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# Insights from a Career at the Border of Developmental Psychology and Cognitive Neuroscience

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## Keywords

executive function, prefrontal cortex, inhibitory control, working memory, creative problem-solving, selective attention, cognitive development, motor development, social–emotional development, dopamine

## Abstract

Much has changed since I started my PhD research in 1980. Neither the field of developmental cognitive neuroscience nor the term “executive functions” existed then. In some ways this piece is backward-looking, such as discussing how our research introduced the importance of the executive function of inhibitory control for cognitive development and that infants and young children are much smarter than we thought. The way our field has queried infants and young children often prevented us from seeing their competencies. That is still too true in studying children from different backgrounds. In other ways, this piece is forward-looking, such as when discussing evidence that the conceptualization of working memory as an executive function and as the key function of dorsolateral prefrontal cortex has been too narrow. It is not just separation in time that must be bridged (traditionally the province of working memory) but also separations in space, and the latter are just as important for cognitive development and just as dependent on the executive function brain network, including dorsolateral prefrontal cortex. It is also forward-looking in discussing the critical importance of motor, social, and emotional development for cognitive development and executive functions, as well as bidirectional relations among these different facets of development. Study of the different aspects of human development is still far too siloed, as are the different fields of science. Examples are

provided of how the fields of neuroscience (including neurochemistry and molecular genetics) and child development inform and complement one another. Implications for educators, parents, and researchers are interwoven throughout.

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## 1. INTRODUCTION

Our conceptions of cognitive development and the brain have changed markedly over the past 50 years. The field of developmental cognitive neuroscience did not exist when I started, and the term “executive functions” (EFs) had not yet been coined.<sup>1</sup> As late as the 1970s and 1980s, there was virtually no cross talk between developmental scientists and neuroscientists. In discussing some of the changes over the past 50 years in how we understand cognitive development and prefrontal cortex (PFC), I highlight changes that I was fortunate enough to play some role in bringing about. Work in developmental science and in neuroscience are interwoven throughout, as insights from neuroscience inform our understanding of child development, and insights from developmental research have pushed neuroscientists to revise their understanding of PFC. Implications for educators and parents are similarly interwoven here.

Key points include the following.

1. Infants and young children are much smarter than we used to think; even in infants, PFC is already subserving important EF abilities, though it is still quite immature.
2. The way we, developmental psychologists, have queried infants and young children has often prevented us from seeing their competencies. That is still too true in studying children from different backgrounds.
3. Development proceeds not only by acquiring more knowledge and better understandings but also through improvements in inhibitory control.
4. The dorsolateral portion of PFC<sup>2</sup> is usually required only when *both* working memory and inhibitory control are needed.
5. Spanning temporal separations (working memory) is probably too narrow a view of PFC and of the EF brain network, as they are also important for spanning spatial separations.
6. We tend to think of cognition as higher or more exalted and motor skills as more lowly or pedestrian, but often it is motor skills that are the limiting factors and later to mature.
7. Similarly, the West has long thought of emotion as more lowly than cognition and something to be controlled, but emotions can power cognition as well as interfere with it.
8. Though we still tend to silo the social and the cognitive, it is a caring, social relationship with an adult in one’s life that is often determinative of how much cognitive progress is made. The different parts of a person (cognitive, emotional, social, spiritual, and physical) are multiply interrelated and affect one another.
9. A final theme is the unusual vulnerability of PFC to the effects of emotional stress and implications of that for understanding individual differences in children’s development.

<sup>1</sup>The term “executive function” first appears, as far as I’ve been able to determine, in Cummings & Benson (1988).

<sup>2</sup>Dorsolateral PFC corresponds to Brodmann’s areas 9 and 46 and to the superior and middle frontal gyri and sulci (Petrides & Pandya 1999).

## 2. A FIRST STEP TOWARD INTEGRATING DEVELOPMENTAL PSYCHOLOGY AND BEHAVIORAL NEUROSCIENCE AND RECOGNIZING THAT, ALREADY IN THE FIRST YEAR, INFANTS ARE USING EXECUTIVE FUNCTIONS

As a graduate student, I realized that developmental psychologists and neuroscientists had been using essentially the same behavioral task since the 1930s without realizing it. Developmental psychologists called it “A-not-B” and used it to study cognitive development in infants; neuroscientists called it “delayed response” and used it to study the functions of PFC in monkeys. In both tasks, the subject watches as a reward is hidden in one of two places that differ only in location; after a few seconds the subject can reach to retrieve the reward. The tasks differ only in that, in A-not-B, the reward is always hidden in the same place until the subject is correct twice in a row, whereas in delayed response, the hiding location is varied randomly. Since delayed response was known to depend on dorsolateral PFC, and since babies improve on A-not-B between 7.5 and 12 months, I hypothesized that maturation in dorsolateral PFC might be partially responsible for some of the cognitive advances we see between 7.5 and 12 months. To test my hypothesis I wanted another task linked to PFC that was as different from delayed response and A-not-B as possible. I adapted a transparent barrier detour task developed by Moll & Kuypers (1977) for use with infants and named it “object retrieval.”

My dissertation documented infants demonstrating the EFs of working memory, inhibitory control, cognitive flexibility, planning, and problem-solving on the A-not-B, delayed response, and object retrieval tasks (Diamond 1983, 1991a,b; Diamond & Doar 1989). An example of creative problem-solving can be seen on the object retrieval task: When a toy is placed inside the object retrieval box, infants even as young as 7 months can successfully retrieve the toy if they are looking along the line of reach, that is, looking through the open side of the box before and during the reach. When the opening of the box is on the right or left side, to look along the line of reach requires infants to bend way over. At 8.5–9 months, if infants sit up in order to reach after looking through the side of the box, they usually cannot succeed. They need to continue to look through the opening to succeed. Staying in that leaning position, the arm ipsilateral to the opening feels sort of caught under the body. Besides, the movement of the contralateral arm can be monitored the whole time, whereas the beginning of the movement of the ipsilateral arm would be out of sight. So, in an example of impressive problem-solving, when the opening of the object retrieval box is on the right or left, infants of roughly 8.5–9 months recruit the arm contralateral to the box opening. It looks extremely awkward (and hence we dubbed it “the awkward reach”), but it is a brilliant act of problem-solving that enables infants to succeed at retrieving the reward (Diamond 1990a, 1991b) (see **Supplemental Figure 1**). It creatively solves the problem of needing to continue to look through the opening. Thus, while it is of course true that infants are developmentally very immature and have much to learn, in some ways they are already brilliant and exercising all of the EFs, albeit in rudimentary form.

This triad of tasks (A-not-B, delayed response, and object retrieval) 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 and retaining that representation despite distraction (“Where was the reward hidden this time?”) plus response inhibition (“Although I’ve been rewarded twice for reaching to A, now I need to resist reaching back there because the reward has been hidden at B, or, even though I can see the toy through the walls of the transparent box, I need to resist reaching at a closed side and instead detour around to the opening”). People used to think that babies under one year were not capable of such complex thought, but they are.

As a postdoctoral fellow, I demonstrated that success on these tasks depends on dorsolateral PFC in both adult and infant monkeys (Diamond 1990a,b, 1991a,b; Diamond & Goldman-Rakic

Supplemental Material >

1989; Diamond et al. 1989). This established a strong link between early cognitive development and the functions of a specific brain system. It gave encouragement to others that rigorous experimental work addressing brain–behavior relations was possible in infants. It also fundamentally altered the scientific understanding of PFC early in development; clearly it was not silent, as accepted wisdom had held. It was an important stride toward the creation of the field of developmental cognitive neuroscience (Casey 2023), where insights from developmental psychology inform our understanding of the brain, and insights from neuroscience inform our understanding of child development.

### **3. CHANGING OUR UNDERSTANDING OF THE DEVELOPMENTAL TIMETABLE FOR PREFRONTAL CORTEX SUBSERVING SOPHISTICATED COGNITIVE FUNCTIONS: PREFRONTAL CORTEX IS ALREADY SUBSERVING EXECUTIVE FUNCTIONS IN INFANTS**

Although PFC is very immature early in life (e.g., Deoni et al. 2012, Kouider et al. 2013) and takes a very long time to develop, my early work suggested that dorsolateral PFC and interconnected regions are already subserving elementary versions of the highest cognitive functions (EFs) during the first year of life. Further confirmation of this came from neuroimaging studies, such as those by Bell (Bell & Fox 1992, Bell & Wolfe 2007, Cuevas et al. 2012), Baird (Baird et al. 2002), and Emberson, Richards, and Aslin (2015).

People used to think that babies under one year were not capable of complex thought, and that PFC, which is not fully mature until our mid-20s (Gogtay et al. 2004), is too immature during the first years of life to support complex cognition. We now know babies actively reason and problem-solve beginning in the first months. How can that be since PFC is so immature? Just because a neural region is not yet fully functional does not mean that it is not functional at all. Consider 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. Similarly, an immature PFC can still subserve working memory, response inhibition, focused attention, cognitive flexibility, planning, problem-solving, and reasoning—most certainly not at their full adult levels, but to some extent (Diamond 1991b).

Although most people believe that plasticity is greater earlier in life, they tend to assume that if a neural region is very immature in the early years (as is PFC), it makes little sense to try to improve skills in young children that rely on that region, thinking there is too little biological substrate (the brain region is too immature) to be able to improve functions dependent on that region. Thus, early educators often assume that young children are incapable of exercising self-control, self-regulation, or inhibitory control, or of using working memory, and so try to organize the classroom such that those abilities are rarely required. That deprives children of the opportunity to try to exercise self-control or working memory and thus of the practice and challenges that would improve these abilities. Indeed, it has been demonstrated that if supports are initially provided in class to help children exercise these abilities, even preschoolers can exercise them and improve at them, allowing the supports to be progressively removed as the children get better (Bodrova & Leong 2007).

### **4. THE ROLE OF INHIBITORY CONTROL IN INFANCY**

One change in our thinking about cognitive development that I played a role in helping to engender is the realization that development proceeds not only through acquiring more knowledge and more sophisticated understandings but also through the increasing ability to inhibit inappropriate reactions that get in the way of demonstrating what a child in fact knows. To some

extent, cognitive competencies are there early; it is the control of action that comes in later. We tend to think of cognition as higher or more exalted and motor skills as more lowly or pedestrian, but often it is motor skills that are the limiting factors and the later to mature.

A child may know what he or she should do, and want to do that, but still not be able to act accordingly. It is not enough to know what you should do; you must do it. Sometimes an inability to inhibit prepotent reflexive or habitual reactions gets in the way. People had assumed that if children knew what they should do, they would do it. However, between knowing the correct response and acting accordingly, another step, long ignored, is often needed. When a strong competing response is present, that response must be inhibited. A child may not have sufficient inhibitory control to do that. Children can get stuck in a behavioral rut from which they cannot easily extricate themselves despite their best intentions. Because young children can have difficulty getting their actions to reflect their intentions, adults may label them as bad, intentionally difficult, or willful when that is not the case. My lab has demonstrated that the biggest challenge for young children is not recall or recognition memory (young children are excellent at that) but inhibiting strong pulls to act a certain way. In this sense, development proceeds not only by acquisition but also by inhibition (Davidson et al. 2006, Diamond 2012b).

I first illustrate this below with infants' performance on the A-not-B task when the place where an object is hidden changes after the infant has successfully found the object at the original hiding place, next on the object retrieval transparent barrier detour task when two objects are contiguous, then with preschoolers' performance on a Stroop-like task (the day–night task), and lastly with children and teens' performance on a type of spatial Stroop or Simon task (the hearts and flowers task).

#### **4.1. Example 1 of the Role of Inhibitory Control: Infants Searching for a Hidden Object**

One of the earliest examples of having the necessary cognitive understanding and sufficient memory, but insufficient inhibitory control, comes from studies of infants performing Piaget's A-not-B task. Beginning at around 7–8 months, infants can successfully find the reward at the first place it is hidden, but when the reward is next hidden at a second location, even though the infants clearly see the hiding, they often reach back to the first location for the reward. Occasionally, you can see infants clearly looking at the second location (the correct hiding place) but still being unable to inhibit repeating the rewarded response of reaching back to the first hiding location (Diamond 1990a) (see **Supplemental Figure 2**).

This interpretation (that sufficient understanding and memory are present but insufficient inhibitory control prevents infants from demonstrating that in their reaching behavior) fits well with evidence from violation-of-expectation paradigms (e.g., Margoni et al. 2024) showing that from an early age, infants can remember in which of two locations an object was hidden (Baillargeon 1987, Baillargeon et al. 1985) and, on the A-not-B task, expect an experimenter to correctly search at the second hiding location on reversal (B) trials (Baillargeon & Graber 1988), even though they themselves reach to the first hiding location on B trials. It is also consistent with the finding that infants show a similar error pattern on the A-not-B task, even when transparent covers are used (Butterworth 1977), although they err less often. Memory should not be taxed at all when the toy remains visible under a transparent cover.

#### **4.2. Example 2 of the Role of Inhibitory Control: Infants Reaching for Contiguous Objects**

Piaget (1954) theorized that infants do not understand the concept of contiguity; they do not understand that an object continues to exist as a separate, independent entity when it shares

a boundary with another object. Piaget based this conclusion on observations of 5-month-old infants' performance when a small desired object was placed on a slightly larger base (e.g., a matchbox on a book). Bower (1974) extended this to situations where one object is in front of, or behind, another. He demonstrated, for example, that infants will retrieve a small object if it is several inches behind a transparent screen, but not if it is directly behind the screen. Bower (1977) concluded, "It seems that what the baby does not understand is that two objects can be in a spatial relationship to one another, so that they share a common boundary. Evidently it is the common boundary that is critical" (pp. 116–17).

