# Role of Dopamine in the Motivational and Cognitive Control of Behavior

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Brain dopamine has often been implicated in impulsive and/or inflexible behaviors, which may reflect failures of motivational and/or cognitive control. However, the precise role of dopamine in such failures of behavioral control is not well understood, not least because they implicate paradoxical changes in distinct dopamine systems that innervate dissociable neural circuits. In addition, there are large individual differences in the response to dopaminergic drugs with some individuals benefiting from and others being impaired by the same drug. This complicates progress in the understanding of dopamine's role in behavioral control processes, but also provides a major problem for neuropsychiatry, where some individuals are disproportionately vulnerable to the adverse effects of dopamine-enhancing drugs on motivation and cognition. Recent progress is reviewed from cognitive and behavioral neuroscience research on motivation and cognitive control, which begins to elucidate the factors that mediate the complex roles of mesolimbic, mesocortical, and nigrostriatal dopamine in behavioral control. NEUROSCIENTIST 14(4):381–395, 2008. DOI: 10.1177/1073858408317009

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The ability to adapt to our constantly changing environment requires, on the one hand, the suppression of inappropriate behavior associated with punishment, and, on the other hand, the selection and maintenance of appropriate behavior associated with reward. Such behavioral control necessitates a motivated and goal-directed mind that is both stable and flexible at the same time. These processes are well established to be modulated by dopamine, which innervates frontostriatal and limbic-striatal brain circuits. However, the relationship between dopamine and behavioral control is complex, with large variability in the effects of dopamine both across and within different individuals. This article reviews factors that mediate this complex relationship.

One approach to addressing the role of dopamine in behavioral control is by investigating neuropsychiatric abnormalities that implicate dopamine, such as attention deficit hyperactivity disorder (ADHD) or drug addiction. However, most neuropsychiatric abnormalities are spectrum disorders, with each individual patient suffering from a unique constellation of deficits. Perhaps not surprisingly, there is currently no consensus regarding the neurobiological basis of these neuropsychiatric disorders or the mechanism of action of drugs that alleviate the symptoms. The lack of understanding likely reflects the heterogeneity of the disorders as well as the lack of neurochemical specificity of therapeutic drugs.

In this article, the issue will be approached by focusing on the effects of dopamine on frontostriatal and limbic-striatal processing, measured with laboratory tasks, as a function of one constituent feature of a range of neuropsychiatric abnormalities, namely trait impulsivity. Trait impulsivity may relate more directly to relevant neurocognitive and genetic variability than the clinical spectrum disorders themselves (Ernst and others 2006b). A subcomponent process approach is adopted, by which adequate behavioral control is thought to depend on the interplay between, on the one hand, motivational processes that implicate ventral limbic-striatal circuitry with, on the other hand, "higher order" cognitive processes that implicate dorsal fronto-striatal circuitry (Fig. 1*a*). Although this article focuses on impulsivity as one expression of behavioral control failure, it is not meant to provide an exhaustive overview of the mechanisms associated with impulsivity. The reader is referred to previous articles for reviews of the role of trait impulsivity in neuropsychiatric disorders (Verdejo-Garcia and others, in press), neurocognitive aspects of impulsivity other than motivational and cognitive control processes (e.g., response disinhibition and delay gratification; Cardinal and others 2004; Congdon and Canli 2005; Aron 2007), and the role of other neurotransmitters (e.g., serotonin) in impulsivity (Evenden 1999; Winstanley 2007).

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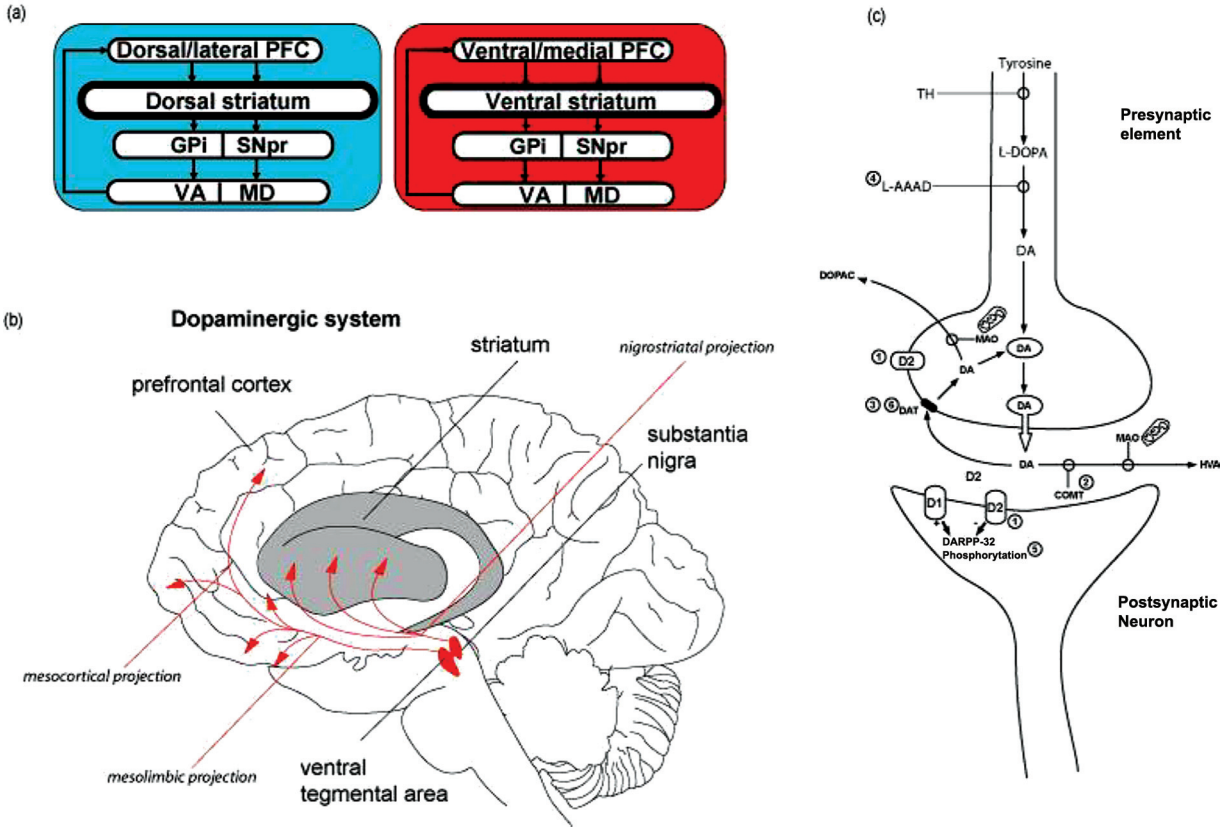


**Fig. 1.** (*a*) Functionally distinct dorsal and ventral frontostriatal circuits. For further details, see Alexander and others (1986). (*b*) Major dopamine projections. The mesolimbic dopamine projection originates in the ventral tegmental area (VTA; A10) and innervates primarily mesolimbic regions including the nucleus accumbens and olfactory tubercle. The nigrostriatal dopamine projection originates in the substantia nigra (SN; A9) and innervates primarily the striatum (caudate nucleus and putamen). The mesocortical dopamine projection originates primarily in the VTA and innervates the prefrontal cortex. This segregation is not absolute (Cooper and others 2003). (*c*) Dopamine synthesis, uptake, and metabolism. TH = tyrosine hydroxylase; DOPAC = dihydroxyphenylacetic acid; MAO = monoamine oxidase; L-AAAD = L-aromatic amino acid decarboxylase; D1 = postsynaptic dopamine D1 receptor (the D1 family includes the D1 and D5 receptor subtypes); D2 = dopamine D2 receptor (the D2 family includes the D2, D3, and D4 receptor subtypes); DAT = dopamine transporter (maintains transmitter homeostasis; its expression is more abundant in the striatum than in the prefrontal cortex); HVA = homovanillic acid; COMT = catechol-O-methyltransferase; DARPP-32 = dopamine and cAMP-regulated phosphoprotein of 32 kDA (enhances (post)synaptic plasticity in the striatum). Circled numbers: 1) Sites of modulation by dopamine receptor agonists (e.g., bromocriptine) and antagonists. 2) Site of action of the COMT Val$^{158}$Met polymorphism. 3) Likely site of action of the DAT1 polymorphism (or one in linkage disequilibrium). 4) Site of action of the PET tracer fluorometatyrosine (FMT), a substrate of AAAD, thus reflecting dopamine synthesis capacity (primarily in striatal terminals). 5) Site of action of the DARPP-32 haplotype. For further details, see Cooper and others (2003).

