Dopaminergic Modulation of Cognitive Control: Distinct Roles for the Prefrontal Cortex and the Basal Ganglia

Article *in* Current Pharmaceutical Design · April 2010

DOI: 10.2174/138161210791293097 · Source: PubMed

3 authors, including:

Martine van Schouwenburg
University of Amsterdam
35 PUBLICATIONS **974** CITATIONS

SEE PROFILE

Esther Aarts
Radboud University
100 PUBLICATIONS **2,682** CITATIONS

SEE PROFILE

Dopaminergic Modulation of Cognitive Control: Distinct Roles for the Prefrontal Cortex and the Basal Ganglia

Martine van Schouwenburg[1,2,*], Esther Aarts[1,2] and Roshan Cools[1,2]

[1]*Radboud University Nijmegen, Donders Institute for Brain, Cognition and Behaviour, Centre for Cognitive Neuroimaging, Kapittelweg 29, 6525 EN, Nijmegen, The Netherlands,* [2]*Radboud University Nijmegen Medical Centre, Department of Psychiatry, Reinier Postlaan 10, 6525 GN, Nijmegen, The Netherlands*

Abstract: Evidence from psychopharmacological functional neuroimaging begins to elucidate the neurochemical mechanisms of cognitive control. Here the role of dopamine in two subcomponent processes of cognitive control is discussed: the active maintenance and the flexible updating of goal-relevant representations. A range of studies have highlighted a role for the prefrontal cortex (pFC) and its modulation by dopamine in the active maintenance of distractor-resistant goal-relevant representations. This work suggests that dopamine might modulate top-down signals from the pFC, thereby increasing the activity of posterior cortical regions that process goal-relevant representations and rendering them distractor-resistant. Conversely, other studies highlight a role for dopamine in the basal ganglia in cognitive switching, which might reflect a modulation of the selective gating of cortical cognitive and motor programs. We present a working hypothesis that integrates these two disparate literatures and states that the flexible adaptation of current goal-relevant representations is mediated by modulatory influences of activity in the dopamine-sensitive basal ganglia on connectivity between the prefrontal cortex and posterior cortex.

Keywords: Working memory, task-switching, pharmacological fMRI, Parkinson's disease.

COGNITIVE CONTROL AND THE ROLE OF THE PREFRONTAL CORTEX

Our environment is changing constantly. However, only some of the changes around us are relevant and require the flexible updating of current cognitive and motor programs. Most other changes are irrelevant and should be ignored. In the latter case adaptive behavior depends on the active maintenance rather than on the flexible updating of current cognitive and motor programs. Here we review studies that begin to elucidate the neurochemical mechanisms that underlie these abilities.

The complex cognitive control processes necessary for adaptive behaviour have been associated most commonly with the anterior part of the brain, the prefrontal cortex (pFC). In particular, the pFC has been reliably implicated in the active on-line maintenance of goal-relevant representations, an ability that is commonly referred to as working memory [1]. The importance of the pFC for working memory was first demonstrated by Jacobsen [2], who showed that monkeys with frontal lobe lesions were impaired on the well-known delayed response task. Subsequent research showed that this deficit was reversed when monkeys were tested in the dark, suggesting that it reflected increased vulnerability to visual distraction [3]. Consistent with a role for the pFC in distractor-resistance were findings from studies with patients with lesions in the pFC, revealing increased distractibility by irrelevant sensory input [4]. Electrophysiological work with monkeys supports this human and non-human primate lesion work by demonstrating that the firing of pFC neurons persists throughout the delay of delayed response tasks [5], even in the face of distraction [6]. Finally, functional magnetic resonance imaging (fMRI) studies with human volunteers have revealed similarly persisting responses in the human pFC during delayed response tasks [7].

What might be the mechanism by which the pFC contributes to the active maintenance of distractor-resistant representations that are relevant for current goals? Desimone & Duncan [8] have proposed the biased competition model of visual attention that speaks to this question. These authors assume that brain regions in posterior cortex, known to process different aspects of our environment (such as V4, V5, the fusiform face area [FFA] and the parahippocampal place area [PPA]), compete with each other via mutually inhibitory interactions. Brain regions in posterior cortex, which process goal-relevant aspects of the environment exhibit higher levels of activity than those with which they share inhibitory interactions. In this model, attention to current goal-relevant representations results from the influence of excitatory top-down signals in the pFC, which bias the competition among brain regions in posterior cortex, increasing the activity of brain regions processing goal-relevant representations and, by virtue of mutual inhibition, suppressing activity of brain regions processing irrelevant representations [9]. Support for the hypothesis that similar mechanisms play a role during working memory tasks comes from fMRI studies, such as that by Gazzaley *et al*. [10]. In this study, subjects were presented a series of four sequentially presented stimuli, two faces and two scenes. They were asked to remember either the faces or the scenes. BOLD responses in the parahippocampal place area (PPA), known to process scenes [11] were increased and suppressed when subjects attended and ignored scenes during working memory encoding respectively. In addition, consistent with the hypothesis that the pFC controls processing in the posterior cortex, connectivity between the pFC and the PPA was significantly enhanced during the encoding of scenes, and suppressed when subjects ignored scenes [10]. This observation that the active maintenance of goal-relevant information is mediated by persistent coactivation of the pFC and posterior cortex is further supported by a recent fMRI study using a delayed response paradigm with distraction [12]. In that study, delayed recognition of faces was disrupted by the presentation of distracting faces during the delay. Critically, this behavioural disruption after distracting faces was accompanied by a perturbation of functional connectivity between the pFC and the FFA during the delay that followed these distractor faces. These data concur with the hypothesis that the pFC supports the online maintenance of goal-relevant information by increasing the activity of brain regions that process goal-relevant representations, and by rendering it resistant to disruption by distracting, goal-irrelevant information.

