NEURONAL PATHWAYS IMPLICATED IN EXECUTIVE DYSFUNCTION

Thomas L. Schwartz and Nikhil Nihalani

Abstract

Executive dysfunction refers to impairment in the set of cognitive skills that enable a person to plan, initiate, sequence, monitor, and inhibit complex, goal-directed behavior. Executive dysfunction typically reflects an impairment in working memory, the component of cognition responsible for the temporary storage and manipulation of information used in goal-directed behavior. Several lines of evidence suggest that dopamine plays a key role in working memory and that working memory deficits are related to impaired dopaminergic signaling. In vitro studies have demonstrated that dopamine plays a modulatory role in the prefrontal cortex, regulating the signal-to-noise ratio of inhibitory and excitatory microcircuits via activation of D_1 versus D_2 dopamine receptors. In behavioral studies, executive function has been linked with the activity of catechol-O-methyltransferase (COMT), one of the principal enzymes responsible for dopamine metabolism, which plays a major role in regulating dopamine levels in the prefrontal cortex. In general, individuals with a COMT genotype polymorphism that promotes increased enzymatic activity exhibit inferior working memory and attentional control. They also exhibit inappropriately increased activation of the prefrontal cortex during memory-related task performances, suggesting less-efficient neuronal processing. Clinical studies implicate dopaminergic signaling impairment in executive dysfunction across a broad range of psychiatric and neurologic disorders, including schizophrenia, depression, Alzheimer's disease, vascular dementia, traumatic brain injury, Parkinson's disease, Huntington's disease, progressive supranuclear palsy, and subcortical vasculopathy. Executive dysfunction has also been reported in individuals with substance abuse problems, sleep deprivation, ADHD, fibromyalgia, chronic fatigue syndrome, as well as in persons experiencing normal aging. Collectively, the available data support a potential role for dopaminergic therapies in conditions with executive impairment as a prominent feature.

Key Words: executive dysfunction, cognitive skills, working memory, schizophrenia, depression, Alzheimer's disease, vascular dementia, traumatic brain injury, Parkinson's disease, Huntington's disease, progressive supranuclear palsy, and subcortical vasculopathy

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Introduction

Executive function comprises a set of cognitive skills that enable a person to plan, initiate, sequence, monitor, and inhibit complex goal-directed behavior. These skills include attention control, interference control, error monitoring, response selection, and working memory.[1] Executive function coordinates aspects of higher cognitive function, such as insight, will, abstraction, and judgment, and also assists with the behavioral regulation of nonexecutive processes vital to normal human behavior ie. basic drives and instincts like fight, flight, feeding, reproduction. Impairment in executive function causes problematic behavior and disability in various neuropsychiatric and neurologic disorders such as: schizophrenia, depression, Alzheimer's disease, vascular dementia, traumatic brain injury, Parkinson's disease, Huntington's disease, progressive supranuclear palsy, and subcortical vasculopathy (Royall et al. 2002). Executive dysfunction is also associated with substance abuse, sleep deprivation, chronic fatigue syndrome Dobbs et al. 2001, Durmer and Dinges 2005, Ersche et al. 2006), and normal aging (Royall et al. 2002).

Executive dysfunction has been linked to deficits in working memory, the component of cognition responsible for the temporary storage and manipulation of information necessary for guiding behavior. An accumulating body of evidence has linked working memory, which is measured using a variety of cognitive and neuropsychological tests, and dopamine levels in the prefrontal cortex. Genetic studies suggest that interindividual variability with respect to working memory capacity is influenced by certain genes, where, as an example the activity of catechol-O-methyltransferase (COMT), the principal extraneuronal synaptic enzyme responsible for dopamine metabolism may influence executive processes. Executive dysfunction, impaired prefrontal cortical dopaminergic signaling, and a high-activity variant of the COMT

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genotype have been identified in populations ranging from the healthy elderly to patients with schizophrenia, raising questions about the potential value of dopaminergic therapies in patients with conditions characterized by executive dysfunction.

