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CHAPTER 18

# Biological and social influences on cognitive control processes dependent on prefrontal cortex

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**Abstract:** Cognitive control functions ("executive functions" [EFs] such as attentional control, self-regulation, working memory, and inhibition) that depend on prefrontal cortex (PFC) are critical for success in school and in life. Many children begin school lacking needed EF skills. Disturbances in EFs occur in many mental health disorders, such as ADHD and depression. This chapter addresses modulation of EFs by *biology* (genes and neurochemistry) and the *environment* (including school programs) with implications for clinical disorders and for education. Unusual properties of the prefrontal dopamine system contribute to PFC's vulnerability to environmental and genetic variations that have little effect elsewhere. EFs depend on a late-maturing brain region (PFC), yet they can be improved even in infants and preschoolers, without specialists or fancy equipment. Research shows that activities often squeezed out of school curricula (play, physical education, and the arts) rather than detracting from academic achievement help improve EFs and enhance academic outcomes. Such practices may also head off problems before they lead to diagnoses of EF impairments, including ADHD. Many issues are not simply education issues or health issues; they are both.

**Keywords:** executive functions; self-regulation; dopamine; COMT; interventions; dopamine transporter; ADHD; gender difference.

## Introduction

Executive functions (EFs; also called "cognitive control" functions) are needed for reasoning, problem-solving, and whenever "going on automatic" would be insufficient or worse. They depend on a neural circuit in which prefrontal cortex (PFC) plays a central role and are impaired by damage to, or dysfunction in, PFC. They are critical for mental health, achievement in school, and successful functioning in the world. The three core EFs from which more complex ones (like reasoning) are built are (1) *inhibitory control* (resisting a strong inclination to do one

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thing and instead do what is most needed or appropriate, e.g., focused or selective attention, being disciplined and staying on task, exercising self-control, and not saying or doing something socially inappropriate), (2) *working memory* (holding information in mind and working with it: mentally manipulating ideas, relating what you are learning, hearing, or reading now to what you learned, heard, or read earlier and relating an effect to the cause that preceded it), and (3) *cognitive flexibility* (being able to change perspectives or the focus of attention, thinking outside the box to come up with other ways to solve a problem) (Diamond, 2006; Huizinga et al., 2006; Lehto et al., 2003; Miyake et al., 2000).

Both biology (genes and neurochemistry) and the environment (including school programs) modulate the functioning of PFC and thus affect EFs. Unusual properties of the dopamine system in PFC contribute to PFC's vulnerability to environmental and genetic variations that have little effect elsewhere, and some of those variations appear to differentially affect males and females. The relevance of this to disorders such as ADHD and PKU are discussed in the section below, as well as how genotype and gender can moderate which environment is most beneficial.

What we are learning about the brain is turning some ideas about education on their heads. "Brain-based" does not mean immutable or unchangeable. EFs depend on the brain, yet they can be improved by the proper activities. PFC is not fully mature until early adulthood (Gogtay et al., 2004), yet EFs can be improved even during the first year of life and certainly by 4–5 years of age. Neuroplasticity is not just a characteristic of the immature brain. PFC remains plastic even into old age, and EFs remain open to improvement. Many children today, regardless of their backgrounds, are behind on crucial EF skills compared to past generations (Smirnova, 1998; Smirnova and Gudareva, 2004), yet these skills can be improved without specialists and without great expense. Research shows that activities often squeezed out of school curricula (play, physical education, and the arts), rather than detracting from academic achievement, help improve EFs and enhance academic achievement. Such practices may also help to head off problems before they lead to diagnoses of EF impairments, such as ADHD, and may have dramatic effects on children's life trajectories. Improving key EF skills early gets children started on a trajectory for success. Conversely, letting children start school when they are behind on these skills may launch them on a negative trajectory that can be extremely difficult and expensive to reverse.

## Special properties of the dopamine system serving Prefrontal Cortex

The dopamine system in PFC is unusual. First, compared with the dopamine systems in most other brain regions, PFC has a relative dearth of dopamine transporter (DAT) protein. This means that while variations in the DAT1 gene that codes for DAT have important consequences elsewhere in the brain, such polymorphisms have little or no direct consequence for PFC.

This also means that unlike other brain regions that have a plentiful supply of DAT, PFC has to rely on mechanisms other than DAT to clear released dopamine. DAT provides the best way to clear released dopamine; those brain regions rich in DAT have little need for secondary mechanisms for clearing dopamine. PFC, because it has little DAT and the DAT it has is not ideally situated (being some distance from synaptic sites), is unusually dependent on the catechol-*O*-methyltransferase (COMT) enzyme for dopamine clearance. Thus variations in the COMT gene that codes for the COMT enzyme have important, direct consequences for PFC, but not for most other brain regions. As estrogen downregulates COMT transcription, there are gender (and menstrual phase) differences in the effects of variations in the COMT gene.

The dopamine system in PFC is also unusual in that, the dopamine neurons projecting to PFC have a higher baseline rate of firing and a higher rate of dopamine turnover. This makes the PFC dopamine system highly sensitive to small changes in the availability of the precursor, tyrosine (Tyr). Other brain regions, such as in the striatum, are unaffected by small changes in the amount of available Tyr.

## Consequence of the relative dearth of DAT in PFC for understanding differences among subtypes of attention deficit hyperactivity disorder (ADHD)

Current diagnostic guidelines list three subtypes of ADHD: primarily inattentive, primarily hyperactive/impulsive, and a combination of the two (DSM-IV; American Psychiatric Association, 1994). Most studies have focused on the combined type. There is much evidence that when ADHD involves hyperactivity (the combined and hyperactive types), the primary disorder is in the striatum and involves a striatal-frontal loop (Casey et al., 1997; Filipek et al., 1997; Hynd et al., 1993; Schrimsher et al., 2002; Soliva et al., 2010; Teicher et al., 1996; Vaidya et al., 1998). As DAT plays an important role in dopamine clearance in the striatum, it follows that polymorphisms of the DAT1 gene should have important consequences for these subtypes of ADHD. That is, in fact, the case (Barr et al., 2001; Bedard et al., 2010; Cook, 2000; Cook et al., 1995; Daly et al., 1999; Gill et al., 1997; Schrimsher et al., 2002; Shook et al., 2011; Swanson et al., 2000; Waldman et al., 1998; Yang et al., 2007).

