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By

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Abstract

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The integrity of the dopamine system is critical for high-level cognitive functions such as attentional processing. Patients with dopaminergic disorders demonstrate deficits across numerous tasks manipulating the allocation of attentional resources, and individual differences in dopamine activity correlate with task performance in healthy subjects. This dissertation uses positron emission tomography (PET), functional magnetic resonance imaging (fMRI), neuropsychological testing, and functional genetic polymorphisms to investigate how dopamine modulates brain networks to influence cognitive performance and specific attentional processes.

The first finding presents a model of the mechanism, at the systems level, whereby a genetic polymorphism in the dopamine system influences cognition. Catechol-O-methyltransferase (COMT) is an enzyme that degrades dopamine in the prefrontal cortex (PFC) and is polymorphic with alleles differing in enzymatic activity. The results show that COMT genotype determined dopamine synthesis, such that individuals with greater COMT activity synthesized more dopamine. Dopamine synthesis in the midbrain and ventral striatum affected functional connectivity in the default mode network, likely through the mesocorticolimbic pathway, in an inverted-U pattern with greater functional connectivity in medial PFC associated with intermediate levels of COMT activity and dopamine. Greater functional connectivity correlated with greater deactivation during performance of a set-shifting task that engaged the PFC. Greater deactivation was in turn associated with better performance. These results suggest that COMT affects prefrontal function by a mechanism involving dopaminergic modulation of the default mode network. The model features the well-known inverted-U function between dopamine and performance and supports the hypothesis that dopamine and the default mode network shift attentional resources to influence prefrontal cognition.

The second finding shows that dopamine influences the shifting of attentional resources between the internal and the external environment by modulating the coupling of brain networks involved in attentional processes. fMRI studies of attention have revealed the importance of three brain networks: a dorsal

attention network (DAN), a default mode network (DMN), and a fronto-parietal control network (FPCN). The dorsal attention network is involved in externally focused attention whereas the default mode network is involved in internally directed attention. The fronto-parietal control network has been proposed to mediate the transition between external and internal attention by coupling its activity to either the dorsal attention network or the default mode network depending on the attentional demand. Dopamine is hypothesized to modulate attention and has been linked to the integrity of these three attention-related networks. We found that in the resting state where internal cognition dominates, dopamine enhances the coupling between the fronto-parietal control network and the default mode network while reducing the coupling between the fronto-parietal control network and the dorsal attention network. These results add a neurochemical perpective to the role of network interaction in modulating attention.

The third finding shows that, in addition to supporting the transition between internal and external attention, dopamine also modulates the shifting of attention between perceptual features of objects. Attentional shifting can be conceptualized as at least two processes: one for shifting between perceptual features of objects and another for shifting between the abstract rules governing the selection of these objects. Object and rule shifts are believed to engage distinct anatomical structures and functional processes. Dopamine activity has been associated with attentional shifting, but patients with dopaminergic deficits are not impaired on all tasks assessing attentional shifting, suggesting that dopamine may have different roles in the shifting of objects and rules. The results did not associate shifts of abstract rules with activation in any brain region, and dopamine did not correlate with rule shift performance. Shifting between object features deactivated the medial prefrontal cortex and the posterior cingulate and activated the lateral prefrontal cortex, posterior parietal areas, and the striatum. FMT signal in the striatum correlated negatively with object shift performance and deactivation in the medial prefrontal cortex, a component of the default mode network, suggesting that dopamine influences object shifts via modulation of activity in the default mode network.

The integration of these findings shows that a gene in the dopamine system influences cognition via dopamine synthesis capacity, resting state fMRI activity and task-related fMRI activity, and that the specific role of dopamine in cognition may be the modulation of attentional processes.

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1. Background

1.1 Dopamine, the neurotransmitter

Dopamine synthesis begins with tyrosine, which is converted to L-DOPA and subsequently to dopamine. Dopaminergic neurons are found in the substantia nigra and the ventral tegmentum of the midbrain. These neurons send their nerve terminals to the striatum and the prefrontal cortex, which are areas with high dopamine receptor density. Released dopamine binds to receptors on postsynaptic neurons to activate the signaling cascade and receptors on presynaptic neurons to regulate dopamine synthesis and release. Dopamine is removed from the synapse by reuptake transporters and degraded by monoamine oxidase or catechol-*O*-methyltransferase or recycled by the vesicular monoamine transporter 2 (Bjorklund and Dunnett, 2007; Cooper et al., 2003).

1.2 Brief history

A humble beginning

Dopamine was independently synthesized by Barger and Ewens in England and by Mannich and Jacobsohn in Germany in 1910 (Barger and Ewens, 1910; Mannich and Jacobsohn, 1910), but until the mid-1950s, it was considered simply an intermediate in the biosynthesis of other catecholamines; in fact, dopamine did not acquire its current name until 1952 (Hornykiewicz, 2002). Research on the physiological effects of neurotransmitters in the early part of the 20th century was often conducted in the peripheral nervous system, where effects of adrenaline and noradrenaline are more salient. Polish chemist Casimir Funk was studying the formation of adrenaline when he synthesized DOPA in 1911 (Funk, 1911). Around the same time, Italian chemist Torquato Torquati isolated the natural L-form of DOPA from the *Vicia faba* bean (Torquati, 1913). The discovery by Peter Holtz and colleagues that the enzyme aromatic-L-amino-acid decarboxylase converts L-DOPA to dopamine led Holtz and Hermann Blaschko at Cambridge to independently propose that dopamine is an intermediate in the synthesis of adrenaline and noradrenaline (Blaschko, 1939; Holtz, 1939; Holtz et al., 1938).

Blaschko first suggested that dopamine might have a physiological function independent of its role as a precursor to noradrenaline at a meeting of the Swiss Society of Physiology, Biochemistry, and Pharmacology in 1956 (Blaschko, 1957). The next year, while researching the pharmacological effects of reserpine, previously shown to deplete noradrenaline in the body, Arvid Carlsson and colleagues in Sweden found that injections of DOPA reversed the sedative effects of reserpine in animals. To their surprise, they did not find a concurrent increase in noradrenaline with DOPA injections, suggesting that dopamine is not simply a precursor for noradrenaline (Carlsson et al., 1957).

Until that period, researchers had been using a flourimetric method in which fluorescence from dopamine and adrenaline have similar characteristics. In 1958, Carlsson and Waldeck developed another flourimetric method whereby the fluorescence spectra of dopamine differ greatly from those of noradrenaline (Carlsson and Waldeck, 1958). Carlsson's students, Ake Bertler and Evald Rosengren, used the new technique to show that dopamine and noradrenaline had clearly different distributions in the brain. Areas with the highest concentration of dopamine turned out to have the lowest concentration of noradrenaline (Bertler and Rosengren, 1959). These results firmly established dopamine as an endogenous agonist with distinct physiological functions. Carlsson later received the Nobel Prize in Physiology or Medicine for his achievements.

Motor focus

Interests in dopamine grew with the recognition of its important role in Parkinson's disease. Several lines of evidence connected dopamine to the motor disease James Parkinson first described in a pamphlet published in 1817 (Parkinson, 2002). Firstly, dopamine was found in large amounts in the striatum, a known component of the motor system. Secondly, reserpine depletes dopamine in the striatum. Lastly, DOPA attenuates the hypokinesis induced by reserpine (Carlsson, 1959).

Oleh Hornykiewicz was a postdoctoral fellow in Blaschko's lab when speculations of a dopaminergic function distinct from noradrenaline were debated. After Hornykiewicz returned to Vienna, he began measuring dopamine levels in postmortem brains of people with Parkinson's disease, Huntington's disease, and other motor disorders. In 1960, he published results showing dopamine depletion in the striatum of only parkinsonian brains. After several more papers on the biochemistry of Parkinson's disease, Hornykiewicz proposed an association between dopamine deficiency in the striatum and motor deficits in Parkinson's patients. Hornykiewicz and a clinical neurologist, Walther Birkmayer, experimented with administering L-DOPA to Parkinson's patients. The duo reported, "Bedridden patients who were unable to sit up, patients who could not stand up from a sitting position, and patients who, when standing, could not start walking, performed all these activities after L-DOPA with ease" (Hornykiewicz, 1992; Roe, 1997). The dramatic results heralded the arrival of L-DOPA therapy as a treatment for Parkinson's disease.

1.3 Dopamine and cognition

Lesion and pharmacological evidence

The success of L-DOPA therapy focused initial attention on the role of dopamine in motor control. As progress was made in improving the efficacy of L-DOPA therapy, pharmacologists began to notice the link between dopaminergic drugs and changes in non-motor behavior. Antipsychotic drugs used to improve schizophrenia were found to work by blocking dopamine receptors, and dopamine agonists could induce psychosis (Swerdlow and Koob, 1987). Subsequent lesion

studies in monkeys and rodents established the importance of dopamine in working memory and other cognitive functions involving the prefrontal cortex and the striatum (Feeser and Raskin, 1987; Whishaw and Dunnett, 1985). A classic study by Patricia Goldman-Rakic and colleagues showed that depletion of dopamine by 6-hydroxydopamine in the principal sulcus of monkeys impaired performance on a delayed response task of spatial working memory. These deficits were reproduced by surgical removal of the same area, and dopamine agonists reversed these deficits (Brozoski et al., 1979). Further evidence linking dopamine and cognition were found in studies whereby bilateral lesions to the substantia nigra rendered rats unable to switch attention between targets and a unilateral lesion of the substantia nigra in baboons produced sensory neglect on the contralateral side (Baunez and Robbins, 1999; Viallet et al., 1983).

Similar findings were also found in pharmacological studies of humans. After subjects received dopaminergic antagonists or a mixture free of dopamine precursors, working memory, attentional shifting, and other executive functions were significantly impaired (Harmer et al., 2001; Mehta et al., 2004; Mehta et al., 1999). In contrast, dopamine agonists improved performance across a range of cognitive measures (Luciana et al., 1992; Muller et al., 1998; Powell et al., 1996). Moreover, cognitive deficits are now well documented in Parkinson's disease and other dopamine-related disorders such as schizophrenia (Braver and Cohen, 1999; Cools et al., 2001b; Lewis et al., 2003). These accumulating studies provide direct evidence that changes in dopamine activity lead to changes in cognitive performance.

Inverted-U effect

Relationships between dopamine and neural activity or cognitive performance follow an inverted-U shaped profile, with too little or too much dopamine resulting in worse outcome. Local field potential recordings in brain slices of rats bathed in dopamine or a dopamine agonist found high neuronal network coherency in samples with moderate levels of dopamine relative to samples with dopamine concentration in the low or high ends (Stewart and Plenz, 2006). In monkeys, stimulation of dopamine receptors in the prefrontal cortex improved working memory but only when the stimulation was within a narrow dose range (Vijayraghavan et al., 2007). Psychopharmacological studies with human volunteers revealed a similar dose-response effect. Administration of amphetamine, a dopamine agonist, improved performance in individuals with low endogenous dopamine level but impaired performance in those with high endogenous dopamine level (Mattay et al., 2003). Bromocriptine, another dopamine agonist, interacted with the baseline working memory capacity of subjects, such that the drug improved working memory in subjects with a low baseline performance but impaired working memory in subjects with a high baseline (Kimberg et al., 1997).

Such nonlinear effects of dopamine have tremendous implications for treating dopaminergic disorders. Dopamine depletion in the striatum of Parkinson's disease patients begins in the dorsal striatum and progresses ventrally. In patients where dopamine function in the ventral striatum was still intact, L-DOPA therapy

improved cognitive functions involving the dorsal striatum while simultaneously impaired functions that engage the ventral striatum (Cools et al., 2001a, 2003). These findings underscore the importance of recognizing the interaction between medication and baseline dopamine activity in treatments of diseases like Parkinson's.

Modulating attention

The specific role of dopamine in cognition has been proposed to be the modulation of attentional processes (Matthysse, 1978; Nieoullon, 2002; Rose et al., 2010). Evidence for this proposal comes from studies in which lesioning of the dopamine system led to suppression of electrophysiological rhythms associated with attention and deficits in attentional aspects of behavior (Montaron et al., 1982; Viallet et al., 1983). Additionally, difficulties in focusing attention have been documented in patients with Parkinson's disease, and treatments for attention deficit disorder often target the dopamine system (Solanto, 1998; Wright et al., 1990). Recently, dopamine release was observed during performance of a task assessing attentional setshifting (Monchi et al., 2006).

Attention has been dichotomized as internally directed versus externally directed as well as discriminating between object features versus abstract rules, presumably a lower-order and a higher-order process, respectively (Carver, 1979; Roberts and Wallis, 2000). Several studies have shown that Parkinson's disease patients are not uniformly impaired on externally- and internally-driven tasks, and the specificity of the impairment may correlate with disease severity (Brown and Marsden, 1988; Fimm et al., 1994; Hsieh et al., 1995). These results suggest that the dopamine system discriminates between internal and external attention. Dopamine also contributes to the ability to distinguish between object features and abstract rules. Patients with lesions in the striatum exhibited deficits in shifting between object features but the shifting of abstract rules appeared intact (Cools et al., 2006). Similarly, shifting between object features but not abstract rules engaged the striatum in healthy subjects (Cools et al., 2004). These findings support an anatomical specificity to the relationship between dopamine and attentional processing. Thus, dopamine seems to not only modulate attention but is also sensitive to the multidimensionality of attention.

1.4 Experimental techniques

Lesion and pharmacological studies provide evidence for a cause-and-effect relationship, but these approaches carry the possibility of disturbing the dopamine system in ways that might alter the endogenous relationship between dopamine and behavior. Alternative techniques for assessing dopamine function without introducing artifacts into the system have been employed. Neuroimaging provides both structural and functional information that together can localize effects of dopamine activity to different regions of the brain with great specificity. Functional genetic polymorphisms, on the other hand, are consistent indicators of individual

differences in dopamine activity. These techniques have proven reliable in studies of dopamine and cognition.

Positron emission tomography (PET)

PET measures endogenous dopamine activity *in vivo*. 6-[^{18}F]fluoro-L-dopa (FDOPA) is a tracer that has been widely used since the 1980s to quantify dopamine synthesis capacity (Garnett et al., 1983). FDOPA is a substrate of aromatic L-amino acid decarboxylase, an enzyme whose activity provides an estimate of the ability of dopaminergic neurons to synthesize dopamine when provided with optimal substrates. Uptake of FDOPA correlates with performance on dopamine-related tasks such as the Stroop test and the Wisconsin card sorting test (Bruck et al., 2001; Tiihonen et al., 1998; Vernaleken et al., 2007), and changes in FDOPA uptake have been documented in dopaminergic disorders such as Parkinson's disease and schizophrenia (Huttunen et al., 2008; Rinne et al., 2001).

One disadvantage of using FDOPA is the metabolism of FDOPA in the peripheral system. This enzymatic process reduces the amount of FDOPA reaching the central nervous system and thus reducing FDOPA uptake by neuronal tissues. It also produces radiolabeled metabolites which complicate interpretation of images and kinetic data. An FDOPA analog, 6-[^{18}F]fluoro-l-m-tyrosine (FMT), was later synthesized to address the issue of peripheral metabolism and improve the signal to noise ratio in the quantification of dopamine synthesis capacity (DeJesus, 2003; Jordan et al., 1997). Like FDOPA, FMT uptake correlates with cognitive functions such as working memory (Cools et al., 2008; Landau et al., 2009) and is sensitive to changes in the dopamine system (Braskie et al., 2008). Hence, PET-FMT is preferred for the quantification of endogenous dopamine activity in humans.

Functional magnetic resonance imaging (fMRI)

The low spatial resolution of PET limits the identification of brain areas and networks mediating the effects of dopamine on behavior. fMRI complements PET by bringing high resolution spatial information to the investigation. fMRI studies of dopamine-related cognitive tasks identified the involvement of several interregional brain networks. Two such networks are the fronto-parietal control network and the default mode network. Both working memory and attentional shifting tasks activate the fronto-parietal control network and deactivate the default mode network, and the degree of activation and deactivation in these networks correlates with task performance (Chee and Choo, 2004; Lie et al., 2006; Nystrom et al., 2000). More recently, fMRI activity in the resting state has been shown to fluctuate in spatial patterns that resemble those activated by cognitive tasks, and the temporal coherence, called functional connectivity, in these spatial patterns correlates with performance, suggesting that these networks are functional and intrinsic to the brain (De Luca et al., 2006).

When PET is combined with fMRI, relationships between dopamine, brain networks, and performance can be assessed. Relationships between dopamine and brain networks have already been demonstrated in both healthy subjects and patients with dopamine deficits. Dopamine depletion impairs functional connectivity between nodes in a network (Nagano-Saito et al., 2008). Similarly,

Parkinson's disease patients exhibit functional disconnection (van Eimeren et al., 2009). Recently, studies from our lab reported associations between PET-FMT uptake and network activity that are consistent with the literature on dopamine and brain networks (Braskie et al., 2010; Klostermann et al., 2012).

