapone component matrix to match the bromocriptine matrix was followed by computation of Tucker's coefficient of congruence, a cosine similarity measure (Lorenzo-Seva Δ ten Berge, 2006). PCA analysis was conducted using the R *psych* library (Revelle, 2018).

RESULTS

Participant Data

Our sample included 80 participants belonging to the following COMT/Taq1A genotype groups: Met/A1+ (n = 20, 10 female, age [mean ± SD] = 20.6 ± 2.4 years), Val/A1+ (n = 21, 15 female, age = 21.0 ± 1.7 years), Met/A1− (n = 19, 15 female, age = 21.8 ± 3.6 years), and Val/A1− (n = 20, 11 female, age = 21.3 ± 2.2 years). For illustrative purposes, untransformed mean RTs, error rates, and switch rates by genotype group are provided in Table 1.

Reaction Time

All F values are presented in Table 2, and estimated mean RT scores are presented in Figure 3. Consistent with previous results using this task (Armbruster et al., 2012), the analysis of RT yielded a simple effect of Trial Type, $F(2, 93.26) = 479.74, p < .0001$, such that costs were incurred for both switch (estimated marginal effect = 355 msec; $z = 28.75, p < .0001$) and distractor (130 msec; $z = 17.57$, $p < .0001$) trials relative to ongoing trials on placebo. We also observed effects of Study Session, $F(1, 140.1) = 50.97$, $p < .0001$, and Task Block, $F(1, 75.29) = 63.14$, $p < .0001$; in both cases, ongoing task responses were faster with each subsequent session or task block (within session).

There were no effects of Drug, $F(2, 113.78) = 2.36$, $p = .1$; COMT Genotype, $F(1, 72.99) = 2.26$, $p = .14$; or Taq1A Genotype, $F(1, 72.99) = 0, p = .99$, on ongoing task RT, nor a significant Drug × Trial Type interaction, $F(4, 1605.2) = 1.77$, $p = .13$. However, we identified a three-way interaction of Drug, Trial Type, and COMT Genotype on RT, $F(4, 1605.21) = 2.63$, $p = .03$; tolcapone increased distractor cost (i.e., distractor RT vs. ongoing task RT) in Met homozygotes (estimated marginal effect = +27 msec, $z = 2.96, p = .01$; Figure 2, top) but not in Val homozygotes (+1 msec, $z = 0.1$, $p = .92$).

Table 2. ANOVA Table for Mixed Model of RT

Effect	*df*	*F*	*p*
Taq1A	1, 72.99	0.00	.99
COMT	1, 72.99	2.26	.14
Drug	2, 113.78	2.36	.10
Type	2, 93.26	479.74	<.0001
Block	1, 75.29	63.14	<.0001
Session	1, 140.10	50.97	<.0001
Version	1, 75.17	2.89	.09
Taq1A × Drug	2, 113.81	0.07	.93
COMT × Drug	2, 113.82	4.81	.01
Taq1A × Type	2, 93.27	1.95	.15
COMT × Type	2, 93.28	0.84	.44
Drug × Type	4, 1605.20	1.77	.13
Taq1A × Block	1, 75.31	0.00	.99
COMT × Block	1, 75.31	0.03	.86
Drug × Block	2, 1625.72	3.33	.04
Type × Block	2, 1605.51	55.91	<.0001
Taq1A × Drug × Type	4, 1605.20	0.67	.61
COMT × Drug × Type	4, 1605.21	2.63	.03
Taq1A × Drug × Block	2, 1625.93	0.22	.80
COMT × Drug × Block	2, 1626.13	8.21	.0003
Taq1A × Type × Block	2, 1605.52	0.15	.86
COMT × Type × Block	2, 1605.48	0.05	.95
Drug × Type × Block	4, 1605.11	0.76	.55
Taq1A × Drug × Type × Block	4, 1605.11	0.43	.79
COMT × Drug × Type × Block	4, 1605.13	1.56	.18

No comparable Tolcapone × COMT genotype effect was found for switch cost, nor were there significant Bromocriptine × COMT genotype effects for either distractor or switch cost (all $|z|$s ≤ 2, ps > .1).

Though not of central focus to the current study, our RT model indicated that dopaminergic drugs may influence the dynamics of performance over time. We include a description of these results here for completeness, as well as to demonstrate that such temporal dynamics do not fully account for the Drug × Trial type × COMT genotype interaction reported above. Specifically, a Drug × Task Block interaction, $F(2, 1625.72) = 3.33$, $p = .04$, revealed that, relative to placebo, the two drugs differed in their modulation of ongoing task RT change across blocks; whereas bromocriptine tended to reduce the negative slope of ongoing task RT change across blocks

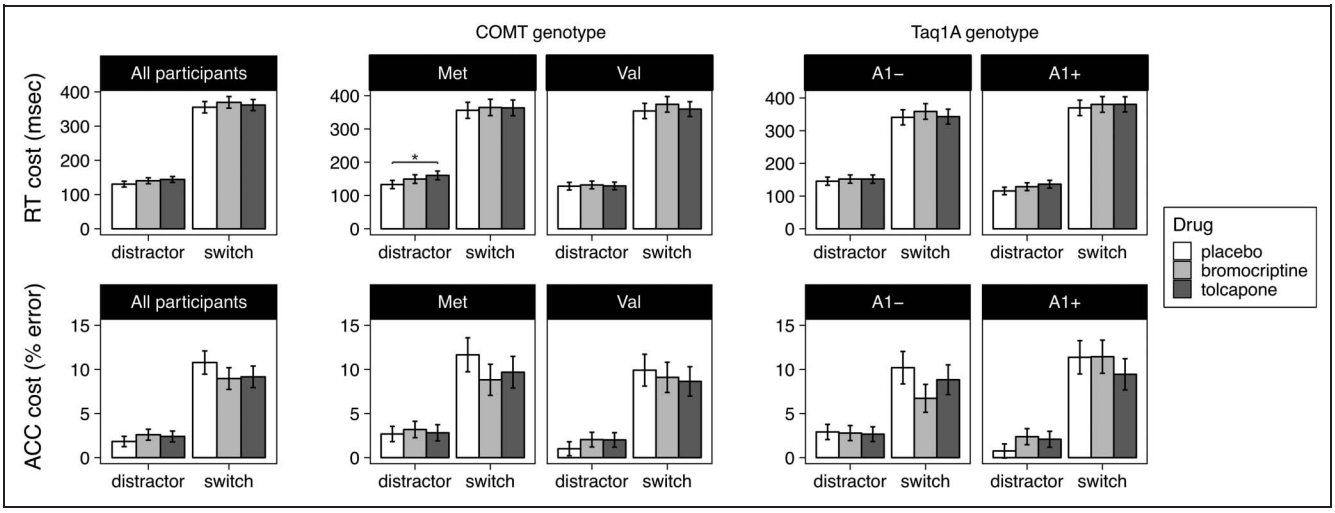

Figure 2. Estimated RT (top) and accuracy (ACC; bottom) costs by trial type for each drug condition (placebo, bromocriptine, tolcapone) and genotype (Taq1A, COMT). Estimates are back-transformed and reflect differences in RT or error rate from the ongoing task condition. Error bars represent back-transformed standard errors estimated from the corresponding mixed models with the "emmeans" package in R. *$p < .05$.

(estimated marginal trend = +2.73 msec, $z = 0.65, p = .51$; less improvement over time), tolcapone tended to increase it (−5.07 msec, $z = -1.21$, $p = .46$; greater improvement over time), though neither drug effect on its own reached statistical significance. This interaction was qualified by a three-way interaction of Drug, Task Block, and COMT Genotype, $F(2, 1626.13) = 8.21$, $p = .0003$, such that a significant difference in the effects of bromocriptine and tolcapone on ongoing task RT slope was present in COMT Met ($z = 2.03$, $p = .04$) but not in Val ($z = 0.60, p = .55$) participants. Importantly, the four-way interaction of Drug, Task Block, COMT Genotype, and Trial Type was insignificant, $F(4, 1605.13) = 1.56, p = .18$, indicating that the interaction of drug, trial type, and COMT genotype (reported above) was likely not driven by incremental deterioration in attention or other nonspecific drug-related changes over time. Similarly, the three-way interaction of COMT Genotype, Drug, and Trial Type remained significant when either prescan, $F(4, 1597.69) = 2.47, p = .04$, or postscan, $F(4, 1597.24) = 2.61, p = .03$, delta scores for both fatigue and drowsiness were included as covariates in the model.