Prefrontal cortex: key anatomical site involved in working memory

Research has identified the prefrontal cortex as the center for working memory. A study of 9 neurologically normal subjects was performed using blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI). For this study, imaging studies were conducted while subjects performed an "*n*-back" task, which employs a variable load of working memory (Callicott et al. 1999). Subjects were presented with a random sequence of visual stimuli, in this case the numbers 1 to 4 at points of a diamond-shaped box, and were then asked to recall previously seen stimuli; "*n*" refers to how far back in a sequence the subject was asked to recall. This task requires subjects to continually encode incoming stimuli while responding to previously seen stimuli. The "no-back" control is a sensorimotor control that involves the identification of the current stimulus without multiple distractors. Results of this study indicated that the prefrontal cortex plays a pivotal role in the performance of increasing working memory load. In particular, the investigators identified specific loci within the dorsolateral prefrontal cortex (DLPFC) that showed an inverted U-shaped pattern of activation with increasing working memory load, indicative of capacity constraint (**Figure 1**). Regions outside the dorsolateral prefrontal cortex showed a more heterogeneous response, usually involving an early plateau or continually increasing response, which was not indicative of capacity constraint (Callicott et al. 1999).

Using a similar event-related fMRI design, a second study compared the relative contributions of the dorsal and ventral prefrontal cortices during different memory-load conditions. For this study, fMRI scans were performed in 6 healthy right-handed subjects during the following behavioral task: where 2 or 6 letters were simultaneously presented in random order for 4 seconds, followed by a 12-second delay, after which a probe letter appeared for 2 seconds. Subjects were asked to press a button with their right thumb if the probe letter was part of their memory set, and with their left thumb if it was not part of their memory set. This task was followed by a 16-second intertrial interval. All subjects completed 10 series of 8 trials each. The investigators found that the subjects with the highest reaction time and lower accuracy showed greater spatial extent, greater change in signal, and slower increase in signals across task components, compared with the subject with the shortest reaction time slope and greater accuracy (**Figure 2**) Rypma and D'Esposito 1999). These results suggest that reductions in working memory are related to increases in dorsal prefrontal cortex activation, possibly due to diminished efficiency in neural processing or an early degradation in the quality of mnemonic representations. In other words, prefrontal structures appear to be engaged in excessive, inappropriate, and erroneous activity which allowed for more impulsive and error prone responses. The brain was working harder but achieving less. Several lines of evidence suggest similarly that impaired dopaminergic signaling may play a key role in working memory deficits.

The role of dopamine in working memory: in vitro studies

Evidence suggests that dopamine plays a modulatory role in the prefrontal cortex, regulating the signal-to-noise ratio of inhibitory and excitatory microcircuits via activation of D_1 versus D_2 dopamine receptors. In medium-sized striatal neurons, which project from the ventral tegmental area (VTA) to the cortex, pharmacologic activation of dopamine D_1 receptors with the selective agonist SKF 81297 enhances currents mediated by *N*-methyl-D-aspartate (NMDA) glutamate receptors (Flores-Hernandez et al. 2002) which up until a certain point may allow better efficient processing. On the other hand, activation of

