Malleable Minds:
Translating Insights From Psychology and Neuroscience to Gifted Education

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Chapter 5

How I Came Full Circle From the Social End of Psychology, to Neuroscience, and Back Again in an Effort to Understand the Development of Cognitive Control

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I had no interest in science and certainly no intention to go into neuroscience. I avoided biology and chemistry in college. My interests were in people's stories and their reasons for what they did, in understanding the world through their eyes, and in social and cultural influences on thought and action. I majored in sociology-anthropology and psychology as an undergraduate.

Though officially a Ph.D. candidate in psychology, the first 3 years of graduate school were spent working primarily in sociology and anthropology. I had a 3-year dissertation fellowship: one year to prepare to go into the field, one year to go anywhere in the world I wanted to do my fieldwork (I chose the South Pacific because it seemed the most idyllic), and one year to write it up. I had a great thesis topic (Is the need to be master of your fate intrinsically human or a product of Western culture?), but did not feel I was coming up with a good way to study it and did not feel that the wonderful people advising me were coming up with a good way to study it neither. That did not seem to bother them. They said, "You will do great work," but I thought, "What is the point of going to paradise and being miserable, thinking, 'How will I ever get a dissertation out of this?' " I gave back the money, explaining that if I ever came up with a good research design, I would re-apply for funding. Having given up my dissertation topic, I needed another.

I turned back to questions that had been raised in a seminar my first year in graduate school by Jerome Kagan. Jerry was brimming over with enthusiasm at findings that children worldwide showed the same cognitive changes (like being able to uncover a hidden object or separation distress) at roughly the same ages though their experiences were markedly different. "It cannot all be learning and the effect of experience," Jerry exclaimed, "Their experiences are too different. There must be a maturational component." Clearly the maturational component in cognitive changes would be in the brain. But where? It so happens that the classic Piagetian task for studying infants' emerging ability to find a hidden object (A-not-B) and the classic task used by neuroscientists to

study the functions of dorsolateral prefrontal cortex (delayed response) are virtually the same (though neither field had realized that). This made my hypothesis easy: Perhaps maturational changes in dorsolateral prefrontal cortex (PFC) help to make possible cognitive improvements (such as improved performance on the A-not-B task) between 7-12 months of age. So, I came to neuroscience motivated by wanting to answer the question Jerry Kagan had so enticingly posed. It was never that I wanted to enter the field of neuroscience per se.

Prefrontal Involvement in Cognitive Changes Between 7-12 Months of Age

I studied babies' developmental progressions on the A-not-B and delayed response tasks with the kind of careful, painstaking observation of behavior that an anthropologist would bring to fieldwork, following the same babies every 2 weeks from 6-12 months, but I also wanted to see if I could get converging evidence from a very different behavioral task. The A-not-B and delayed response paradigms require holding in mind where a reward was hidden and updating that on each trial (*working memory*). When the reward is hidden in a different place, infants must inhibit the tendency to repeat the rewarded response of reaching back to where the reward had been before (*inhibitory control*). I wanted a third task that did not require hiding anything, imposing any delay, or placing much demand on memory, yet still dependent on frontal cortex. I adapted Moll and Kuypers' (1977) transparent barrier detour task for children, calling it "object retrieval." The object retrieval task involves placing a reward inside a transparent box open on one side. It requires first and foremost inhibiting the strong tendency to reach directly for the visible reward (*inhibitory control*). *Working memory* played a role as well in that the memory of having looked along the route they would have to reach aided infants in integrating looking through a closed side while reaching into the opening.

The dissertation showed that although A-not-B and object retrieval looked superficially so different, important advances on those tasks occur during the same brief time window, and further, individual children first show that they can uncover a hidden object in the A-not-B paradigm at almost exactly the same age as when they show the first advance on the object retrieval task ("Phase 1b").

The results were intriguing but provided no direct evidence on the brain function or maturation. To obtain such direct evidence I joined the neuroscience laboratory of Patricia Goldman-Rakic at Yale. That was in the 1980s and neuroimaging had not yet advanced to the point where one could investigate such questions in the human brain, so I worked with rhesus monkeys. As a postdoctoral fellow I systematically charted the developmental progression of infant monkeys and the effects of brain lesions to dorsolateral PFC and elsewhere on adult and infant monkeys' performance using exactly the same 3 tasks that I had administered to babies (A-not-B, delayed response, & object retrieval). This provided a solid body of evidence consistent with the hypothesis that maturation of dorsolateral PFC is critical for developmental improvements in the working memory and inhibitory control abilities assessed by my triad of tasks.

Important Take-Home Messages to Bear in Mind

Note that this triad of tasks requires problem-solving ("If the obvious route to the reward is blocked, how else might I try to get into the box to get it?"), updating one's mental representation ("Where was the reward hidden *this* time?"), and retaining the representation despite distraction, plus other quite sophisticated cognitive abilities. People used to think that babies under one year were not capable of such complex thought, and that PFC, which is not fully mature until an individual's mid-20s (Gogtay et al., 2004), is too immature during the first years of life for such complex cognition. We now know babies actively reason and problem-solve beginning in their first months of life. How can that be since PFC is so immature? Well, think of a 2-year-old's legs. Certainly they are not at their full adult length and will not be for another 10-15 years. With those immature legs, however, a 2-year-old can walk and even run. That is to say that an immature PFC can still subserve working memory, inhibition, planning, problem-solving, and reasoning—most certainly not at their full adult levels—but to some extent.

Moreover, exercising prefrontal cognitive abilities (the "executive functions" [EFs]) even in the first year of life, improves them (Kovács & Mehler, 2009a; 2009b), in much the same way that exercise improves physical skills. The exercise that appears best is that which occurs naturally in the course of daily living, such as being around people who speak different languages. Certainly flash cards and oppressive drills, or any feedback that makes a child feel embarrassed or ashamed, has been shown to be detrimental for cognitive development (Hirsh-Pasek & Golinkoff, 2003).

Most important is to reinforce and support children's developing self-confidence, feelings of self-efficacy, curiosity, and love of exploring the world around them and of challenging themselves. No one needs to force an infant to learn to walk or talk. All infants want to do this and will succeed, unless we get in their way or they are biologically unable. Why should we think mastering anything else should be different? Do you want children to excel? Do you want their gifted potential to shine through? Then give them a loving, secure foundation and help nature take its course, much as a midwife helps at a birth. It is the children's journey; help them along the way (that is very important), but do not try to force them along this way or that or try to rush them before they are ready.