The primary cause of the cognitive deficits in ADHD (such as inattention and poor working memory) lies in PFC, not the striatum. DAT is sparse in PFC and plays only a minor role there (Durston et al., 2005; Lewis et al., 2001; Sesack et al., 1998). It follows that polymorphisms in DAT1 should have little effect on the cognitive problems that can plague persons with ADHD and little effect on ADHD of the inattentive type. Indeed, that is the case. For example, levels of hyperactive–impulsive symptoms are correlated with the number of DAT1 high-risk alleles but levels of inattentive symptoms are not (Waldman et al., 1998) and DAT binding is related to motor hyperactivity but not to inattentive symptoms (Jucaite et al., 2005).

A role for polymorphisms of the DAT1 gene in the forms of ADHD where hyperactivity is present is consistent with the efficacy of methylphenidate in treating those forms of ADHD, as methylphenidate acts directly on DAT function (Dresel et al., 2000; Seeman and Madras, 1998; Shenker, 1992; Volkow et al., 2002, 2005, 2007). DAT clears released dopamine through reuptake of released dopamine back into presynaptic neurons. Methylphenidate attaches to DAT protein, blocking it from being able to take up dopamine (see Fig. 1). Most children with the combined or hyperactive subtypes of ADHD (as high as 90%) respond positively to methylphenidate; over 67% respond positively to methylphenidate in moderate to high doses (Barkley, 2001; Barkley et al., 1991; Milich et al., 2001; Weiss et al., 2003). That is consistent with methylphenidate acting directly on DAT, DAT being particularly important in the striatum, and the striatum being the site of the primary disturbance in forms of ADHD where hyperactivity is present.

However, a significant proportion of children with the inattentive subtype of ADHD are not helped by methylphenidate or are helped at low doses (Barkley, 2001; Barkley et al., 1991; Milich et al., 2001; Weiss et al., 2003). This is consistent with the different actions of methylphenidate at low doses. At low doses, methylphenidate preferentially increases dopamine neurotransmission in PFC (Berridge et al., 2006).

In humans the dopamine receptor type 4 (DRD4) is present in PFC but not in the striatum (Meador-Woodruff et al., 1996). It follows that polymorphisms in the DRD4 gene should then affect prefrontal function and be related to the inattentive subtype of ADHD, but should not directly affect striatal function. There is evidence to support this. Single-nucleotide polymorphisms (SNPs) in the promoter region of DRD4 have been found to be strongly and primarily

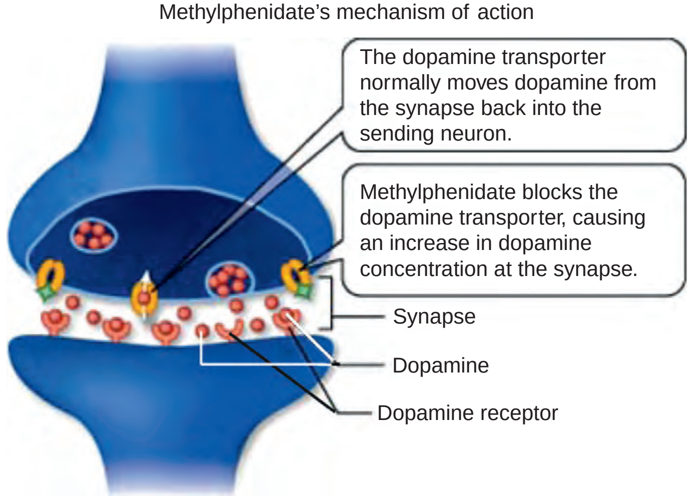



Fig. 1. Mechanism of action of methylphenidate.

associated with inattentive symptoms in ADHD (Lasky-Su et al., 2008), the inattentive subtype of ADHD seems to be the subtype most strongly correlated with the DRD4 7-repeat allele (Rowe et al., 1998), and attentional and working memory deficits have been reported in children with a 7-repeat allele of DRD4 (Auerbach et al., 2001). Moreover, evidence shows a lack of relation between the presence of the 7-repeat allele variant of DRD4 and hyperactivity or impulsivity, deficits which reflect a striatal abnormality (Bellgrove et al., 2005; Johnson et al., 2008; Kramer et al., 2009).

Where hyperactivity is prominent, children with ADHD tend to be frenetic. Children with the inattentive subtype of ADHD, however, are often the opposite; they can be hypoactive, sluggish, and slow to respond (Carlson and Mann, 2002; Carlson et al., 1986; Milich et al., 2001). Where hyperactivity is prominent, children with ADHD tend to be insufficiently self-conscious. Children with the inattentive subtype of ADHD can be overly self-conscious.

Both groups have social problems, but for different reasons. Where the ADHD includes hyperactivity or impulsivity, the child can alienate others by failing to wait his or her turn, butting in line, and acting without first considering others' feelings. Where the ADHD includes no hint of hyperactivity, the child is more likely to have social problems because of being too passive or shy. Such children are not so much easily distracted as easily bored. Their problem is more in motivation (underarousal) than in inhibitory control. Rather than distraction derailing them, they go looking for distraction because their interest in what they had started has dwindled. Having lost interest in their current project, their attention drifts as they look for something to engage their interest. Challenge or risk, something to literally get their adrenaline pumping, can be key to keeping their attention and optimum performance.

It is no coincidence that methylphenidate in low doses (the dosage most efficacious for such children), not only inhibits dopamine reuptake (as it does at high doses) but also preferentially stimulates release of dopamine and norepinephrine (Ishimatsu et al., 2002). Children with ADHD are often given untimed exams to help them, but children with the inattentive subtype often perform better when challenged by presenting test items at a quick rate.