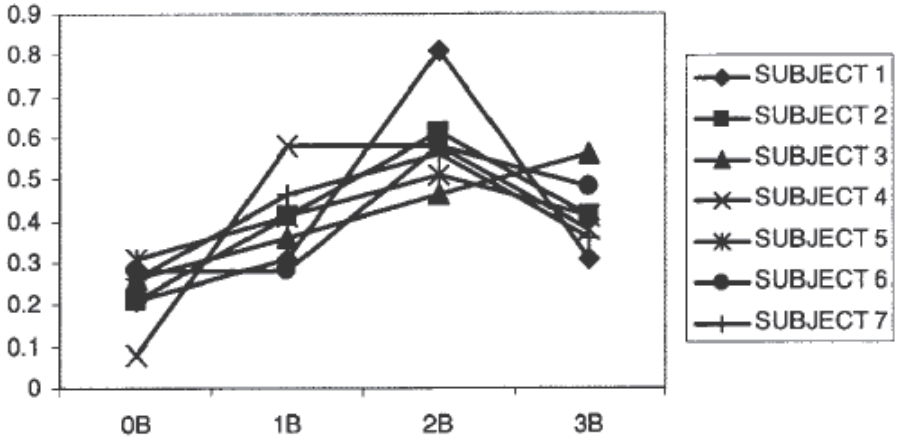
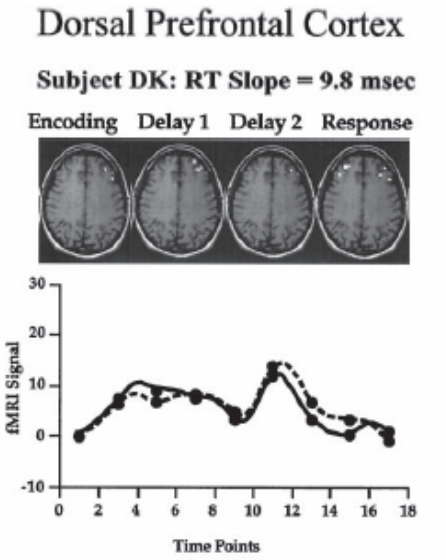


Figure 1. *Capacity-constrained physiological response in the dorsolateral prefrontal cortex with increasing working memory load. Working memory is optimized and peaks, only to a certain extent with increasing task demands. Eventually maximal workload creates inefficient cortical processing and working memory worsens* (Callicott et al. 1999)

A.



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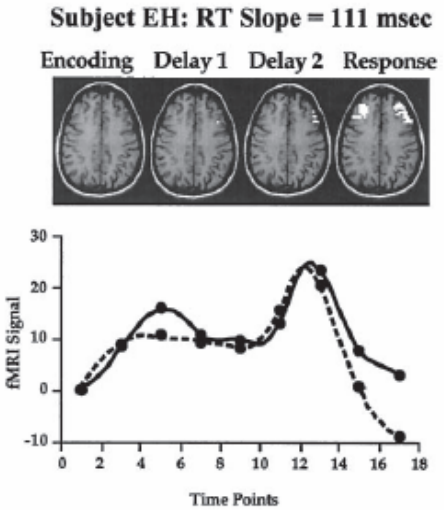

Figure 2. (A). *Optimal, efficent engamement of the dorsolateral prefrontal cortex*. (B) *Greater engagement of the dorsolateral prefrontal cortex with inferior performance of a working memory task, suggesting less efficient neural processing* (Rypma et al. 1999)

D_2 receptors inhibits NMDA receptor-mediated currents and significantly reduces D_1 receptor-mediated enhancement of NMDA currents (Flores-Hernandez et al. 2002) which, in theory may cause a worsening of processing. D_1 effects on NMDA receptor-mediated currents may be modulated by direct interaction between the two types of receptors on the same cells (Lee et al. 2002). Another mechanism of D_1 enhancement of NMDA receptor-mediated currents may be up-regulation of a-amino-3-hydroxy-5-methylisoxazole-4-propionic acid glutamate receptors (Smith et al. 2005).

Dopamine also bidirectionally modulates inhibitory neurotransmission. On pyramidal neurons of the prefrontal cortex, lower concentrations of dopamine stimulate D_1 receptors, resulting in enhancement of the amplitude of ^{3}-aminobutyric acid (GABA) receptor-mediated currents; higher concentrations stimulate D_2 receptors, resulting in reduction of these currents (Trantham-Davidson et al. 2004).