Error Rates

All *F* values are presented in Table 3, and estimated mean error rates are presented in Figures 2 and 3. As expected, we obtained a simple effect of trial type on error rates, $F(2, 191.75) = 62.4$, $p < .0001$, such that relative to ongoing trials, more errors were made on distractor (estimated marginal effect = +1.8%; $z = 3.23$, $p = .001$) and switch (+10.8%; $z = 10.35$, $p < .0001$) trials on placebo. We found no effects of Drug or Genotype, nor any significant interactions among Drug, Genotype, and Trial Type (all Fs ≤ 2.3, ps ≥ 0.1; Figure 2, bottom).

Next, we investigated the effects of drug and genotype on a particular category of errors: those in which

Table 3. ANOVA Table for Mixed Model of Error Rates

Effect	*df*	*F*	*p*
Taq1A	1, 70.70	2.64	.11
COMT	1, 70.71	1.77	.19
Drug	2, 198.65	0.13	.88
Type	2, 191.75	62.40	<.0001
Block	1, 73.02	0.06	.81
Session	1, 152.49	3.83	.05
Version	1, 76.41	4.24	.04
Taq1A × Drug	2, 198.71	2.28	.11
COMT × Drug	2, 198.74	0.65	.52
Taq1A × Type	2, 191.79	0.82	.44
COMT × Type	2, 191.82	1.27	.28
Drug × Type	4, 1678.03	0.71	.59
Taq1A × Block	1, 73.05	0.59	.45
COMT × Block	1, 73.04	2.46	.12
Drug × Block	2, 1700.56	0.16	.85
Type × Block	2, 1678.60	10.95	<.0001
Taq1A × Drug × Type	4, 1678.03	0.89	.47
COMT × Drug × Type	4, 1678.05	0.65	.63
Taq1A × Drug × Block	2, 1700.75	0.86	.43
COMT × Drug × Block	2, 1700.89	2.96	.05
Taq1A × Type × Block	2, 1678.63	0.06	.94
COMT × Type × Block	2, 1678.54	0.59	.56
Drug × Type × Block	4, 1677.91	0.62	.65
Taq1A × Drug × Type × Block	4, 1677.91	0.43	.79
COMT × Drug × Type × Block	4, 1677.95	0.58	.68

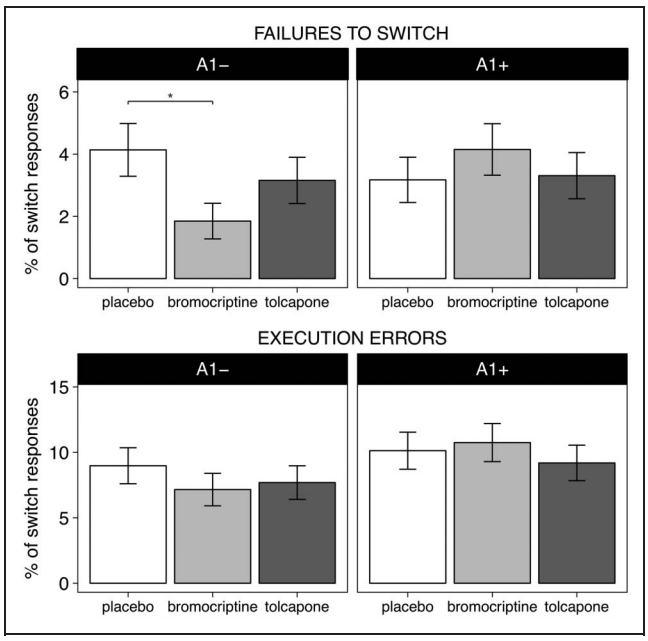

Figure 3. Estimated switch trial errors (percentage of total switch trial responses) by error type, Taq1A genotype, and drug (placebo, bromocriptine, tolcapone). Errors of commission were classified according to whether participants switched to the correct response set (middle fingers) but pressed the wrong button ("execution errors") or failed to switch to the correct response set ("failures to switch"). Error bars represent back-transformed standard errors estimated from the corresponding mixed models with the "emmeans" package in R. *$p < .01$.

participants responded to a switch cue as if they were performing the ongoing task or "failures to switch." Such errors, comprising 0–100% of all switch trial errors (range: 0–14 instances per session), are hypothesized to result from relatively reduced striatal activation of D2 receptors and therefore to be susceptible to remediation by D2 agonists. Analysis of this specific error rate revealed no effects of Drug, $F(2, 153) = 0.90$, COMT Genotype, $F(1, 76) = 0.15$, or Taq1A Genotype, $F(1, 76) = 0.46$, all ps $> .1$, but a significant interaction of Drug and Taq1A Genotype, $F(2, 153) = 4.64$, $p = .01$. Relative to placebo, bromocriptine reduced failures to switch in A1− homozygotes (estimated marginal effect = −2.3%; $z = -3.02$, $p = .005$), but not in A1+ carriers (+1%; $z = 1.18$, $p > .1$; Figure 3). There was no effect of tolcapone on switch failures in either Taq1A group (A1−: −1%, $z = -1.16$, $p > .1$; A1+: +0.1%, $z = 0.17$, $p > .1$) nor an interaction of Drug × COMT Genotype on failure to switch, $F(2, 153) = 0.1$, $p = .9$. By contrast, when considering switch "execution errors," the proportion of switch trials on which participants correctly switched response set but still made an incorrect button response, there were effects of session number, $F(1, 153) = 18.94$, $p < .0001$, and ongoing task version, $F(1, 76) = 13.17$, $p = .0005$, but no effect of Drug, Genotype, or Drug × Genotype interaction (all Fs < 1.65, ps $> .1$).

In summary, our RT results suggest that tolcapone selectively influenced cognitive stability and only in individuals with putatively high baseline PFC DA levels. By contrast, our analysis of error rates demonstrated that bromocriptine reduces a particular class of switch trial errors in Taq1A A1− homozygotes, but not in A1+ carriers. Tolcapone did not alter error rates, either across the sample or in interaction with either genotype. This pattern suggests that bromocriptine may interact with baseline striatal DA system function (or more globally with D2 receptor signaling) to facilitate cognitive flexibility.

Spontaneous Switch Rate

Across sessions, the average (untransformed) switch proportion among accurate ambiguous trials was 24.9% (range: 0–100%), considerably lower than the 54.8% originally reported by Armbruster et al. (2012). However, in the prior study, only a single block of data was collected. Considering just the first block of the first session in the current study, irrespective of drug condition, we obtain an average accurate switch proportion (41.5%) much closer to their estimate, indicating that the ambiguous condition produced similar sample-level results as it has in the past. This finding also highlights the fact that, in the current context, decisions regarding which task to perform vary with exposure to ambiguous trials. Indeed, aggregated across blocks, our analysis of accurate trials

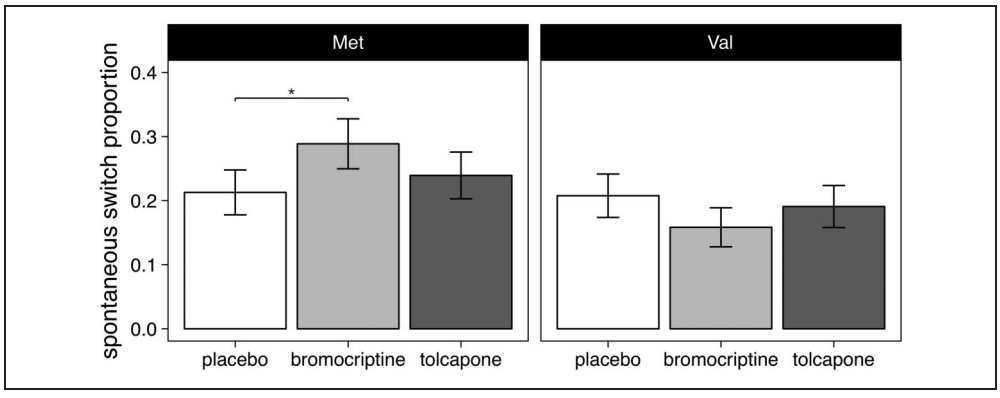

Figure 4. Estimated spontaneous switch proportions for accurate, ambiguous trials by COMT genotype and drug (placebo, bromocriptine, tolcapone). Higher values indicate that a greater proportion of ambiguous trials were treated as switch trials, as indicated by the use of middle fingers for responding. Means and error bars reflect back-transformed estimates from the corresponding mixed model with the *emmeans* package in R. *$p < .05$.

yielded a main effect of Session, $F(1, 152.19) = 15.49$, $p = .001$, on transformed switch rates, such that, on average, switch proportion decreased with each subsequent session.

