Brain Development and Cognition: A Reader, Second Edition
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A Model System for Studying the Role of Dopamine in Prefrontal Cortex During Early Development in Humans

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Dorsolateral prefrontal cortex (DL-PFC) undergoes an extremely protracted period of maturation and is not fully mature until adulthood (Yakovlev and Lecours, 1967; Huttenlocher, 1979, 1984, 1990; Orzhekhovskaya, 1981; Huttenlocher et al., 1982; Thatcher et al., 1987; Rosenberg and Lewis, 1994; Sowell et al., 1999). Growing evidence indicates, however, that some of the cognitive advances seen as early as the first year of life (6–12 months) are made possible, in part, by early changes in DL-PFC (e.g., Fox and Bell, 1990; Diamond, 1991a, b; Bell and Fox, 1992, 1997). One maturational change in DL-PFC that might help make possible these early cognitive advances is increasing levels of the neurotransmitter, dopamine, in DL-PFC.

Prefrontal cortex is richer in dopamine than any other region of the cerebral cortex (e.g., Bjorklund et al., 1978; Brown et al., 1979; Levitt et al., 1984; Lewis et al., 1988; Gaspar et al., 1989; Williams and Goldman-Rakic, 1993, 1995; Lewis et al., 1998). Not surprisingly, given its high concentration in prefrontal cortex, dopamine plays an important role in DL-PFC function in adult human and non-human primates (e.g., Brozoski et al., 1979; Sawaguchi et al., 1988; Sawaguchi and Goldman-Rakic, 1991; Luciana et al., 1992; Watanabe et al., 1997; Akil et al., 1999).

We know that during the period that infant rhesus macaques are improving on tasks dependent on DL-PFC (the A-not-B, delayed response, and object retrieval tasks) the level of dopamine is increasing in their brain (Brown et al., 1976; Brown and Goldman, 1977), the density of dopamine receptors in their prefrontal cortex is increasing (Lidow and Rakic, 1992), and the distribution within their DL-PFC (Brodmann's area 9) of axons containing the rate-limiting enzyme for the production of dopamine (tyrosine hydroxylase) is markedly changing (Lewis and Harris, 1991; Rosenberg and Lewis, 1995). Moreover, in adult rhesus macaques, the cognitive abilities that depend on DL-PFC (as indexed by tasks such as delayed response) rely critically on the dopaminergic projection to prefrontal cortex (e.g., Brozoski et al., 1979; Sawaguchi et al., 1990; Taylor et al., 1990; Taylor et al., 1990; Sawaguchi and Goldman-Rakic, 1991).

Evidence such as that summarized here makes it plausible that one change in the prefrontal neural circuit helping to make possible some of the cognitive advances that occur in infants between 6–12 months of age might be changes in the dopaminergic

innervation of prefrontal cortex. Maturational changes in the prefrontal dopamine system are protracted, and therefore it is conceivable that later maturational changes in that system might help make possible subsequent improvements in the cognitive abilities dependent on prefrontal cortex as well. (To propose that changes in the dopamine innervation of prefrontal cortex play a role in making possible some of the cognitive advances during development is not to negate the role of experience nor the role of other maturational changes in the prefrontal neural system, such as in the communication between prefrontal cortex and other neural regions.)

To begin to look at the role of the dopamine projection to DL-PFC in helping to subserve cognitive functions early in life in humans, we have been studying children who, the evidence suggests, have reduced levels of dopamine in prefrontal cortex but otherwise remarkably normal brains. These are children treated early and continuously for a genetic disorder called "phenylketonuria" (PKU), who have levels of an amino acid (phenylalanine [Phe]) in their bloodstream that are 3–5 times normal (6–10 mg/dl).

Where is DL-PFC?

The cerebral cortex is distinguished from subcortex by generally having six different layers of cells (subcortical regions have fewer layers) and by being the outer mantle of the brain (closer to the surface), whereas subcortical structures are buried deep inside the brain below the cortex. In general, cortical regions are phylogenetically newer regions of the brain than subcortical regions, mature later during development, and receive more highly processed information that has already passed through subcortical structures. During primate evolution, the cerebral cortex changed from being smooth to having marked "hills" (called "gyri") and "valleys" (called "sulci"). This infolding made possible the extraordinary expansion in size of the cerebral cortex within a cranium that expanded much less markedly in size. This was a very adaptive solution to getting much more surface area into a limited space.

The central sulcus divides the front of the brain from the back. All of the cerebral cortex in front of the central sulcus is frontal cortex (see figure 22.1). The most posterior region of frontal cortex, directly in front of the central sulcus, is primary motor cortex (Brodmann's area 4). The anterior boundary of motor cortex is the precentral sulcus. In front of that is premotor cortex and the supplementary motor area (SMA), two distinct subregions of Broadmann's area 6. All of the cortex in front of that is prefrontal cortex (areas 8, 9, 10, 12, 44, 45, 46, 47, and 9/46). Prefrontal cortex is not only the most anterior region of frontal cortex, but the only region of frontal cortex with a granule cell layer.

While the brain as a whole has increased in size during evolution, the proportion of the brain devoted to prefrontal cortex has increased much more dramatically, especially in humans (Brodmann, 1912). For example, prefrontal cortex makes up 25 percent of the cortex in the human brain, but only 15 percent in chimpanzees, 7 percent in dogs, and 4 percent in cats. Prefrontal cortex is an association area; its functions are primarily integrative, neither exclusively sensory nor motor. In accord with its late maturational timetable and massive expansion during primate evolution, prefrontal cortex is credited with underlying the most sophisticated cognitive abilities, often called "executive processes," such as reasoning, planning, problem-solving, and coordinating the performance of multiple tasks (e.g., Warren and Akert, 1964; Goldman-Rakic, 1987; Shallice, 1988; Pennington and Ozonoff, 1996; Postle et al., 1999).

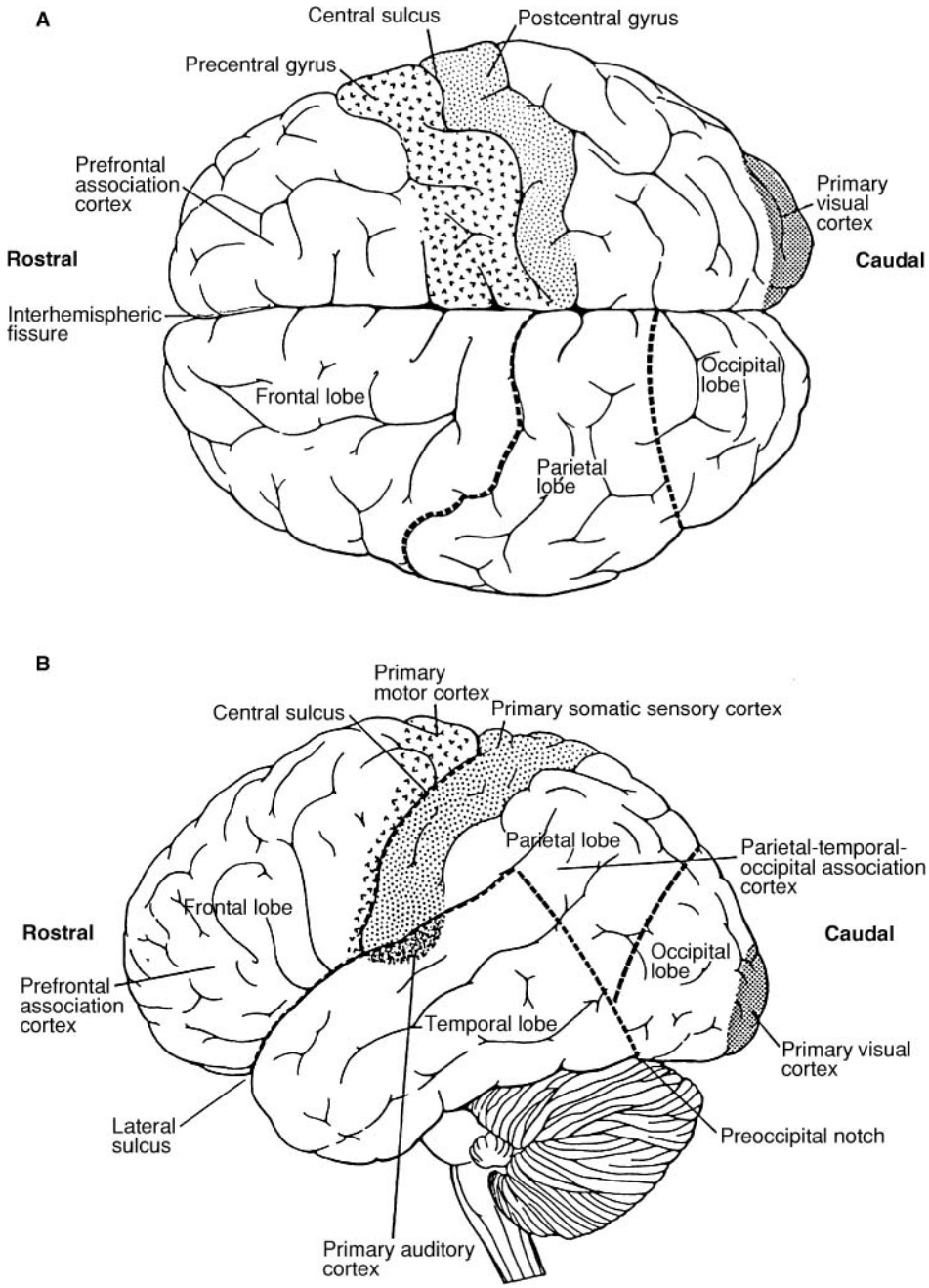


Figure 22.1 Diagram of the human brain, indicating the location of dorsolateral prefrontal cortex.