*Address correspondence to this author at the Radboud University Nijmegen, Donders Institute for Brain, Cognition and Behaviour, Centre for Cognitive Neuroimaging, Kapittelweg 29, 6525 EN, Nijmegen, The Netherlands; Tel: +31 24 3668065; Fax: +31 24 36 10989;
E-mail: martine.vanschouwenburg@donders.ru.nl

1381-6128/10 $55.00+.00

ROLE OF DOPAMINE IN THE PREFRONTAL CORTEX

The pFC is extremely sensitive to its modulation by dopamine (DA), which is not surprising given diffuse ascending inputs from the DA neurons in the midbrain. Unlike classic neurotransmission, which facilitates chemical wiring between neurons by direct influences from one presynaptic neuron onto one postsynaptic partner, this major neuromodulator DA is secreted by a small group of neurons in the midbrain and diffuses through large areas of, primarily the anterior parts of the brain [13]. Brozoski *et al.* [14] provided the first empirical support for a role of DA in working memory by showing that DA and noradrenalin (NA) depletion in the pFC of monkeys impaired delayed response task performance almost to the same degree as did complete ablation of the pFC. Delayed response task performance was also impaired by injection of a DA receptor antagonist (which blocks DA receptors) in the monkey pFC [15], while application of DA and DA receptor agonists (which simulate the effect of endogenous DA on its receptors) to pFC neurons enhanced delayed response task performance [16, 17]. Results from studies with humans are consistent with a role for DA in working memory, showing, for example, that administration of DA receptor agonists and antagonists respectively improved and impaired performance on a working memory task [18, 19]. The importance of the pFC in such dopaminergic modulation of working memory is supported by several fMRI studies showing a modulation by dopaminergic drugs of BOLD signal during working memory tasks, especially in the pFC [20-26]. For example, Willson *et al.* [26] have found a significant effect of dextroamphetamine, which increases both DA and NA levels, on BOLD signal during a working memory task in the dorsolateral pFC, cingulate cortex and insula. Taken together, these data suggest that DA modulates working memory by modulating processing in the pFC. Although the actual mechanism by which DA alters working memory requires further empirical study, hypotheses have been put forward based on *in vitro* electrophysiological and computational modeling work. Specifically, effects of DA on working memory might reflect DA-induced increases in the signal-to-noise ratio of neuronal firing in the pFC [27], leading to increased stabilization of currently goal-relevant representations, and increased robustness of these representations in the face of intervening distractors [28-30]. Pharmacological fMRI studies are in progress to test this hypothesis directly by assessing whether DA receptor stimulation in humans alters the degree to which delay-period activity in the pFC and FFA, measured during a face delayed response task, is perturbed by intervening distractor faces (A. Miyakawa, R. Cools, M. D'Esposito, in preparation).

Although it is clear that working memory depends on DA in the pFC, the precise relationship between DA and working memory is complex and non-linear. An 'inverted U'-shaped relation exists between DA receptor stimulation and working memory with too little as well as excessive DA levels impairing performance [31-33]. Stress, known to increase pFC DA and NA levels, impairs working memory performance in rats and monkeys [34] and this effect of stress can be prevented by pretreatment with a DA receptor antagonist. These data suggest that the detrimental effect of stress on working memory performance is driven, at least partly, by excessive DA receptor stimulation [35]. Further evidence for an 'inverted U'-shaped relationship between DA and working memory performance comes from studies in aged monkeys showing that low doses of a DA receptor agonist improve working memory performance, while higher doses have a detrimental effect on performance [36]. Dose-dependent effects of dopaminergic drugs have also been found on pFC activity in humans [37]. In addition, contrasting effects have been observed in different subgroups of subjects. For example, Kimberg *et al.* [38] found that the DA receptor agonist bromocriptine had opposing effects on cognitive performance in subjects with low versus high working memory capacity, with low capacity subjects benefiting from bromocriptine, but high capacity subjects being impaired by the same drug. Subsequent pharmacological neuroimaging work has shown that these span-dependent behavioral effects can be accompanied by opposite effects on BOLD signals in the pFC [21]. Thus bromocriptine increased pFC signals and impaired performance in high-span subjects, while decreasing pFC signals and improving performance in low-span subjects. Similarly, Mattay *et al.* [24] have found that the effect of dextroamphetamine on the performance on a working memory task and associated neural activity depended on baseline performance on the task. Subjects who had relatively low working memory capacity at baseline improved on dextroamphetamine, while the drug worsened performance in those subjects who had a relatively high working memory capacity at baseline. In a H_2O positron emission tomography (PET) study performed by Mehta *et al.* [25], similar effects were observed after administration of methylphenidate, which increases catecholamine levels; the degree of improvement on a working memory task and associated pFC activity correlated negatively with baseline memory span.

Consistent with the 'inverted U'-shaped relationship between DA and working memory, these span-dependent effects of dopaminergic drugs likely reflect variation as a function of baseline levels of DA. In humans, working memory span was shown to correlate positively with baseline DA synthesis capacity, as indexed by uptake of the radiotracer 6-[^{18}F]fluoro-L-m-tyrosine (FMT) using PET [39, 40]. Furthermore, microdialysis in rats has revealed that performance on a difficult working memory task, which was improved by a DA receptor agonist, was accompanied by low DA levels in the pFC, while performance on an easy task, which was impaired by the drug, was accompanied by high DA levels in the pFC [41, 42]. Finally, evidence for baseline-dependency comes from studies which have made use of common genetic polymorphisms in DA genes to predict dopaminergic drug effects [43, 44]. For example, amphetamine was shown to improve performance on a working memory task and to reduce BOLD signals in the pFC of carriers of the Val allele of the *COMT* Val$^{108/158}$Met genetic polymorphism, which is associated with low baseline DA levels in pFC. By contrast, the same drug impaired performance and increased BOLD signal in subjects who were homozygous for the *Met allele*, which is associated with high baseline DA levels in pFC [43].

COGNITIVE CONTROL AND THE ROLE OF DOPAMINE IN THE BASAL GANGLIA

As reviewed above, DA in the pFC has been implicated in the stabilization and active maintenance of current representations, and in filtering out new input that might be irrelevant to ongoing processing. However, in some cases new input might be relevant. In such cases, we need to shift our attention and existing goal-representations need to be flexibly updated rather than protected. Accumulating evidence indicates that DA is also implicated in the flexible updating of current cognitive as well as motor programs. According to some current theorizing, DA might affect flexible updating not by modulation of pFC processing but rather by modulation of processing in the basal ganglia (BG).

