Psychopharmacology
DOI 10.1007/s00213-014-3741-9

ORIGINAL INVESTIGATION

Dopaminergic modulation of distracter-resistance and prefrontal delay period signal

Mirjam Bloemendaal · Martine R. van Schouwenburg · Asako Miyakawa · Esther Aarts · Mark D'Esposito · Roshan Cools

Received: 31 July 2013 / Accepted: 10 September 2014

Abstract Dopamine has long been implicated in the online maintenance of information across short delays. Specifically, dopamine has been proposed to modulate the strength of working memory representations in the face of intervening distracters. This hypothesis has not been tested in humans. We fill this gap using pharmacological neuroimaging. Healthy young subjects were scanned after intake of the dopamine receptor agonist bromocriptine or placebo (in a within-subject, counterbalanced, and double-blind design). During scanning, subjects performed a delayed match-to-sample task with face stimuli. A face or scene distracter was presented during the delay period (between the cue and the probe). Bromocriptine altered distracter-resistance, such that it impaired performance after face relative to scene distraction. Individual differences in the drug effect on distracter-resistance correlated negatively with drug effects on delay period signal in the prefrontal cortex, as well as on functional connectivity between the prefrontal cortex and the fusiform face area. These results provide evidence for the hypothesis that dopaminergic modulation of the prefrontal cortex alters resistance of working memory representations to distraction. Moreover, we show that the effects of dopamine on the distracter-resistance of these representations are accompanied by modulation of the functional strength of connections between the prefrontal cortex and stimulus-specific posterior cortex.

Keywords Working memory · Distraction · Dopamine · Prefrontal cortex · Connectivity · fMRI

Mirjam Bloemendaal and Martine R. van Schouwenburg contributed equally to the manuscript.

Electronic supplementary material The online version of this article (doi:10.1007/s00213-014-3741-9) contains supplementary material, which is available to authorized users.

M. Bloemendaal (✉) · M. R. van Schouwenburg · E. Aarts · R. Cools
Radboud University Nijmegen, Donders Institute for Brain, Cognition and Behaviour, Centre for Cognitive Neuroimaging, P.O. Box 9101, 6500, HB Nijmegen, The Netherlands
e-mail: mirjambloemendaal@gmail.com

M. R. van Schouwenburg · R. Cools
Radboudumc, Donders Institute for Brain, Cognition and Behaviour, Department of Psychiatry, P.O. Box 9101, 6500, HB Nijmegen, The Netherlands

A. Miyakawa · M. D'Esposito
Helen Wills Neuroscience Institute, University of California, 132 Barker Hall, Berkeley, CA 94720-3190, USA

M. R. van Schouwenburg
Department of Neurology, University of California, San Francisco, CA 94158, USA

Introduction

We live in a demanding, highly distracting environment. The necessary increase in attentional demands can be a particular problem for those who are already easily distracted. Indeed, several psychiatric disorders, including schizophrenia and Attention Deficit Hyperactivity Disorder, have been associated with an inability to filter out distracting information. Recent theoretical frameworks have suggested that dopamine might play an important role in the resistance to distracters by stabilizing task-relevant representations in prefrontal cortex and by rendering them more resistant to new inputs (Durstewitz and Seamans 2008). Here we aim to test this hypothesis in humans.

Studies in non-human primates have long highlighted the importance of the prefrontal cortex (PFC) in working memory and distracter-resistance (Jacobsen 1936; Malmo 1942). These studies have focused primarily on cortex surrounding the principal sulcus, corresponding to the dorsolateral PFC (DLPFC) in humans. Neurons in this PFC region show sustained signal during the delay period of a working memory

Published online: 11 October 2014

delayed response task (Fuster and Alexander 1971; Miller et al. 1996). Moreover, DLPFC lesions in humans as well as ablation of analogue PFC regions in rhesus monkeys are accompanied by reduced distracter-resistance (Jacobsen 1936; Chao and Knight 1995).

The PFC has been suggested to support working memory by selectively enhancing the processing of task-relevant information via excitatory top-down connections to the relevant sensory regions (Miller and Cohen 2001; Feredoes et al. 2011). This hypothesis is corroborated by functional MRI (fMRI) studies in humans. For example, Gazzaley et al. (2004) have shown that the online maintenance of face stimuli was accompanied by significant connectivity between the DLPFC and the fusiform face area (FFA), a region involved in processing of faces (Kanwisher et al. 1997). Thus, DLPFC may support working memory by increasing connectivity with brain regions that process remembered information, thereby rendering this information resistant to distraction.

Distracter-resistance during delayed response tasks of working memory has been shown to depend on the similarity between encoding cues and intervening stimuli. Thus, distracter-resistance is particularly vulnerable when distracters are very similar to the remembered information (Jha et al. 2004; Yoon et al. 2006). It was proposed that maintained information and distracting information are represented by independent patterns in the PFC and that the similarity between these patterns determines how well the PFC can dissociate between them (Durstewitz et al. 1999). Indeed, Yoon et al. (2006) showed that delayed match-to-sample performance with face memoranda was disrupted by (congruent) face distracter stimuli, but not (incongruent) scene distracter stimuli. Moreover, signal in DLPFC and connectivity between DLPFC and FFA were selectively perturbed after face distracters (Yoon et al. 2006).

In the current study, we aimed to assess the role of dopamine in distracter-resistance, using an adapted version of the paradigm used by Yoon and colleagues. Pharmacological studies in both animals and humans have assigned an important role for dopamine in working memory (Brozoski et al. 1979; Sawaguchi and Goldman-Rakic 1991; Luciana and Collins 1992; Collins et al. 2000; Gibbs and D'Esposito 2005; Diamond 2007). However, the precise way in which dopamine alters working memory is still unclear. Based on in vitro electrophysiological and computational modeling work, it has been suggested that the effects of dopamine on working memory reflect dopamine-induced increases in the signal-to-noise ratio of neuronal firing in the PFC (Servan-Schreiber et al. 1990), leading to increased stabilization of representations of remembered information and, importantly, increased robustness of these representations in the face of intervening distracters (Durstewitz et al. 2000; Seamans and Yang 2004; Durstewitz and Seamans 2008). Here we test this hypothesis by assessing the effects of dopaminergic drugs on working memory performance and neural working memory representations in the face of distraction. We predicted that dopaminergic drugs would alter distracter-resistance and, following Yoon et al. (2006), that these effects would be accompanied by modulation of delay period signal in the DLPFC as well as of delay period connectivity between DLPFC and FFA.

