Published in final edited form as:

Cortex. 2013 ; 49(10): . doi:10.1016/j.cortex.2013.04.002.

Dissociable fronto-striatal effects of dopamine D2 receptor stimulation on cognitive vs. motor flexibility

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Abstract

Genetic and pharmacological studies suggest an important role of the dopamine D2 receptor (DRD2) in flexible behavioral adaptation, mostly shown in reward-based learning paradigms. Recent evidence from imaging genetics indicates that also intentional cognitive flexibility, associated with lateral frontal cortex, is affected by variations in DRD2 signaling. In the present functional MRI study, we tested the effects of a direct pharmacological manipulation of DRD2 stimulation on intentional flexibility in a task-switching context, requiring switches between cognitive task rules and between response hands. In a double-blind, counterbalanced design, participants received either a low dose of the DRD2 agonist bromocriptine or a placebo in two separate sessions. Bromocriptine modulated BOLD signal during rule switching: rule-switching-related activity in the left posterior lateral frontal cortex and in the striatum was increased compared to placebo, at comparable performance levels. Fronto-striatal connectivity under bromocriptine was slightly increased for rule switches compared to rule repetitions. Hand-switching-related activity, in contrast, was reduced under bromocriptine in sensori-motor regions. Our results provide converging evidence for an involvement of DRD2 signaling in fronto-striatal mechanisms underlying intentional flexibility, and indicate that the neural mechanisms underlying different types of flexibility (cognitive vs. motor) are affected differently by increased dopaminergic stimulation.

Keywords

bromocriptine; psychopharmacology; intentional flexibility; functional magnetic resonance imaging (fMRI)

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1. Introduction

Flexibility in perception, cognition and action is a prerequisite of managing everyday challenges. Recent theories on the neurochemical basis of individual differences in flexibility suggest a crucial role of the dopamine D2 receptor (DRD2) in modulating the flexible adaptation of behavior (Cools, 2011; Durstewitz and Seamans, 2008; Seamans and Yang, 2004). In humans, this hypothesis is supported by genetic (Aarts et al., 2010; Frank et al., 2007; Jocham et al., 2009; Klein et al., 2007; Stelzel et al., 2010) and pharmacological (Cools et al., 2009; Cools et al., 2007; Frank and O'Reilly, 2006; Jocham et al., 2011; Kimberg et al., 1997; Mattay et al., 2003; van Holstein et al., 2011) studies. Until recently, the association of DRD2 signaling with cognitive flexibility was primarily investigated in learning paradigms where behavioral adaptation was based on feedback including rewards. However, humans are also able to be flexible in a prospective, intentional manner, e.g., when switching back and forth between different tasks is based on instructions without receiving any immediate reward for doing so. DRD2-related modulations of feedbackbased learning have been shown in ventral striatal, anterior cingulate, and orbitofrontal regions (Cools et al., 2009; Jocham et al., 2009; Klein et al., 2007). In contrast, the neural effects of DRD2 on intentional switching can be expected in lateral fronto-parietal control networks (Brass and von Cramon, 2002; Braver et al., 2003), and also striatal regions (Gu et al., 2008; Leber et al., 2008), typically associated with intentional switching (Cools et al., 2007; Mehta et al., 2004; Mehta et al., 1999; Stelzel et al., 2010; van Holstein et al., 2011).

Using fMRI, we showed before that the performance in attentional switching and task-rule switching is associated with the dopamine D2 receptor. In a pharmacological study with the D2 agonist bromocriptine (Cools et al., 2007), participants had to encode stimuli (i.e., faces vs. scenes) during a delayed response task. Stimuli from both categories were presented and a colored cue indicated which stimulus category had to be encoded in each trial. Hence, the same task rule was applied throughout the task (i.e., maintain encoded items for later recall), but from trial to trial, attention had to be either maintained on the currently relevant stimulus category or switched to a different stimulus category. High impulsive individuals improved in attentional switching under the D2 agonist bromocriptine compared to placebo, which was accompanied by increased activity in the putamen. Accordingly, switching attention between stimulus categories can be assumed to be related rather directly to the signaling of the D2 receptor in the striatum.

With respect to task-rule switching, we showed in a recent imaging genetics study (Stelzel et al., 2010) that non-carriers of the A1 allele of the DRD2/ANKK1-TaqIA polymorphism – associated with increased DRD2 density and presumably lower striatal dopamine levels (Laakso et al., 2005) – had increased rule-switching costs, hence cognitive inflexibility, compared to A1 carriers. In that study, subjects were cued to perform different categorization tasks on number stimuli (i.e. odd/even or greater/smaller 5 decisions), which were either repeated or switched from trial to trial. The behavioral effects were accompanied by increased lateral frontal activity and increased fronto-striatal functional connectivity. As the D2 receptor is most abundant in the striatum (Pohjalainen et al., 1998), this finding indicates that successful updating of task representations in the lateral frontal cortex depends on DRD2-modulated fronto-striatal processing. This, in turn, supports models of frontostriatal gating according to which stronger striatal dopamine D2 signals allow more flexible updating of prefrontal cortex (PFC) representations (Durstewitz and Seamans, 2008; Frank et al., 2001) whereas weaker striatal signals might have to be compensated with increased PFC activity. Hence, variations in DRD2 signaling can be assumed to have direct effects in the striatum in the case of attentional switching, but also distant effects in the lateral PFC in the case of task-rule switching.