A Model System for Studying the Role of Dopamine (DA) in Prefrontal Cortex (PFC) During Early Human Development

Having demonstrated that maturational changes in PFC might underlie some of the cognitive advances in early life, I was left with the question, "What was changing in PFC?" One possibility was that the level of dopamine (DA) in PFC was increasing (Brown, Crane, & Goldman, 1979; Brown & Goldman, 1977; Lewis, Sesack, Levey, & Rosenberg, 1998; Rosenberg & Lewis, 1995). As an initial way of studying the role DA plays in modulating prefrontal cortex and the effect of that on cognitive function early in life, I turned to a group of children who there was reason to believe might have lower levels of DA in PFC, but otherwise basically normal brains: children treated early and continuously for the genetic disorder, phenylketonuria (PKU).

Normally one amino acid (phenylalanine, let us call it Phe) is broken down into another amino acid (tyrosine, which happens to be the precursor of dopamine). Unfortunately, if someone has PKU that does not happen. So Phe levels in the bloodstream get terribly high, which is not good. You might think, "Well, just tell people with PKU not to eat foods that contain Phe." The problem is that Phe is a component of protein; the only way to eliminate Phe-containing foods from someone's diet is to eliminate protein from that person's diet—not a good thing. Doctors wisely realized they needed to settle on a compromise between getting some protein into children with PKU without having them ingest too much Phe. But where should that compromise point be set? For many years, medical guidelines maintained that if Phe levels in the bloodstream did not go over 600 μmol/L, children with PKU were on a sufficiently strict diet.[1] Certainly the IQs of children with PKU were in the normal range, and they showed no signs of gross brain damage.

However, there were persistent reports of selective cognitive problems in these children, problems reminiscent of those seen when PFC is damaged or not functioning properly (Faust, Libon, & Pueschel, 1986; Pennington, VanDoornick, McCabe, & McCabe, 1985; Welsh, Pennington, Ozonoff, Rouse, & McCabe, 1990). Doctors replied that those reports made no sense. When amino acids cross from the blood into the brain, the entire brain receives those levels of amino acids. Why should only one brain region be showing any ill effects? No one could imagine a mechanism that could produce what the researchers said they were seeing, so the findings had no effect on medical practice.

Unbeknownst to those working on PKU, researchers in an entirely different sub-field of neuroscience had discovered a mechanism that could produce exactly the selective effect reported in treated PKU children. Phe and tyrosine compete to cross the blood-brain barrier (Pardridge & Choi, 1986). If the ratio of Phe to tyrosine is disturbed because of slightly too much Phe in the bloodstream, then not enough tyrosine will reach the brain, especially since the proteins that carry the amino acids across to the brain happen to prefer Phe over tyrosine (Tyr). So a mild elevation in the amount of Phe in the bloodstream leads to a mild diminution in the amount of Tyr in the brain.

Most brain regions, such as the striatum, are insensitive to small decreases in the amount of the raw material (tyrosine) from which DA is made (Cooper, Bloom, & Roth, 2002). They could care less if a little less tyrosine is available. But, the DA projection to PFC is unusual—it is exquisitely sensitive to even small reductions in the amount of tyrosine. The reason is that the DA neurons that project to PFC have a higher rate of firing and a higher rate of DA turnover (Bannon, Bunney, & Roth, 1981; Bradberry, Karasic, Deutsch, & Roth, 1989; Tam, Elsworth, Bradberry, & Roth, 1990; Thierry et al., 1977). Those special properties of the DA system in PFC provide a mechanism by which

[1] You might be thinking, "What about tyrosine? If a person with PKU is not able to convert Phe into tyrosine, does that person lack tyrosine?" Good question. It turns out that there are two routes to the body getting tyrosine. One route is through the conversion of Phe to tyrosine (that route is inoperative in someone with PKU). The other route is directly through diet. Therefore, someone with PKU only has slightly depressed tyrosine levels. Trying to increase tyrosine levels by taking tyrosine pills does not work very well, so doctors are left with trying to keep Phe levels down.

children treated for PKU could show deficits limited to PFC. If these children have levels of Phe in their blood that results in a small decrease in the amount of tyrosine that reaches the brain, PFC and only PFC would be affected, because only the DA projection to PFC is sensitive to a small decrease in tyrosine availability.

I recruited collaborators for the study. We were able to confirm the selective reduction in DA in and only in PFC in animal models, demonstrating that that reduction produces deficits in cognitive abilities dependent on PFC, and that those cognitive deficits are closely linked to how much DA is reduced in PFC (Diamond, Ciaramitaro, Donner, Djali, & Robinson, 1994). I also led a large study of children with PKU (Diamond, 2001; Diamond, Prevor, Callender, & Druin, 1997). Those children treated for PKU whose Phe levels were 360-600 μmol/L performed below average on all six tasks that required working memory plus inhibition (executive functions [EFs] dependent on PFC) and the higher their Phe levels, the worse they performed on those tasks (Diamond et al.). These same children performed fine on all 10 control tasks, most of which required functioning of the parietal cortex or the medial temporal lobe. Thus, as long as their average Phe levels were about 360-600 μmol/L, they had cognitive deficits but only in those abilities (the EFs) dependent on PFC, though the entire brain received a modest reduction in Tyr.

The wonderful news is that deficits in EFs are preventable and reversible. They can be completely prevented in young children with PKU if their Phe levels are kept from early infancy to 120-360 μmol/L (Diamond et al., 1997; Stemerdink et al., 1995). Cognitive deficits in children and adults with PKU can be somewhat reversed by a stricter dietary regimen that brings Phe levels down (Koch et al., 1999). Our work, building on that of many others, changed medical guidelines for the treatment of PKU throughout North America and Europe. Subsequent research has shown that this change has improved children's lives (Huijbregts, de Sonneville, Licht, van Spronsen, & Sergeant, 2002; Stemerdink et al., 1999).