Traditionally, the BG have been associated with the flexible control of movement. The anatomy of the BG is perfectly suited to function as a selective gate, such that it can gate a desired motor command (via the thalamus) to the motor cortex for execution, while simultaneously inhibiting competing motor action plans [45]. Specifically, the tonic inhibitory output of the BG to the thalamus, which prevents it from activating the motor cortex, is focally released by the so-called direct (Go) pathway, while the indirect (NoGo) pathway is thought to further inhibit the remaining thalamic areas involved in competing motor actions. Disruption of this selective gating mechanism might underlie effects of BG dysfunction on motor switching, e.g. in experimental rodents [46, 47] and in Parkinson's disease (PD), which is characterized by

severe DA depletion in the BG [48, 49]. Critically, it has long been recognized that classification of the BG strictly as motor is untenable [50-52] and the role of the BG in the selective gating of motor action programs [45] likely extends to the selective gating of cognitive programs [53]. The BG might provide a mechanism by which currently goal-relevant representations are flexibly updated in response to new input, thus enabling both cognitive as well as motor flexibility.

Empirical evidence supports a role for the BG in the updating of cognitive programs. BOLD signals in the BG have been found to increase during task-switching, attentional set-shifting and reversal learning, processes that require the flexible updating of current goal representations [54-57]. Evidence that the BG are not just activated, but in fact *necessary* for cognitive switching comes from studies with PD patients and patients with focal BG lesions. These patients show deficits on a range of tasks requiring the ability to switch cognitive set [48, 58-62]. Consistent with the importance of DA in the BG for cognitive switching are observations that task-switching is impaired by acute administration of the DA receptor antagonist sulpiride, which blocks primarily D2 receptors that are most abundant in the BG [19]. In keeping with this observation, we have recently found that acute administration of the DA D2 receptor agonist bromocriptine improved task-switching in young healthy volunteers (M. van Holstein, E. Aarts, M. van der Schaaf, M. van Schouwenburg and R. Cools, unpublished observations). Intriguingly, we also found, in the same sample of subjects, that pretreatment with sulpiride blocked the bromocriptine-induced improvement in task-switching, so that performance on switch trials differed no longer from that in the placebo session. These data demonstrate an important role for D2 receptors in cognitive switching and, given abundance of D2 receptors in the BG, provide indirect evidence for an important role of the BG. More direct evidence for the importance of DA in the BG comes from pharmacological neuroimaging work. For example, Cools *et al.* [63] have shown that effects of dopaminergic medication withdrawal during switch trials of a probabilistic reversal learning paradigm in PD patients were restricted to BOLD signal in the BG, and did not extend to BOLD signal in the pFC. Similar selective effects were observed in young healthy volunteers after administration of methylphenidate, which blocks the DA transporter thereby increasing DA levels [64]. Like dopaminergic medication (levodopa and DA receptor agonists) in PD patients, methylphenidate reduced BOLD signal in the BG, and not the pFC during switch trials of the probabilistic reversal learning paradigm (Fig. **1A**). Finally, evidence for an important role of the BG in the dopaminergic modulation of task-switching was also provided by recent genetic imaging data, showing that the modulation of task-switching costs by incentive motivation depended on genetic variation in the DA transporter (Aarts E, Roelofs A, Franke B, Rijpkema M, Fernandez G, Helmich R, Cools R, *et al.* Neuropsychopharmacology (in press) [83]. In this study we made use of a common polymorphism in the DA transporter gene (*DAT1, SLC6A3*), which is thought to affect DA transmission primarily in the BG. Results revealed that carriers of the 9-repeat allele, associated with high DA levels in the BG, exhibited greater decreases of switch-costs when they anticipated being rewarded for correct performance, than did 10-allele homozygotes. Critically, this modulatory effect on task-switching was accompanied by significant modulation of BOLD signal in the BG.

Like drug effects on BOLD signals in the pFC, drug effects on BOLD signals in the BG are highly variable between subjects. For example, in a recent study by Cools *et al.* [65], bromocriptine improved cognitive switching and potentiated BOLD signals in the BG, but only in subjects who scored highly on a self-report measure of trait impulsivity (Fig. **1B**). The enhancing effects of bromocriptine on cognitive switching and associated BG signals were restricted to high-impulsive subjects, while low-impulsive subjects exhibited, if anything, the opposite effect. This observation concurs with findings from another recent study showing that effects of methylphenidate on probabilistic reversal learning were predicted by trait impulsivity, such that high-impulsive subjects benefited most from the drug [66]. Greater cognitive benefits of DA-enhancing drugs in high-impulsive subjects are consistent with methylphenidate's beneficial effects on cognition in attention deficit hyperactivity disorder and might reflect suboptimal baseline levels of DA transmission in high-impulsive subjects [67, 68]. More direct evidence for a relationship between baseline levels of DA in the BG and bromocriptine's effects on flexible updating comes from a recent study, in which we combined neurochemical PET imaging with psychopharmacology [69]. In this study, subjects underwent a PET scan with the radiotracer FMT, a substrate for DA synthesis, with uptake of the tracer reflecting the degree to which DA is synthesized in the BG. Results revealed that the effects of bromocriptine on reversal learning could be predicted from baseline levels of DA synthesis capacity in the BG. Bromocriptine improved reversal learning in subjects with low baseline synthesis capacity, but impaired it in subjects with high baseline synthesis capacity.

In addition to evidencing baseline-dependency, the above reviewed studies also suggest that the effects of DA in the BG might be quite different from those in the pFC. For example, in the study by Cools *et al.* [65], bromocriptine modulated BG signals during cognitive switching, but pFC signals during distractor-resistance in the delay. Specifically, in this study, subjects were shown two faces or two scenes, presented sequentially. They were instructed to memorize either the faces or the scenes depending on the color of a fixation cue. After a delay subjects were presented with either a face or a scene, which they had to categorize as either a match or non-match to the encoding stimuli. Face and scene trials were randomized so that probe performance on switch trials (face-to-scene and scene-to-face) could be compared with performance on non-switch trials (face-to-face and scene-to-scene). Bromocriptine improved switching between faces and scenes, as evidenced by reduced switch costs (measured at probe), and these effects on switching were accompanied by modulation of BOLD signals during switching in the BG. By contrast, no effects were observed in the pFC during switching. Interestingly, although bromocriptine did not modulate pFC signals during switching, it did modulate pFC signals during a different task period: it increased pFC signals during the processing of a distractor stimulus presented during the delay of the task. Therefore, these data demonstrate that the same dopaminergic drug might modulate distinct cognitive functions, i.e. task-switching and distractor-resistance, by acting on dissociable brain regions, i.e. the BG and the pFC respectively. Furthermore, the data might have implications for the interpretation of results from other studies in which more complex paradigms have been employed. For example, effects of dopaminergic drugs on BG signals during complex working memory tasks might reflect modulation of the flexible updating rather than the active maintenance of goal-relevant representations [70].