While genetic variations in the DRD2 system provide a well-established proxy for showing an association of this specific dopamine sub-system with specific cognitive processes, it is not known whether these phenotypical differences are directly related to differences in striatal DRD2 stimulation. Alternatively, adaptive long-term mechanisms over the lifetime may have changed the dopamine system more fundamentally in individuals with high versus low DRD2 density. For example, there is evidence that genetically determined low DRD2 density is associated with higher striatal dopamine synthesis capacity (Laakso et al., 2005), presumably based on altered presynaptic autoreceptor availability in the midbrain (Bello et al., 2011; Buckholtz et al., 2010). This might result in impulsivity and impulse-related disorders in the extreme case, characterized by excessive distractibility (Buckholtz et al., 2010; Voon et al., 2011). As a consequence, the two reported studies on pharmacological modulation of attentional switching vs. genetic modulation of task rule switching are difficult to compare. To conclude that variations in DRD2 stimulation are expressed in distant lateral prefrontal regions and/or striatal regions for task rule switching, a direct pharmacological manipulation is required.

In the present study, we manipulated DRD2 stimulation experimentally using the D2 receptor agonist bromocriptine in a task-switching paradigm. Besides switches between task rules, switches between response hands were included in the paradigm to test for potentially dissociable effects of DRD2 stimulation on cognitive vs. motor flexibility. Motor flexibility is known to be crucially affected by dopaminergic medication in Parkinson's disease (Galea et al., 2012). Anatomical evidence for distinguishable fronto-striatal circuits between sub-regions of the striatum and subregions of the frontal cortex (Alexander et al., 1986; Haber and Calzavara, 2009) suggests that distinct fronto-striatal sub-regions might be more relevant for cognitive vs. motor flexibility, respectively. In a previous study, we showed partly overlapping but also separable frontal and superior parietal activity for rule switching and hand switching (Stelzel et al., 2011). Whether DRD2 stimulation has distinct vs. overlapping effects on both types of intentional flexibility in fronto-striatal regions is not known yet. In a placebo-controlled double blind design, we tested whether or not the administration of bromocriptine modulates task-rule and hand switching and whether or not this is associated with frontal activity or rather with striatal activity as it was shown previously for attentional switching in high impulsive individuals (Cools et al., 2007).

2. Methods

2.1 Participants

24 participants were included in the study. Three individuals had to be excluded due to high error rates (> 30 %) and three further individuals due to high movement (> 3 mm) during MRI. Unfortunately, the six drop-out individuals could not be replaced due to organizational reasons. The final sample consisted of 18 righthanded participants (10 females, age: $M = 25.6$, $SD = 2.8$; 8 males, age: $M = 26.5$, $SD = 6.7$), all from the UC Berkeley community, of Caucasian ethnicity, without neurological or psychiatric history, and with normal or corrected-to-normal vision. Participants were selected from a larger sample of genotyped individuals ($n = 101$) based on their genotype (half A1-, half A1+ - final sample: $n = 8$ A1+, $n = 10$ A1-), gender, and ethnicity. However, due to small sample sizes genotype was not considered in the present analyses. The study was approved by the local ethics committee and participants gave written consent according to the Declaration of Helsinki and were paid for participation.

2.2 General procedure

All participants visited the Helen Wills Neuroscience Institute twice, with two identical sessions that only differed in whether they received a lactose placebo or an oral dose of the

D2 receptor agonist bromocriptine (1.25 mg). Drug versus placebo administration was double blind, and the order of administration was counterbalanced across individuals and genetic groups. Individuals started with the task-switching paradigm in the MRI 75 minutes after drug versus placebo intake. The time of the MRI session was chosen to ensure that bromocriptine plasma concentration was high and did not begin to decay during testing (Deleu et al., 2002). After the task switching experiment, two additional tasks and a resting-state scan (5 minutes) were performed in the scanner. One task was a working memory task requiring the maintenance and updating of letter stimuli (20 minutes). The other task was a face recognition task (5 minutes). All tasks were performed in the same order for all subjects. Results will be reported elsewhere. Before consuming the drug or placebo pill, blood pressure was measured. Immediately after drug intake participants filled out a visual analogue scale involving 8 state items about being anxious, happy, sad, nauseous, drowsy, jittery, fatigued, or dizzy. After scanning, blood pressure and the visual analogue scale were measured again. All relevant control measures were submitted to repeated measures ANOVAs with within subject factors: (1) drug (bromocriptine vs. placebo), and (2) time (pre vs. post MRI measurement).

2.3 Behavioral Procedure

In the task switching experiment, participants performed two different tasks on visually presented number stimuli (i.e., 1–9, excluding 5) depending on a task cue presented 300 msec before the number stimuli. The task cue remained on the screen until the end of the trial (see Figure 1), and participants had to respond quickly and accurately. A diamond cue indicated that participants had to decide whether the number stimulus was greater or less than five. A square indicated to decide whether the number was odd or even. The number stimulus was presented in the center of the cue symbol for 1700 msec, followed by a variable inter trial interval of 2, 4, or 6 sec. In addition to the sequence of the two tasks, the location of the task cues was varied. Cues were presented either to the left or the right of the fixation cross, indicating the response hand for the present trial. If cue and stimulus appeared to the left of the fixation cross, the response was to be given with the middle or index finger of the left hand, if they appeared to the right of the fixation cross, participants were to respond with the right middle or index finger. This revealed 4 different task conditions (1) rule repetition - hand repetition, (2) rule repetition - hand switch, (3) rule switch -hand repetition and (4) rule switch - hand switch.

Participants responded with the left finger of the respective response hand if the stimulus was less than five or even and with the right finger if it was greater than five or odd. The task sequence was pseudo-randomized with the restriction that not more than 3 task repetitions, 2 stimulus repetitions, and 3 response repetitions occurred in sequence. Participants performed 2 runs of 96 trials each, resulting in 47 to 48 trials in each of the four conditions. Transitions between conditions were balanced evenly. Participants received two blocks of training (64 trials each) with the task directly before each MRI session. Behavioral data were analyzed with repeated measures ANOVAs with within subject factors: (1) rule switch (repetition vs. switch), and (2) hand switch (repetition vs. switch) and (3) drug (bromocriptine vs. placebo).