When I was testing infants on the object retrieval task longitudinally every 2 weeks from 6 months of age to 12 months, I found that they could succeed by about 7 months when the top of the transparent box was open. I began to experiment with how that condition might be made more challenging for them. I tried putting a Lego brick directly behind the front wall of the box. Infants performed exactly as Bower described: They could retrieve the Lego if it were in the center of the box but not if it bordered the front wall. I was curious, and a bit skeptical of Bower's explanation, so I systematically varied parameters such as the distance of the Lego from the front wall of the box and whether the Lego could be obtained by a straight line of reach or whether the child had to reach in one direction to avoid the front wall and then change direction to obtain the toy (a bidirectional reach) (Diamond & Gilbert 1989). We found that infants' success varied independently of contiguity, and depended entirely on whether a simple, straight reach would suffice to reach the Lego (Diamond & Gilbert 1989) (see **Figure 1**).

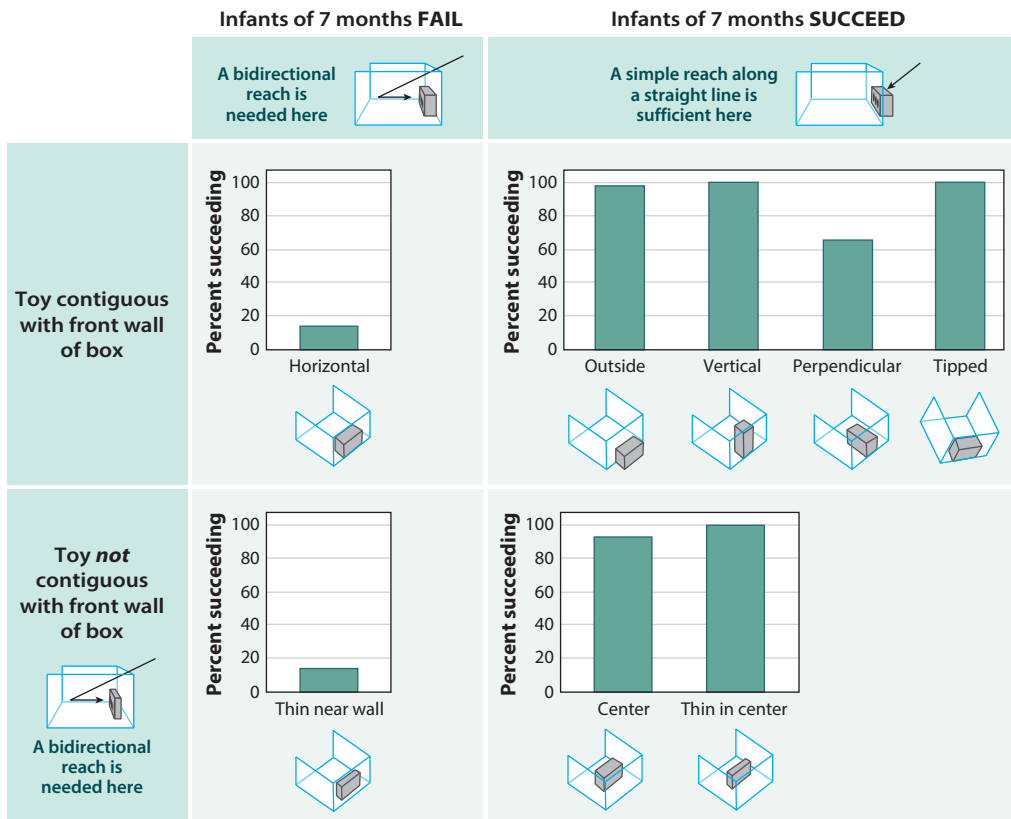
Why do 7-month-old infants fail when a bidirectional reach is required? That reach is complex enough that infants often graze the top edge of the front wall of the box en route to the Lego. They typically react to touching that edge by reflexively grasping it (about 75% of the time) or reflexively withdrawing their hand (about 20% of the time). They rarely continue a reach after grazing the edge of the box or after grasping the box. Instead, they pull their hand back to the starting position and begin the reach again. Infants of 10 months, on the other hand, are much better at aiming their bidirectional reach to avoid the front wall, are less likely to react reflexively when they touch the front wall (grasping the edge only 25% of the time and almost never reflexively pulling their hand back), and are much more likely to continue their reach despite contacting the front wall (Diamond & Gilbert 1989).

Thus, 7-month-olds do seem to understand the concept that an object continues to exist as a separate entity when it shares a boundary with another object. Their behavior often fails to reflect that understanding, however, because of imprecise aim in the execution of motor actions (reaching) and because of their imperfect ability to inhibit reflexive or habitual motor reactions. By 10 months, and perhaps earlier, infants have sufficient control of their actions to enable them to demonstrate in their behavior the conceptual understanding that seems to be present already by at least 7 months.

This was a rebuttal of Bower, but not necessarily of Piaget, since I had not investigated the condition on which Piaget had based his conclusions and I had studied older infants. Initially, we could not replicate Piaget's observation that infants of 5–6 months cannot retrieve a matchbox placed on top of a book. We used a smaller rectangular block placed upon a larger rectangular block. Whatever one may think of Piaget's theorizing, he was an excellent and accurate observer of children's behavior. If we could not replicate what he observed, we were doing something wrong.

It dawned on me that we were simulating presenting a matchbox on a book with the binding side of the book facing the child. Piaget never mentioned the orientation of the book. Maybe Piaget had presented the matchbox on a book with the pages facing the child. That could matter because the binding would be too thick for an infant to grasp, whereas the thin cover would be





**Figure 1**

Whether infants were able to retrieve a Lego block from behind the front wall of the object retrieval box depended not on whether the Lego was contiguous with the front wall, but rather on whether a straight line of reach was sufficient to reach the Lego or an arced or two-directional reach was required.

easily graspable. Sure enough, we replicated Piaget's observation with the larger block shaped like a hardcover book with its cover extending slightly beyond the pages.

Piaget's observations were absolutely correct, but his conclusion was not. The problem is not conceptual, as Piaget thought. Systematically varying parameters such as whether the toy and base were touching and the distance between the toy and the front edge of the base showed that success in retrieving an object placed atop another varies independently of contiguity. It depends, instead, on whether an imprecise reach might accidentally touch a graspable edge of the base en route to the toy (Diamond & Lee 2000). Success in retrieving objects close in size and fully contiguous with their bases is seen even at 5 months, when demands on the skill of reaching are reduced.

At least by 5 months, when infants see one object placed upon another, they understand that the two objects continue to exist independently as separate objects even though they share a border. Lack of a conceptual understanding of contiguity is not the problem. Further confirmation came from later research on object segregation that showed that by 4–5 months of age, infants correctly parse displays composed of two contiguous objects into two independent objects. For example, when an experimenter pulls on one of the objects, infants are surprised if the other one moves with it as if the two were a single unit (Aguilar & Baillargeon 2000).



The problem infants have on tasks with contiguous objects (especially if they have seen them even momentarily as separate) is motor: imprecise visually guided reaching and incomplete inhibition of the grasp reflex. Five-month-old infants lack the skill to reach precisely for the top object without accidentally touching an edge of the base en route; if that edge is graspable, it stimulates the infants' grasp reflex. When infants fail, it is because they react reflexively to touching the edge of the base.

### 4.3. Example 3 of the Role of Inhibitory Control: Infants Exercising Bimanual Coordination

Often, infants of 7.5–8 months would raise the front of the object retrieval box with both hands (the rear of the box being held down on the table). That enabled them to see through the opening and have a straight shot in reaching to the toy inside the box. However, with both hands thus occupied, there was no free hand with which to retrieve the toy. When infants removed one hand from gripping the front of the box, lowering that hand to reach in, the darn box came down, halting the reach since the toy was no longer seen through the open front (see **Supplemental Figure 3**). The box came down because when one hand was lowered to reach for the toy, infants had great difficulty not lowering the other. They would try repeatedly to raise the box and reach in, but the hand left to hold up the box kept failing at its task (Diamond 1990b). Bruner et al. (1968) noted something similar with a slightly different task. Their apparatus was a box with a transparent lid, mounted on sliding ball bushings. To retrieve the toy, an infant had to slide the lid up its track, which was tilted 30° from the horizontal and would fall back down if not held. Bruner et al. (1968) observed that infants of 7 months had “great difficulty holding the panel with one hand while reaching underneath with the other. Indeed, the first compromise solutions to the problem consist of pushing the panel up with both hands, then attempting to free one hand in order to slip it under the panel. One notes how often the infant fails because the two hands operate in concert” (p. 222).

I found that infants at 8.5–9 months could solve this problem sequentially by first raising the box and looking along the line of reach, then reaching in while looking through the closed transparent top (improvement in working memory making it possible to remember the route along which the hand will reach while no longer looking along that route). Infants still could not simultaneously keep the box raised with one hand while the other hand released hold of the box and reached inside. By 11 months, however, infants could raise the front of the box with both hands and keep the front raised while one hand let go and reached in. Such sweet success!

The emergence of such bimanual coordination (being able to do simultaneous, but different, movements of the two hands) is probably made possible, at least in part, by maturational developments in the supplementary motor area (SMA), the pre-SMA, and the callosal connections between the two SMAs and two pre-SMAs, one in each hemisphere of the brain. See the **Supplemental Text** for a further discussion of this.

The three examples presented here illustrate some themes in my work. (a) Infants and young children often know and understand more than they can demonstrate. (b) We tend to think of so-called higher-level skills (such as appreciating that two separate objects are present even though they are contiguous) as maturing later than so-called lower-level skills (such as the motor skills required for detouring to reach a goal object). However, often it is the motor skills that are the limiting factors and the later to mature. (c) Development proceeds both by the acquisition of new knowledge and by the increasing ability to inhibit reflexive or habitual reactions that get in the way of demonstrating knowledge that is already present. I see this as very much related to the development of the ability to exercise choice and control over what we do. (d) Imperfect inhibitory

**Supplemental Material** >

control prevents infants from demonstrating knowledge they, in fact, possess because of the way we, psychologists, query them.

People tend to think of cognition as higher and later-maturing and of motor as lower and earlier-maturing. However, motor development shows as long a period of development as cognitive skills (Diamond 2000). Fine motor control, bimanual coordination, and visuomotor skills are not fully developed until late adolescence (Marion et al. 2003, Rueckriegel et al. 2008), just as EFs continue maturing into late adolescence and early adulthood. One of the best ways to practice and improve the EF of focused attention is through motor activities. Kitchen chores such as pouring, grating, scooping beans, cutting vegetables, or carrying a tray with items that might spill require careful, focused attention, as do other household chores like hammering a nail, watering a plant, or handling fragile items. Crafts such as weaving, beadwork, sewing, or crocheting similarly require careful, focused attention. Practicing these can improve both fine motor skills as well as the EF of selective, focused attention. Walking on a log, walking while balancing something on your head, or racing while holding an egg in a spoon also require careful attention. Indeed, Raver and colleagues (2011, 2008) used walking on a balance beam as one of their measures of focused attention. Studies consistently find balance and EFs to be related (e.g., children and adults with better balance have better EFs) (Haynes et al. 2018, Mihara et al. 2008, St George et al. 2021).

The ability to inhibit making the impulsive or dominant response frees us to exercise choice and control over what we do. Thus, it makes possible the emergence of intentionality. All organisms have prepotent response tendencies, innate and conditioned. It is not clear, however, that all organisms have the capacity to resist or overcome the strongest response of the moment or an engrained habit. That seems to depend upon the highest levels of cortical control and may not be possible for organisms without a frontal cortex.

## **5. THE ROLE OF INHIBITORY CONTROL IN PRESCHOOLERS AND YOUNG CHILDREN**

### **5.1. Inhibitory Control During the Preschool Period: Evidence from the Day-Night Task**

Children 3–4 years old are so eager to respond that they often blurt out what comes to mind first, though it is often incorrect. They can respond correctly, however, when they take their time or when some way can be found to cause them to delay responding for just a few moments. An example of that can be seen with the day–night task (Gerstadt et al. 1994), which requires saying the opposite of what the stimulus cards represent (saying “day” when shown a black card with a moon and stars and saying “night” when shown a white card with a sun). Children of 3–4 years err on this task (Gerstadt et al. 1994; for a review, see Montgomery & Koeltzow 2010).

We (Gerstadt et al. 1994) demonstrated that children are not erring simply because of the task’s memory demands, because if abstract shapes are used as the stimuli and the response options remain the same, children of 3–4 years succeed. Similarly, if the original stimuli are used, but the response options change (say “dog” to the daytime scene and “pig” to the nighttime scene), children of 3–4 years also succeed (Diamond et al. 2002). Since memory demands are the same in both of these variants as in the standard condition, the fact that children succeed in these variants means that insufficient working memory does not appear to be why they fail the standard condition. Further, the dog–pig manipulation teaches us that 4-year-olds can inhibit saying what a stimulus represents, even when they must hold two rules in mind.

I thought the problem lay in inhibiting saying a word semantically related to the word they should say. In the dog–pig condition, preschoolers succeeded, I thought, because the response-to-be-inhibited was not semantically related to the response-to-be-activated.

Simpson & Riggs (2005) proved me wrong. They showed that preschoolers fail even if the two responses are not semantically related (say “car” to an image of a book and “book” to an image of a car). The factor that determines how difficult a response is to inhibit is whether that response is valid for the task. Thus, if preschoolers are primed to say “car” because it is a valid response to a stimulus other than a car, they have difficulty not saying “car” when the stimulus is a car and they are supposed to say a different word.

The responses one plans to make for a task are held in an activated state during that task; they are prepotent for that period of time. Responses become prepotent because of one’s intention to make them (for a similar analysis of tasks with adults, see Hommel 2000). Evidence from the Stroop task also supports that if a response is in the response set, it takes effort to inhibit it, but other responses are easy to inhibit (Milham et al. 2001, Proctor 1978, Stirling 1979). For example, if red and blue are in the response set, it is challenging to say “blue” when shown the word “red” printed in blue ink. However, if purple is not in the response set, it is not challenging to say “blue” when shown the word “purple” printed in blue ink. Similarly, on the flanker task (where one is to focus on the center stimulus and ignore flanking stimuli, called “flankers”), flankers interfere with performance only if there is a valid response associated with them (Munro et al. 2006). For example, if response options for the center stimulus are left and right, flankers interfere if they are pointing in the opposite direction but not if they are pointing up or down. Thus, the ability to selectively attend to the center stimulus (screening out flankers) is inextricably intertwined with whether response inhibition (inhibiting the response associated with where the flankers are pointing) is needed.