## The Intricacies of Dopamine

How does brain dopamine regulate behavioral control? The answer to this question is not straightforward, partly because behavioral control comprises multiple subcomponent processes that implicate distinct neural circuits. For example, failures of behavioral control, such as impulsivity and/or inflexibility, may result from abnormal motivational processes, which implicate the ventral striatum (particularly the nucleus accumbens) and the strongly connected ventral/medial parts of the prefrontal cortex (PFC). However, behavioral control also depends on complex cognitive control processes, which implicate a different frontostriatal circuit that connects the dorsal striatum (caudate nucleus and putamen) with the dorsolateral PFC (Fig. 1*a*).

In addition, the dopaminergic system itself is complex, with multiple pathways innervating multiple brain regions (Fig. 1*b*). The system is highly dynamic and constantly regulates itself to maintain equilibrium both at the molecular and at the systems level (Fig. 1*c*). This is illustrated by the stimulation by dopamine receptor agonists of presynaptic D2 receptors, which inhibits cell firing, release, and/or synthesis, thus paradoxically reducing dopaminergic activity. A presynaptic mechanism of action of dopamine receptor agonists is likely

more pronounced in subjects with already high baseline levels of synaptic dopamine than in subjects with suboptimal baseline levels of dopamine (Torstenson and others 1998). Furthermore, high baseline levels of synaptic dopamine may induce desensitization of postsynaptic D2 receptors, thereby further reducing the postsynaptic efficacy of dopamine receptor agonists. A final complexity pertains to regulation at the systems level, so that changes in dopaminergic activity in one structure (e.g., the PFC) induce adaptive changes in dopaminergic activity in another structure (the striatum; Pycock and others 1980; Meyer-Lindenberg and others 2002; Akil and others 2003; Meyer-Lindenberg and others 2005).

The implication of this complexity is that dopamine and dopamine receptor agonists have contrasting effects on the expression of function depending on, among other factors, the brain region that is implicated by the process under study, the baseline levels of dopamine in that brain region and receptor specificity. We will illustrate the importance of these factors by reviewing data from three approaches toward studying the role of dopamine in behavioral control. First, we review studies on individual genetic differences in dopamine function (i.e., uptake by dopamine transporter [DAT], D2 receptor density, and metabolism by catechol-*O*-methyltransferase [COMT]). Second, a select set of neurochemical imaging studies will be reviewed that reveal correlations between performance and dopamine function (i.e., dopamine synthesis capacity). Third, we review psychopharmacological studies on the effects of relatively selective dopamine D2 receptor agonists (i.e., bromocriptine). Results from these studies will be considered in the context of evidence from behavioral neuroscience studies with experimental animals.

## Mesolimbic Dopamine: Motivation, Reward, and Punishment

For decades, neuropsychopharmacological research of one of the most salient disorders of behavioral control, that is, drug addiction, has focused on neural circuits associated with incentive motivation. Incentive motivation refers to the state triggered by external stimuli that have appetitive (rewarding) or aversive (punishing) properties and implicates the ventral striatum and its innervation by mesolimbic dopaminergic neurons (Ikemoto and Panksepp 1999; Jentsch and Taylor 1999; Robbins and Everitt 2003). Specifically, mesolimbic dopamine has been argued to promote impulsive drug seeking by potentiating the capacity of a reward to elicit (approach) behavior (Robbins and others 1989). In keeping with this emphasis, classic personality theory has long highlighted motivational bias and enhanced reward sensitivity as a core feature of trait impulsivity, that is, the most salient temperament associated with behavioral control failure (Gray 1982; Dawe and Loxton 2004). Healthy high-impulsive individuals respond faster in anticipation of reward and exhibit greater neural activity in the ventral striatum during reward than do low-impulsive subjects (Wallace and Newman 1990; Cools and others 2005; Forbes and others 2007). An underemphasized, but potentially complementary, aspect of impulsivity, which some have defined as behavior that occurs despite its harmful consequences, is reduced efficacy of the process that opposes appetitive motivation (Konorski 1967): aversive motivation (e.g., Ernst and others 2006a; Potts and others 2006). Reduced aversive motivation induces a failure to avoid punishment-associated stimuli and behaviors.

The motivational control of behavior by appetitive and aversive stimuli (reinforcement) requires the anticipation of biologically relevant events (reward and punishment) by learning signals of their occurrence: prediction. Preliminary support for a bias away from punishment prediction toward reward prediction in trait impulsivity was provided in a recent study, in which the impact of unexpected reward and punishment was assessed using a reversal learning paradigm (Fig. 2; Cools R, D'Esposito M, unpublished observations, 2008). In this study more than 1000 healthy college-aged UC Berkeley students were prescreened on the self-report Barratt Impulsiveness Scale–Version 11 (BIS-11; Patton and others 1995), one of the most widely used measures of trait impulsivity. From the tail ends of the normal distribution of total BIS-11 scores, we selected a group of high-impulsive individuals and a group of low-impulsive individuals. These two groups were tested on an observational reversal learning paradigm that required subjects to learn to predict reward and punishment. On each trial of this task, one of two stimuli was highlighted, and subjects had to predict, based on trial-and-error learning, whether this highlighted stimulus would lead to reward (a smiley face, point bonus, and a pleasant sound) or punishment (a sad face, point loss, and an unpleasant sound). The stimulus-outcome contingencies reversed multiple times during the task. Critically, these reversals were signaled to subjects by the presentation of unexpected reward or unexpected punishment (Fig. 2*a*). Accordingly, the task enabled the separate assessment of reversal based on unexpected reward and reversal based on unexpected punishment. Preliminary data from 10 volunteers (Fig. 2*b*) indicate that high-impulsive subjects had greater difficulty with reversal based on unexpected punishment than with reversal based on unexpected reward ($F_{1,4} = 11.7$, $P = 0.027$). Conversely, low-impulsive subjects had greater difficulty with reversal based on unexpected reward than with reversal based on unexpected punishment ($F_{1,4} = 16.6$, $P = 0.015$). There was a highly significant interaction between impulsivity and outcome valence ($F_{1,8} = 24.5$, $P = 0.001$), indicating that trait impulsivity was accompanied by a shift away from punishment sensitivity toward reward sensitivity. This finding is intriguing particularly in the context of observations that trait impulsivity, measured with BIS-11, predicts increased vulnerability to addictive disorders such as alcoholism (Dawe and Loxton 2004), which have been characterized by enhanced appetitive motivation (i.e., greater motivational impact of reward on behavior), but reduced aversive motivation (i.e., reduced impact of punishment). What role might dopamine play in this imbalance between reward sensitivity and punishment sensitivity?