The hypothesis that the effects of DA in the BG are quite different from DA in the pFC is supported by work on attentional set-switching with non-human primates (here: marmosets). In these studies, animals had to discriminate between two-dimensional stimuli, consisting of shapes as well as lines. Initially they were rewarded for attending to and discriminating according to one of the two dimensions (e.g. shapes) and for ignoring the other dimension (e.g. lines). When it became clear that subjects had formed and could maintain an attentional set, the rule changes, after which they were rewarded for attending to the previously non-rewarded dimension. This critical rule-change required the animals to make an attentional set-switch. DA lesions in the BG impaired switching back to a previously irrelevant attentional set [71], while DA lesions in the pFC actually improved attentional set switching [72]. Furthermore, an adapted version of the paradigm also enabled

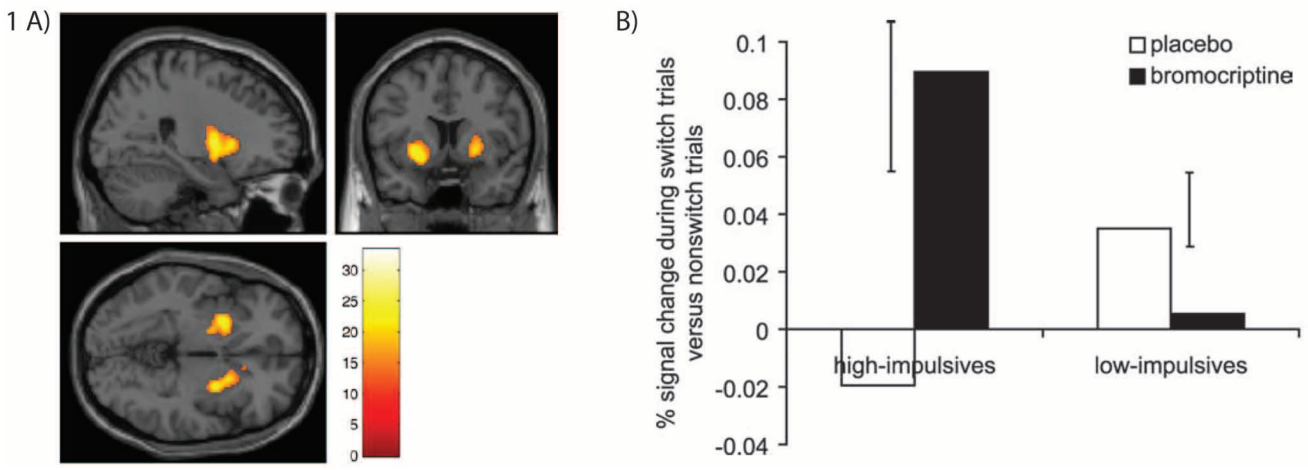

Fig. (1). Dopaminergic drugs modulate BOLD signal in the basal ganglia (BG) during cognitive switching. A) Oral administration of methylphenidate reduced switch-related activity in the BG during switch trials of a probabilistic reversal learning paradigm (Figure thresholded at P <0.05, FDR corrected for multiple comparisons). Figure reproduced with permission from *The Journal of Neuroscience* [64]. Higher intensity values represent a greater methylphenidate-induced *decrease* in BOLD response. The colour scale represents F-values. The right putamen was also activated at the more conservative threshold of $p < 0.05$ FWE corrected.

B) Administration of the dopamine receptor agonist bromocriptine increased BOLD signal in the BG during switch trials of a working memory paradigm requiring attention to faces or scenes. This effect was restricted to high-impulsive subjects with low working memory capacity (associated with low baseline dopamine synthesis capacity) and did not extend to low-impulsive subjects with high working memory capacity (associated with high baseline dopamine synthesis capacity). Figure reproduced with permission from *The Journal of Neuroscience* [65].

the measurement of distractor-resistance. In this adapted version, the experimenter replaced the exemplars of the irrelevant dimension (e.g. lines) while subjects were forming and maintaining attentional set to the relevant dimension (e.g. shapes). DA lesions in marmoset pFC increased distractibility by these changes in the irrelevant dimension during discrimination learning. Conversely, DA lesions in the BG actually reduced distractibility [73]. Thus DA in the pFC might promote cognitive stability by increasing distractor-resistance, while conversely, DA in the BG might promote flexibility, by allowing the updating of newly relevant representations. The observation that DA in the BG has different effects from DA in the pFC is not surprising for a number of reasons. First, effects of a neuromodulator likely depend on the function of the target region that is innervated, and the pFC and the BG are known to subserve distinct cognitive functions. Second, there are differences between the pFC and the BG in terms of receptor distribution, with D2 receptors being abundant in the BG and D1 receptors being abundant in the pFC. Third, the mechanism of action of DA differs between the BG and the pFC. Specifically, there are very few DA reuptake transporters and autoreceptors to rapidly terminate or regulate the phasic action of DA released in the pFC. This is different from the BG where the DA transporter and autoreceptors are abundant. One possible implication of this is that effects of DA on pFC function might be more sustained than those on BG function. The working hypothesis that DA in the pFC and DA in the BG regulate the balance between two functionally opponent processes (stability versus flexibility) concurs with proposals that there is neurochemical reciprocity between DA in the pFC and DA in the BG, with increases and decreases in prefrontal DA being associated respectively with decreases and increases in terms of DA in the BG [74, 75].