Despite this systematic variation in switch rates across sessions, we obtained a significant Drug × COMT Genotype interaction, $F(2, 152.13) = 5.62$, $p = .004$ (Figure 4) that was driven by an increase in switch proportion on bromocriptine (relative to placebo) for Met (estimated marginal effect = +7.6%; $z = 2.66$, $p = .016$) but not Val (−4.9%; $z = -2$, $p = .09$) homozygotes. No other factors were predictors of spontaneous switch rate (all Fs < 2, ps > .1). Including both accurate and inaccurate ambiguous trials in the calculation of switch proportion did not change the overall pattern of significant results. Our control analysis (see Table 4) indicated that luminance differences linearly influenced trial-wise decisions to either switch tasks or repeat the ongoing task, $\chi^2(1) = 36.97$, $p < .0001$; however, we found no evidence for interactions of Luminance × Drug, $\chi^2(2) = 4.13$, $p = .13$; Luminance × COMT Genotype, $\chi^2(1) = 0.01$, $p = .91$; Luminance × Taq1A Genotype, $\chi^2(1) = 1.28$, $p = .26$; Luminance × Drug × COMT Genotype, $\chi^2(2) = .05$, $p = .97$; or Luminance × Drug × Taq1A Genotype, $\chi^2(2) = 1.39$, $p = .5$. Importantly, the interactive effect of Drug and COMT Genotype remained significant with luminance included in the model, $\chi^2(2) = 13.18$, $p = .001$.

In summary, our exploration of spontaneous switching behavior revealed that bromocriptine induced a bias toward greater spontaneous switching in COMT Met, but not Val, homozygotes that were unrelated to altered visual perception but did not interact with Taq1A genotype to predict drug-related changes in spontaneous switching, contrasting with the previous finding of bromocriptine-modulated change in cued task switching (see Error Rates section).

Table 4. ANOVA Table for Generalized Mixed Model of Spontaneous Switching

Effect	*df*	χ^2	*p*
Taq1A	1	1.84	.17
COMT	1	0.00	.98
Drug	2	0.27	.87
Luminance	1	36.97	<.0001
Session	1	12.70	.0004
Version	1	1.13	.29
Taq1A × Drug	2	1.07	.58
COMT × Drug	2	13.18	.001
Taq1A × Luminance	1	1.28	.26
COMT × Luminance	1	0.01	.91
Drug × Luminance	2	4.13	.13
Taq1A × Drug × Luminance	2	1.39	.50
COMT × Drug × Luminance	2	0.05	.97

Additional Explanatory Variables

Trait-like measures of working memory span and impulsivity have been found to moderate the effects of dopaminergic manipulations (e.g., Cools et al., 2007). Thus, we examined the extent to which genotypic differences in our drug effects could be explained by variability in these more proximal phenotypes. Neither baseline working memory (listening span score), $t(77) = 0.46$, $p = .64$ (Val: mean = 3.0, $SD = 0.8$; Met: mean = 2.9, $SD = 0.9$), nor trait impulsivity (Barrett Impulsivity Scale score), $t(78) = 1.04$, $p = .30$ (Val: mean = 56.2, $SD = 8.1$; Met: mean = 58.3, $SD = 9.4$), varied by COMT genotype. Furthermore, COMT genotype was the sole predictor of tolcapone-related change in (log-transformed) distractor RT cost ($b = 0.022$, $t = 2.11$, $p = .038$) when all three measures were entered as predictors in a linear regression model. Similar results were obtained for the effect of COMT genotype on bromocriptine-related change in (arcsin-transformed) spontaneous switch rate ($b = 0.07$, $t = 3.06$, $p = .003$).

Listening span score did not differ between Taq1A genotypes, $t(77) = 0.08$, $p = .9$ (A1−: mean = 3, $SD = 0.9$; A1+: mean = 3, $SD = 0.9$). However, impulsivity score was marginally associated with Taq1A genotype, $t(78) = 1.84$, $p = .07$. Consistent with previous work (Eisenberg et al., 2007), A1+ carriers were more impulsive (mean = 59.0, $SD = 8.25$) than were A1− homozygotes (mean = 55.4, $SD = 9.04$). As the sole factor in a regression model, impulsivity score predicted bromocriptine-related change in (arcsin-transformed) switch failure proportion ($b = 0.03$, $t = 2.04$, $p = .045$). However, adding Taq1A genotype to the model fully reduced this contribution to insignificance (impulsivity: $t = 1.51$, $p = .14$; Taq1A: $t = 2.82$, $p = .006$), suggesting that Taq1A genotype likely gives rise to concurrent variation in impulsivity score and behavioral drug effect.

Interactions among Facets of Cognitive Control

Across the sample, correlations among drug effects did not provide evidence for antagonistic effects of dopaminergic drugs on cognitive stability and cognitive flexibility. Changes (from placebo) in distractor RT cost and switch RT cost were uncorrelated for both drugs (bromocriptine: $\rho = -0.1$, $p = .4$; tolcapone: $\rho = 0.1$, $p = .3$). On the other hand, Δ distractor accuracy cost and Δ switch accuracy cost were positively correlated for both bromocriptine ($\rho = 0.25$, $p = .03$) and tolcapone ($\rho = 0.42$, $p = .0001$). This result indicates that indices of task accuracy may generally track together. However, to investigate whether there is additional structure in the drug effects suggestive of a subtler anticorrelation pattern among task components, we conducted PCA on the set of drug-

related change scores separately for bromocriptine and tolcapone. PCA of bromocriptine-related effects yielded two factors with eigenvalues greater than 1 (Table 5, top). The first component accounted for 34% of the variance and was characterized by unidirectional loadings of distractor and switch accuracy change, consistent with the obtained positive correlation between these two metrics. The second component accounted for 27% of the variance and was characterized by loadings of Δ distractor and switch RT cost in opposing directions. PCA of tolcapone-related effects yielded a single component with an eigenvalue greater than 1 that accounted for 41% of the variance. Nonetheless, we retained the second component (eigenvalue = 0.93; 27% of variance) to facilitate comparison with bromocriptine-related changes (Table 5, middle). Both distractor-related metrics and Δ switch accuracy cost loaded unidirectionally onto the first component, whereas Δ switch RT cost loaded highly on the second component with some contribution from Δ switch accuracy cost. Procrustes rotation of the tolcapone components to match the bromocriptine components revealed greater similarity of the second components: For tolcapone, strong loading of Δ switch RT cost was met by opposing, albeit considerably weaker, loading of distractor RT and accuracy costs (Table 5, bottom). Tucker's congruence coefficient was 0.94 and 0.88 for Components 1 and 2, respectively. These values indicate more evidence for concordance between drugs on the first component, although both fall within the [0.85–0.94] range indicative of "fair similarity" (Lorenzo-Seva & ten Berge, 2006). The lower congruence coefficient for the second component, combined with the relatively low eigenvalue for the tolcapone data, suggests that there is more evidence for opposing drug-elicited effects on cognitive stability and flexibility with bromocriptine than with tolcapone. Of note, scores on the second component did not vary by COMT or Taq1A genotype for either bromocriptine or tolcapone (all $|t|$s < 1.3, ps $> .1$).