In 2005, colleagues and I laid out the evidence that ADHD that includes hyperactivity and ADHD that is exclusively inattentive are fundamentally different disorders, with different genetic and neural bases, cognitive profiles, responses to medication, and patterns of comorbidity (Diamond, 2005). It resonated deeply with clinicians and patients. Almost overnight, the number of Web sites devoted to ADHD inattentive (ADD) rose from four to thousands. The Founder and Head of the Dutch ADD Assoc. (Stichting ADD Nederland), Karin Windt, wrote, "Many people with attention deficits have great talents, often a high IQ, and are innovative and creative. However, they are seen as daydreamers who cannot concentrate well. In the old days, we would be called stupid or lazy .... Through [Diamond's] work we are now able to explain to others why ADD is so different from ADHD. This question remained unanswered until her article appeared in 2005." Although DSM-V has not yet been released, it appears that the upcoming edition of the diagnostic manual will list ADD and the forms of ADHD that include hyperactivity in separate categories, as fundamentally different disorders.

**Consequence of the higher rate of dopamine turnover in PFC for understanding why dietary treatment for phenylketonuria (PKU), if insufficiently rigorous, results in deficits limited to the cognitive abilities (the "executive functions") that depend on PFC**

PKU is an inborn (i.e., genetic) error of metabolism usually caused by any of a family of point mutations or microdeletions of the phenylalanine hydroxylase gene, which codes for the enzyme, phenylalanine hydroxylase (DiLella et al., 1986; Lidsky et al., 1985; Woo et al., 1983). Phenylalanine hydroxylase is essential for hydroxylating the amino acid, phenylalanine (Phe), into the amino acid, Tyr. In persons with PKU, phenylalanine hydroxylase activity is either absent or markedly reduced.

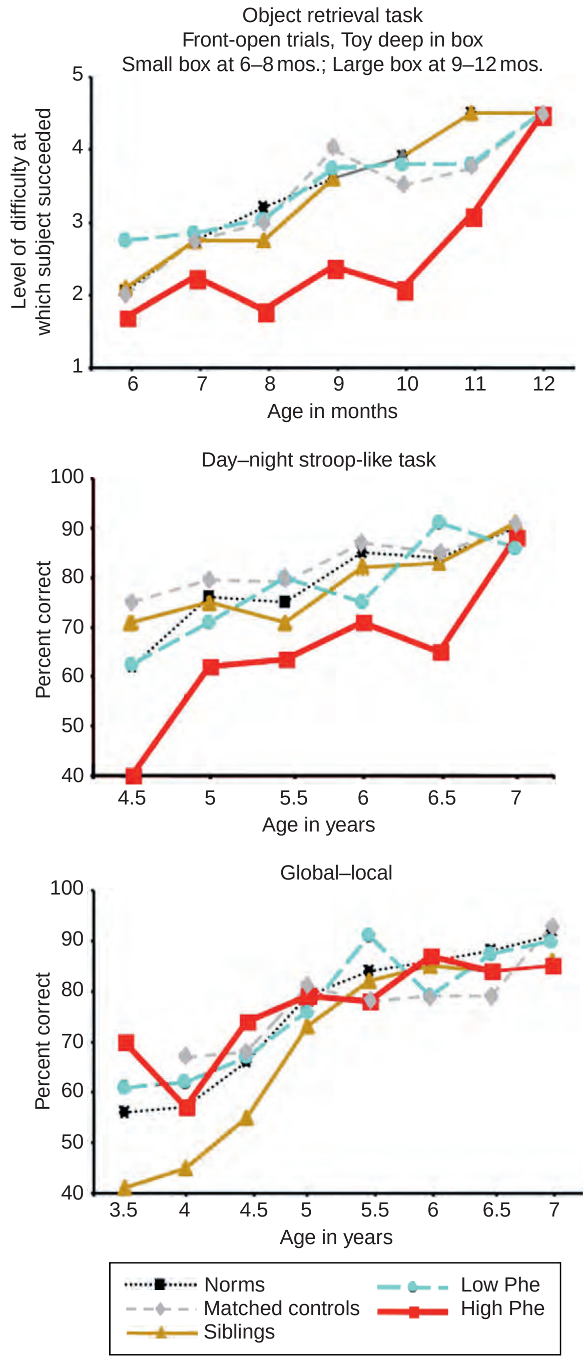
As little, if any, Phe is metabolized, Phe levels in the bloodstream skyrocket. If this drastic increase in blood levels of Phe is not corrected early, it causes widespread brain damage and severe mental retardation (Cowie, 1971; Hsia, 1967; Koch et al., 1982; Krause et al., 1985; Tourian and Sidbury, 1978). It would be ideal if the intake of Phe could be reduced to almost trace levels, but the only way to reduce Phe intake is to reduce protein intake, so dietary treatment for PKU must necessarily be a compromise between the need to minimize Phe intake and the need for protein. For this reason, the low-Phe diet rarely results in fully normal blood levels of Phe; Phe levels are reduced but remain moderately elevated. Further, blood levels of Tyr are moderately reduced, as little or no Tyr is produced from Phe, and oral supplements of Tyr only slightly increase blood Tyr levels. The upshot is that dietary treatment for PKU results in a mild imbalance in the ratio of Phe to Tyr in the bloodstream (without dietary treatment, the ratio of Phe to Tyr would be grossly elevated).

When PKU is treated early and continuously by a diet low in Phe, gross brain damage and severe mental retardation are averted (Bickel et al., 1971; Holtzman et al., 1986). However, young children on such treatment still show deficits if their blood levels of Phe are only brought down to 6–10 mg/dL (360–600 mmol/L)—roughly three to five times normal—levels considered safe worldwide until the late 1990s. Those deficits are specific to and limited to the functioning of PFC and the cognitive abilities dependent on PFC (DeRoche and Welsh, 2008; Diamond, 2001; Diamond et al., 1994, 1997; Smith et al., 2000; Welsh et al., 1990). The reason is as follows:

Phe and Tyr compete for the same limited supply of transporter proteins to cross the blood–brain barrier. Indeed, those protein carriers have a higher affinity for Phe than for Tyr (Miller et al., 1985; Oldendorf, 1973; Pardridge, 1977; Pardridge and Oldendorf, 1977). Elevations in blood levels of Phe relative to Tyr thus result in less Tyr reaching the brain. Because the ratio of Phe to Tyr in the bloodstream is only modestly increased in PKU children on dietary treatment, the decrease in Tyr levels in the brain is only modest. Unlike dopamine systems in most brain regions, which are robust in the face of modest decreases in available Tyr, the dopamine system in PFC is profoundly affected. (Tyr is the precursor of dopamine.) The higher rates of firing and of dopamine turnover of the dopamine neurons that project to PFC result in PFC being acutely sensitive to even a modest decrease in available Tyr. Reductions in Tyr too small to affect dopamine systems in other brain regions, such as the striatum, profoundly reduce prefrontal dopamine levels (Bannon et al., 1981; Bradberry et al., 1989; Tam et al., 1990; Thierry et al., 1977).