INTEGRATING THE DISTINCT ROLES OF THE PREFRONTAL CORTEX AND THE BASAL GANGLIA

So far we have reviewed relatively separate lines of evidence for effects of DA in the domains of working memory, top-down attention and cognitive switching. These separate lines of evidence suggest that the pFC and the BG likely mediate different cognitive effects of DA[1]. Next we aim to integrate evidence from studies on the role of the pFC in working memory and top-down attention with those on the role of DA in the BG in cognitive switching. Specifically, based on the existence of strong anatomical connections between the pFC and the BG [76], we propose that DA in the BG might facilitate cognitive switching by regulating interactions between the pFC and posterior cortex, thus controlling the top-down biasing of competition between goal-relevant and goal-irrelevant representations (Fig. **2**). Evidence for this hypothesis came from a recent fMRI study, in which subjects were instructed to switch their attention as soon as they detected a change in an irrelevant dimension of two-dimensional stimuli. Specifically, on each trial, subjects were presented with two adjacent compound stimuli, each consisting of a face overlapping a scene. They selected one of the two compound stimuli based on one of the two dimensions (faces or scenes). On some trials, exemplars of the unattended dimension were unexpectedly replaced with novel exemplars. These changes elicited an attention switch to the novel exemplars on some trials, but not on other trials. This enabled the comparison of BOLD signals during changes in the environment that elicited an attention switch with signals during changes in the environment that did not elicit an attention switch (van Schouwenburg M, den Ouden H, Cools R, in revision). The results demonstrated that BOLD signals in the BG and the pFC were increased when novel stimuli triggered attention switches. Strikingly, BOLD signal in these regions also increased in response

1 In fact DA's effects on cognitive function can be disentangled at a much finer spatial scale. Distinct ventromedial and dorsolateral parts of the pFC and of the BG are well known to subserve dissociable cognitive functions. Thus DA's effects will also critically depend on where it acts *within* the pFC and *within* the BG. However, this distinction goes beyond the aim of the current review, which we acknowledge provides only one small step towards elucidating the mechanisms underlying the flexible adjustment of behaviour.

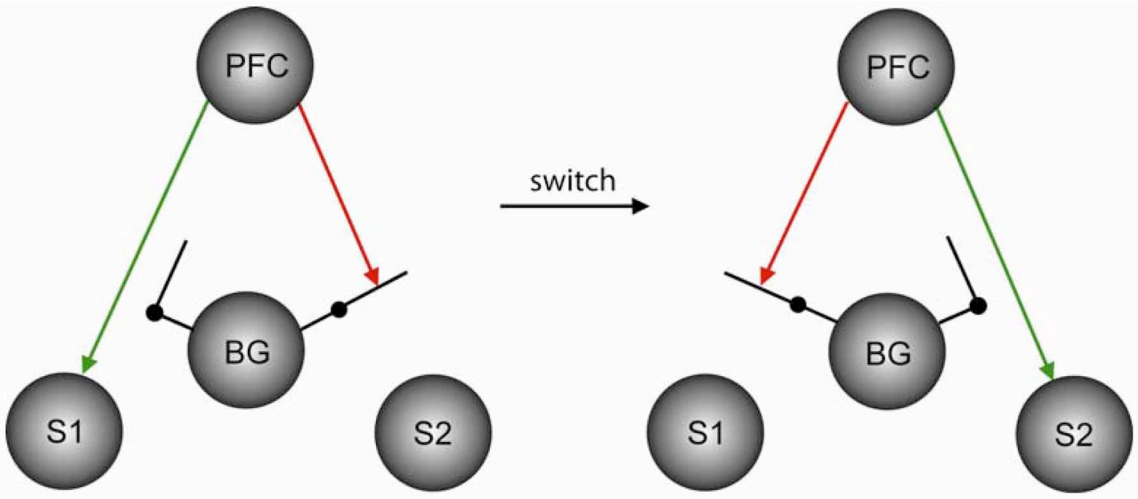

Fig. (2). Schematic illustration of the working hypothesis that the basal ganglia (BG) control cognitive switching by regulating top-down projections from prefrontal cortex (PFC) to posterior sensory areas. The PFC biases information processing in favour of posterior sensory regions that support currently goal-relevant representations (e.g. S1) away from regions that support currently goal-irrelevant representations (e.g. S2). In our model, this top-down control mechanism mediated by the PFC is in turn regulated by the BG, which implement a switch in attention, for example in response to novel salient stimuli, by closing the gate to one region (e.g. S1) while simultaneous opening the gate to another region (e.g. S2).

to novel stimuli that did not elicit flexible attention switching. By contrast, posterior visual regions (including the FFA and the PPA) were silent during novel stimuli that failed to trigger attention switches; these regions responded only when those novel stimuli elicited switches in attention. These data suggest that the BG and the pFC control cognitive switching by modulating the processing of visual information in posterior cortex. Application of nonlinear dynamic causal modeling (DCM) [77] enabled us to disentangle the separate contribution of the pFC and the BG to the control of cognitive switching. As described above, we hypothesized that the BG gate top-down biasing of the pFC on stimulus-specific posterior cortex. Consistent with this prediction, we found that our data was best explained by a model that included a modulatory influence of the BG on connectivity between the pFC and stimulus-specific posterior visual regions. Thus we hypothesize that salient information is processed in the BG, and that a certain salience threshold must be reached for the BG to open a top-down gate from pFC to posterior visual cortex, which, when closed, protects ongoing processing from distracting input (Fig. **2**). A similar mechanism in the BG has been suggested for action selection, where evidence for a certain action accumulates until a threshold is reached, upon which the action is executed [78, 79]. The present data suggest that the BG might play similar roles in the domain of attention and action.

One mechanism by which salient stimuli might influence the selective gating of attention is the regulation of BG activity by DA, which is released in the BG during salient events [80]. DA is thought to increase activity in the direct BG pathway while suppressing activity in the indirect BG pathway, thus lowering the threshold for a response to be executed. This hypothesis is in line with suggestions that short-latency DA signals mediate the switching of attention to unexpected, behaviourally relevant stimuli [81] and concurs with pharmacological functional imaging studies showing that dopaminergic manipulations modulate connectivity between the BG and the pFC during attention switching [82]. An intriguing question for further research is whether the modulatory influence of the BG on fronto-posterior connectivity during the performance of the present paradigm is altered by administration of dopaminergic drugs.