Important Take-Home Message to Bear in Mind

We hear a lot about how biology and biochemistry affect our behavior and our cognitive abilities. PKU provides a striking example of the reverse—how our behavior (what we eat) affects our biology and biochemistry. By monitoring what their babies and young children eat, parents of children with PKU can prevent gross brain damage and mental retardation by keeping blood Phe levels $\leq$ 600 μmol/L. By keeping infants and young children on an even stricter dietary regimen that keeps average Phe levels at 120-360 μmol/L, parents of a child with PKU can prevent deficits even in the sophisticated EF skills dependent on PFC. And, even if Phe levels are too high early in life, or become too high later, adopting a strict dietary regimen can erase much of the cognitive impairment, and sometimes all of it.

The brain remains remarkably plastic throughout life. Such lifelong neuroplasticity means it is never too late (though it can be harder later). A middle-aged couch potato can become a marathon runner if he or she puts in the sustained effort. Children mature at vastly different rates; we should not rush to pigeonhole children too early. Einstein

spoke late (at age 3 years); by most definitions he would have been considered delayed and even language-impaired. Yet, Einstein was a genius, and perhaps his verbal delay was somehow intrinsically linked to, and indeed enabled, the superior development of his spatial giftedness.

Genetic Effects on the Cognitive Abilities (Executive Functions [EFs]) Dependent on PFC

Scientific results are rarely perfectly neat and clean. It is true that children with PKU whose Phe levels were 360-600 µmol/L were impaired on all six of our tasks that require working memory plus inhibition, but they performed well on three other tasks that tax working memory (two self-ordered pointing tasks[2] and one temporal order memory task). There is solid evidence that these three tasks also depend on PFC based on work with patients with damage to PFC (Petrides & Milner, 1982), neuroimaging in adults (Petrides, Alivisatos, Meyer, & Evans, 1993), and animal studies (Petrides, 1995). I had predicted that performance on *all* tasks dependent on PFC would be impaired in PKU children with mildly elevated Phe levels of 360-600 µmol/L. Why on earth were they not impaired on these 3 tasks? I had no clue.

Collins and colleagues published a finding that seemed to offer a possible explanation (Collins, Roberts, Dias, Everitt, & Robbins, 1998). They showed that taking out PFC in monkeys impairs performance on self-ordered pointing, just as it impairs performance on other tasks like A-not-B and delayed response. However, Collins et al. showed that reducing the amount of DA in PFC does *not* impair performance on self-ordered pointing, although they replicated the finding that it does impair performance on tasks like A-not-B and delayed response. No one had ever looked before at the effect of reducing the amount of DA in PFC on self-ordered pointing. The results of Collins et al. were consistent with our PKU findings. I had predicted that a small reduction in the amount of Tyr reaching the brain would reduce the amount of DA in PFC and therefore cause deficits on tasks dependent on PFC. If self-ordered pointing and temporal order memory are not sensitive to the amount of DA in PFC, then it would make perfect sense that performance on those tasks would not be impaired in PKU children with mildly elevated Phe levels.

An opportunity arose to further test whether self-ordered pointing was really insensitive to variations in PFC DA levels. There is a way that the amount of DA, specifically in PFC, naturally varies—and that is by variations in the COMT gene (Karoum, Chrapusta, & Egan, 1994).[3]

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[2] On self-ordered pointing tasks, you are to touch all the items, one at a time, not repeating a choice; after each touch where the pictures are scrambled.

[3] Variations in the COMT gene do not matter so much for most other brain regions because they have lots of DA transporter. DA transporter provides the best way to clear DA once a neuron has released it. Poor PFC has less DA transporter (Durston et al., 2005; Lewis et al., 2001; Sesack, Melchitzky, & Lewis, 1998). Since it does not have enough of the best mechanism for clearing DA, it has to rely on secondary mechanisms. You guessed it—COMT provides just such a secondary mechanism. A secondary mechanism for clearing DA is very important in PFC but less important in most of the rest of the brain because those other brain regions have lots of the best mechanism for clearing DA (DA transporters).

The more quickly the COMT enzyme clears DA away, the less DA remains in PFC. The COMT gene tells the body how to make the COMT enzyme (i.e., the COMT gene "codes for" the COMT enzyme). It is the COMT enzyme that does the clearing of DA, but it is variations in the COMT gene that determine how quickly or slowly the COMT enzyme works.

A common variation in the COMT gene involves which amino acid (methionine [we will call that Met] or valine [we will call that Val]) is at a particular location on the gene (location: "codon 158"). When Met is at location "codon 158," the COMT gene codes for a slower-acting COMT enzyme that clears DA much more slowly from PFC. Conversely, when Val is at that location, the COMT enzyme works much more quickly (Lotta et al., 1995; Tenhunen et al., 1994). Remember, the slower the COMT enzyme works, the more DA remains in PFC. Hence, the Met variant of the COMT gene results in more DA in PFC. The Met variant of the COMT gene in adults had been shown to result in better EF performance (Egan et al., 2001; Malhotra et al., 2002).

Well, I thought, polymorphisms of the COMT gene should affect children's performance on tasks that are sensitive to the amount of DA in PFC (like A-not-B or delayed response) but should *not* affect children's performance on tasks that are *not* sensitive to the amount of DA in PFC. *If* self-ordered pointing really is insensitive to the level of DA in PFC, performance on it should not vary by COMT genotype. That is indeed what we found! Children homozygous[4] for the COMT Met-158 genotype (which leaves more DA in PFC) performed better than children homozygous for the COMT Val-158 genotype on the Dots-Mixed task, which requires working memory plus inhibition, but COMT genotype did not matter for performance on self-ordered pointing (Diamond, Briand, Fossella, & Gehlbach, 2004).

Gender Differences in Reaction to Stress and in Which Version of the COMT Gene Is Most Beneficial for the Cognitive Abilities [Executive Functions (EFs)] Dependent on PFC

Not one to leave well enough alone, I asked, "How come variations in COMT genotype do not produce larger effects? Sure, the effects are significant, but should they be larger?" The optimum level of DA in PFC is an intermediate level; too much or too little is not good (Mattay et al., 2003; Zahrt, Taylor, Matthew, & Arnsten, 1997). Perhaps results at the group level were not larger because in some young adults and children being homozygous for the COMT Met-158 genotype results in too much DA in PFC (i.e., more than optimal).