Thus, infants and young children treated early and continuously for PKU show deficits in the cognitive abilities dependent on PFC if their phenylalanine levels are not kept at 2–6 mg/dL (120–360 μmol/L; see Fig. 2), and the higher their Phe levels, the worse their performance on EF tasks that require PFC (Diamond et al., 1997). As long as Phe levels in young children do not exceed 10 mg/dL, the deficits appear to be exclusively in those abilities dependent on PFC. What affects how much Tyr reaches the brain is not simply the level of Phe in the bloodstream but also the level of Tyr. It follows that EF deficits in children with PKU are even more closely related to the Phe : Tyr ratio in blood than to either blood Phe or Tyr levels alone (Luciana et al., 2001).

The wonderful news is that deficits in EFs are preventable and reversible. When average blood Phe levels of children with PKU are kept between 2 and 6 mg/dL, cognitive function seems to be completely normal. EFs deficits can be completely prevented in young children with PKU if their Phe levels are kept between 2 and 6 mg/dL (120–360 μmol/L; Diamond et al., 1997; Stemerdink et al., 1995), and EF deficits in children and adults with PKU can be reversed by a strict dietary regimen that brings Phe levels down



(Schmidt et al., 1994). Also, there are individual differences in the kinetics of the blood–brain barrier that result in variation in the permeability of the blood–brain barrier to different amino acids. Some people have unusual protection against how much Phe reaches the brain and so show little or no deficits from sky-high ratios of Phe to Tyr in their bloodstreams (Koch et al., 2000; Moller et al., 1998, 2000; Weglage et al., 2001).

There were reports in the 1970s and 1980s of cognitive deficits in some PKU children despite treatment and that those deficits appeared to be limited to the cognitive skills requiring PFC. The effect of those reports was muted, however, because no one could imagine a mechanism that would produce such a selective effect. Luckily, unbeknownst to those working on inborn errors of metabolism, a discovery by neuropharmacologists in the 1970s and 1980s—the special sensitivity of prefrontally projecting dopamine neurons to small decreases in Tyr—provided such a mechanism. Neurochemical and behavioral work in an animal model (Diamond et al., 1994) and extensive neurocognitive testing of children (DeRoche and Welsh, 2008; Diamond et al., 1997) confirmed that this mechanism did, indeed, account for PFC cognitive deficits in treated PKU patients. By 2000, the guidelines for the treatment of PKU in young children were changed worldwide, requiring stricter dietary compliance so that average plasma Phe levels remain 2–6 mg/dL, and that has enabled many thousands of children with PKU to lead more productive lives.

### Consequences of the relative dearth of DAT, and hence dependence on COMT, for PFC

With less extensive reuptake of dopamine by DAT, PFC is more dependent on secondary mechanisms for terminating the action of released dopamine, such as the COMT enzyme, which deactivates dopamine by adding a methyl group (Napolitano et al., 1995; Weinshilboum et al., 1999). The COMT enzyme accounts for >60% of dopamine degradation in PFC, but <15% of dopamine degradation in the striatum (Karoum et al., 1994). Administering an inhibitor of COMT (Tolcapone) to Parkinson patients improves their EFs (Gasparini et al., 1997) because it results in more dopamine in PFC, but it does not improve their motor problems, which are due to striatal dysfunction (Chong et al., 2000).

Variations in the COMT gene disproportionately affect PFC. A common variation in the COMT gene, a guanine to adenine missense mutation (a single base pair substitution [C**G**TG for C**A**TG]), results in a substitution of methionine (Met) for valine (Val; AG**V**KD vs. AG**M**KD) in the coding sequence of the gene (Lachman et al., 1996). Met at codon 158 of the COMT gene codes for a more sluggish COMT enzyme in brain; it methylates dopamine four times more slowly than the COMT enzyme coded from the Val-158 version of the COMT gene (Lotta et al., 1995; Tenhunen et al., 1994). The slower COMT works, the longer the temporal and spatial presence of dopamine at PFC synapses.

The variant of the COMT gene that prolongs the action of dopamine in PFC (Met-158) has been shown in both adults and children to result

Fig. 2. Comparison of the performance of PKU children whose blood Phe levels were 6–10 mg/dL (360–600 mmol/L; labeled the "High Phe" group) with the performance of four comparison groups on tasks that assess executive functioning (the top and middle panels) and a task that does not tax EFs (bottom panel). At each age range investigated (the top panel shows one of the age ranges and the middle panel shows another), and on all EF measures requiring working memory and inhibitory control, the PKU children with relatively high Phe levels (though still within the clinically accepted range at the time) performed significantly worse no matter who they were compared with (other PKU children with lower Phe levels [Phe levels of 2–6 mg/dL, 120–360 mmol/L; labeled the "Low Phe" group], their own siblings, matched controls, or children from the general population). They were not impaired on any of the ten control measures (one shown in bottom panel), most of which required the functions of parietal cortex or the medial temporal lobe. (Modified with permission from Diamond et al., 1997).

in superior performance on cognitive tasks requiring EFs (Diamond et al., 2004; Egan et al., 2001; Malhotra et al., 2002) and to result in more efficient prefrontal functioning holding cognitive performance constant (Egan et al., 2001; Winterer et al., 2006). This effect is specific to PFC function. There is no relation between the Met versus Val COMT genotype and IQ or other cognitive abilities not centrally dependent on PFC, such as recall or recognition memory (Diamond et al., 2004; Egan et al., 2001; see Fig. 3).