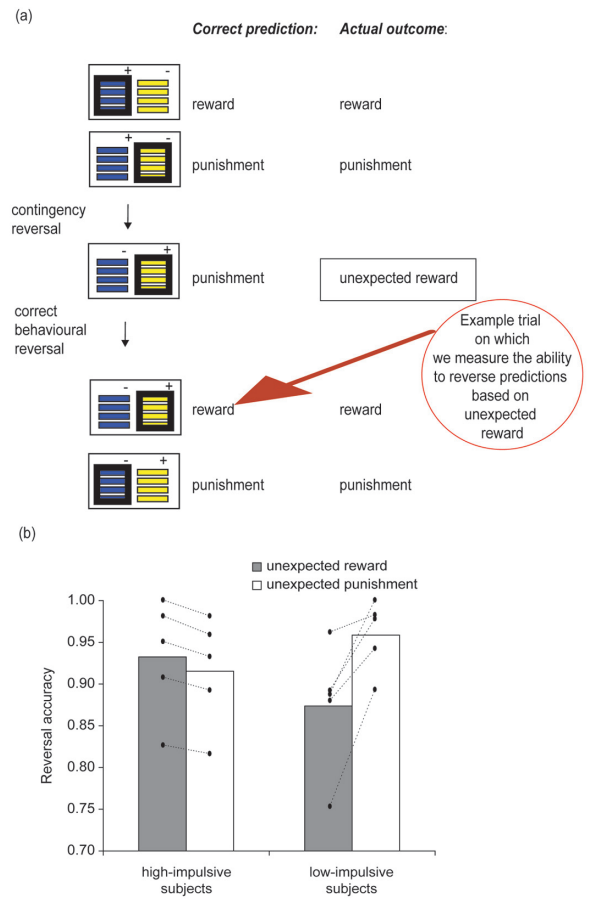


**Fig. 2.** Trait impulsivity is associated with greater reward sensitivity relative to punishment sensitivity. (*a*). Example trial sequence from the unexpected reward condition of the observational reversal learning task, used to assess reward sensitivity and punishment sensitivity as a function of trait impulsivity. Predictions were made by left or right button presses. See text for details. (*b*). Trait impulsivity was associated with enhanced reward relative to punishment sensitivity. Data represent the proportion of correct reversals of outcome predictions in response to unexpected reward and unexpected punishment as a function of trait impulsivity. High-impulsive subjects made significantly more prediction errors after unexpected punishment than after unexpected reward. Conversely, low-impulsive subjects made significantly fewer prediction errors after unexpected punishment than after unexpected reward. (Cools R, D'Esposito M, unpublished observations, 2008.)

### *Imaging Genetics of Reward*

Considerable progress in the understanding of the role of dopamine in reward has been made by recent imaging genetics studies, which have combined blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) with a genetic approach. Reward-related activity in the ventral striatum was modulated by genetic variation in several steps of dopamine transmission (Fig. 3*a*, *b*; Cohen and others 2005; Kirsch and others 2006; Cohen and others 2007; Forbes and others 2007; Frank and others 2007; Klein and others 2007; Yacubian and others 2007). Specifically, Forbes and others (2007) have observed reduced reward-related activity in the ventral striatum in subjects homozygous for the 10-repeat allele of a 40-bp variable number of tandem repeats (VTR) polymorphism in the 3′-untranslated region of the DAT gene (SLC6A3; Fig. 3*a*). The 10-repeat allele (10R) has been associated with increased gene expression and presumably lower levels of synaptic dopamine in the striatum relative to carriers of the 9-repeat allele (9R; Heinz and others 2000; Mill and others 2002; VanNess and others 2005; but see van Dyck and others 2005). This finding indicates that increased synaptic dopamine levels promote reward-related activity in the ventral striatum. Interestingly, the Forbes study also revealed a strong association between reward-related activity in the ventral striatum and a single nucleotide polymorphism (SNP4) in the promoter region (–141C insertion/deletion, Ins/Del) of the DRD2 gene (Fig. 3*a*). Greater activity was seen in subjects with the deletion variant of this polymorphism, which has been associated with reduced D2 receptor density. Thus reward-related activity in the ventral striatum appeared to depend on high synaptic dopamine levels, but also on low D2 receptor density. This apparent paradox can be reconciled by recognizing that reduced D2 receptor density may lead to reduced self-regulation via autoreceptors. Reduced self-regulation diminishes inhibition of dopamine synthesis and release, and thus indirectly increases synaptic dopamine levels.

It is important to note that the effects reported by Forbes and others (2007) reflect modulation of activity during blocks of high reward probability relative to that during blocks of low reward probability. Accordingly, the effects might well be due to modulation of reward prediction rather than modulation of reward receipt. It is essential to take into account the precise reward-related process under investigation, because different effects of DRD2 polymorphisms have been observed during reward prediction and during reward receipt. For example, subjects with the A1 allele of the DRD2 Taq1A polymorphism (SNP23), associated with reduced DRD2 density (Pohjalainen and others 1998), have been shown to exhibit decreased neural activity in the ventral striatum during the receipt but not during the prediction of reward (Cohen and others 2005; Kirsch and others 2006; Cohen and others 2007; Klein and others 2007). Thus, subjects with genetically determined low D2 receptor density may exhibit increased neural activity in the ventral striatum during reward prediction, but decreased neural activity in the ventral striatum during reward receipt. How to account for this apparent discrepancy? To resolve this paradox, it is necessary to consider evidence obtained from studies with experimental animals.

### *Behavioral Neuroscience of Reward*

The contrasting effects on reward prediction and receipt are highly reminiscent of a long accepted distinction between two aspects of motivated behavior (Robbins