Table 5. Component (C) Loadings from Principal Component Analysis of Bromocriptine (Top) and Tolcapone (Middle, Bottom) Drug Effects

Bromocriptine	*C1*	*C2*
Δ distractor acc cost	0.78	
Δ distractor RT cost		0.74
Δ switch acc cost	0.77	
Δ switch RT cost		−0.73

Tolcapone	*C1*	*C2*
Δ distractor acc cost	0.88	
Δ distractor RT cost	0.74	
Δ switch acc cost	0.57	0.39
Δ switch RT cost		0.96

Tolcapone (Rotated)	*C1′*	*C2′*
Δ distractor acc cost	0.79	0.38
Δ distractor RT cost	0.65	0.35
Δ switch acc cost	0.69	
Δ switch RT cost	0.50	−0.82

For each analysis, four input variables included drug-related change scores (i.e., drug − placebo) for distractor and switch costs (i.e., distractor/switch performance − ongoing task performance). Bottom panel depicts tolcapone component loadings after Procrustes rotation was used to best match bromocriptine components. Loadings are thresholded at |0.3|.

DISCUSSION

Few studies to date have directly compared the effects of mechanistically divergent dopaminergic drugs on distinct facets of cognitive control within the same healthy human sample. Here, we assessed the relative influences of tolcapone, an inhibitor of the catecholamine-catabolizing enzyme COMT, and bromocriptine, a monoamine agonist with strong affinity for the DA D2 receptor, on cognitive stability (i.e., the ability to maintain task and response rule information in the presence of salient and directly competing distractors), cognitive flexibility (i.e., the ability to quickly respond to changing environmental cues by reallocating attention and remapping response contingencies), and their relative anticorrelation. Exploiting putative baseline dependence of DA effects on human cognitive performance, we attempted to better characterize drug effects by examining their interaction with known genetic polymorphisms affecting PFC and striatal DA system function. We observed a dissociation in the influence of the two drugs on domains of cognitive control, such that tolcapone impacted distractor resistance whereas bromocriptine promoted both spontaneous and cued task switching. In both cases, drug effects were found only in genotypically defined subgroups, consistent with the previously documented baseline dependence of DA treatment responses (Cools & D'Esposito, 2011). Together, our results support the view that the cognitive effects of DA drugs vary not only as a function of the DA system component upon which they act, but also on subtle differences in task demands and context.

Tolcapone Perturbs Distractor Resistance in High-DA Participants

Based on current models of the role of DA in stabilizing PFC representations, we hypothesized that tolcapone would differentially impact distractor resistance in COMT Met and Val homozygotes, enhancing performance on distractor trials in putatively low-DA Val homozygotes and

worsening it in high-DA Met homozygotes. Although tolcapone did not demonstrably improve cognitive stability in Val homozygotes in the current study, we found that tolcapone induced response slowing on distractor (but not switch) trials in Met homozygotes. This latter finding is consistent with reports of performance impairment following tolcapone administration (or "overdosing") in Met homozygotes across a range of paradigms that require cognitive stability, including the *n*-back task (Farrell et al., 2012; Giakoumaki, Roussos, & Bitsios, 2008) and the intradimensional set-shifting task (Apud et al., 2007), which assesses the extent to which individuals can form and stably maintain attentional sets, and on tests of prepulse inhibition, a metric thought to reflect the filtering out of irrelevant incoming sensory information at early stages of processing (Giakoumaki et al., 2008). Similarly, in mice expressing humanized Val or Met alleles, tolcapone induces improvement in Val/Val mice but performance decrements in Met/Met mice on a test of delayed spatial working memory (Risbrough, Ji, Hauger, & Zhou, 2014).

By inhibiting the enzyme COMT, tolcapone increases the accumulation of extracellular DA but does not selectively target D1 or D2 receptors. Given the relative paucity of DA transporters in the PFC, it is suspected that accumulating cortical DA tends to diffuse from the synaptic cleft to influence extrasynaptic D1 receptor binding (Slifstein et al., 2008; Bilder et al., 2004). Thus, a supraoptimal level of D1 receptor stimulation may be a primary contributor to poorer performance in the high baseline DA group. The mechanisms underlying the deleterious effects of D1 overdose on cognitive performance are still being investigated; however, it has been argued that, although PFC D1 receptor stimulation within the optimal range stabilizes and tunes sensory or rule representations in part by enhancing lateral inhibition and opening hyperpolarization-activated cyclic nucleotide-gated channels, at higher levels of stimulation these inhibitory processes may suppress neuronal firing more globally, including responses to currently relevant rules or preferred stimulus features (Arnsten et al., 2015; Vijayraghavan et al., 2007). By extension, D1 overdose in Met participants may interfere with distractor trial performance by diminishing the ability to shield the ongoing task rule from interference by salient distractors (i.e., reducing rule selective firing) or by impairing the ability to efficiently respond to incoming stimulus information (i.e., by reducing overall firing).

This account is in contrast to the logic of the dual-state theory (Durstewitz & Seamans, 2008), which might hold that, by broadly increasing DA availability, the active cortical network in Met homozygotes was shifted from a D1-dominant to a D2-dominant state, characterized by reduced shielding of representations from distraction, and more frequent switches between representations. Although enhancement of D2 signaling (i.e., following administration of bromocriptine) did increase spontaneous switching in these participants (see below), a comparable effect was not obtained with tolcapone. Cued task-switching cost, a presumptively D2-mediated facet of behavior, was likewise unaffected by tolcapone in these individuals, and tolcapone did not interact with Taq1A genotype (a putative marker of D2 receptor density) to influence behavior. Together, this pattern of results suggests that poorer distractor resistance in Met homozygotes was unlikely to have been driven simply by a transition to a D2-dominant state.

In a departure from our prediction that DA augmentation would improve cognitive stability in lower DA participants, COMT Val homozygotes did not show behavioral enhancement by tolcapone treatment. If Val carriers do, in truth, benefit cognitively from tolcapone, as has been found in certain studies of humans and rodents (Risbrough et al., 2014; Farrell et al., 2012; Apud et al., 2007), it is possible that elements of task design (such as relative difficulty) play an outsized role in determining the presence or absence of treatment effect. For example, using a version of an *n*-back task, Farrell et al. (2012) observed tolcapone-induced perturbations in Met participants' performance at low levels of difficulty (i.e., 0-back and 1-back) but improvements in Val participants' performance only at higher levels of cognitive demand (i.e., 2-back and 3-back). Thus, the distractor trials in our task may have been sufficient to drive poorer drug-related performance in Met homozygotes but insufficiently demanding to reveal benefits for Val homozygotes. Indeed, it is possible that the optimal level of cortical DA (or optimal D1/D2 ratio) required for performing our distractor task may be lower than for other paradigms. As such, Val homozygotes may already approach the apex of a putative inverted-U-shaped curve linking DA levels and performance at baseline; augmentation of DA with tolcapone might shift these participants to the opposite side of such an apex while leaving the D1/D2 ratio itself (and consequently the behavior) virtually unchanged. Alternatively, distraction at the level of task rule (rather than at the level of an individual item) may not follow the anticipated inverted-U-shaped pattern with respect to DA, either within the range of DA levels tested, for the current paradigm, or at all. Indeed, recent work (Floresco, 2013) highlights the multitude of functions relating PFC DA neuromodulation to cognition.

Bromocriptine Enhances Spontaneous Switching in High-DA Participants

In contrast to the deleterious effect of tolcapone on distractor resistance, bromocriptine did not significantly perturb task maintenance nor did it improve cued task switching differentially in COMT Met and Val homozygotes. This result bolsters the interpretation that the tolcapone-induced worsening of distractor resistance in Met homozygotes, reviewed above, was mediated primarily by D1, rather than D2, receptor actions. Furthermore,

it accords with rat and nonhuman primate work demonstrating no net effect of PFC D2 agonism on working memory (Romanides, Duffy, & Kalivas, 1999; Sawaguchi & Goldman-Rakic, 1994; but see Druzin, Kurzina, Malinina, & Kozlov, 2000) or set switching (Floresco, Magyar, Ghods-Sharifi, Vexelman, & Tse, 2006) and human PET results indicating no relationship between PFC D2 receptor binding potential and scores on a neuropsychological battery probing immediate and delayed stimulus recall as well as perseveration on the Wisconsin Card Sorting Task (Takahashi et al., 2008).