Genetic polymorphism

In addition to neuroimaging, another approach for assessing endogenous dopamine function in humans is to exploit existing genetic polymorphisms. One of the most well-researched single nucleotide substitution in the dopamine system is on the gene coding for catechol-*O*-methyltransferase (COMT). COMT metabolizes dopamine, and in the prefrontal cortex where dopamine reuptake transporters are expressed in low abundance, COMT influences synaptic dopamine activity (Karoum et al., 1994). Knocking out COMT in rodents significantly increased dopamine level in prefrontal cortex (Gogos et al., 1998).

A guanine/adenine substitution in the COMT gene changes the amino acid at codon 158 from a valine (Val) to a methionine (Met). COMT is more thermostable in the Val/Val genotype, making this genotype four times more efficient at metabolizing dopamine than the Met/Met genotype. The result is three levels of COMT activity: high activity in Val/Val, intermediate activity in Val/Met, and low activity in Met/Met. COMT polymorphism has been associated with dopamine synthesis capacity, fMRI activity in the prefrontal cortex, and cognitive performance (Akil et al., 2003; Malhotra et al., 2002; Meyer-Lindenberg et al., 2005; Tan et al., 2007).

1.5 Specific aims

The goal of this dissertation is to combine the three aforementioned techniques (PET, fMRI, and genetic polymorphism) to extend current knowledge of relationships between dopamine, brain activity as seen with fMRI, and cognitive performance, particularly on tasks involving attentional processes. Specifically, the first aim is to characterize relationships between COMT, dopamine synthesis capacity, resting state fMRI activity, task-related fMRI activity, and cognitive performance to derive a model, at the systems level, of how COMT influences performance through these measures of brain activity. Numerous studies have associated COMT polymorphism with behavior, but the results have been inconsistent (Egan et al., 2001; Mattay et al., 2003). COMT influences behavior though many downstream processes, making direct COMT-behavior associations unstable, leading to inconsistent reports. Knowing the effects of COMT on neurochemistry and neural networks is critical to understanding COMT function and reconciling current inconsistencies regarding COMT in the literature. Additionally, this study will investigate the inverted-U shaped effect of dopamine that psychopharmacological studies have reported but using an *in vivo* measure of endogenous dopamine activity.

The second and third aims investigate the specific brain areas and networks mediating dopaminergic modulation of attentional processes. As previously

discussed, the dopamine system discriminates between internal and external attention as well as between object features and abstract rules. The second aim explores the role of dopamine in the shifting of attention between internal and external environments. The third aim investigates the relationship between dopamine and the shifting of attention between object features and the abstract rules guiding the selection of those features.

The three aims are addressed in the three chapters of this dissertation. Each chapter includes an introduction to the aim, the materials and methods employed, the results, and a discussion of the findings. These findings provide a framework for understanding the mechanism of gene-behavior associations and the multidimensional relationship between dopamine and attention. I hope our results demonstrate the power of combining different techniques and motivate other researchers to consider a multimodal approach in their investigations.

2. Aim 1 - Genetic effects on behavior are mediated by neurotransmitters and large-scale neural networks

2.1 Introduction

Dopamine is critical for cognitive functions involving the prefrontal cortex (PFC) (Braver and Cohen, 2000). Catechol-O-methyltransferase (COMT) degrades dopamine in the PFC (Dickinson and Elvevag, 2009). A nucleotide substitution in the COMT gene replaces a valine (Val) with a methionine (Met), resulting in a less active enzyme that quadruples the concentration of dopamine in the PFC (Lachman et al., 1996). Studies relating COMT genotype to prefrontal function yield conflicting results (Egan et al., 2001; Mattay et al., 2003), demonstrating that a direct correlation between gene and behavior reflects a partial relationship that is unstable without knowledge of the mechanism of COMT function.

The immediate function of COMT in the PFC is dopamine degradation, suggesting that COMT modulates neural activity and cognition via dopamine activity. Human autopsy studies found an association between the Val allele and increased expression of a dopamine-synthesizing enzyme (Akil et al., 2003). We therefore used positron emission tomography (PET) to measure dopamine synthesis capacity *in vivo* to assess the influence of COMT polymorphism on dopamine activity.

Dopamine may affect cognition by facilitating neuronal synchrony. Local field potential recordings showed that dopamine modulates oscillations in the γ-band proposed to support cortical activity relating to perceptual and cognitive performance (Sharott et al., 2005; Ward, 2003). Neuronal synchrony may be the cellular basis of temporal coherence seen with functional magnetic resonance imaging (fMRI) (Fox et al., 2005). Without an externally driven task, brain activity seen with fMRI fluctuates in coherent patterns called resting state networks (RSNs) (Biswal et al., 1995). RSNs are thought to reflect functional systems involved in cognitive processes (De Luca et al., 2006). Similar to γ-band oscillations, temporal coherence within RSNs, known as functional connectivity, decreases after dopamine depletion (Nagano-Saito et al., 2008). We therefore acquired fMRI signal in the absence of a task and related these to our PET measures of dopamine to assess the role of this neurotransmitter in modulating functional connectivity in RSNs.

RSNs may arise from the "idling state" of functional networks and can be predictive of task-induced fMRI activity (De Luca et al., 2006; Mennes et al., 2010). We acquired fMRI signal during performance of a prefrontal function task to explore the relationship between resting state and task-related activity. A prefrontal function associated with COMT and dopamine is cognitive flexibility, or the ability to change behavior in response to relevant changes in the environment (Cools et al., 2001b; Nolan et al., 2004). Setshift tasks probe cognitive flexibility by assessing the subject's response as the rule of the task changes unpredictably (Monchi et al., 2004). We hypothesized that individual differences in setshift performance would

relate to fMRI activity during task performance and, indirectly, functional connectivity in RSNs and dopamine function.

Lastly, we propose a model of how COMT influences prefrontal cognition through dopamine synthesis, resting state fMRI activity, and task-related fMRI activity. A complex multimodal assessment of this sort will be necessary for a full understanding of the relationships between genetics and behavior that will improve prediction of genetic effects on behavior and their role in disease.

2.2 Materials and Methods

Subjects

Fifteen right-handed, young adults between 20 and 30 years old, inclusive, (mean age 25.3 ± 2.8 years, 8M/7F) were recruited via flyers and online postings. Subjects were excluded if they had a Mini Mental State Exam (Folstein et al., 1975) score less than 28, a known major systemic disease, a history of psychiatric or neurological disorder, a history of substance abuse, current usage of medication known to affect dopaminergic or any neurological function, current or prior symptoms of depression, a serious head injury, or any contraindications to MR imaging. Subjects gave written informed consent prior to undergoing a PET scan with 6-[^{18}F]fluoro-l-m-tyrosine (FMT), a resting state fMRI scan, task-related fMRI scans, and genotyping. The current study was approved by institutional review boards at University of California, Berkeley and Lawrence Berkeley National Laboratory.

Genotype

Blood samples were collected from subjects and stored at the DNA Bank at the University of California, San Francisco (UCSF). UCSF's Genetics Core Facility performed COMT genotyping (Lachman et al., 1996). Of the fifteen subjects, 5 were met/met, 4 were met/val, and 6 were val/val.

PET data acquisition

PET imaging and FMT synthesis were performed at Lawrence Berkeley National Laboratory. FMT synthesis has been described previously (VanBrocklin et al., 2004). FMT is a substrate of aromatic L-amino acid decarboxylase (AADC), a dopamine-synthesizing enzyme whose activity provides an estimate of the ability of dopaminergic neurons to synthesize dopamine when provided with optimal substrate (DeJesus, 2003). FMT is metabolized by AADC to 6-[^{18}F]fluorometatyramine, which is oxidized to 6-[^{18}F]fluorohydroxyphenylacetic acid (FPAC). FPAC is visible on PET-FMT scans. Signal intensity on PET-FMT scans is thus indicative of dopamine synthesis capacity.

Subjects received an oral dose of carbidopa (2.5mg/kg) approximately 60 minutes before FMT injection. Carbidopa inhibits peripheral decarboxylation of FMT, resulting in a higher PET signal. Carbidopa does not cross the blood brain barrier (Clark et al., 1973) and has no detectable clinical effects in the dose range used in this study.

PET scans were acquired on a Siemens ECAT-HR PET camera with a 3.6-mm in-plane spatial resolution, 47 parallel imaging planes, and retractable septae for 3D imaging. Subjects were positioned in the scanner for a 10-min transmission scan used for attenuation correction. Following the scan, approximately 2.5 mCi of FMT was injected as a bolus into an antecubital vein. Eighty-nine minutes of dynamic acquisition was acquired in the following sequence of frames: 4 x 60s, 3 x 120s, 3 x 180s, and 14 x 300s. FMT images were reconstructed with an ordered subset expectation maximization algorithm with weighted attenuation, scatter corrected, and smoothed with a 4mm full width half maximum kernel.

Regions of interest (ROIs)

We drew ROIs by visual inspection on each subject's mean MPRAGE MRI scan using FSLview. Dorsal caudate, dorsal putamen, and ventral striatum ROIs were drawn according to previously published guidelines (Mawlawi et al., 2001). Midbrain ROIs were drawn on five consecutive axial slices, the most caudal being the slice on which frontopontine fibers were separated into left and right bundles and the substantia nigra was clearly outlined (Fig. 1A). Both intrarater and interrater reliability were greater than 95%. The cerebellum grey matter was the reference region for calculating PET-FMT values. Because the cerebellum is located posterior and adjacent to the midbrain, limited PET spatial resolution introduces blurring and causes signal to spill onto neighboring regions. To avoid contamination of FMT signal from the midbrain, only the posterior ¾ of the cerebellum was included in the ROI.

PET data analysis

Movement correction was achieved in two steps. In the first step, during the reconstruction of emission images, the sum of the first 5 minutes of data served as the reference image. If the transmission image was not aligned with the reference image, we used SPM to align these images. We then used SPM to calculate the matrix for aligning each subsequent emission image to the reference image and applied these matrices to the transmission image to move it to each emission image space for image reconstruction. This processing was done "offline" after forward projecting the PET data, reorienting as needed, and then performing the reconstruction of correctly aligned transmission and emission data. In the second step, we used SPM to align all emission images to the middle (12^{th}) image. Realigning all emission images to the middle image minimizes extreme displacement of the first and last few images in the scan.

ROIs were mapped to FMT space using the matrix calculated by FSL-FLIRT for coregistering the mean MPRAGE to the mean image of the realigned FMT frames (http://www.fmrib.ox.ac.uk/fsl/, version 4.1.2). After coregistration, ROI masks were thresholded at 0.5 to ensure high tissue probability. An in-house graphical analysis program implementing Patlak plotting (Patlak and Blasberg, 1985) with the cerebellum as the reference region created K_i images (Fig. 1A), which represent the amount of tracer accumulated in the brain relative to the cerebellum and are comparable to K_i images obtained using a blood input function but scaled to the volume of distribution of the tracer in the cerebellar reference region. K_i values

from the ROIs were extracted.

MRI data acquisition

MRI data were acquired on a Siemens 1.5T Magnetom Avanto System with a 12-channel head coil. Foam cushions and headphones were provided to enhance comfort and reduce head movement. T2*-weighted echo planar images were collected for task-related fMRI (repetition time=2020ms, echo time= 50ms, flip angle=90°, voxel dimensions=3x3x3.5mm) and resting state fMRI (repetition time=1890ms, echo time=50ms, flip angle=90°, voxel dimensions=3x3x3.5mm). During the resting state scan, subjects were instructed to relax and think of nothing in particular. Three structural images were acquired: one T1-weighted structural scan in plane to the fMRI scans (repetition time=2000 ms; echo time=11ms; flip angle=150°; voxel dimensions=0.9x0.9x3.5 mm) and two T1-weighted volumetric magnetization prepared rapid gradient echo (MPRAGE) images (repetition time=2120 ms; echo time=3.58 ms; inversion time=1100 ms; flip angle=15°; voxel dimensions=1x1x1mm). MPRAGE images were averaged to obtain a high-quality structural image. T1-weighted images in plane to the fMRI data were used to improve coregistration of fMRI data to the mean MPRAGE, which was used to normalize fMRI data to standard MNI space for group level analyses.

fMRI task

The setshift task was adapted from a design by Cools and colleagues (Cools et al., 2004). On each trial, a star and an hourglass appeared simultaneously on left and right sides of the computer screen; the location was counterbalanced. Bordering the star and hourglass was either a red or blue window. A blue window cued the subject to choose the target figure in the previous trial; if the target in the previous trial was a star, the correct answer was also a star. A red window cued the subject to choose the figure that was *not* a target in the previous trial; if the target in the previous trial was a star, the correct answer was an hourglass. The correct answer held true even if the subject made a wrong response. The first trial of every run included an arrow indicating the target figure. The subject began responding on the second trial. A red window followed by a blue window represented a shift: the rule changed. A red window followed by a red window represented a shift: the target figure changed. A blue window followed by a red window represented a shift; both the rule and the target figure changed. A blue window followed by a blue window represented no shift in rule or target figure (Fig. 2A).

Each subject performed 4 runs of 100 trials each. Each trial lasted 2950ms. On each trial, the stimulus appeared for 2000ms, during which the subject was instructed to make a response by pressing the response key in the left or right hand corresponding to the position of the target figure on the left or right side of the screen; the number of trials in which the target was on the left or right side of the screen was balanced so that each trial type had similar number of left and right hand responses. Feedback then appeared for 500ms: a yellow happy face appeared if the response was correct, and a purple sad face appeared if the response was wrong. The subject was instructed to adjust his or her response according to the feedback. If the subject did not make a response within the 2000ms stimulus period,

the purple sad face appeared, indicating that the response period had lapsed. A fixation cross appeared after the feedback, until the end of the trial. Each trial type had equal probability of appearing. Trial order was pseudorandomized such that no trial type appeared consecutively more than 3 times; the number of repeat trials was counterbalanced across trial type.

Subjects practiced the task for 5 min before the experimental session commenced. After the practice session, the subject had to verbally confirm that s/he understood the task as well as achieving at least 95% accuracy on the practice session. If either condition were not satisfied, the subject had to repeat the practice session. No subject had to repeat the practice session more than once.

Response times from shift and no shift trials were averaged separately to form mean response times for each of the two trial types for each subject.

Task-related fMRI analysis

We used FSL for preprocessing and statistical analyses. Preprocessing included motion correction with MCFLIRT, brain extraction with BET, spatial smoothing with a 7mm full width half maximum Gaussian kernel, and high-pass temporal filtering (100s). Statistical analyses were performed using a general linear model implemented by FEAT. FILM prewhitening was applied to correct for temporal autocorrelation. Temporal derivatives and temporal filtering were included to improve fitting of the model to the data. Events were modeled at the time of stimulus presentation after convolution with a gamma hemodynamic response function. In the first level analyses, for each subject and each scan, one regressor representing shift trials and one regressor representing no shift trials were modeled separately. Only correct trials were modeled. The feedback and fixation events were not modeled and thus functioned as the implicit baseline.

For group-level analyses, we first coregistered each functional scan to the T1-weighted structural image and then to the mean MPRAGE using 6 degrees of freedom rigid body transformations. The mean MPRAGE and its associated T1-weighted structural image and functional scans were normalized to MNI space using 12 degrees of freedom affine transformations. For each subject, first level results were combined in a paired t-test contrasting shift versus no shift trials. Subject-level results were averaged to obtain group-level contrast maps showing activation and deactivation during shift trials relative to no shift trials. Group-level contrast maps were thresholded at $z > 2.3$ with cluster thresholding to correct for multiple comparisons.

Because COMT degradation of dopamine occurs in the PFC (Dickinson and Elvevag, 2009), and because dopamine afferents to the PFC are concentrated in the medial PFC (Emson and Koob, 1978), we used the medial PFC cluster showing deactivation in the group-level contrast map as a region of interest from which to extract a mean deactivation value for each subject. To determine whether the relationship between task-related fMRI activity and performance of a task involving dopamine is specific to the medial PFC, we also extracted mean deactivation values from the posterior cingulate cluster. The cluster of voxels showing deactivation in the medial PFC was clearly separate from the cluster in the posterior cingulate.

Mean deactivation values were calculated by averaging z-statistics extracted from subject-level maps using the medial PFC and posterior cingulate ROIs.

Resting state fMRI analysis

To control for effects of scanner artifacts and physiological processes such as respiratory and cardiac functions, signal associated with the white matter, cerebrospinal fluid (CSF), and the global signal were entered as covariates in the regression of resting state fMRI data. To extract signal associated with white matter and CSF, each subject's mean MPRAGE was segmented into grey matter, white matter, and CSF using FSL-FAST. Signal intensity in CSF and white matter images was then thresholded at 90% and 99%, respectively, to ensure high tissue probability. Each individual's resting state fMRI scan was masked with the thresholded CSF and white matter images, and the mean time series was extracted for CSF and white matter. Global signal was calculated by averaging across all voxels in the whole brain.