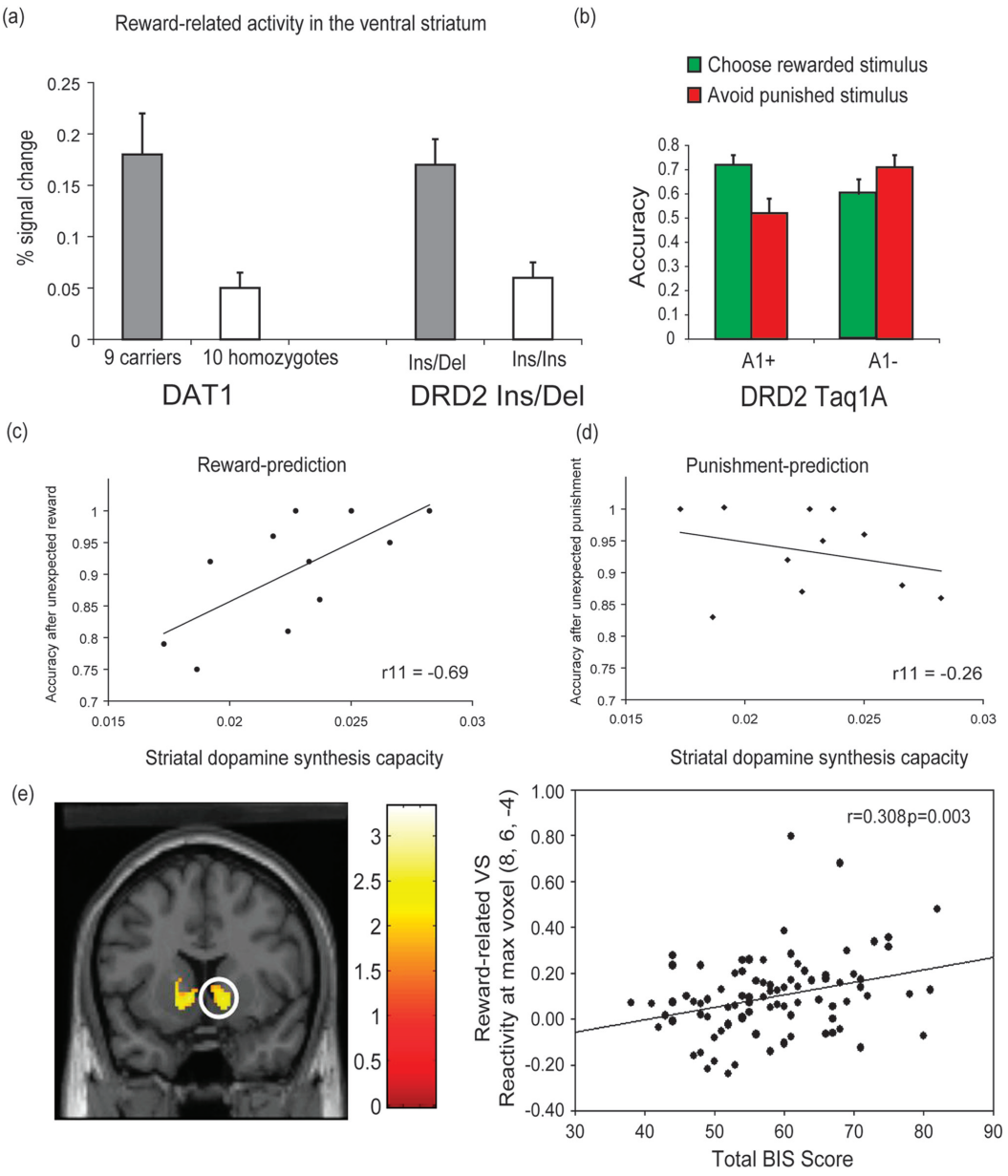


**Fig. 3.** Evidence for the importance of synaptic dopamine and the DRD2 in reward sensitivity, and its relation to trait impulsivity. (*a*) Reward-related activity in the ventral striatum depends on genetic variation in the dopamine transporter (DAT) and DRD2 genes (Forbes and others 2007). It is enhanced in subjects who carry the 9-repeat allele of the DAT gene, associated with low DAT expression (and presumably high synaptic DA levels), and also in subjects with the DRD2 insertion/deletion polymorphism, associated with reduced DRD2 expression. Figure adapted with permission from Forbes and others (2007) (*b*) The DRD2 Taq1A polymorphism biases subjects away from punishment-based learning, but did not affect reward-based learning, as measured using the probabilistic selection task devised by Frank and others (2004). Figure reproduced with permission from Klein and others (2007). (*c*) Reward sensitivity (measured with the task depicted in Fig. 2) correlates positively with dopamine synthesis capacity in the striatum (measured with PET; Cools R, Frank MJ, Gibbs SE, Miyakawa A, Jagust W, D'Esposito M, unpublished observations, 2008). (*d*) No correlation was obtained between punishment sensitivity and synthesis rates. (*e*) Correlation (*right*) between trait impulsivity, as measured with the Barratt Impulsiveness Scale, and reward-related activity (*left*) in the ventral striatum. Reprinted with permission from Macmillan Publishers Ltd: Neuropsychopharmacology (Forbes and others 2007), copyright 2007.

and Everitt 1992; Berridge and Robinson 1998; Ikemoto and Panksepp 1999; Baldo and Kelley 2007). In one instantiation of this distinction, "reward" can be "parsed" into, on the one hand, its impact on conditioned (learned) preparatory behavior (e.g., drug seeking) by virtue of its activating, energizing, or invigorating effect, and, on the other hand, its impact on unconditioned (innate) consummatory behavior (e.g., eating; Robbins

and Everitt 1992; Salamone and others 2007). In another strongly related instantiation, reward is parsed into, on the one hand, its motivational impact on "wanting" (by modulation of expected reward representations) and, on the other hand, its hedonic impact on "liking" (by modulation of sensory signals accompanying reward consumption; Berridge and Robinson 1998). It is only the former conditioned preparatory process related to wanting that is impaired by decreases and potentiated by increases in mesolimbic dopamine neurotransmission. By contrast, the consummatory process that relates to liking has been found to be, in fact, increased after decreases in mesolimbic dopamine transmission (Koob and others 1978). Intriguingly, it has been proposed that reciprocal inhibitory interconnections exist between these preparatory and consummatory systems, by which preparatory systems, associated with mesolimbic dopamine, exert inhibitory control over consummatory systems (Baldo and Kelley 2007). In keeping with this notion of antagonism, preparatory and consummatory behaviors are mutually incompatible in terms of their behavioral strategy requirement. Whereas preparatory reward-directed behavior is characterized by increased flexibility and exploration, consummatory reward-maintaining behavior is characterized by inflexible, repetitive behavior and exploitation (Baldo and Kelley 2007). In this context, the hypothesis that preparatory behavior during reward prediction corresponds to increased striatal dopamine concurs with the classical view that striatal dopamine mediates behavioral and cognitive flexibility (see below; Lyon and Robbins 1975; Cools 1980; Cools and others 1984; Oades 1985).

This evidence highlights the importance of taking into account the fact that reward comprises multiple components, which are likely mediated by dissociable, possibly antagonistic mechanisms. Furthermore, it may provide a partial resolution to the observation that genetically determined reduction of DRD2 availability (which may disinhibit dopamine release; see Fig. 4) implicates two apparently contradictory, but possibly related changes: 1) deficient (or blunted) response to reward receipt (at least when it is not entirely unexpected [Schultz 2000]), but 2) excessive response during reward anticipation. The above-reviewed opposite directions of the effect of DRD2 polymorphisms on reward anticipation and receipt concur with the reward deficiency hypothesis of disorders associated with reduced DRD2 availability and impulsivity (i.e., addiction). According to this hypothesis, greater motivational drive to obtain rewards results from an understimulated hedonic reward system (Volkow and others 1997; Reuter and others 2005). In keeping with this observation is the finding that a reduction of ventral striatal activity in A1-carriers (with putatively low DRD2 availability, and possibly high synaptic dopamine) during reward receipt is accompanied, if anything, by increased rather than decreased selection (and thus prediction) of rewarded stimuli (Cohen and others 2007; Klein and others 2007).

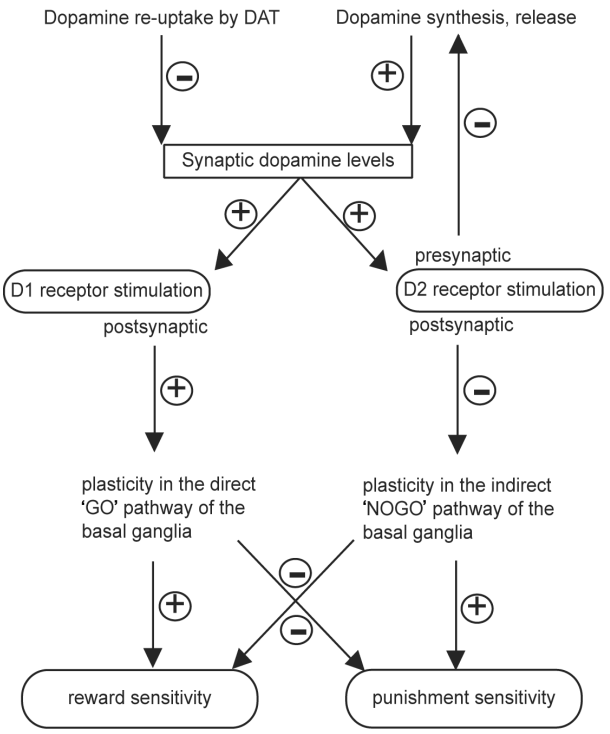


**Fig. 4.** Schematic of hypothesized mechanisms of dopamine transmission in the (ventral) striatum that mediate the impact of reward and punishment on learning. This schematic is based on a theoretical model proposed by Frank (2005) of the role of dopamine in the basal ganglia in reinforcement learning. According to this model, high levels of synaptic dopamine (e.g., as a result of phasic bursting of dopamine neuron firing) support reward-based learning by modulating plasticity in the direct pathway of the basal ganglia via action at D1 receptors. Conversely, decreases of synaptic dopamine levels (e.g., as a result of phasic inhibition of dopamine neuron firing) support punishment-based learning, by modulating plasticity in the indirect pathway of the basal ganglia via action at D2 receptors. The data reviewed in this article highlight that reward-based learning can also be modulated by D2 receptor stimulation (i.e., by bromocriptine), suggesting that changes in the direct and indirect pathway may have complementary effects.