Within prefrontal cortex, the mid-dorsolateral subregion (areas 9, 46, and 9/46) has increased disproportionately in size during evolution even compared to the other regions of prefrontal cortex. Mid-DL-PFC consists of the middle section of the superior and middle frontal gyri, extending from behind the frontal pole (area 10) to area 8 (see figure 22.1; Petrides and Pandya, 1999). DL-PFC has historically been defined by its reciprocal connections with the parvocellular subdivision of the mediodorsal nucleus of the thalamus (Walker, 1940; Rose and Woolsey, 1948; McLardy, 1950; Akert, 1964; Kievit and Kuypers, 1977; Tobias, 1975; Jacobson et al., 1978; Goldman-Rakic and Porrino, 1985; Siwek and Pandya, 1991). The size of the parvocellular portion of the mediodorsal nucleus has increased phylogenetically in proportion to the increase in size of DL-PFC and disproportionately compared even to other regions of the mediodorsal nucleus (Pines, 1927; Clark, 1930; Khokhryakova, 1979).

No area of the brain acts in isolation. A neural region functions as part of a system of functionally and anatomically interrelated structures. Through its reciprocal connections with the *superior temporal cortex* (Petrides and Pandya, 1988; Seltzer and Pandya, 1989), *posterior parietal cortex* (area 7a; Goldman-Rakic and Schwartz, 1982; Schwartz and Goldman-Rakic, 1984; Petrides and Pandya, 1984; Selemon and Goldman-Rakic, 1988; Cavada and Goldman-Rakic, 1989; Johnson et al., 1989), *anterior and posterior cingulate* (Vogt et al., 1987), premotor cortex (Künzle, 1978; Barbas and Mesulam, 1985, 1987), SMA (Wiesendanger, 1981; McGuire et al., 1991), *retrosplenial cortex* (Morris et al., 1999; Morris et al., 1999; see also Petrides and Pandya, 1999, concerning all of these interconnections), and the *neocerebellum* (Sasaki et al., 1979; Leiner et al., 1989; Yamamoto et al., 1992; Middleton and Strick, 1994; Middleton and Strick, 1997; Schmahmann and Pandya, 1995; Diamond, 2000), mid-DL-PFC can modulate the activity of those regions, as well as receive information from, and be modulated by, these regions. In addition, mid-DL-PFC sends a strong projection to the caudate nucleus (Kemp and Powell, 1970; Goldman and Nauta, 1977; Selemon and Goldman-Rakic, 1985; Arikuni and Kubota, 1986). The projections from DL-PFC, posterior parietal cortex, and the superior temporal cortex are intricately interdigitated throughout the brain, including in the caudate nucleus, providing multiple opportunities for these neural regions to communicate with, and influence, one another (Goldman-Rakic and Schwartz, 1982; Schwartz and Goldman-Rakic, 1984; Selemon and Goldman-Rakic, 1985, 1988; Johnson et al., 1989).

Evidence that DL-PFC subserves Cognitive Abilities even during Infancy

The "A-not-B" task has been used in scores of laboratories throughout the world to study cognitive development in infants since it was first introduced by Piaget (1954 [1936]). Under the name "delayed response," an almost-identical task has been the classic paradigm for studying the functions of DL-PFC in macaques since it was first introduced for that purpose by Jacobsen (1935, 1936). In the A-not-B/delayed response task, the participant watches as a desired object is hidden in one of two hiding places that differ only in their left–right location, and then a few seconds later is allowed to reach to find that object. The participant must hold in mind over those few seconds where the object was hidden. Over trials, the participant must update his or her mental record to reflect where the reward was hidden last. When the participant reaches correctly, he or she is rewarded by being allowed

to retrieve the desired object. In this manner, the behavior of reaching to that hiding location is reinforced and hence the tendency to emit that response is strengthened. When the reward is then hidden at the other location, the participant must inhibit the natural tendency to repeat the rewarded response and instead respond according to the representation held in mind of where the reward was just hidden. Thus, the A-not-B task requires holding information in mind (where the reward was last hidden) and inhibition of a prepotent response tendency. By roughly $7\frac{1}{2}-8$ months of age, infants reach correctly to the first hiding location with delays as long as 3 sec. When the reward is then hidden at the other hiding place, however, infants err by going back to the first location (called the "A-not-B error"). As infants get older, they are able to succeed at longer and longer delays. Thus, for example, one sees the A-not-B error (correct at the first location, but incorrectly repeating that response on the reversal trials) at delays of 5 sec in infants of 9 months and at delays of 7–8 sec in infants of 10 months (Diamond, 1985; Diamond and Doar, 1989).

In the object retrieval task (Diamond, 1981, 1988, 1990a), nothing is hidden and there is no delay. A toy is placed within easy reach in a small, clear box, open on one side. Difficulties arise when the infant sees the toy through one of the closed sides of the box. Here, the infant must integrate seeing the toy through one side of the box with reaching through a different side. There is a strong pull to try to reach straight for the toy; that prepotent response must be inhibited when a detour reach is required. The following variables are manipulated: (a) which side of the box is open (top, front, left, or right), (b) distance of the toy from the box opening, (c) position of the box on the testing surface (e.g., near the front edge of table or far), (d) box size, and (e) box transparency. The experimental variables jointly determine through which side of the box the toy is seen. Initially, infants reach only at the side through which they are looking. They must look through the opening, and continue to do so to reach in and retrieve the toy. As they get older, the memory of having looked through the opening is enough; infants can look through the opening, sit up, and reach in while looking through a closed side. Still older infants do not need to look along the line of reach at all. Infants progress through a well-demarcated series of 5 stages of performance on this task between 6 and 12 months of age (e.g., Diamond, 1981, 1988, 1990a).

Although the A-not-B/delayed response task and the object retrieval task appear to share few surface similarities, human infants improve on these tasks during the same age period (6–12 months; Diamond, 1988, 1991a, b) and so do infant rhesus macaque ($1\frac{1}{2}$–4 months; Diamond and Goldman-Rakic, 1986; Diamond, 1988, 1991a, b). Indeed, although there is considerable individual variation in the rate at which different infants improve on any of these tasks, the age at which a given infant reaches "Phase 1B" on the object retrieval task is remarkably close to the age at which that same infant can first uncover a hidden object in the A-not-B/delayed response paradigm (Diamond, 1991a, b). Developmental improvements on both in human infants are related to the same changes in the EEG pattern over frontal leads and in frontal-parietal EEG coherence (*re: A-not-B*: Fox and Bell, 1990; Bell and Fox, 1992, 1997; *re: object retrieval*: Fox, personal communication) Both the A-not-B/delayed response task and the object retrieval task depend on DL-PFC and are sensitive to the level of dopamine there.