The removal of the global signal served two purposes in this study. The first purpose was to control for global effects common to all fMRI studies, such as scanner artifacts, gross body movement, and physiological processes. The second purpose was to control for effects of peripheral dopamine activity. Dopamine receptors are present in peripheral arteries, carotid bodies, and the endocrine system. Stimulation of these receptors has been found to affect vasodilation and myocardial contractility (Cavero et al., 1982). The global signal was removed to remove effects of peripheral dopamine from effects in the central nervous system.

The medial PFC is a component of the default mode network (DMN), a group of brain areas known to deactivate during task performance relative to baseline (Buckner et al., 2008). To explore the relationship between resting state and task-related activity, we calculated functional connectivity between the medial PFC and the DMN. Resting state fMRI scans were preprocessed in FSL using the following operations: motion correction with MCFLIRT, removal of non-brain matter with BET, spatial smoothing with a Gaussian kernel of 5 mm, and high-pass temporal filtering removing frequencies below 0.01Hz. We defined the DMN with a posterior cingulate (PCC) seed. Using the seed-based approach, Greicius and colleagues reported that peak connectivity in the PCC had MNI coordinates -2 -51 27 (Greicius et al., 2003). We generated an 8x8x8 mm^3 ROI around the peak connectivity voxel, coregistered the ROI to individual subject's resting state fMRI scan, and extracted the mean time series for voxels in the ROI mask. To extract the DMN mask, for each subject, we performed a regression in FSL-FEAT with the PCC mean time series and the three covariates discussed above. z-statistic maps from the regressions were averaged to generate the group-level DMN, which showed correlations between each voxel's time series and the PCC time series. To calculate functional connectivity between the medial PFC and the whole DMN for each subject, we coregistered the DMN mask to the resting state fMRI scan, extracted the mean times series for the whole DMN, and performed a regression with the DMN mean time series and the three covariates. The results were z-statistic maps showing correlations between each voxel's time series and the mean DMN time series. We extracted the mean z-statistic in the medial PFC using the identical ROI used to extract task-related

deactivation. The mean z-statistic represented functional connectivity between the medial PFC and the DMN.

In addition to calculating functional connectivity from a DMN mask defined with a posterior cingulate seed, to confirm the results, we also calculated functional connectivity using a DMN mask extracted with independent component analysis. In addition to the 15 subjects in this study, we have resting state fMRI scans from an additional 13 subjects that participated in a different study in our lab but were recruited using the same criteria as this study; these 13 subjects were not included in other analyses in this study because they were not genotyped or did not perform the fMRI task. We performed independent component analysis on these 28 resting state fMRI scans and identified the component corresponding to the default mode network. Resting state fMRI scans were preprocessed as described above. Preprocessed scans were decomposed into separate spatial and temporal patterns using FSL-MELODIC multi-session temporal concatenation. From the list of outputs, we identified the DMN as the component that has the most voxels overlapping with a DMN template from a previous study in the lab (Mormino et al., 2011). The spatial pattern corresponding to the DMN was coregistered to individual subject's resting state fMRI scan, and a mean time series for all voxels in the DMN mask was extracted for each subject from their preprocessed resting state scan. Functional connectivity was then calculated using the same approach as described above for the DMN mask defined with a posterior cingulate seed.

Statistics

Statistical tests were performed in R (Team, 2011). We used trend analyses to evaluate relationships between COMT, FMT, and functional connectivity. We used Pearson's correlations to relate resting state functional connectivity, task-related deactivation, and response time. FMT, functional connectivity, task-related deactivation, and response time were confirmed to be normally distributed using the Shapiro-Wilk normality test with an alpha of 0.05.

We used an automated variable selection method and bootstrap resampling to identify independent predictors of response time, task-related deactivation, and resting state functional connectivity. Automated variable selection methods are often used to identify independent predictors. However, the approach sometimes mistakenly identifies noise variables as independent predictors or yields models that are not reproducible. Bootstrapping repeatedly samples from the data to estimate the weight of evidence for a variable being an independent predictor. Validation of the approach found that selecting variables identified as independent predictors by at least 60% of the bootstrap samples yields an effective predictive model (Austin and Tu, 2004).

In the initial model, we included COMT, FMT, resting state functional connectivity, and task-related deactivation as predictors of response time. The method generated 1000 bootstrap samples from the dataset, used the Akaike information criterion to develop a parsimonious predictive model for each sample, and calculated the percentage of bootstrap samples in which a variable was identified as an independent predictor. In the next model, the variable identified as an independent predictor in the initial model became the outcome variable, and the

other predictors in the initial model remained as predictors. The process continued until all independent predictors have been identified. Table 1 shows the models employed and the outcome independent predictors. Column 1 shows the input model. Column 2 shows the percent of bootstrap samples in which each variable appeared in the parsimonious model. Column 3 shows the independent predictor of that model or the variable that appeared in more than 60% of the bootstrap samples.

2.3 Results

COMT and dopamine

Trend analyses showed that the number of Val alleles present correlated with increased FMT signal in the midbrain (Pearson's r = 0.62, p-value = 0.025), ventral striatum (Pearson's r = 0.70, p-value = 0.005), and putamen (Pearson's r = 0.62, p-value = 0.024). Correlations between COMT and FMT signal in the caudate were not significant (Pearson's r = 0.33, p-value = 0.808) (Fig. 1B-E).

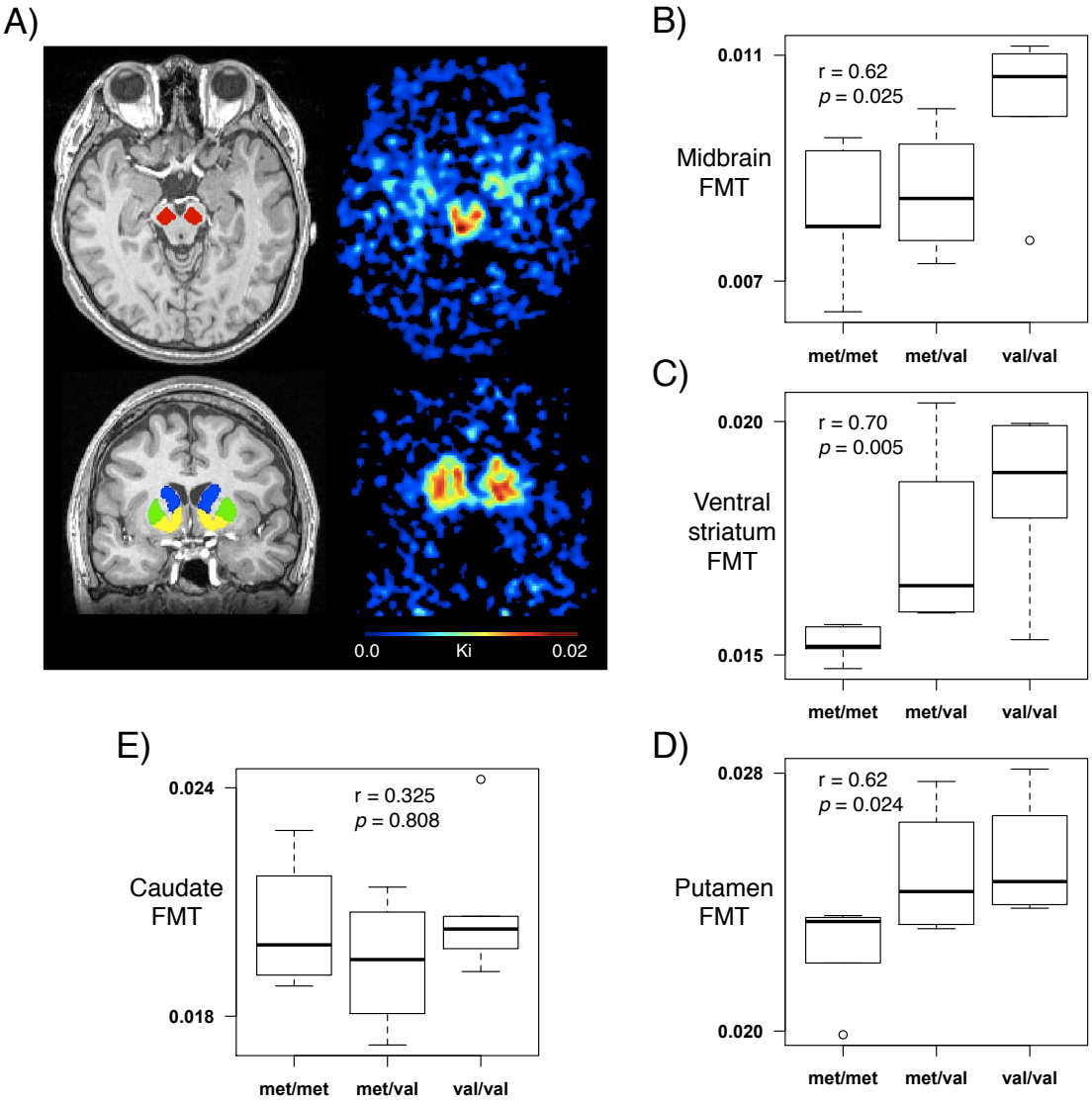

Fig 1: Regions of interest. A) Examples from one subject. Left column shows midbrain (red), caudate (blue), putamen (green), and ventral striatum (yellow) ROIs superimposed on the mean MPRAGE. Right column shows FMT uptake in the midbrain and striatum. B-D) FMT uptake in the midbrain, ventral striatum, and putamen increased as the number of Val alleles increased. E) No relationship between COMT and FMT uptake in the caudate.

Task-related fMRI activity and setshift performance

Relative to no-shift trials, setshift trials deactivated the medial PFC and posterior cingulate and activated the dorsolateral PFC and parietal lobule. Greater medial PFC deactivation correlated with faster response time during shift trials (Pearson's r = 0.59, p-value = 0.020). Deactivation in the posterior cingulate did not correlate with response time during shift trials (Pearson's r = 0.39, p-value = 0.156) (Fig. 2B-D). There was no relationship between task-related activation and response time during shift trials.

Greater deactivation in the medial PFC also correlated with faster response time during no shift trials (Pearson's r = 0.56, p-value = 0.029). Response times during no shift and shift trials were highly correlated (Pearson's r = 0.87, p-value = 2.0×10^{-5}). Given the collinearity, it was unclear whether the relationship between task-related fMRI activity and response time during no shift trials was dependent or independent of the relationship between response times during shift and no shift trials. To address the question of independent versus dependent effect, we used an automated variable selection method in conjunction with bootstrap resampling to identify independent predictors; results are shown below.

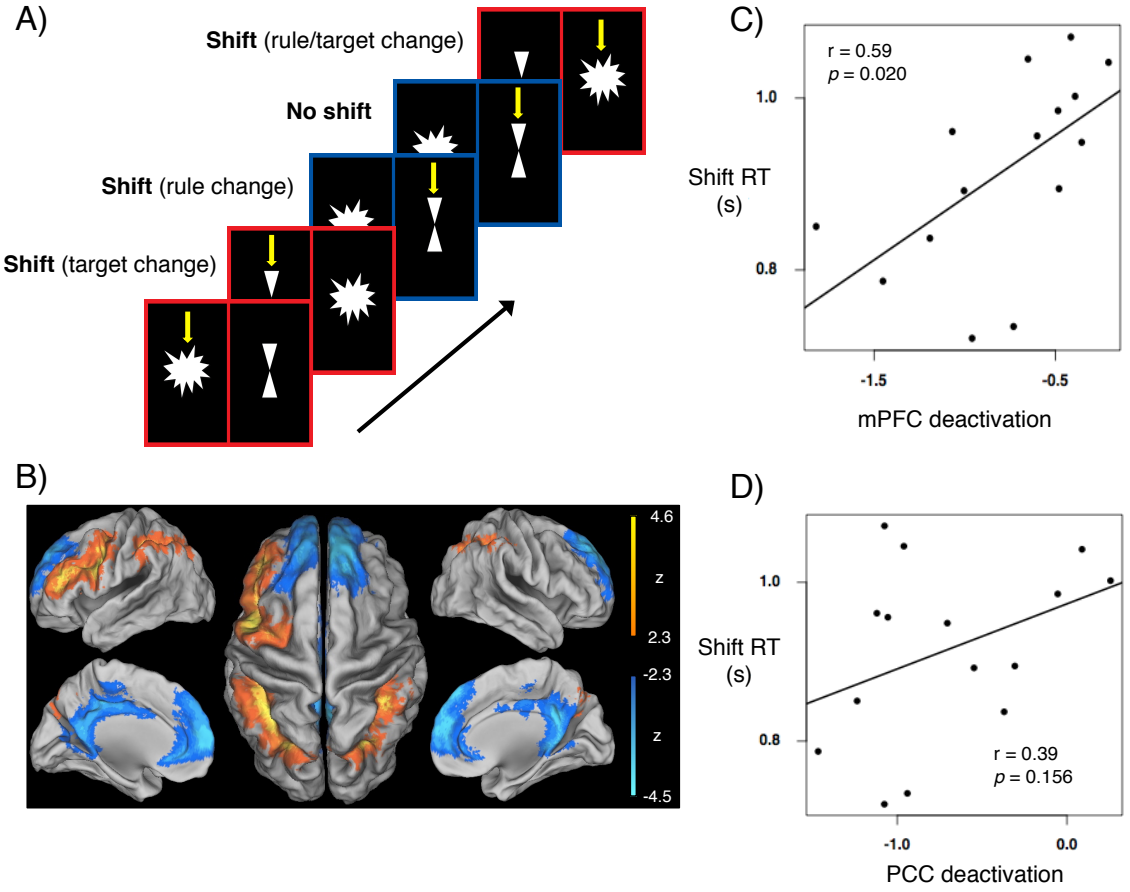

Fig 2: Performance of the setshift task. A) Schematic of the task showing shift and no shift trials. Yellow arrows indicate the correct answer for each trial. B) Voxelwise analysis contrasting shift minus no shift trials found activation (orange) in the left PFC and bilateral parietal lobule and deactivation (blue) in the medial PFC (mPFC) and posterior cingulate. C) Greater deactivation in the mPFC correlated with faster response time (RT) during shift trials. D) Deactivation in the posterior cingulate (PCC) did not correlate with RT during shift trials.

Relationships with resting state functional connectivity

The DMN extracted with a posterior cingulate seed included the medial PFC, posterior cingulate, lateral parietal and left superior temporal cortices (Fig. 3A).

Greater medial PFC functional connectivity correlated with greater medial PFC deactivation during setshift performance (Pearson's r = 0.62, p-value = 0.013). Greater medial PFC functional connectivity also correlated with faster response time during shift trials (Pearson's r = 0.57, p-value = 0.028) (Fig. 3B-C). We used the automated variable selection method to determine whether the relationship between functional connectivity and performance was independent or dependent of the relationship between performance and task-related deactivation, with which functional connectivity was correlated (Pearson's r = 0.62, p-value = 0.013).

A trend analysis showed that Met/Val individuals had greater functional connectivity in the medial PFC than either Met/Met or Val/Val individuals (Pearson's r = 0.58, p-value = 0.030) (Fig. 3D).

Subjects were evenly divided into low, medium, and high FMT groups. Trend analyses showed that subjects with mid-range FMT values had higher functional connectivity than those with low or high FMT values in both the midbrain (Pearson's r = 0.63, p-value = 0.019) and ventral striatum (Pearson's r = 0.89, p-value = 1.4×10^{-4}). Correlations between functional connectivity and FMT values in the putamen (Pearson's r = 0.53, p-value = 0.056) and caudate (Pearson's r = 0.37, p-value = 0.222) were not significant (Fig. 3E-H).

To confirm that functional connectivity results were not affected by the approach with which we defined the DMN, we repeated these analyses using an independent components analysis method of defining the DMN, and all the significant relationships reported above remained (Fig. 4).