2.5 MRI Data Acquisition

All images were acquired with a 3 Tesla Siemens Trio MRI scanner equipped with a fast gradient system for echo-planar imaging. We used a 12-channel head coil and stabilized participants with cushions to restrict head motion comfortably. Functional images were acquired in 2 runs, using a whole brain one-shot gradientecho, echo-planar sequence (TE = 28 msec, matrix size = 64×64 , FOV = 24 cm, flip angle = 70° , TR = 2 sec). Each functional volume consisted of 32 axial slices with 3 mm thickness and 0.45 mm inter-slice gap. We

also acquired a structural T1-weighted 3-D MPRAGE scan at the end of the experiment (matrix size 256×230 , slice thickness: 1.0 mm, flip angle: 9°). Anatomical images were used for the normalization of the functional data to the Montreal Neurological Institute (MNI) atlas space.

2.6 Functional MRI Data Analyses

All analyses were carried out with SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>). First, each participant's functional data set was slice-time corrected, motion corrected and then coregistered to the anatomical data. After segmentation, the data were spatially normalized into the standard MNI atlas space. Data were then smoothed with an 8-mm FWHM Gaussian kernel and high-pass filtered during statistical analysis. We applied the general linear model for serially auto-correlated data (Friston et al., 1995), included one covariate for each task type in relation to the preceding trial: task repetition/hand repetition; task repetition/hand switch; task switch/hand repetition, task switch/hand switch. In addition, we included one covariate for error trials. Second level analyses were conducted in several steps: First, two flexible factorial models were created independently for each switch type, i.e., rule vs. hand switching, with three factors each (model 1: (1) subject (2) drug (placebo vs. bromocriptine), (3) rule switch (repetition vs. switch); model 2: (1) subject, (2) drug, (3) hand switch). Baseline contrasts for each factor combination were included into the model. Effects of switching vs. repetition in each of these models were analyzed, applying an FWE-corrected threshold of $p < .05$ (cluster size $k > 5$ voxels). To increase sensitivity for drug effects, a more liberal threshold of $p < .005$, uncorrected, $k > 20$ voxels (see (Lieberman and Cunningham, 2009)) was used for the analysis of interaction effects between condition (repetition vs. switch) and drug (placebo vs. bromocriptine). While this is a rather liberal threshold, we believe that this is superior to a pure ROI approach applied by many previous studies in the field, as it represents more fully the effect of bromocriptine in all task-related regions. To protect against false positives, the analysis of the drug interaction was restricted to a functionally defined mask of brain regions showing switching-related activation in the respective domain (i.e., rule switching or hand switching), defined at the same statistical threshold (see transparent red areas in Figure 2). Finally, to test the complete 3-way interaction, we calculated the interaction effects of rule switching and hand switching on the first level in each subject and then used paired t-tests to compare the interaction effects between drug vs. placebo sessions. This approach was chosen as the flexible factorial model in SPM is restricted to a maximum of three factors (including the subject factor). This model was also thresholded at $p < .005$, uncorrected, $k > 20$ voxels and masked by the respective interaction effect of rule switch and hand switch ($p < .005$, uncorrected, $k > 20$).

To visualize interaction patterns, parameter estimates from clusters showing an interaction effect were extracted. This was done by saving the clusters as binary masks using xjview (<http://www.alivelearn.net/xjview8/>) and then extracting and averaging the parameter estimates per task condition for all voxels included in this mask. To additionally test for effects in the striatum, an anatomical ROI approach was used, defining the caudate and putamen as ROI via the Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002), dilated by 2 voxels and then testing for interaction effects within this ROI.

Psycho-physiological Interaction

To explore whether switching-related frontostriatal interactions differ between placebo and bromocriptine we used the method of psychophysiological interactions (Friston et al., 1997). The aim of a PPI analysis is to explain neural responses in one brain region in terms of the interaction between the neural responses in another brain region and a specific psychological context. We performed two different PPI analyses, one with rule switching as psychological context and one with hand switching as psychological context. The respective frontal

clusters that showed an interaction effect with bromocriptine were used as seed regions. The psychophysiological interaction term was calculated as the product of the mean time course in this region and the respective psychological variable (i.e., rule switch vs. repetition or hand switch vs. repetition). All three variables (time course in seed region, psychological variable, and interaction term) were entered into new general linear models for each subject, i.e., one for task switching and one for hand switching. Then, one-sample t-tests were performed on the psycho-physiological interaction term, separately for the bromocriptine and the placebo conditions, respectively. We restricted the analysis to the striatum by applying an anatomical mask of this region (see above).

3. Results

3.1 Behavioral data

As expected, pooled across hand-switching conditions, task-rule switching elicited performance costs, i.e., increased response times (RT; $58.7 \text{ msec} \pm 9.6$, s.e.m; $F(1, 17) = 37.38$, $p < .001$) and error rates (4.4% , $\pm .8$; $F(1, 17) = 32.9$, $p < .001$) compared to task-rule repetitions (see Table 1). Hand switching, pooled across rule-switching conditions, was not associated with increased RTs, $F(1, 17) = 2.8$, $p = .11$ or increased error rates, $F(1, 17) = 0.02$, $p = .88$. A significant interaction between the two switching factors, $F(1, 17) = 10.06$, $p = .006$, however, reflected that hand switching effects differed between task-rule repetition and rule-switch trials: while significant hand-switching costs were present when the task rule was repeated ($30.7 \text{ msec} \pm 9.6$; $t(17) = 3.19$, $p = .005$), they were absent in rule-switch trials (7.9 ± 8.5 , $t(17) = 0.93$, $p = .36$). Likewise, rule-switching costs were stronger in handrepetition-trials ($77.9 \text{ msec} \pm 11.1$; $t(17) = 6.98$, $p < .001$) compared to hand-switch trials ($39.4 \text{ msec} \pm 11.5$; $t(17) = 3.41$, $p = .003$). This interaction effect was not present in the error rates, $F(1, 17) = 3.47$, $p = .08$.

