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Genetic effects on behavior are mediated by neurotransmitters and large-scale neural networks

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ABSTRACT

Claims of gene–behavior associations are complex and sometimes difficult to replicate because these relationships involve many downstream endogenous and environmental processes that mediate genetic effects. Knowing these mediating processes is critical to understanding the links between genes and behavior and how these factors differ between people. We identified and characterized the effects of a gene on neurochemistry and neural networks to elucidate the mechanism, at the systems level, whereby genes influence cognition. Catechol-O-methyltransferase (COMT) degrades dopamine in the prefrontal cortex (PFC) and is polymorphic with alleles differing in enzymatic activity. We found 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. The integration of these results yields a model whereby 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.
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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). 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;

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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., 2001; 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.

Materials and methods

Subjects

Fifteen right-handed, young adults between 20 and 30 years old (mean age 25.3 ± 2.8 years, 8 M/7 F) 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, and 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 (2.5 mg/kg) approximately 60 min 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: 4×60 s, 3×120 s, 3×180 s, and 14×300 s. FMT images were reconstructed with an ordered subset expectation maximization algorithm with weighted attenuation, scatter corrected, and smoothed with a 4 mm 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 reliability and interrater reliability were greater than 95%. The cerebellum gray 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

FMT frames were realigned to the middle frame, the twelfth frame, to correct for movement during scanning. 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 1.5 T 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 = 2020 ms, echo time = 50 ms, flip angle = 90°, voxel dimensions = 3×3×3.5 mm) and resting state fMRI (repetition time = 1890 ms, echo time = 50 ms, flip angle = 90°, voxel dimensions = 3×3×3.5 mm). 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 = 11 ms; flip angle = 150°; voxel dimensions = 0.9×0.9×3.5 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 = 1×1×1mm). 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.

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