### *Neurochemical Imaging of Reward*

Further insight into the dopaminergic mechanisms of reward sensitivity in humans has come from recent work using neurochemical PET with the tracer fluorometatyrosine (FMT). FMT is a substrate of aromatic amino acid decarboxylase (AAAD; Fig. 1) and thus indexes dopamine synthesis capacity, primarily in striatal nerve terminals. We have recently assessed the relationship between dopamine synthesis capacity in the striatum using FMT PET and performance on the observational reversal learning paradigm that enables the separate investigation of reward sensitivity and punishment sensitivity (Fig. 2*a*). Results indicate that reward sensitivity,

but not punishment sensitivity, depended on dopamine synthesis capacity (Fig. 3*c*, *d*; Cools R, Frank M, Gibbs S, Miyakawa A, Jagust W, D'Esposito M, unpublished data, 2008). This observation is consistent with prior findings that expression of the dopamine transporter, which regulates the reuptake of dopamine from the synapse (see Figs. 1 and 4) correlates with reward-related activity in the ventral striatum (Forbes and others 2007; Yacubian and others 2007). Accordingly, this PET work strengthens the hypothesis that reward sensitivity benefit from high levels of mesolimbic dopamine in the synapse.

### *Imaging Genetics of Punishment*

What about the role of dopamine in punishment sensitivity? At least some of the above-reviewed imaging genetics studies confounded reward processing and punishment processing. For example, the effect of interest in the Forbes study represented a correlation with activity during reward minus activity during punishment. Accordingly, it is not possible to determine whether, and if so which distinct mechanisms mediate reward versus punishment sensitivity. Advance was made in a recent series of studies that disentangled learning to choose reward-associated stimuli from learning to avoid punishment-associated stimuli (Frank and others 2004). Interestingly, Frank and others (2007) observed that punishment-based learning, but not reward-based learning, correlated with genetic variation in the C957T polymorphism (exonic SNP21) of the DRD2 gene (see Klein and others [2007] and Figure 3*b* for a similar effect of the DRD2 Taq1A polymorphism). Carriers of the C-allele, which is associated with low D2 receptor density (Hirvonen and others 2004), had selective difficulty with punishment-based avoidance. Critically, this polymorphism affects only postsynaptic D2 receptor density and not presynaptic dopamine synthesis (Laakso and others 2005). Thus the effects on punishment-based avoidance could not reflect altered self-regulation of synaptic dopamine via autoreceptors, but must reflect changes in postsynaptic receptor density. These data provide an alternative account of the Ins/Del effect in the Forbes study, which revealed enhanced reward-related activity, relative to punishment-related activity, in subjects with genetically determined low D2 receptor expression: Thus, the increase in reward-related activity in the ventral striatum in Ins/Del subjects (low D2 density) may in fact reflect a reduction in punishment-related activity.

### *Interim Summary*

Together, these studies provide detailed information about different steps in dopamine transmission that may mediate the balance between reward versus punishment sensitivity in the domain of learning (Table 1). On the one hand, reward-based learning may reflect synaptic dopamine levels, which are regulated by dopamine synthesis capacity, dopamine reuptake by the DAT, and (D2) autoreceptor-mediated self-regulation. On the other hand, punishment-based learning may reflect (postsynaptic) D2 receptor density (Frank and others 2007; Klein and others 2007), which is in turn regulated (i.e., desensitized) by synaptic dopamine levels. These data are remarkably consistent with a recent theoretical model (Fig. 4; Frank 2005), according to which reward-based learning depends on the impact of phasic dopamine release in the synapse on D1 receptors. Conversely, the theory states that punishment-based learning depends on the impact of the phasic inhibition of dopamine firing on postsynaptic dopamine D2 receptors. In the context of regulation of synaptic dopamine levels by D2 receptors (and vice versa), it is perhaps not surprising that enhanced reward sensitivity often co-occurs with reduced punishment sensitivity. In other words the functional opponency between reward prediction and punishment prediction parallels neurochemical reciprocity between synaptic dopamine levels and DRD2 density.

### *Human Psychopharmacology of Reward and Punishment*

A third approach toward addressing the role of dopamine is by studying the effects of administration of selective dopamine receptor agents to healthy volunteers. Several studies have recently adopted this psychopharmacological approach to the study of reward and punishment (Pessiglione and others 2004; Frank and O'Reilly 2006; Kirsch and others 2006; Cohen and others 2007). However, there is large variability in the direction and extent of these dopaminergic drug effects. In fact, contrasting effects of dopamine receptor agents have been observed, so that drug effects vary across different individuals as well as different tasks (Cools and Robbins 2004). Specifically, dopamine receptor agonists (such as bromocriptine and cabergoline) improve function in subjects with low baseline performance levels, but impair function in subjects with already optimized baseline performance levels (Kimberg and others 1997; Gibbs and D'Esposito 2005; Frank and O'Reilly 2006; Cools and others 2007). This dependency on baseline performance levels has been argued to reflect quantitative variation in baseline levels of dopamine neurotransmission, so that an inverted U-shaped relationship exists between dopamine receptor stimulation and performance (Williams and Goldman-Rakic 1995; Zahrt and others 1997; Arnsten 1998). To test this hypothesis, we have combined FMT PET with psychopharmacology in healthy volunteers (Cools R, Frank M, Gibbs S, Miyakawa A, Jagust W, D'Esposito M, unpublished data, 2008). Specifically, we have assessed the effects of the dopamine D2 receptor agonist bromocriptine on reward sensitivity and punishment sensitivity in relation to baseline levels of dopamine synthesis capacity in the striatum. As predicted, bromocriptine improved reward sensitivity in subjects with low baseline synthesis capacity, but impaired it in subjects with high baseline synthesis capacity. Remarkably, the opposite relationship was observed for punishment prediction: bromocriptine

**Table 1.** Summary of Reviewed Dopaminergic Effects on Reward Sensitivity and Punishment Sensitivity

| | Putative Neurochemical Effect | Reward Impact | Punishment Impact |
|---|---|---|---|
| 9-repeat allele of the DAT1 polymorphism (Forbes and others 2007) | High DA | Up | Down (?) |
| A1-allele of the DRD2 Taq1A polymorphism (Klein and others 2007) | Low DRD2 | — | Down |
| DRD2 Ins/Del polymorphism (Forbes and others 2007) | Low DRD2 | Up | Down (?) |
| C-allele of the DRD2 C957T polymorphism (Frank and others, 2007) | Low DRD2 | — | Down |
| FMT uptake (Cools R, Frank M, Gibbs S, Miyakawa A, Jagust W, D'Esposito M, unpublished data, 2008) | High DA | Up | — |

Note that these studies assess different reward-related processes: Forbes and others describe effects on the neural responsiveness to reward/punishment, Klein and others and Frank and others describe effects on choice based on reward/punishment learning, and we describe effects on reward/punishment prediction. Modulation of all these processes might affect conditioned (preparatory) rather than unconditioned (consummatory) behavior. DA = dopamine; Ins/Del = insertion/deletion; FMT = fluorometatyrosine.

impaired punishment sensitivity in subjects with low baseline synthesis capacity, but improved it in subjects with high baseline synthesis capacity.

To understand the basis of these paradoxical effects, we need to take into account the complex nature of dopamine neurotransmission. We argue that, in the high-dopamine subjects, bromocriptine impaired reward sensitivity by reducing dopamine release via modulation of presynaptic D2 receptors. Conversely, in the low-dopamine subjects, bromocriptine enhanced reward sensitivity by increasing dopaminergic function, hypothetically via modulation of postsynaptic dopamine D2 receptors (and inhibition of the indirect pathway; see Fig. 4). The finding that the effects on punishment sensitivity contrasted with those on reward sensitivity suggests that, unlike reward prediction, punishment sensitivity benefits from low rather than high synaptic dopamine levels. This concurs with prior neuropsychological evidence, showing that patients with Parkinson's disease (characterized by severe striatal dopamine depletion) exhibit a bias away from reward sensitivity toward punishment sensitivity, whereas dopamine-enhancing medication in these patients induced the reverse bias (Frank and others 2004; Cools and others 2006).