There was no main effect of bromocriptine on overall RTs, $F(1,17) = .29$, $p = .60$, or error rates, $F(1, 17) = 1.54$, $p = .23$. Also, rule switching was not affected by bromocriptine in the RTs, $F(1,17) = .27$, $p = .61$, or error rates, $F(1,17) = .06$, $p = .82$, neither was hand switching in the RTs, $F(1,17) = .51$, $p = .49$ or error rates, $F(1, 17) = 1.29$, $p = .27$. The 3-way interaction of drug, rule and hand switching approached significance in the RTs, $F(1,17) = 4.33$, $p = .053$ but not in the error rates, $F(1, 17) = 0.61$, $p = .45$. This was due to a differential effect of bromocriptine on rule-switching depending on the hand switching condition: while rule switch costs increased numerically under bromocriptine in the hand-repetition condition (placebo: 59.4 msec , ± 12.5 ; bromocriptine: $96.5 \text{ msec} \pm 22.6$; Table 1), rule-switching costs under bromocriptine were numerically decreased in the hand-switching condition (placebo: 47.6 ± 16.1 ; bromocriptine: 31.2 ± 12.5). Hence, the RT interaction pattern of rule switch and hand switch tended to be stronger under bromocriptine compared to placebo, albeit not significantly. The error rates tended to be affected in the opposite direction, suggesting a potential speed-accuracy trade-off for the processing of the combined switching demands under bromocriptine.

3.2 fMRI data

In accordance with our previous study (Stelzel et al., 2011) and based on the reported interaction patterns in the behavioral data, subsequent analyses of switching effects in the fMRI data and interaction effects with the bromocriptine manipulation were calculated for the pure switching contrasts, that is, rule switching versus repetition when the hand remained the same and hand switching versus repetition when the abstract task rule remained the same, respectively. Note that there was no interaction effect between rule switching and hand switching on the brain level present that passed the statistical threshold.

In line with previous reports (Brass and von Cramon, 2002; Derrfuss et al., 2004; Kim et al., 2011; Stelzel et al., 2010), task-rule switching (compared to rule repetition) was associated with increased activity in fronto-parietal regions, including the left inferior frontal junction (IFJ) region at the intersection of the inferior frontal sulcus (IFS) and the precentral sulcus, a region in the left superior frontal sulcus/ presupplementary motor area, and left inferior parietal regions ($p < .05$, FWE corrected, $k > 5$ voxels; see Table 2). At a more lenient threshold of $p < .005$, uncorrected, $k > 20$ voxels, increased rule-switching-related activity was present in a more extended, mostly left lateralized fronto-parietal network also involving activation clusters more anteriorly in the left IFS, in the right superior frontal sulcus, the pre-supplementary motor area, in regions surrounding the intraparietal sulcus and in the putamen (see Figure 2A, left panel, transparent red). This more extended activation map was used as mask to restrict subsequent analyses of drug effects on switching-related activations.

Hand switching was associated with strong ($p < .05$ FWE-corrected, $k > 5$) activity increases in visual and motor areas, i.e., bilateral calcarine sulci, central and precentral sulci, and superior frontal and right superior parietal regions (Table 2). At $p < .005$, uncorrected, $k > 20$, a wide bilateral network involving medial and lateral (pre-) motor regions, the left IFJ, left posterior putamen, inferior parietal regions and a wide range of visual regions were involved in switching between response hands compared to hand repetitions (see Figure 2B left panel, transparent red).

To address the question whether switching-related brain activity was affected by bromocriptine, we tested the interaction of switching (i.e., switch vs. repetition) with drug (placebo vs. bromocriptine), again separately for rule switching and hand switching. Results were masked by the respective task contrasts isolating switchingspecific activations, as described above (but see Supplemental Table S1 for unmasked whole brain results). There was only one cluster in the left IFJ / precentral sulcus within the rule-switching network that showed an interaction effect at the applied threshold of $p < .005$, $k > 20$ ($k = 30$ voxels, peak 1: $x = -33$, $y = +11$, $z = +46$, $t_{\max} = 3.28$, peak 2: $x = -42$, $y = -8$, $z = +49$, $t_{\max} = 3.15$; see Figure 2A, left panel, red color code). Parameter estimates were extracted from this cluster to visualize the interaction pattern. As can be seen from Figure 2A (right panel) ruleswitching-effects were increased under bromocriptine compared to placebo, which resulted from signal increases in rule-switch trials and signal decreases in rulerepetition trials.

For hand switching, drug-dependent effects were also present, but in the opposite direction (see Figure 2B). Within the hand-switching network, reduced activity differences between hand-switch and hand-repetition trials under bromocriptine were present in the SMA at $p < .005$, $k > 20$ ($x = +12$, $y = -1$, $z = +52$, $t_{\max} = 4.28$, $k = 43$ voxels) and the postcentral gyrus ($x = +48$, $y = -19$, $z = +28$, $t_{\max} = 5.25$, $k = 54$ voxels). Thus, bromocriptine had distinguishable effects on both types of switching - in terms of anatomical location as well as directionality of the effects.

Finally, we tested also for the presence of a 3-way interaction of rule switch (repetition vs. switch) x hand switch (repetition vs. switch) x drug (placebo vs. bromocriptine), restricted to those regions showing interaction effects between rule switching and hand switching (see Methods section for details). Within this search space, we found no region in which the interaction effect of rule switching and hand switching was modulated by bromocriptine (but see Supplementary Table 1 for the unmasked results).