There is no behavioral task more firmly linked to DL-PFC than the A-not-B/delayed response task. Lesions that destroy DL-PFC disrupt performance of A-not-B and delayed response in adult macaques (e.g., Butters et al., 1969; Goldman and Rosvold, 1970; Diamond and Goldman-Rakic, 1989) and infant macaques (Goldman et al., 1970; Diamond

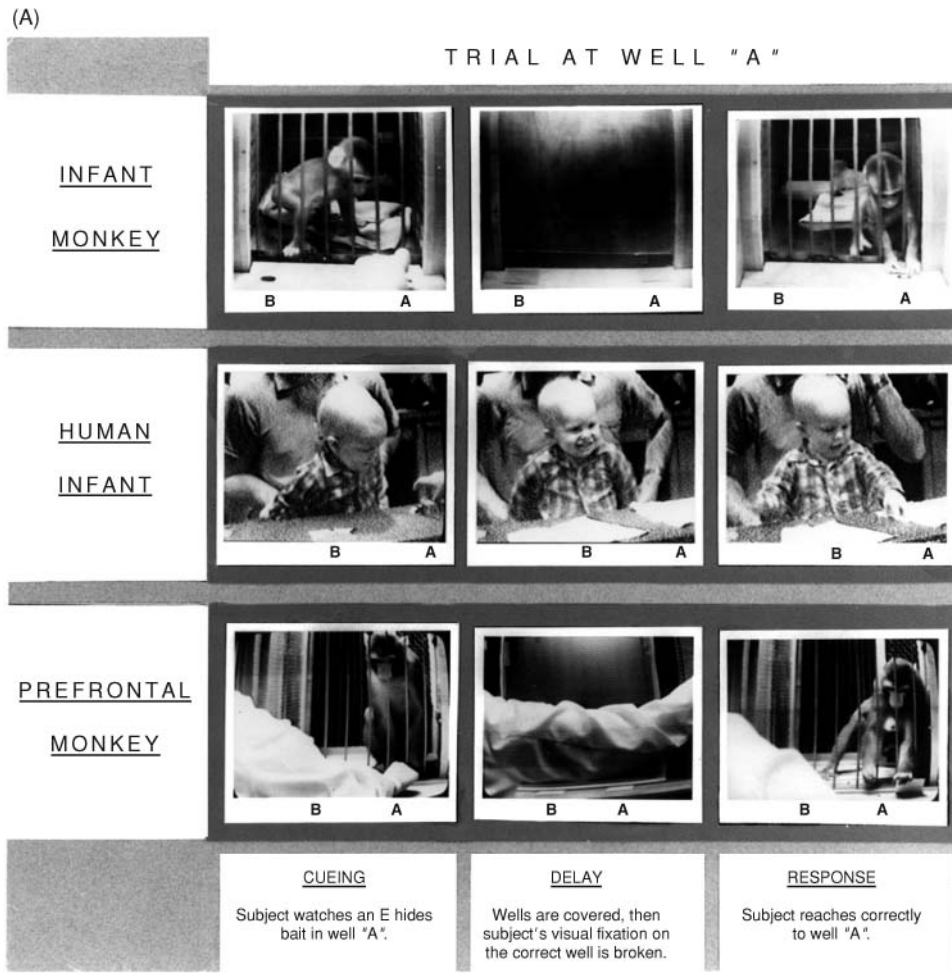
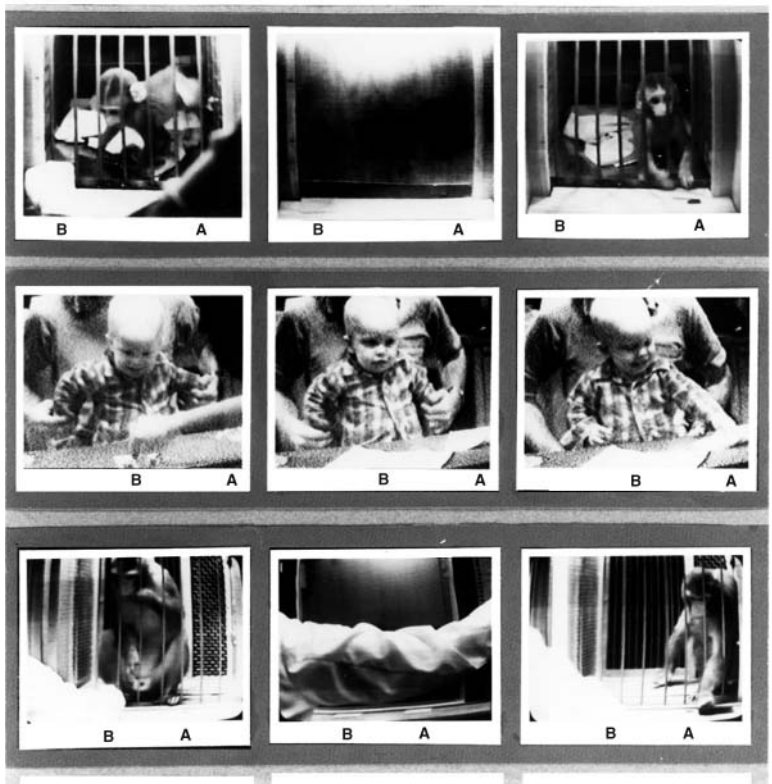


Figure 22.2 Illustration of a $1\frac{1}{2}$-month-old infant rhesus macaque, 8-month-old human infant, and an adult rhesus macaque in whom dorsolateral prefrontal cortex had been removed bilaterally performing the A-not-B/delayed response task. All are correct at the first hiding place (A). After 2 trials, there is a switch and the reward is hidden at the second hiding place (B). Although they all watch the hiding at B, and although the delay at B is no longer than at A, they all err by reaching back to A. This error is called the "A-not-B error" because they are correct on the A trials, but not on the B trials; they reach to A, not B.

(B)

TRIAL AT WELL "B"



CUEING

Subject watches an E hides bait in well "B".

DELAY

Wells are covered, then subject's visual fixation on the correct well is broken.

RESPONSE

Subject reaches incorrectly to "A," which is now empty.

and Goldman-Rakic, 1986; Diamond, 1990b), while performance of other tasks such as delayed nonmatching to sample (Bachevalier and Mishkin, 1986) and visual discrimination (Goldman et al., 1970) is unimpaired. Lesions of other brain regions do not affect A-not-B or delayed response performance at the same brief delays (e.g., medial temporal lobe [Diamond et al., 1989]; posterior parietal cortex [Harlow et al., 1952; Diamond and Goldman-Rakic, 1989; Bauer and Fuster, 1976]). Successful delayed response performance has been linked to dorsolateral PFC by techniques as varied as *reversible cooling* (where function is only temporarily disrupted, and an animal can serve as his own control; e.g., Fuster and Alexander, 1970; Bauer and Fuster, 1976), *single unit recording* (where the functions of individual neurons are studied in the intact brain; e.g., Niki, 1974; Fuster and Alexander, 1971; Fuster, 1973), and *2-deoxyglucose metabolic labeling* (where the functions of diverse neural regions are studied in the intact brain; Bugbee and Goldman-Rakic, 1981). Blocking dopamine receptors in DL-PFC produces deficits on the delayed response task as severe as when DL-PFC is removed altogether (Brozoski et al., 1979). Indeed, there is a precise dose-dependent relation between how large a dose of the dopamine antagonist is injected and performance on the delayed response task (Sawaguchi and Goldman-Rakic, 1991). Disruption of the prefrontal dopamine system by injections of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropy-ridine) also impairs performance on the task (Schneider and Kovelowski, 1990). Destruction of the dopamine neurons in the ventral tegmental area (VTA) that project to prefrontal cortex impairs performance on the task as well (Simon et al., 1980). Pharmacological activation of D2 dopamine receptors in normal human adults has been found to facilitate performance on the task (Luciana et al., 1992).

DL-PFC lesions in the macaque also disrupt performance on the object retrieval task (Diamond and Goldman-Rakic, 1985; Diamond, 1990b), while lesions of the medial temporal lobe (Diamond et al., 1989) or of posterior parietal cortex (Diamond and Goldman-Rakic, 1989) do not. MPTP injections, which reduce the level of dopamine in prefrontal cortex, also produce deficits on the task (e.g., Saint-Cyr et al., 1988; Taylor et al., 1990a, b; Schneider and Roeltgen, 1993). (MPTP also affects the level of dopamine in the striatum, but lesions of the striatum do not impair performance on the object retrieval task [Crofts et al., 1999].) Cumulative doses of 15–75 mg of MPTP do not produce Parkinsonian-type motor deficits in rhesus macaques, although larger doses do. At the lower doses of MPTP [15–75 mg], monkeys are impaired on the object retrieval and A-not-B/delayed response tasks [e.g., Schneider and Kovelowski, 1990; Taylor et al., 1990], although they perform normally on other tasks such as visual discrimination.)

Importantly, human infants, infant rhesus macaques, and infant and adult rhesus macaques with lesions of DL-PFC fail the A-not-B/delayed response task under the same conditions and in the same ways. The same is true for the object retrieval task. Thus, for example, on A-not-B: macaques with lesions of DL-PFC and human infants of $7\frac{1}{2}-9$ months succeed when there is no delay (*macaques*: Harlow et al., 1952; Bättig et al., 1960; Goldman et al., 1970; *infants*: Harris, 1973; Gratch et al., 1974), succeed when allowed to circumvent the memory requirements by continuing to stare at or strain toward the correct well during the delay (*macaques*: Bättig et al., 1960; Miles and Blomquist, 1960; Pinsker and French, 1967; *infants*: Cornell, 1979; Fox et al., 1979), succeed if a landmark reliably indicates where the reward is located (*macaques*: Pohl, 1973; *infants*: Butterworth et al., 1982), fail even at brief delays of only 2–5 sec (*macaques*: Goldman and Rosvold, 1970; Diamond and Goldman-Rakic, 1989; *infants*: Gratch and Landers, 1971; Fox et al., 1979; Diamond, 1985; Diamond and Doar, 1989) and fail if the hiding places differ either in left–

right or up–down location (*macaques*: Goldman et al., 1970; Fuster, 1980; *infants*: Gratch and Landers, 1971; Butterworth, 1976). See figure 22.2.