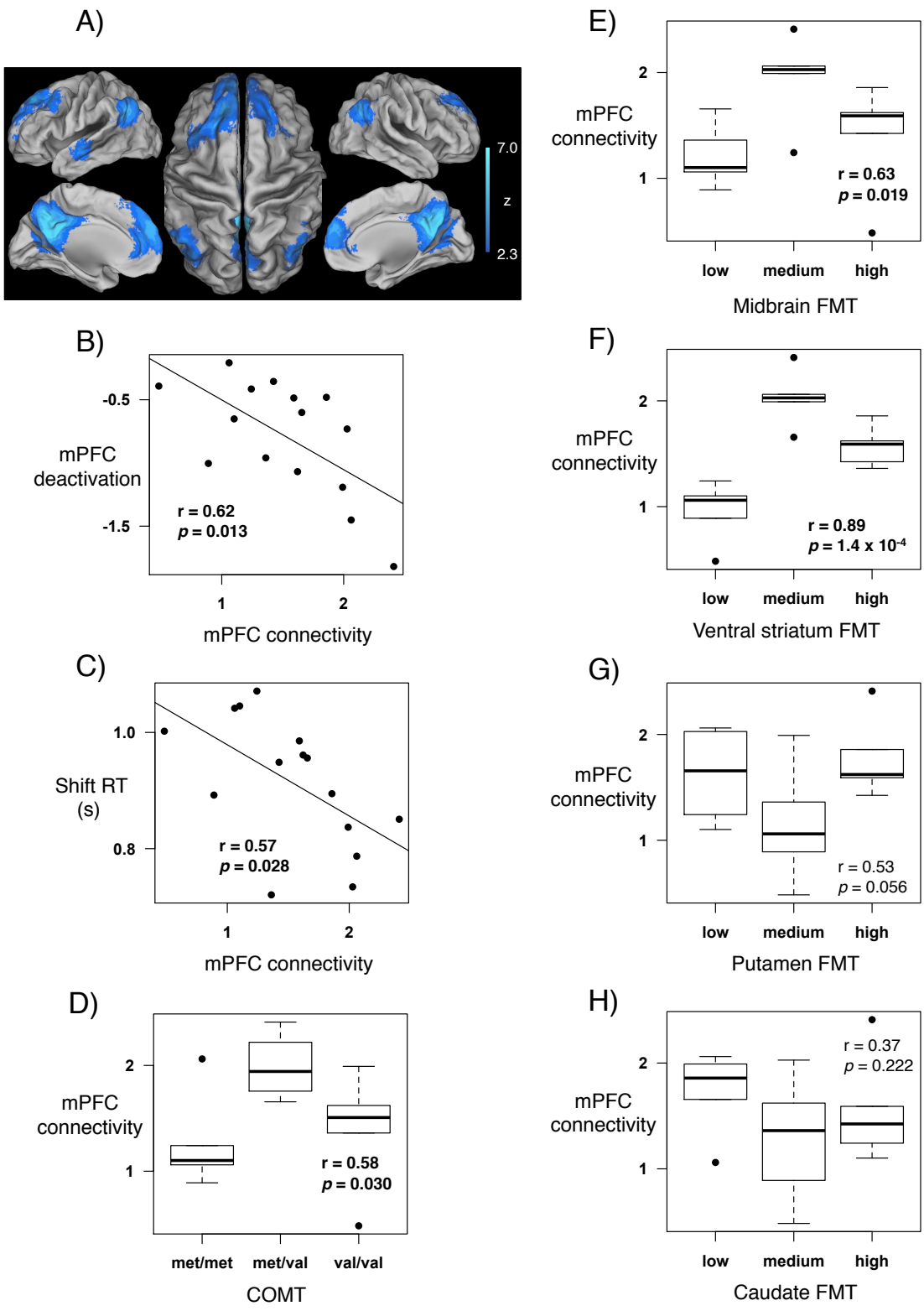
A)
7.0
z
2.3
B)
-0.5
-1.5
mPFC deactivation
r = 0.62
p = 0.013
1
2
mPFC connectivity
C)
1.0
0.8
Shift RT (s)
r = 0.57
p = 0.028
1
2
mPFC connectivity
D)
2
1
mPFC connectivity
r = 0.58
p = 0.030
met/met
met/val
val/val
COMT
E)
2
1
mPFC connectivity
r = 0.63
p = 0.019
low
medium
high
Midbrain FMT
F)
2
1
mPFC connectivity
r = 0.89
p = 1.4 x 10-4
low
medium
high
Ventral striatum FMT
G)
2
1
mPFC connectivity
r = 0.53
p = 0.056
low
medium
high
Putamen FMT
H)
2
1
mPFC connectivity
r = 0.37
p = 0.222
low
medium
high
Caudate FMT

Fig 3: Relationships with functional connectivity. A) Default mode network, extracted with a posterior cingulate/precuneus seed, included the medial PFC, posterior cingulate/precuneus, lateral parietal and superior temporal areas. B) Greater mPFC functional connectivity correlated with greater mPFC deactivation. C) Greater mPFC functional connectivity correlated with faster RT during shift trials. D-F) Inverted-U relationships between mPFC functional connectivity and COMT, midbrain FMT, and ventral striatum FMT. G-H) Relationships between mPFC functional connectivity and caudate and putamen FMT were not significant.

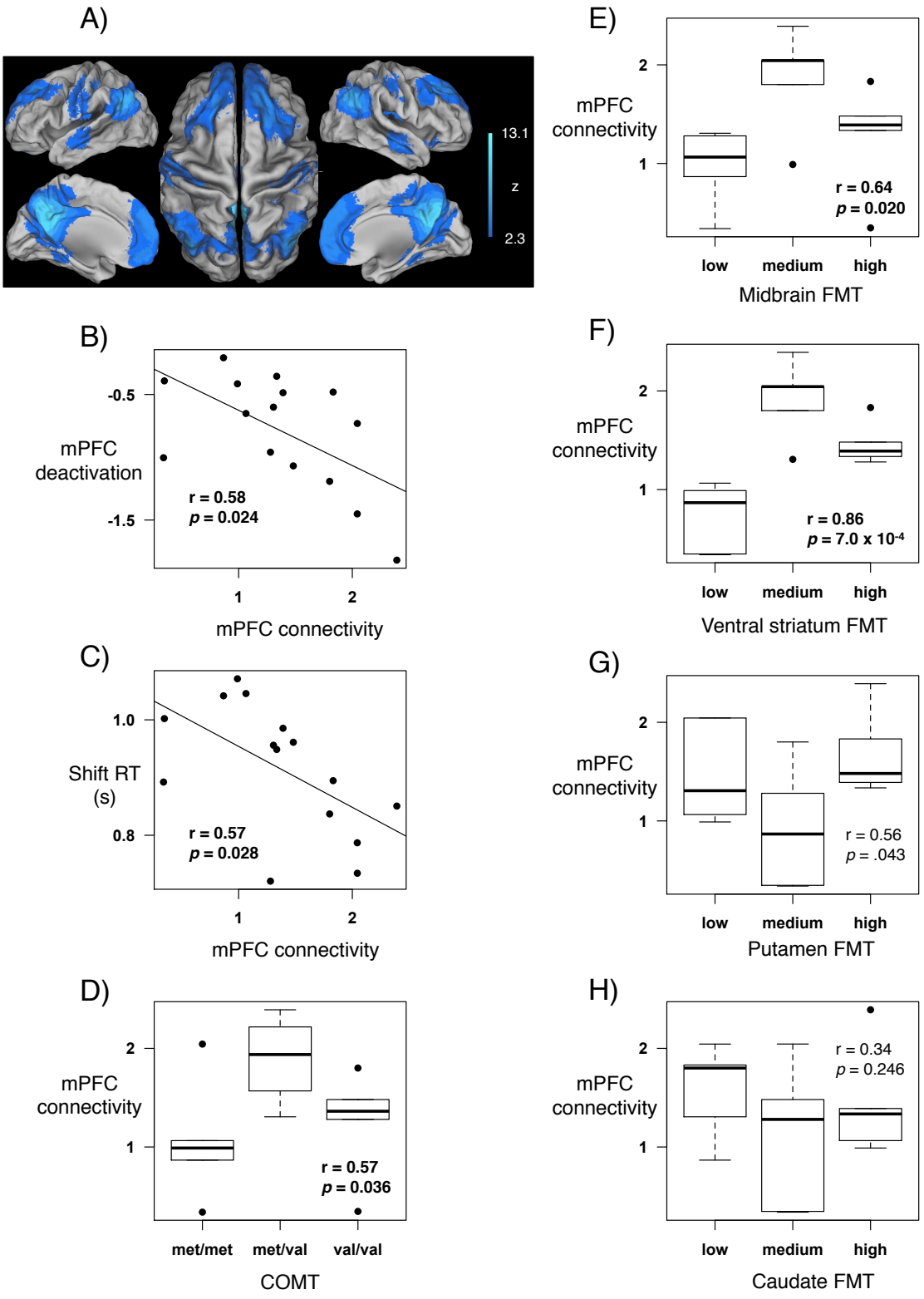

Fig 4: Functional connectivity results replicated. The DMN mask extracted with independent component analysis yielded similar functional connectivity results as the DMN mask defined with a posterior cingulate seed.

Automatic variable selection analysis

Figure 5A summarizes the significant correlations between COMT, FMT, functional connectivity, task-related deactivation, and response time. Figures 5B and 5C show the predictive models for response time during shift trials after elimination of dependent predictors when midbrain or ventral striatum FMT was in the model, respectively. Outputs from the automated variable selection method are presented in Table 1. Results did not differ whether functional connectivity was calculated from the DMN defined with a posterior cingulate seed or extracted by independent component analysis. For predicting response time during shift trials, task-related fMRI activity was the independent predictor of response time, and functional connectivity was the independent predictor of task-related fMRI activity. COMT and FMT were both independent predictors of functional connectivity when midbrain FMT was in the model. When ventral striatum FMT replaced midbrain FMT in the model, ventral striatum FMT was the only predictor of functional connectivity, and COMT was the predictor of ventral striatum FMT. No independent predictor was identified for response time during no shift trials.

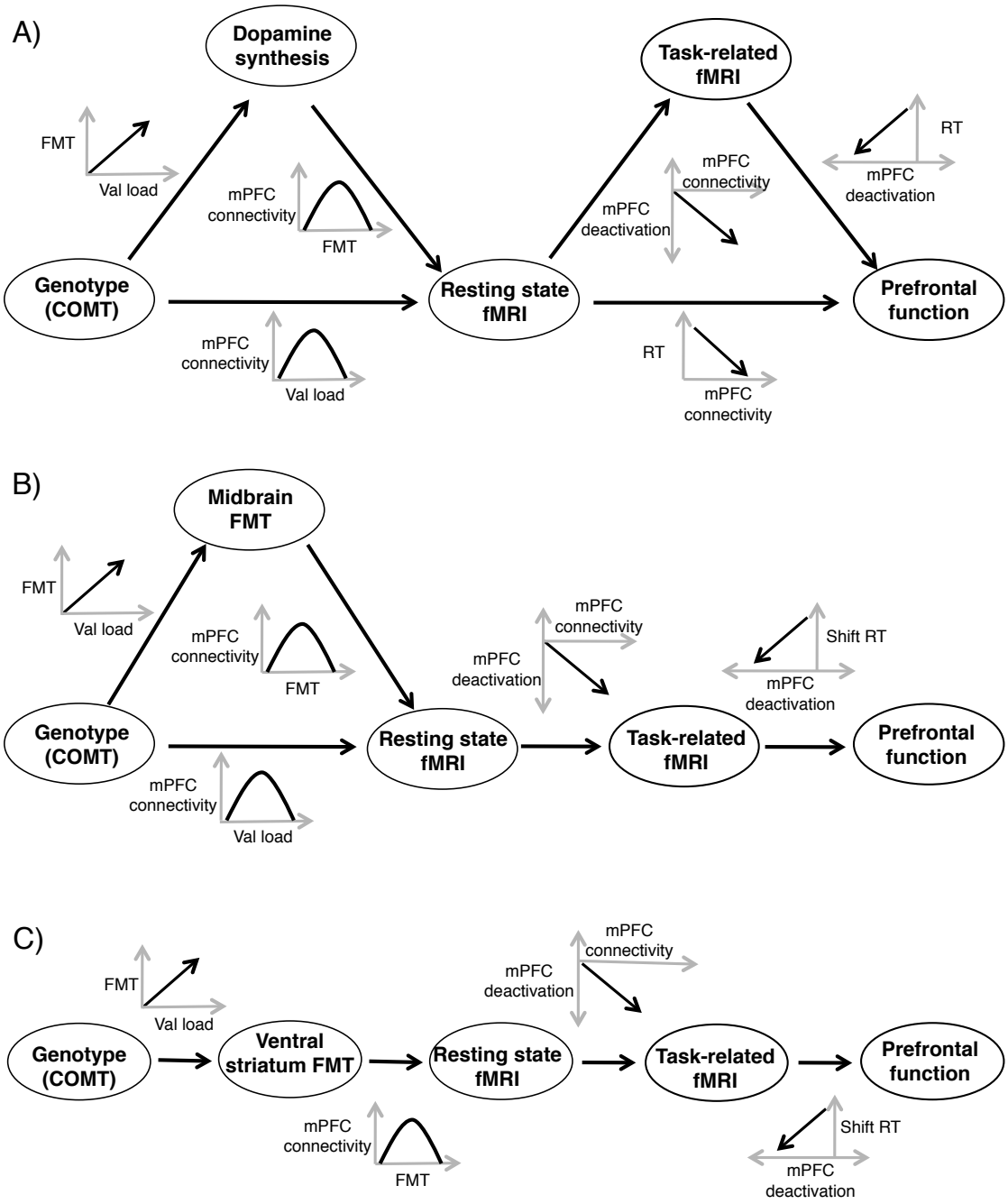

Fig 5: Correlation diagrams. A) Correlations between COMT, FMT, resting state fMRI activity, task-related fMRI activity, and response time. Next to each arrow connecting 2 correlated variables are plots showing the direction and shape of the correlation. B) Predictive model with midbrain FMT after elimination of dependent predictors. C) Predictive model with ventral striatum FMT after elimination of dependent predictors.

Identification of independent predictors by the automated variable selection method and bootstrap resampling

Initial model	% bootstrap samples	Independent predictor
1) Predicting shift RT with midbrain FMT		
shift RT = task fMRI + FC + midbrain FMT + COMT	task fMRI = 70.9 FC = 34.1 FMT = 40.9 COMT = 40.7	task fMRI
task fMRI = FC + midbrain FMT + COMT	FC = 75.9 FMT = 37.6 COMT = 45.4	FC
FC = midbrain FMT + COMT	FMT = 88.3 COMT = 88.8	FMT, COMT
2) Predicting no shift RT with midbrain FMT		
no shift RT = task fMRI + FC + midbrain FMT + COMT	task fMRI = 58.4 FC = 29.4 FMT = 49.4 COMT = 57.9	no independent predictor selected
3) Predicting shift RT with ventral striatum FMT		
shift RT = task fMRI + FC + ventral striatum FMT + COMT	task fMRI = 71.6 FC = 28.2 FMT = 36.9 COMT = 37.0	task fMRI
task fMRI = FC + ventral striatum FMT + COMT	FC = 67.8 FMT = 56.7 COMT =55.9	FC
FC = ventral striatum FMT + COMT	FMT = 91.38 COMT = 54.44	FMT

4) Predicting no shift RT with ventral striatum FMT		
no shift RT = task fMRI + FC + ventral striatum FMT + COMT	task fMRI = 53.5 FC = 25.8 FMT =55.6 COMT = 44.0	no independent predictor selected

Table 1: Identification of independent predictors for response time, task-related fMRI activity, and functional connectivity (FC). Independent predictors for each model were variables identified as predictors in more than 60% of the bootstrapped samples. This table shows the percentage of bootstrapped samples in which each variable was identified as a predictor in each model. Column 1 shows the initial model with the outcome variable and its predictors. Column 2 shows the percentage of bootstrap samples, out of 1000 samples, that each predictor was selected in the parsimonious model, the outcome model of the automated variable selection method. Column 3 shows the independent predictor identified by being selected in more than 60% of the bootstrap samples. For predicting RT during shift trials when midbrain FMT was in the model, a) task-related fMRI activity was the independent predictor of RT, b) FC was the independent predictor of task-related fMRI activity, and c) COMT and FMT were independent predictors of FC. These results are summarized in Fig. 4B. For predicting RT during shift trials when ventral striatum FMT was in the model, a) task-related fMRI activity was the independent predictor of RT, b) FC was the independent predictor of task-related fMRI activity, c) FMT was the independent predictor of FC, and d) COMT was the predictor of FMT. These results are summarized in Fig. 4C. No variable was identified as an independent predictor of response time during no shift trials.

2.4 Discussion

Genetic effects on behavior are undoubtedly mediated by a host of biochemical and physiological processes. We studied the downstream processes whereby the COMT gene influences prefrontal cognition. We performed fMRI with a setshift task to identify brain areas associated with cognitive flexibility, a function previously shown to engage the prefrontal cortex and the dopamine system (Cools et al., 2004; Monchi et al., 2006). We found that setshift performance deactivated the medial PFC and posterior cingulate, two nodes in the DMN (Buckner et al., 2008; Raichle et al., 2001). Setshift performance also activated the dorsolateral PFC and parietal lobule; these areas form the fronto-parietal control network, which consistently activates during performance of tasks probing the prefrontal cortex (Vincent et al., 2008). The deactivation and activation profile of the setshift task resembles results from previous fMRI studies of prefrontal function, assuring us that the setshift task engaged brain regions involved in prefrontal cognition (Chee and Choo, 2004).

We found that greater deactivation in the medial PFC correlated with faster response time during shift trials. These results were not found in the posterior cingulate, suggesting that the relationship was specific to the medial PFC component of the DMN. The DMN is believed to support a variety of internal mental processes. In studies of spontaneous internal cognition, subjects with frequent mindwandering

show higher DMN activity (Mason et al., 2007). In tasks where mindwandering is suppressed in favor of focused attention on external cues, the DMN consistently deactivates (Buckner et al., 2008). Our result supports the hypothesis that optimal task performance involves successful reallocation of attentional resources from the DMN to areas involved in task performance, such as the fronto-parietal control network (McKiernan et al., 2003). Furthermore, the DMN is hypothesized to comprise two subsystems: a medial temporal lobe subsystem that facilitates memory retrieval and a medial PFC subsystem that simulates interactions between retrieved memories (Buckner et al., 2008). Performance of the setshift task requires greater attention to forming associations between task cues than retrieving long term memory. The specificity of the relationship between medial PFC deactivation and setshift performance suggests that subsystems of the DMN have independent roles and that cognitive flexibility preferentially involves the medial PFC subsystem.

