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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.*

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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 <u>different</u> 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 periarcuate 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, Derfuss, Forstmann, & von Cramon, 2005; Derfuss, 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 periarcuate, 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 µmol/L. By keeping infants and young children on an even stricter dietary regimen that keeps average Phe levels at 120-360 µmol/L, parents of a child with PKU can prevent 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^{158}, 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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