Val and Met are equiprobable at codon 158 in COMT alleles of persons of European descent (Palmatier et al., 1999). As COMT Met-158 is associated with better PFC function, you might wonder why it has not been selected for over the course of evolution and become the more common version of the gene. The reason is likely that COMT Val-158 also confers certain advantages. Persons homozygous for the Val variant of the COMT gene tend to be calmer in the face of stress, whereas those homozygous for COMT Met-158 tend to be more sensitive to stress, have higher anxiety, and have higher pain stress responses (Diatchenko et al., 2005; Zubieta et al., 2003).

The reason homozygosity for COMT Met-158 (which results in more dopamine in PFC) is associated with weathering stress less well is probably because even mild stress markedly increases dopamine levels in PFC (though not elsewhere in the brain; Del Acro et al., 2007; Deutch and Roth, 1990; Roth et al., 1988; Reinhard et al., 1982; Thierry et al., 1976). Persons homozygous for

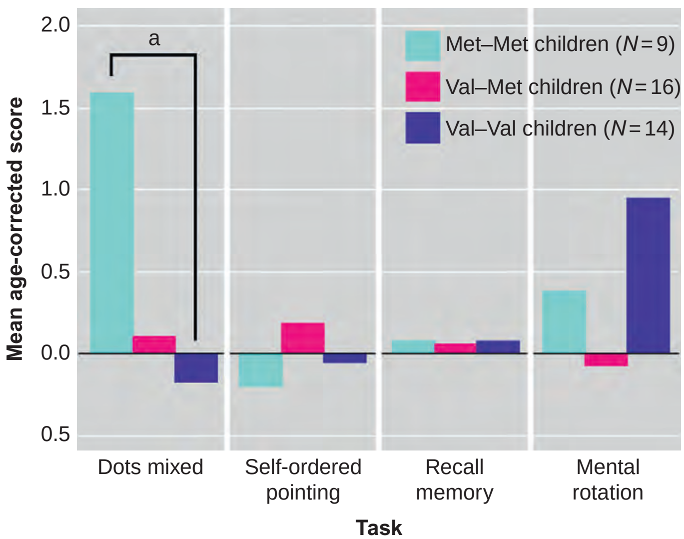



Fig. 3. Performance of children by COMT genotype on four cognitive measures. Children homozygous for COMT Met-158 performed significantly better (Wilcoxon $t = 126.0$, $p < 0.01$) than children homozygous for the COMT Val-158 genotype on the Dots-Mixed task, which requires holding two higher-order rules in mind and switching between inhibiting a prepotent response and making it, and is sensitive to the level of dopamine in PFC. All groups performed comparably on all control tasks (i.e., there was no effect of COMT genotype on any control task): (1) self-ordered pointing, which depends on PFC but is not sensitive to the level of dopamine in PFC; (2) recall memory, which depends on the medial temporal lobe; and (3) mental rotation, which depends on parietal cortex. To control for the effect of age, age mean difference scores were used. For each task, the mean percentage of correct responses for the subject's age in years was subtracted from the subject's percentage of correct responses, yielding an age difference score. This partialled out any effect of age. Gender was not significantly related to performance on any of these three cognitive tasks. (From Diamond et al., 2004, with permission).

COMT Val-158 have a bit more room for stress to increase PFC dopamine levels before detrimental effects are seen because their fast-acting COMT enzyme is quickly clearing away released dopamine. Persons homozygous for COMT Met-158 have relatively high PFC dopamine levels even when calm because of their sluggish COMT enzyme; stress can easily push their PFC dopamine levels well past optimal.

It has long been known that some of the brightest people also have the most fragile personalities and are highly reactive to stress. Here is a possible mechanism for why the two might go together. A person homozygous for COMT Met-158 might have outstanding executive functioning but might be highly vulnerable to stress and anxiety. Boyce (2007; Boyce and Ellis, 2005) has talked about "orchid" and "dandelion" children. "Dandelions" are children who do okay wherever they are planted. They are often identified as models of resilience. Yet research shows that some of the children who look the worst when they are in an unsupportive, stressful environment are exactly those who blossom the most when in a good environment (e.g., Belsky and Beaver, 2011). Perhaps children homozygous for COMT Val-158 are the dandelions; they are more robust in the face of stress but do not have the fine-tuning of PFC to achieve the brilliance of which a COMT Met-158 child might be capable. Perhaps some children homozygous for COMT Met-158 are among the orchids—they might look like a disaster when in a stressful environment, but might blossom brilliantly in the right environment.

Most studies of the effect of COMT genotype have included all males, mostly males, or have not investigated possible gender differences. Yet estrogen downregulates human COMT transcription in a dose- and time-dependent manner (Ho et al., 2008; Jiang et al., 2003; Xie et al., 1999) and results in COMT enzymatic activity being 30% lower in women than men (Boudikova et al., 1990; Chen et al., 2004; Cohn and Axelrod, 1971). The story that being homozygous for Met at codon 158 of COMT confers a cognitive advantage is not true for women during the portion of their menstrual cycle when their estrogen levels are high. COMT activity varies inversely with estrogen levels. With estrogen reducing COMT activity, when estrogen levels are high, being homozygous for the Met variant of the COMT gene (and so having a more sluggish COMT enzyme) confers no cognitive advantage for women, indeed, just the opposite. During the midluteal phase of the menstrual cycle (when estrogen levels are high), young women (ages 19–35) show better executive functioning if they are homozygous for Val at codon 158 than if they are homozygous for COMT Met-158 (Evans et al., 2009). During the follicular phase of the menstrual cycle (when estrogen levels are low), women show the male pattern of better EFs by those homozygous for Met at codon 158 (Evans et al., 2009).