At this point, we have oversimplified COMT and dopamine effects into simple, 'all-or-none' categories. Unfortunately the brain is extremely more complex. These multi-directional effects of dopamine on excitatory and inhibitory neurotransmission are thought to have an overall effect of modulating the signal-to-noise ratio of these microcircuits, which may for example lead to variability in one's ability to sustain attention or vigilance, as an example. For example, when D_1 activation predominates over D_2 activation, D_1-mediated increases in NMDA currents would enhance the persistent state of activity of neurons relative to changes resulting from incoming signals.[10] This improves 'signal' and diminishes 'noise' in the proposed model. In this state, there would be a decreased likelihood that interfering input would interrupt persistent activity, and working memory representations would be more robust and efficient. In contrast, when D_2 activation predominates, there would be a decrease in signal-to-noise ratio, reflecting a decrease in the efficiency as there is greater 'noise' in the signaling network for the brain to contend with (Seamans et al. 2001). As this executive functioning 'circuit' has multiple inputs and control segments a balance of dopaminergic activity is needed for good processing and thinking as either too little, or even too much, dopamine activity may be deleterious.

The role of dopamine in working memory: behavioral studies

COMT plays a prominent role by catalyzing dopamine and reducing levels in the prefrontal cortex (Axelrod and Tomchick 1958). COMT accounts for approximately 60% of extracellular dopamine degradation in the prefrontal cortex, compared to no more than 15% in the striatum, as assessed by measuring the levels of the byproduct 3-methoxytyramine using mass fragmentography (Karoum et al. 1994). Furthermore, COMT may also regulate dopamine release: in rats, administration of the brain-penetrating COMT inhibitor tolcapone significantly and selectively potentiates evoked release of dopamine in the medial prefrontal cortex (Tunbridge et al. 2004). Experimental disruption of the gene encoding COMT (COMT knockout mice) results in a region-specific, 2- to 3-fold increase in dopamine levels in the frontal cortex (Gogos et al. 1998).

In contrast to COMT, dopamine transporters (DAT) appear to play a lesser role in regulating prefrontal dopamine. In the prelimbic prefrontal cortex, compared to the striatum, there are, in fact, very low levels of dopamine transporters, and they are localized away from synaptic release sites (Sesack et al. 1998). Dopamine reuptake in the frontal cortex depends primarily on the norepinephrine transporter instead; this finding was demonstrated by an in vivo pharmacologic study using microdialysis and in another pharmacologic study assessing uptake in synaptosomes from knockout mice with a targeted disruption of the DAT gene (Mazei et al. 2002, Moron et al. 2002). However, even with this available mechanism of dopamine uptake via the

norepinephrine transporter, the prefrontal cortex exhibits a lower capacity for dopamine clearance, compared with the striatum (Sesack et al. 1998).

Studies support a role of COMT in executive cognition; performance of tasks requiring executive cognition is affected by levels of COMT activity. This was observed in studies of normal individuals with a COMT polymorphism, resulting in a substitution of Val with Met at amino acid position 158 of membrane-bound COMT (position 108 of soluble COMT), which was associated with about 40% lower enzyme activity and therefore presumably a higher level of dopaminergic availability and signaling in the dorsolateral prefrontal cortex due to this variant's less aggressive catabolism (Chen et al. 2004).

As observed with dopaminergic modulation of NMDA and GABA currents in the prefrontal cortex, COMT also appears to regulate physiological efficiency (Blasi et al. 2005). In general, individuals with the less catabolic COMT Met allele, compared with the Val allele, demonstrate superior performance of attentional control task (**Figure 3A**) and lesser activation of the