**5.1.1. How can young children be helped when inhibitory control is needed?** I noticed that those children who took their time continued to do well throughout the day–night test and that children who did well on only the first few trials took much longer on those trials than on later ones they got wrong. It seemed that when preschoolers took their time they could succeed. How could we get them to take their time?

We (Diamond et al. 2002) came up with the strategy of having the tester chant a short ditty after showing the stimulus card (“Think about the answer; don’t tell me”). This imposed a momentary delay between when the stimulus was revealed and when a child could respond. It had a dramatic effect! Four-year-olds went from responding at chance (56% correct) to being 89% correct. When the same ditty was chanted between trials (before the stimulus was revealed), it did not significantly aid performance. We concluded that imposing a brief waiting period between stimulus and response (while the ditty was chanted) scaffolds preschoolers’ incipient inhibitory control, enabling them to resist the prepotent response and make the considered one instead.

Munakata (2013) had a different hypothesis—that the problem for preschoolers was in holding the two rules in mind with sufficient clarity throughout all the test trials. Thus, Munakata argued that the ditty helped because its content reminded children of task-relevant information, not because the ditty imposed a waiting period. If the ditty’s content were the determining factor, then whether the ditty was chanted between trials or after the stimulus was presented should not matter. Although chanting the ditty between trials did not significantly improve performance, there was a slight trend for performance to be better there than in the standard condition, which would be consistent with Munakata’s hypothesis. So, we tested our hypothesis against Munakata’s.

To test between the two competing hypotheses, we used a ditty that had no task-relevant information (“I hope you have a nice time; I like you”) in one condition, the ditty we had used before in another, and the standard condition (Diamond et al. 2002). If children only benefited, or benefited more, from the original, task-relevant ditty, then the content was helping. The results showed, however, that both ditties aided performance similarly. Thus, the beneficial effect of the

ditty appears to be due to it taking time to chant and children waiting until the chanting is over to respond (i.e., it provides a way to get children to wait a few seconds before responding).

Diamond and colleagues (2002), Simpson & Riggs (2005), Simpson et al. (2012), and Montgomery & Fosco (2012) have all replicated the finding that helping preschoolers wait before responding on the day–night task enables them to reveal a competence that had appeared absent when they could respond as quickly as they wanted. Indeed, using very different experimental paradigms (all of which, I would argue, require inhibitory control), investigators have also repeatedly found that when more time (just a few moments) is interposed between stimulus presentation and when children can respond, preschoolers consistently do better than if allowed to respond right away (for theory of mind tests, see Heberle et al. 1999; for go/no-go, see Jones et al. 2003; for Piagetian search, see Riviere & Lecuyer 2003; and for a box-opening task, see Simpson et al. 2012).

**5.1.2. Why does imposing a momentary delay between stimulus and response enable preschoolers to succeed when otherwise they would not?** We reasoned that a momentary delay between stimulus and response helps because the day–night task is sufficiently difficult for young children that it takes them several seconds to compute the answer, and they often do not take the time they need. Simpson & Riggs (2007) proposed a different hypothesis: Imposing a momentary delay between stimulus and response helps simply because the incorrect, prepotent response (which activates faster) needs time to passively fade, enabling the correct answer to compete more successfully. They hypothesized that children were not using the extra time to compute anything. The incorrect response (naming the image), being prepotent, had a shorter rise time and raced to the response threshold before the correct response was computed. Imposing a delay after stimulus presentation, according to Simpson and Riggs, gave that incorrect response time to passively dissipate and the correct response time to become ascendant.

I contacted Simpson and suggested we collaborate in testing between the two hypotheses: Does a momentary delay help because children need that additional time to compute the thoughtful response (active computation) or does it help simply because the incorrect dominant response needs time to passively decay (passive dissipation)? Our collaboration (Simpson et al. 2012) demonstrated it is the latter; Simpson and Riggs were correct and I was wrong. We found that distracting children during the delay did not reduce the benefit of the delay. Children successfully inhibited their prepotent response despite not being able to compute anything during the delay as they were occupied with a guessing game. Good performance in the distraction-during-delay condition is consistent only with the passive-dissipation hypothesis.

Just as I thought imposing a brief delay helps young children because they need those few moments to compute the correct answer, Zelazo has emphasized the importance of reflection (reflecting before responding) for successful performance when needing to override a prepotent or habitual response, for example: “The development of EF is made possible, in part, by increases in the efficiency of *reflection*, which refers to children’s ability to notice challenges, pause, consider their options, and put things into context prior to responding. Having reflected on their situation, children are then in a position to exercise their EF skills” (Zelazo et al. 2016, p. 6). The results of our collaboration with Simpson, however, shows that simply pausing or waiting often can be sufficient in and of itself, without reflecting. We occupied children during the momentary pause, thus they could not reflect, and yet after the pause they performed correctly when without the pause they often erred.

Similarly, the stratagem used by *Tools of the Mind* teachers for getting rid of mirror reversal writing—to have children put down their pencil and pick up a red pencil whenever they need to write the number or letter they have been reversing—works, not because children are reflecting on how to write the number or letter while changing writing implements, but simply because the act

of changing writing implements takes a few moments. The simple passage of time, independent of attention or effort, allows the prepotent response to subside (making it easier to inhibit) and gives the considered response more time to rise to the response threshold (which, since it requires computation, takes longer to reach that threshold). Simply imposing a brief delay between stimulus and response thus scaffolds children's inchoate inhibitory control. By the time children are allowed to respond, less inhibitory control is needed (the incorrect response that popped into mind first has already begun to subside).

Children may know how they should behave, but if something in the environment brings to mind another action (e.g., seeing crayons might make them think of drawing), that action can become primed. Under such circumstances, young children (whose inhibitory control is still immature) may incorrectly make the primed response even though they know better. To help them, we can scaffold their emerging inhibitory control by finding something, anything, that causes them to delay responding for just a few moments. Identifying what enables young children to succeed in such situations can provide guidance for parents and teachers. For example, finding creative ways to help a child wait before responding (since saying "wait" would be ignored) serves to reduce inhibitory demands by giving the prepotent, incorrect response time to activate and then passively dissipate, which improves preschoolers' performance.

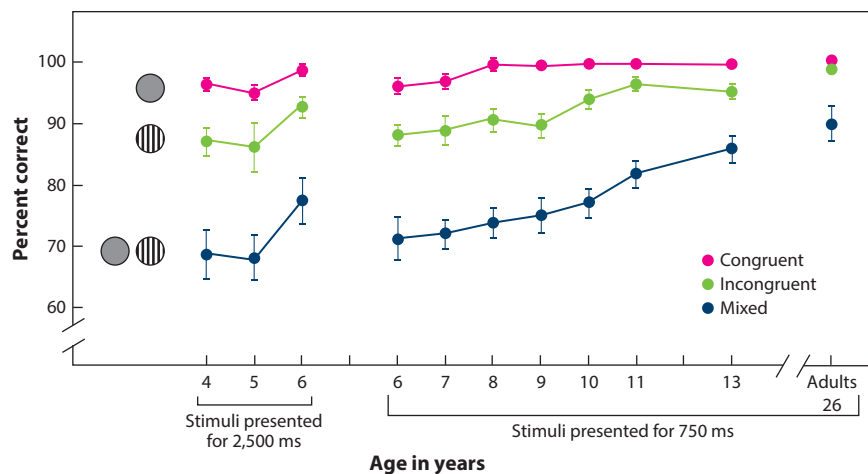
One excellent example of this can be seen in the Providing Alternative Thinking Strategies (PATHS) school program (Domitrovich et al. 2005, Kusché & Greenberg 2001). In PATHS, children are taught that when they get upset they should do what a turtle does (cross their arms and wrap them tightly around their body, hugging themselves) and take a deep breath before starting to plan how they will respond. This strategy is far more effective than asking young children to wait before responding. Young children are no good at waiting; asking them to wait is asking them to do something that is beyond their developmental level. PATHS gives children something to do while waiting (doing what turtles do). Doing this accomplishes two very important things: (a) it allows time to pass between the upsetting event and when the child responds, permitting the intensity of the annoyance to subside, and (b) it asks children to do something that helps them calm down. Children who have learned to "do turtle" at school really take to it and bring the practice back home, calling out to a parent when that parent starts getting upset at someone, "Do turtle!"

Encouraging the use of a strategy that imposes a delay before responding might not only help young children but could also benefit anyone facing an inhibitory-control challenge [such as someone with attention-deficit/hyperactivity disorder (ADHD), traumatic brain injury, or a decline in prefrontal function] resist doing something that would be inappropriate, be incorrect, or upset others. It gives them time to do what they know they should do, rather than be at the mercy of prepotent tendencies.

## 5.2. Inhibitory Control in Young Children: Evidence from the Hearts and Flowers Task

As discussed above, often the biggest challenge for young children is not recall or recognition memory, but inhibitory control. Although inhibiting a prepotent response is demanding, if that is required on all trials of a block, adults are as fast and accurate as on the corresponding block where the prepotent response is correct on every trial. We (Davidson et al. 2006) found that this is not true of children.

In the hearts and flowers task, for the first block of trials, participants are to press on the side (left or right) where a heart appears; for the second block, they are to press on the side opposite wherever a flower appears; for the third block, heart and flower trials are intermixed. Heart and flower trials have the same memory demands [there is only one rule to remember: Either press on the same side as the stimulus (for hearts) or the opposite side (for flowers)]. The only difference



**Figure 2**

Accuracy over age on the hearts and flowers task with gray and striped discs as the stimuli. Children, at all ages tested, performed worse on the incongruent (striped disc) block than on the congruent (gray disc) block, although adults performed comparably on both blocks. The same pattern is seen with reaction time: worse performance by children at all ages tested on the incongruent block than on the congruent one, but comparable performance on both blocks by adults.

between the heart and flower blocks is that for hearts, the prepotent response is correct (you need simply do what comes naturally and press on the same side as the stimulus), whereas for flowers, that response must be inhibited so you can press on the opposite side.

Even over many trials, adults are as fast and as accurate on the block of flower trials (incongruent trials) as they are on the block of heart trials (congruent trials). Children, however, at all ages tested (4–13 years) are slower and less accurate on the block requiring inhibition on every trial (the flower block) than on the block where no inhibition is needed (the heart block) (Davidson et al. 2006) (see **Figure 2**). Thus, just increasing the demand on inhibitory control, without any additional demand on working memory or cognitive flexibility, takes a toll on children's performance that is completely absent in adults. Indeed, increasing demands on inhibitory control is more difficult for children 4–9 years old than increasing demands on how much information they must hold in mind from two items to six (Davidson et al. 2006). The opposite is true for adults. Not until 10 years of age are the differences in speed or accuracy of holding two versus six arbitrary, hard-to-verbalize rules in mind greater than the differences between consistently inhibiting the tendency to respond on the same side as the stimulus [the incongruent (flower) block] versus when inhibiting that tendency is not required [the congruent (heart) block]. Children are not miniature adults. Adults may not appreciate how inordinately difficult inhibition is for young children because it is so much less difficult for us.

Studies that use only steady-state conditions and compare across only single-task blocks (as in many Stroop studies that compare blocks of reading the words with blocks of saying the color of the ink) underestimate effects because maintaining inhibition in steady state is not that difficult for adults.

Normally the congruent (heart) block is administered first and then the incongruent (flower) block. Children's performance in the incongruent block is virtually identical, however, whether it is administered first (before the congruent one) or second (Wright & Diamond 2014), as they are slower and make more errors on incongruent trials regardless of which block is administered first.



This shows that increasing inhibitory demands alone is sufficient to impair children's performance in the face of no change in working memory demands.

Everyone, at all ages, finds switching back and forth between the two rules in a task-switching block far more difficult than exercising inhibitory control in steady state (see **Figure 2**). Adults (but not young children) seem to reset their default response when inhibition of the same tendency is required throughout a block. Thus, adults have little difficulty consistently exercising inhibition on all trials in a single-task block (e.g., the flower block), but children of all ages tested displayed a cost for doing so, albeit a much smaller cost than when exercising inhibition intermittently is required.

## **6. CENTRALITY FOR COGNITIVE DEVELOPMENT OF IMPROVEMENTS NOT JUST IN BRIDGING TEMPORAL SEPARATIONS BUT ALSO IN BRIDGING SPATIAL SEPARATIONS**

Infants reach correctly for a hidden toy in the A-not-B task if allowed to reach immediately and can retrieve a toy from the object retrieval box if the toy is sitting in the box opening. Infants run into difficulty, however, if a temporal gap is imposed between when the toy is hidden and when they are allowed to reach or if a spatial gap is imposed between the toy and box opening by placing the toy deep inside the transparent object retrieval box.

The object retrieval task requires infants to relate the opening of the box to the reward inside over a spatial separation. When reward and opening are superimposed (as when the reward is in the opening, partially out of the box), even infants of only 5–6 months (and even monkeys without dorsolateral PFC) succeed. However, as the spatial separation between the reward and the opening widens (i.e., as the reward is placed deeper inside the box), the age at which infants succeed progressively increases. In the A-not-B task, when there is no delay between hiding and retrieval, even infants of only 7–8 months (and even monkeys without dorsolateral PFC) succeed. As the time interval between hiding and retrieval increases, the age at which infants succeed progressively increases.<sup>3</sup>

I suggest that developmental psychologists and neuroscientists take more seriously physicists' notion that time and space are inextricably intertwined and are perhaps even aspects of the same thing. "Space by itself, and time by itself, are doomed to fade away into mere shadows, and only a kind of union of the two will preserve an independent reality" (Minkowski 1952, p. 75).