Increasing the level of dopamine in PFC is beneficial only up to a point. The optimal level of dopamine in PFC is an intermediate level; too much dopamine is as bad as too little (Mattay et al., 2003; Zahrt et al., 1997). This inverted-U dopamine dose–response curve has been observed in mice, rats, monkeys, and humans (Arnsten et al., 1994; Cai and Arnsten, 1997; Gibbs and D'esposito, 2005; Lidow et al., 2003; Vijayraghavan et al., 2007). Thus, a double boost to PFC dopamine levels—high estrogen levels reducing COMT activity and COMT Met-158 homozygosity reducing COMT activity—evidently increases PFC dopamine levels too much, past the optimal level for PFC functioning.

Elderly women homozygous for COMT Val-158 perform better on the Wisconsin Card Sort (a measure of executive functioning) than do elderly women homozygous for Met-158, while elderly men tend to show the pattern so often reported in the literature, with those homozygous for COMT Met-158 performing better than elderly Val-158 men (Diamond, 2007). Elderly, postmenopausal women do not have menstrual-cycle mediated estrogen surges in their body.

The gender difference here is probably due to setting effects of the sex hormones very early in development (Shansky et al., 2004; Shors and Miesegaes, 2002).

Male animals perform better on tasks dependent on PFC when they are mildly stressed than when they are calm, but female animals do not; they perform worse when even slightly stressed than when calm (Arnsten and Goldman-Rakic, 1998; Shansky et al., 2004; Shors, 2001; Shors and Leuner, 2003; Wood and Shors, 1998; Wood et al., 2001). This gender difference appears to be estrogen-mediated. Female animals show the male pattern in response to mild stress when their estrogen levels are low, but mild stress impairs cognitive functions dependent on PFC in female animals during the point in the estrus cycle when estrogen levels are high (Shansky et al., 2004).

Perhaps there is a gender difference, not hereto considered or reported before, in the baseline levels of dopamine in PFC. Females may have higher baseline levels of dopamine in PFC (an optimum level) and males may have slightly too little dopamine in PFC at baseline. That would be consistent with slight stress bringing males' PFC dopamine levels up to optimal but raising females' PFC dopamine levels past optimum (see Fig. 4).

If so, this would have important practical implications for gender differences in the effective dosages of medications that affect PFC dopamine levels. Women may need lower dosages than men, at least when their estrogen levels are high. Certainly, there already appears to be evidence of menstrual-phase differences in the optimal dosage levels of drugs that affect PFC dopamine; when a woman's estrogen levels are high, she has more dopamine in PFC than when her estrogen levels are low; hence, the same dosage of medication affecting PFC dopamine levels that is beneficial during certain times of the month might be detrimental during other times of the month.

It is also important to remember the general principle that a genotype that is beneficial in

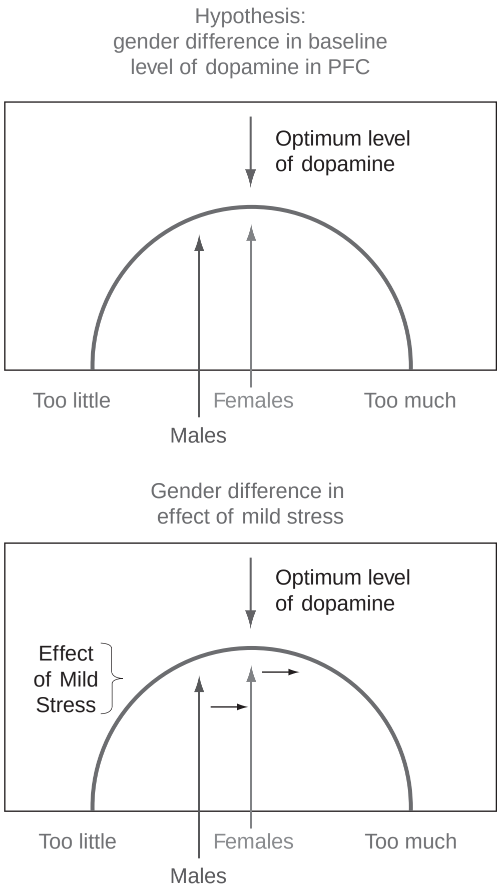



Fig. 4. Illustration of how, if males and females have different baseline levels of dopamine in PFC, that would account for the differential effects of slight stress on males and females (with slight stress being beneficial for males' EFs but detrimental for females' EFs).

one environment may not be beneficial in another. The COMT Met-158 genotype is probably not beneficial in a highly stressful environment. Yet this same genotype that confers risk on individuals when they are in adverse, stressful circumstances holds out promise of extraordinary potential if only the right fit of circumstances can be found for the individual. When working with children living in disadvantaged, at-risk conditions, it is important to bear this in mind.

## Environmental conditions and interventions that enhance the development of the cognitive control processes dependent on PFC

Just as we can improve our physical fitness through exercise, through challenging ourselves to push our limits, and through a regular practice regimen, so too, our EFs can be improved through exercising them, challenging them, and using them throughout the day, every day. Research shows this is true throughout life, from infancy to old age, and that it does not require anything expensive, highly technical, or complicated.

Bilingualism places heavy demands on inhibitory control and cognitive flexibility (two core components of EFs). A bilingual speaker needs to inhibit using a language the listener would not understand (even if only that language has the perfect word for what the speaker wants to express), one needs to shift from the perspective and mindset implied by one language to that implied by another, and one may need to flexibly switch languages in a conversation with a person who speaks Language A and person who speaks Language B (Green, 1998; Hermans et al., 1998; Klein et al., 1995; Paradis, 1997; Perani et al., 1998). Thus bilingualism taxes executive functioning and early bilingualism exerts environmental pressure for the accelerated development of EFs.

Children only 4–7 years old, who are fluently bilingual, are 1–2 years ahead of their monolingual peers on cognitive tasks that require inhibiting distractors or prepotent responses, changing perspectives, or flexibly adapting to changed rules (Bialystok, 1999; Bialystok and Majumder, 1998; Bialystok and Martin, 2004; Bialystok and Shapero, 2005; Martin-Rhee and Bialystok, 2008). Even infants show advanced executive functioning if bilingual (Kovács and Mehler, 2009a,b). Indeed, before infants are even speaking, simple comprehension seems to produce this effect, for it has been elegantly demonstrated that infants of only 7 months, exposed to bilingual input from one parent speaking one language and the other parent speaking another, show more advanced executive functioning than their peers exposed to only one language (Kovács and Mehler, 2009a). These effects are specific; bilingual children are not ahead on recognition or recall memory, learning, or IQ. Older adults who continue to be actively bilingual preserve their executive functioning longer into old age than do monolingual older adults matched for IQ, SES, and health (Bialystok et al., 2005, 2004, 2006).