Neither medial PFC deactivation nor response time during shift trials correlated with COMT genotype. Although fMRI activity and task performance have been associated with COMT, the immediate function of COMT is dopamine degradation, suggesting that the direct effect of COMT is on dopaminergic function. We found that FMT signal in the midbrain, ventral striatum, and putamen increased with the number of Val alleles, consistent with a previous study that employed PET with [18F]fluorodopa and found that Val carriers had greater dopamine synthesis than Met homozygotes (Meyer-Lindenberg et al., 2005). Dopamine activity is regulated by multiple feedback mechanisms in the dopamine system. For instance, lower dopamine receptor density is offset by greater dopamine synthesis capacity (Laakso et al., 2005), and effects of excessive receptor stimulation are negated by receptor desensitization (Cooper et al., 2003). Our findings suggest that individuals with the Val allele show greater dopamine synthesis. This may represent, in part, compensation for lower dopamine concentration in the PFC.

Dopamine has been proposed to enhance the neural response by suppressing noisy spontaneous activity from neurons, thus increasing the signal to noise ratio in the system (Grace, 2000). Electrophysiological recordings in monkeys found that stimulation of dopamine receptors reduces the width of tuning curves of prefrontal neurons and suppresses responses to nonpreferred directions in a spatial working memory task, resulting in better memory performance (Vijayraghavan et al., 2007). Local field potential recordings found that dopamine increases neuronal synchrony in frequencies associated with cognitive functions (Brown, 2003), perhaps by tuning the response curve of disparate neurons to the relevant frequency band. fMRI may capture dopaminergic modulation of neuronal synchrony via functional connectivity in RSNs. Functional connectivity has been shown to be highly susceptible to manipulation of endogenous dopamine level. Dopamine agonists increase functional connectivity (Kelly et al., 2009) while dopamine depletion reduces functional connectivity and its relationship to cognitive performance (Nagano-Saito et al., 2008). Our finding of a relationship between endogenous dopamine activity and functional connectivity encourages future studies to investigate neuronal synchrony as a possible cellular mechanism for functional connectivity.

Specifically, we found an inverted-U relationship whereby subjects with mid-range FMT values had significantly higher functional connectivity than those with

low or high FMT values. These relationships were present in the midbrain and the ventral striatum but not the caudate or putamen. Dopaminergic neurons in the midbrain are localized in the substantia nigra and the ventral tegmentum. Because nigral neurons project to dorsal caudate and putamen, and ventral tegmental neurons project to the ventral striatum and PFC, our results suggest that it is the ventral tegmental system, and thus the mesocortical and mesolimbic systems that are involved in these relationships.

We also found that Met/Val individuals, who had mid-range dopamine synthesis, had greater functional connectivity than both Met/Met individuals who had low dopamine synthesis and Val/Val individuals who had high dopamine synthesis. Both COMT and FMT were identified as independent predictors of functional connectivity by the automated variable selection method when midbrain FMT was in the model, suggesting that COMT also influences functional connectivity by a mechanism that we did not measure, such as dopamine release or receptor behavior. When ventral striatum FMT replaced midbrain FMT in the model, ventral striatum FMT was identified as the only predictor of functional connectivity, and COMT was the predictor of ventral striatum FMT. Midbrain FMT reflects the synthesis capacity of the whole dopamine system whereas ventral striatum FMT reflects the mesocorticolimbic pathway. These results suggest that the mesocorticolimbic pathway dominates effects on functional connectivity and COMT effects become less visible. These dynamics between dopamine synthesis and its distribution in the different pathways deserve further investigation in future studies.

The relationship between dopamine and a variety of neural and behavioral responses has previously been characterized as an inverted-U shape (Dickinson and Elvevag, 2009), indicating that optimal dopamine levels result in maximum efficiency in the PFC. Deviations from the optimal level toward the low or high ends both result in decreased efficiency. Support for the inverted-U hypothesis has come from studies manipulating endogenous dopamine level. In humans, administration of dopamine agonists improve performance in individuals with low endogenous dopamine level but impairs performance in those with high endogenous dopamine level (Mattay et al., 2003). In monkeys, both too much and too little stimulation of dopamine receptors in the prefrontal cortex impairs performance (Vijayraghavan et al., 2007). Our results suggest that both COMT genotype and dopamine synthesis are associated with an inverted-U function that is instantiated in the brain at the level of the prefrontal components of a resting-state default mode network.

Furthermore, we found that functional connectivity correlated with task-related deactivation in the medial PFC. Several studies have remarked on the similarities between RSNs and patterns of task-induced activity and suggested that RSNs reflect functional networks in their idling state (Mennes et al., 2010; Smith et al., 2009; Thomason et al., 2008). Our results support the hypothesis that the integrity of functional networks at "rest", as measured by functional connectivity, determines the ability of the network to perform the task, as measured by task-related fMRI (De Luca et al., 2006). We also found a correlation between functional connectivity and response time during shift trials. Resting state functional connectivity has been directly correlated with behavioral performance (Nagano-

Saito et al., 2008). However, functional connectivity was not identified as an independent predictor of performance by the automated variable selection method, suggesting that the relationship between functional connectivity and performance stems from the relationship between performance and task-related fMRI activity, with which functional connectivity is correlated.

The integration of our results through the models in Fig. 5B and C demonstrates that COMT modulates dopamine synthesis, which supports functional connectivity in resting state networks in an inverted-U pattern. COMT may also influence functional connectivity in the same pattern by a mechanism independent of dopamine synthesis. Functional connectivity affects task-related deactivation, which modulates performance of prefrontal functions. These results form a model for the mechanisms whereby genetic drivers of dopamine synthesis modulate a system in which intermediate levels of dopaminergic function result in optimal performance.

In this study, changes in BOLD activity were observed in both the default mode network and the fronto-parietal control network during setshift performance, but the relationship between performance and BOLD activity was only found in the default mode network. Previous studies assessing prefrontal functions have also associated BOLD activity in the fronto-parietal control network with performance (Klingberg et al., 1997; Naghavi and Nyberg, 2005). Currently it is not clear how the default mode network and the fronto-parietal control function together to modulate cognition. Spreng and colleagues showed that activities in the fronto-parietal control network and the default mode network are coupled during internally driven cognition and uncoupled during externally driven cognition (Spreng et al., 2010). Vincent and colleagues observed that the fronto-parietal control network is anatomically adjacent to both the default mode network and the dorsal attention network, leading them to propose that the fronto-parietal control network flexibly couples to the default mode network or the dorsal attention network depending on the current cognitive task (Vincent et al., 2008). More research is needed to determine whether the default mode network and the fronto-parietal control network are equal partners in influencing cognition or that one network is secondary to the other. Furthermore, dopamine has also been associated with the fronto-parietal control network (Landau et al., 2009; Tan et al., 2007; Wimber et al., 2011). It is not known whether dopamine affects the default mode network and the fronto-parietal control network equally or that dopamine plays a direct role in one network, and since the two networks are related, dopamine also correlates with activity in the other network. It is also possible that the role of dopamine in these two networks varies with the task. This study assessed the role of dopamine in setshifting, and it remains to be investigated whether our findings can be generalized to other executive functions. Future studies should investigate not only how dopamine affects the default mode network and the fronto-parietal control network individually but also how the fronto-parietal control network and the default mode network interact to affect cognition and the role of dopamine in this interaction.

Dopamine has been proposed to perform a gating function allowing or blocking afferent information into the prefrontal cortex, thus modulating attention

(Montague et al., 2004). Also involved in attention, the DMN deactivates to reallocate processing resources from self- referential to external goal-directed behavior (Buckner et al., 2008). Patients with dopamine disorders exhibit not only DMN disconnection but also deficits on tasks requiring attention to shift between existing and incoming information (Cools et al., 2001b; van Eimeren et al., 2009), suggesting that dopamine modulates attention via the DMN. Our results support the role of dopamine in this system and show that genetic factors affect dopamine synthesis, which in turn affect the resting state and brain activation in the anterior medial prefrontal cortex component of this network.

3. Aim 2 - Dopamine supports coupling of attention-related networks

3.1 Introduction

Functional magnetic resonance imaging (fMRI) studies of attention have revealed the importance of three brain networks: a dorsal attention network (DAN), a default mode network (DMN), and a fronto-parietal control network (FPCN). The DAN is hypothesized to modulate externally directed attention by amplifying or attenuating the saliency of relevant cues and irrelevant cues, respectively (Corbetta and Shulman, 2002; Ptak and Schnider, 2010). This network includes the intraparietal sulcus, frontal eye fields, inferior parietal lobule, dorsal lateral prefrontal cortex, insula, supplementary motor area, and middle temporal area (Fox et al., 2005). These areas routinely activate when subjects search and detect visual targets among nontargets (Shulman et al., 2003). In contrast, the DMN, which includes the posterior cingulate, precuneus, medial prefrontal, lateral parietal and medial temporal cortices, is associated with internal cognitive processes and deactivates when attention is focused on the external environment (Greicius et al., 2003; Raichle et al., 2001). Analysis of resting state fMRI signal revealed that activity in the DAN is anticorrelated with that of the DMN (Fox et al., 2005). Additionally, fMRI signal acquired during task performance showed that goal-directed behavior is associated with increased activity in the DAN and decreased activity in the DMN whereas stimulus-independent thoughts are associated with increased activity in the DMN and decreased activity in the DAN (Corbetta et al., 2002; McKiernan et al., 2003; Raichle and Snyder, 2007). These results led to the proposal that competition between these two networks underlies the transition between task-focused attention and stimulus-independent thought.

Mediating the allocation of resources between the DAN and the DMN may be the FPCN, which encompasses the anterior prefrontal, dorsolateral prefrontal, dorsomedial superior frontal/anterior cingulate, anterior inferior parietal lobule, and anterior insular cortex. The FPCN is engaged by task paradigms assessing conflict monitoring, planning, and reasoning (Kroger et al., 2002; van den Heuvel et al., 2003; Wager et al., 2004). Many of the network's components exhibit sustained activity over the duration of the task, suggesting a role for the FPCN in maintaining task sets and integrating information across time (Velanova et al., 2003; Yarkoni et al., 2005), necessary functions for facilitating competition between the DAN and the DMN. Vincent and colleagues noticed that the FPCN is physically interposed between the DAN and the DMN and suggested that the FPCN may flexibly couple to the DMN or the DAN depending on the attentional demand of the task (Vincent et al., 2008). Spreng and colleagues provided support for this proposal by showing that the FPCN is coupled to the DMN during internal cognition and uncoupled during external cognition (Spreng et al., 2010).

Also connecting the DAN, DMN, and FPCN is their mutual association with the neurotransmitter dopamine. Methylphenidate, a drug inhibiting reuptake of

monoamines like dopamine, has been shown to increase activation of the DAN during performance of visual attention and memory tasks (Muller et al., 2005; Tomasi et al., 2011). Methylphenidate also influences deactivation of the DMN, and apomorphine, a dopamine receptor agonist, alters the relationship between DMN activity and performance (Nagano-Saito et al., 2009; Tomasi et al., 2011). The DMN has also been associated with dopamine synthesis and a polymorphism affecting expression of the dopamine transporter that clears dopamine from the synapse (Braskie et al., 2010; Gordon et al., 2011). Activity in the FPCN is also influenced by functional polymorphisms in the dopamine system (Gordon et al., 2011; Tan et al., 2007), and depletion of dopamine impairs FPCN function and its association with performance (Nagano-Saito et al., 2008).

Given the influence of dopamine on these three networks, we hypothesized that dopamine plays a role in the cross-network interactions that other researchers have identified. Specifically, in the absence of external stimulation, dopamine would influence the degree of correlation between the FPCN and the DMN and anticorrelation between the FPCN and the DAN. We used positron emission tomography (PET) with 6-[^{18}F]fluoro-L-m-tyrosine (FMT) to measure dopamine synthesis capacity *in vivo* and fMRI to acquire stimulus-independent brain activity.

3.2 Methods

Subjects

Twenty-eight healthy, right-handed subjects between 20 and 30 years old, inclusive, (mean age 24.3 ± 3.0, 12M/16F) participated in the study. PET data from twelve subjects in this study were reported in two previous studies on different topics (Braskie et al., 2010; Braskie et al., 2008). Recruitment and exclusionary criteria were as described in Aim 1. All subjects gave written informed consent prior to participating in the study, which includes a PET-FMT scan, a resting state fMRI scan, and structural MRI scans. The current study was approved by institutional review boards at University of California, Berkeley and Lawrence Berkeley National Laboratory.

PET data acquisition and analysis

As described in Aim 1.

MRI data acquisition

As described in Aim 1.

Regions of interest (ROIs)

Midbrain and cerebellum ROIs were drawn described in Aim 1. A figure showing midbrain ROIs superimposed on an MPRAGE and FMT uptake in the midbrain is reproduced below (Fig. 6).

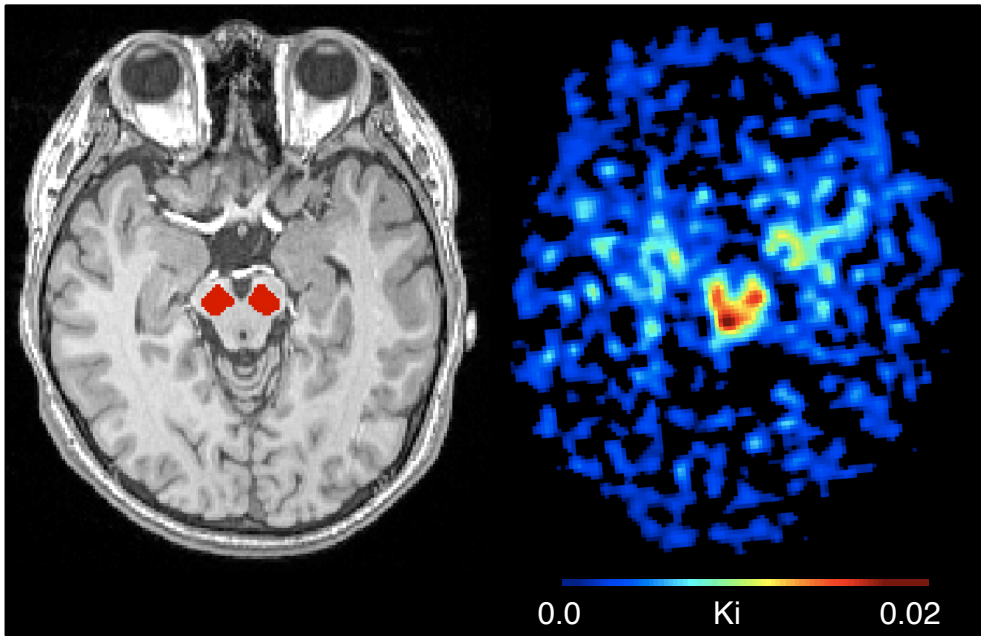

Fig 6. One subject's scans. Left image shows midbrain ROIs superimposed on a structural scan. Right image shows FMT uptake in the midbrain.

MRI data analysis

Network identification

We extracted the DAN, DMN, and FPCN using seeds from previous publications. Specifically, Fox and colleagues used seeds at the intraparietal sulcus (-25, -57, -46), the frontal eye field (25, -13, 50), and the middle temporal region (-45, -69, -2) to generate the DAN (Fox et al., 2005). Greicius and colleagues used the posterior cingulate to define the DMN; the posterior cingulate voxel showing peak functional connectivity in their network had coordinates (-2, -51, 27) (Greicius et al., 2003). Vincent and colleagues used left and right dorsolateral prefrontal cortex seeds to extract the FPCN; in their network, peak functional connectivities for left and right seeds had coordinates (-50, 20, 34) and (46, 14, 43), respectively.

We generated an 8x8x8 mm^3 ROI around each of the coordinates above and coregistered the ROIs to individual subject's resting state fMRI scan. Resting state fMRI scans were preprocessed in FSL using the following operations: motion correction (Jenkinson et al., 2002), removal of non-brain matter (Smith, 2002), spatial smoothing with a Gaussian kernel of 5 mm, and high-pass temporal filtering removing frequencies below 0.01Hz. For each ROI, for each subject, we extracted the mean time series for voxels in the ROI, performed a regression in FSL-FEAT with the mean time series and three nuisance covariates discussed below. z-statistic maps from the regressions were averaged across subjects to generate group-level maps showing correlations between each voxel's time series and the mean time series for each ROI. Group-level maps for ROIs in the intraparietal sulcus, frontal eye field, and middle temporal region were averaged to create the DAN. Since the

DMN was defined solely with a posterior cingulate seed, the group-level z-statistic map for the posterior cingulate seed was the DMN. The FPCN was the average of group-level maps from left and right prefrontal cortex ROIs.