### **6.1. Changing Our Understanding of the Functions of Dorsolateral Prefrontal Cortex: It Is Typically Needed When Both Holding Information in Mind and Inhibitory Control Are Taxed**

Early work on the functions of dorsolateral PFC relied heavily on the delayed response task, where the location at which the reward is hidden is randomly varied. Because that task does not allow one to tease apart the contributions of memory and inhibition, and because some neurons in dorsolateral PFC maintain firing over the delay, early researchers studying dorsolateral PFC emphasized its contribution to working memory (Fuster et al. 1982, Kojima & Goldman-Rakic 1982, Quintana et al. 1988). That interpretation unfortunately continues to have an outsized influence on the field.

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<sup>3</sup>Note that for preschoolers, who unlike infants can easily remember something for a few seconds, imposing a brief delay (3–4 s) between seeing the stimulus revealed and being able to respond in the day–night task helps them to give the correct answer, while for infants, imposing a brief delay (e.g., 3–4 s) during which they must remember where they saw a reward hidden makes the A-not-B and delayed response tasks more challenging. The day–night task does not require remembering anything (except the rules); that is, it does not require holding any information in mind over a delay, while the A-not-B and delayed response tasks do.



One challenge to thinking that dorsolateral PFC is required specifically and primarily for working memory came when I showed that performance on object retrieval (the transparent barrier task, where nothing is hidden) improves over the same period of infancy as does performance on the A-not-B and delayed response tasks for both monkeys and humans (Diamond & Doar 1989, Diamond & Goldman-Rakic 1989) and that lesions of dorsolateral PFC, but not of parietal cortex or the hippocampus, impair performance on the task (Diamond 1990c, Diamond et al. 1989). The main requirement of the object retrieval task is to inhibit the pull to try to reach straight to a visible target through a closed side of the transparent box. Infants must instead reach around to the opening. Thus, infants perform better with an opaque box, where the toy cannot be seen through a closed side (Diamond 1983, 1990c). The counterintuitive finding that the task is easier when the goal is not visible is consistent with the task being more difficult when seeing the goal through a closed side, since the pull to reach straight to the goal must then be inhibited. Since this task requires dorsolateral PFC, that brain region cannot be required only for working memory.

Another challenge to thinking that *the* function of dorsolateral PFC is to subserve working memory is that just holding information in mind (as neurons firing during a delay period make possible) is short-term memory, not working memory. When neuroscientists studying the classic tasks of dorsolateral PFC function in animals (such as delayed response or delayed alternation) quote an authority on working memory, they typically cite Baddeley (e.g., Baddeley 1992). However, their tasks do not meet Baddeley's definition of working memory, as these tasks do not require manipulating or working with the information held in mind. Holding information in mind without manipulating it is short-term memory. These tasks also require inhibition of proactive interference (cognitive inhibition or interference control). A way to still consider these tasks as requiring working memory would be to adopt the definition of working memory put forward by either Hasher & Zacks (1988) or Kane & Engle (2000), as they incorporate cognitive inhibition as part of working memory (defining working memory as holding information in mind plus interference control). Another way to think about these tasks is to say that they require short-term memory plus cognitive inhibition (interference control) and to stop saying that they require working memory. In any case, there are other demands on inhibitory control in these tasks: resisting going to one's preferred side and resisting repeating a response that was just rewarded.

Dorsolateral PFC appears to be required for tasks where subjects must (*a*) integrate information that is separated in space (as in the object retrieval task) or time (as in the A-not-B, delayed response, and delayed alternation tasks) and (*b*) exercise inhibitory control. If only one of these abilities is required, usually dorsolateral PFC is not required.

What is the evidence that inhibitory control is required for A-not-B or that working memory is required for object retrieval? We have already seen an example of evidence for the role of inhibitory control in A-not-B in **Supplemental Figure 2**. An example of evidence for the role of working memory in the object retrieval task can be seen at 8.5–9 months, when infants can look through the top of the box while reaching through the open front for the first time, or at 10–10.5 months, when infants can look through the top of the box while reaching through the open left or right side. At both ages, infants still need to have seen the toy through the opening on the current trial to succeed, but success no longer depends on maintaining that line of sight. The memory of having seen the toy through the opening is enough.

This changes how scientists conceive of dorsolateral PFC, expanding its role. It is not only needed for bridging temporal gaps (whether one calls that working memory or short-term memory) but also needed for bridging spatial gaps. Moreover, it is required when inhibitory control is needed in addition to that. When a task requires just inhibitory control or just short-term memory, it typically requires ventrolateral PFC (i.e., the inferior frontal gyrus in humans).

## 6.2. Importance of a Physical Connection (No Spatial Separation) for Infants and Toddlers to Grasp How Two Objects Are Related to One Another

The most extreme reduction in spatial separation is to be physically connected. That can sometimes aid young children's cognition in quite powerful ways.

A classic task in behavioral neuroscience for assessing recognition memory dependent on the medial temporal lobe is the delayed nonmatching to sample (DNMS) task. Originally designed for work with monkeys, a new sample object is presented on each DNMS trial. The participant displaces it to retrieve a small reward from the well underneath. After a brief delay, the sample is again presented, but this time along with a novel object, and the reward is now under that novel object. Hence, the participant needs to deduce the rule: always go to the new (nonmatching) object. No stimulus is ever used on more than one trial (to preserve the novelty of the nonmatching stimuli). Since monkeys (and young children) have a natural preference for novelty, researchers assumed that if participants remembered the sample, they would pick the new object. Indeed, because of that novelty preference, it takes monkeys 10 times longer to learn delayed matching (Brush et al. 1961, Harlow 1950), and children do not succeed at delayed matching until years after they succeed at delayed nonmatching (Luciana & Nelson 1998; N. Wusnich & N. Levy, unpublished manuscript). (Delayed matching to sample requires inhibiting the novelty preference and instead reaching back to the familiar, and therefore more boring, sample.)

Children generally do not succeed at DNMS, even with delays of only 5 or 10 s, until they are almost 2 years old (20–21 months) (Diamond 1990c, Diamond et al. 1994, Overman 1990, Overman et al. 1992), whether tested only once (Diamond 1990c) or daily beginning at 12 months (Overman 1990). Some prominent neuroscientists took this to indicate that the medial temporal lobe memory system matures late in humans, given what DNMS was designed to assess. However, robust recognition memory is present in human infants long before 21 months, so late success on DNMS must be due to the late emergence of another ability (Diamond 1990c, 1995; Diamond et al. 1994). Moreover, when a child first succeeds on DNMS with a 5-s delay, that child also succeeds at delays of 30 and 60 s in the same session (Diamond et al. 1994).

Since children's performance on DNMS is insensitive to the length of delay (at least within the range of 5–60 s; Diamond et al. 1994), and since there is abundant evidence that infants  $\leq 6$  months are capable of remembering something for far longer than 5 s, infants of 6–19 months must fail DNMS for some reason other than inadequate recognition memory. While DNMS is an excellent test of recognition memory in adult monkeys, or even human adults, infants and toddlers fail the task for reasons other than poor recognition memory. That is, the developmental progression of improved DNMS performance in infants and toddlers does not chart the developmental progression of recognition memory nor the maturation of the memory system on which it depends, even though the same task when used with adult humans and monkeys is a measure of recognition memory dependent on the medial temporal lobe.

Although most children fail the standard DNMS task until they are almost 2 years old, even infants of only 6 months succeed when there are no extrinsic rewards. That is, when infants reached—not to obtain something else, but to obtain the stimulus itself (i.e., the stimulus itself being the reward)—even 6-month-olds consistently chose the novel object (Diamond 1995). Similarly, when no wells or hidden rewards were used, but instead the experimenter cheered and applauded, infants also succeeded at DNMS (Diamond et al. 1999). It seems that something about the rewards being real objects in their own right confuses infants and toddlers.

Infants also succeed in the Velcro condition, where the rewards are separate objects but are attached to the base of the stimuli with Velcro (Diamond et al. 1999). As in the standard DNMS task, the stimuli are still atop wells, and the rewards are still out of sight in the wells, but instead of the reward remaining in the well when a stimulus is displaced, the reward moves with the stimulus

(see **Supplemental Figure 4**). In this condition, where the rewards are physically connected to (although detachable from) the stimuli, the youngest infants tested (9 months old) succeeded even at delays of 1 min (Diamond et al. 1999). Thus, introducing a physical connection between the stimulus and reward more than halved the age at which infants succeed at DNMS.

Such a physical connection also seems to greatly aid nonhuman primates. Jarvik (1956) asked why it takes chimpanzees hundreds of trials to learn a simple color discrimination. He varied whether the reward was in a well under a plaque or pasted to the plaque's underside (analogous to our Velcro condition). When the reward was attached to the plaque, though detachable, Jarvik found that chimpanzees learned the task in one trial.

Infants at all ages tested (9, 12, and 15 months) succeeded in a jack-in-the-box condition, where the stimuli and rewards were all part of a single, large white box. A puppet (the jack-in-the-box) popped up the moment an infant moved the correct stimulus (Diamond et al. 2003). Perhaps the stimulus seemed like a lever, which when pulled, made the jack-in-the-box pop up (see **Supplemental Figure 5a**). Even with a delay of 2 or 5 s between acting on the stimulus and the jack-in-the-box popping up, infants succeeded (Diamond et al. 2003). Apparently, when the stimuli and rewards are perceived to be components of a single thing, even if the stimuli and rewards are not directly attached to one another, the connection between them is understood by infants.

When each jack-in-the-box was housed in its own little box, however, despite the stimuli being positioned directly in front of their associated boxes, infants of 9, 12, and 15 months failed even when the reward appeared immediately upon touching the stimulus (Diamond et al. 2003) (see **Supplemental Figure 5b**). Thus, in the absence of the perception that the stimulus and reward were components of a single thing, even having both close temporal and spatial proximity was insufficient here. We tried two other conditions where the reward appeared immediately upon acting on the correct stimulus, but stimulus and reward were not physically connected. Infants failed both of those conditions as well (Shutts et al. 2001) (see **Figure 3**).

It appears that infants and toddlers have difficulty grasping that two objects are conceptually connected if they are not physically connected. Physical connection, even if indirect, appears to be key.

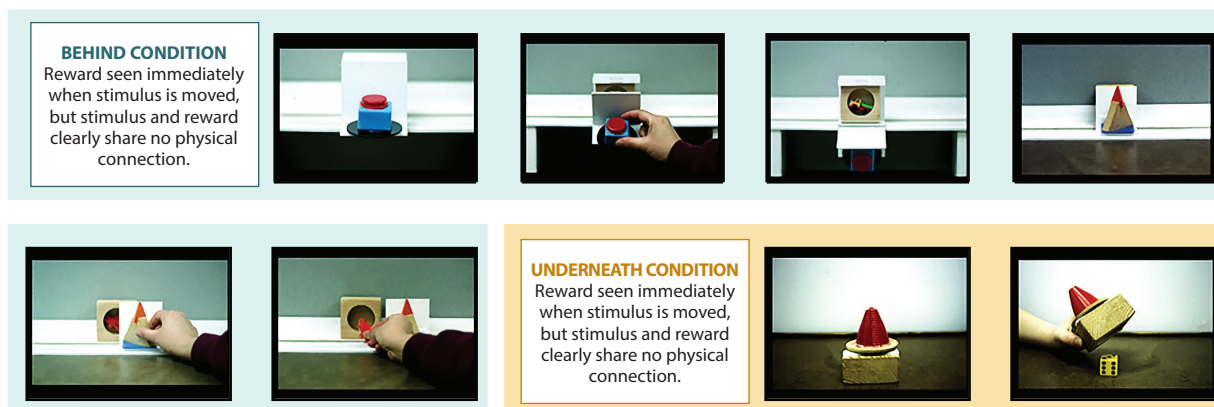
Most behavioral training with children with developmental delays has not considered whether a physical connection is present or not. Making such a simple change in training methods might enable children to grasp concepts previously thought far beyond their ability.

Other developmental psychologists have shown that the problem of grasping relations between things is not fully solved by 21 months and continues for some years. For example, Rudel (1955) found when children of 1.5–3.5 years were tested with the reward placed *inside* stimulus boxes, they learned to choose on the basis of relative size in far fewer trials than even older children who were tested with the reward *underneath* the stimulus. DeLoache & Brown (1983) found that 18–22-month-olds performed significantly better on a search task when a reward was hidden in a piece of furniture rather than near it; by 24–30 months, performance was equally good in both conditions. In DeLoache's work with models (DeLoache 1989, 1995, 2000), she found that while children of 2.5 years have difficulty relating a small model of a room to the full-size room (two separate things), they have no difficulty relating those same two things if they are told the model and room are one space that magically changes size (no longer two separate things in the child's mind).