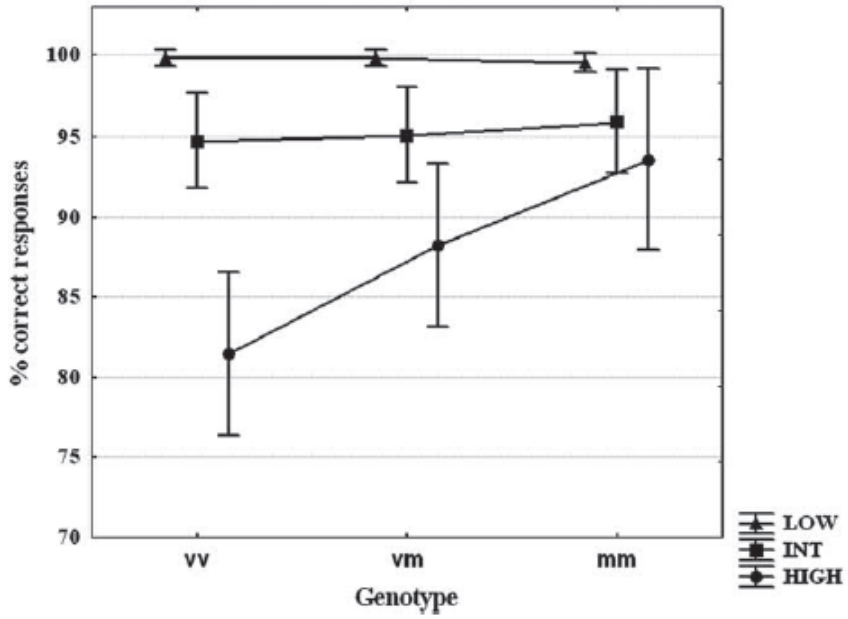

Figure 3A. *Superior performance of an attentional control task with the COMT 158met allele, compared with the Val allele (Blasi et al. 2005)*

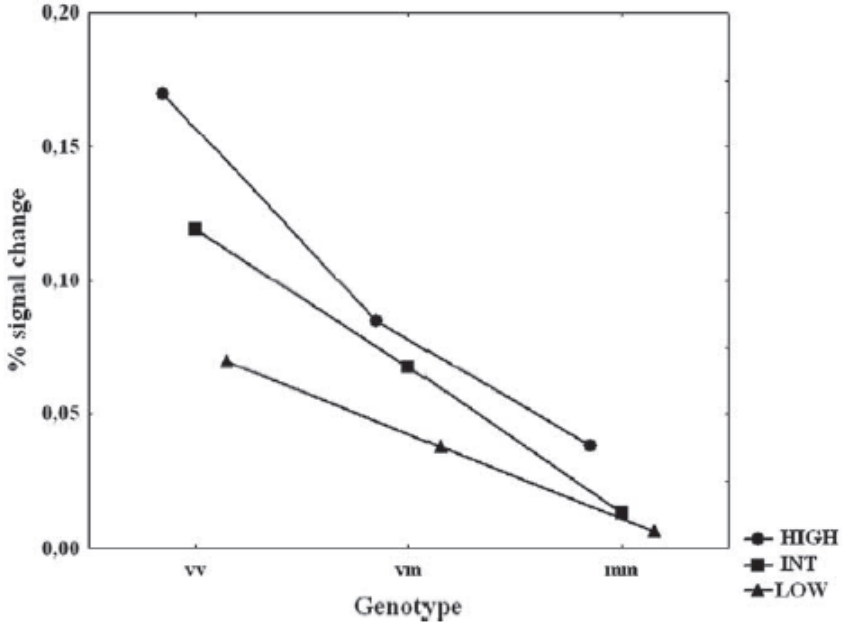

Figure 3B. *Optimal (lesser) activation of the dorsal cingulated cortex during performance of an attentional control task with the COMT 158met allele (Blasi et al. 2005)*

dorsal cingulate cortex during task performance, as detected by BOLD fMRI (**Figure 3B**) (Blasi et al. 2005). These subjects efficiently use smaller areas of cortex to accomplish tasks. Individuals with the COMT Met allele also demonstrate superior performance of the *n*-back test of working memory, shorter reaction time**,** and lesser activation of the dorsolateral prefrontal cortex while performing the *n*-back test, suggesting faster, more efficient physiological processing than individuals with the more dopamine catabolic Val allele (Goldberg et al. 2003, Egan et al. 2001). This increase in physiological efficiency with the COMT Met allele is additive to an increase in efficiency associated with a polymorphism of the gene encoding the DAT (Bertolino et al. 2006).