Nuisance variables

As described in Aim 1.

Cross-network connectivity

From the three networks we extracted, we identified the nodes in each network by first eroding voxels with low intensities to remove voxels that overlapped between nodes and then applying a cluster algorithm to identify individual clusters of voxels. We also referenced previous studies to ensure that the clusters in our networks resemble published findings (Fox et al., 2005; Greicius et al., 2003; Vincent et al., 2008). We identified the voxel with the highest z-statistic in each cluster or node in the network and created an 8x8x8 mm^3 ROI around the peak voxel. For each node in each network, we extracted the mean time series from the resting state fMRI data. To calculate how activity in one network is related to activity in one of the other two networks, we calculated Pearson's correlations between the mean time series of each node in each network with the time series of each node in the other network. Since the objective was to understand, within each subject, how different networks relate to one another, we standardized all the Pearson's correlations for each subject to derive a relative measure of coupling; thus a negative correlation value now means that the strength of coupling is less than the subject's average correlation, not that the coupling is anticorrelated. We then averaged the cross-network Pearson's correlations to form a coupling value for any two networks. For example, the DMN has 5 nodes and the FPCN has 8 nodes. We calculated Pearson's correlations between each of 5 nodes in the DMN with each of 8 nodes in the FPCN and averaged the resulting 40 Pearson's correlations to derive a measure of how activity in the DMN is correlated with activity in the FPCN.

Statistics

Statistical tests were performed using R (http://www.r-project.org/). We used Pearson's correlations to compare cross-network coupling values with midbrain FMT K_i values.

3.3 Results

Figure 7 shows the DAN, DMN, and FPCN extracted with the seed-based approach. Table 2 lists the coordinates and intensity of the peak voxel in each cluster of each network.

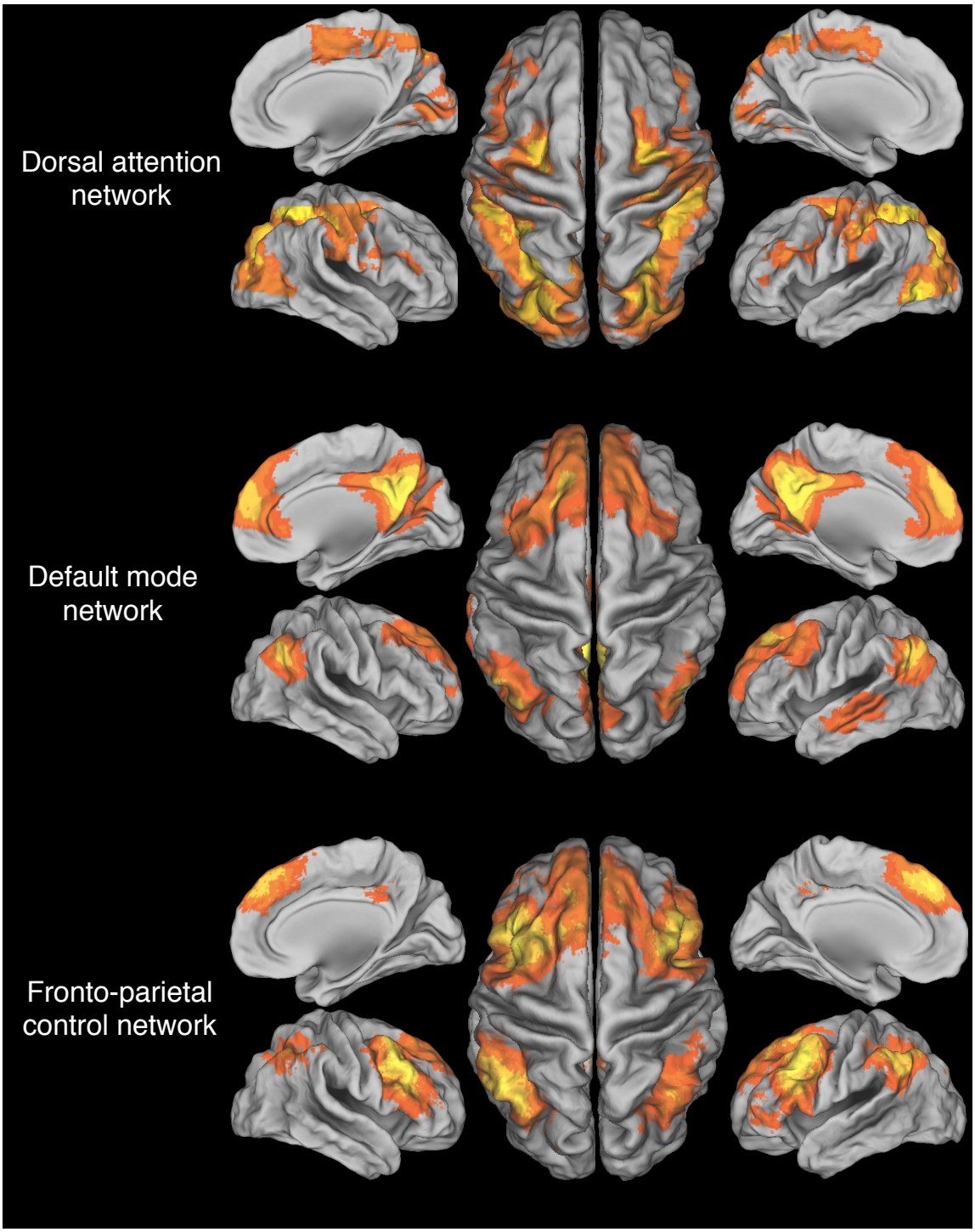

Fig 7. Brain networks. The dorsal attention, default mode, and fronto-parietal control networks were extracted using a seed-based approach.

Nodes in the dorsal attention, default mode, and fronto-parietal control networks				
	MNI coordinates			max z
	x	y	z	
Dorsal attention network				
precentral area: L	-26	-2	54	3.06
precentral area: R	28	-12	50	4.20
superior parietal lobule: L	-28	-54	58	4.38
superior parietal lobule: R	30	-56	50	4.32
middle temporal area: L	-44	-66	-4	4.22
Default mode network				
posterior cingulate/precuneus	0	-54	28	10.08
medial prefrontal	2	62	22	6.85
lateral parietal: L	-46	-64	32	7.44
lateral parietal: R	52	-64	34	7.68
medial temporal: L	-62	-10	-16	5.09
Fronto-parietal control network				
dorsomedial frontal/anterior cingulate	-4	38	38	5.59
dorsolateral prefrontal: R	50	16	42	7.45
dorsolateral prefrontal: L	-50	14	36	6.98
lateral parietal: R	44	-54	56	4.94
lateral parietal: L	-40	-62	54	5.71

Table 2. MNI coordinates and maximum intensity of the peak voxel in each node in the DAN, DMN, and FPCN.

FMT K_i values in the midbrain correlated positively with coupling between the DMN and FPCN (Pearson's r = 0.38, p-value = 0.046) but negatively with coupling between the DAN and the FPCN (Pearson's r = 0.39, p-value = 0.038). No significant correlation existed between midbrain FMT K_i values and coupling between the DAN and the DMN (Pearson's r = 0.17, p-value = 0.395) (Fig. 8).

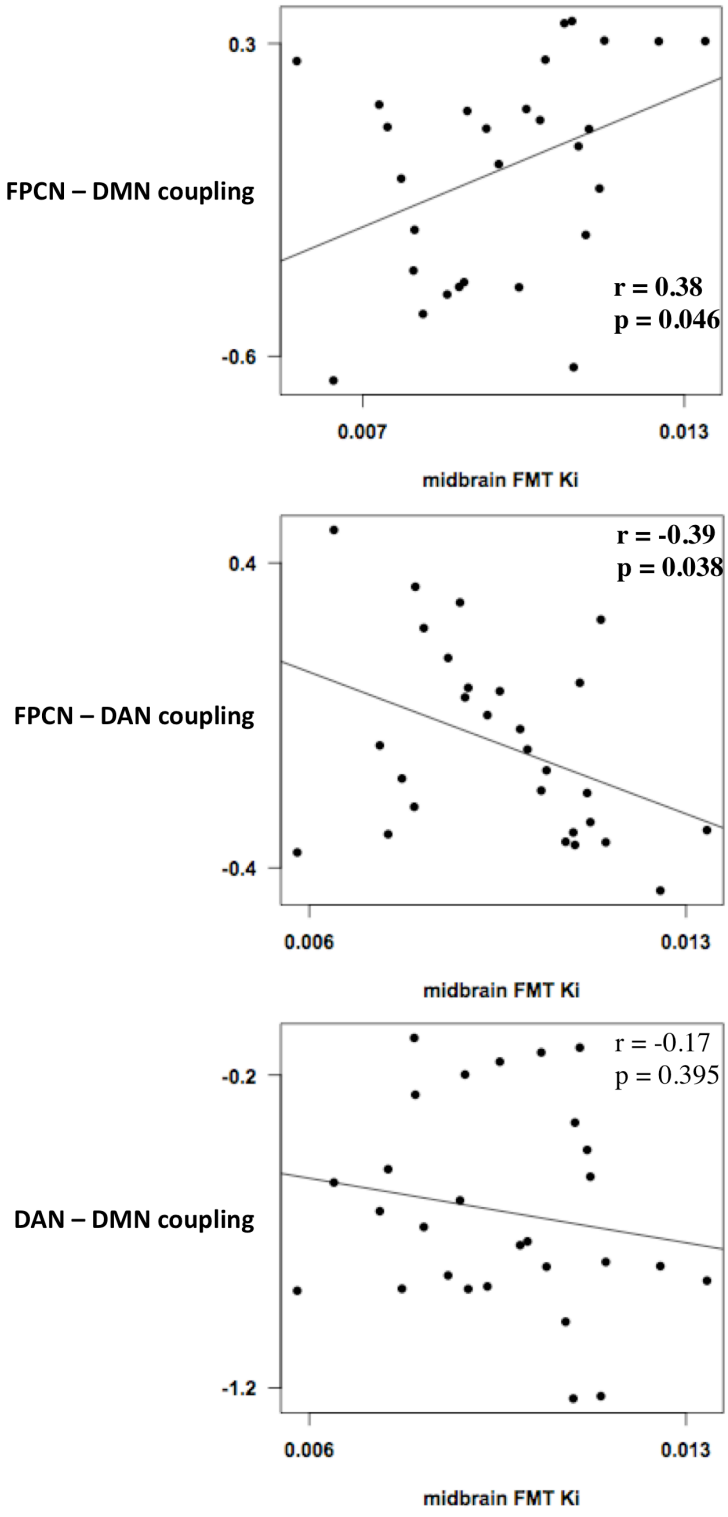

Fig 8. Dopamine and network coupling. FMT uptake in the midbrain correlated positively with coupling between the FPCN and DMN (top) and negatively with coupling between the FPCN and the DAN (middle). No relationship found between FMT uptake and coupling between the DAN and the DMN (bottom).

3.4 Discussion

Previous findings suggest that externally focused attention involves the DAN whereas internally directed attention involves the DMN, and the FPCN supports the transition between external and internal attention by coupling its activity with either the DAN or the DMN during externally- or internally-driven tasks, respectively (Spreng et al., 2010). Here we show that dopamine is involved in this interaction between the three networks. Specifically, in the resting condition, when internal cognitive processes presumably dominate and the DMN is engaged, we found that dopamine synthesis capacity correlates positively with the correlation between activity in the DMN and activity in the FPCN. We also found that dopamine synthesis capacity correlates negatively with the coupling between the FPCN and the DAN in the resting state, when the DAN is not activated. These results suggest that during internal cognition, dopamine not only strengthens the relationship between the FPCN and the DMN but also helps to disengage the FPCN from the DAN.

Dopamine has long been proposed to play a role in the modulation of attention. Initial evidence came from observations of patients with dopaminergic disorders. Parkinson's disease patients are particularly impaired at shifting between mental sets, as shown by performance on setshifting tasks like the Wisconsin card sorting test (Lees and Smith, 1983). Schizophrenic patients often exhibit mental rigidity when they fail to ignore irrelevant cues (Sarter, 1994). Treatments for attention deficit hyperactivity disorder, such as methylphenidate and amphetamine, target the dopamine system (Solanto, 1998). Additional support comes from animal lesion studies and neuroimaging of humans. Lesioning of dopaminergic terminals in the prefrontal cortex of primates impairs the animal's ability to acquire attentional sets (Crofts et al., 2001), and positron emission tomography shows dopamine release in humans during setshifting (Monchi et al., 2006).

The mechanism whereby dopamine modulates attention has been proposed for both the cellular and the systems level. At the cellular level, activation of dopamine D1 receptor subtype increases neuronal response to excitatory neurotransmitters whereas activation of the D2 receptor subtype decreases this response (Nicola et al., 2000). This paradoxical action of dopamine leads to the hypothesis that dopamine modulates attention via a gating mechanism that involves both updating and maintenance of information. Stimulation of D1 receptors would enhance maintenance but impair updating of cortical representations, while stimulation of D2 receptors would destablize the current representations, rendering them vulnerable to modification by incoming stimulation (Cohen et al., 2002). Results from lesion studies and neuroimaging support this hypothesis. D1 receptors are the dominant receptor subtype in the prefrontal cortex. Lesion of dopaminergic terminals in the PFC increases distractibility and impairs maintenance of attentional sets. In contrast, animals with lesions in the striatum, the site of D2 receptors concentration, are less distractible and exhibit greater focusing on the relevant stimuli (Crofts et al., 2001). Similarly, inhibiting D2 receptors with the antagonist sulpiride impairs performance on setshifting but improves performance during the maintenance condition (Mehta et al., 2004). These opposing effects may underline

the maintenance and shifting of attention between the internal and external environment.

At the systems level, the cumulative effect of dopamine action on D_1 and D_2 receptors may be on the properties of large-scale, interregional networks (Walters et al., 2000). Local field potential recordings found that dopamine modulates brain oscillations in frequencies thought to support perception and cognition (Ward, 2003). Dopamine agonists increase temporal coherence seen in fMRI BOLD fluctuations (Kelly et al., 2009), and dopamine depletion reduces this coherence and its relationship to cognitive performance (Nagano-Saito et al., 2008). Gordon and colleagues recently reported an association between network coupling and dopamine, using a polymorphism affecting expression of dopamine transporters as a marker of dopamine function (Gordon et al., 2011). The present finding of an association between dopamine and cross-network couplings between the DAN, DMN, and FPCN are consistent with the proposed effects of dopamine on network properties.

In summary, the current study adds a neurochemical perspective to previous observations of the interaction between the DAN, DMN, and FPCN by showing that, in the absence of external stimulation, dopamine enhances coupling between the FPCN and DMN while reducing the coupling between the FPCN and the DAN.

4. Aim 3 - Striatal dopamine influences the default mode network to affect shifting between object features

4.1 Introduction

Cognitive flexibility characterizes the ability to shift attention between different stimuli in accordance with situational context (Cools et al., 2006; Rogers et al., 2000). One may shift attention between perceptual features of objects, abstract task rules regarding selection of these objects, or a combination of the two, as in the Wisconsin Card Sorting Test (WCST), a set-shift task commonly used to probe cognitive flexibility. Impaired performance on the WCST is generally associated with deficits in the prefrontal cortex (PFC) (Barcelo and Knight, 2002; Dias et al., 1996b; Merriam et al., 1999), but accumulating evidence suggests that the mechanisms involved in shifting between object features and abstract rules are anatomically and functionally distinct. Abstract rule shift seems to involve the dorsolateral PFC whereas shifting between object features might be processed by the orbitofrontal cortex (Dias et al., 1996a; O'Reilly et al., 2002; Ravizza and Carter, 2008). Cools and colleagues proposed that the dopamine-rich striatum, which receives projections from the frontal cortex, also distinguishes shifting of object features from abstract rules. In a study of patients with focal striatal lesions, deficits in shifting between object features were detected but shifting between abstract rules appeared intact (Cools et al., 2006). Additionally, functional magnetic resonance imaging (fMRI) of healthy subjects found activation in the striatum during performance of object shifts but not abstract rule shifts (Cools et al., 2004).

Patients with dopamine deficits, such as those with Parkinson's disease, demonstrate deficits on the WCST (Alevriadou et al., 1999; Beatty and Monson, 1990; Kulisevsky et al., 1996; Lees and Smith, 1983; Monchi et al., 2004). However, studies using alternative assays of cognitive flexibility either found no shifting deficits in these patients or reported no relationships between dopaminergic status and shifting performance (Kehagia et al., 2010; Lewis et al., 2005; Rogers et al., 1998; Woodward et al., 2002). The inconsistency suggests that the role of dopamine in cognitive flexibility differs based on the specific demand of the set-shift task, such as shifting between object features versus abstract rules. Furthermore, Parkinson's disease patients performing the WCST exhibited decreased cortical activity and task performance only in stages of the task that effectively solicit the striatum in control subjects (Monchi et al., 2004). Correspondingly, striatal dopamine depletion in marmosets changes susceptibility to task-irrelevant distractions (Crofts et al., 2001), supporting the idea that striatal dopamine is critical in set-shifting, specifically between object features.