Interestingly, bromocriptine induced a higher frequency of spontaneous task switches when explicit task cues were ambiguous, but only in Met homozygotes. This effect is not likely attributable to drug-related changes in Met participants' use of residual luminance difference to guide decision-making. Although the difference in luminance between the two stimuli presented on ambiguous trials was strongly predictive of the choice to maintain the ongoing task or switch tasks on a given trial, it did not interact with COMT genotype, drug, or the interaction of genotype and drug to explain variability in spontaneous switching. We propose several factors that may bear on the extent to which D2 stimulation facilitates cognitive flexibility as a function of COMT genotype. First, the influence of dopaminergic activity, particularly in the PFC, may be enhanced during the performance of more novel actions relative to highly familiar tasks (Puig & Miller, 2014). Although switch and ambiguous trials occurred with equal frequency across the task, ambiguous trials were not included in participants' training nor did they convey clear information about the type of response that should occur, rendering mastery unlikely. Second, it is possible that higher levels of uncertainty during ambiguous trials elicit changes in bottom–up signaling, such as increases in mesocortical DA release (de Lafuente & Romo, 2011), which in turn may be sufficient to drive cognitive flexibility for the high-DA Met group even in the absence of equivalent changes during unambiguous trials. Finally, the difference in drug effects may be due to variation in the levels of hierarchical cognitive control engaged across trial types. That is, because ambiguous trials lack a discrete mapping between presented stimuli and task rule, responses may rely on the biasing influence of top–down control signals from regions encoding higher order policies or levels of task abstraction (Badre & D'Esposito, 2009). Given the proposal that the distribution of DA receptor density varies across PFC regions involved in supporting hierarchical levels of cognitive control (Vogelsang & D'Esposito, 2018), future work should examine systematically how the impact of DA drugs, such as bromocriptine, varies as distinct levels of hierarchical control are invoked.

It is important to note the possibility that the bromocriptine-related change in spontaneous switching rate was due to D2 actions in the striatum as well as in the PFC. Indeed, COMT genotype may indirectly affect levels of DA synthesis in populations of dopaminergic neurons projecting to the striatum; the Val allele has been associated with increased expression of midbrain tyrosine hydroxylase, the rate-limiting enzyme for DA synthesis, an effect hypothesized to result from DA actions within the PFC (Akil et al., 2003). Thus, if striatal DA synthesis (and perhaps, release) is lower in Met homozygotes, administration of an agonist targeting striatal DA receptors could improve cognitive flexibility (see discussion below), though it remains to be determined why this pattern would only be observed for ambiguous trials.

Bromocriptine Enhances Cued Switching in Low-DA Participants

We hypothesized that bromocriptine would modulate cognitive flexibility through actions of the DA D2 receptor. We found that bromocriptine reduced the proportion of cued switch trials during which Taq1A A1− homozygotes continued to perform the ongoing task (i.e. "failures to switch") but did not significantly affect the overall accuracy of switch trial responses nor any measure of distractor trial performance. This dissociation supports the idea that D2 signaling is more involved in the gating of newly relevant task sets into working memory or in the updating of attentional targets than in the accumulation of evidence in favor of a particular response or the deployment of higher order control more broadly. Indeed, PET studies of healthy adults have implicated striatal D2 family receptor binding in giving rise to successful task and rule switching. For example, Monchi, Ko, and Strafella (2006) reported that striatal D2 binding potential was reduced when participants performed a card classification task in which the relevant attribute switched every trial compared with when they performed the same task without trial-wise switches, suggesting that, when cognitive flexibility demands increase, so too do striatal DA release and D2 binding. Complementing this result, Samanez-Larkin et al. (2013) observed that increases in striatal DA release (and D2 family binding) following amphetamine administration correlated with drug-related improvements in cued task switching. Importantly, our drug effect was mediated by Taq1A genotype: Only A1− homozygotes, associated with lower striatal DA in the healthy human striatum (Laakso et al., 2005), showed bromocriptine-related improvements in cognitive flexibility. Such baseline dependency accords well with other work probing the influence of striatal DA on cognitive flexibility (van Holstein et al., 2011; Cools et al., 2007). In these studies, the effect of D2 agonists on cognitive flexibility has typically favored individuals posited to have lower relative striatal DA neurotransmission, leading to the hypothesis that, as with D1 receptor stimulation in the PFC, the relation between striatal DA and performance follows an inverted-U-shaped function.

In addition to reduced DA synthesis, the Taq1A A1− genotype has been repeatedly associated with greater striatal D2 receptor density in healthy adults (Gluskin & Mickey, 2016; Savitz et al., 2013). Enhanced D2 receptor density—a phenotype associated with impaired rule reversal in transgenic mice (Kellendonk et al., 2006)—may, in fact, trigger the downregulation of DA synthesis observed in A1− carriers (Laakso et al., 2005). Speculatively, by increasing striatal D2 autoreceptor density, the Taq1A A1− genotype may attenuate phasic DA release (Laakso et al., 2005) and consequently reduce direct pathway excitation in response to salient environmental stimuli (or explicit switch cues). Administering a D2 agonist could rectify the bias toward direct pathway-mediated cognitive flexibility in the context of salient task cues by acting on inhibitory postsynaptic D2 receptors within the indirect pathway. This hypothesis is partially supported by recent evidence that stimulation of D2 family receptors in the marmoset striatum exerts a triphasic dose-dependent effect on cognitive flexibility that may depend on relative levels of autoreceptor stimulation (Horst, Jupp, Roberts, & Robbins, 2019). Specifically, following infusion of quinpirole (a D2 agonist) across a wide range of doses, nonhuman primates exhibited a general trend of impaired reversal learning at relatively low and high doses and a boost in performance at medium doses. At low doses, it was posited that behavioral decline is related to preferential occupancy of inhibitory, presynaptic D2 autoreceptors leading to reduced striatal DA release, whereas at mid-range doses, flexibility is facilitated by an optimal balance of pre- and postsynaptic D2 receptors. The absolute doses at which performance changed varied considerably across monkeys and were related to hemispheric differences in D2 receptor binding. Thus, it is plausible that the nonlinear relationship between striatal DA and cognitive performance in humans is also mediated by relative pre-/postsynaptic D2 binding, and as such, genetic variability in D2 receptor density would be expected to significantly affect the outcome of a single dose of agonist across participants. Future work exploiting genetic variation in the expression of D2 autoreceptors (Zhang et al., 2007) may lead to a better understanding of the neural mechanisms underlying the baseline-dependent effect of D2 agonists on cognitive flexibility, as it has with working memory (Gelao et al., 2014; Zhang et al., 2007) and outcome-based learning (Frank & Hutchison, 2009).

Opposing Drug Effects on Cognitive Flexibility and Stability

Finally, we examined the extent to which DA drug administration produces opposing effects on cognitive stability and flexibility. This idea follows from the recognition that D1 and D2 receptors exert opposing effects on downstream signaling pathways in the PFC and striatum and from work in humans demonstrating antagonistic effects of drug on behavioral domains (e.g., impaired performance on task switching but improved performance on distractor resistance; Mehta, Manes, Magnolfi, Sahakian, & Robbins, 2004). In seeming contradiction to this proposal, the most prominent relationship between the drug-driven changes in these facets of cognitive control was one of positive correlation. However, PCA revealed a secondary structure characterized by antagonism between drug effects on switch and distractor costs (specific, here, to RT costs) that was not evident from simple correlation analysis. Thus, it is important to note that more global change in performance of complex tasks from session to session may mask subtler drug effects. Bromocriptine, in particular, emerged as an elicitor of opposing influences on cognitive flexibility and stability, despite its apparent lack of significant effect on either domain across the entire sample and its simple effects being limited to a single domain (i.e., flexibility) when considering genotypic subgroups. Whether this pattern is evoked to the same extent by tolcapone is less clear; for these data, the eigenvalue associated with the relevant component was < 1, loadings on this component were highly imbalanced across domains, and direct comparison with bromocriptine's "antagonism" component yielded low (though present) evidence for similarity. Given that our measure of component similarity was computed across only four values, subsequent work with a larger set of variables is needed to determine with confidence whether these drugs vary in their ability to elicit opposing effects on cognitive stability and flexibility. Nonetheless, these preliminary results suggest that dopaminergic drugs shift the balance between flexibility and stability and that this may be particularly true for drugs impacting function in both striatum and cortex or targeting D2 receptor signaling. Importantly, the direction and magnitude of these shifts vary across individuals. This raises the possibility that, as with the putatively "primary" effect of a drug on performance metrics (e.g., tolcapone's influence on distractor RT cost or bromocriptine's effect on switch errors), baseline differences in neurobiological structure, connectivity, and function may moderate a particular drug's influence. The nature of these particular differences, as well as their relationship to phenotypes contributing to primary effects of drug in humans, comprise a promising area for future research.