### 6.3. Importance of Integrating Color and Shape in the Visual Display for Aiding 3-Year-Olds When the Task Requires Conceptually Integrating Those Dimensions

An example of the power of eliminating spatial separation is that 3-to-4-year-olds can more readily integrate dimensions if they are presented as aspects of the same object than if they are attributes

a



b

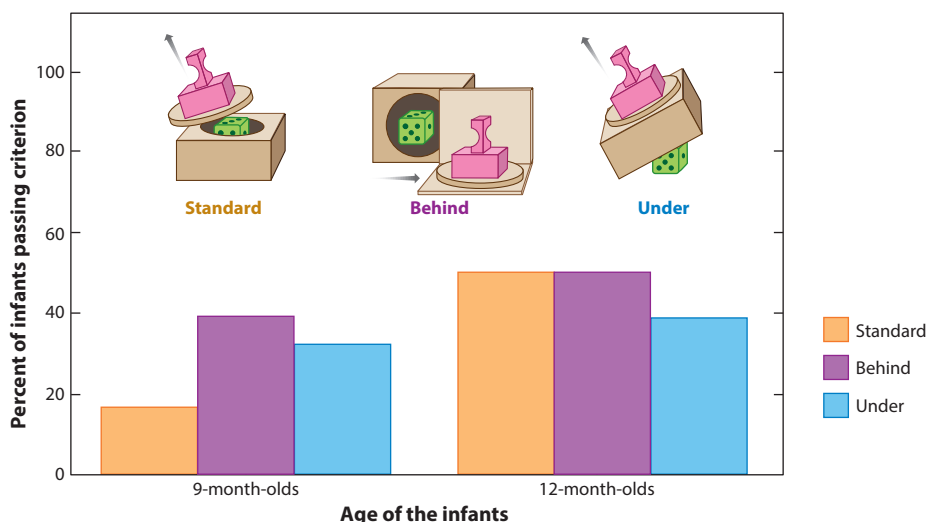


Figure 3

(a) Behind and underneath conditions of the delayed nonmatching to sample (DNMS) task. (b) The percentage of infants passing criterion at the 5-s delay in the standard, behind, and underneath conditions of DNMS. Note that in the behind and underneath conditions, even though the reward appeared immediately upon acting on the correct stimulus, infants performed no better than in the standard condition (i.e., most failed to demonstrate learning of the nonmatching rule). The behind and underneath conditions share the property of the stimulus and reward not being physically connected with the standard condition.

of separate entities, despite all being on the same stimulus card. Children younger than 4.5–5 years typically fail the conditional discrimination reasoning task, where which color (or shape) is correct is contingent on which shape (or color) is present (Andrews et al. 2012, Gollin 1965, Gollin & Liss 1962). Here, when Color 1 is present, Shape X is correct, and when Color 2 is present, Shape Y is correct. Children are not told the rules; they must deduce them based on feedback. To know which choice is correct, one must take into account both color and shape.

Conditional discrimination had always been administered with color and shape separated on the stimulus cards (e.g., a colorless truck on a blue background or with a blue border around the

card) (Andrews et al. 2012, Gollin 1965, Gollin & Liss 1962). Most children younger than 4 years fail that. We reasoned that integrating color and shape in the stimuli (e.g., a blue truck on a white background, so the stimulus is both a truck and blue in color) would enable 3-year-olds to succeed, and in fact they do (Ling et al. 2021). We think the integrated-dimensions condition enables 3-year-olds to succeed because it bootstraps them perceptually in their task of conceptually relating the two dimensions to one another.<sup>4</sup>

Thus, I have described how the age of success on both DNMS and conditional discrimination was significantly reduced by introducing a physical connection between the items to be conceptually related. Elsewhere, I have proposed that a border region partially overlapping lateral PFC and Brodmann's area 6 (the periarculate area in the monkey brain) is critical for the ability to grasp that physically separate things are related (Diamond 2006). See the **Supplemental Text** for more on the border region I have proposed.

#### **6.4. The Flip Side: Separating Color and Shape in the Visual Display Aids 3-Year-Olds in Ignoring One Dimension When Asked to Focus on Another in the Dimensional Change Card Sort Task**

While conditional discrimination requires cognitively integrating color and shape, the dimensional change card sort (DCCS) task devised by Zelazo and colleagues (Zelazo et al. 1996) requires keeping those same dimensions cognitively separate. Here, children are to sort a deck of cards first by one dimension (color or shape) and then switch to sorting by the other dimension. One sorting bin might display a blue-star model card, for example, while a red-truck model card might be displayed on the other. When sorting by color, the blue truck would go in the bin with the blue-star model card, but when sorting by shape, the same stimulus card should go in the bin with the red-truck model card (see **Figure 4**).

By 2–3 years of age, children can sort the cards correctly by color or shape. However, when asked to switch and sort by the other dimension, they tend to continue to sort by the initial dimension, even though they can correctly indicate on each trial what the new sorting dimension is and how to sort by it. Not until 4.5–5 years of age does that error disappear. This task presents the simplest possible task-switching paradigm. First a short block of trials of one task is presented (e.g., sort by shape), then a single task switch is introduced and a short block of trials of the other task is presented (e.g., sort by color). DCCS procedures often minimize memory demands by providing a reminder of which dimension is currently relevant at the start of each trial.

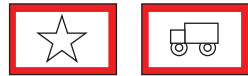
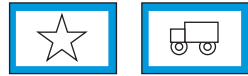
Central to success on the DCCS task is keeping the two dimensions cognitively separate, that is, inhibiting attention to one (e.g., shape) when sorting by the other (e.g., color). Correctly switching requires that children understand that the attributes of a single entity can be conceptually separated and the entity redescribed from another perspective (Kirkham et al. 2003; and more fully elaborated in Kloo & Perner 2005). For example, when sorting by color, children should think of a stimulus as a blue thing and look for the bin with a model card that has blue, but when sorting by shape, that same stimulus now needs to be thought of as a truck and placed in the bin with a model card showing a truck. Certainly, much evidence from many paradigms has shown that preschoolers have great difficulty thinking about the same thing from two different perspectives [e.g., evidence from research on ambiguous objects (Gopnik & Rosati 2001), appearance–reality (Flavell et al. 1983), and false belief (Perner et al. 1987); for a review, see Diamond & Kirkham 2005].

<sup>4</sup>One caveat to note is that we did not use multiple versions of trucks or stars or multiple versions of the colors red or blue. It is possible that infants learned to associate the blue truck with a reward and the red star with a reward, rather than learning the rules: “when blue is present, choose the truck, and when red is present, choose the star.” Further studies with varied stimuli are needed to disambiguate these two explanations (simple stimulus–response learning versus conditional-rule learning).

**a**

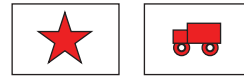
- For **CONDITIONAL DISCRIMINATION**, color and shape must be integrated because which shape is correct depends on the color of the stimuli.
- For example, when the stimuli are blue the correct response might be to select the truck, but when the stimuli are red the correct response would be to select the star.

**Example of standard (separated dimensions) conditional discrimination stimuli**



Correct choice in this example

**Example of integrated-dimensions conditional discrimination stimuli**



Correct choice in this example

Children tend **not to be able** to succeed here until they are 4.5–5 years old.

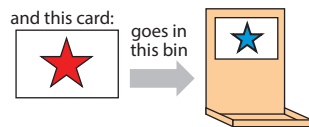
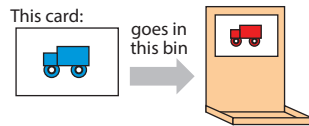
Most children **are able** to succeed here at only 3 years old.

**b**

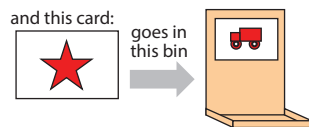
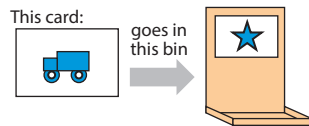
- The **DIMENSIONAL CHANGE CARD SORT** task requires attending only to color or shape at any given time, ignoring the other dimension.
- For example, when sorting by color, the blue truck goes in the bin with a blue model card (ignore that the model card shows a star) and the red star goes in the bin with the red model card (ignore that the model card shows a truck).
- When sorting by shape, however, the color on the cards needs to be ignored and one should focus only on the shape displayed.

**Example of standard (integrated dimensions) dimensional change card sort stimuli**

When sorting by **SHAPE**:



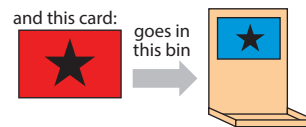
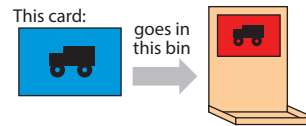
But when sorting by **COLOR**:



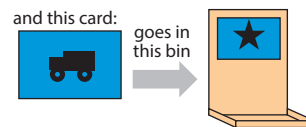
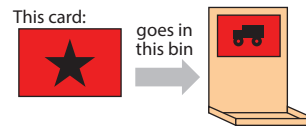
Children tend **not to be able** to succeed here until they are 4.5–5 years old.

**Example of separated dimensions card sort stimuli**

When sorting by **SHAPE**:



But when sorting by **COLOR**:



Most children **are able** to succeed here at only 3 years old.

**Figure 4**

Illustration of the rules for the (a) conditional discrimination and (b) dimensional change card sort tasks.



If color and shape are separated on the stimulus cards—that is, if color is a property of the background and the stimulus object is “colorless” (being only black or white)—then children only 3 years old can switch from sorting by color to sorting by shape and vice versa (Diamond et al. 2005). Shortly after we showed this, Kloo & Perner (2005) reported similar results with colorless shapes and a color patch on each card.

Evidently, children of 3 years have difficulty mentally separating dimensions (e.g., color and shape) of the same object and difficulty mentally integrating dimensions that are not part of the same object. Scaffolding their emerging conceptual skills with just a superficial change to the stimuli enables 3-year-olds to demonstrate cognitive abilities long thought beyond their grasp. They are then able to succeed at DCCS and conditional discrimination a full 12–18 months earlier than on canonical versions of those tasks. *Separating* color and shape in the stimuli enables 3-year-olds to conceptually separate them and thus switch sorting dimensions on the DCCS task. *Integrating* color and shape enables 3-year-olds to conceptually integrate them, required for the conditional discrimination task (Diamond et al. 1999, Ling et al. 2021).

Although adults experience Stroop interference when color and word attributes are integrated, they find the task far easier when those attributes are spatially separated (MacLeod 1991, 1998). On the Simon task, for Stimulus A, one is to press on the left, and for Stimulus B, one is to press on the right, regardless of where the stimulus appears. Although the location of the stimulus is irrelevant, children and adults are slower when a stimulus appears on the side opposite the response associated with that stimulus (Hasbroucq & Guiard 1991, Lu & Proctor 1995). Evidently, even for adults, it is easier to take into account all salient aspects of a stimulus than just one aspect, such as identity, color, or shape (Diamond 2009, Pratt & Hommel 2003). In this context, unbinding (rather than binding) is the problem.

## 7. SOCIAL AND EMOTIONAL INFLUENCES ON COGNITIVE DEVELOPMENT

We are not just intellects; we also have emotions, social needs, and bodies. The different parts of a person (cognitive, emotional, social, spiritual, and physical) are multiply interrelated and affect one another (Diamond 2012b, 2014; Diamond & Ling 2019; for a more recent discussion of this, see Stodden et al. 2023). No one’s EFs work as well when that person is lonely or isolated, sad or stressed, or ill or not physically fit (Diamond 2012a, 2014).

Western philosophy and psychology have long regarded cognition and emotions as independent, with emotions as more lowly, something to be controlled, regulated, or inhibited [e.g., Bachelard 1964 (1958)]. Yet, emotions can be as sophisticated as cognition and can power cognition as well as interfere with it. While emotions can certainly impair EFs, they can also aid EFs. For example, when one is highly motivated to succeed or thoroughly enjoying an activity, one works harder to exercise the very best EFs that one is capable of.

One’s emotional state affects one’s EF performance (e.g., Cohen & Pressman 2006, Lupien et al. 2007, Okon-Singer et al. 2015). As Okon-Singer et al. (2015, p. 8) said, “The distinction between the ‘emotional’ and the ‘cognitive’ brain is fuzzy and context-dependent.... [P]utatively emotional and cognitive regions influence one another via a complex web of connections.... [E]motion and cognition are deeply interwoven in the fabric of the brain.”

A few weeks of stress in preparation for a major exam impairs EFs and, at the neural level, disrupts functional connectivity between PFC and other brain regions (Liston et al. 2009). When people are more stressed, they are 37% more likely to show poorer working memory and problem-solving, and chronic stress can lead to a loss of gray matter in prefrontal cortex (Kulshreshtha et al. 2023). Stress impairs all EFs, including selective attention (Sänger et al. 2004) and self-control



(Maier et al. 2015). Copious evidence documents that a happy mood leads to greater creativity, specifically in the sense of greater cognitive flexibility (Ashby et al. 1999, Isen et al. 1987). For example, when we are happier, we are more willing to consider alternatives or to see relations among things we would not normally group together (Hirt et al. 2008). When we are sad or depressed, we have worse working memory (Mammott et al. 2018) and selective attention (Desseilles et al. 2013), and the functional connectivity in our frontostriatal network is disrupted (Gupta et al. 2024). When we are happy, we have better working memory (Yang et al. 2013) and selective attention (Gable & Harmon-Jones 2008).

Though we still tend to silo the social and the cognitive, it is a caring social relationship with an adult in one's life that is often determinative of how much cognitive progress is made (e.g., Melhuish 2006). Feeling socially excluded or that you do not belong has been shown to impair EFs (specifically selective attention in the face of distraction, reasoning and decision-making, and persistence on difficult tasks) (Baumeister et al. 2005, Cacioppo & Patrick 2008, Twenge et al. 2002). One reason why perceived social support aids EFs is that it helps reduce one's levels of stress (Gerin et al. 1992, Gottlieb & Bergen 2010, Pilcher & Bryant 2016, Uchino et al. 1996), and stress impairs EFs (Cerqueira et al. 2007, Zareyan et al. 2021). Since feeling socially supported or excluded affects EFs, it is hardly surprising that loneliness or feeling socially excluded impairs academic performance (Benner 2011). Given the behavioral findings, it is also not surprising that feeling socially isolated disrupts functional connectivity in the EF brain network (Layden et al. 2017).

These effects are bidirectional. Not only does a greater sense of social belonging and support help one exercise better EFs, but better EFs help one have more harmonious social relations (Hughes et al. 2000, Tangney et al. 2004, Zeytinoglu et al. 2023). Similarly, while stress impairs EFs, exercising good EFs can help minimize stress, such as by planning ahead or using cognitive flexibility to change the way one thinks about something and thereby reduce its emotional impact (cognitive reappraisal) (Lantrip et al. 2016, Toh & Yang 2022).