Empirical data (Sawaguchi and Goldman-Rakic 1991; Wang et al. 2004) and current theories (Seamans and Yang 2004; Durstewitz and Seamans 2008) suggest that the effects of dopamine on working memory are receptor-specific, with D1 and D2 modes of PFC corresponding with enhanced and reduced distracter-resistance, respectively. To assess such receptor-specific effects, we administered both the selective D2-receptor agonist bromocriptine (Kvernmo et al. 2006) as well as the (non-selective) dopamine precursor L-DOPA.

Methods

Subjects

Data analysis was performed on 16 healthy subjects (eight men, mean age 19.8, SD 1.1). Twenty-four subjects were recruited from the University of California Berkeley community and screened following a similar procedure used previously (Cools et al. 2007). All subjects gave written informed consent and were compensated for their participation. This study was approved by the Committee for the Protection of Human Subjects at the University of California Berkeley.

From the 24 subjects who participated in the study, eight were excluded due to scanner problems, head movement, or abnormal performance on the task, leading to our final sample of 16 subjects, included in the analysis (Supplementary Material).

Our original aim had been to assess dopaminergic drug effects as a function of trait impulsivity, to certify prior findings showing that dopaminergic drug effects are more pronounced in high-impulsive subjects (Cools et al. 2007). For that reason, subjects on both ends of the Barratt Impulsiveness Scale (Patton et al. 1995) were selected; high-impulsive subjects had a Barratt score between 77 and 87 and a mean score of 81, and low impulsive subjects had a Barratt score between 44 and 54 and a mean score of 50. Unfortunately, the size of our final sample (nine low and seven high-impulsive subjects) did not allow us to assess impulsivity-dependent effects. Accordingly, we report effects irrespective of trait impulsivity.

General procedure

Subjects were invited to visit the Helen Wills Neuroscience Institute on four sessions: on the first screening session, they were interviewed for suitability, administered background neuropsychological tests, and explained the procedure. On the remaining sessions, subjects were scanned, after oral

intake of a lactose placebo, the dopamine receptor agonist bromocriptine (1.25 mg), or the dopamine precursor L-DOPA (100 mg with 25 mg carbidopa), according to a double-blind, crossover design (Supplementary Material).

Experimental paradigm

Subjects performed a modified version of a three-item delayed match-to-sample working memory task while being scanned (Fig. 1). They were instructed to encode three face stimuli and make a match/non-match discrimination on the probe stimulus. The probe matched one of the cues 50 % of the time. In the middle of the delay period, a distracter stimulus, either a face or scene, was presented. Thus, the delay period was separated into two components, pre- and post-distraction. When a distracter stimulus was presented, subjects had to indicate whether the distracter stimulus was one of two pre-learned targets. This was the case on one out of three trials.

The design included two trial types of interest: cue/distracter congruent (i.e., face distracter) and cue/distracter incongruent (i.e., scene distracter) trials. Furthermore, the design included a trial type of no interest. In this trial type, the images in the encoding, distracter, and probe phase were scrambled images. Subjects had to press any button during the "distracter" and the "probe" phase to match conditions for motor demands. This trial type was inserted to provide an interpretable baseline condition. It was not included in our contrasts of interest, which compared different working memory conditions with distinct levels of distraction. Subjects were presented with an equal number of trials for each of the three conditions. The task was scanned in six runs of 18 trials each.

Localizer task

In addition to the delayed match-to-sample task, subjects performed a one-back task using alternating blocks of face, scene, objects, and scrambled stimuli to localize the FFA (Kanwisher et al. 1997) (Supplementary Material).

Behavioral data analysis

Reaction times and error rates were calculated for the face distracter and scene distracter conditions separately. Subjects who had (1) a response count less than 80 % or (2) had error rates above 50 % on one of the conditions on either the distracter or probe task were excluded from analysis (final sample $n=16$). For the reaction time analysis, the first trial of each run was excluded as well as trials with an incorrect response on either the distracter or probe task. In addition, trials following an incorrect probe trial were excluded to avoid a potential bias across trial types in the reaction time data owing to differential rates of "post-error slowing" (Rabbit 1966). A drug (3)×distracter (2) repeated measures ANOVA was performed on mean reaction times and error rates on the probe task. The critical measure of interest, the distracter cost, was defined as error rates on face distracter trials minus error rates on scene distracter trials. Note that this measure reflects a "relative" distracter cost that was chosen based on previous