Note on Reliability

Our study included well-balanced genotype groups, direct comparison of effects between two drugs putatively acting on components of the DA system associated with these genotypes, strong a priori hypotheses, and a task optimized to dissociate components of hypothesized drug effects. We note that, although the genotype-mediated results present in the data were in the anticipated direction based on inverted-U-shaped and dual-state models, the absence of other effects predicted by these same models and reported in other studies (e.g., lack of tolcapone-related benefit in Val homozygotes) may be

due to low power or sources of variability that remain unaccounted for. Future work aimed at developing more direct estimates of baseline D1 and D2 density across the human brain (i.e., optimized PET measures) will likely enhance our ability to evaluate and characterize baseline-dependent effects of DA manipulations. Although the reliability of the observed effects will only be determined by replication, we believe that the results of this study demonstrate an important dissociation in the effects of bromocriptine and tolcapone on distinct cognitive control processes.

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REFERENCES

Aarts, E., Nusselein, A. A., Smittenaar, P., Helmich, R. C., Bloem, B. R., & Cools, R. (2014). Greater striatal responses to medication in Parkinson's disease are associated with better task-switching but worse reward performance. *Neuropsychologia*, *62*, 390–397.

Akil, M., Kolachana, B. S., Rothmond, D. A., Hyde, T. M., Weinberger, D. R., & Kleinman, J. E. (2003). Catechol-*O*-methyltransferase genotype and dopamine regulation in the human brain. *Journal of Neuroscience*, *23*, 2008–2013.

Apud, J. A., Mattay, V., Chen, J., Kolachana, B. S., Callicott, J. H., Rasetti, R., et al. (2007). Tolcapone improves cognition and cortical information processing in normal human subjects. *Neuropsychopharmacology*, *32*, 1011–1020.

Armbruster, D. J., Ueltzhöffer, K., Basten, U., & Fiebach, C. J. (2012). Prefrontal cortical mechanisms underlying individual differences in cognitive flexibility and stability. *Journal of Cognitive Neuroscience*, *24*, 2385–2399.

Armbruster-Genç, D. J., Ueltzhöffer, K., & Fiebach, C. J. (2016). Brain signal variability differentially affects cognitive flexibility and cognitive stability. *Journal of Neuroscience*, *36*, 3978–3987.

Arnsten, A. F., Wang, M., & Paspalas, C. D. (2015). Dopamine's actions in primate prefrontal cortex: Challenges for treating cognitive disorders. *Pharmacological Reviews*, *67*, 681–696.

Badre, D., & D'Esposito, M. (2009). Is the rostro-caudal axis of the frontal lobe hierarchical? *Nature Reviews Neuroscience*, *10*, 659–669.

Barkus, C., Korn, C., Stumpenhorst, K., Laatikainen, L. M., Ballard, D., Lee, S., et al. (2016). Genotype-dependent effects of COMT inhibition on cognitive function in a highly specific, novel mouse model of altered COMT activity. *Neuropsychopharmacology*, *41*, 3060–3069.

Barr, D. J., Levy, R., Scheepers, C., & Tily, H. J. (2013). Random effects structure for confirmatory hypothesis testing: Keep it maximal. *Journal of Memory and Language*, *68*, 255–278.

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting linear mixed-effects models using lme4. *Journal of Statistical Software*, *67*, 1–48.

Berry, A. S., Shah, V. D., & Jagust, W. J. (2018). The influence of dopamine on cognitive flexibility is mediated by functional connectivity in young but not older adults. *Journal of Cognitive Neuroscience*, *30*, 1330–1344.

Berryhill, M. E., Wiener, M., Stephens, J. A., Lohoff, F. W., & Coslett, H. B. (2013). COMT and ANKK1-Taq-Ia genetic polymorphisms influence visual working memory. *PLoS One*, *8*, e55862.

Bestmann, S., Ruge, D., Rothwell, J., & Galea, J. M. (2015). The role of dopamine in motor flexibility. *Journal of Cognitive Neuroscience*, *27*, 365–376.

Bilder, R. M., Volavka, J., Lachman, H. M., & Grace, A. A. (2004). The catechol-*O*-methyltransferase polymorphism: Relations to the tonic–phasic dopamine hypothesis and neuropsychiatric phenotypes. *Neuropsychopharmacology*, *29*, 1943–1961.

Bloemendaal, M., van Schouwenburg, M. R., Miyakawa, A., Aarts, E., D'Esposito, M., & Cools, R. (2015). Dopaminergic modulation of distracter-resistance and prefrontal delay period signal. *Psychopharmacology*, *232*, 1061–1070.

Brandies, R., & Yehuda, S. (2008). The possible role of retinal dopaminergic system in visual performance. *Neuroscience & Biobehavioral Reviews*, *32*, 611–656.

Brozoski, T. J., Brown, R. M., Rosvold, H. E., & Goldman, P. S. (1979). Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. *Science*, *205*, 929–932.

Cameron, I. G. M., Wallace, D. L., Al-Zughoul, A., Kayser, A. S., & D'Esposito, M. (2018). Effects of tolcapone and bromocriptine on cognitive stability and flexibility. *Psychopharmacology*, *235*, 1295–1305.

Camps, M., Cortés, R., Gueye, B., Probst, A., & Palacios, J. M. (1989). Dopamine receptors in human brain: Autoradiographic distribution of D2 sites. *Neuroscience*, *28*, 275–290.

Colzato, L. S., Waszak, F., Nieuwenhuis, S., Posthuma, D., & Hommel, B. (2010). The flexible mind is associated with the catechol-*O*-methyltransferase (COMT) Val158Met polymorphism: Evidence for a role of dopamine in the control of task-switching. *Neuropsychologia*, *48*, 2764–2768.

Cools, A. R. (1980). Role of the neostriatal dopaminergic activity in sequencing and selecting behavioural strategies: Facilitation of processes involved in selecting the best strategy in a stressful situation. *Behavioural Brain Research*, *1*, 361–378.

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2001). Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cerebral Cortex*, *11*, 1136–1143.

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2003). L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. *Neuropsychologia*, *41*, 1431–1441.

Cools, R., & D'Esposito, M. (2011). Inverted-U-shaped dopamine actions on human working memory and cognitive control. *Biological Psychiatry*, *69*, e113–e125.

Cools, R., Sheridan, M., Jacobs, E., & D'Esposito, M. (2007). Impulsive personality predicts dopamine-dependent changes in frontostriatal activity during component processes of working memory. *Journal of Neuroscience*, *27*, 5506–5514.

Costa, A., Peppe, A., Mazzù, I., Longarzo, M., Caltagirone, C., & Carlesimo, G. A. (2014). Dopamine treatment and cognitive functioning in individuals with Parkinson's disease: The "cognitive flexibility" hypothesis seems to work. *Behavioural Neurology*, *2014*, 260896.

Crofts, H. S., Dalley, J. W., Collins, P., Denderen, J. C. M. V., Everitt, B. J., Robbins, T. W., et al. (2001). Differential effects of 6-OHDA lesions of the frontal cortex and caudate nucleus on the ability to acquire an attentional set. *Cerebral Cortex*, *11*, 1015–1026.

de Lafuente, V., & Romo, R. (2011). Dopamine neurons code subjective sensory experience and uncertainty of perceptual decisions. *Proceedings of the National Academy of Sciences, U.S.A.*, *108*, 19767–19771.