Levels of DA in the brain decrease with aging (e.g., Suhara et al., 1991; Volkow et al., 1996, 1998; Wong, Young, Wilson, Meltzer, & Gjedde, 1997). Certainly the COMT Met-158 genotype should be beneficial for PFC functioning in virtually all older adults, right? (Since older adults have less DA in their brains almost all of them should benefit from

[4] Homozygous means both versions of the COMT gene in a person are the same. You can have one Met-158 and one Val-158 version of the COMT gene or you can be homozygous for the COMT gene, which means you have either 2 Met-158 or 2 Val-158 versions.

the Met version of COMT as it is associated with more DA in PFC). Maybe if we studied older adults we could find much larger effects than seen with young adults or children. I persuaded Art Kramer, an expert on cognitive aging, to collaborate.

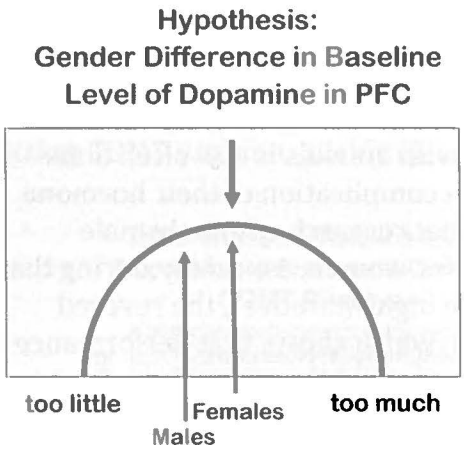
So sure was I of the reasoning behind my prediction, that I was ready to write the paper before we had the results. I was therefore dumbfounded when Art's lab reported to me that not only did older adults not show a stronger effect of COMT genotype, they showed *no* effect of COMT genotype.

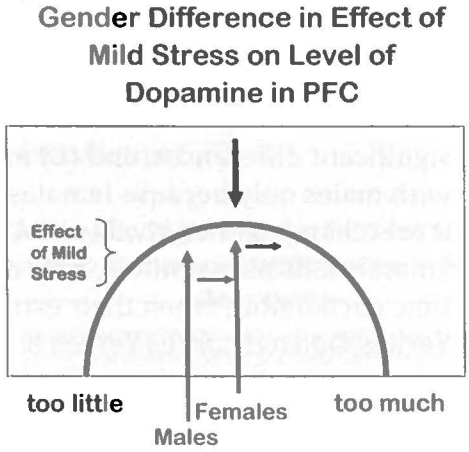
How could one make sense of this? Well, I remembered that the percentage of females in the population increases with advancing age. There is much evidence that male animals perform better (or no worse) on cognitive tasks requiring PFC when they are mildly stressed than when they are calm. However, female animals perform worse when even slightly stressed than when calm (Arnsten & Goldman-Rakic, 1998; Shansky et al., 2004; Shors, 2001; Shors & Leuner, 2003; Shors & Miesegaes, 2002; Wood, Beylin, & Shors, 2001; Wood & Shors, 1998). The DA system in PFC is acutely sensitive to stress. Stress increases prefrontal DA levels (Arnsten, 1998; Cerqueira, Mailliet, Almeida, Jay, & Sousa, 2007; Roth, Tam, Ida, Yang, & Deutch, 1988). Maybe females have higher (more nearly optimal) baseline levels of DA in PFC, while males have slightly too little DA in PFC. That would explain why slight stress (which raises prefrontal DA levels) would be helpful for males' EFs but detrimental to females' EFs (see Figure 5.1). This would also be consistent with males being more susceptible to disorders of too little prefrontal DA (e.g., ADHD; Rucklidge, 2008; St. Sauver et al., 2004) and females being more susceptible to disorders of too much prefrontal DA (e.g., anxiety or depression; Hyde, Mezulis & Abramson, 2008; Leach, Christensen, Mackinnon, Windsor, & Butterworth, 2008).

If this line of reasoning were correct, then having a still more sluggish COMT enzyme (a COMT Met-158 genotype) might not be beneficial to women. Indeed, whereas the more sluggish Met-158 COMT enzyme might be beneficial to men, the faster-acting Val-158 COMT enzyme might be more beneficial to women. I contacted Art's lab, "Quick, analyze the results separately for men and women." Everything fell into place. Older women homozygous for COMT Val-158 showed superior EF performance to older women homozygous for COMT Met-158, whereas older men showed the pattern that had always been reported in the literature (better EF performance in COMT-158 homozygotes than those homozygous for Val-158; Diamond, 2006).

Why might females have higher prefrontal DA levels than males? Remember, the less active or the slower the COMT enzyme, the more DA there is in PFC. It so happens that estrogen causes the COMT enzyme to work more slowly (that should result in higher prefrontal DA levels in females). Estrogen down-regulates human COMT gene transcription in a dose- and time-dependent manner (Ho et al., 2008; Jiang, Xie, Ramsden, & Ho, 2003; Xie, Ho, & Ramsden, 1999). Therefore, the COMT enzyme is 30% less active in women than in men (Boudikova, Szumlanski, Maidak, & Weinshilboum, 1990; Chen et al., 2004; Cohn & Axelrod, 1971). Postmenopausal women no longer have menstrual-cycle-mediated estrogen surges in their body. The gender difference among

older adults is probably due to the setting effects of sex hormones early in development (Shansky et al., 2004; Shors & Miesegaes, 2002).





	Suboptimal EF performance	Optimal EF performance	Suboptimal EF performance
Males	when calm	when mildly stressed	
Females when their estrogen levels are LOW	when calm	when mildly stressed	
Females when their estrogen levels are HIGH		when calm	when mildly stressed

Figure 5.1. Illustration of how gender differences in baseline levels of DA in PFC could account for the observed gender differences in the effect of mild stress on cognitive tasks that require PFC.

If the gender difference we discovered in the effects of COMT genotype on EFs is mediated by estrogen, then this gender difference should be even greater in young adults. Young women have higher circulating levels of estrogen than do post-menopausal women. Indeed, we discovered that the story that being homozygous for the Met -158 version of the COMT gene confers a cognitive advantage is not true for young women during the portion of their menstrual cycle when their estrogen levels are high. COMT activity varies inversely with estrogen levels (the more estrogen the slower the COMT enzyme works). When estrogen levels are high, being homozygous for COMT Met-158 (and so having an even more sluggish COMT enzyme) confers no cognitive advantage for women—indeed, just the opposite. When women are menstruating, however, and their estrogen levels are low, young women show the male pattern of better EFs if homozygous for COMT Met-158 (Evans, Fossella, Hampson, Kirschbaum, & Diamond, 2009).