The human being is an integrated whole. Sadness, stress, chronic lack of sleep, chronic infections, or marked physical inactivity can mask remarkable giftedness potential, causing it to potentially be missed altogether. I have put forward the hypothesis that focusing exclusively on training EF skills is less efficient, and ultimately less successful, than also addressing emotional, social, spiritual, and physical needs (Diamond 2010, 2014). While training and challenging EFs is needed for them to improve, I have hypothesized that indirectly supporting EFs by lessening things that impair them (such as stress and sadness) and enhancing things that support them (such as social support and physical vitality) is also critical (Diamond 2012a, Diamond & Ling 2019). It follows that even if one's goal is only to improve academic outcomes, the best way to achieve that is probably not to focus narrowly on academics alone but to also address children's emotional, social, and physical needs (Diamond 2010, 2013; Diamond & Lee 2011). Most researchers studying how to improve EFs have focused almost exclusively on directly training EFs (or improving aerobic fitness to improve EFs), ignoring powerful emotional and social factors that affect EFs.

I have argued for years that the distinction between so-called academic and so-called enrichment activities is arbitrary and that EF skills can all be taught through music-making, theater, martial arts, dance, sports, carpentry, auto mechanics, activities in the great outdoors, and more (Diamond 2014, Diamond & Ling 2019). More and more research is demonstrating the value of these activities for EFs and for doing well academically (e.g., Jylänki et al. 2022, Kasuya-Ueba et al. 2020). Importantly, many neurodiverse students excel at these activities. Often they are spatially or musically gifted, but our academic education is so heavily verbally oriented that they often look less bright than their peers. These activities can give them an opportunity to shine, and these activities teach important skills to all children.

### 7.1. Educational Programs Show that Focusing Equally on Social–Emotional Development, Executive Functions, and Academics Does Not Detract from Academic Success but Enhances It

*Tools of the Mind* (*Tools* for short) is a preschool and kindergarten curriculum, developed by Bodrova & Leong (2007) based on the work of Vygotsky (1962, 1978), that directly trains and challenges EFs while also lessening things that impair them (such as peer rejection) and promoting things that support them (such as students working together and being kind to and supporting one another). It emphasizes active, hands-on learning and play. Vygotsky emphasized that cognitive and social development are fundamentally intertwined and that social interactions are key to developing EFs and cognitive skills; thus, rather than having separate activities for academics and social–emotional learning, *Tools* activities address both. *Tools* teachers are taught how to foster an atmosphere of cooperation and mutual support. Compared with traditional kindergarten, *Tools* makes far greater use of peer social interaction for learning. Children learn to help bootstrap one another's EFs, providing helpful reminders to each other. For Vygotsky, engaging in mature, dramatic social pretend play (e.g., playing doctor and patient or grocery store) was the major mechanism for developing EFs, as all the principles Vygotsky (1962, 1978) emphasized can be incorporated there. Thus, this type of play features prominently in *Tools*. It requires working memory (to remember what role you picked and what roles your friends picked), inhibitory control (to avoid acting out of character), and cognitive flexibility (to adjust in real-time as your friends take the play scenario in directions you never imagined)—all three of the core EFs.

In 2007 we published a report in *Science* (Diamond et al. 2007) of the results of the first study of the efficacy of *Tools*. We compared the *Tools* preschool curriculum with another new curriculum developed by the school district and of which the school district was quite proud. Both programs were instituted at the same time, had identical resources, and covered the same academic content. The students in the two curricula came from low-income homes and were closely matched on demographic variables. We found that children from the *Tools* classes showed better EFs (better selective attention on the flanker task) than closely matched peers and that the better children's EFs were, the better their performance on standardized academic measures. Whether children were in *Tools* or not accounted for more variance in EFs than did age or gender. One school was so impressed by how much better children in *Tools* were performing that they dropped out of the study and switched all their preschool classes to *Tools*, feeling it unethical to deprive any students of *Tools*.

These findings were important for a few different reasons. One, they showed for the first time that it was possible to intervene early to improve EFs (many had thought 4–5 years of age was too early because PFC was still too immature). Two, they showed for the first time that EFs can be improved in regular public-school classes (without expensive high-tech equipment, one-to-one attention, or specialists). The materials used were simple, inexpensive, and readily available. Three, they suggested that dramatic pretend play and attention to social and emotional well-being may be critical for young children to have the best EFs and best academic performance. That flew directly in the face of pressure on preschool teachers to limit play and devote more time to direct academic instruction. Four, these findings ignited worldwide interest in intervening early to improve EFs to head off mental health problems and school failure and to give children a better chance in life. Indeed, as a result of this study, four countries (Chile, Ecuador, Indonesia, Peru), the Ktunaxa First Nation, and three US states (Arizona, Maryland, Washington) started to reform their early education systems.

That first study was followed by a much larger randomized control trial by Blair and colleagues (Blair & Raver 2014, Blair et al. 2018) of *Tools* in kindergarten. That study found better and more improved teacher–child relationships and emotion regulation and lower levels of stress in children in *Tools* than in children in comparison classes. Partly because of that, the study also found

better and more improved vocabulary, math, and EFs (working memory and reasoning)—though inhibitory control and cognitive flexibility did not differ between groups. Academic benefits were even larger the following year (grade 1), where gains in reading first became apparent. Effect sizes were roughly eight times larger in low-income schools.

A third study compared a daycare-based *Tools* program for 3-to-4-year-olds to a high-quality, existing play-based program (Solomon et al. 2018). Children in *Tools* whose parents rated them as highly hyperactive and/or inattentive in the fall showed greater gains on an inhibitory control task of self-control than control children. The authors concluded that “*Tools* may be advantageous in classrooms with children experiencing greater challenges with self-regulation, at no apparent cost to those less challenged in this regard” (p. 2).

In the first randomized control trial of *Tools* in Canada (Diamond et al. 2019), we replicated the finding that *Tools* improves reading and showed for the first time that it also improves writing (far exceeding levels the schools had seen before) and that it improves EFs in the real world (e.g., time on task without supervision) as opposed to just on laboratory tests. Children in *Tools* showed less bullying and peer ostracism and more kindness and helping behavior than students in more traditional classes. Students and teachers were happier, teacher enthusiasm for teaching soared, and teacher burnout was absent in *Tools* classes. By the spring, *Tools* teachers were still enthusiastic about teaching; control teachers were exhausted.

Because students in *Tools* are helped to have better EFs, teachers do not have to worry about discipline problems; they can relax. Without having to worry about being disciplined, students can relax. *Tools* also minimizes the chance that a child is made to feel ashamed. *Tools* teachers provide scaffolds to help children succeed and use materials that indicate themselves whether a child is right or wrong so that mistakes can be a private matter. There is more calm in *Tools* classes. More learning occurs in happy, joyous classrooms, where children feel safe, secure, and accepted and where they feel the teacher sees them for who they are and genuinely cares (Gregory & Weinstein 2004, Harter 1996, Jethwani-Keyser 2008, Little & Ellison 2015). Children can then dispense with the dual tasks of, on the one hand, always looking over their shoulder and trying to contain their anxiety, anger, or hurt, while on the other hand, trying to learn. They can risk trying something new and being wrong. Children need to feel safe enough to push the limits of what they know, venture into the unknown, and risk looking foolish.

Children across the board benefited from *Tools*—whether higher or lower socioeconomic status (SES) and whether more or less advanced in academic skills or EFs at school entry. Regardless of the SES of students in the class or the experience of the teacher, by May, over half the children in *Tools* were able to read and write independently. Principals and resource teachers reported that they were unable to identify the special needs students when they visited *Tools* classrooms in the spring, much to their amazement. Evidence from this study has been used to persuade Ministries of Education and school boards to do more to address students’ social and emotional well-being.

Initially, Bodrova and Leong had tried *Tools* as an add-on to existing curricula. Children improved on what they practiced in that module, but the benefits did not transfer. Clements & Sarama (2008) replicated that when adding only the pretend play portion of *Tools* to the regular curriculum, it does not yield EF or academic benefits. I think that is because you need the whole package; you need to address classroom climate and social-emotional well-being, and you need to train, challenge, and support EFs in all activities throughout the school day.

A large, national study called Head Start CARES randomly assigned three preschool programs (Preschool PATHS, The Incredible Years, and Tools of the Mind—Play) to roughly 100 Head Start programs (Morris et al. 2014). They found that Tools of the Mind—Play did not produce the expected EF gains. Perhaps that was because only a subset of *Tools* was introduced, as others have demonstrated that implementing only part of *Tools* produces few benefits (Bodrova &

Leong 2007, Clements & Sarama 2008). Perhaps the lack of gains was because *Tools* (not being a cookbook method, unlike *The Incredible Years*, for example) may require better-educated teachers than Head Start normally attracts given its low salaries. Perhaps the lack of gains was because *Tools* seems to work better in kindergarten, as it may be too demanding for preschoolers. Both Preschool PATHS and *The Incredible Years* improved social-emotional outcomes at no cost to academic ones.

Goble et al. (2021) reanalyzed data from the Head Start CARES study. They found a significant main effect of implementation fidelity to *Tools* on EF gains. Teachers with more experience (i.e., >10 years) had attended more of the *Tools* trainings and showed better adherence to *Tools* than novice teachers. Goble et al. also found that teachers' educational backgrounds significantly moderated the relation between implementation quality and EF gains. *Tools* yielded greater benefits for teachers with child development training; Goble et al. speculated that perhaps that was because such training gave teachers a stronger understanding of children's development. This is consistent with the speculation that many Head Start teachers might not have the training or years of experience to adequately realize the gains possible from *Tools*.<sup>5</sup>

Melhuish (2006) and Melhuish & Petrogiannis (2006) looked at what makes the best early childhood education by getting data from every program in every country they could locate. They found that the variable that matters most is not the number of children, nor the adult-to-child ratio, nor the quality of the materials. Those matter, but they are not what matters most. What matters most is the relationship between the adults and the children. If the children felt cared about, the results were the best. Regardless of the program, a deeply caring relationship was essential for the best outcomes. Kiuru and colleagues (2015) also found that teachers' positive affect toward the students and peer acceptance in grades 1–3 predict better reading and math scores in grade 4. In her book, Noddings (2005) presents a strong argument for cultivating an environment of caring, rather than competition, in schools.

What nourishes the human spirit also appears to be best for EFs. Supporting the other aspects of an individual (emotional, social, spiritual, and physical) that support optimal EFs may be key to seeing EF benefits and/or seeing them last and thus key for school and job success (Diamond 2013). 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 friends, for fresh air and being in nature, and for generally nourishing their whole being, which is what we all need.

Programs nominally the same can obtain markedly different results because of how the programs were delivered. It could be that the critical difference between studies where greater or

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<sup>5</sup>Null results for *Tools* versus comparison conditions were reported at a Society for Research on Educational Effectiveness Conference in 2012 (Lonigan 2012, Wilson & Farran 2012). Lonigan (2012) reported no differential benefit to EFs comparing preschool *Tools* to his program (Literary Express™), but Lonigan's team never assessed EFs. I was supposed to do the EF assessments for that study, but in the end no EF assessments were able to be done.

Wilson & Farran (2012) reported null results from year 1 of their study of prekindergarten *Tools* in Tennessee and North Carolina. Nine years later their results were published in *SRCD Monographs* (Nesbitt & Farran 2021). The research design was absolutely outstanding, but some of their outcome measures were prone to ceiling and floor effects (e.g., most 5-year-olds pass the DCCS test), and the training provided to *Tools* teachers was not of the usual quality. Even so, one school district in the study was so impressed by the markedly better writing of *Tools* children that the district used its own funding to have all its teachers trained in *Tools* (assessment of writing had not been part of the research study). Other school districts that had been in the study did likewise because principals and kindergarten teachers felt they observed better social skills and readiness for learning in kindergarten children who had attended *Tools* prekindergartens versus children from other prekindergartens. (The research study had not evaluated children in kindergarten, only at the beginning and end of prekindergarten.)

fewer EF benefits were found has to do with variables that few studies have looked at, such as (a) whether those implementing the program want to be doing that and believe in the program (versus, for example, teachers being forced to deliver something they feel ill-prepared to implement); (b) other characteristics of those implementing the program (such as fidelity of implementation, being supportive and not punitive, and having unwavering faith in participants and the ability of the program to produce EF benefits); (c) whether the activity is personally meaningful and relevant to participants, inspiring a deep commitment and emotional investment in the activity and to one another (versus, for example, being randomly assigned to something they were not really interested in); (d) whether the group of participants develops significant camaraderie or not; and (e) whether the atmosphere created is one that fosters risking making a mistake or one where participants worry about being embarrassed (Diamond & Ling 2019). I have predicted that the way an activity is done will prove more decisive than what the activity is. It is critical to look at what actually happens in a program. I have hypothesized that what is needed is to engage people in activities they really care about, where improving EFs is needed for what they want to do, and where mentors and experiences inspire and instill self-confidence (Diamond & Ling 2019).

## 7.2. The Unique Sensitivity of PFC to Even Quite Mild Stress

Dopamine (DA) is a critically important neurotransmitter in PFC and other brain regions. One of the many ways in which the PFC DA system is unusual is that, compared with the DA systems in most other brain regions, PFC has a relative dearth of DA transporter (Durstun et al. 2005, Sesack et al. 1998). DA transporter is the best mechanism for clearing away excess DA (that is, the DA released by transmitting neurons that is not picked up by receiving neurons).

Having less DA transporter, PFC must rely on secondary mechanisms for clearing DA, in particular the catechol-*O*-methyltransferase (COMT) enzyme. The COMT enzyme accounts for over 60% of the DA clearance in PFC but less than 5% in other brain regions, such as the striatum (Karoum et al. 1994, Männistö & Kaakkola 1999). The gene that codes for the COMT enzyme is called the *COMT* gene. Thus, variations in the *COMT* gene affect PFC more than other brain regions. A single substitution of one amino acid (methionine or Met) for another amino acid (valine or Val) at codon 158 of the *COMT* gene results in a more sluggish COMT enzyme. Indeed, the COMT enzyme is about 30% less active in COMT-Met<sup>158</sup> homozygotes than in COMT-Val<sup>158</sup> homozygotes (Boudíková et al. 1990, Chen et al. 2004). The slower the COMT enzyme, the longer the temporal and spatial presence of DA at PFC synapses.