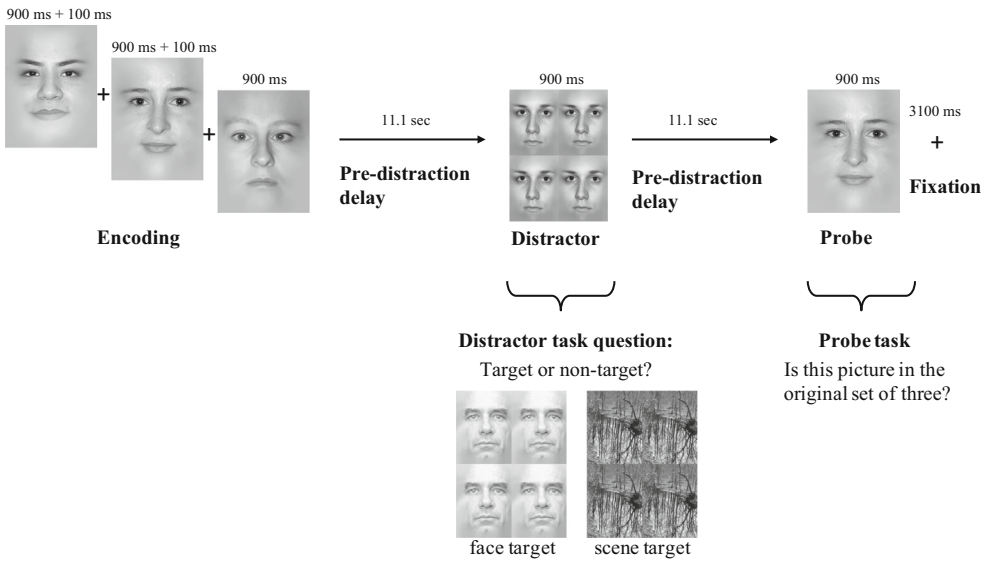

Fig 1 Schematic diagram of the delayed match-to-sample working memory task. During the encoding phase (duration 2.9 s), subjects were presented with three face stimuli (sequentially). After an 11.1-s delay period, they were shown a face or scene distracter (duration 0.9 s). Subjects pressed a right or left button to indicate whether this stimulus matched a pre-learned target face or scene. After another delay period of 11.1 s, the probe stimulus appeared and the subject made a left/right button press to indicate whether this probe stimulus matched one of the encoded stimuli. Thus, two responses were recorded per trial: one for the delayed response task at probe and one for the distracter target detection task

literature showing that congruent distracters are more distracting than incongruent distracters (e.g., Yoon et al. 2006). Next, we calculated the drug effect on the distracter cost (distracter $cost_{drug}$ − distracter $cost_{placebo}$) and used this measure for brain–behavior correlations.

MRI data acquisition and analysis

Whole-brain functional images and a T1-weighted anatomical scan were obtained on a Siemens 3-T MR scanner (for scanning parameters, see Supplementary Material). fMRI preprocessing was conducted using SPM8 (Statistical Parametric Mapping, Wellcome Trust Centre for Cognitive Neuroimaging, London, UK). Data was visually inspected for spikes and signal stability. Slice timing correction was performed using the first slice as a reference slice. Anatomical images were spatially coregistered to the mean of the functional images and normalized using a unified segmentation approach. These normalization parameters were then applied to the functional images that were spatially smoothed using a Gaussian kernel (8 mm full-width at half-maximum).

In a general linear model, we included 15 regressors of interest, five for each of the three trial types: face distracter trials, scene distracter trials, and scrambled trials. The five task phases were modeled at the onset of stimulus (encoding, distracter, and probe) or in the middle of the delay period (pre-distraction and post-distraction delay periods). This approach minimizes the contamination of the delay period covariate by residual cue period signal and has been used to successfully model delay period signal in numerous published studies (Postle et al. 2000; Pessoa et al. 2002; Barde and Thompson-Schill 2002; Druzgal and D'Esposito 2003; Curtis et al. 2004; Ranganath et al. 2004). Thus, to minimize collinearity between temporally adjacent regressors, the delay period was not modeled as a boxcar function beginning immediately after the offset of the cue stimulus and extending until the onset of the probe stimulus. Rather, care was taken to ensure that the onsets of temporally adjacent regressors were spaced at least 4 s apart (Zarahn et al. 1997). All regressors of interest were modeled as delta functions and convolved with a canonical hemodynamic response function. In addition, the six realignment parameters were modeled as regressors of no interest. Time series were high-pass filtered using 128 s cut-off. Parameter estimates for the regressors of interest, derived from the mean least-squares fit of the model to the data, were estimated at the (subject-specific) first level and were used in a second-level random effects analysis.

This study aimed to find a link between dopaminergic drug effects on behavioral distracter-resistance and concurrent effects on brain signal. We found no effect of L-DOPA on behavior. Therefore, we decided to focus our fMRI analyses on the bromocriptine versus placebo contrast, which revealed a behavioral effect. Nevertheless, for completeness, we conducted supplementary analyses to compare the L-DOPA and placebo sessions, from which we report analogous contrasts. The effect of bromocriptine on BOLD signal was assessed at the voxel level, corrected for multiple comparisons in our search volumes (see below) ($p_{fwe}<0.05$). We predicted that bromocriptine would alter the effect of face versus scene distracters on delay period signal. Accordingly, we assessed drug×distracter interaction effects on post-distraction delay period signal. We assessed this interaction on a whole brain level as well as within those regions that exhibited signal during the pre-distraction delay. To select these regions, a volume of interest (VOI) was selected from the second-level contrast representing the pre-distraction delay period (averaged across face distracter and scene distracter conditions and placebo and bromocriptine drug sessions). A lenient threshold was used to identify such delay period signal (height threshold $p<0.05$ uncorrected for multiple comparisons, extent threshold 25 voxels), but it should be noted that this procedure did not bias our subsequent statistical test of interest (drug × distraction on post-distraction delay signal). Specifically, it should be noted that the VOI is independent because the selection is based on a main effect (face distracter and scene distracter conditions across drug sessions) and we test for an interaction effect (drug × distracter). In addition, the VOI was selected from a separate (independent) task phase. This selection procedure revealed 15 clusters across the brain, which were combined into a single VOI (for a list of clusters and graphical overview of the pre-distracter VOI see Supplementary Material). In addition to assessing the drug× distracter interaction across all subjects, we also assessed a brain–behavior correlation for the same interaction.

For illustration purposes, we display for each phase of the task the main effects of task (i.e., collapsed across face distracter and scene distracter conditions and placebo and bromocriptine drug sessions), at a threshold of $p<0.001$ or $p<0.05$ uncorrected.