The current study tests the hypothesis that cognitive flexibility is sensitive to dopaminergic modulation if the task assesses shifting between object features and if the dopamine-rich striatum is involved in task performance. We used fMRI with a set-shift task that, unlike the WCST, differentiates shifting between object features from shifting between abstract rules to identify brain areas engaged by each type of

set-shift. To quantify striatal dopamine activity, we used positron emission tomography (PET) with 6-[^{18}F]-fluoro-l-m-tyrosine (FMT), a substrate for aromatic L-amino acid decarboxylase, a dopamine-synthesizing enzyme whose activity correlates with dopamine synthesis capacity (DeJesus, 2003). PET-FMT measures dopamine activity *in vivo*, bypassing the issue of artifacts introduced by lesion studies that could alter endogenous dopamine function and its relationship to cognition. We predicted that a) object feature shifts and abstract rule shifts would activate different brain regions, particularly engagement of the striatum in object feature shifts, and b) striatal FMT signal would correlate with fMRI activity and performance measures for shifts between object features but not abstract rules.

Deficits in higher level abstract rule shifts and lower level perceptual feature shifts have very different implications for the ability to perform functions in daily life. Failure to control attention using top-down signals derived from abstract rules greatly impairs decision making whereas failure to process bottom-up signals from object features inhibits the execution of behavior. The results of this study not only yield important insight into the neural basis of cognitive flexibility but also aid in the diagnosis and treatment of individuals with dopamine deficits.

4.2 Methods

Subjects

Sixteen right-handed, cognitively healthy subjects (mean age ± SD: 25 ± 2.5 years, 7 females) were recruited via online postings and flyers. Exclusionary criteria were as described in Aim 1. Subjects gave informed consent prior to undergoing a PET-FMT scan and fMRI scans. The study was approved by institutional review boards at University of California, Berkeley and Lawrence Berkeley National Laboratory.

fMRI task

We adapted the setshift task from a design by Cools and colleagues (Cools et al., 2004; Cools et al., 2006). The task paradigm is described in Aim 1 and shown again below in figure 9. Briefly, the sequence of consecutive red and blue windows allowed for the differentiation of four trial types:

(1) No shift: When a blue window trial followed another blue window trial, neither the target figure nor the task rule changed.
(2) Object feature shift: When a red window trial followed another second red window trial, the target figure changed, but the task rule remained constant.
(3) Abstract rule shift: When a blue window trial followed a red window trial, the task rule changed, but the target figure remained constant.
(4) Both shifts: When a red window trial followed a blue window trial, both the target figure and the task rule changed.

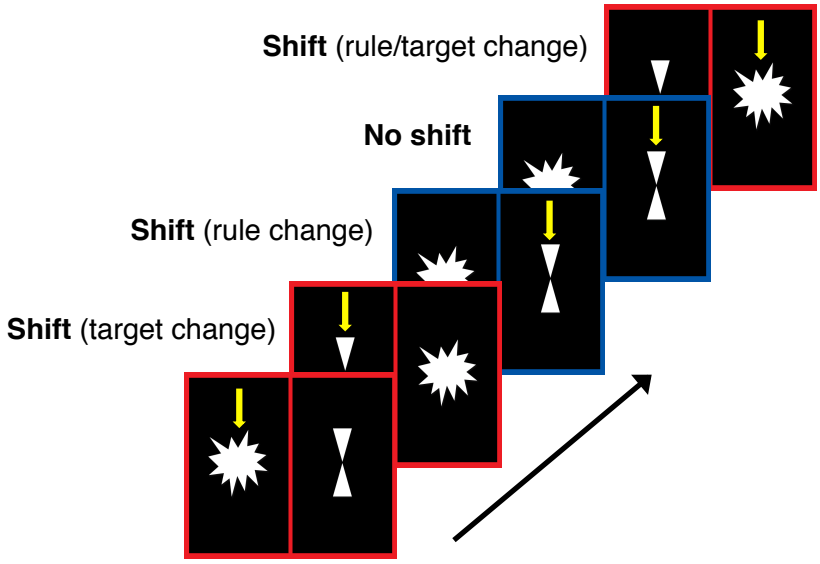

Fig 9. Sample sequence of slides shown to the subject. A blue border cued the subject to choose the figure that was the target in the previous trial. A red border cued the subject to select the figure that was NOT the target in the previous trial. Yellow arrows indicate the correct answer for each trial.

Composite set-shift score

Accuracy, response time (RT), and response time standard deviation (RTSD) were averaged over four runs for each subject. Accuracy and RT were not independent measures, as subjects might have sacrificed one for the other. Measures of intra-individual variability such as RTSD have been shown to provide information not detectable by the mean and may even be better at differentiating inter-individual variability (Hervey et al., 2006; Klein et al., 2006; MacDonald et al., 2006). To evaluate performance, we created a composite score whereby better performance was characterized by high accuracy, low RT, and low RTSD. Accuracy scores, RT, and RTSD were standardized. RT and RTSD were then subtracted from accuracy scores to yield the composite score.

MRI data acquisition

As described in Aim 1.

Task-related fMRI analysis

We used FSL for preprocessing and statistical analyses (http://www.fmrib.ox.ac.uk/fsl/, version 4.1.2). Preprocessing included motion correction with MCFLIRT, brain extraction with BET, spatial smoothing with a 7mm full width half maximum Gaussian kernel, and high-pass temporal filtering (100s). Statistical analyses were performed using a general linear model implemented by FEAT. FILM prewhitening was applied to correct for temporal autocorrelation. Temporal derivatives and temporal filtering were included to improve fitting of the model to the data. Events were modeled at the time of stimulus presentation after

convolution with a gamma hemodynamic response function. In the first level analyses, for each subject and each scan, three regressors representing object shift trials, rule shift trials, and no shift trials were modeled separately. Only correct trials were modeled. The feedback and fixation events were not modeled and thus functioned as the implicit baseline.

For group-level analyses, we first coregistered each functional scan to the T1-weighted structural image in plane to the fMRI data and then to the mean MPRAGE using 6 degrees of freedom rigid body transformations. The mean MPRAGE and its associated structural and functional scans were normalized to MNI space using 12 degrees of freedom affine transformations. For each subject, we grouped first level results from each scan and performed paired t-tests contrasting object shift trials with no shift trials and rule shift trials with no shift trials to isolate patterns of activity specific to the cognitive components of object and rule shifting. Contrast maps were thresholded at $z > 2.3$ with cluster thresholding to correct for multiple comparisons. We regressed subject-level contrast maps against FMT values in a voxelwise analysis with age and sex as covariates of non-interest.

PET-FMT data acquisition and analysis

As described in Aim 1.

Regions of interest (ROIs)

Cognitive flexibility engages the frontal cortex, which is anatomically connected to the caudate component of the striatum (Alexander et al., 1986). We drew dorsal caudate ROIs on each subject's mean MPRAGE using FSLview according to guidelines published previously (Fig. 10) (Mawlawi et al., 2001). The cerebellum grey matter was the reference region for calculating PET-FMT values. Limited PET spatial resolution introduces blurring and causes signal to spill onto neighboring regions. Because the cerebellum is located posterior and adjacent to the midbrain, to avoid contamination of FMT signal from the midbrain, only the posterior 3/4 of the cerebellum was included in the ROI.

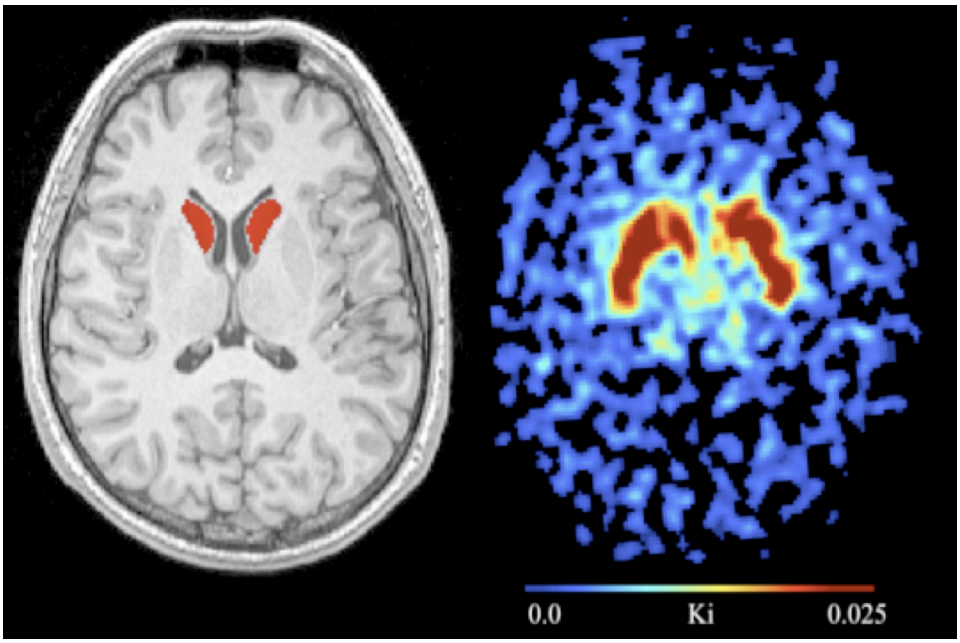

Fig 10: One subject's scans. Right image shows FMT uptake in the striatum. Left image shows the manually defined dorsal caudate region of interest superimposed on a high-resolution structural scan.

Statistics

Statistical tests were performed using Stata 10 (Stata Corp, College Station, TX). We used Pearson's correlations to relate FMT values, task-related fMRI activity, and cognitive scores, all of which were confirmed to be normally distributed using the Shapiro-Wilk normality test with an alpha of 0.05.

4.3 Results

fMRI activity

Relative to no shift trials, object shift trials increased activation in the dorsolateral PFC, posterior parietal cortex, and striatum and deactivated the medial PFC and the posterior cingulate (Fig. 11). Coordinates of peak activation and deactivation voxels for each of these areas are presented in Table 3. No significant activation or deactivation was observed when contrasting rule shift with no shift trials.

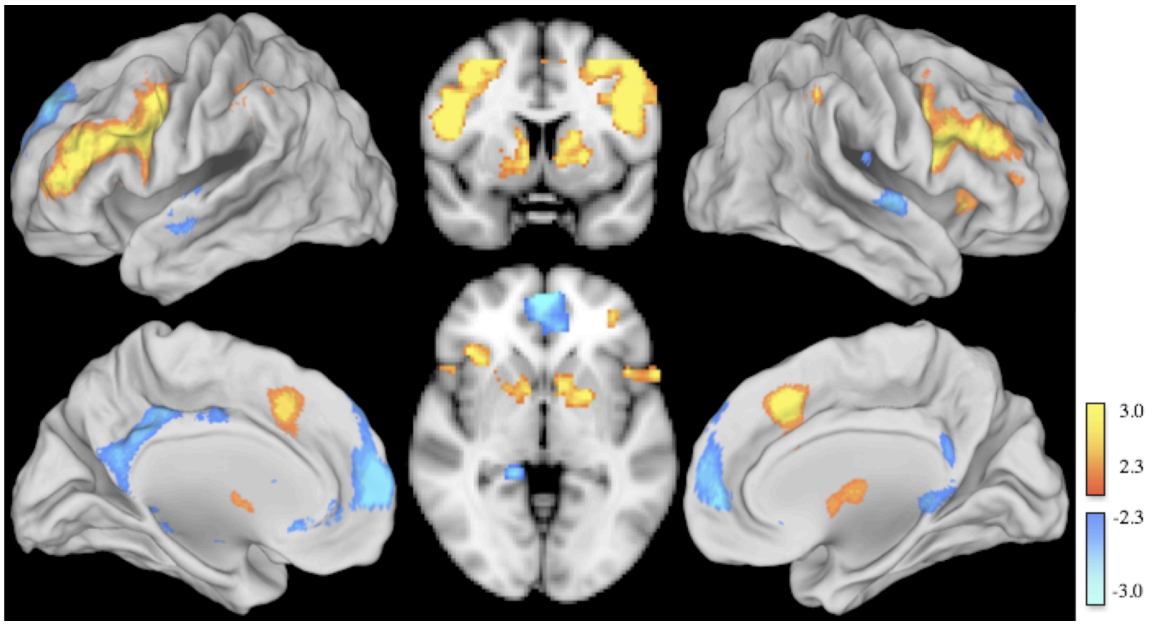

Fig 11: Object shift minus no shift contrast displayed on an MNI standard brain. Object shift activated (yellow) the dorsolateral PFC, posterior parietal cortex, and striatum and deactivated (blue) the medial PFC (mPFC) and posterior cingulate.

MNI coordinates of peak voxels in object shift vs no shift contrast

Areas of activation (Object shift > No shift)	Maximum z-score	MNI coordinates		
		x	*y*	*z*
Right dorsolateral PFC	4.53	50	8	20
Left dorsolateral PFC	4.26	-44	36	16
Right posterior parietal	4.85	44	-40	46
Left posterior parietal	4.67	-36	-46	44
Right striatum	3.40	12	2	14
Left striatum	3.98	-16	2	8
Areas of deactivation (No shift > Object shift)				
Medial PFC	3.95	-8	62	8
Posterior cingulate	3.42	-2	-36	40

Table 3: Areas of activation and deactivation during object shift. Relative to no shift trials, object shift increased BOLD activity in the dorsolateral PFC, posterior parietal cortex, and the striatum while decreasing BOLD activity in the medial PFC and posterior cingulate.

fMRI activity and FMT

A voxelwise analysis revealed that deactivation in the medial prefrontal cortex (mPFC) during object shift trials correlated inversely with FMT K_i values in the right dorsal caudate such that greater deactivation was associated with less dopamine synthesis (Fig. 12A).

Behavioral data

Composite cognitive scores for object shift trials and rule shift trials were not significantly different (p-value = 0.879, R^2 = 0.010). The object shift composite score correlated negatively with FMT Ki values in the right dorsal caudate (p-value = 0.018, R^2 = 0.257) (Fig. 12B). High FMT Ki values correlated with both low accuracy (p-value = 0.016, R^2 = 0.308) and long response time (p-value = 0.02, R^2 = 0.328), confirming the relationship shown by the composite score. The correlation between FMT Ki values and response time standard deviation was not significant (p-value = 0.704, R^2 = 0.011). Deactivation in the medial PFC during object shift did not correlate with the composite score (p-value = 0.160, R^2 = 0.136). No significant correlation was observed between FMT values and the rule shift composite score (p-value = 0.369, R^2 = 0.125).

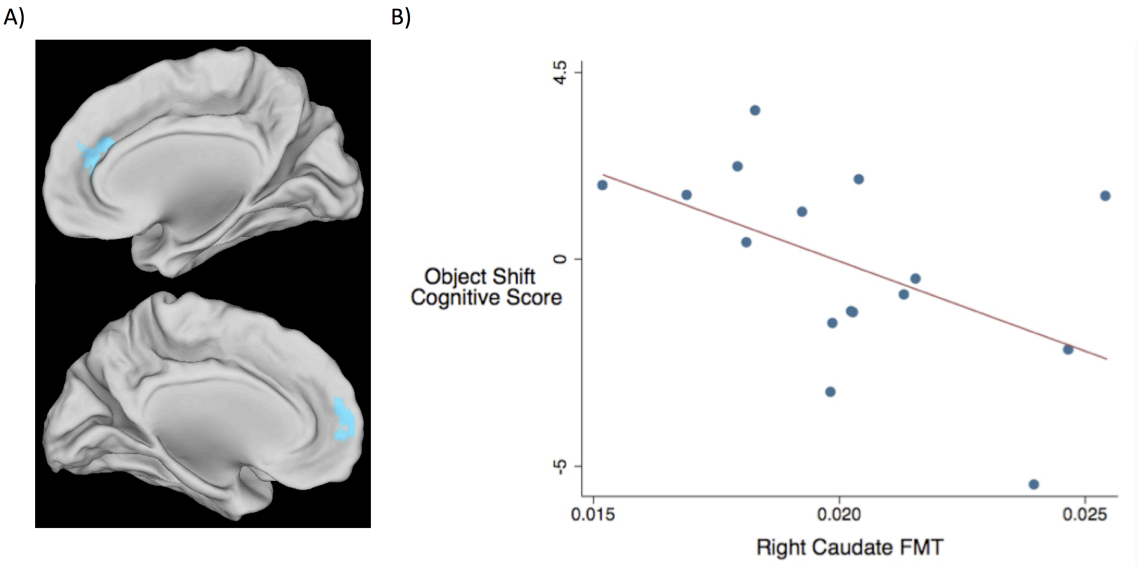

Fig 12: FMT uptake and object shift. A) High FMT values in the right dorsal caudate correlated with less mPFC deactivation during object shift relative to no shift. B) Negative correlation between object shift composite score and right caudate FMT K_i values (p-value = 0.028, R^2 = 0.264).