The Met polymorphism of the *COMT* gene is generally associated with better EF performance (e.g., Diamond et al. 2004, Egan et al. 2001, Malhotra et al. 2002) and more efficient prefrontal functioning (Egan et al. 2001, Winterer et al. 2006) at baseline. This effect is specific to EFs and PFC function. COMT-Met<sup>158</sup> has a downside, however. Persons homozygous for COMT-Met<sup>158</sup> tend to be more sensitive to stress, have higher anxiety, and show heightened pain stress responses (Diatchenko et al. 2005, Zubieta et al. 2003).

Too much DA in PFC is as detrimental to EFs as too little (Arnsten & Li 2005, Cools & D'Esposito 2011, Vijayraghavan et al. 2007). Even quite mild stress floods PFC with DA, impairing EF performance (Cerqueira et al. 2007, Roth et al. 1988). It can make it difficult to concentrate, learn anything new, or exercise discipline or self-restraint. This is a unique feature of PFC; mild stress does not raise DA levels elsewhere in the brain. Stress (such as that before a major exam) also disrupts the functional communication between PFC and other brain regions, impairing EFs (Liston et al. 2009). That communication is restored and EFs return to normal once the stress is over.

It has long been assumed that mild stress is beneficial for performance on challenging cognitive tasks (e.g., Middlebrooks & Audage 2008), portrayed by the classic Yerkes–Dodson curve (Yerkes

& Dodson 1908). That curve had never been tested in humans, however. Indeed, we found that for most people, the Yerkes–Dodson curve does not hold.

Many scholars predicted that, by raising PFC DA levels, mild stress should aid the EFs of persons with PFC DA levels lower than optimal at baseline, such as COMT-Val<sup>158</sup> homozygotes (COMT-Vals), bringing their PFC DA levels up closer to optimal, and that stress should impair the EFs of persons with PFC DA levels close to optimal at baseline, such as COMT-Mets<sup>158</sup> homozygotes (COMT-Mets), raising their PFC DA levels past optimal. Two teams tried to find this, but only found stress to impair the EFs of COMT-Mets, not to improve the EFs of COMT-Vals (Buckert et al. 2012, Qin et al. 2012). Using a far milder stressor, we succeeded in finding the double dissociation—COMT-Vals performed better when mildly stressed than when calmer, while those with at least one COMT-Met allele performed worse when mildly stressed (Zareyan et al. 2021).

Putting the results from all three studies together, it is clear that stress (even if mild) impairs the EFs of most people. No level of stress was good for the EFs of most people. Some people (COMT-Vals)<sup>6</sup> are better able to tolerate it, but they are not helped by it unless it is very mild. That is, stress and anxiety, even if quite mild, only help a minority and impair most people's EFs. Feeling stressed because you are worried about what others might think of you (social evaluative stress) or your performance (performance anxiety) is not beneficial for EFs. There is a difference between the excitement and exhilaration of a challenge and the anxiety of feeling stressed or fearing embarrassment. This has important implications for teaching students and supervising employees. Many workplaces and graduate programs intentionally impose stress, thinking it will improve performance. If a student or employee is stressed, however, that person's performance will likely suffer. Indeed, reducing stress in the classroom not only improves classroom climate but also has been shown to lead to better academic outcomes (Denham & Brown 2010, Diamond et al. 2019, Jennings & Greenberg 2009).

This does not mean that children should not be exposed to any stress. Children need to learn how to handle stress and to reduce how much they let it affect them. It does mean, however, that while they are feeling stressed, their EFs will probably not be at their best.

Most studies of the effect of COMT genotype included only or mostly males or did not investigate possible sex differences. We pioneered evidence that mild stress is more detrimental to the EFs of women when their estrogen levels are higher than it is for men or for women during the portion of the menstrual cycle when estrogen levels are lower (Zhang 2016). Estrogen down-regulates *COMT* gene transcription (Ho et al. 2008, Xie et al. 1999), resulting in a slower COMT enzyme (Chen et al. 2004), which leaves more DA in PFC. Since stress, even if mild, increases DA in PFC, the combination of more estrogen plus stress can push PFC DA levels past optimal, impairing EFs. Might we be missing giftedness in some girls and women because of the assumption that keeping students a little on edge is beneficial for all? Similarly, while the COMT-Met genotype is generally associated with better EFs in the absence of stress, during the portion of the menstrual cycle when estrogen levels are higher, women with the COMT-Val genotype have better EFs (Diamond 2011, Evans et al. 2009).

Our work on COMT also shows it is not sufficient to know a person's genotype or whether the person is stressed or not. It is the interaction of biology and environment that is determinative. The COMT-Met genotype is associated with better EFs when calmer and estrogen levels are lower; the COMT-Val genotype is associated with better EFs when stressed or estrogen levels are higher. Another example of this principle is that the version of the serotonin-regulatory

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<sup>6</sup>In our study, as in a prevalence study in India (Kumar et al. 2017), the incidence of homozygosity for COMT-Val was about 45%. An incidence study among Europeans found COMT-Val homozygosity in only 25% of the population (Palmatier et al. 1999).

gene (*SLC6A4*) associated with better EFs depends on an environmental factor (mother's mood) (Park et al. 2018, Weikum et al. 2013). Among children whose mothers exhibited some depressive affect during pregnancy, we found a child's EFs at age 6 were a function of the child's *SLC6A4* genotype plus the mother's mood. The EFs of children with at least one short allele of the gene stayed fine regardless of their mother's mood. For children with two long forms of the gene, however, if their mother was sadder, they showed worse EFs than anyone else; but if their mother was happier, they showed better EFs than anyone else.

Because stress selectively increases levels of the neurotransmitter DA in PFC, persons with optimal levels of DA in PFC at baseline can show poor EFs under stress. (Remember, PFC functions best and EF performance is best when PFC DA levels are at an intermediate level.) There are multiple implications of that. For example, someone who looks distracted, unable to think clearly or problem solve well because they are stressed, might be the one with the greatest potential to be a star if that stress can be lessened or removed. On the other hand, a person who looks great at baseline might actually not function as well as needed under real-life stressful circumstances, just when it is most important that a person be able to think clearly and quickly problem solve. In those situations, a student who did not impress you so much (e.g., a COMT-Val) might be the real hero. A genotype beneficial in one environment may not be beneficial in another.

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. Boyce & Ellis (2005) have talked about "orchid" and "dandelion" children. Dandelions are children who do OK wherever they are planted. They are often 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 & Beaver 2011, Weikum et al. 2013). Perhaps children homozygous for COMT-Val<sup>158</sup> are dandelions. Their fast-acting COMT enzyme quickly clears away released DA so they have a bit more room for stress to increase PFC DA levels without detrimental effects being seen. Perhaps children homozygous for COMT-Met<sup>158</sup> or for the long form of *SLC6A4* are orchids. Since COMT-Mets have higher PFC DA levels even when calm because of their sluggish COMT enzyme, stress can easily push their PFC DA levels past optimal. Thus, while they might look like a disaster in a stressful environment, they might blossom brilliantly in the right environment. The COMT-Met genotype, or homozygosity for the long form of *SLC6A4*, 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. 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.

Because stress negatively impacts the EFs of most people, programs and activities that reduce stress have been found to be particularly beneficial for EFs. In the most comprehensive review to date of all the different methods tried for improving EFs and at all ages, we (Diamond & Ling 2019) found that a relatively understudied approach, mindfulness practices involving movement (including tai chi, tae kwon do, and Chinese mind-body practices), showed by far the best results for improving EFs. These activities were far more effective at improving EFs than any other type of physical activity or computerized cognitive training. That is likely because of the role of mindful movement in reducing how stressed or anxious a person feels. Indeed, second in efficacy were (a) school programs that build community and reduce stress and (b) more sedentary mindfulness practices, which also reduce stress.

Colleagues and I investigated an elementary school program called MindUp (Schonert-Reichl et al. 2015), which emphasizes using mindfulness to reduce stress as well as caring for others (social responsibility). Classrooms of fourth and fifth graders were randomly assigned to MindUp or



the existing social-responsibility curriculum. Children who received training in mindfulness plus social responsibility (*a*) improved more in mindfulness, EFs, stress regulation, empathy, optimism, and emotion control; (*b*) tended to have better math grades and less school absenteeism; (*c*) showed greater decreases in depression and aggression; and (*d*) were rated by peers as more trustworthy, kind, and helpful than children who received only the regular social-responsibility curriculum (Schonert-Reichl et al. 2015).

In this section, I have discussed the implications of two unusual properties of the DA system in PFC. One unusual property is that even stress too mild to increase DA elsewhere in the brain increases DA specifically in PFC. That makes EF performance particularly vulnerable to the effects of stress. Another unusual property of the PFC DA system is that its relative lack of DA transporter (the best mechanism for clearing DA) makes PFC more dependent on a secondary mechanism for clearing DA (the COMT enzyme) than other brain regions. Hence, polymorphisms of the *COMT* gene disproportionately affect PFC and EFs, and which variant of the gene a person has affects how stress affects that person's EFs. In the **Supplemental Text**, I elaborate on these and other unusual properties of the prefrontal DA system and their implications: The relative lack of DA transporter means that the dosages of drugs that target DA transporters [as do psychostimulants, such as methylphenidate (Ritalin® or Biphentin®)] needed to address ADHD of the inattentive type are different from the dosages that best address ADHD that includes hyperactivity (Diamond 2005) (see the **Supplemental Text**). Another unusual property of PFC's DA system is its higher rate of firing and thus its higher rate of turning over DA, which makes PFC unusually sensitive to small decreases in the availability of tyrosine (the precursor of DA) that do not affect other brain regions. That is why children who are on a special diet for the genetic disorder phenylketonuria that is insufficiently strict have deficits specifically and exclusively in their EFs, which are prevented or reversed by going on a stricter diet (Diamond et al. 1997, Diamond 2001). The mechanism of how PFC's unusual sensitivity to small decreases in the availability of tyrosine leads to impaired EFs is discussed in the **Supplemental Text**. Finally, in the **Supplemental Text**, I point out something that I do not think many people realize, which is that while DA is a critically important neurotransmitter in PFC, not all EFs are sensitive to the level of DA in PFC.

## 8. CONCLUSIONS

Dorsolateral PFC is the kingpin of the brain network subserving EFs. The importance of this network, and specifically of dorsolateral PFC, for spanning spatial divides has been underappreciated. Focus has traditionally been on spanning temporal separations in working memory; it should be enlarged to also encompass spanning separations in space. The emphasis on working memory has unfortunately blinded many from seeing that if only working memory is required (especially if the amount of information to hold in mind is not excessive), dorsolateral PFC is not recruited; it is usually recruited only when *both* holding information in mind and inhibitory control are needed.

A recurrent theme in this article is that immature inhibitory control, often in combination with immature motor skills, has often prevented infants and young children from demonstrating their understanding of important concepts or their memory of what they have seen. We, developmental psychologists, have often erroneously concluded that infants or children did not understand something or did not yet have a cognitive competence because the ways we queried infants or children did not allow them to show us what they understood or remembered.

Infants and children are much smarter than most people used to think. For example, we have seen that even in the first year of life, infants are capable of impressive problem-solving, as with the awkward reach on the object retrieval task (see **Supplemental Figure 1**). When queried by where they look, infants can show they know where a toy has been hidden on B trials in the A-not-B paradigm, even though they reach back to the place where the toy used to be. We have seen

in Section 6 that if the items infants are meant to relate conceptually are presented as physically connected, infants of only 9–12 months appear to grasp their conceptual relation. People used to think that babies under 1 year were not capable of such complex thought. Other examples of fairly sophisticated reasoning and problem-solving by infants have since been elegantly demonstrated by others, including Holmboe et al. (2008), Gweon & Schulz (2011), and Téglás et al. (2011). Indeed, through many elegant experiments, Baillargeon and her students have demonstrated that infants less than 6 months old can reason about rather advanced physics concepts (e.g., Baillargeon et al. 1985, Luo & Baillargeon 2005a,b).

Abilities not thought to be present until later have been shown to be present far earlier just by modifying the tasks used to assess those abilities. Similarly, sometimes a child who cannot grasp something when it is taught one way can readily grasp it when it is presented a different way. Thus, educators should be wary about giving up on a child and should instead try different strategies and approaches so a child who is having difficulty can succeed.

Often we, developmental psychologists, have erroneously concluded that a cognitive competence was not yet present when the real problem was that the motor requirements of the task were the limiting factor (e.g., Diamond & Gilbert 1989, Diamond & Lee 2000, Diamond 1995). Altering the motor demands enables the cognitive competence to be revealed. For example, as we have seen in the second example in Section 4, infants of only 5 months know that an object placed on top of a slightly larger one is a separate object, and infants of 7 months know to reach through the open top of the object retrieval box when an object is placed inside, contiguous with the front wall of the box, but that they were unable to demonstrate this knowledge and understanding because their immature motor control and immature inhibition of reflexive reactions to touch prevented them from demonstrating this on the tasks we gave them.

Other times we, developmental psychologists, have erroneously assumed that a cognitive competence was not yet present because the way we presented the stimuli made it difficult for children to focus on only one attribute when they were supposed to ignore other properties of the stimulus, or we made it difficult for children to grasp that a conceptual connection existed between two attributes or stimuli because in the visual display they were separated.

More and more research is now focusing on how EF assessments need to be culturally appropriate so that children are not erroneously labeled as having EF deficits when the problem is instead that they did not understand what was being asked of them or that what was asked made no sense in their cultural context (Cho et al. 2023, Gaskins & Alcalá 2023, Jukes et al. 2024).