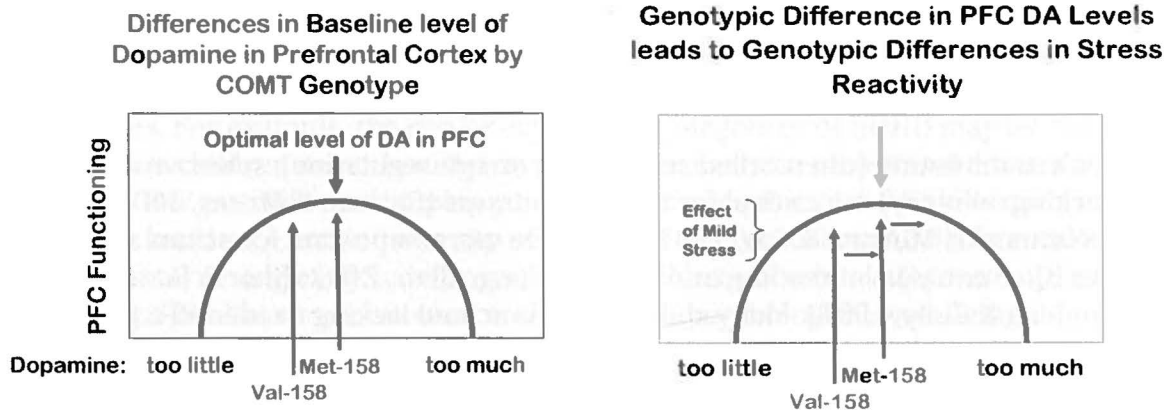
Important Take-Home Messages to Bear in Mind

1. Too much of a good thing is almost always no better than too little of a good thing. The golden mean pertains to almost everything. Thus, a double-boost to

prefrontal DA levels—from (a) COMT Met-158 homozygosity reducing COMT enzyme activity and (b) high estrogen levels reducing COMT enzyme activity—seems to increase prefrontal DA levels too much, past the golden mean for optimal PFC functioning.

2. Women are different from men. You say, "That is obvious." Yet to this day (a) research on humans often pools the results for males and females without seriously looking for differences or having too few of each gender to find significant differences, and (b) much research with animals is still often done with males only because females have the extra complication of their hormone levels changing. Yet, levels of DA medications that research with only male animals tells us is optimal, may not be optimal for women, especially during that time each month when their estrogen levels are high. Moreover, the revered Yerkes-Dodson curve (Yerkes & Dodson, 1908), which shows that performance on any difficult cognitive task is better when one is slightly stressed, may not be true of females, at least during the portion of each month when their estrogen levels are high. Female animals show the male pattern in response to mild stress when their estrogen levels are low, but mild stress impairs their performance on EF tasks when their estrogen levels are high (Shansky et al., 2004). Might we be missing giftedness in some girls because of the assumption that keeping students a little on edge is beneficial for all?
3. Take heart when your hypothesis is *not* confirmed. It is perfectly okay to be wrong. When our prediction is confirmed, we learn only that we were probably correct. When our prediction is not confirmed, it is a great opportunity to learn something new, to make a whole new discovery! Look at how much we learned when my prediction that variations in COMT genotype would have larger effects in older adults was not confirmed.
4. All students need to develop general cognitive skills (such as clear thinking, sound reasoning, and creative problem-solving) that will serve them well regardless of what they do, and they need the confidence to venture into the unknown and to follow where their discoveries and unanswered questions take them. I never in my wildest dreams imagined I would be a neuroscientist. Having ventured into behavioral neuroscience from developmental psychology, I certainly never expected I would do work in neurochemistry on neurotransmitters and amino acids, nor that I would do any work related to molecular genetics or visual science (Diamond & Herzberg, 1996). We cannot know where interest and/or opportunity will take any of our students. We need to give all of them the basic tools to succeed at things we, and they never imagined.
5. A genotype beneficial in one environment may not be beneficial in another. Moreover, when two versions of a gene occur with equal probability (as the Val-158 and Met-158 variants of the COMT gene do in persons of European descent [Palmatier, Kang, & Kidd, 1999]), it is likely that there are advantages and disadvantages of each variant. Otherwise one would have been selected for and become the more dominant form.

The COMT Met-158 genotype is generally associated with better EFs, except if you are female, at least during a portion of each month. The COMT Val-158 genotype, on the other hand, is generally associated with being calmer in the face of stress; persons homozygous for COMT Met-158 tend to be more sensitive to stress, have higher anxiety, and higher pain stress responses (Diatchenko et al., 2005; Zubieta et al., 2003). Perhaps this is because persons homozygous for COMT Val-158 have a bit more room for stress to increase prefrontal DA levels before detrimental effects are seen, since their fast-acting COMT enzyme quickly clears released DA (see Figure 5.2).



Genotype	Suboptimal EF performance	Optimal EF performance	Suboptimal EF performance	EF performance
COMT Met-158 homozygotes			when calm	when mildly stressed
COMT Val-158 homozygotes		when calm	when mildly stressed	

Figure 5.2. The Met-158 COMT genotype codes for a more sluggish COMT enzyme that clears dopamine from PFC more slowly, resulting in more dopamine in PFC. This is beneficial in an un-stressful environment, but stress is more disruptive to persons with the Met-158 COMT genotype precisely because they start out with more dopamine in PFC.

A person homozygous for COMT Met-158 might have outstanding EFs but be highly vulnerable to stress and anxiety. Boyce (2007; Boyce & Ellis, 2005) identified "orchid" and "dandelion" children. "Dandelions" are children who do okay wherever they are planted. They are often seen as models of resilience. Yet research shows that some children who look the worst when they are in unsupportive, stressful environments are exactly those who blossom the most when in a good environment (e.g., Belsky & Beaver, 2011). Perhaps children homozygous for COMT Val-158 are the dandelions; they will do okay even in a stressful environment, but might lack the exquisite fine-tuning of PFC needed 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 in a stressful environment, yet blossom brilliantly in the right environment.

The COMT Met-158 genotype, which 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. When working with children it is important to remember this. A child who is not doing well in one environment, or does not respond to a particular instructional style, might shine in another environment or with a different teaching approach.