3.3 Analysis of striatal bromocriptine effects

In the masked analyses of bromocriptine effects, no striatal interaction effects were present at the applied statistical threshold, neither for rule switching nor for hand switching or their interaction, presumably because the task-related activity in the striatum was very small. As previous studies strongly suggest that bromocriptine acts at the level of the striatum to modulate attentional flexibility (Cools et al., 2007), we intended to test the hypothesis that bromocriptine modulates striatal activity during intentional flexibility in more detail. For this, we used an anatomical striatal ROI comprising the caudate nucleus and the putamen as a mask for testing the main effect of drug as well as the interaction with the switching effects, at a statistical threshold of $p < .005$, $k > 5$ voxels. As a first result, we found a general increase in activity bilaterally in the caudate nucleus under bromocriptine compared to placebo across rule-switching conditions, i.e. a main effect of drug in the rule-switching model ($x = +3$, $y = +14$, $z = +4$, $t_{\max} = 4.64$, $k = 70$ voxels, see Figure 3A, left panel). In addition, decreases in activity under bromocriptine were present in the bilateral posterior putamen when pooled across the rule-switching conditions (left: $x = -24$, $y = -22$, $z = +4$, $t_{\max} = 3.91$, $k = 15$; right: $x = +27$, $y = -19$, $z = -2$, $t_{\max} = 3.25$, $k = 19$, see Figure 3A, right panel). As for the interaction between drug and rule switching, a small cluster in the left caudate nucleus ($x = -18$, $y = 29$, $z = 1$, $t_{\max} = 2.93$, $k = 6$ voxels, see Figure 3B, left panel) exhibited stronger rule-switching-related activity under bromocriptine compared to placebo. Likewise, a cluster in the posterior putamen exhibited stronger rule-switching-related activity under placebo than under bromocriptine ($x = -33$, $y = -1$, $z = -2$, $t_{\max} = 3.16$, $k = 7$ voxels see Figure 3B, right panel).

For hand switching, the only bromocriptine-related effect in the striatum was reduced switching-related activity under bromocriptine compared to placebo in the putamen ($x = -27$, $y = 14$, $z = -11$, $t_{\max} = 3.01$, $k = 9$ voxels). See also supplementary Figure S1 for the 3-way interaction of the full 2 (rule switch) x 2 (hand switch) x 2 (drug) model in the striatal ROI.

Taken together, strongest effects of bromocriptine in the striatum were present in the caudate nucleus, in a mostly unspecific manner, i.e. increased activity in switch- and repetition trials. The interaction effects were small and suggest that activity in the interaction clusters in the caudate nucleus are best described as increased rule-switching-related activity under bromocriptine compared to placebo, while the putamen exhibits the reverse pattern with reduced switching-related activity under bromocriptine.

3.4 Psychophysiological Interaction

To additionally assess whether switching-related bromocriptine effects in the frontal cortex were directly associated with activity changes in the striatum, we performed PPI analyses with the respective frontal clusters from the drug x switching effects in the IFJ (rule switching) and SMA (hand switching) as seed regions and the anatomical mask of the striatum as region of interest.

Interestingly, for rule switching, there was increased functional connectivity between the IFJ and the caudate nucleus under bromocriptine ($x = +15$, $y = +17$, $z = +10$, $t_{\max} = 3.57$, $k = 15$ voxels, see Figure 3C, left panel), which was not present under placebo. However, the difference between bromocriptine and placebo was not significant. For hand switching, there was no reliable connectivity effect present.

3.5 Control measures

Blood pressure—Neither the placebo versus bromocriptine sessions nor the time of measurement differed with respect to blood pressure measured before and after MRI

measurement. The only interaction present was between drug and time for systolic blood pressure, $F(1, 16) = 5.62$, $p = .031$, with slightly decreased values after scanning under bromocriptine only (pre: 123.3, post: 116.5, $t(16) = 1.98$, $p = .06$), which were, however, still in a normal range.

Self report (Visual analogue scale)—Of the self-report measures, only self-reported anxiety changed over time, $F(1, 17) = 15.1$, $p < .001$, with lower values after scanning (pre: 26.7 (3.3); post: 15.6 (2.3)).

To assure that bromocriptine effects on brain activity were not just related to more basic physiological effects of bromocriptine, which might produce drops in blood pressure, as well as drowsiness or nausea, we correlated the control measures assessed after MRI measurement with the rule-switching-related IFJ activity and hand-switching-related SMA/postcentral activity in the bromocriptine session. None of the self-report scales or the blood pressure values correlated with switching-related activity. Additionally, we tested whether any of these measures was related to performance (i.e. mean error rates) in the switching paradigm or the other demanding Sternberg task (not reported here). No correlations with behavior were present.

4. Discussion

In the present study, we aimed at further elucidating the role of the dopamine D2 receptor in intentional flexibility. Consistent with previous research (Brass and von Cramon, 2002; Stelzel et al., 2011; Stelzel et al., 2010) and quantitative meta analyses (Derrfuss et al., 2005), fronto-parietal regions exhibited reliable activity during intentional switching between task rules and response hands. For rule switching, the D2 receptor agonist bromocriptine modulated this activity in the left IFJ region in the lateral frontal cortex, such that slightly greater switching-related activity was elicited under bromocriptine relative to the placebo control condition. In addition, at a more lenient statistical threshold, bromocriptine also increased activity in the left dorsal striatum, as indicated by the striatal ROI analysis. Functional connectivity data revealed increased rule-switching-related connectivity between the IFJ and the striatum under bromocriptine but not under placebo. For hand switching, activity in sensorimotor regions (SMA, postcentral gyrus) was affected by the D2 agonist -activity in these regions was decreased under bromocriptine compared to placebo. In addition there was reduced hand-switching related activity under bromocriptine in the left putamen.

These findings provide converging evidence for the assumption that variations in DRD2 signaling, most likely originating in the DRD2-rich striatum, affect intentional flexibility associated with activity changes in the frontal cortex. While our previous findings demonstrated that long-term genetic differences in DRD2 density between individuals affect fronto-striatal BOLD signals during the flexible switching between task rules (Stelzel et al., 2010), the present pharmacological manipulation revealed that a direct, transient modulation of DRD2 stimulation with bromocriptine has a comparable neural effect on rule switching. In addition, the finding that bromocriptine effects in the lateral frontal cortex were specific to rule switching support the predominant role of dopaminergic transmission to the lateral frontal cortex for intentional flexibility in the cognitive domain.