We also need to do a far better job of appreciating the centrality of social and emotional well-being for EFs and good cognitive performance. If a child is stressed in school or at home; feels socially insecure, misunderstood, or ostracized; or is hurting in some other way, that child's EFs and school work will suffer. Often, a cognitive competence is assumed to be deficient when the problem is really the person's emotional state. To fulfill their academic mission, schools need to care about the whole child. If school staff ignore that students are stressed, sad, lonely, or not physically fit, the very academic performance they are trying to improve will take a hit.

When a child seems not to be grasping something, we need to ask what role we (the experimenters or teachers) are playing in that and what we can do differently so the child can grasp that concept. If we start with the bedrock conviction that every child is capable of succeeding, then we can push ourselves to use the cognitive flexibility and creative problem-solving that EFs make possible to find a way for every child to succeed.

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## Supplemental Text

for

**Adele Diamond (2024). Insights from a Career at the Border of Developmental Science and Cognitive Neuroscience. *Annual Review of Developmental Psychology*, 7.**

## Table of Contents

### Supplementary Sections

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## Role of the Supplementary Motor Area (SMA) and callosal connections in the emergence of bimanual coordination in Infants

The emergence of such bimanual coordination (being able to do simultaneous, but different, movements of the two hands) is probably made possible, at least in part, by maturational developments in the SMA, pre-SMA, and in the callosal connections between the two SMAs and pre-SMAs in hemisphere's of the brain. See supplementary online material for a further discussion of this.

SMA is a brain region within frontal cortex, just posterior to dorsolateral prefrontal cortex (PFC). SMA and the pre-SMA occupy the anterior, medial portion of Brodmann's Area 6, the pre-SMA (Area 6ab) being immediately in front of SMA (Area 6aa); Kim et al., 2010; Nachev et al., 2007).

In adults results in lasting deficits when simultaneous, but different, movements of the two hands are required (Laplane, Talairach, Meininger, Bancaud, & Orgogozo, 1977; Luria, 1973). People either do the same thing with both hands or execute the movements sequentially - similar to the behavior of infants of 7½-10½ months. More recent neuroimaging ties doing different movements with the two hands simultaneously more to the pre-SMA than to the SMA proper (Obhi, Haggard, Taylor, & Pascual-Leone, 2002; Wilson, Kurz, & Arpin, 2014). Inhibitory projections via the corpus callosum are needed to stop one hand from doing the same thing as the other. That is, the default is for both hands to do the same thing; to resist that requires inhibition via the corpus callosum. For example, adults born without a corpus callosum have difficulty inhibiting one hand from doing what the other is doing (i.e., they have difficulty suppressing "associated movements;" Dennis, 1976; Takeuchi et al., 2012). The same is true of patients who undergo removal of the anterior corpus callosum (Preilowski, 1972). Thus improvements in the ability to inhibit one hand from doing what the other is doing probably is made possible in part by maturation of SMA, pre-SMA, and callosal connections between the two SMAs (Diamond, 1990; 1991). Of course, neither SMA, the pre-SMA, or the corpus callosum mature fully during infancy. Even preschoolers of 4 or 5 years find it difficult to avoid associated movements (called mirror movements or motor overflow). This is normal until children are almost 8 years old (Lazarus & Todor, 1987; Mayston, Harrison, & Stephens, 1999).

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### **Role of a border region partially overlapping lateral PFC and Area 6 for the ability to grasp a relation between physically separate things**

I have proposed that a border region partially overlapping lateral PFC and Area 6 (the periarculate area in the monkey brain) is critical for the ability to grasp that physically separate things are related (Diamond, 2006). Brass and colleagues (Amunts, 2004; Brass, Derrfuss, Forstmann, & von Cramon, 2005; Derrfuss, Brass, Neumann, & von Cramon, 2005) independently proposed a distinct functional and anatomical region (which they called “inferior frontal junction”) located within the area I have proposed that they argue is important for learning and using abstract rules.

A great deal of early research (e.g., Crowne, Dawson, & Richardson, 1989; Petrides, 1985, 1990) documented lesions of the border area in the periarculate, but not lesions limited to dorsolateral PFC or ventrolateral PFC proper, produce deficits in learning conditional associations (in the presence of one cue, Response X is correct but in the presence of another cue, Response Y is correct). Recently, Wallis and Miller (2003) found that more cells in this border area than in any other frontal region in the monkey encode the abstract delayed-nonmatching and delayed-matching-to-sample rules.

Like human infants, monkeys with lesions of ventrolateral PFC that extend into Area 6 have great difficulty deducing the nonmatching rule even with no delay, but once they have figured out the rule they perform well even at long delays (Bachevalier & Mishkin, 1986; Kowalska, Bachevalier, & Mishkin, 1991; Rushworth, Nixon, Eacott, & Passingham, 1997), just as human infants do (Diamond et al., 1994; Overman, 1990). As with human infants, their difficulty appears to be in acquiring the delayed non-matching to sample rule, not in remembering the sample over a delay. This pattern of performance is not seen in monkeys with other brain lesions, including lesions carefully restricted to only ventrolateral PFC. Consistent with this, neuroimaging studies in humans implicate this border area encompassing posterior ventrolateral PFC and dorsolateral PFC and anterior Area 6 (premotor cortex and pre-SMA) in delayed-nonmatching and delayed-matching-to-sample rule learning in adults (Bunge, Kahn, Wallis, Miller, & Wagner, 2003; Elliott & Dolan, 1999).

In a lovely series of experiments, Halsband and Passingham (1982, 1985) studied the ability of monkeys with lesions of this border area (lesions of premotor cortex extending into ventrolateral PFC) to learn a visual–motor conditional association: if blue cue, pull a handle; if red, turn the handle. If the cue was the color of the handle itself they succeeded. However, if the cue was the color of the panel in front of the handle (which the monkey had to displace to reach the handle) or the color of the panel behind the handle, monkeys with lesions in this border area failed. They failed even though they could make the requisite

movements and discriminate the color cues, and showed no strong preference for either movement. Whereas Halsband and Passingham focused on premotor cortex, Wang, Zhang, and Li (2000) have shown that disrupting neuronal activity in ventrolateral PFC severely impairs monkeys' ability to master a very similar task with the cue just above the handle. I would argue that the focus of both Halsband and Passingham and Wang et al. is partially correct, but that the crucial region is the transitional area that partially overlaps both premotor cortex in Area 6 and lateral PFC. I suggest this border area is crucial for rule learning (such as conditional associations) because it is necessary for something more elementary – perceiving conceptual connections in the absence of a physical connection.

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## **Other Unusual Properties of the Prefrontal Dopamine (DA) System that Contribute to PFC's Vulnerability to Environmental and Genetic Variations that Have Little Effect Elsewhere in the Brain**

### **A. Consequences of the Relative Dearth of Dopamine Transporter in PFC for Understanding Differences among Subtypes of Attention Deficit Hyperactivity Disorder (ADHD)**

PFC is most linked to the cognitive deficits in ADHD (such as inattention and poor working memory), whereas the striatum is most linked to behavioral deficits in ADHD (such as hyperactivity; Diamond, 2005). It follows that polymorphisms in the gene for dopamine transporter (the DAT1 gene) 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 dopamine transporter binding is related to motor hyperactivity but not to inattentive symptoms (Jucaite, Fernell, Halldin, Forssberg, & Farde, 2005).

This is consistent with findings concerning the effective doses of ADHD medications. Methylphenidate (MPH) is a psychostimulant widely used for treating ADHD. MPH works by "blocking reuptake," which means it works by locking onto dopamine transporter proteins, blocking them from taking up DA to clear it, thus bringing DA levels up closer to normal (Dresel et al., 2000; Volkow, Fowler, Wang, Ding, & Gatley, 2002; Volkow, Wang, Fowler, & Ding, 2005; Volkow et al., 2007). Consistent with MPH working on DAT, DAT being plentiful in the striatum, and lower DA in the striatum being linked to behavioral problems in ADHD like hyperactivity, most children with ADHD that includes hyperactivity respond positively to MPH in moderate to high doses (Barkley, 2001; Barkley, DuPaul, & McMurray, 1991; Milich, Balentine, & Lynam, 2001). On the other hand, a significant percentage of children with the inattentive subtype of ADHD are not helped by MPH or are helped at low doses. At low doses, MPH preferentially increases DA neurotransmission in PFC (Berridge et al., 2006).

In 2005, 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; the number of websites devoted to ADHD-inattentive sky-rocketed from four to thousands. The Founder and Head of the Dutch ADD Association, 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" (Windt Van Der Berg, 2009).

**B. Consequences of the higher rate of DA turnover in PFC for understanding why dietary treatment for phenylketonuria (PKU), if insufficiently rigorous, results in deficits in, and only in, Executive Functions (EFs)**

Another unusual property of the PFC DA system is that DA neurons in PFC have a higher baseline rate of firing and a higher rate of DA turnover than other brain regions (Bannon, Bunney, & Roth, 1981; Tam, Elsworth, Bradberry, & Roth, 1990; Thierry et al., 1977). This makes the PFC DA system uniquely sensitive to small changes in the availability of the precursor of DA, tyrosine (Tyr; Bradberry et al., 1989). Other brain regions, such as the striatum, are unaffected by small changes in the amount of available Tyr.

In the genetic disorder called phenylketonuria (PKU), the body is unable to break down the amino acid, phenylalanine (Phe), into Tyr (Woo et al., 1983). Tyr is still available directly through diet, but the important indirect route to Tyr is not functional, and the elevated levels of Phe out-compete Tyr for entry from the bloodstream into the brain (Pardridge & Oldendorf, 1977). If PKU is treated by reducing the intake of Phe in foods, the result is a reduction in the amount of Tyr reaching the brain too small to affect brain regions other than PFC. At Phe levels previously thought medically safe, we found that DA levels were lower in PFC (though not elsewhere in the brain; Diamond et al., 1994) and EF deficits were evident, while other cognitive functions were unaffected. The EF deficits were directly, inversely related to Phe level (the higher the levels of Phe in a child's bloodstream, the worse that child's EF performance; Diamond, Prevor, Callender, & Druin, 1997).

Parents and clinicians had been reporting for decades that children supposedly well-treated for PKU had EF deficits, but no one could imagine a mechanism by which a global insult to the entire brain (less Tyr crossing the blood-brain barrier) would have an effect specifically and exclusively in PFC, so the larger medical and research communities dismissed those reports. We changed things by hypothesizing, and then scientifically demonstrating, the mechanism whereby this could happen and providing detailed empirical evidence that EFs were indeed impaired (Diamond, 2001). We showed that when Phe levels were kept lower, the EF deficits were absent. Almost overnight guidelines around the world for the treatment of PKU changed to lower Phe intake (American Psychological Association, 2003).

The most wonderful part of this story is that not only could EF deficits in children with PKU now be completely prevented, but subsequent research has shown that EF deficits, even in adults with PKU, can be reversed, at least in part, by a stricter dietary regimen that brings Phe levels down further (Koch et al., 1999; Schmidt et al., 1994).

One hears a lot about how biology and biochemistry affect behavior and cognition. 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 intellectual disability by keeping blood Phe levels < 600  $\mu\text{mol/L}$ . By keeping infants and young children on an even stricter dietary regimen that keeps average Phe levels at 120-360  $\mu\text{mol/L}$ , parents of a child with PKU can prevent EF deficits altogether. If Phe levels are too high early, or become too high later, adopting a strict dietary regimen can erase much of the cognitive impairment.

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### **Although DA is a critically important neurotransmitter in PFC, not all cognitive functions dependent on PFC are sensitive to the level of DA in PFC**

When we tested children with PKU, I had predicted we would find deficits on all cognitive tasks linked to PFC in children whose Phe levels were not sufficiently low. We found that for six tasks dependent on PFC (like the a-not-b, object retrieval, and day-night tasks), but we found no relation between Phe level and performance on another task dependent on PFC – self-ordered pointing (Diamond et al., 1997). I would have loved to have been able to say that self-ordered pointing does not really depend on PFC, or the same region of PFC, as the other tasks, but that is not what the data showed. Self-ordered pointing has been shown to depend specifically on dorsolateral PFC by lesion studies in monkeys (Petrides, 1995), studies of human adults with naturally occurring brain damage (Petrides & Milner, 1982; Wiegersma, Van der Scheer, & Hijman, 1990), and neuroimaging studies in intact human adults (Petrides, Alivisatos, Meyer, & Evans, 1993)

I had no idea why we had not found an effect on self-ordered pointing until a study from Robbins' lab appeared (Collins, Roberts, Dias, Everitt, & Robbins, 1998). They showed that while lesions of PFC impair self-ordered pointing, depleting PFC of DA did not impair self-ordered pointing. Remember that the mechanism we hypothesized for why EF deficits would be found in children treated for PKU with a slightly too lenient diet is that slightly too high levels of Phe block some of the Tyr from reaching the brain, causing reduced DA levels in PFC. We knew that reduced DA in PFC impairs tasks like a-not-b and delayed response (Brozoski, Brown, Rosvold, & Goldman, 1979) and we, along with everyone else, assumed that if a cognitive task depended on PFC then changes in the level of DA in PFC would affect performance on that task. Collins and colleagues taught us that that is not necessarily the case. That was a sea change. No one had considered that possibility before.

To further test that, we tested children on self-ordered pointing, the hearts and flowers task (which should be sensitive to the level of DA in PFC), a task dependent on parietal cortex, and a task dependent on the medial temporal lobe, and analyzed which variant of the COMT gene each child had (Diamond et al., 2004). Consistent with the findings of Collins et al. (1998) and our own PKU findings (Diamond et al., 1997), we found that performance on the hearts and flowers task was better in persons homozygous for COMT-Met<sup>158</sup>, but that performance on the three other tasks (including self-ordered pointing) was insensitive to COMT genotype, i.e., insensitive to the level of DA in PFC. The differential sensitivity of distinct cognitive abilities to specific neurotransmitters opens up possibilities for targeted pharmacological interventions.

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