EFs are Critically Important for Academic Success and Much More

By 2000, I had been doing basic laboratory-based cognitive neuroscience for 20 years. It was becoming more and more apparent to me that EFs were too important for people's lives to remain content with just doing basic research, without seeing if there might be a way to help the EF development in the real world.

EFs (such as inhibition [often called self-control or self-regulation], selective attention, and working memory) are critical for school readiness (Carlson & Moses, 2001; Hughes, 1998; Kochanska, Murray, & Coy, 1997). They are more important for school readiness than are IQ or entry-level reading or math skills (e.g., Blair, 2002; Blair & Razza, 2007; Normandeau & Guay, 1998). Many children begin school lacking needed EFs (Raver & Knitzer, 2002). Might they just catch up later? Evidence indicates that rather than early EF deficits disappearing, they often tend to grow larger (Brody et al., 2003; Nagin & Tremblay, 1999).

Consider children who start school with poor EFs: They blurt out the answer, jump out of their seats, have trouble paying attention and completing assignments, impulsively butt in line, and grab things from other children. They get poor grades and are always getting scolded. School is no fun for them; before long they would rather 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 called upon, 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. No wonder children at risk fall progressively farther behind other children each year they are in school (O'Shaughnessy, Lane, Gresham, & Beebe-Frankenberger, 2003). That widening achievement gap may result from two opposing dynamisms (feedback loops) going in opposite directions. Being able to aid EF development early in a child's life may be an enormous help to that child doing well in school and in life thereafter. Early intervention (heading off problems before they develop) costs less and achieves more than trying to correct problems once they have been allowed to develop.

EF skills are critical for school success. A plethora of studies have found that EFs predict both math and reading competence throughout the school years (e.g., De Beni & Palladino, 2000; Gathercole, Pickering, Knight, & Stegmann, 2004). We found that the more EF-demanding an experimental condition was, the more highly it correlated with academic outcome measures (Diamond, Barnett, Thomas, & Munro, 2007).

Poorer EFs (less persistence, greater impulsivity, and poorer attention regulation) at ages 3-11 predict worse health, lower earnings, and more run-ins with the law 30 years later when the children are adults, controlling for IQ, gender, social class, and their home lives and family circumstances growing up (Moffitt et al., 2011). Early EF gains can reduce the later incidence of aggression and anti-social behavior (Nagin & Tremblay, 1999) and increase marital harmony (people with poor EFs are less easy to get along with, less dependable, and more likely to act on impulse [Eakin et al., 2004]). EF development is part of being able to demonstrate social intelligence (Goleman, 1995), such as being able to exercise the self-discipline needed to think first and thus avoid putting your foot in your mouth or hurting another's feelings.

Improving EFs might buffer children against diverse health and social problems caused by poor EFs. For example, the recent explosion in diagnoses of ADHD may be due in part to some children never having learned how to exercise attentional control and self-discipline. It is possible that helping young children acquire such EF skills early might reduce the incidence and/or severity of disorders of EFs, such as ADHD or conduct disorder. Intervening early to improve EFs should benefit school achievement, mental and physical health, career success, and social and psychological well-being.

Ways to Aid the Development of the EFs

If aiding EF development is of such importance, it seemed something worth devoting my time and effort to. An opportunity arose when Dr. Deborah Leong, the co-developer of an early education curriculum called Tools of the Mind, that intentionally aims to aid EF development, asked me to objectively evaluate the program (Bodrova & Leong, 2007). I was skeptical (I often hear grand claims), but agreed to visit a school. First Deb took me to a non-Tools preschool class. It was noisy and slightly chaotic, but seemed a perfectly normal preschool class. Then she took me to a Tools of the Mind preschool class. The difference was night and day. It was as if I had walked into a Grade 2 class. The children were intently working together with one or two peers on independent projects. They did not need the teacher to keep asking for order or directing them back to the task at hand. I agreed to do a rigorous, though small-scale, scientific study of Tools of the Mind.

To evaluate the effect of Tools of the Mind on EF development, I compared it to another new, high-quality program just developed by the school district, and chose EF measures different from anything the children had done before. To see a difference between children in the Tools of the Mind and district curricula, Tools children would need 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 of the Mind performed better on our measures of EFs than their peers in the district's curriculum. Other children in Tools in other schools and states, with different comparison programs, have been found to consistently outperform other children on standardized academic measures (Barnett et al., 2008). Staff at one school in our study

became so convinced that children in Tools classes were so outperforming other children that they halted the study early in their school and switched all classes to the Tools curriculum. Lillard and Else-Quest (2006), in a lovely randomized control study, similarly found that children in a good Montessori program showed better EFs than their peers who attended other schools. What about these two programs (Tools and Montessori) might be enabling EF development to flourish more than in other teaching environments?

The Importance of Action for Learning

If I asked you who learns and remembers a route better—the driver or the passenger in the car, you would know the answer—it is the driver—and you would know why—because the driver has to actively use the information while the passenger is just passively sitting there. Much psychological research has demonstrated this principle and ancient traditions have long known it. We seem to forget this when it comes to schooling, however, where we have students passively listening with only the teacher active in the front of the room.

The best way to educate is through doing, through hands-on, problem-based learning. We evolved to learn to help us do what we want to do. We pay attention to information, and learn it when we need it. We need it when it is important for what we want to do. If information is not relevant for action, we do not pay attention in the same way. We learn something when we need it for something we want to do (Olson, 1964). My son demonstrated how to program the VCR and I thought I understood. Later, when I went to program it I realized I had not understood at all. The same applies when we teach children in school. They will want to learn, and will understand quicker and in far greater depth, if they need to use the information than if they do not.

A core aspect of Tools and of Montessori is that minimal time is devoted to "whole group activities" (where the teacher is talking and the children are gathered as a group, passively listening). Rather, they emphasize learning through doing (Montessori, 2007).

Importance of Child-to-Child Tutoring

Child-to-child teaching has been found repeatedly to produce better (often dramatically better) outcomes than teacher-led instruction (Cohen, Kulik, & Kulik, 1982; Greenwood, Delquadri, & Hall, 1989; Mastropieri et al., 2001). Montessori often works better with class sizes of 30-40 than 15-20 because when the child to teacher ratio is large, older children in mixed 3-year age-groups perceive the need to help instruct younger ones, and such child-to-child mentoring is invaluable. In Tools children take turns instructing or checking one another.