PPI analysis

Functional connectivity during the post-distraction delay period was assessed using psycho-physiological interaction (PPI) analysis. Individual DLPFC seed regions were based on coordinates of the DLPFC cluster that exhibited a significant brain–behavior correlation (see "Results" and Supplementary Material). Time series were extracted from these individual seed regions and multiplied by a vector coding for the experimental conditions (face distracter condition minus scene distracter condition) to obtain the PPI. On the subject level, we included the PPI as a regressor of interest in a general linear model. The experimental condition and the extracted time series were modeled as additional regressors of no interest in order to assess the PPI estimates in the brain

over and above shared functional activation and task-independent correlations in BOLD signal between the seed and other regions. This approach ensures that any obtained PPI results are independent of univariate results. The extracted time series (deconvolved in SPM) and experimental condition regressors were convolved with a canonical hemodynamic response function and high-pass filtered (128 s). In addition, the six realignment parameters were modeled. The PPI analysis was performed for the drug sessions separately.

As described in the "Introduction", we predicted that dopaminergic drug effects on distracter-resistance would be accompanied by drug effects on PFC–FFA connectivity. Because of large individual variation in the anatomical location of the FFA, it can be challenging to find whole brain effects at the group level. Therefore, we defined VOIs for the FFA individually using an independent localizer task conform prior studies (Kanwisher et al. 1997; Gazzaley et al. 2004; Yoon et al. 2006) (for details see Supplementary Material). Beta values were extracted from these individual VOIs and tested for bromocriptine-induced changes in PFC–FFA connectivity using a paired *t* test. This analysis effectively tests for a drug×distracter interaction, similar to the univariate analysis, because the contrast face minus scene distracter condition was already included in the PPI analysis. In addition to the VOI analysis, we performed an exploratory whole-brain PPI analysis, again using the DLPFC as a seed.

Results

Behavioral results

An initial omnibus ANOVA of error rates with three drug levels (L-DOPA, bromocriptine, and placebo) failed to reveal the predicted interaction effect between drug and distracter ($F_{2,30}=1.52$; $p=0.24$). Subsequent ANOVA with two drug levels (bromocriptine and placebo), however, did reveal a significant interaction effect between drug and distracter ($F_{1,15}=5.39$; $p=0.04$), which was due to bromocriptine significantly increasing the face (vs. scene) distracter cost compared with the placebo condition ($t_{(15)}=2.3$, $p=0.04$). There was also a main effect of distracter ($F_{1,15}=6.62$; $p=0.02$). Across drug conditions, more errors were made in the congruent (face) condition than in the incongruent (scene) condition. Post hoc *t* tests confirmed that the face (vs. scene) distracter cost did not differ between placebo and L-DOPA ($t_{(15)}=1.0$, $p=0.35$) or between L-DOPA and bromocriptine ($t_{(15)}=0.64$, $p=0.53$) (Fig. 2, Table S1). An ANOVA of reaction times did not reveal any effects.

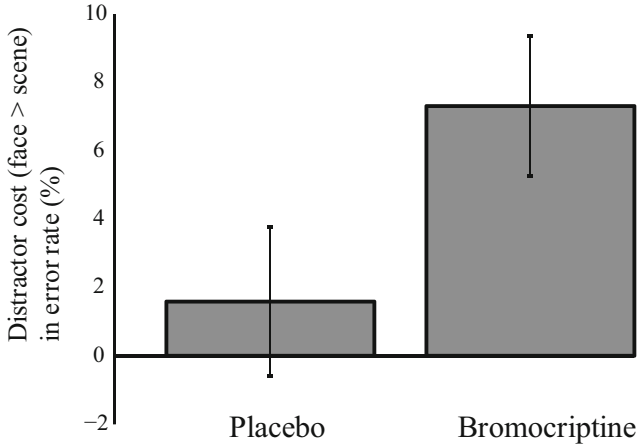

Fig 2 Distracter cost in error rate (face > scene distracters) for each drug condition. *Error bars* represent standard errors of the difference between face and scene distracter conditions

fMRI results

Inspection of the main effects of task (averaged across face distracter and scene distracter conditions and across bromocriptine and placebo drug sessions) revealed the expected network during encoding, distraction, and probe (Fig. 3). As is often reported, our group analyses were somewhat less sensitive to detecting delay period signal, presumably because such delay period signal is more variable between individual subjects than is signal during task periods that are accompanied by visual input (e.g., Druzgal and D'Esposito 2003). As outlined above, we had anticipated that the degree to which post-distracter delay period signal is modulated after distraction would vary as a function of both the type of distraction (face vs. scene) as well as drug. Testing this hypothesis by means of a drug×distracter ANOVA did not reveal any such effects when all subjects were collapsed into one group (whole brain $p_{FWE}<0.05$). Restricting our search volume to the VOI of the pre-distraction delay period also did not show such a drug×distracter interaction. The lack of a drug effect across the group as a whole concurs with many previous studies showing individual differences in dopaminergic drug effects (for review see Cools and D'Esposito 2011; Mehta and Riedel 2006). In fact, regression analysis within the pre-distracter VOI revealed a significant brain–behavior correlation in the left DLPFC ($p_{svc}=0.04$, $T=5.57$, MNI coordinates x, y, $z=-24$ 40 26) (Fig. 4a, encircled region). In this region, a decrease in face- (> scene) related delay period signal after administration of bromocriptine was associated with a greater bromocriptine-induced distraction by faces> scenes (Fig. 4b).

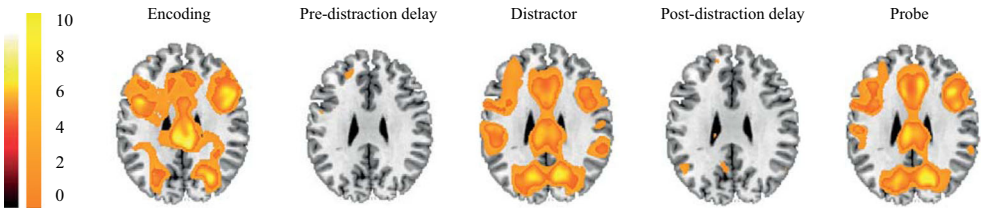

Fig 3 Main effect of task for all task phases; encoding, pre-distraction delay, distracter (face and scene), post-distraction delay, and probe. For all task phases, T-maps are thresholded at $p=0.001$ uncorrected (smaller network in the red to yellow gradient, *left bar* in the legend) and $p=0.05$ uncorrected (more widespread network in the orange gradient, *right bar* in the legend)

Similar analyses for L-DOPA-induced effects showed no results at the whole brain level or the VOI level.