Similar close parallels in the parameters determining success or failure, and in the characteristics of performance, hold for the object retrieval task (*infants*: Diamond, 1981; 1990b, 1991a; *macaques with lesions of DL-PFC*: Diamond and Goldman-Rakic, 1985; Diamond, 1990b; 1991a; *MPTP-treated macaques*: Saint-Cyr et al., 1988; Taylor et al., 1990a, b; Schneider and Roeltgen, 1993). Human infants of $7\frac{1}{2}-9$ months, rhesus macaques with lesions of DL-PFC, and macaques treated with MPTP all succeed on the object retrieval task when they are looking through the open side of the box. They fail when they are looking through a closed side, and they fail by trying to reach straight through the transparent barrier instead of detouring around it. Human infants of $7\frac{1}{2}-9$ months, rhesus macaques with lesions of DL-PFC, and macaques treated with MPTP perform better when the box is opaque than when the box is transparent. They lean over to look in the box opening when the left or right side of the box is open and recruit the contralateral hand to reach in the opening (see figure 22.3), and show that "awkward reach" on both the left and right sides of the box.

The Cognitive Abilities Subserved by DL-PFC and Required for Success on the A-not-B and Object Retrieval Tasks

Note that many of the manipulations discussed above for the A-not-B task indicate that the presence of the delay is critical, since even very young infants and prefrontally-lesioned macaques perform well when there is no delay or when the requirements of the delay can be circumvented. This suggests that the ability to hold in mind the information on where the reward was last hidden (this might be termed "sustained attention" or the information-maintenance component of "working memory" [Baddeley, 1992]) is critical to success on this task. The information that must be held in mind is relational (Was the reward hidden on the right or the left most recently? "Left" is only left in relation to right and, similarly, "recent" implies a before and after relation.) There is also a characteristic pattern to the errors made by infants and by prefrontally-lesioned macaques on the A-not-B task: Their errors tend to be confined to the reversal trials and to the trials immediately following a reversal error when the reward continues to be hidden at the new location (Diamond, 1985, 1990a, 1991a, b). If the only source of error on the task were failure to keep the critical information in mind, then one would expect errors to be random, but they are not (Diamond et al., 1994a). The non-random pattern of errors, and the fact that participants occasionally look at the correct location (as if they remember that the reward is there) while at the same time reaching back to the previously correct location (Diamond, 1990a, 1991a; see also Hofstadter and Reznick, 1996) suggests that success on the task also requires resisting, or inhibiting, the tendency to repeat the previous response. (I have suggested that there is a predisposition to repeat the previous response because it had been rewarded. Smith et al. (1999) suggest that there is a predisposition to repeat the previous response simply because the response was made before [not because of reinforcement], just as it is easier for neurons in visual cortex to process a visual stimulus if they have previously processed that visual stimulus. Either account of the source of the predisposition works equally well for my theoretical position. The important point is that there is a tendency to repeat the previous response; the source of that predisposition is unimportant for my argument.)

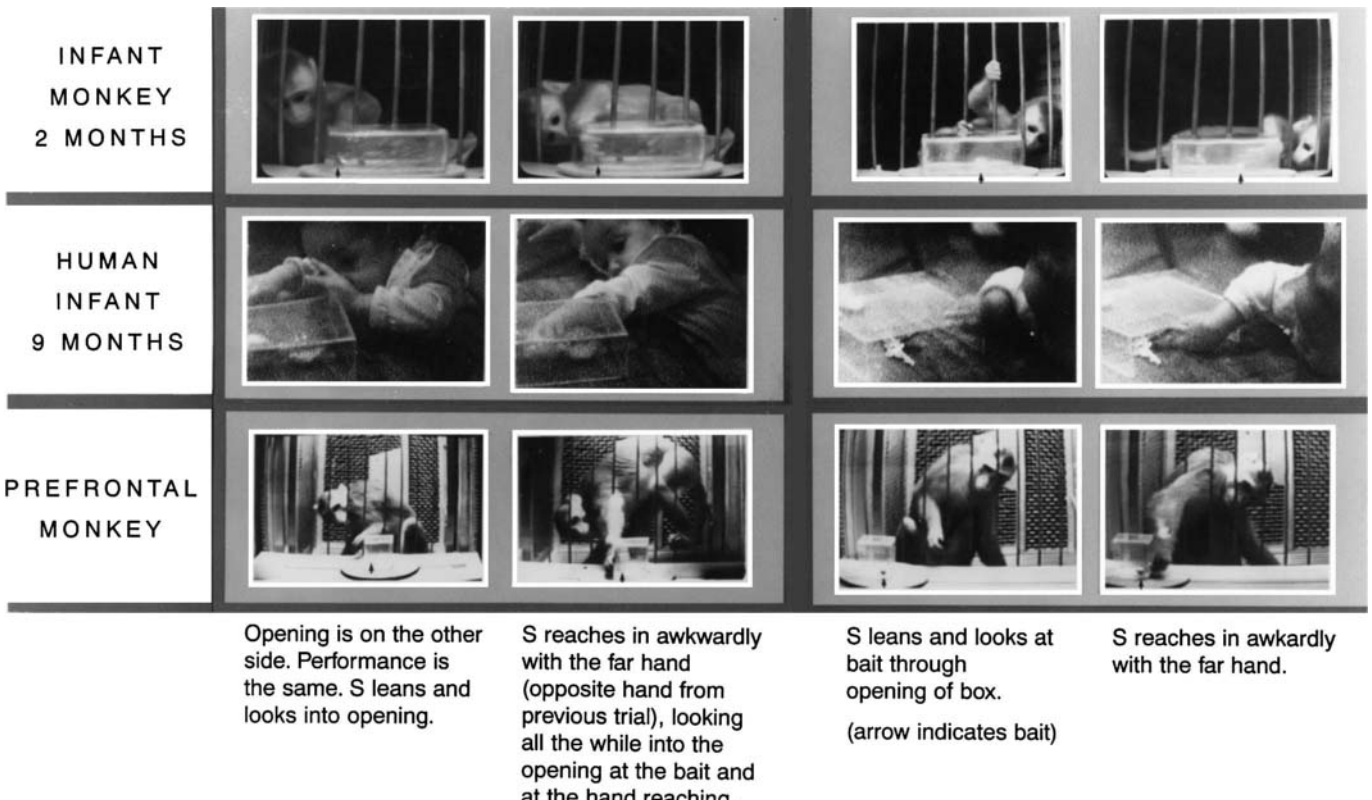


Figure 22.3 Illustration of a 2-month-old infant rhesus macaque, 9-month-old human infant, and an adult rhesus macaque in whom dorsolateral prefrontal cortex had been removed bilaterally performing the object retrieval task. They lean and look in the side opening of the transparent box, and then while continuing to look through the opening, recruit the contralateral hand to reach in and retrieve the reward. This is seen on both sides of the box and does not reflect a hand preference. Because of its appearance, the recruitment of the contralateral arm is dubbed the "awkward reach."

A few errors can be elicited simply by taxing how long information must be held in mind even when no inhibition is required, such as by using a long delay at the first hiding location (e.g., Sophian and Wellman, 1983). Similarly, a few errors can be elicited simply by taxing inhibitory control even when the participant does not have to remember where the reward was hidden; for example, a few infants err on the reversal trial even when the covers are transparent (e.g., Butterworth, 1977; Willatts, 1985). However, the overwhelming majority of errors occur when participants must both hold information in mind and also exercise inhibitory control (i.e., on reversal trials when the covers are opaque and a delay is imposed).

A fragile memory of where the reward was hidden would be sufficient on the initial trials at A because there is no competition. However, when the side of hiding is reversed, the fragile memory of where the reward was hidden now has to compete with the conditioned tendency to repeat the rewarded response of reaching to A, and so sometimes that fragile memory is not sufficient to win the battle. At the core of my hypothesis about the cause of the A-not-B error has always been the notion of a competition or battle between the information held in mind (i.e., where the toy was last hidden) and the prepotent tendency (a type of procedural or implicit memory) formed by the experience of previous trials. The key element is conflict: What is required is not simply holding in mind the newest information, but that stored information has to win against a competitor (a conditioned tendency), which is probably subcortical in origin, since even extremely simple organisms can show conditioned tendencies.