The Importance of Practice, Repeated Practice

PFC (to which I have devoted my life's work) is over-rated. It is true that to learn something new, we need PFC. Thus, among novices, those who recruit PFC most usually perform best (Duncan & Owen, 2000; Durston et al., 2006; Kane & Engle, 2002). However, after something is no longer new, those who recruit PFC *least* usually perform best (Garavan, Kelley, Rosen, Rao, & Stein, 2000; Jansma, Ramsey, Slagter, & Kahn,

2001). Why? PFC is the evolutionarily newest region of the brain. Other brain regions have had hundreds of thousands more years of evolutionary time to perfect their functioning. They can subserve task performance much more efficiently than can PFC. Thus, I need PFC to learn a new dance step, but later if I try to think about what my feet are doing while dancing, I will not dance well. Similarly, children need PFC to learn what sound goes with what letter, but when a fifth grader reads, we no longer want the child to be thinking about letter-sound mapping; we want that to become automatic. A child may know intellectually (at the level of PFC) that he should not hit another, but in the heat of the moment if that knowledge has not become automatic (passed on from PFC to subcortical regions) the child will do exactly what he should not (and exactly what, if you asked him, he knows he should not do). Montessori (2007) emphasized the critical importance of the child's repetition over and over again for education.

The only way something becomes automatic (becomes passed off from PFC) is through action—repeated action. The only way we become really good at something (whether it is piano playing or chess) is through repeated practice. Nothing else will do. Aristotle commented on this back in the 4th century BC:

> We are what we repeatedly do. Excellence, then, is not an act, but a habit. We do not act rightly because we have virtue or excellence, but we rather have these because we have acted rightly; "these virtues are formed in man by his doing the actions"; we are what we repeatedly do. (*Ethica Nicomachea*)

Tools of the Mind is based on the theories and work of Vygotsky (1967, 1978). He emphasized the importance of social pretend play (e.g., playing doctor and patient) for the early development of EFs. 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 impromptu play scenario in directions they never imagined. Social pretend play exercises and challenges all 3 core EFs (inhibitory control, working memory, and cognitive flexibility). It is a central component of Tools. 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 benefits did not generalize. To get generalization, supports for, training in, and challenges to EFs had to be part and parcel of what the children did all day long. Children needed EF exercise throughout the day to really see progress. Thus, besides providing activities whose primary focus was to improve EFs, Tools interweaves EF training into all academic activities.

A Tools literacy activity with an embedded EF involves preschoolers each selecting a book, getting into pairs, and taking 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 the listener succeed at exercising inhibitory control (one of the EFs), the teacher gives the child a drawing of an ear and explains, "Ears do not talk; ears listen." With that concrete, visible reminder, the child is able to listen. Without it, the child would not be able to do that. After a few months, children have internalized this and are able to succeed without a visual reminder.

Scaffolds, such as the simple line drawing of an ear, 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 beyond their reach), and through repeated practice, improve. Instead of feeling embarrassed 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 is required of them.

Importance of Educating the Whole Child: Cognitive, Emotional, Social, and Physical

We are not just intellects. We also have emotions, social needs, and bodies. Our EFs do not work as well when we are sad or stressed, feel lonely or isolated, are ill or not physically fit. The best, most efficient way to improve academic achievement is probably *not* to focus narrowly on academics alone, but to address children's emotional, social, and physical development as well.

Stress, even mild stress, floods PFC with DA and impairs EF performance (Arnsten, 1998; Cerqueira et al., 2007; Roth et al., 1988). It can make it almost impossible to concentrate, learn anything new, or exercise discipline or self-restraint. Reducing stress in the classroom not only reduces teacher burn-out and improves classroom climate, it also leads to better academic outcomes (Denham & Brown, 2010; Downer, Sabol, & Hamre, 2010; Jennings & Greenberg, 2009).

There are strong reciprocal relations between emotion and cognition. When children's EFs are better, the teacher can stop worrying about what out-of-control behavior might happen; she can relax. The children can stop worrying about being scolded; they can relax. Both Tools and Montessori also minimize the chance that a child will be made to feel ashamed. They provide scaffolds to help children succeed and use materials that indicate in themselves if one is right or wrong so that mistakes can be a private matter. More learning occurs in happy, joyous classrooms, where children feel safe, secure, and accepted, and where they feel the teacher sees them for whom they are and genuinely cares (Gregory & Weinstein, 2004; Harter, 1996; Jethwani-Keyser, 2008; Roeser, Eccles, & Sameroff, 2000). Children can then dispense with the dual-task of always looking over their shoulders, of trying to contain their anxiety, anger, or hurt while they are trying to learn. They can risk trying something new and maybe being wrong. Children need to feel safe enough to push the limits of what they know, to venture into the unknown, to risk looking foolish. Anything is learned more quickly when students are passionately interested in it. Emotions can be the engine to power great strides in learning.

We are not just thinking and feeling beings, we are also social. Just as our brains work better when we are not feeling stressed, our brains work better when we are not feeling

lonely or socially isolated—and that is particularly true of PFC and EFs. Feeling excluded or as if you do not belong has been scientifically shown to impair reasoning and decision-making, decrease persistence on difficult problems, and impair selective attention in the face of distraction (Baumeister, DeWall, Ciarocco, & Twenge, 2005; Cacioppo & Patrick, 2008; Twenge, Catanese, & Baumeister, 2002). In one study, Baumeister, Twenge, and Nuss (2002) told some participants they would have close relationships throughout their lives, told others the opposite, and told yet others unrelated bad news. On simple memorization problems that do not require EFs, the groups performed comparably. On logical reasoning problems, however, where EFs are needed, those told they would be lonely performed significantly worse than the other groups. Campbell et al. (2006) just asked people how they felt; they did not try to manipulate that. They found that PFC worked less efficiently in those who felt lonely.

Just as our brains work better when we are not feeling stressed or lonely, our brains (especially PFC) work better when we get exercise. "[T]he positive effects of aerobic physical activity on cognition and brain function [are evident] at the molecular, cellular, systems, and behavioral levels"(Hillman, Erickson, & Kramer, 2008, p. 58). "Physical activity-related modulation is disproportionately larger for task components that necessitate greater amounts of executive control" (Hillman et al., p. 61). For example, aerobic games (e.g., running games, jump rope, basketball, and soccer), with an emphasis on enjoyment rather than competition have been found to improve the EF skills and mental math of 7-11 year olds in a dose-dependent manner (40 minutes a day most, 20 minutes intermediate, regular physical education least), with no effect on non-EF skills (Davis et al., 2011; see also Kamijo et al., 2011; Tuckman & Hinkle, 1986).