Together, the data suggest that in the domain of learning reward sensitivity benefits from high levels of synaptic dopamine and low D2 receptor density, whereas punishment sensitivity benefits from high D2 receptor density and low levels of synaptic dopamine. The functional opponency between reward sensitivity and punishment sensitivity corresponds to neurochemical homeostasis mechanisms, by which synaptic dopamine levels are adaptively regulated by D2 receptor function and vice versa. The reviewed findings raise the question whether trait impulsivity, which has been associated with high reward sensitivity, but low punishment sensitivity (Fig. 2), is accompanied by high synaptic dopamine levels, but low D2 receptor density. Intriguingly, a significant correlation between trait impulsivity (as measured with the BIS) and genetic variation in the expression of the DAT was recently obtained, with the 9-repeat allele being positively associated with BIS scores: High impulsivity was associated with genetically determined low DAT expression, and thus presumably high synaptic dopamine levels (Fig. 3*e*; Forbes and others 2007). In addition, a recent neurochemical PET study with the tracer [$^{18}$F]fallypride (a D2/3 receptor antagonist) in experimental animals revealed that high-impulsive rats have significantly lower D2/3 receptor density in the ventral striatum than do low-impulsive rats (Dalley and others 2007). Future neurochemical imaging research is necessary to demonstrate similar changes in human trait impulsivity. Finally, future research should address the question whether the administration of dopamine receptor agonists helps vulnerable impulsive subjects by attenuating reward anticipation and potentiating punishment sensitivity.

## Mesocortical and Nigrostriatal Dopamine: Cognitive Control

The study of behavioral control has benefited not only from an understanding of the role of mesolimbic dopamine in motivation and reward, but also from that of mesocortical and nigrostriatal dopamine in "higher order" cognitive functions (Fig. 2). These pathways innervate primarily the PFC and the dorsal striatum, which direct behavior toward abstract goals that are out of sight.

The importance of the mesocortical dopamine projection to the dorsolateral PFC for cognitive control has been established since the seminal observation that dopamine depletion from the PFC impaired performance on the classic delayed response task to the same extent as did ablation of the PFC (Brozoski and others 1979). Together with subsequent neurophysiological data (Sawaguchi and Goldman-Rakic 1991; Wang and Goldman-Rakic 2004; Vijayraghavan and others 2007), this finding indicated that prefrontal dopamine supports the active maintenance of goal representations in working memory, a form of cognitive control that is clearly critical for the active suppression and selection of irrelevant and relevant behaviors.

The importance of the active maintenance of goal representations in working memory for behavioral control is illustrated by recent data from nonhuman primates (James and others 2007). This work has shown that naturalistic measures of impulsivity predicted individual differences in performance on the classic delayed response task: High-impulsive monkeys exhibited a delay-dependent deficit on this task relative to low-impulsive monkeys. A different study revealed that, in patients with ADHD, performance on the self-ordered spatial working memory task was negatively associated with impulsive, disinhibited responding (Clark and others 2007). We recently demonstrated a similar relationship between working memory capacity and trait impulsivity (as measured with the BIS-11) in healthy human volunteers (Cools and others 2007). High-impulsive subjects had significantly lower working memory capacity as measured with the listening span test than did low-impulsive subjects, thus further strengthening the (inverse) relationship between impulsivity and working memory.

It should be noted that the active maintenance process of working memory is only one subcomponent process of cognitive control that is necessary for behavioral control. Behavioral control requires not only the active maintenance and stabilization of goal representations, but also the flexible updating of those goal representations. Although prior models of cognitive control and working memory have considered almost exclusively the role of the PFC, more recent theorizing highlights a critical role in cognitive control for an additional brain region, the striatum (Frank and others 2001; Bilder and others 2004; Gruber and others 2006; Meyer-Lindenberg and others 2007; Zhang and others 2007; McNab and Klingberg 2008). Specifically, whereas dopamine (D1) receptor stimulation in the PFC is thought to promote goal stability by increasing distractor resistance (Durstewitz and others 2000), dopamine receptor stimulation in the striatum has been hypothesized to promote goal flexibility, by allowing the updating of newly relevant representations (Fig. 5; Frank 2005). The newly recognized importance of striatal dopamine for cognitive flexibility (and set shifting) by cognitive neuroscientists concurs with the classic view of behavioral neuroscientists that striatal dopamine is essential for behavioral flexibility and switching, that is, that striatal dopamine increases the number of categories in which effort is expended (Lyon and Robbins 1975; Cools 1980).

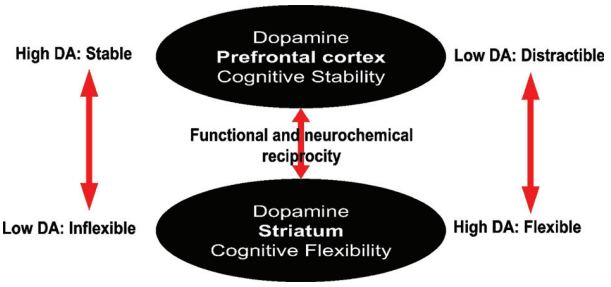


**Fig. 5.** The working hypothesis stating that dopamine in the prefrontal cortex promotes cognitive stability, whereas dopamine in the striatum promotes cognitive flexibility. The functional opponency between stability and flexibility parallels neurochemical reciprocity between dopamine in the prefrontal cortex and dopamine in the striatum. DA = dopamine.

The functional opponency between stability and flexibility maps well onto the neurochemical reciprocity between dopamine in the PFC and the striatum: Increases and decreases in PFC dopamine lead to decreases and increases in striatal dopamine respectively, possibly reflecting compensatory regulation at the systems level (Pycock and others 1980; Akil and others 2003; Meyer-Lindenberg and others 2005). Thus, high levels of striatal dopamine that are good for cognitive flexibility might be bad for cognitive stability. Similarly, high levels of PFC dopamine that are good for cognitive stability might be bad for flexibility. One implication of this model is that cognitive stability and flexibility, mediated by prefrontal and striatal dopamine respectively, trade off in the healthy brain, where dopamine levels interact dynamically. Of course, in the diseased brain, dopamine dysregulation in both the PFC and the striatum may independently disrupt subcomponent processes, sometimes causing the apparently paradoxical combination of instability (distractibility) and inflexibility (e.g., in trait impulsivity or ADHD).

### *Imaging Genetics of Cognitive Control*

Various studies have provided evidence that can be reconciled with this working hypothesis**.** For example, Nolan and others (2004) have assessed the effects on reversal learning of the $Val^{108/58}$Met polymorphism of the COMT gene. This polymorphism regulates the expression of COMT, an enzyme that breaks down dopamine released into the synapse, and is thought to have regionally selective effects on dopamine in the PFC. The Met allele of the this polymorphism has been associated with reduced activity of the COMT enzyme and thus higher dopamine in the PFC than the Val allele (Lotta and others 1995; Chen and others 2004; Bertolino and others 2006). Val/Val homozygotes exhibited a performance pattern that was interpreted to reflect enhanced cognitive flexibility (reversal learning) but reduced cognitive stability (acquisition) relative to Met/Met homozygotes (see also Bilder and others 2004). fMRI studies on working memory have also

provided results that are consistent with the hypothesis: Complementary changes in neural activity were seen as a function of genetic variation in dopamine metabolism in the PFC, by COMT, and in the striatum, by DAT (Bertolino and others 2006; Caldu and others 2007). As mentioned above, the 10-repeat allele of the DAT gene has been associated with lower dopamine in the striatum relative to the 9-repeat allele. On the other hand, the Met allele of the $Val^{158}Met$ polymorphism in the COMT gene has been associated with higher dopamine in the PFC relative to the Val allele. Remarkably, Bertolino and others (2006) have observed similar effects on neuronal activity of the 10-repeat allele of the DAT1 gene and the Met allele of the COMT gene, so that the activity pattern of subjects with putatively low striatal dopamine levels resembled that seen in subjects with putatively high dopamine levels in the PFC: Both alleles induced more focused activity in the PFC during the n-back task. These studies concur with the hypothesis that there are distinct optimal levels of dopamine transmission for dissociable neural regions subserving different components of working memory (Cools and Robbins 2004).