Connectivity results

Psycho-physiological interaction analyses revealed, similar to the univariate analyses, significant brain–behavior associations. Specifically, there was a negative correlation between drug-related changes in the distracter cost and drug-related changes in post-distraction delay-related connectivity between the DLPFC and the FFA (VOI analyses within the individually defined FFA—$r=-0.62$; $p=0.01$). In other words, a decrease in face- (> scene-) related DLPFC–FFA connectivity after administration of bromocriptine was accompanied by greater bromocriptine-induced increases in the face (> scene) distracter cost. Thus, the effect on connectivity resembled the effect on DLPFC signal (Fig. 5a, bottom). Similar to the univariate results, we found no main effect of drug on DLPFC–FFA connectivity (individual VOIs), and there was no significant DLPFC–FFA connectivity when the placebo or bromocriptine sessions were assessed separately. Therefore, we conducted exploratory whole-brain analyses. These did reveal an effect of bromocriptine on connectivity between the DLPFC and the visual association cortex (Brodmann area 17) across the group as a whole (Fig. 5b, top, $p=0.001$ uncorrected for multiple comparison). Thus, bromocriptine increased face- (> scene-) related connectivity between the DLPFC and the visual association cortex. Simple effects analyses revealed that there was no significant connectivity between DLPFC and FFA under placebo or bromocriptine separately. Critically, as in the individually localized FFA ROIs, a negative correlation ($r=-0.69$ $p=0.005$) was seen between the drug effect on connectivity and the drug effect on behavior (Fig. 5b, bottom).

Thus, both ROI and whole-brain analysis of brain–behavior correlations confirmed that individual differences in the drug effect on behavior were associated with individual differences in the drug effect on DLPFC–FFA connectivity. Bromocriptine increased face- (> scene-) related delay-period connectivity in subjects who were not affected by bromocriptine behaviorally. Conversely, bromocriptine did not increase face- (> scene-) related connectivity in subjects where bromocriptine increased distracter vulnerability.

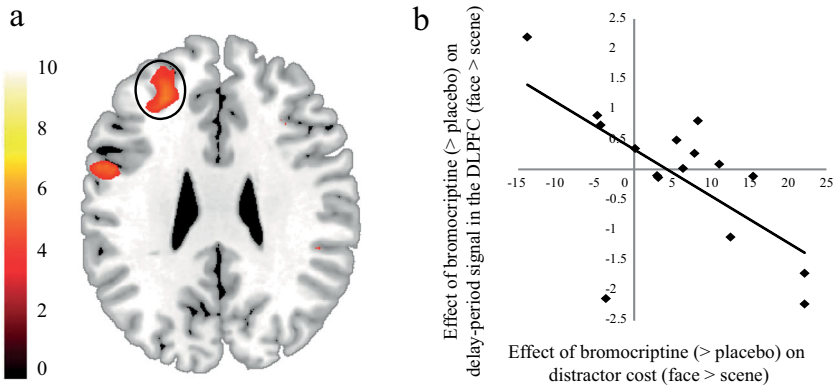

Fig 4 Brain–behavior correlation. **a** Whole-brain results of a regression analysis between drug effects on behavioral distracter cost and drug effects on neural distracter cost. The *bar* indicates *T* values and figures are thresholded for a *T* value of 3.79, corresponding to a *p* value of 0.001 uncorrected for multiple comparisons. **b** Data were extracted and plotted from the peak voxel in the DLPFC cluster that was found in the whole-brain correlation analysis (encircled in **a**) for illustrative purposes. Only the DLPFC cluster revealed a significant brain–behavior correlation when correcting for multiple comparisons across the VOI (see "Methods")

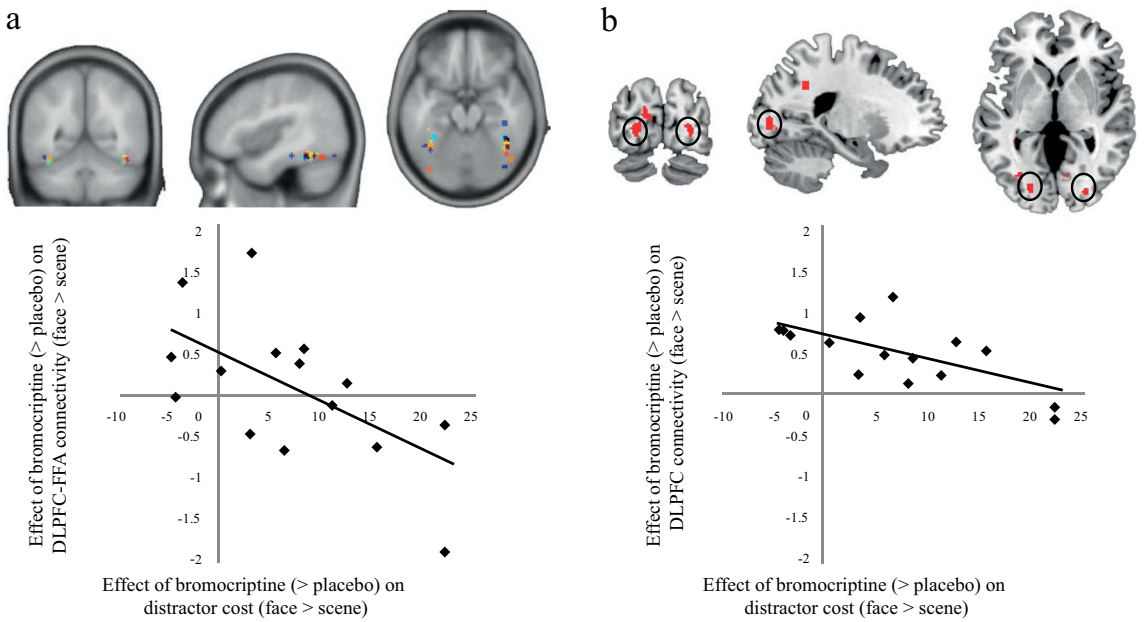

Fig 5 **a** *Top panel*: localizer-based individual FFA VOIs (see Supplementary Material); *bottom panel*: correlation between drug effects on DLPFC and individual FFA VOI connectivity during the post-distraction delay phase as a function of distracter (face > scene) and drug effect on the behavioral distracter cost (face > scene). **b** *Top panel*: effect of bromocriptine (> placebo) on connectivity (whole-brain) with the DLPFC; *bottom panel*: brain–behavior correlation. Data extracted from the encircled region (visual association cortex)