Dodds, C. M., Müller, U., Clark, L., van Loon, A., Cools, R., & Robbins, T. W. (2008). Methylphenidate has differential

effects on blood oxygenation level-dependent signal related to cognitive subprocesses of reversal learning. *Journal of Neuroscience*, *28*, 5976–5982.
Druzin, M. Y., Kurzina, N. P., Malinina, E. P., & Kozlov, A. P. (2000). The effects of local application of D2 selective dopaminergic drugs into the medial prefrontal cortex of rats in a delayed spatial choice task. *Behavioural Brain Research*, *109*, 99–111.
Durstewitz, D., & Seamans, J. K. (2008). The dual-state theory of prefrontal cortex dopamine function with relevance to catechol-*O*-methyltransferase genotypes and schizophrenia. *Biological Psychiatry*, *64*, 739–749.
Eisenberg, D. T., MacKillop, J., Modi, M., Beauchemin, J., Dang, D., Lisman, S. A., et al. (2007). Examining impulsivity as an endophenotype using a behavioral approach: A DRD2 TaqI A and DRD4 48-bp VNTR association study. *Behavioral and Brain Functions*, *3*, 2.
Ellwood, I. T., Patel, T., Wadia, V., Lee, A. T., Liptak, A. T., Bender, K. J., et al. (2017). Tonic or phasic stimulation of dopaminergic projections to prefrontal cortex causes mice to maintain or deviate from previously learned behavioral strategies. *Journal of Neuroscience*, *37*, 8315–8329.
Farrell, S. M., Tunbridge, E. M., Braeutigam, S., & Harrison, P. J. (2012). COMT Val158Met genotype determines the direction of cognitive effects produced by catechol-*O*-methyltransferase inhibition. *Biological Psychiatry*, *71*, 538–544.
Floresco, S. B., (2013). Prefrontal dopamine and behavioral flexibility: Shifting from an "inverted-U" toward a family of functions. *Frontiers in Neuroscience*, *7*, 62.
Floresco, S. B., Magyar, O., Ghods-Sharifi, S., Vexelman, C., & Tse, M. T. (2006). Multiple dopamine receptor subtypes in the medial prefrontal cortex of the rat regulate set-shifting. *Neuropsychopharmacology*, *31*, 297–309.
Frank, M. J., & Hutchison, K. (2009). Genetic contributions to avoidance-based decisions: Striatal D2 receptor polymorphisms. *Neuroscience*, *164*, 131–140.
Frank, M. J., & O'Reilly, R. C. (2006). A mechanistic account of striatal dopamine function in human cognition: Psychopharmacological studies with cabergoline and haloperidol. *Behavioral Neuroscience*, *120*, 497–517.
Gelao, B., Fazio, L., Selvaggi, P., Di Giorgio, A., Taurisano, P., Quarto, T., et al. (2014). DRD2 genotype predicts prefrontal activity during working memory after stimulation of D2 receptors with bromocriptine. *Psychopharmacology*, *231*, 2361–2370.
Giakoumaki, S. G., Roussos, P., & Bitsios, P. (2008). Improvement of prepulse inhibition and executive function by the COMT inhibitor tolcapone depends on COMT Val158Met polymorphism. *Neuropsychopharmacology*, *33*, 3058–3068.
Gibbs, S. E., & D'Esposito, M. (2005). Individual capacity differences predict working memory performance and prefrontal activity following dopamine receptor stimulation. *Cognitive, Affective, & Behavioral Neuroscience*, *5*, 212–221.
Gluskin, B. S., & Mickey, B. J. (2016). Genetic variation and dopamine D2 receptor availability: A systematic review and meta-analysis of human in vivo molecular imaging studies. *Translational Psychiatry*, *6*, e747.
Hall, H., Sedvall, G., Magnusson, O., Kopp, J., Halldin, C., & Farde, L. (1994). Distribution of D1- and D2-dopamine receptors, and dopamine and its metabolites in the human brain. *Neuropsychopharmacology*, *11*, 245–256.
Horst, N. K., Jupp, B., Roberts, A. C., & Robbins, T. W. (2019). D2 receptors and cognitive flexibility in marmosets: Tri-phasic dose–response effects of intra-striatal quinpirole on serial reversal performance. *Neuropsychopharmacology*, *44*, 564–571.
Hurd, Y. L., Suzuki, M., & Sedvall, G. C. (2001). D1 and D2 dopamine receptor mRNA expression in whole hemisphere sections of the human brain. *Journal of Chemical Neuroanatomy*, *22*, 127–137.
Jaspers, R., Schwarz, M., Sontag, K. H., & Cools, A. R. (1984). Caudate nucleus and programming behaviour in cats: Role of dopamine in switching motor patterns. *Behavioural Brain Research*, *14*, 17–28.
Jorga, K. M., Fotteler, B., Heizmann, P., & Zürcher, G. (1998). Pharmacokinetics and pharmacodynamics after oral and intravenous administration of tolcapone, a novel adjunct to Parkinson's disease therapy. *European Journal of Clinical Pharmacology*, *54*, 443–447.
Käenmäki, M., Tammimäki, A., Myöhänen, T., Pakarinen, K., Amberg, C., Karayiorgou, M., et al. (2010). Quantitative role of COMT in dopamine clearance in the prefrontal cortex of freely moving mice. *Journal of Neurochemistry*, *114*, 1745–1755.
Kellendonk, C., Simpson, E. H., Polan, H. J., Malleret, G., Vronskaya, S., Winiger, V., et al. (2006). Transient and selective overexpression of dopamine D2 receptors in the striatum causes persistent abnormalities in prefrontal cortex functioning. *Neuron*, *49*, 603–615.
Kimberg, D. Y., D'Esposito, M., & Farah, M. J. (1997). Effects of bromocriptine on human subjects depend on working memory capacity. *NeuroReport*, *8*, 3581–3585.
Klanker, M., Feenstra, M., & Denys, D. (2013). Dopaminergic control of cognitive flexibility in humans and animals. *Frontiers in Neuroscience*, *7*, 201.
Kvernmo, T., Härtter, S., & Burger, E. (2006). A review of the receptor-binding and pharmacokinetic properties of dopamine agonists. *Clinical Therapeutics*, *28*, 1065–1078.
Laakso, A., Pohjalainen, T., Bergman, J., Kajander, J., Haaparanta, M., Solin, O., et al. (2005). The A1 allele of the human D2 dopamine receptor gene is associated with increased activity of striatal L-amino acid decarboxylase in healthy subjects. *Pharmacogenetics and Genomics*, *15*, 387–391.
Laatikainen, L. M., Sharp, T., Harrison, P. J., & Tunbridge, E. M. (2013). Sexually dimorphic effects of catechol-*O*-methyltransferase (COMT) inhibition on dopamine metabolism in multiple brain regions. *PLoS One*, *8*, e61839.
Lachman, H. M., Papolos, D. F., Saito, T., Yu, Y. M., Szumlanski, C. L., & Weinshilboum, R. M. (1996). Human catechol-*O*-methyltransferase pharmacogenetics: Description of a functional polymorphism and its potential application to neuropsychiatric disorders. *Pharmacogenetics*, *6*, 243–250.
Lenth, R. (2018). emmeans: Estimated marginal means, aka least-squares means (R package version 1.3.1). https://CRAN.R-project.org/package=emmeans.
Lorenzo-Seva, U., & ten Berge, J. M. (2006). Tucker's congruence coefficient as a meaningful index of factor similarity. *Methodology*, *2*, 57–64.
Matsumoto, M., Weickert, C. S., Akil, M., Lipska, B. K., Hyde, T. M., Herman, M. M., et al. (2003). Catechol *O*-methyltransferase mRNA expression in human and rat brain: Evidence for a role in cortical neuronal function. *Neuroscience*, *116*, 127–137.
Mehta, M. A., Manes, F. F., Magnolfi, G., Sahakian, B. J., & Robbins, T. W. (2004). Impaired set-shifting and dissociable effects on tests of spatial working memory following the dopamine D 2 receptor antagonist sulpiride in human volunteers. *Psychopharmacology*, *176*, 331–342.
Monchi, O., Ko, J. H., & Strafella, A. P. (2006). Striatal dopamine release during performance of executive functions: A [11C] raclopride PET study. *Neuroimage*, *33*, 907–912.
Müller, U., von Cramon, D. Y., & Pollmann, S. (1998). D1- versus D2-receptor modulation of visuospatial working memory in humans. *Journal of Neuroscience*, *18*, 2720–2728.
Neville, M. J., Johnstone, E. C., & Walton, R. T. (2004). Identification and characterization of ANKK1: A novel kinase