4.4 Discussion

We found that shifting between object features was associated with an increase in BOLD activity in the dorsolateral PFC, posterior parietal cortex, and striatum and a decrease in BOLD activity in the medial PFC and posterior cingulate. Higher dopamine activity in the striatum, specifically the right dorsal caudate,

correlated with less medial PFC deactivation and lower performance of object shifts. In contrast, shifting between abstract rules was not associated with any specific brain region, and performance of rule shifts did not correlate with striatal dopamine activity.

Cognitive flexibility and neural networks

The dorsolateral PFC, posterior parietal areas, and striatum form an interregional pattern that has been referred to as the fronto-parietal control network (Vincent et al., 2008). The medial PFC and posterior cingulate are two nodes of the default mode network (Greicius et al., 2003). Activation of the fronto-parietal control network and deactivation of the default mode network during object shifts not only mirror results of previous studies employing the WCST and other setshift tasks but also studies that assessed working memory and cognitive control (Chee and Choo, 2004; Lie et al., 2006; Nystrom et al., 2000; Persson et al., 2007). These cognitive functions are grouped as executive function, which is often loosely defined as processes that initiate and coordinate goal-directed behavior (Miyake et al., 2000). Our results support the proposal that activities in the fronto-parietal control network and default mode network facilitate performance of cognitive flexibility and other executive functions.

The default mode network consistently exhibits greater activity during the resting condition in which no task is administered than during performance of tasks employing externally oriented stimuli; this phenomenon is not specific to executive functions (Buckner et al., 2008). In a study of stimulus-independent thoughts, Mason and colleagues showed that individuals with greater daydreaming tendencies had greater activity in the default mode network (Mason et al., 2007), leading to the hypothesis that the default mode network supports internally driven cognition, and deactivation of the default mode network reallocates processing resources from self-referential to goal-directed behavior. Unlike the default mode network, the fronto-parietal control network often shows greater activity during performance of executive tasks than during the control condition (Klingberg et al., 1997; Naghavi and Nyberg, 2005). Recently, Spreng and colleagues found the fronto-parietal control network and default mode nework are coupled during a task of autobiographical planning and decoupled during a task with external stimuli (Spreng et al., 2010), analogous to our finding of opposing activity, activation and deactivation, between these two networks during shifting of object features.

Object feature shifts and striatum

Cognitive flexibility has been differentiated into shifting between object features and shifting between the rules governing the shift, presumably a lower-order shift and a higher-order shift, respectively (Dias et al., 1996a; Wager et al., 2004; Wallis et al., 2001). The neural marker of this differentiation is often the presence or absence of activity in the striatum (Cools et al., 2006; Crofts et al., 2001; Crone et al., 2006). Cools and colleagues found that patients with focal lesions in the striatum, but not in the PFC, were impaired at shifting between object features. Parkinson's disease patients, who also exhibit striatal deficits, experienced difficulty during set-shifting only when selecting between two competing responses but not

when selecting between two rule sets (Ravizza and Ciranni, 2002). fMRI studies on young healthy adults similarly found that striatal BOLD activity is sensitive to changes in stimuli features rather than rule representation (Cools et al., 2004; Crone et al., 2006). Our observation of striatal BOLD activity during shifts of object feature affirms previous findings that the striatum plays an important role in shifting attention between object features.

Furthermore, we found that object shifts activated both dorsal and ventral striatum. These results are congruent with a study by Cools and colleagues, whose task paradigm we adopted, showing similar effects in a group of patients with lesions in both dorsal and ventral striatum (Cools et al., 2006). However, in a different study with healthy subjects, Cools and colleagues found that the activation was restricted to the ventral striatum (Cools et al., 2004). In contrast, Crone and colleagues also tested healthy subjects and identified activity in the dorsal striatum as the locus where mapping of stimulus features to response occurs (Crone et al., 2006). It remains to be investigated whether cognitive flexibility engages only certain component of the striatum or the whole striatum whereby information is processed in parallel in the various parts of the striatum (Haber, 2003; Voorn et al., 2004).

The striatum receives inputs from the cortex and several sensory and motivational systems and sends outputs to the substantia nigra and the globus pallidus, which project to the different sensorimotor systems. Neurons in these output targets are inhibitory and, without signal from the striatum, prevent the sensorimotor systems from sending commands to the motor circuitry, therefore impeding voluntary action (Alexander et al., 1990). The striatum thus serves as a filter whereby afferents of intrinsic and extrinsic origins compete for access to the motor system, leading to the proposal that the striatum is the center for resolving the issue of stimuli-response mapping (Gurney et al., 2001; Mink, 1996). Our results suggest that one selection mechanism computed by the striatum is between perceptual features of objects.

Object feature shifts and dopamine

Our finding that subjects with higher FMT signal in the dorsal caudate performed worse on object shifts than subjects with lower FMT signal suggests that striatal function in object shifts is mediated by dopamine. Dopaminergic receptors have the highest density in the striatum, and dopaminergic depletion has been found to impair set shifting. Additionally, Monchi and colleagues documented dopamine release in the striatum during performance of the WCST (Monchi et al., 2006). Although object shifts activated both the dorsal and ventral striatum, the relationship between FMT uptake and performance lies in the dorsal striatum. Successful execution of behavior has been proposed to involve the coordination of limbic, cognitive, and motor circuits, which are associated with different regions of the striatum and their connected counterparts in the cortex. In the striatum, emotions driving behavior are thought to be processed in the ventral striatum, which signals the caudate to plan strategies for the desired behavior, leading to the execution of that behavior by the putamen (Haber, 2003). In Monchi and colleagues' study where reward and motor demands were balanced across conditions,

dopamine release was observed only in the dorsal striatum. Together with their findings, our result suggests that although both ventral and dorsal striatum are involved in setshifting, the relationship between dopamine and the cognitive component of setshifting lies in the caudate.

Relationships between dopamine and performance are often explained in the context of two models: the tonic/phasic model and the inverted-U shaped model. The tonic/phasic model characterizes the role of two distinct patterns of dopamine release: 1) phasic bursts in response to stimuli and 2) low tonic activity in the absence of such stimuli (Cohen et al., 2002; Cools et al., 2001a; Grace, 1995). Tonic and phasic dopaminergic activity are proposed to be antagonistic, with high tonic dopamine creating a strong background signal that raises the threshold for phasic firing triggered by a change in the environment (Grace, 1995; Vijayraghavan et al., 2007). While our FMT measure does not give information about the strength of phasic activity during our task, it may reflect tonic dopamine activity. FMT Ki is a steady state parameter assessed during a 90min resting state scan. Previous researchers using FMT and its analog, [^{18}F]DOPA, have interpreted uptake of these tracers as indicative of the long-lasting, tonic activity rather than the dynamic variations of dopaminergic neurotransmission (Braskie et al., 2010; Dreher et al., 2008; Kienast et al., 2008; Schlagenhauf et al., 2012; Siessmeier et al., 2006). Evidence for a positive relationship between [^{18}F]DOPA uptake and tonic dopamine release comes from a study with non-human primates (Doudet et al., 2004). PET imaging of these animals in the anaesthetized state found that increased [^{18}F]DOPA uptake was associated with reduced raclopride binding, suggesting increased dopamine release. The tonic/phasic model suggests that individuals with higher FMT signal in our study are less likely to release the phasic bursts necessary for optimal task performance and consequently perform worse.

The inverted-U shaped model proposes that maximum efficiency in neural and behavioral performance results from having an optimal dopamine level, and deviation from this optimum in either direction results in decreased efficiency (Dickinson and Elvevag, 2009). Support for this model comes from both human and animal studies. In humans, administration of dopamine agonists improves performance in individuals with low endogenous dopamine function but impairs performance in those with high endogenous dopamine function (Mattay et al., 2003). Similar inverse relationships also have been reported *in vivo* without drug manipulation (Meyer-Lindenberg et al., 2005). In monkeys, both too much and too little stimulation of dopamine receptors in the prefrontal cortex impairs performance (Vijayraghavan et al., 2007). In this context, studies reporting relationships between high dopamine and low performance have proposed an "overdosing" effect whereby high dopamine is indicative of a deviation from the optimal dopamine level and thus optimal performance (Cools et al., 2001a; Mehta et al., 2001). Our results in Aim 1 support this proposal by showing that high FMT uptake correlates with low functional connectivity, reduced task-related deactivation, and long response time. Here, our finding of a correlation between high FMT signal and worse performance provides additional support for the possibility that subjects on the high extreme of dopaminergic function may be functioning at non-optimal levels.

Additionally, we found that subjects with higher caudate FMT signal showed less task-induced deactivation in the medial PFC during shifts of object features. Given that the medial PFC is a node within the default mode network, the integration of this finding with the negative relationship between FMT signal and object shift performance suggests that striatal dopaminergic activity influences set shifting through modulation of default mode network activity. Default mode network deactivation is indicative of the suspension of ongoing internal processing and the reallocation of finite brain resources in response to new task demands (McKiernan et al., 2003). Several studies have found unusual patterns of default mode network deactivation in patients with dopaminergic disorders like schizophrenia and Parkinson's disease (Harrison et al., 2007; Tinaz et al., 2008). Additionally, reduced default mode network deactivation in Parkinson's disease patients is associated with reduced connectivity between the medial PFC and the striatum (van Eimeren et al., 2009). Our observation that steady-state, presumably tonic striatal dopamine measurements correlate inversely with medial PFC deactivation during object shifts suggests that a high background dopamine signal may impair cognitive flexibility by interfering with this reallocation process.

Using a working memory paradigm, Nagano-Saito and colleagues found that dopamine depletion via phenylalanine/tyrosine depletion (APTD) in healthy adults reduced the degree of deactivation in the medial PFC and posterior cingulate (Nagano-Saito et al., 2008). While our results seem to conflict with this finding, it is important to note that APTD reduces both tonic and phasic dopamine release (Leyton et al., 2004; Montgomery et al., 2003), suggesting that the resulting effects on cognition with this method may be more complex (Mehta et al., 2005). Furthermore, dopaminergic mediation of working memory may differ from cognitive flexibility, as different subtypes of dopamine receptors in the medial PFC are activated during these two processes (Floresco et al., 2006). Future studies should investigate whether our results are specific to cognitive flexibility or can be generalized to other executive functions involving dopaminergic activity.

Furthermore, we found that FMT signal in the right caudate, but not left caudate, correlated with BOLD activity and performance of object shifts. The striatum is highly asymmetric. In Parkinson's disease patients exhibiting unilateral motor symptom onset, preservative errors on the WCST have been associated with left-onset Parkinson's disease (Tomer et al., 2007), suggesting that dopaminergic activity in the right hemisphere plays a larger role in set-shifting (Tomer et al., 1993). Other studies also observed greater right frontal cortex activity during set-shifting (Aron et al., 2004; Swainson et al., 2003). This lateralization may extend to subcortical structures as well, as Parkinson's disease patients with right, but not left, caudate denervation exhibit deficits in object alternation (Cheesman et al., 2005; Marie et al., 1999). In the context of these findings, our results suggest a greater role of the right hemisphere in shifting of object features.

Object feature shift vs. abstract rule shift

We did not find any specific pattern of BOLD activity showing significant correlations with shifting between abstract rules. It is unlikely that the lack of activation specific to rule shift is an effect of inadequate statistical power since a

previous study using this paradigm also did not find specific activation for rule shifts (Cools et al., 2004). While it is possible that rule shifts elicited a similar yet less robust pattern of activation that was not detected by our study, the difference in the strength of BOLD responses nevertheless supports the hypothesis that these two types of set-shifts elicit distinct brain activity. These effects cannot be ascribed to differential working memory demands between object and rule shifts, as each type of shift required the subject to remember their previous selection. Additionally, we observed no significant difference in accuracy, response time, or response time standard deviation between shift types, implying that task difficulty remained constant across both shifts.

Results from previous studies have been mixed regarding brain activity during such abstract higher-order shifts. Cools and colleagues also did not find any brain region specific to rule-shifting in healthy subjects (Cools et al., 2004). In contrast, other studies reported greater overall task-related fMRI signal change in the PFC during higher-order shifting of perceptual dimensions (analogous to a simultaneous object and rule shift in our study) compared to lower order reorganization of stimulus-response associations (analogous to object shift) (Cools et al., 2004; Nagahama et al., 2001; Rogers et al., 2000). However, the higher-order shifting tasks in these studies also placed greater demands on working memory, unlike in our study. It is possible that the greater PFC activity found in these studies reflects greater working memory load, not cognitive flexibility. Lastly, Kehagia and colleagues observed no correlation between dopaminergic status and performance on rule shifting in Parkinson's disease patients, postulating that not all types of attentional shifts rely on dopaminergic activity (Kehagia et al., 2009). Our results present no conclusion regarding the differential effects of dopamine on object shift versus rule shift as we did not observe significant BOLD activity related to rule shift.

4.5 Conclusions

We demonstrated that object feature shifts activate the fronto-parietal control network and deactivate the default mode network. Dopamine function in the dorsal striatum influences shifting of object features via modulation of default mode network activity through the medial PFC. While further research is needed regarding the role of dopamine in shifting between abstract rule, this study sheds light on the neurochemical basis of one important aspect of cognitive flexibility.

5. Concluding remarks

5.1 Summary

This dissertation presents three findings. Firstly, a genetic polymorphism in the COMT gene, which codes for an enzyme that affects dopamine levels in the prefrontal cortex, influences cognition via a mechanism that involves dopamine synthesis capacity, fMRI activity in the resting state, and fMRI activity during task performance. Secondly, the specific role of dopamine in cognition may be the modulation of resources supporting the transition between internally directed and externally directed attention. Thirdly, the dopamine system distinguishes the shifting of attention between perceptual features of objects and between the abstract rules guiding the selection of those objects. Furthermore, there exists a regional specificity to the relationship between dopamine and attention such that dopamine in the striatum is sensitive to attentional shifts between object features but not abstract rules.

5.2 Final thoughts

Optimal cognition involves a delicate balance between focusing attention on the current task and shifting attention in response to relevant changes in the environment. Such paradoxical processes require an inverted-U shaped function where peak performance is characterized by an intermediate level of attention. This modulatory precision seems to involve the dopamine system. Results from Aim 1 suggest that intermediate levels of dopamine enhance cognitive performance by increasing functional connectivity within brain networks and improving the efficiency of their response during task performance. Aim 3 shows the effect of deviating from these intermediate levels of dopamine. As expected from the inverted-U shaped profile, high FMT uptake correlated with low task-related fMRI response and low cognitive scores. The term "overdosing" describes this state of high dopamine past the tipping point between focusing and flexibility towards mental rigidity or instability, both of which are detrimental to performance.

In addition to influencing within network activity, results in Aim 2 show that dopamine also modulates the coupling of networks. High FMT uptake correlated with strong coupling between the fronto-parietal control network and the default mode network in the resting state. Although the relationship between cognitive performance and network coupling was not directly investigated, the finding of an association between high FMT uptake and worse performance in Aim 3 suggests that strong coupling between the fronto-parietal control network and the default mode network might not lead to better performance. The fronto-parietal control network is hypothesized to flexibly couple to the default mode network when attention is directed internally and to the dorsal attention network when attention is oriented externally. Strong network coupling may indicate a less flexible fronto-

parietal control network.

In terms of practical applications, the inverted-U shaped profile of dopamine function implies that individual assessments of baseline dopamine activity and specific deficits are necessary before administration of any dopaminergic drug. L-DOPA therapy has been shown to both enhance and impair performance, depending on the individual and the pathology. The effect of a dopamine drug is not known until the recipient is known.

5.3 Future directions

The present results demonstrate that dopamine synthesis capacity modulates large-scale brain networks to influence cognitive performance, but many questions concerning these findings remain. For example, relationships between individual differences in the synthesis of dopamine and its downstream signaling cascade are not yet known, as is the role this signaling cascade in brain networks. What is the relationship between dopamine synthesis and dopamine release or dopamine receptor function? Does dopamine release correlate with network activity differently than dopamine synthesis? The relationship between neuronal network activity and brain networks seen with fMRI also needs to be investigated. Dopamine has been shown to modulate neuronal synchrony and, as our results show, functional connectivity. Does functional connectivity reflect neuronal synchrony? If not, what is the process mediating dopamine function and functional connectivity?

This dissertation also ignored any effect of the environment on neurochemistry and brain activity. Each day, every one of us inhales and consumes numerous chemical compounds, natural and synthetic, but the present studies, like many others, assumed that the brain exists in a closed environment. Questions like the following were not considered but might be pertinent. How does tea, my favorite indulgence, affect the relationship between dopamine and performance or between fMRI activity and behavior? What is the role of physical activity? Can the present results be generalized to a population suffering nutritional deficiency? And many others.

Although the findings presented here are a small contribution, I hope they help serve as a launching pad for many future studies, with some culminating in meaningful applications.

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