To conclude, we have reviewed evidence for a role of the pFC and its modulation by DA in the active maintenance of distractor-resistant goal-relevant representations. Such a role might reflect modulation of excitatory top-down signals in the pFC, which increase the activity of posterior cortical regions that process goal-relevant representations and, by virtue of mutual inhibition, suppress activity of brain regions that process irrelevant representations. Second, we have reviewed the role of DA in cognitive switching, which might reflect a modulation of a selective gating mechanism triggered by salient stimuli, leading to changes in stimulus-driven release of cortical cognitive and motor programs. Our working hypothesis integrates these two hitherto disparate literatures and states that the flexible adaptation of current goal-relevant representations in response to salient stimuli is mediated by modulatory influences of activity in the DA-sensitive BG on connectivity between the pFC and stimulus specific posterior visual regions. Future studies should provide further evidence in support of this working hypothesis.

ACKNOWLEDGEMENTS

RC and MvS were supported by a VIDI grant to RC from the Innovational Research Incentives Scheme of the Netherlands Organization for Scientific Research (NWO).

REFERENCES

[1] Baddeley AD. Working Memory. Oxford: Clarendon Press 1986.
[2] Jacobsen C. Studies of cerebral functions in primates. Comp Psychol Monographs 1936; 13: 1-60.
[3] Malmo R. Interference factors in delayed response in monkeys after removal of frontal lobes. J Neurophysiol 1942; 5: 295-308.
[4] Chao L, Knight R. Human prefrontal lesions increase distractibility to irrelevant sensory inputs. NeuroReport 1995; 6(12): 1605-10.
[5] Fuster J, Alexander G. Neuron activity related to short-term memory. Science 1971; 173: 652-4.
[6] Miller E, Erikson C, Desimone R. Neural mechanisms of visual working memory in prefrontal cortex of the macaque. J Neurosci 1996; 16: 5154-67.
[7] Curtis C, D'Esposito M. Persistent activity in the prefrontal cortex during working memory. Trends Cogn Sci 2003; 7(9): 415-23.
[8] Desimone R, Duncan J. Neural mechanisms of selective visual attention. Annu Rev Neurosci 1995; 18: 193-222.
[9] Miller E, Cohen J. An integrative theory of prefrontal cortex function. Annu Rev Neurosci 2001; 24: 167-202.
[10] Gazzaley A, Rissman J, Cooney J, Rutman A, Seibert T, Clapp W, *et al.* Functional interactions between prefrontal and visual