The pattern of performance discussed above for the object retrieval task highlights the importance, for success at that task, of being able to inhibit the strong tendency to reach straight in the side of the box through which one is looking. Behaviors such as the "awkward reach" also highlight the importance of holding the location of the box opening in mind when looking at the reward and holding the location of the reward in mind when looking at the box opening, and of integrating the two pieces of information. Focusing exclusively on the reward or the box will not work for this task; both must be taken into account. Reaching through the opening when looking through a closed side requires integrating in one's mind looking at the reward along one route with reaching for the reward along a completely different route. Infants of $8\frac{1}{2}$–9 months and prefrontally-lesioned macaques are only able to succeed when the left or right side of the transparent box is open by simplifying the task. They lean over to look in the opening, hence lining up the opening and the reward so that they can see both at once and so that their line of sight is the same as the line along which they will reach.

I have emphasized that DL-PFC is recruited when one must both hold information in mind and inhibit a prepotent response. Other investigators have characterized the functions of DL-PFC more broadly, proposing that when one must both hold information in mind and manipulate or process that information, then DL-PFC becomes critical (Petrides, 1994; 1995b; Owen et al., 1996; Smith et al., 1998; D'Esposito et al., 1999; Owen et al., 1999; Postle et al., 1999; Smith and Jonides, 1999). Under such conceptualizations, holding information in mind plus inhibiting a dominant response becomes part of a subset of "holding information in mind + another cognitive operation." I am in full accord with such formulations. In general, tasks that require DL-PFC are more difficult than tasks that do not. Tasks that require simply holding one piece of information in mind (such as delayed nonmatching to sample) are too easy to require DL-PFC (e.g., Bachevalier and Mishkin, 1986). However, if one increases how much information must be held in mind so that the task is as difficult as one that requires both holding information in mind plus inhibition

(Diamond et al., 1998) or as difficult as one that requires alphabetizing the information held in mind (Postle et al., 1999) then that task, too, will activate DL-PFC.

In sum, human infants of $7\frac{1}{2}-9$ months, infant macaques of $1\frac{1}{2}-2\frac{1}{2}$ months, adult macaques with bilateral removals of DL-PFC, infant macaques of 5 months in whom DL-PFC was removed at 4 months, and adult macaques who have received MPTP injections to disrupt the prefrontal dopamine system fail the A-not-B/delayed response and object retrieval tasks under the same conditions and in the same ways (see table 22.1). This does not prove that maturational changes in DL-PFC during infancy contribute to the emergence of success on these tasks during infancy, but this body of work makes that hypothesis plausible.

Evidence of Improvement in the Cognitive Abilities that depend on DL-PFC during Early Childhood

DL-PFC continues to mature until early adulthood. Marked improvements on tasks that require working memory + inhibition (tasks thought to require the functions of DL-PFC) are seen in children between 3 and 6 years of age. At 3 years of age, one can see errors reminiscent of the A-not-B error seen in infants and in prefrontally-lesioned macaques, but with a slightly more difficult task. On this task, children who are 3 years old can sort cards correctly by the first criterion they are given (*either color or shape*: Zelazo et al., 1996; Zelazo et al., 1995; Kirkham et al., submitted), just as infants of $7\frac{1}{2}-9$ months and prefrontally-lesioned macaques are correct at the first hiding place, and just as adults with prefrontal cortex damage are correct at sorting cards according to the first criterion (*Wisconsin Card Sort test*: Milner, 1963, 1964; Drewe, 1974). Three-year-old children err when correct performance demands switching to a new criterion, i.e., when cards previously sorted by color (or shape) must now be sorted according to the other criterion (shape or color), just as infants of $7\frac{1}{2}-9$ months and prefrontally-lesioned macaques err when required to switch and search for the reward at the other location, and just as adults with prefrontal cortex damage err when required to switch to a new sorting criterion.

Although 3-year-old children fail to sort by the new sorting criterion (sticking steadfastly to the previously correct criterion), they can correctly state the new sorting criterion (Zelazo et al., 1996; Kirkham et al., submitted). Similarly, infants of $7\frac{1}{2}-9$ months can sometimes tell you with their eyes that they know the reward is in the new hiding place even as they persist in reaching back to the previously correct location (Diamond, 1990a, 1991a, b; Hofstadter and Reznick, 1996), and patients with prefrontal cortex damage can sometimes tell you correctly the new sorting criterion even as they persist in sorting by the previously correct criterion (Milner, 1963, 1964; Luria and Homskaya, 1964). When there are only two sorting criteria (color and shape) and only two values for each criterion (e.g., red/blue, truck/star) children are able to succeed at the card sorting task by $4–4\frac{1}{2}$ years of age. If the task is made more complicated, by, for example, adding a third sorting dimension, then children cannot succeed until they are $5–5\frac{1}{2}$ years old. The problem for the children appears to be in relating two or more dimensions to a single stimulus (thinking of a stimulus as either red or blue and also thinking about that same stimulus as either a truck or a star) and in inhibiting the tendency to repeat their previously correct way of categorizing the stimulus.

Similarly, children 3 years old have great difficulty with "appearance–reality" tasks (e.g., Flavell, 1986, 1993) where, for example, they are presented with a sponge that looks like a

Table 22.1 Performance of human infants, infant rhesus monkeys, and adult rhesus monkeys with selective ablations on the same three tasks

	A-not-B	*Delayed Response*	*Object Retrieval*
Human infants show a clear developmental progression from $7\frac{1}{2}$ to 12 months.	Diamond, 1985	Diamond & Doar, 1989	Diamond, 1988
Adult monkeys with lesions of prefrontal cortex fail.	Diamond & Goldman-Rakic, 1989	Diamond & Goldman-Rakic, 1989	Diamond & Goldman-Rakic, 1985
Adult monkeys with lesions of parietal cortex succeed.	Diamond & Goldman-Rakic, 1989	Diamond & Goldman-Rakic, 1989	Diamond & Goldman-Rakic, 1985
Adult monkeys with lesions of the hippocampal formation succeed.	Diamond, Zola-Morgan, & Squire, 1989	Squire & Zola-Morgan, 1983	Diamond, Zola Morgan, & Squire, 1989
Infant monkeys show a clear developmental progression from 1 to 4 months.	Diamond & Goldman-Rakic, 1986	Diamond & Goldman-Rakic, 1986	Diamond & Goldman-Rakic, 1986
5-month-old infant monkeys, who received lesions of prefrontal cortex at 4 months, fail.	Diamond & Goldman-Rakic, 1986	Diamond & Goldman-Rakic, 1986	
Disruption of the prefrontal dopamine system impairs performance in monkeys.		Taylor et al., 1990a, b; Schneider & Roeltgen, 1993	Schneider & Kovelowski, 1990; Sawaguchi & Goldman-Rakic, 1991

rock. Three-year-olds typically report, for example, that it looks like a rock and really is a rock, whereas a child of 4–5 years correctly answers that it looks like a rock but really is a sponge. The problem for the younger children is in relating two conflicting identities to the same object (e.g., Rice et al., 1997) and in inhibiting the response that matches their perception (thus manipulations that reduce the perceptual salience, by removing the object during questioning, find significantly better performance by children of 3–4 years [e.g., Heberle et al., 1999]). "Theory of mind" and "false belief" tasks are other tasks that require holding two things in mind about the same situation (the true state of affairs and the false belief of another person) and inhibiting a prepotent impulse (in this case, to give the veridical answer). For example, the child must keep in mind where the hidden object is now and where another person saw it placed before, and the child must inhibit the inclination to say where the object really is and instead say where the other person would think it is, even though the child knows that answer to be "wrong" because the object is not there now. Here, as well, manipulations that reduce the perceptual salience of the true state of affairs aid children of 3–4 years (Fritz, 1991; Zaitchik, 1991). Carlson et al. (1998) reasoned that pointing veridically to true locations and identities is likely to be a well-practiced and reinforced response in young children, and that children of 3–4 years have trouble inhibiting that tendency when they should point to the false location, as is required on false belief tasks. Carlson et al. (1998) found that when they gave children a novel response by which to indicate the false location, children of 3–4 years performed much better on the false belief task.