gene closely linked to DRD2 on chromosome band 11q23.1. *Human Mutation*, *23*, 540–545.
Nicola, S. M., Surmeier, D. J., & Malenka, R. C. (2000). Dopaminergic modulation of neuronal excitability in the striatum and nucleus accumbens. *Annual Review of Neuroscience*, *23*, 185–215.
Ott, T., Jacob, S. N., & Nieder, A. (2014). Dopamine receptors differentially enhance rule coding in primate prefrontal cortex neurons. *Neuron*, *84*, 1317–1328.
Ott, T., & Nieder, A. (2019). Dopamine and cognitive control in prefrontal cortex. *Trends in Cognitive Sciences*, *23*, 213–234.
Patton, J. H., Stanford, M. S., & Barratt, E. S. (1995). Factor structure of the Barratt impulsiveness scale. *Journal of Clinical Psychology*, *51*, 768–774.
Price, P., Debono, A., Parkes, J. D., Marsden, C. D., & Rosenthaler, J. (1978). Plasma bromocriptine levels, clinical and growth hormone responses in Parkinsonism. *British Journal of Clinical Pharmacology*, *6*, 303–309.
Puig, M. V., & Miller, E. K. (2014). Neural substrates of dopamine D2 receptor modulated executive functions in the monkey prefrontal cortex. *Cerebral Cortex*, *25*, 2980–2987.
Revelle, W. (2018) psych: Procedures for personality and psychological research (R package version 1.8.12). https://CRAN.R-project.org/package=psych.
Risbrough, V., Ji, B., Hauger, R., & Zhou, X. (2014). Generation and characterization of humanized mice carrying COMT158 Met/Val alleles. *Neuropsychopharmacology*, *39*, 1823–1832.
Roberts, A. C., De Salvia, M. A., Wilkinson, L. S., Collins, P., Muir, J. L., Everitt, B. J., et al. (1994). 6-Hydroxydopamine lesions of the prefrontal cortex in monkeys enhance performance on an analog of the Wisconsin card sort test: Possible interactions with subcortical dopamine. *Journal of Neuroscience*, *14*, 2531–2544.
Romanides, A. J., Duffy, P., & Kalivas, P. W. (1999). Glutamatergic and dopaminergic afferents to the prefrontal cortex regulate spatial working memory in rats. *Neuroscience*, *92*, 97–106.
Salthouse, T. A., & Babcock, R. L. (1991). Decomposing adult age differences in working memory. *Developmental Psychology*, *27*, 763–776.
Samanez-Larkin, G. R., Buckholtz, J. W., Cowan, R. L., Woodward, N. D., Li, R., Ansari, M. S., et al. (2013). A thalamocorticostriatal dopamine network for psychostimulant-enhanced human cognitive flexibility. *Biological Psychiatry*, *74*, 99–105.
Savitz, J., Hodgkinson, C. A., Martin-Soelch, C., Shen, P. H., Szczepanik, J., Nugent, A. C., et al. (2013). DRD2/ANKK1 Taq1A polymorphism (rs1800497) has opposing effects on D2/3 receptor binding in healthy controls and patients with major depressive disorder. *International Journal of Neuropsychopharmacology*, *16*, 2095–2101.
Savitz, J., Solms, M., & Ramesar, R. (2006). The molecular genetics of cognition: Dopamine, COMT and BDNF. *Genes, Brain and Behavior*, *5*, 311–328.
Sawaguchi, T., & Goldman-Rakic, P. S. (1994). The role of D1-dopamine receptor in working memory: Local injections of dopamine antagonists into the prefrontal cortex of rhesus monkeys performing an oculomotor delayed-response task. *Journal of Neurophysiology*, *71*, 515–528.
Schacht, J. P. (2016). COMT val158met moderation of dopaminergic drug effects on cognitive function: A critical review. *Pharmacogenomics Journal*, *16*, 430–438.
Singmann, H., Bolker, B., Westfall J., & Aust, F. (2018). afex: Analysis of factorial experiments (R package version 0.22-1). https://CRAN.R-project.org/package=afex.
Slifstein, M., Kolachana, B., Simpson, E. H., Tabares, P., Cheng, B., Duvall, M., et al. (2008). COMT genotype predicts cortical-limbic D1 receptor availability measured with [11C] NNC112 and PET. *Molecular Psychiatry*, *13*, 821–827.
Stelzel, C., Basten, U., Montag, C., Reuter, M., & Fiebach, C. J. (2010). Frontostriatal involvement in task switching depends on genetic differences in D2 receptor density. *Journal of Neuroscience*, *30*, 14205–14212.
Stelzel, C., Fiebach, C. J., Cools, R., Tafazoli, S., & D'Esposito, M. (2013). Dissociable fronto-striatal effects of dopamine D2 receptor stimulation on cognitive versus motor flexibility. *Cortex*, *49*, 2799–2811.
Syvänen, A. C., Tilgmann, C., Rinne, J., & Ulmanen, I. (1997). Genetic polymorphism of catechol-*O*-methyltransferase (COMT): Correlation of genotype with individual variation of S-COMT activity and comparison of the allele frequencies in the normal population and parkinsonian patients in Finland. *Pharmacogenetics*, *7*, 65–71.
Takahashi, H., Kato, M., Takano, H., Arakawa, R., Okumura, M., Otsuka, T., et al. (2008). Differential contributions of prefrontal and hippocampal dopamine D1 and D2 receptors in human cognitive functions. *Journal of Neuroscience*, *28*, 12032–12038.
van Holstein, M., Aarts, E., van der Schaaf, M. E., Geurts, D. E. M., Verkes, R. J., Franke, B., et al. (2011). Human cognitive flexibility depends on dopamine D2 receptor signaling. *Psychopharmacology*, *218*, 567–578.
van Schouwenburg, M. R., Zwiers, M. P., van der Schaaf, M. E., Geurts, D. E. M., Schellekens, A. F. A., Buitelaar, J. K., et al. (2013). Anatomical connection strength predicts dopaminergic drug effects on fronto-striatal function. *Psychopharmacology*, *227*, 521–531.
Vijayraghavan, S., Major, A. J., & Everling, S. (2016). Dopamine D1 and D2 receptors make dissociable contributions to dorsolateral prefrontal cortical regulation of rule-guided oculomotor behavior. *Cell Reports*, *16*, 805–816.
Vijayraghavan, S., Major, A. J., & Everling, S. (2017). Neuromodulation of prefrontal cortex in non-human primates by dopaminergic receptors during rule-guided flexible behavior and cognitive control. *Frontiers in Neural Circuits*, *11*, 91.
Vijayraghavan, S., Wang, M., Birnbaum, S. G., Williams, G. V., & Arnsten, A. F. (2007). Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. *Nature Neuroscience*, *10*, 376–384.
Vogelsang, D. A., & D'Esposito, M. (2018). Is there evidence for a rostral-caudal gradient in fronto-striatal loops and what role does dopamine play? *Frontiers in Neuroscience*, *12*, 242.
Wang, M., Vijayraghavan, S., & Goldman-Rakic, P. S. (2004). Selective D2 receptor actions on the functional circuitry of working memory. *Science*, *303*, 853–856.
Winterer, G., & Weinberger, D. R. (2004). Genes, dopamine and cortical signal-to-noise ratio in schizophrenia. *Trends in Neurosciences*, *27*, 683–690.
Yavich, L., Forsberg, M. M., Karayiorgou, M., Gogos, J. A., & Männistö, P. T. (2007). Site-specific role of catechol-*O*-methyltransferase in dopamine overflow within prefrontal cortex and dorsal striatum. *Journal of Neuroscience*, *27*, 10196–10209.
Zahrt, J., Taylor, J. R., Mathew, R. G., & Arnsten, A. F. (1997). Supranormal stimulation of D1 dopamine receptors in the rodent prefrontal cortex impairs spatial working memory performance. *Journal of Neuroscience*, *17*, 8528–8535.
Zhang, Y., Bertolino, A., Fazio, L., Blasi, G., Rampino, A., Romano, R., et al. (2007). Polymorphisms in human dopamine D2 receptor gene affect gene expression, splicing, and neuronal activity during working memory. *Proceedings of the National Academy of Sciences, U.S.A.*, *104*, 20552–20557.