Since brain activity changes related to bromocriptine administration were not associated with performance benefits, i.e. reduced switching costs, but if anything, with an increase in behavioral rule-switching costs (cf. also Stelzel et al., 2010), these findings suggest that rule-switching efficiency was reduced, i.e. subjects have invested more neural effort in the lateral frontal cortex for switching between two task rules under bromocriptine. Note that this

interpretation is based on a non-significant behavioral difference between bromocriptine vs. placebo, which would be interesting to test for robustness in a larger sample. However, as the numerical direction of RT effects indicated increased rule-switching effects under bromocriptine, a reversal into a benefit seems to be very unlikely. This might indicate that subjects unsuccessfully attempted to reach a better performance level for rule switching by investing more effort. In contrast, activity in the SMA and postcentral gyrus indicates that hand switching was related to less neural effort under bromocriptine, showing an improvement, which, however was not strong enough to be reflected behaviorally (Meyer-Lindenberg and Weinberger, 2006). It is important to note that all interactions with drug were only found at a lenient statistical threshold of $p < .005$ combined with a cluster threshold of $k > 20$. Accordingly, the present findings can only be considered as first evidence for bromocriptine-related modulation of rule and hand switching and require replication in a larger sample.

4.1 Neurocognitive mechanisms for different types of switching

The predominant effect of bromocriptine on lateral frontal activity during ruleswitching in the present study seems to be at odds with our previous study on attentional switching (Cools et al., 2007) where bromocriptine increased striatal activity and performance selectively during switching, but did not affect lateral frontal switching-related activity. Importantly, the types of switching required in the current task differ from this previous bromocriptine study, where individuals had to switch their visual attention to different stimulus categories depending on a cue, thereby still performing the same task. Switching attention between visual objects can be assumed to share some common processing demands with switching between cognitive task rules. However, these common processes seem to be mainly associated with the parietal cortex and not with the striatum (Chiu and Yantis, 2009). Depending on the specific neurocognitive architecture for these two types of switching, manipulations of dopaminergic signaling might have different effects on both types of switching, i.e. more pronounced effects either directly in the striatum or in distant cortical regions. The present dissociation of dopaminergic effects on rule switching as compared to hand switching supports the notion that effects of dopaminergic stimulation depend on the task-relevant switching-related networks.

We have previously shown that switching between task rules overlaps anatomically with switching between response hands in the IFJ and in superior frontal and superior parietal cortices (Stelzel et al., 2011). In contrast, a recent study demonstrated that the only overlap for switching between rules and switching between response modalities is located in the inferior parietal cortex (Philipp et al., 2012). This suggests that response-modality switching and rule switching might be less similar than hand switching and rule switching, both of the latter requiring the switch between relatively distinct task-set elements (Logan and Bundesen, 2004). This, in turn, raises the question whether the seemingly low-level switch between response hands might require similar control mechanism as rule switching. In general, the degree to which task switching requires cognitive control is still under discussion and certainly depends on the specific tasks, the nature of task cueing, preparation intervals, ITIs and many other variables (Kiesel et al., 2010; Monsell, 2003). Depending on these variables either more proactive control, i.e. preparatory control that facilitates task processing via preparation, or reactive control, i.e. control evoked by the task demand at the time of target presentation, might be involved in switching (Braver, 2012). Due to the long ITIs and short cue-target intervals (300 ms), in the present study the focus was more on reactive than proactive control (Meiran et al., 2000). It is likely that this was particularly the case for rule switching where preparation requires more time compared to hand switching. Note that for hand switching the laterality of the task cue indicated very directly the

upcoming response hand. This difference might additionally contribute to the differential effects of bromocriptine on both types of switching and the involvement of the IFJ.

While both types of switching were related to the IFJ, bromocriptine effects in the IFJ and connectivity of the IFJ with the dorsal striatum were only present for rule switching. For hand switching, bromocriptine affected switching-related activity in sensorimotor regions such as SMA. This indicates that even though the IFJ seems to have a more general role for different switching processes, its dopamine-dependent interaction with the dorsal striatum is specific for the cognitive switching between task rules.

4.2 Comparison of pharmacological and genetic effects

The convergence of the bromocriptine effects on rule switching in the present study with our previously reported genetic effects for task-rule switching (Stelzel et al., 2010) has important implications for the understanding of the role of DRD2 signaling in cognitive flexibility. For example, the finding that transient increases in DRD2 stimulation via bromocriptine lead to comparable neural effects as genetically determined increases in DRD2 density, associated with lower striatal dopamine, seems to indicate that pharmacological DRD2 stimulation and high DRD2 density are associated with similar neurophysiological mechanisms. One such mechanism could be that both - pharmacological DRD2 stimulation and high DRD2 density - lead to increased striatal DRD2 signaling to the lateral PFC which is not beneficial but rather detrimental for switching between representations in the PFC. This, however, is at odds with the assumption of a fronto-striatal gating mechanism, according to which stronger striatal DRD2 signals are associated with enhanced updating of PFC representations (Cohen et al., 1996; Frank et al., 2001). This interpretation would also contradict computational models suggesting that the flexible switching between representations relies on D2-dominated system states (Durstewitz and Seamans, 2008).