association cortex contribute to top-down modulation of visual processing. Cereb Cortex 2007; 17 (Suppl 1): i125-35.
[11] Epstein R, Kanwisher N. A cortical representation of the local visual environment. Nature 1998; 392(6676): 598-601.
[12] Yoon JH, Curtis CE, D'Esposito M. Differential effects of distraction during working memory on delay-period activity in the prefrontal cortex and the visual association cortex. NeuroImage 2006; 29(4): 1117-26.
[13] Stahl S. Stahl's Essential Psychopharmacology. Neuroscientific Basis and Clinical Applications. 3rd ed. Cambridge: Cambridge University Press 2008.
[14] Brozoski TJ, Brown R, Rosvold HE, Goldman PS. Cognitive deficit caused by regional depletion of dopamine in the prefrontal cortex of rhesus monkeys. Science 1979; 205: 929-31.
[15] Sawaguchi T, Matsumura M, Kubota K. Effects of dopamine antagonists on neuronal activity related to a delated response task in monkey prefrontal cortex. J Neurophysiol 1990; 63(6): 1401-12.
[16] Sawaguchi T, Matsumura M, Kubota K. Catecholaminergic effects on neuronal activity related to a delayed response task in monkey prefrontal cortex. J Neurophysiol 1990; 63(6): 1385-99.
[17] Sawaguchi T, Goldman-Rakic PS. D1 dopamine receptors in prefrontal cortex: involvement in working memory. Science 1991; 251: 947-50.
[18] Luciana M, Depue RA, Arbisi P, Leon A. Facililtation of working memory in humans by a D2 dopamine receptor agonist. J Cogn Neurosci 1992; 4(1): 58-68.
[19] Mehta MA, Sahakian BJ, McKenna PJ, Robbins TW. Systematic sulpiride in young adult volunteers simulates the profile of cognitive deficits in Parkinson's disease. Psychopharmacology 1999; 146: 162-74.
[20] Gibbs SE, D'Esposito M. A functional MRI study of the effects of bromocriptine, a dopamine receptor agonist, on component processes of working memory. Psychopharmacology 2005; 180(4): 644-53.
[21] Gibbs SE, D'Esposito M. Individual capacity differences predict working memory performance and prefrontal activity following dopamine receptor stimulation. Cogn Affect Behav Neurosci 2005; 5(2): 212-21.
[22] Gibbs SE, D'Esposito M. A functional magnetic resonance imaging study of the effects of pergolide, a dopamine receptor agonist, on component processes of working memory. Neuroscience 2006; 139(1): 359-71.
[23] Mattay VS, Berman KF, Ostrem JL, Esposito G, Van Horn JD, Bigelow LB, *et al.* Dextroamphetamine enhances 'neural network-specific' phyiological signals: a Positron-Emission Tomography rCBF study. J Neurosci 1996; 16(15): 4816-22.
[24] Mattay VS, Callicot JH, Bertolino A, Heaton I, Frank JA, Coppola R, *et al.* Effects of dextroamphetamine on cognitive performance and cortical activation. NeuroImage 2000; 12(3): 268-75.
[25] Mehta M, Calloway P, Sahakian B. Amelioration of specific working memory deficits by methylphenidate in a case of adult attention deficit/hyperactivity disorder. J Psychopharm 2000; 14(3): 299-302.
[26] Willson MC, Wilman AH, Bell EC, Asghar SJ, Silverstone PH. Dextroamphetamine causes a change in regional brain activity *in vivo* during cognitive tasks: a functional magnetic resonance imaging study of blood oxygen level-dependent response. Biol Psychiatry 2004; 56(4): 284-91.
[27] Servan-Schreiber D, Printz H, Cohen J. A network model of catecholamine effects: gain, signal-to-noise ratio, and behavior. Science 1990; 249: 892-5.
[28] Durstewitz D, Seamans J, Sejnowski T. Dopamine-mediated stabilization of delay-period activity in a network model of prefrontal cortex. J Neurophysiol 2000; 83: 1733-50.
[29] Durstewitz D, Seamans JK. The dual-state theory of prefrontal cortex dopamine function with relevance to catechol-o-methyl-transferase genotypes and schizophrenia. Biol Psychiatry 2008; 64(9): 739-49.
[30] Seamans JK, Yang CR. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. Prog Neurobiol 2004; 74(1): 1-58.
[31] Arnsten AFT. Catecholamine modulation of prefrontal cortical cognitive function. Trends Cogn Sci 1998; 2(11): 436-46.
[32] Zahrt J, Taylor JR, Mathew RG, Arnsten AFT. Supranormal stimulation of D1 dopamine receptors in the rodent prefrontal cortex impairs spatial working memory performance. J Neurosci 1997; 17(21): 8528-35.
[33] Williams GV, Goldman-Rakic PS. Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. Nature 1995; 376: 572-5.
[34] Arnsten AF, Goldman-Rakic PS. Noise Stress Impairs Prefrontal Cortical Cognitive Function in Monkeys. Arch Gen Psychiatry 1998; 55: 362-8.
[35] Murphy FC, Arnsten AF, Goldman-Rakic PS, Roth RH. Increased dopamine turnover in the prefrontal cortex impairs spatial working memory performance in rats and monkeys. Proc Natl Acad Sci USA 1996; 93(3): 1325-9.
[36] Cai JX, Arnsten AF. Dose-dependent effects of the dopamine D1 receptor agonists A77636 or SKF81297 on spatial working memory in aged monkeys. J Pharmac Exp Ther 1997; 282: 1-7.
[37] Tipper CM, Cairo TA, Woodward TS, Phillips AG, Liddle PF, Ngan ET. Processing efficiency of a verbal working memory system is modulated by amphetamine: an fMRI investigation. Psychopharmacology 2005; 180(4): 634-43.
[38] Kimberg DY, D'Esposito M, Farah MJ. Effects of bromocriptine on human subjects depend on working memory capacity. Neuroreport 1997; 8: 3581-5.
[39] Cools R, Gibbs S, Miyakawa A, Jagust W, D'Esposito M. Working memory capacity predicts dopamine synthesis capacity in the human striatum. J Neurosci 2008; 28: 1208-12.
[40] Landau SM, Lal R, O'Neil JP, Baker S, Jagust WJ. Striatal dopamine and working memory. Cereb Cortex 2009; 19(2): 445-54.
[41] Floresco S, Phillips A. Delay-dependent modulation of memory retrieval by infusion of a dopamine D1 agonist into the rat medial prefrontal cortex. Behav Neurosci 2001; 115(4): 934-9.
[42] Phillips A, Ahn S, Floresco S. Magnitude of dopamine release in medial prefrontal cortex predicts accuracy of memory on a delayed response task. J Neurosci 2004; 14(2): 547-53.
[43] Mattay V, Goldberg T, Fera F, Hariri A, Tessitore A, Egan M, *et al.* Catechol *O*-methyltransferase Val158 -*met* genotype and individual variation in the brain response to amphetamine. Proc Natl Acad Sci USA 2003; 100(10): 6186-91.
[44] Cohen MX, Krohn-Grimberghe A, Elger CE, Weber B. Dopamine gene predicts the brain's response to dopaminergic drug. Eur J Neurosci 2007; 26(12): 3652-60.
[45] Mink JW. The basal ganglia: focused selection and inhibition of competing motor programs. Prog Neurobiol 1996; 50: 381-425.
[46] Cools AR. Role of the neostriatal dopaminergic activity in sequencing and selecting behavioural strategies: facilitation of processes involved in selecting the best strategy in a stressful situation. Behav Brain Res 1980; 1: 361-78.
[47] van den Bos R, Cools A. Switching to cue-directed behavior: specific for ventral striatal dopamine but not ventral pallidum/ substantia innominata gaba as revealed by a swimming-test procedure in rats. Neuroscience 2003; 118(4): 1141-9.
[48] Cools AR, Van Den Bercken JHL, Horstink MWI, Van Spaendonck KPM, Berger HJC. Cognitive and motor shifting aptitude disorder in Parkinson's disease. J Neurol Neurosurg Psychiatry 1984; 47: 443-53.
[49] Hayes AE, Davidson MC, Keele SW. Towards a functional analysis of the basal ganglia. J Cogn Neurosci 1998; 10(2): 178-98.
[50] Barbeau A. Biology of the Striatum. In: Gaull G, Ed. Biology of Brain Dysfunction. New York: Plenum Press 1973; pp. 333-50.
[51] Battig K, Rosvold H, Mishkin M. Comparison of the effects of frontal and caudate lesions on delayed response and alternation in monkeys. J Comp Physiol Psychol 1960; 53: 400-4.
[52] Packard MG, Knowlton BJ. Learning and memory functions of the basal ganglia. Annu Rev Neurosci 2002; 25: 563-93.
[53] Frank MJ. Dynamic dopamine modulation in the basal ganglia: a neurocomputational account of cognitive deficits in medicated and nonmedicated Parkinsonism. J Cogn Neurosci 2005; 17(1): 51-72.
[54] Leber AB, Turk-Browne NB, Chun MM. Neural predictors of moment-to-moment fluctuations in cognitive flexibility. Proc Natl Acad Sci USA 2008; 105(36): 13592-7.
[55] Cools R, Clark L, Robbins TW. Differential responses in human striatum and prefrontal cortex to changes in object and rule relevance. J Neurosci 2004; 24(5): 1129-35.
[56] Cools R, Clark L, Owen AM, Robbins TW. Defining the neural mechanisms of probabilistic reversal learning using event-related

functional magnetic resonance imaging. J Neurosci 2002; 22(11): 4563-7.

[57] Rogers RD, Andrews TC, Grasby PM, Brooks DJ, Robbins TW. Contrasting cortical and subcortical activations produced by attentional-set shifting and reversal learning in humans. J Cogn Neurosci 2000; 12(1): 142-62.