### *Psychopharmacology of Cognitive Control*

To test directly the hypothesis that the dopaminergic modulation of flexibility and stability is mediated by distinct brain regions (Fig. 5), we have investigated the effects of the dopamine receptor agonist bromocriptine on neural activity with fMRI (Fig. 6; Cools and others 2007). During scanning, subjects performed a working memory task that enabled the separate investigation of cognitive flexibility during encoding of information in working memory and cognitive stability necessary to resist distraction during the subsequent delay. Bromocriptine potentiated striatal activity, particularly in the dorsal striatum, when subjects flexibly switched between task-relevant representations during encoding. Conversely, the same drug potentiated activity in the PFC during distraction in the delay (Fig. 6). These data concur with the theoretical model and suggest that dopamine receptor stimulation modulates the striatum and the PFC during flexibility and stability respectively.

However, as was the case for the reversal learning task, the drug effects on the working memory task differed greatly between different individuals. Specifically, the effects of bromocriptine on the ability to switch between task-relevant representations and associated striatal activity depended on trait impulsivity (Fig. 7*a*). Bromocriptine improved cognitive switching and potentiated associated striatal activity in high-impulsive subjects. By contrast, there was no significant drug effect in low-impulsive subjects. If anything, the direction of the effect in the low-impulsive subjects was in the opposite direction. These contrasting effects were reminiscent of earlier studies that had revealed contrasting effects of bromocriptine in subjects with high and low working memory capacity, as measured with the listening span test (Kimberg and others 1997; Gibbs and D'Esposito 2005). In fact, it turned out that the high-impulsive subjects in our study, who benefited from bromocriptine, had significantly lower working memory capacity than did the low-impulsive subjects (Cools and others 2007). As described above, this dependency on baseline performance levels has been argued to reflect quantitative variation in baseline levels of dopamine neurotransmission.

### *Neurochemical Imaging of Cognitive Control*

The hypothesis that dopaminergic drug effects on cognitive control depend on baseline levels of dopamine in the striatum was recently strengthened by observations from a neurochemical PET study with the tracer FMT (Cools and others 2008). This study revealed that working memory capacity predicts dopamine synthesis capacity in the striatum, particularly in the caudate nucleus (part of the dorsal striatum), so that subjects with higher working memory capacity, as measured with the listening span, had higher synthesis capacity (Fig. 7*c*). Working memory capacity, in turn, predicted the direction of the effects of bromocriptine on cognitive switching and dorsal striatal activity (Cools and others 2007). Thus the PET data support the hypothesis that the dependency of dopaminergic drug effects on baseline working memory capacity reflects dependency on quantitative variation in baseline dopamine synthesis capacity in the striatum. The data also highlight a further issue. Low working memory capacity, as measured with the listening span, was associated not only with low dopamine synthesis capacity in the striatum, but also with trait impulsivity. Although there was no significant association between trait impulsivity and dopamine synthesis capacity in this small sample PET study, the association between working memory span and trait impulsivity suggests, at least indirectly, that trait impulsivity might be accompanied by reduced nigrostriatal dopamine in the dorsal striatum. How to reconcile this observation with the hypothesis, described in the first section of this article, that trait impulsivity is associated with increased synaptic levels of mesolimbic dopamine in the ventral striatum? Might impulsivity be accompanied by an imbalance between dopamine in the ventral striatum and dopamine in the dorsal striatum?

In fact, a functional imbalance between mesolimbic dopamine in the ventral striatum and nigrostriatal dopamine in the dorsal striatum has been previously observed after 6-hydroxydopamine (6-OHDA) lesions in the substantia nigra in rats (van Oosten and Cools 2002; van Oosten and others 2005) as well as in Parkinson's disease (Kish and others 1988). Specifically, nigral dopamine lesions cause a functional shift away from nigrostriatal dopamine in the dorsal striatum toward mesolimbic dopamine in the ventral striatum (van Oosten and others 2005). Like trait impulsivity, Parkinson's disease is associated with increased risk for addiction and pathological gambling (Voon and others 2007). Therefore, an intriguing hypothesis is that trait impulsivity is characterized by a shift away from nigrostriatal dopamine in the dorsal striatum toward mesolimbic dopamine in the ventral striatum. This would