The bidirectional effects of dopamine on excitatory and inhibitory neurotransmission observed in in vitro studies is paralleled by bidirectional effects on performance of behavioral tasks that employ executive cognition. In rats and monkeys, pharmacologic enhancement of dopamine turnover and dopamine release in the prefrontal cortex with systemic administration of the inverse benzodiazepine agonist FG7142 results in impaired performance of spatial working memory tasks that depend on prefrontal cortical functioning (eg, delayed alternation testing in rats and relayed response testing in monkeys) (Murphy et al. 1996a, Murphy et al. 1996b, Murphy et al. 1997. This effect is mediated by activation of D_1 receptors: it is prevented by pretreatment with an agent that blocks the FG7142-mediated increase in dopamine turnover and by nonselective and D_1-selective dopamine receptor antagonists. Similarly, in rats, administration of the noncompetitive NMDA antagonist ketamine disrupts performance of a spatial working memory task, and systemic administration of dopamine receptor antagonists reverses this effect (Verma and Moghaddam 1996). On the other hand, experimentally reducing dopaminergic neurotransmission in the prefrontal cortex results in impaired performance of tasks involving executive cognition (Murphy et al. 1996a).

A bidirectional effect of dopamine on executive cognition was also demonstrated in a pharmacologic study of the influence of COMT genotype in healthy people. In subjects with the *val*/*val* more catabolic genotype and therefore presumably low baseline synaptic dopamine, treatment with amphetamine—a psychostimulant that increases prefrontal dopamine—resulted in enhanced efficiency of the prefrontal cortex (assessed with fMRI) while performing the Wisconsin Card Sorting Task, a test of executive cognition (**Figure 4**) (Mattay et al. 2003). In subjects with the *met*/*met* genotype and therefore presumably higher baseline synaptic dopamine availability, amphetamine had no effect on cortical efficiency at low-to-moderate working memory load and caused deterioration at high-working memory load. These results are consistent with an inverted U-shaped dose-response curve for the effect of dopamine on prefrontal cortex function. Baseline dopaminergic tone, which is affected by COMT genotype, determines response to dopaminergic agents.

Role of prefrontal cortex dopamine in executive dysfunction

Research has implicated that decreased levels of dopamine in the prefrontal cortex may lead to deficits in executive function. This has been observed in several patient populations, and genetic studies link these deficits to the high-catabolic activity *val/val* COMT genotype discussed in the previous section. In a study of 292 nondemented men (aged 35-85 years), subjects with the COMT *val/val* genotype demonstrated decreased performance in tests of executive function and exhibited cognitive decline over a 5-year period compared with subjects with the *met/met* genotype and therefore presumably higher levels of prefrontal dopamine. The investigators concluded that these results were consistent with data showing that cognitive tasks that require executive control (eg, working memory) are sensitive to levels of dopamine in the dorsolateral prefrontal cortex (de Frias et al. 2005).