[58] Owen AM, James M, Leigh JM, Summers BA, Marsden CD, Quinn NP, *et al.* Fronto-striatal cognitive deficits at different stages of Parkinson's disease. Brain 1992; 115: 1727-51.

[59] Downes JJ, Roberts AC, Sahakian BJ, Evenden JL, Morris RG, Robbins TW. Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease: evidence for a specific attentional dysfunction. Neuropsychologia 1989; 27: 1329-43.

[60] Cools R, Ivry R, D'Esposito M. The human striatum is necessary for responding to changes in stimulus relevance. J Cogn Neurosci 2006; 18(12): 1959-72.

[61] Cools R, Barker RA, Sahakian BJ, Robbins TW. Mechanisms of cognitive set flexibility in Parkinson's disease. Brain 2001; 124: 2503-12.

[62] Cools R, Barker RA, Sahakian BJ, Robbins TW. Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. Cereb Cortex 2001; 11: 1136-43.

[63] Cools R, Lewis S, Clark L, Barker R, Robbins TW. L-DOPA disrupts activity in the nucleus accumbens during reversal learning in Parkinson's disease. Neuropsychopharmacology 2007; 32: 180-9.

[64] Dodds CM, Muller U, Clark L, van Loon A, Cools R, Robbins TW. Methylphenidate has differential effects on blood oxygenation level-dependent signal related to cognitive subprocesses of reversal learning. J Neurosci 2008; 28(23): 5976-82.

[65] Cools R, Sheridan M, Jacobs E, D'Esposito M. Impulsive personality predicts dopamine-dependent changes in frontostriatal activity during component processes of working memory. J Neurosci 2007; 27(20): 5506-14.

[66] Clatworthy PL, Lewis SJ, Brichard L, Hong YT, Izquierdo D, Clark L, *et al.* Dopamine release in dissociable striatal subregions predicts the different effects of oral methylphenidate on reversal learning and spatial working memory. J Neurosci 2009; 29(15): 4690-6.

[67] Dalley JW, Fryer TD, Birchard L, Robinson ES, Theobald DE, Laane K, *et al.* Nucleus accumbens D2 receptors predict trait impulsivity and cocaine reinforcement. Science 2007; 315(5816): 1267-70.

[68] Oswald LM, Wong DF, Zhou Y, Kumar A, Brasic J, Alexander M, *et al.* Impulsivity and chronic stress are associated with amphetamine-induced striatal dopamine release. NeuroImage 2007; 36(1): 153-66.

[69] Cools R, Frank M, Gibbs S, Miyakawa A, Jagust W, D'Esposito M. Striatal dopamine synthesis capacity predicts dopaminergic drug effects on flexible outcome learning. J Neurosci 2009; 29(5): 1538-43.

[70] Dodds CM, Clark L, Dove A, Regenthal R, Baumann F, Bullmore E, *et al.* The dopamine D2 receptor antagonist sulpiride modulates striatal BOLD signal during the manipulation of information in working memory. Psychopharmacology 2009; 207(1): 35-45.

[71] Collins P, Wilkinson LS, Everitt BJ, Robbins TW, Roberts AC. The effect of dopamine depletion from the caudate nucleus of the common marmoset (Callithrix jacchus) on tests of prefrontal cognitive function. Behav Neurosci 2000; 114(1): 3-17.

[72] Roberts AC, De Salvia MA, Wilkinson LS, Collins P, Muir JL, Everitt BJ, *et al.* 6-Hydroxydopamine lesions of the prefrontal cortex in monkeys enhance performance on an analog of the wisconsin card sort test: possible interactions with subcortical dopamine. J Neurosci 1994; 14(5): 2531-44.

[73] Crofts HS, Dalley JW, Van Denderen JCM, Everitt BJ, Robbins TW, Roberts AC. Differential effects of 6-OHDA lesions of the frontal cortex and caudate nucleus on the ability to acquire an attentional set. Cerebral Cortex 2001; 11(11): 1015-26.

[74] Pycock CJ, Kerwin RW, Carter CJ. Effect of lesion of cortical dopamine terminals on subcortical dopamine receptors in rats. Nature 1980; 286: 74-7.

[75] Akil M, Kolachana BS, Rothmond DA, Hyde TM, Weinberger DR, Kleinman JE. Catechol-O-methyltransferase genotype and dopamine regulation in the human brain. J Neurosci 2003; 23(6): 2008-13.

[76] Alexander G, DeLong M, Stuck P. Parallel organisation of functionally segregated circuits linking basal ganglia and cortex. Ann Rev Neurosci 1986; 9: 357-81.

[77] Stephan KE, Weiskopf N, Drysdale PM, Robinson PA, Friston KJ. Comparing hemodynamic models with DCM. NeuroImage 2007; 38(3): 387-401.

[78] Bogacz R, Wagenmakers EJ, Forstmann BU, Nieuwenhuis S. The neural basis of the speed-accuracy tradeoff. Trends Neurosci 2010; 33(1): 10-6.

[79] Forstmann BU, Dutilh G, Brown S, Neumann J, von Cramon DY, Ridderinkhof KR, *et al.* Striatum and pre-SMA facilitate decision-making under time pressure. Proc Nat Acad Sci USA 2008; 105(45): 17538-42.

[80] Schultz W. Multiple reward signals in the brain. Nat Rev 2000; 1: 199-207.

[81] Redgrave P, Prescott TJ, Gurney K. The basal ganglia: a vertebrate solution to the selection problem? Neuroscience 1999; 89(4): 1009-23.

[82] Nagano-Saito A, Leyton M, Monchi O, Goldberg YK, He Y, Dagher A. Dopamine depletion impairs frontostriatal functional connectivity during a set-shifting task. J Neurosci 2008; 28(14): 3697-706.

[83] Aarts E, Roelofs A, Franke B, Rijpkema M, Fernandez G, Helmich RC, *et al.* Striatal dopamine mediates the interface between motivation and cognition in humans: Evidence from genetic imaging. Neuropsychopharmacology (in press).

Received: March 2, 2010 **Accepted: March 26, 2010**