Many of the advances of Piaget's "preoperational" child of 5–7 years over a child of 3–4 years, who is in the stage of "concrete operations," similarly reflects the development of the ability to hold more than one thing in mind and to inhibit the strongest response tendency of the moment. Evidence that children 3 or 4 years old have difficulty keeping two things in mind at the same time, or that they tend to focus on only one aspect of a problem, can be seen in (a) their failure on tests of liquid conservation (they fail to attend to both height and width, attending only to height), (b) their difficulty on tests of perspective-taking where they must mentally manipulate a scene to say what it would look like from another perspective and must inhibit the strong tendency to give the most salient response (i.e., their current perspective), (c) their difficulty in comparing an old idea with a new one and hence seeing the contradiction, and (d) their difficulty in working through a two-step problem without losing track of what they are doing. By 5 or 6 years of age, children are capable of doing all of these things. Certainly, part of the difficulty posed by Piaget's liquid conservation task (Piaget and Inhelder, 1941) is the salience of the visual perception that the tall, thin container appears to have more liquid in it. Thus, if an opaque screen is placed between the child and the containers before the child answers, younger children are much more likely to answer correctly (Bruner, 1964).

Many investigators have similarly found evidence of improved ability to exercise inhibitory control over one's behavior between 3 and 6 years of age, especially when children must hold two things in mind and relate them to one another. For example, in the delay of gratification paradigm, when faced with the choice of a smaller, immediate reward or a later, larger reward, children of 3–4 years are unable to inhibit going for the immediate reward although they would prefer the larger one. By 5–6 years of age, children are much better at waiting for the bigger reward (Mischel and Mischel, 1983). Similarly, on the windows task, where children are rewarded for pointing to a box that is visibly empty, and are not rewarded for pointing to a box in which they can see candy, 3-year-olds fail to inhibit the tendency to point to the baited box (Russell et al., 1991). Children 3–4 years of

age also tend to fail go/no-go tasks because they cannot inhibit responding. They appear to understand and remember the task instructions (e.g., they can verbalize the instructions), but cannot get themselves to act accordingly. By 5–6 years, they succeed on these tasks (Bell and Livesey, 1985; Livesey and Morgan, 1991).

Difficulty in holding two things in mind can also be seen in persons with frontal cortex damage. For example, they can have difficulty when asked to do two things (such as clean the windshield and change the oil). They are inclined to focus on only one aspect of a story, instead of on the story as a whole. Indeed, Goldstein (1936, 1944) considered the fundamental disorder caused by damage to the frontal lobe to be an "inability to grasp the entirety of a complex situation." Patients with frontal cortex damage also have a well-documented difficulty inhibiting a strong response tendency. For example, they are impaired on the Stroop task, which requires inhibiting the normal tendency to say the word one is reading; one is instructed instead to say the color of the ink in which the word is printed (Perret, 1974; Richer et al., 1993). They fail a perspective-taking task much like Piaget's, and make the same error as do the younger children (they give as their answer their current perspective, when the current answer is the scene as viewed from a different perspective; Price et al., 1990).

We have followed the developmental improvement in these abilities between $3\frac{1}{2}$–7 years of age using three tasks, the "day–night Stroop-like" task (Gerstadt et al., 1994), the tapping task (Diamond and Taylor, 1996), and the three pegs task (Diamond et al., 1997). These three tasks were also used in our research on the role of dopamine in prefrontal cortex function early in life in treated PKU children and so will be described briefly here.

For the day–night task, children must hold two rules in mind ("Say 'night' when you see a white card with a picture of the sun, and say 'day' when you see a black card with a picture of the moon and stars") and must inhibit the tendency to say what the stimuli really represent; instead they must say the opposite. Children of $3\frac{1}{2}$–$4\frac{1}{2}$ years find the task terribly difficult; by 6–7 years of age the task is trivially easy. Children younger than 6 years of age err often, whereas children of 6–7 years are correct on roughly 90 percent of the trials (see figure 22.4). Children of 3Ω and 4 years show long response latencies on the task (approximately 2 sec); older children take roughly half as long (1 sec). The age-related increase in the percentage of correct responses is relatively continuous from $3\frac{1}{2}$ to 7 years of age, but the decrease in speed of responding occurs primarily between $3\frac{1}{2}$ and $4\frac{1}{2}$ years. Passler, Isaac, and Hynd (1985) tested children on a similar, though slightly easier variant of this task, which required children to recognize the correct answer, whereas our task requires that they recall the correct answer. They found that children of 6 years were performing at ceiling on their task, which is consistent with the excellent performance that we found at 6–7 years of age.

To test whether the requirement to remember two rules alone is sufficient to cause the younger children difficulty, we tested a version of our day–night test where each card contained one of two abstract designs (Gerstadt et al., 1994). Children were instructed to say "day" to one design and "night" to the other. Here the children were still required to hold two rules in mind, but they did not also have to inhibit the tendency to say what the stimuli really represented because the stimuli were abstract designs. Even the youngest children performed superbly here. Thus, the requirement to learn and remember two rules is not in itself sufficient to account for the poor performance of the younger children on the day–night task.

Moreover, children's difficulty with the task depends critically on the correct responses being semantically related to the responses that must be inhibited. When we used the same

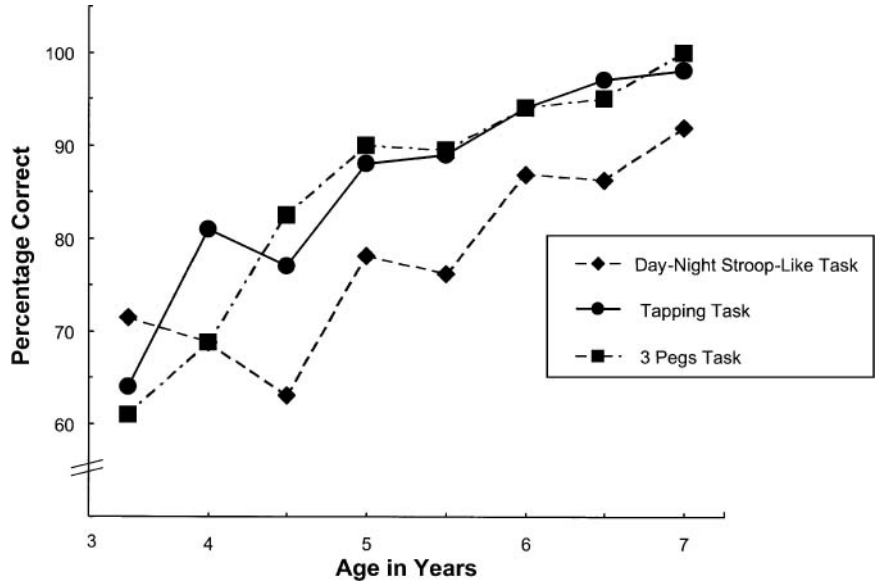


Figure 22.4 Performance of children, $3\frac{1}{2}$ through 7 years of age, on the day–night, tapping, and three pegs task. Note the close parallels in performance on all three tasks throughout this age range.

white/sun and black/moon cards, but instructed the children to say "dog" to one and "pig" to the other, even the youngest children again performed well (Diamond et al., submitted). The task of holding two rules in mind and inhibiting one's natural inclination is sufficiently hard for the younger children that they need a long time to formulate their answers in order to respond correctly. Although we gave children unlimited time, they tended to speed up their responses over the 16 test trials, and the accuracy of the youngest children correspondingly fell. When we made the children wait to respond, by singing a brief ditty to them on each trial after the stimulus was presented, the younger children were able to perform well, even though the period before their response was filled with potentially interfering verbal stimulation (Diamond et al., submitted). It is not simply that slowing down the testing helped, because when the children were made to wait before the start of each trial, they performed poorly. The day–night task is sufficiently difficult for young children that it takes them several seconds to compute the answer; often they do not take the needed time; when forced to take extra time they can perform well.

Luria's tapping test (Luria, 1966) also requires (a) remembering two rules and (b) inhibiting the response you were inclined to make, making the opposite response instead. Here, one needs to remember the rules, "Tap once when the experimenter taps twice, and tap twice when the experimenter taps once," and one needs to inhibit the tendency to mimic what the experimenter does. Children improve on this task over the same age period as they do on the day–night task (see figure 22.4). Over the period of $3\frac{1}{2}-7$ years, children improve in both speed and accuracy on the tapping task, with most of the improvement occurring by the age of 6 (Diamond and Taylor, 1996; Passler et al., 1985; Becker et al., 1987).

Adults with large frontal lobe lesions fail this same tapping task (Luria, 1966). They have similar problems when instructed to raise their finger in response to the experimenter making a fist and to make a fist in response to the experimenter raising a finger (Luria, 1966). The most common error by young children is to always tap once, or always tap twice, regardless of what the experimenter does. It may be that the young children are able to keep in mind only one of the two rules. Or, it may be that they lack the ability to flexibly switch between the two rules, although they remember both. (It cannot be because they do not understand what they should do because no child is tested who does not demonstrate understanding during training of what he or she should do when the experimenter taps once or twice.) This error is reminiscent of a characteristic error Luria (1966) observed in his patients. For example, when asked to alternately draw a circle and a cross, patients with extensive frontal lobe damage start out performing correctly (as do even the youngest children), but the patients soon deteriorate into following only one of the rules (i.e., drawing only circles or only crosses).