Discussion

The present study provides empirical evidence for an important role for dopamine in distracter-resistance in humans. The dopamine D2 receptor agonist bromocriptine modulated behavioral distracter-resistance, and this was accompanied by changes in prefrontal BOLD signal. This finding is in line with experimental animal and human work showing that dopamine acts on the PFC to modulate working memory (Brozoski et al. 1979; Sawaguchi and Goldman-Rakic 1991; Mattay and Tessitore 2002; Cools et al. 2002; Gibbs and D'Esposito 2005). Here we significantly extend this prior work by showing that distracter-resistance might be one mechanism by which dopamine alters working memory.

Our finding concurs with theoretical models suggesting that dopamine in the PFC modulates the stability of online working memory representations by changing the signal-to-noise ratio of neuronal firing (Seamans and Yang 2004; Durstewitz and Seamans 2008). According to these models, PFC networks can be in one of two alternative states: a closed state with high neuronal firing in which representations are robust and resistant to distraction, and an open state in which there is a low signal-to-noise ratio with unstable neuronal firing. In an open state, new information can easily interfere with currently active representations, such that these active representations are vulnerable to distraction. The particular state of the PFC has been suggested to depend on the ratio by which dopamine binds to prefrontal D1 versus D2 receptors. When D2 receptor stimulation dominates the PFC, it is in an open state, while a closed state is present when D1 receptor stimulation dominates (Durstewitz and Seamans 2008). Our results are consistent with this model: administration of the D2 receptor agonist bromocriptine decreased distracter-resistance in our subjects. Thus, across subjects, bromocriptine presumably increased prefrontal D2 receptor stimulation, thereby switching the PFC to an open state, in which representations are unstable and vulnerable to distraction. This model might also explain why we did not find effects of the dopamine precursor L-DOPA. An increase in dopamine levels might increase overall dopamine receptor stimulation, but not change the D1/D2 binding ratio, thereby leaving the PFC state unchanged.

The effect of bromocriptine on distracter-resistance also correlated negatively with drug effects on functional PFC–FFA connectivity. Indeed, working memory representations are thought to be maintained through simultaneous activation of a network of regions, rather than activation of the PFC alone. For instance, neuroimaging studies in humans have shown delay period signal in parietal cortex, caudate nucleus, thalamus, and visual cortex (Jha and McCarthy 2000; Gazzaley et al. 2004). Here we focused analyses specifically on the visual association cortex following previous studies showing that connectivity between the PFC and this region predicts behavioral working memory performance (Yoon et al. 2006; Clapp et al. 2010). Future studies might investigate how the network as a whole interacts during working memory maintenance and distraction using more advanced connectivity analyses such as dynamic causal modeling.

The effect of bromocriptine on the behavioral distracter cost, which was significant when analyzed across the whole group of subjects, was not accompanied by supra-threshold neural effects across the group as a whole. Instead, a significant neural effect was revealed only when taking into account individual differences in the behavioral drug effects. Indeed, in some subjects, bromocriptine did not increase but rather decreased the distracter cost (Figs. 4 and 5). In these subjects, face- versus scene-distracter-related DLPFC signal and connectivity was not decreased but rather enhanced by bromocriptine. The presence of individual differences is perhaps less surprising when considering accumulating evidence that there is large individual variability in drug effects, which at least in part reflects individual variability in baseline levels of dopamine (Cools et al. 2007; Cools et al. 2009; Cools and D'Esposito 2011; Floresco 2013). Thus, bromocriptine might have opposite effects in subjects with sub- versus supra-optimal baseline levels of dopamine, with bromocriptine acting predominantly at post- versus presynaptic D2 receptors, leading to a net increase versus decrease in receptor stimulation, respectively. As such, bromocriptine might push performance towards versus away from an optimal D2 state in subjects with sub- versus supra-optimal baseline levels of dopamine.

Exploratory whole-brain connectivity analyses strengthened our observation from the connectivity analyses within the individually defined localizer FFAs that the correlation between drug effects on connectivity and drug effects on behavioral distractibility was negative. However, it also highlighted that in most subjects bromocriptine in fact increased connectivity. Bromocriptine increased face-related connectivity to a greater extent in subjects who were less affected by bromocriptine behaviorally. Conversely, bromocriptine did not increase face-related connectivity in subjects where bromocriptine increased distracter-vulnerability. Together, these findings suggest that drug-induced increases in face-related BOLD signal in the DLPFC and in face-related connectivity between the DLPFC and the FFA (more generally visual association cortex) protected against drug-induced distraction by faces.

We had hypothesized that bromocriptine would increase distracter vulnerability of working memory representations by reducing the robustness of (and thus disrupting) delay-period activity in prefrontal cortex. Our observation that bromocriptine increased rather than decreased connectivity across the group as a whole does not seem consistent with this hypothesis. However, one possibility is that our univariate analysis approach with its focus on persistent delay-period activity was not appropriate for measuring neural patterns in prefrontal cortex that encode stable working memory representations. Indeed, recent work indicates that the neural patterns of stable working memory representations might well be spatially distributed and varying across time, thus detectable only using multivariate pattern classification techniques (Sreenivasan et al. 2014). Accordingly, any disruptive effect of bromocriptine on prefrontal representations might have gone unnoticed. Instead, our approach might have been more optimized for measuring (effects of bromocriptine on) cognitive control processes in prefrontal cortex that are key for protecting against distraction. In future work, multivariate analysis techniques might be employed to assess whether the observed effects of bromocriptine on protective prefrontal control processes are accompanied by disruptive effects on (multivariate) prefrontal working memory representations.