Our current findings may be better reconciled with these models by taking into account (i) that striatal dopamine synthesis has been observed to be relatively reduced in individuals with genetically determined high DRD2 density (Laakso et al., 2005) and (ii) the observation that bromocriptine at low dosages, as it was administered in the present study, might primarily act on presynaptic D2 receptors (Frank and O'Reilly, 2006; Luciana and Collins, 1997; Skirboll et al., 1979), thus stimulating inhibitory autoreceptors and decreasing striatal dopamine release. The first would be in line with our previous finding of high IFJ activity during task-rule switching in A1 allele non-carriers (A1-). If high DRD2 density in the striatum decreases striatal dopamine release, weak updating signals to the PFC should result in stronger prefrontal control demands during task switching. Despite this strong PFC involvement, A1- individuals, however, were unable to reach a comparable performance level as A1 allele carriers. This suggests a moderately successful attempt to compensate for the weak striatal gating signals by investing additional processing resources in the PFC. This detrimental effect of high DRD2 density is in line with the finding that striatal DRD2 overexpression in transgenic mice, which affects the D1:D2 balance in the striatum and D1 signaling in the PFC, impairs cognitive flexibility (Kellendonk et al., 2006). As for bromocriptine, we found evidence for stronger rule-switching-related activity in the IFJ following bromocriptine administration compared to placebo, which might also be associated with the compensation for weak striatal signals under bromocriptine. As outlined above there is evidence that bromocriptine at low dosages might primarily act on presynaptic D2 autoreceptors, thus decreasing striatal dopamine release. This, in turn should weaken postsynaptic phasic signaling from the basal ganglia which is relevant for updating PFC representations, and thus lead to higher compensatory demands in the PFC for successful switching.

Importantly, our fine-grained analysis of striatal bromocriptine effects revealed a signal increase for task-rule switching only in the dorsal caudate nucleus, which is known to be linked to lateral frontal regions (Alexander et al., 1986; Haber and Calzavara, 2009). The caudate nucleus also showed increased functional connectivity with the IFJ during rule switching under bromocriptine, supporting the role of the interaction of the two regions for rule switching. Psychophysiological interactions do not allow inference about directionality. Accordingly, it is unclear whether the increased connectivity reflects increased signaling from the striatum to the IFJ or increased signaling from the IFJ to the striatum. Following the argument outlined above, we speculate that bromocriptine decreases dopamine signaling in the striatum. Accordingly, we would suggest that it is rather the fronto-striatal and not the striato-frontal connectivity which is increased, but this should be further addressed in future studies. Importantly, this result converges with our earlier finding of increased IFJ-caudate functional connectivity during task-rule switching in A1 allele non-carriers who are characterized by greater DRD2 receptor densities and were also less efficient during task switching.

In contrast, the putamen, which is connected to motor regions, such as the SMA via the thalamus, showed decreased activity under bromocriptine. While the differential effects of bromocriptine on the caudate vs. putamen merit further investigations on the neurophysiological level, the finding of reduced putamen activity under bromocriptine fits nicely to our finding of reduced SMA and postcentral activity for hand switching. Considering that the inhibitory effect of the putamen on the thalamus would be reduced under bromocriptine one might expect that flexible motor behavior would be facilitated, which is what we found. Note, however, that the nature of these interactions and the relation of the present imaging results to previous findings in patients with Parkinson's disease (Kehagia et al., 2009), are certainly complex and need to be investigated in more detail in future studies.

Hence, as the exact relationships between transient increases in DRD2 stimulation, striatal dopamine levels, and BOLD responses are still under investigation (Buckholz et al., 2010; Knutson and Gibbs, 2007; Schott et al., 2008), the interpretation of the finding of additional BOLD increases in the caudate vs. BOLD decreases in the putamen remains somewhat speculative. For example, the striatal effects might be related to striatal presynaptic DRD2 activity or to other postsynaptic effects caused by the increase in presynaptic DRD2 stimulation. While more direct evidence for the proposed autoreceptor mechanisms, e.g. on their locus in the midbrain versus striatum or interactive effects with D1 receptor stimulation, is needed (Bello et al., 2011), in our view the consideration of autoreceptor effects provides a highly plausible account for the present findings of increased compensatory PFC activity associated with bromocriptine, which converges with the findings in individuals with genetically determined high DRD2 density. Both - low doses of bromocriptine and long-term, genetically determined high DRD2 density - seem to be associated with relatively reduced striatal dopamine synthesis, ultimately leading to increased lateral frontal activity during intentional rule switching.

4.3 Dependence on baseline dopamine levels

In the present study, we did not assess differences in baseline dopamine levels between subjects. According to the inverted U-curve model of dopamine function formulated for the PFC and recently for the striatum (Cools and D'Esposito, 2011; Williams and Castner, 2006), individuals with low baseline dopamine levels would benefit from additional dopamine release, shifting them towards the performance maximum of the inverted U. In contrast, individuals with high baseline dopamine levels are shifted to the descending part of the curve with additional dopamine release leading to performance decrements and/or compensatory brain activity. Many recent pharmacological studies suggest that the effects of

DRD2-related drugs (D2 receptor agonists vs. antagonists) depend on variations in baseline dopamine levels (for review see (Cools and D'Esposito, 2011)), a hypothesis that was recently confirmed using PET (Cools et al., 2009). For example, it was shown (Cools et al., 2007) that administration of bromocriptine improved attentional switching between stimulus categories via increased striatal activity exclusively in high impulsive subjects, presumably characterized by low DRD2 density and high striatal dopamine levels at baseline (Bello et al., 2011; Buckholtz et al., 2010). Similarly, in a rewarded task-switching paradigm, exclusively individuals with presumably low striatal dopamine levels (i.e., homozygous carriers of the 10-repeat allele of the dopamine transporter gene DAT1) had lower task-switching costs in the error rates after bromocriptine administration compared to placebo (van Holstein et al., 2011). This effect could specifically be attributed to DRD2 stimulation since it was reversed when subjects were pre-treated with sulpiride, a selective D2 receptor antagonist. Hence, baseline dopamine levels are a crucial factor in predicting individual variability in cognitive flexibility (Cools et al., 2008). Combining the idea of baseline-dependent pharmacological effects with the assumption that bromocriptine at low dosage actually decreases striatal dopamine levels might reconcile the present findings with those previous studies that showed better performance in attentional (Cools et al., 2007) and rewarded cognitive switching (van Holstein et al., 2011) under bromocriptine compared to placebo. We suggest that the hypothesized decrease in striatal dopamine release at low bromocriptine dosages might actually be beneficial for subjects with overly high dopamine levels, such as high impulsive subjects (Cools et al., 2007) or in situations where dopamine levels are high due to other task variables such as the expectation of a reward (van Holstein et al., 2011). In contrast, in the present study, participants were not overly impulsive and were not offered a reward, and thus might be closer to the optimum of the inverted U at baseline and would be shifted to the left by the autoreceptor effects of bromocriptine, resulting in less optimal dopamine levels.