Other errors by the children seem more clearly to reflect inadequate inhibitory control. One common error among the younger children is to be unable to resist tapping many times, instead of just once or twice. Again, this error is reminiscent of behavior Luria noted in patients with excessive damage to the frontal lobe: "[When asked] to tap three times or to squeeze the doctor's hand three times . . . although the patient retains the verbal instruction and repeats it correctly, he taps many times or squeezes the doctor's hand five, six, or more times instead of three" (Luria, 1966: 252). Another error made by the younger children is to match what the experimenter does, instead of doing the reverse. Luria (1966; Luria and Homskaya, 1964) has extensively described such "echopractic" errors in frontal lobe patients. Indeed, on the tapping task itself, Luria found that although the patients could correctly comply with the instructions for a short while (like the younger children), they very soon began to imitate the experimenter's movements. Luria also found that the frontal patients could verbalize the rules even as they failed to act in accord with them.

Since Luria first introduced the tapping test over 30 years ago, it has been widely used in neurological assessments of frontal lobe damage in patients. However, much of the work with this test comes from old studies with patients with massive damage. It is not clear from such studies which regions within frontal cortex are critical for the task, or even whether the cortex, rather than the basal ganglia, is the critical site.

For the three pegs task (Balamore and Wozniak, 1984) a child is shown a pegboard containing three pegs arranged in the order: red, yellow, green. The child is asked to tap the pegs in the order: red, green, yellow. This task requires remembering a 3-item sequence and inhibiting the tendency to tap the pegs in their spatial order. The tapping and day–night tasks are more similar to one another than is the three pegs task. Although it, too, requires acting counter to one's initial tendency on the basis of information held in mind. Children show developmental improvements on the three pegs task during the same age period that they are improving on the tapping and day–night tasks (see figure 22.4; Diamond et al., 1997), and performance on the three tasks is correlated (tapping & three pegs tasks: $r[144] = .53$, $p = .0001$; tapping & day-night: $r[144] = .35$, $p = .0001$; day-night & three pegs: $r[151] = .20$, $p = .01$; Diamond et al., 1997).

Clearly, improvement in the performance of tasks requiring memory plus inhibition occurs between 3 and 6 years of age. Perhaps that improvement is made possible, in part, by maturational changes in DL-PFC, although that remains to be demonstrated. Perhaps one

of those maturational changes in DL-PFC is in its dopamine system, although little is known about what is happening in the dopamine system in prefrontal cortex during this period. To begin to look at the role of the dopamine innervation of DL-PFC in helping to subserve cognitive functions during infancy and early childhood, we have been studying children who, we had good reason to believe, have reduced levels of dopamine in prefrontal cortex but otherwise remarkably normal brains – children treated early and continuously for phenylketonuria (PKU), whose phenylalanine (Phe) levels are 3–5 times normal (6–10 mg/dl [360–600 mmol/L]).

At the time we began this work, there were almost no data on the role of dopamine in prefrontal function *in humans*, and no data on the role of dopamine in aiding prefrontal function *early in development* in any species. As an initial way of beginning to look at the role of dopamine in prefrontal cortex function in humans early in development, we conducted a large, longitudinal study of children treated early and continuously for PKU (Diamond et al., 1997). We complemented that with work with an animal model of early- and continuously-treated PKU, where we could investigate the underlying biological mechanism (Diamond et al., 1994b). Additionally, we sought to obtain converging evidence from a study of visual contrast sensitivity in children treated early and continuously for PKU (Diamond and Herzberg, 1996), where we postulated that the same underlying mechanism was at work.

The Reasoning and Evidence Leading to the Hypothesis of a Selective Deficit in Dopamine in Prefrontal Cortex in Children Treated Early and Continuously for PKU

Phenylketonuria (PKU) defined

The core problem in PKU is a mutation of the gene on chromosome 12 (12q22 – 12q24.1) that codes for the enzyme phenylalanine hydroxylase. Phenylalanine hydroxylase is essential for hydroxylating (i.e., converting) the amino acid phenylalanine (Phe) into the amino acid tyrosine (Woo et al., 1983; Lidsky et al., 1985; DiLella et al., 1986; see figure 22.5). In the roughly 1 in every 10,000 people born with PKU, phenylalanine hydroxylase activity is either absent or markedly reduced. Hence, PKU is a member of the class of disorders called "inborn [i.e., genetic] errors of metabolism." In the case of PKU, the error is in the metabolism of Phe.

Since little, if any, Phe is metabolized, Phe levels in the bloodstream reach dangerously high levels. Indeed, when PKU is untreated, levels of Phe in the bloodstream rise to well over 10 times normal (>20 mg/dl [>1200 mmol/L]). Since little or no tyrosine is produced from Phe, the level of tyrosine in the bloodstream is low (e.g., Nord et al., 1988). (Tyrosine levels would be still lower were it not for the availability of tyrosine directly through the foods we eat.) This imbalance in blood levels of Phe and tyrosine, if not corrected early, causes widespread brain damage and severe mental retardation (Hsia, 1967; Cowie, 1971; Tourian and Sidbury, 1978; Koch et al., 1982; Krause et al., 1985). Indeed, PKU is the most common biochemical cause of mental retardation. The primary cause of the widespread brain damage is thought to be the toxic effects of grossly elevated levels of Phe in the brain.

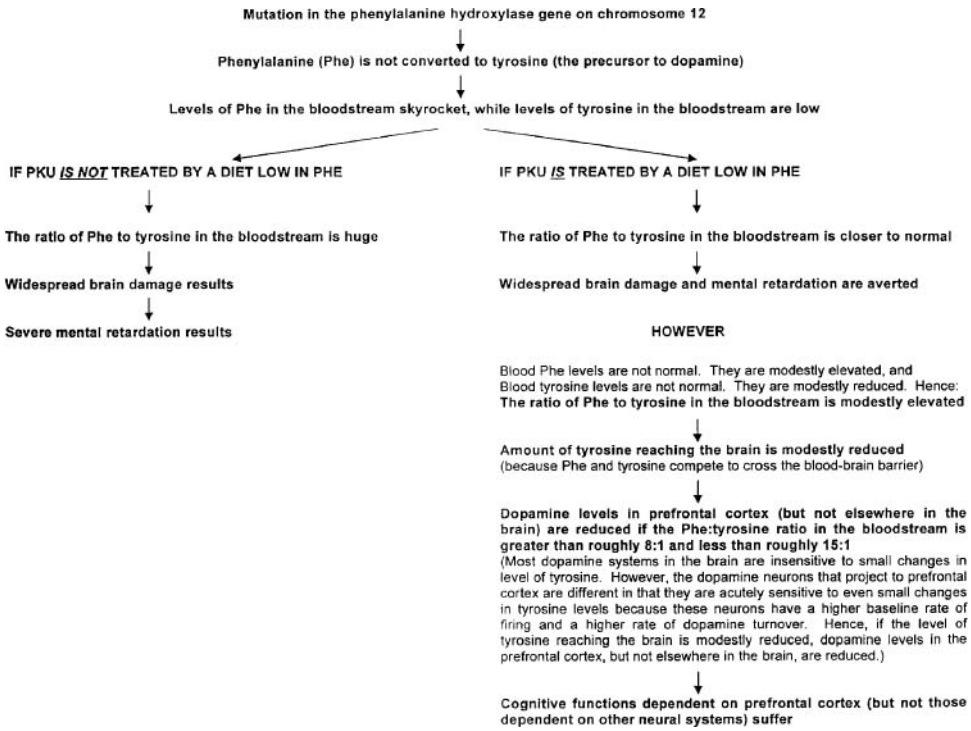


Figure 22.5 Diagram illustrating the reasoning leading to the hypothesis that children treated early and continuously for PKU, whose blood Phe levels are 6–10 mg/dl, would have a selective decrease of dopamine in prefrontal cortex and a selective deficit in the cognitive abilities dependent on prefrontal cortex.

The treatment for PKU: A diet low in phenylalanine

The treatment for PKU consists of a diet low in Phe. Since Phe is a constituent of protein, the low-Phe diet severely restricts the intake of milk and milk products (such as ice cream, butter, and cheese), and all meat and fish. When PKU is treated early and continuously by a diet low in Phe, gross brain damage and severe mental retardation are averted (e.g., Bickel et al., 1971; Holtzman et al., 1986). Note that here is an example of how a behavioral change (changing what you eat) can profoundly affect your biochemistry and your brain.