A number of caveats should be noted. First, bromocriptine increased the behavioral distracter cost by decreasing error rate in the incongruent (scene) condition rather than by increasing error rate in the congruent (face) condition (Table S1). Here we would like to point out that task-specific drug effects are best interpretable in terms of difference scores rather than absolute scores. Thus, it is well possible that the drug also had non-specific effects, for example on vigilance or motivation, leading to an overall global performance improvement. Such a global improvement could be superimposed on a more task-selective (i.e., distracter-dependent) impairment, which would then surface as a selective improvement on the control trial type rather than a selective impairment on the experimental trial type. For this reason, and following many other studies, we here focused on drug effects on the relative measure (i.e., face vs. scene, referred to as distracter cost) which controls for such non-specific effects. A second caveat of the present study is that we failed to replicate previous research showing that dopaminergic drug effects were most pronounced in high-impulsive subjects (Cools et al. 2007). We were not able to replicate this finding here, probably because our sample sizes for the low- and high-impulsive groups were too small. In fact, supplementary analyses revealed that the results presented in this paper were mostly driven by subjects in the high-impulsive group, although the full interaction did not reach significance.

In addition, in contrast to previous findings (Jha et al. 2004; Yoon et al. 2006), we did not find a significant face (vs. scene) distracter cost in the placebo condition. Thus, after placebo, subjects showed no differences in performance between the face and scene condition. Although we do not have a good account of this lack of sensitivity in some of our subjects, we speculate that this might reflect individual variability in the existence of compensatory/complementary systems that can help protect against distractibility.

Finally, we also note that we cannot make definitive claims about the D2 receptor selectivity of the observed effect. Although bromocriptine is a D2 receptor agonist, it also has low affinity for D1, D3, D4, noradrenalin, and serotonin receptors (Kvernmo et al. 2006). This means that bromocriptine might have also exerted its effects via other receptor types. Nevertheless, bromocriptine has the highest affinity for D2

receptors (Seeman and van Tol 1994), and as such, our results concur with theoretical predictions as described above. To conclusively assess receptor specificity, future work might assess whether D2 antagonists, e.g., sulpiride or haloperidol, show opposite effects on distracter-resistance. A design in which subjects are pre-treated with a D1 or D2 receptor antagonist can also be used to assess effects of D2 receptors specifically.

In conclusion, the present study supports the hypothesis that dopamine-induced changes in working memory performance reflect changes in distracter-resistance of working memory representations. In addition, it establishes an important role for the prefrontal cortex and its connectivity with stimulus-specific visual regions in posterior cortex in this effect of dopamine on distracter-resistance. Bromocriptine modulated delay period PFC signal and connectivity with visual areas possibly reflecting a compensatory and/or protective effect on prefrontal regions that are key for protection against distraction.

Funding and disclosure The authors declare no conflict of interest. This work was supported by the National Institute of Health (R01-DA20600 to M.D.), Niels Stensen foundation to E.A., a Dorothy Hodgkin research fellowship of the Royal Society of the UK to R.C., a Human Frontiers Science Program grant to R.C., a Vidi grant of the Netherlands Organisation for Scientific Research (NWO) to R.C., and a James McDonnell scholar award to R.C. R.C. has been a consultant to Abbott Laboratories, but she is not an employee or a stock shareholder.

References

Barde LHF, Thompson-Schill SL (2002) Models of functional organization of the lateral prefrontal cortex in verbal working memory: evidence in favor of the process model. J Cogn Neurosci 14:1054–1063. doi:10.1162/089892902320474508

Brozoski T, Brown R, Rosvold H, Goldman P (1979) Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. Science 205(80):929–932

Chao LL, Knight RT (1995) Human prefrontal lesions increase distractibility to irrelevant sensory inputs. Neuroreport 6:1605–1610

Clapp WC, Rubens MT, Gazzaley A (2010) Mechanisms of working memory disruption by external interference. Cereb Cortex 20:859–872. doi:10.1093/cercor/bhp150

Collins P, Wilkinson LS, Everitt BJ et al (2000) The effect of dopamine depletion from the caudate nucleus of the common marmoset (*Callithrix jacchus*) on tests of prefrontal cognitive function. Behav Neurosci 114:3–17

Cools R, D'Esposito M (2011) Inverted-U-shaped dopamine actions on human working memory and cognitive control. Biol Psychiatry 69: e113–e125. doi:10.1016/j.biopsych.2011.03.028

Cools R, Frank MJ, Gibbs SE et al (2009) Striatal dopamine predicts outcome-specific reversal learning and its sensitivity to dopaminergic drug administration. J Neurosci 29:1538–1543. doi:10.1523/JNEUROSCI.4467–08.2009

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. J Neurosci 27: 5506–5514. doi:10.1523/JNEUROSCI.0601-07.2007

Cools R, Stefanova E, Barker RA et al (2002) Dopaminergic modulation of high-level cognition in Parkinson's disease: the role of the prefrontal cortex revealed by PET. Brain 125:584–594. doi:10.1093/brain/awf052

Curtis CE, Rao VY, D'Esposito M (2004) Maintenance of spatial and motor codes during oculomotor delayed response tasks. J Neurosci 24:3944–3952. doi:10.1523/JNEUROSCI.5640–03.2004

Diamond A (2007) Consequences of variations in genes that affect dopamine in prefrontal cortex. Cereb Cortex 17(Suppl 1):i161–i170. doi:10.1093/cercor/bhm082