Vygotsky (1967, 1978) emphasized the importance of social pretend play (e.g., playing doctor and patient, or grocery store) for the early development of EFs. If you think about it, during dramatic make-believe play, children must *inhibit* acting out of character, *hold in mind* the role they have chosen and those of others, and *flexibly adjust* in real-time as their friends take the play scenario in directions they never imagined. Thus, social pretend play exercises and challenges all three of the core EFs (inhibitory control, working memory, and cognitive flexibility).

Bodrova and Leong (2007) developed an early education program, *Tools of the Mind*, based on the theories and research findings of Vygotsky and his protégés. Bodrova and Leong initially tried social dramatic play as an add-on to existing curricula. Children improved on what they practiced in those modules, but the benefits did not generalize. They did not generalize to other contexts or other demands on EFs. For benefits to generalize, supports for, training in, and challenges to EFs had to be part and parcel of what the children did all day long. The children's actions throughout the day had to be exercising EFs to really see a benefit. Thus, Bodrova and Leong embedded aspects of EF training in all academic activities, including literacy and math, as well as having activities whose primary focus was to improve EFs.

A *Tools of the Mind* literacy activity with an embedded EF component is *Buddy Reading*. Children of 4 or 5 years each select a book, get into pairs, and take turns "reading" the story in their picture books. With each child eager to tell his or her story, no one wants to listen. To help them succeed at exercising inhibitory control (one of the EFs), the teacher gives one child a drawing of lips and the other a drawing of an ear, explaining, "Ears don't talk; ears listen." With the concrete, visible reminder, the child with the ear is able to inhibit talking, wait his or her turn, and listen (see Fig. 5). Otherwise the child would not be able to do that. After a few months, the pictures are no longer needed; the children have internalized the instructions and are able to listen and wait their turn without the visible reminders.

Scaffolds, such as the simple line drawing for *Buddy Reading*, enable children to practice skills they would not otherwise be able to practice. If a teacher assumes that children are not capable of something and so structures the class so that the children never need to do that, children do not get the benefit of practice to help them improve. If a teacher, with the same assumption, scaffolds or supports children to help them perform at a level they could not perform at on their own, then they get practice (and the pride of doing something that may have seemed far beyond their reach) and through repeated

Fig. 5. Photograph of two children engaged in *Buddy Reading*. Note the line drawing of an ear in the hand of the girl listening to the other girl. Photograph by Morey Kitzman, reprinted from the supplementary online material for Diamond et al. (2007) with permission.

practice, they improve. In the *Buddy Reading* example, instead of being scolded or ashamed for being a poor listener (as would happen without the visual "ear" reminder), children have the boost to their self-esteem from having been able to be a good listener, and increased self-confidence that they can successfully do what's required of them.

When we evaluated the effect of *Tools of the Mind* on EF development compared with a high-quality program newly developed by the school district, we specifically chose EF measures quite different from anything the children had ever done before. To see a difference by condition, the children would have to transfer their training in EFs to utterly new situations. All children came from the same neighborhood and were closely matched on demographics. Stratified random assignment of teachers minimized confounds due to teacher characteristics.

Our results reported in *Science* (Diamond et al., 2007) showed that children in *Tools* performed better on measures of EFs than their peers in the district's curriculum (see Fig. 6). This difference increased as the EF requirements of the tasks increased. Other children in *Tools of the Mind* in other schools and states, with different comparison programs, have been found to consistently outperform comparison children on standardized academic measures (Barnett et al., 2008). Staff at one school in our study became so convinced that children in *Tools of the Mind* classes were so markedly outperforming other children that they halted the study early in their school and switched all classes to the *Tools of the Mind* curriculum.

The significance of these findings is that they indicate that (1) EFs can be improved in preschoolers. Some had thought preschool too early to try to improve EFs, but this research indicates it is not. (2) EFs can be improved in regular public-school classes, without expensive, high-tech equipment or specialists. (3) The program that embraced the importance of play produced better EFs and academic outcomes than

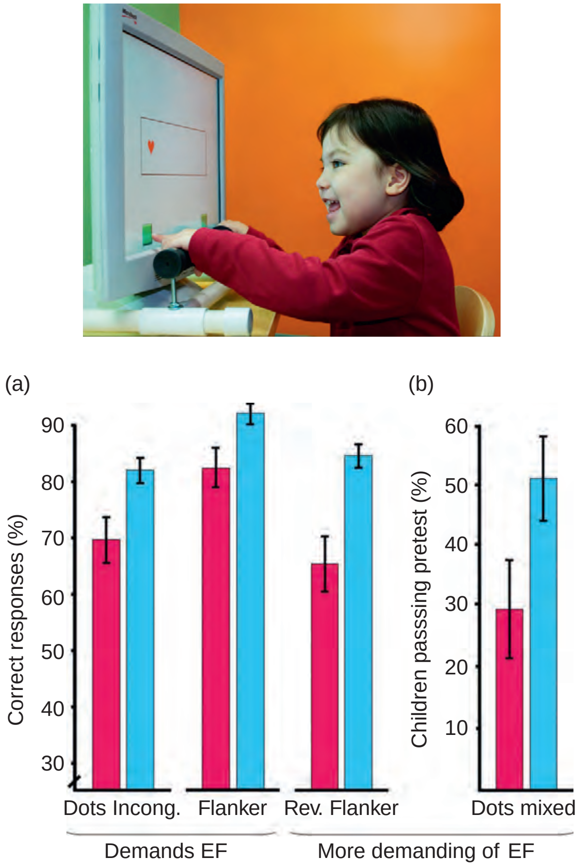



Fig. 6. Photograph of a child performing the Hearts & Flowers task (which used to be called Dots-Mixed [see Fig. 3]) and comparison of the performance of Kindergarten children in *Tools of the Mind* (lighter gray in print version; blue in online version) with the performance of children from the same neighborhood, closely matched on demographics, in a different kindergarten program (darker gray in print version; pink in online version) on tasks that assess EFs. All differences are significant, but the benefit of *Tools of the Mind* on the easier conditions (Hearts & Flowers Incongruent and Flanker) was much smaller than on the more EF-demanding conditions (Hearts & Flowers Mixed and Reverse Flanker). For the first set of three graphs (A), the dependent measure is percentage of correct responses. For the last graph (B), the dependent measure is percentage of children. Photograph is by Martin Dee. The graphs are reprinted from Diamond et al. (2007) with permission.