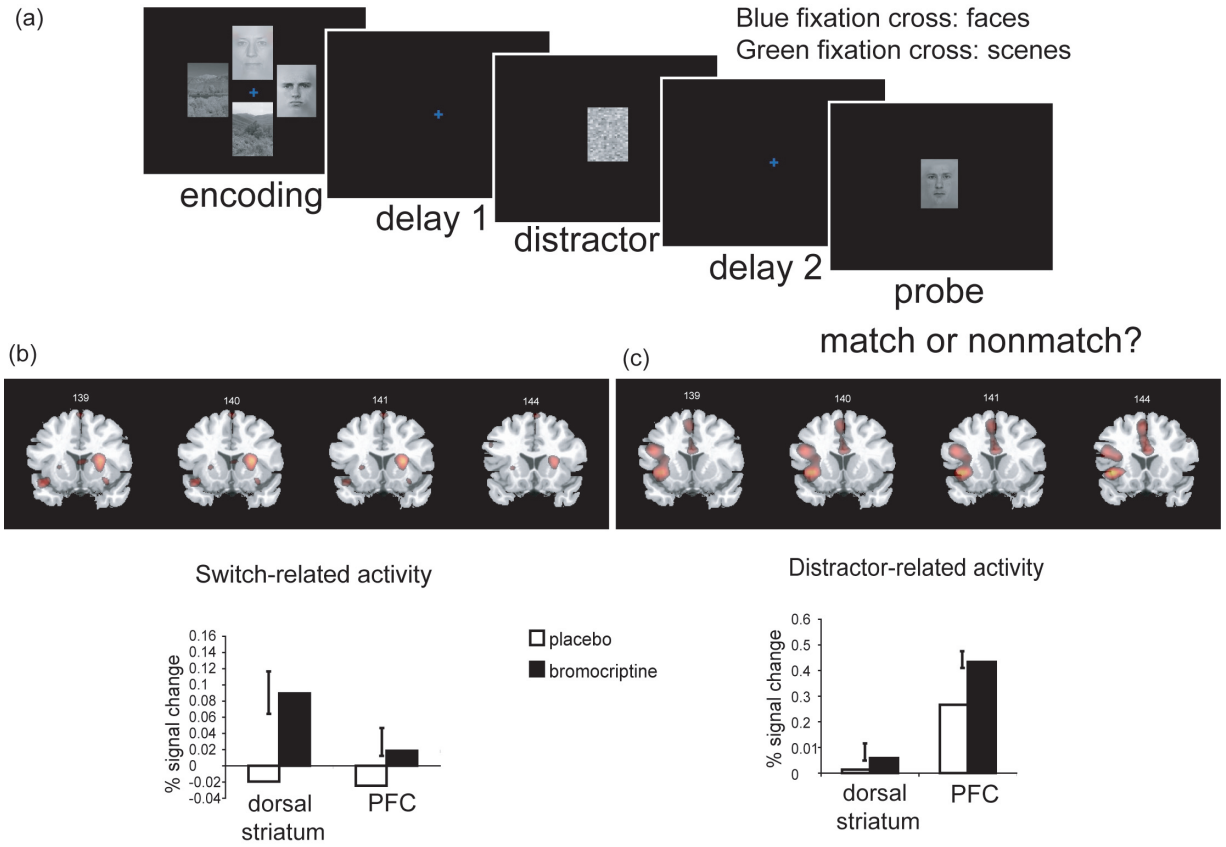


**Fig. 6.** Opposite effects of dopamine receptor stimulation on activity in the striatum and the prefrontal cortex (PFC) as a function of task demands. (*a*) The task enabled the separate investigation of cognitive flexibility and stability. It required subjects to memorize faces if the fixation cross was blue, but scenes if the fixation cross was green. Face-relevant and scene-relevant trials were randomized so that subjects occasionally switched between encoding faces and scenes. The encoding period was following by a delay period, after which a distractor was presented, which subjects were instructed to ignore. The distractor was followed by a second delay, after which a probe was presented. Subjects made a right or left button press depending on whether the probe matched one of the two task-relevant encoding stimuli. (*b*, *top*) Effects of bromocriptine on striatal activity during switching as a function of trait impulsivity (the group × drug interaction effect, whole-brain contrast values [>25] are overlaid on 4 coronal slices [slice numbers displayed on top] from the Montreal Neurological Institute high-resolution single-subject MR image; Abbreviations: L = left; R = right). (*b*, *bottom*) Effects of bromocriptine on switch-related activity in the dorsal striatum and left PFC in high-impulsive subjects only. (*c*, *top*) Effects of bromocriptine on frontal activity during distraction as a function of trait impulsivity (the group × drug interaction effect, all contrast values > 25 shown). (*c*, *bottom*) Effects of bromocriptine on distractor-related activity in the dorsal striatum and left PFC in high-impulsive subjects only. Figure adapted with permission from Cools and others (2007). Copyright 2007 by the Society for Neuroscience.

account for suggestions that trait impulsivity is accompanied by reduced cognitive flexibility on tasks that implicate dopamine in the dorsal striatum (Figs. 6*b*, 7*a*), but enhanced preparatory exploration and reward anticipation that implicates dopamine in the ventral striatum (Fig. 2). Future studies are necessary to test this hypothesis.

## Conclusion

How does brain dopamine regulate behavioral control? The present article illustrates the importance of approaching this question by investigating behavioral control in terms of its subcomponent processes. Behavioral control is a multifactorial phenomenon that requires adaptive recruitment of motivational processes, which enable a dynamic balance between the anticipation of appetitive stimuli (reward) and the anticipation of aversive stimuli (punishment). These motivational processes interact with cognitive control mechanisms that bias ongoing behavior toward goal representations in working memory. The distinct components of behavioral control by external incentive motivational stimuli and "internal" representations of future goals implicate dissociable ventral and dorsal striatal regions, the functional outputs of which are adjusted by dopamine to direct behavioral output to current goals (Robbins and Everitt 2003; van den Bos and Cools 2003). Notably, the optimal direction of behavioral output to current goals requires not only the flexible activation of behavior

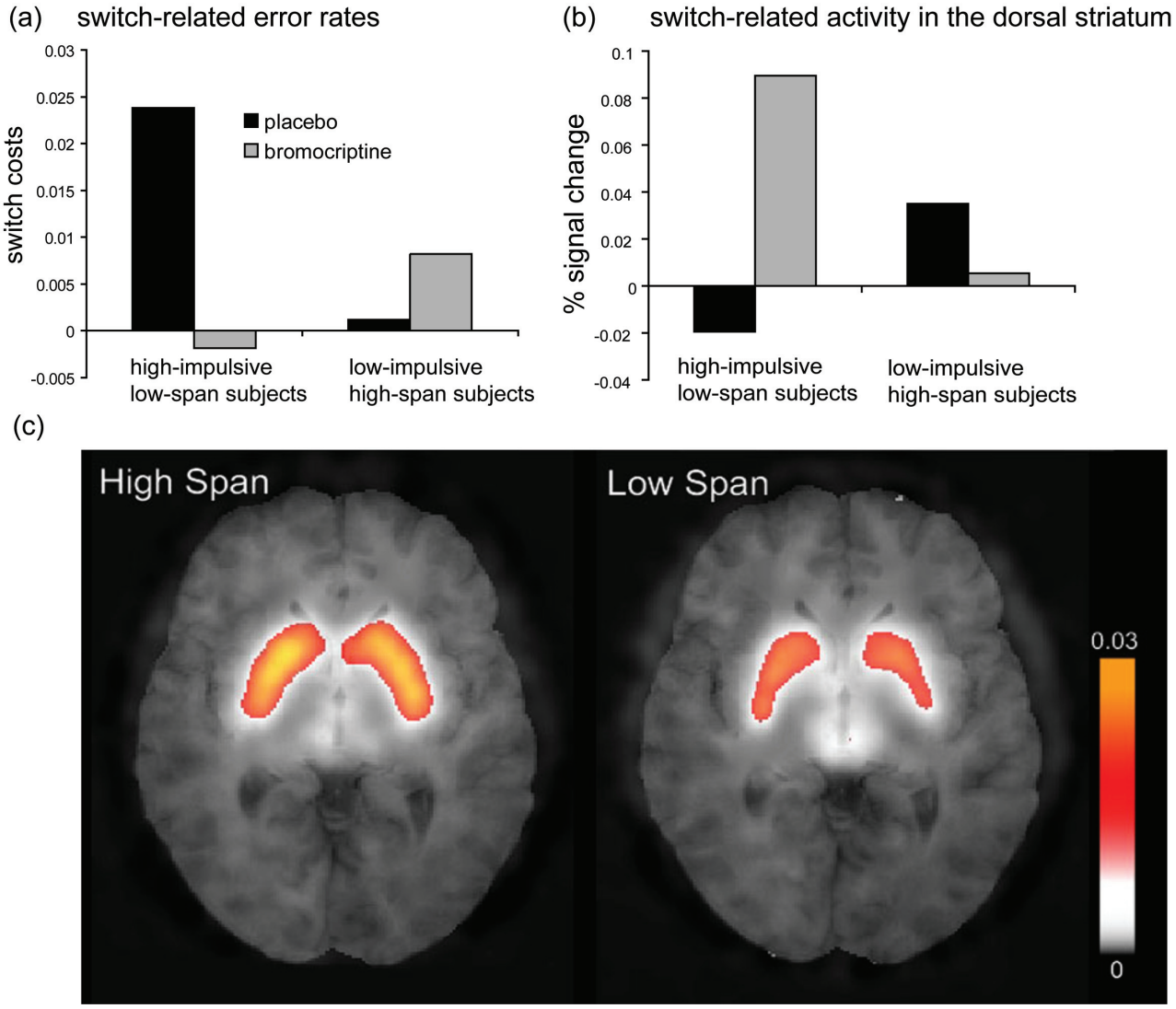


**Fig. 7.** Trait impulsivity predicts contrasting effects of bromocriptine on cognitive flexibility (*a*) and associated dorsal striatal activity (*b*). High-impulsive subjects had significantly lower working memory capacity as measured with the listening span, which in turn predicted dopamine synthesis capacity in the dorsal striatum (*c*). Figure reproduced with permission from Cools and others (2008). Copyright 2008 by Society for Neuroscience.

triggered by relevant stimuli, but also the protective stabilization of behavior in the context of irrelevant stimuli. Dopamine plays an important role in the regulation of this balance between flexibility and stability by adjusting the neurochemical equilibrium between, on the one hand, the ventral and dorsal striatum, and, on the other hand, the prefrontal cortex. The present article highlights the complexity not only of behavioral control, but also of the dopaminergic system, which is characterized by regulatory mechanisms, both at the molecular level of receptors as well as at the systems level. The implication of this complexity is that failures of behavioral control may result from paradoxical changes in dopamine transmission in distinct neural circuits. Furthermore, dopamine receptor agonists have contrasting effects on the expression of function depending on, among other factors, the brain region that is implicated by the type of function under study, the baseline levels of dopamine in that brain region, and receptor specificity.

Together, these hypotheses have clear implications for the manner in which dopamine adjusts the expression of different behavioral control mechanisms. This research begins to elucidate the neurobiological basis of a variety of neuropsychiatric disorders as well as the mechanisms of action of drugs used to treat them.

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