Druzgal TJ, D'Esposito M (2003) Dissecting contributions of prefrontal cortex and fusiform face area to face working memory. J Cogn Neurosci 15:771–784. doi:10.1162/089892903322370708

Durstewitz D, Kelc M, Güntürkün O (1999) A neurocomputational theory of the dopaminergic modulation of working memory functions. J Neurosci 19:2807–2822

Durstewitz D, Seamans JK (2008) The dual-state theory of prefrontal cortex dopamine function with relevance to catechol-o-methyltransferase genotypes and schizophrenia. Biol Psychiatry 64:739–749. doi:10.1016/j.biopsych.2008.05.015

Durstewitz D, Seamans JK, Sejnowski TJ (2000) Dopamine-mediated stabilization of delay-period activity in a network model of prefrontal cortex. J Neurophysiol 83:1733–1750

Feredoes E, Heinen K, Weiskopf N, et al. (2011) Causal evidence for frontal involvement in memory target maintenance by posterior brain areas during distracter interference of visual working memory. PNAS. doi: 10.1073/pnas.1106439108

Floresco SB (2013) Prefrontal dopamine and behavioral flexibility: shifting from an "inverted-U" toward a family of functions. Front Neurosci 7:62. doi:10.3389/fnins.2013.00062

Fuster JM, Alexander G. (1971) Neuron activity related to short-term memory. Science (80) 652–654.

Gazzaley A, Rissman J, D'Esposito M (2004) Functional connectivity during working memory maintenance. Cogn Affect Behav Neurosci 4:580–599

Gibbs SEB, D'Esposito M (2005) A functional MRI study of the effects of bromocriptine, a dopamine receptor agonist, on component processes of working memory. Psychopharmacology (Berl) 180:644–653. doi:10.1007/s00213-005-0077-5

Jacobsen CF (1936) Studies of Cerebral Function in Primates. Psychol, Comp

Jha AP, Fabian SA, Aguirre GK (2004) The role of prefrontal cortex in resolving distractor interference. Cogn Affect Behav Neurosci 4: 517–527

Jha AP, McCarthy G (2000) The influence of memory load upon delay-interval activity in a working-memory task: an event-related functional MRI study. J Cogn Neurosci 12(Suppl 2):90–105. doi:10.1162/089892900564091

Kanwisher N, McDermott J, Chun MM (1997) The fusiform face area: a module in human extrastriate cortex specialized for face perception. J Neurosci 17:4302–4311

Kvernmo T, Härtter S, Burger E (2006) A review of the receptor-binding and pharmacokinetic properties of dopamine agonists. Clin Ther 28:1065–1078. doi:10.1016/j.clinthera.2006.08.004

Luciana M, Collins P (1992) Dopaminergic modulation of working n memory for spatial but not object cues in normal humans. J Cogn Neurosci 330–347

Malmo RB (1942) Interference factors in delayed response in monkeys after removal of frontal lobes. J Neurophysiol 5:295–308

Mattay V, Tessitore A (2002) Dopaminergic modulation of cortical function in patients with Parkinson's disease. Ann Neurol 51:156–164. doi:10.1002/ana.10078

Mehta MA, Riedel WJ (2006) Dopaminergic enhancement of cognitive function. Curr Pharm Des 12:2487–2500

Miller EK, Cohen JD (2001) An integrative theory of prefrontal cortex function. Annu Rev Neurosci 24:167–202. doi:10.1146/annurev.neuro.24.1.167

Miller EK, Erickson CA, Desimone R (1996) Neural mechanisms of visual working memory in prefrontal cortex of the macaque. J Neurosci 16:5154–5167

Patton JH, Stanford MS, Barratt ES (1995) Factor structure of the Barratt impulsiveness scale. J Clin Psychol 51:768–774

Pessoa L, Gutierrez E, Bandettini P, Ungerleider L (2002) Neural correlates of visual working memory: fMRI amplitude predicts task performance. Neuron 35:975–987

Postle BR, Zarahn E, D'Esposito M (2000) Using event-related fMRI to assess delay-period activity during performance of spatial and nonspatial working memory tasks. Brain Res Brain Res Protoc 5:57–66

Rabbit P (1966) Errors and error correction in choice-response tasks. J Exp Psychol 71:264–272

Ranganath C, Cohen MX, Dam C, D'Esposito M (2004) Inferior temporal, prefrontal, and hippocampal contributions to visual working memory maintenance and associative memory retrieval. J Neurosci 24:3917–3925. doi:10.1523/JNEUROSCI.5053-03.2004

Sawaguchi T, Goldman-Rakic PS (1991) D1 dopamine receptors in prefrontal cortex: involvement in working memory. Science 251(80):947–950

Seamans JK, Yang CR (2004) The principal features and mechanisms of dopamine modulation in the prefrontal cortex. Prog Neurobiol 74:1–58. doi:10.1016/j.pneurobio.2004.05.006

Seeman P, van Tol HM (1994) Dopamine receptor pharmacology. TiPS 15:264–270. doi:10.1016/S0072–9752(07)83004–1

Servan-Schreiber D, Printz H, Cohen JD (1990) A network model of catecholamine effects: gain, signal-to-noise ratio, and behavior. Science 249(80):892–895

Sreenivasan KK, Curtis CE, D'Esposito M (2014) Revisiting the role of persistent neural activity during working memory. Trends Cogn Sci 18:82–89. doi:10.1016/j.tics.2013.12.001

Wang M, Vijayraghavan S, Goldman-Rakic PS (2004) Selective D2 receptor actions on the functional circuitry of working memory. Science 303(80):853–856. doi:10.1126/science.1091162

Yoon JH, Curtis CE, D'Esposito M (2006) Differential effects of distraction during working memory on delay-period activity in the prefrontal cortex and the visual association cortex. Neuroimage 29:1117–1126. doi:10.1016/j.neuroimage.2005.08.024

Zarahn E, Aguirre G, D'Esposito M (1997) A trial-based experimental design for fMRI. Neuroimage 6:122–138. doi:10.1006/nimg.1997.0279