one that devoted more time to direct academic instruction, indicating that play may *aid* academic goals rather than taking time away from achieving them. (4) If throughout the school-day EFs are supported and progressively challenged, it appears that benefits generalize and transfer to new activities, as the outcome measures were different from anything the children had done before.

Just as our brains (especially PFC) work better when we are not feeling stressed, our brains (especially PFC) work better when we get exercise and are physically fit. There is considerable evidence that aerobic exercise improves how the brain works (especially PFC) and how we think (with EFs showing the greatest benefit from improved aerobic fitness). "[T]he positive effects of aerobic physical activity on cognition and brain function [are evident] at the molecular, cellular, systems, and behavioral levels" (Hillman et al., 2008: 58). "Physical activity-related modulation is disproportionately larger for task components that necessitate greater amounts of executive control" (Hillman et al., 2008: 61). The positive effects of aerobics on EFs, long demonstrated in adults, can also be seen in children (Hillman et al., 2005, 2009).

Intervention studies show that children's increased participation in physical activity leads to better cognitive skills and grades. For example, a 2-year physical activity intervention with over 4500 elementary-school children produced improvements in children's math and reading scores (Hollar et al., 2010). Children who received extra physical education showed better academic achievement on average than that of a control group (Shephard et al., 1994). Among 6th graders randomly assigned to condition, those who met at least some of the Healthy People 2010 guidelines for vigorous activity had significantly higher grades than those who performed no vigorous activity (Coe et al., 2006). Among 13–16 year olds randomly assigned to physical exercise or a control group, those in the exercise group improved more in selective attention and concentration (Budde et al., 2008). When the results from many studies were pooled in a meta-analysis, a positive clear relation between physical activity and both verbal skills and math emerged for all ages (4–18 years) and especially for those 13 years of age or younger (Sibley and Etnier, 2003).

Dance provides physical exercise and can be quite physically demanding and taxing, but it also directly exercises and challenges EFs by requiring sustained attention and concentration and by requiring that one hold complex sequences in mind. There have been few scientific studies of the benefits of dance for other than fitness, posture, or balance. Two noteworthy studies have been conducted with older adults, however. Verghese et al. (2003) examined the relation between leisure-time cognitive or physical activity and the incidence of dementia. At the study's outset all subjects were over 75 years old and dementia-free. Five years later, reading or doing crossword puzzles was associated with a 35% reduced risk of dementia. Almost none of the physical activities offered protection against dementia—except dance. Dance conferred the greatest risk reduction of any activity studied, cognitive or physical; a 76% reduced risk of dementia. Kattenstroth et al. (2010) studied the impact of many years of regular, amateur ballroom dancing on neurologically healthy elderly subjects, compared to education, gender, and age-matched controls with no record of dancing or sports. The dancers performed better on the Raven Matrices (a measure of fluid intelligence very highly correlated with EFs [Duncan, 1995; Duncan et al., 2008; Jaeggi et al., 2008]) and on a nonverbal test of selective attention and concentration (Gatterer, 1990).

Many different activities can probably improve executive functioning, from tae-kwon-do (Lakes and Hoyt, 2004), tai chi (Lam et al., 2010; Matthews and Williams, 2008; Taylor-Piliae et al., 2010), or yoga (Pradhan and Nagendra, 2010) to playing chess, from storytelling to playing a musical instrument, from sports to choral singing to acting in plays. The most important element is probably that the person loves what he or she is doing, so that doing it brings great joy. If a person enjoys the activity enough he or she will spend a lot of time at it, practicing and pushing him- or herself to do better. It is the discipline, the practice that produces the benefits. Even the best activity for improving EFs if done rarely will produce little benefit.

Why try to improve EFs early? Just because it is possible to improve them early does not necessarily mean that we should. Why not wait? Perhaps slower-developing children will catch up over time. Alas, evidence indicates that rather than early EF delays disappearing, they tend to grow larger (Nagin and Tremblay, 1999; Brody et al., 2003). Consider children who start school with poor EFs: They tend to blurt out answers, jump out of their seats, have trouble paying attention and completing assignments, and impulsively butt in line and grab things from other children. They get poor grades and are always getting scolded. School is no fun and before long they would just as soon not be there. Teachers come to expect poor performance from them, and the children come to expect poor performance from themselves. A self-reinforcing negative feedback loop develops with the frustrated child deciding school is a place of failure.

Conversely, consider children who start school with good EFs: They wait to answer until they are called on, stay in their seats, pay attention, complete their assignments, and are well behaved. For them, school is a place of success and praise. Teachers enjoy them, expect them to do well, and the children expect to succeed. A self-reinforcing positive feedback loop is created.

Small differences at the beginning can lead to bigger and bigger differences over time. A small difference in children's EFs at the outset of schooling could lead to disparities in EFs and achievement that grow larger with each passing year. Children at risk fall progressively farther behind other children in academic achievement over the school years. That "widening achievement gap" (O'Shaughnessy et al., 2003) may result from two opposing dynamisms (negative and positive feedback loops) going in opposite directions. Reducing or erasing the disparity at the outset might nip that dynamic in the bud.

"Brain-based" does not mean immutable or unchangeable. EFs depend on the brain, yet they can be improved by the proper activities. Reducing stress and improving physical fitness yield benefits to EFs. Using your EFs, exercising and challenging them improves them, much as physical exercise hones our physical fitness. Such EF "exercise" may be beneficial for our mental health just as physical exercise is beneficial for our bodily health.

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