There are only so many hours in the day, and teachers have so much academic content to cover, how can they possibly find time to also address social, emotional, and physical development in addition? It does not have to be in addition. For example, instead of teaching high school physics by lecturing, what about having the class restore an old car? That requires applying principles of physics, giving students a good reason to master those principles. Not only is such an activity hands-on, it engages students' enthusiasm and emotions, it requires physical activity, and provides an experience of working collaboratively together toward a shared goal. Imagine the excitement as students are working on the car and imagine the beaming smiles of pride when they have finished.

Tools of the Mind activities also organically involve elements that address the various facets of human development. Many kindergarten programs treat social-emotional development (if at all) as separate from cognitive development. Vygotsky (1978) emphasized, however, that cognitive development and social development are fundamentally intertwined; social interactions are key to developing intentional self-control. Each week, every week, each child is paired with every other for at least one literacy or math activity, reducing social isolation and discouraging cliques. Montessori materials seamlessly and organically embed physical and artistic development into math, science, and reading. For example, simple geometric shapes have small knobs (aiding the early development of the pincer grasp) and the vibrantly colored pieces can

be used to create beautiful works of art. Children practice motor control at the same time they are practicing focused, mindful attention in activities such as walking on a line (perhaps holding a bell that would ring were they not careful).

Important Take-Home Messages to Bear in Mind

1. "Brain-based" does not mean immutable or unchangeable. EFs depend on the brain, yet they can be improved by the proper activities. Exercising and challenging EFs improves them (see review, Diamond & Lee, 2011), 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.
2. Moreover, EFs can be improved in regular public school classrooms by regular teachers, without specialists or expensive equipment.
3. Schools are under pressure to cut back on time allowed for play to provide more time for academic instruction. Children in Tools of the Mind, however, who have more time to play, improve more in EFs (Diamond et al., 2007) and perform better on academic outcome measures (Barnett et al., 2008) than their peers who have more time in direct academic instruction. Similar findings from other programs persuaded the International Association for the Evaluation of Educational Achievement that "young children's cognitive performance at 7 years of age was better for those children who had spent less time in whole-group activities and more time working or playing" (Bracey, Montie, Xiang, & Schweinhart, 2007, p. 2). Play does not have to take away time from improving academic outcomes; play can improve academic outcomes.

   Schools are also cutting funding for the arts. Yet throughout human history, across *all* cultures, the arts (e.g., storytelling, dance, crafts, and music-making) have been part of the human condition. People in all cultures told stories and passed down information by word of mouth, made music, sang, danced, and crafted beautiful creations. If art, music, dance, and crafts are simply frills, why did they spring up everywhere and why have they not been weeded out over the long course of human history? They must serve some important, fundamental human needs. There must be good reasons why those activities have lasted so long and been found so ubiquitous. One of the reasons seems to be that they address the whole person. Music-making, singing, and dancing address our cognitive, emotional, social, and physical needs. They challenge our executive functions, make us happy and proud, address our social needs, and help our bodies develop.
4. Students learn and remember far more when they have to use the information and when they make discoveries for themselves, than when they passively sit and listen to instruction from the teacher.
5. Repeated practice is key to mastery. If we want EF skills to be second nature so that in the heat of the moment they are implemented, they must be practiced enough that their control has moved from PFC to older brain regions so they are executed automatically as one's first reaction. Gifted children need repetition, too, though perhaps not as much, but to master anything from chess to the times tables to tennis requires repeated practice no matter who you are. Indeed, a gift

for something often emerges through, and because of such dedicated repeated practice.

6. We can help children practice even those skills that they are not yet able to do on their own, and we can minimize occasions when children are made to feel ashamed or feel like failures. Rather than letting children flounder and experience failure and criticism, Tools of the Mind teachers provide supports (scaffolds) and Montessori teachers provide materials that contain "control of error" (i.e., allow a child to see his or her own error and correct it) so that each child, whatever his or her level of ability, is able to succeed. The boost to self-confidence and self-esteem from experiencing success may be key to the success of Tools and Montessori. Testers in the Diamond et al. (2007) study said they could tell which children were Tools graduates because when it came to the most difficult test conditions, control children tended to give up, but Tools children kept saying, "I know I can do this. Let me try again."
7. Our expectations often determine outcomes. I suggest that we start with the deeply held conviction that every child is capable of succeeding at what we teach. When a child is not succeeding, ask yourself how you might do something differently so that this particular child is able to succeed. If we believe every child can succeed then we will push ourselves to think outside the box and try something new and different that might, just might, work for a particular child. Sometimes our testing method is the problem; we are not asking the question in a way that allows children to demonstrate the knowledge and abilities they have (Diamond, Churchland, Cruess, & Kirkham, 1999; Diamond & Gilbert, 1989; Diamond, Kirkham, & Amso, 2002; Diamond & Lee, 2000; Diamond, Lee, & Hayden, 2003).
8. The human being is an integrated whole. Being sad or stressed, sleepy, lonely, out of shape, or ill, impairs how clearly we think and our performance on anything that requires thought or self-control. Sadness, stress, chronic lack of sleep, chronic infections, or marked physical inactivity can mask remarkable giftedness potential so that it might be missed altogether. Said another way, just as EFs are amenable to improvement through training and practice, they are also particularly susceptible to disruption by stress, illness, lack of sleep, loneliness, or lack of exercise.

What nourishes the human spirit also appears to be best for EFs. Play, physical activity, and the arts may be critical for achieving the academic outcomes we all want. Children who are intellectually or musically gifted are sometimes pushed to devote inordinate hours to honing their remarkable talents; it is important not to lose sight of those children's needs for social interaction and for friends, for fresh air and being in nature, and generally for nourishing their whole being, which is what we all need.

I am back studying children in real-world social contexts seeing if storytelling and dance do indeed improve EFs as I have predicted. We never know where interest and/or opportunity will take us. Hopefully, we and our children will have the basic cognitive skills to see us through, the self-confidence to have faith in our own efficacy, and the flexibility to take advantage of serendipity.

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