It also has been hypothesized that bromocriptine might act presynaptically in subjects with high dopamine baseline levels only and postsynaptically in subjects with low dopamine levels (Cools et al., 2009). More direct measures of dopamine levels would be needed to directly compare baseline levels in a normal range with extreme groups, in order to test these competing hypotheses directly. Previous research investigating the association of DRD2 binding potential and performance in more complex cognitive control and updating tasks provided mixed evidence for associations with DRD2 binding in the striatum. While no evidence for a direct association of striatal DRD2 binding and behavioral indices for cognitive flexibility was found in a complex set shifting task (MacDonald et al., 2009), increased lateral frontal activity was found for the updating of long-term representations for individuals with high DRD2 availability in the striatum (Nyberg et al., 2009). The direct association of striatal DRD2 availability and striatal dopamine levels with the described neurocognitive processes of intentionally switching between two task sets remains to be addressed accordingly.

In sum, the present study provides converging evidence for the role of DRD2 signaling in intentional flexibility associated with fronto-striatal networks and shows dissociable effects for rule vs. hand switching in these networks. Together with our previous genetic DRD2 effects, a consistent picture emerges, indicating that individual differences in efficient intentional flexibility are strongly related to fronto-striatal interactions involving DRD2 signaling.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by an Emmy Noether grant from the German Research Foundation of CJF (DFG FI 848/3-1) and by National Institute of Health grants MH63901, NS40813, DA02060. CJF and RC are further supported by VIDI grants from the Netherlands Organization for Scientific Research. The authors wish to thank Elaine Laguerta and Asako Miyakawa for assistance in data acquisition, Emily Jacobs for setting up the genetic database, and Jochen Roeper for helpful comments on an earlier version of this manuscript.

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Figure 2.

(A) Rule-switching-related activity (red transparent) and interaction effects with drug (placebo vs. bromocriptine, red). Bar graph illustrates mean parameter estimates for IFJ interaction region, demonstrating increased rule-switching effects under bromocriptine. (B) Hand-switching-related activity (red transparent) and interaction effects with drug (placebo vs. bromocriptine, red). Bar graphs illustrate mean parameter estimates for SMA and postcentral interaction regions, demonstrating decreased rule-switching effects under bromocriptine. All thresholded at $p < .005$, uncorrected, $k > 20$ voxel. Error bars represent standard error of the mean.

A: Striatum: main effect of drug, across rule switching conditions

B: Striatum: Interaction drug x rule switching

C: Functional fronto-striatal connectivity

(seed region: L IFJ (Fig. 2A); psychological factor: rule switch > rule repetition)

Figure 3.

(A) Main effects of bromocriptine in anatomical striatum mask for the rule-switching analysis. Bar graphs illustrate mean parameter estimates for each region.

(B) Interaction effects of drug x rule switching in anatomical striatum mask.

(C) Psychophysiological interaction effects in anatomical striatum mask with drug x rule-switching IFJ cluster as seed region, rule switch vs. rule repetition as psychological factor.

All thresholded at $p < .005$, uncorrected, $k > 5$.

Table 1

Behavioral Results. Rule-switching costs (mean RTs, error rates) and hand-switching costs for placebo vs. bromocriptine sessions (standard error of the mean in parentheses).

	<i>Mean RTs (in msec)</i>		<i>Mean error rates (in %)</i>	
	Placebo	Bromocriptine	Placebo	Bromocriptine
Rule Repetition				
Hand Repetition	834.9 (37.8)	835.1 (32.4)	5.8 (1.8)	7.2 (2.3)
Hand Switch	857.1 (36.4)	874.2 (39.1)	6.2 (1.3)	8.1 (2.4)
Rule Switch				
Hand Repetition	894.3 (40.4)	931.6 (40.7)	11.3 (2.5)	12.0 (2.7)
Hand Switch	904.7 (41.8)	905.4 (40.6)	9.3 (2.0)	12.4 (2.5)

Table 2

Anatomical location and MNI coordinates for task switch versus repetition contrast FWE-corrected ($p < .05$, FWE-corrected, $k > 5$ voxels). Hem, Hemisphere (L, left; R, right); BA, Brodmann's area, incl., included.

Region	Hem	BA	MNI Coordinates			t-value	cluster size
			x	y	z		
Task-rule switching							
Middle Frontal Gyrus / Precentral	L	6/9	-18	-1	58	6.26	167
Sulcus/ Superior Frontal Sulcus/							
Inferior Frontal Junction			-42	5	46	6.12	incl. in 167
Inferior Parietal Lobule	L	40	-48	-40	43	5.55	9
Inferior Parietal Lobule/Precuneus	L	7/40	-33	-52	52	5.40	5
Hand switching							
Calcarine Sulcus /	L/R	17/18/	12	-61	13	8.17	178
posterior Cingulate Gyrus		30/31					
Central Sulcus	R	2/3/6	42	-28	46	6.83	199
Superior Frontal Sulcus	L	6	-27	-7	46	6.41	53
Superior Parietal Lobule	R	7	24	-58	64	5.85	11
Central Sulcus/ Postcentral Gyrus	L	2	-48	-28	40	5.85	18
Cerebellum / Lingual Gyrus	L	19	-12	-55	-5	5.68	11
Supplementary Motor Area	R	24	6	-1	46	5.65	8