DiGeorge/velocardiofacial syndrome (VCFS) is known as 22q11.2 deletion syndrome where individuals have a deletion of genetic sequence on the 22 chromosome and this is the area that codes for the COMT alleles we have spoken of above. Therefore these patients cannot be met-met or val-val in that they will only have one allelic gene copy. They would be classified as

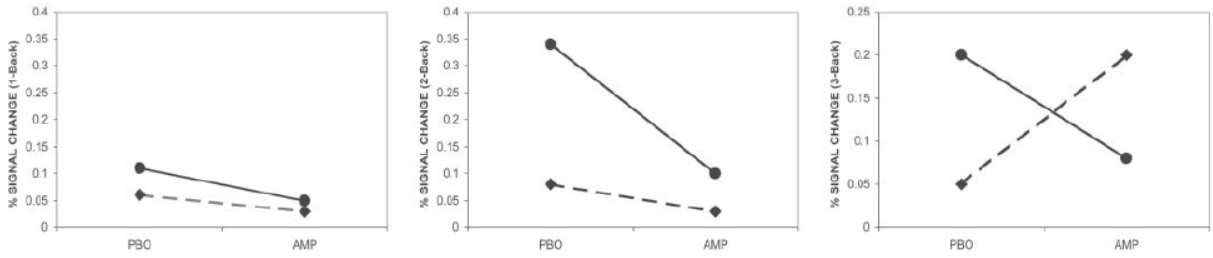

Figure 4. *Influence of COMT genotype on the effects of amphetamine on prefrontal cortex activity during performance of a working memory. Met (♦) individuals function better (left to right) with increasing workload or compared to val allele (●) individuals overall. However, high workload or and high amphetamine load actually leads even, met individuals' performance to degrade, suggesting that optimal dopamine is required for optimal cortical functioning* (Mattay et al. 2003)

homozygous for val- or met- solely instead. Met- patients will show low dopamine catabolism and therefore excess available dopamine similar to normal met-met patients. The val- patients will have poor availability of dopamine. Executive function results in VCFS patients are mixed in that some studies show that excess dopamine may help executive functioning in these patients and other studies will show increases in executive dysfunction. The excess dopamine may also be at the root cause of increased psychosis in VCFS patients. In this very specific patient population it appears that an appropriate balance of bidirectional dopamine is needed and marked excess or deficiency of dopaminergic activity can produce worsening of executive functioning (Bearden et al. 2004, Gothelf et al. 2005). These conflicting findings regarding 'too much' versus 'too little' dopamine activity further drive the point that the DLPFC circuitry requires a balance of dopamine activity and that certain patient populations may have dysfunction to different degrees along this circuitry which may require more or less dopamine depending upon their diagnosis.

Finally, a large trial examined the relationship between COMT genotype and the occurrence of mood disorders in 378 patients with major depressive disorder, 506 patients with bipolar disorder, and 628 healthy controls. An association was found between the *val* allele, and particularly the *val/val* genotype, and early-onset major depressive disorder. The investigators noted that these findings are consistent with other studies showing that patients with mood disorders who have the *val/val* genotype exhibit diminished executive functioning, probably due to impaired prefrontal dopaminergic signaling (Massat et al. 2005).

Summary and Conclusion

Evidence suggests that executive function is regulated in large part by dopamine in the prefrontal cortex. Here, in vitro studies demonstrate that dopamine modulates excitatory (glutamatergic) and inhibitory (GABAergic) microcircuits. Via activation of D_1 receptors, dopamine enhances neuronal signaling and thereby increases the signal-to-noise ratio, or efficiency, of these microcircuits. The opposite effect is mediated by activation of D_2 dopamine receptors. This bidirectional, modulatory role of dopamine in the prefrontal cortex is paralleled by the influence of COMT genotype on the efficiency of engagement of the prefrontal cortex during performance of tasks of executive cognition. This result is observed in healthy people and in patients with various forms of executive dysfunction. The available data strongly support dopamine as a target for treating a number of conditions characterized by executive dysfunction, including normal aging, schizophrenia, depression, attention-deficit/hyperactivity disorder, Alzheimer's disease, vascular dementia, traumatic brain injury, Parkinson's disease, Huntington's disease, progressive supranuclear palsy, substance abuse, sleep deprivation, and chronic fatigue syndrome. The available data also suggest that baseline screening for COMT genotype, a determinant of dopaminergic tone, may be useful in patients with indications for dopaminergic therapy.

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