Limitations of the diet: Why problems might still exist when PKU is treated

The low-Phe diet rarely results in fully normal levels of Phe or tyrosine. This is because the need to minimize Phe intake must be balanced with the need for protein. Eliminating all Phe from the diet would require eliminating all protein. Phe is not present outside of protein in any naturally occurring food. Not only does the human body need to

ingest protein, but the body needs a small quantity of Phe to produce its own protein. Hence, because persons with PKU need protein, blood Phe levels remain somewhat elevated in a person with PKU, even with conscientious adherence to the recommended diet, as an inevitable consequence of consuming even a small amount of protein. The advice of the U.S. National Collaborative Study of Treated PKU has been that as long as Phe levels in the bloodstream do not exceed 5 times normal (10 mg/dl [600 mmol/L]), persons with PKU are considered to be under adequate control (Williamson et al., 1981; Koch and Wenz, 1987). The diet has historically done little to correct the reduction in tyrosine, although recently the companies that manufacture the "formula" that persons with PKU drink instead of milk have added additional tyrosine to their formulas. Still, tyrosine levels are below normal in most children treated for PKU.

Even with a low-Phe diet, there is a moderate elevation in the ratio of Phe to tyrosine levels in the bloodstream and deficits in certain cognitive abilities

Thus, the consequence for PKU children of following a dietary regimen of reduced Phe intake and mild tyrosine supplementation is that they have moderately elevated levels of Phe and moderately reduced levels of tyrosine in their bloodstreams. (Were they not following this dietary regimen, the elevation in their Phe:tyrosine ratio would be huge, rather than moderate, and they would likely incur brain damage and become severely cognitively impaired.)

Given that the low-Phe diet does not return Phe and tyrosine levels fully to normal, one can see how the possibility for problems could still exist. Indeed, a number of studies have found significant cognitive deficits in PKU children on the low-Phe diet (e.g., Dobson et al., 1976; Williamson et al., 1981; Pennington et al., 1985; Faust et al., 1986; Smith and Beasley, 1989). For example, the IQs of these children are often significantly lower than the IQs of their siblings. Children with PKU, even when they have been on the special diet since shortly after birth, typically have IQs in the 80s or 90s – lower than the mean score of 100 of their same-age peers, though still within the normal range (e.g., Dobson et al., 1976; Berry et al., 1979; Williamson et al., 1981).

In the 1980s, studies reported problems in holding information in mind, problem-solving, and "executive functions" in children with PKU on the low-Phe diet (e.g., Krause et al., 1985; Pennington et al., 1985; Faust et al., 1986; Brunner et al., 1987; Smith and Beasley, 1989). These problems are reminiscent of the deficits seen after damage to prefrontal cortex, and that similarity did not escape the notice of others (see, especially, Welsh et al., 1990). Indeed, damage to prefrontal cortex typically results in IQs lowered to the 80s or 90s (Stuss and Benson, 1986, 1987), i.e., the same range as one sees in children treated for PKU. The impact of these findings was muted, however, because people were not sure how to make sense of them. No one had suggested a mechanism whereby the cognitive functions dependent on prefrontal cortex might be impaired in treated PKU children, while other cognitive functions appeared normal. Actually, the facts needed for understanding the underlying mechanism were already available. However, the neuroscientists working on the prefrontal dopamine system in the rat and the cognitive neuropsychologists and pediatricians working with PKU children did not know of one another's work, so no one had put the facts together.

Proposed mechanism: How a modest imbalance in the levels of Phe and Tyr in the bloodstream might produce deficits specific to the cognitive abilities dependent on prefrontal cortex

Children treated early and continuously for PKU have a moderate increase in the ratio of one amino acid (phenylalanine [Phe]) to another (tyrosine [Tyr]) in their bloodstreams. (Tyrosine is the precursor of dopamine.) We predicted that when the imbalance is moderate it would selectively affect the dopamine projection to prefrontal cortex.

Why should a modest imbalance in the levels of Phe and tyrosine in the bloodstream produce deficits in the cognitive abilities dependent on DL-PFC? And, why should deficits be confined to that neural system and not extend to other functions of the brain?

Modest reduction in the level of Tyrosine reaching the brain

The modest elevation in Phe relative to tyrosine in the bloodstream results in a modest reduction in the level of tyrosine reaching the brain. This is because Phe and tyrosine compete for the same limited supply of proteins to transport them across the blood-brain barrier (Chirigos et al., 1960; Oldendorf, 1973; Pardridge, 1977). Indeed, those transport proteins have a higher binding affinity for Phe than for tyrosine (Pardridge and Oldendorf, 1977; Miller et al., 1985). Thus, elevations in blood levels of Phe relative to tyrosine place tyrosine at a competitive disadvantage in finding transport into the brain. Because the ratio of Phe to tyrosine in the bloodstream is only modestly increased in those on dietary treatment for PKU, the decrease in the amount of tyrosine reaching the brain is correspondingly modest. In this way, the moderate plasma imbalance in Phe:tyrosine ratio results in modestly reduced tyrosine levels in the brain.

The dopamine neurons that project to prefrontal cortex are unusually sensitive to modest reductions

The special properties of the dopamine projection to prefrontal cortex make prefrontal cortex more sensitive to small changes in the level of tyrosine than other brain regions. The brain needs tyrosine to make dopamine (see figure 22.6). Indeed, the hydroxylation of tyrosine is the rate-limiting step in the synthesis of dopamine. Most dopamine systems in the brain are unaffected by small decreases in the amount of available tyrosine. Not so prefrontal cortex. The dopamine neurons that project to prefrontal cortex are unusual in that they have a higher firing rate and higher rate of dopamine turnover than other dopamine neurons (e.g., Thierry et al., 1977; Bannon et al., 1981; Roth, 1984). These unusual properties of the prefrontally-projecting dopamine neurons in the ventral tegmental area (VTA) make prefrontal cortex acutely sensitive to even a modest change in the supply of tyrosine (e.g., Wurtman et al., 1974; Tam et al., 1990). Reductions in the availability of tyrosine too small to have much effect on other dopamine systems in other neural regions (such as the striatum) have been shown to profoundly reduce dopamine levels in prefrontal cortex (Bradberry et al., 1989).

Reducing the level of dopamine in prefrontal cortex produces deficits in the cognitive abilities dependent on prefrontal cortex

As mentioned above, selectively depleting DL-PFC of dopamine can produce cognitive deficits as severe as those found when DL-PFC is removed altogether (Brozoski et al., 1979). Local injection of dopamine antagonists into DL-PFC impairs performance in a

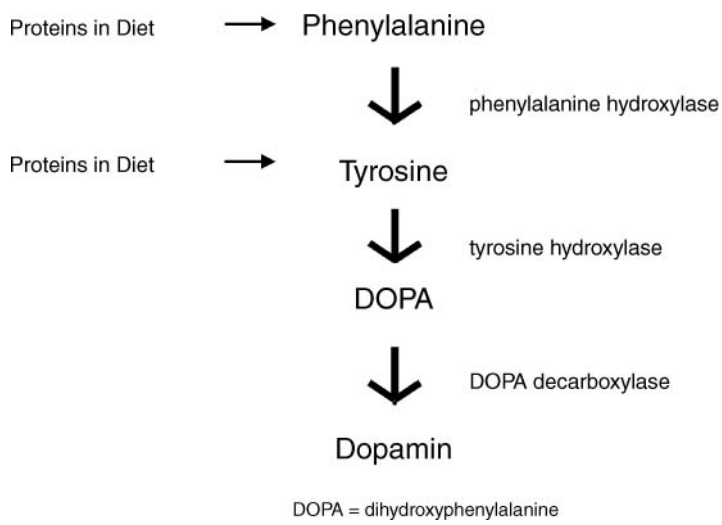


Figure 22.6 Diagram illustrating the mechanism by which the neurotransmitter, dopamine, is produced in the body. Persons with PKU either lack the enzyme phenylalanine hydroxylase, or have it in an inactive form. Note that the body acquires tyrosine via two routes, the hydroxylation of Phe and directly through diet. The hydroxylation of tyrosine is the rate-limiting step in the production of dopamine.

precise, dose-dependent manner (Sawaguchi and Goldman-Rakic, 1991). Destruction of the dopamine neurons in the VTA that project to prefrontal cortex also impairs performance on tasks dependent on DL-PFC (Simon et al., 1980). Similarly, injections of MPTP that disrupt the dopamine projection to prefrontal cortex, but are of sufficiently low dose that motor deficits are avoided, impair performance on the A-not-B/delayed response and object retrieval tasks (e.g., Schneider and Kovelowski, 1990; Taylor et al., 1990a, b).

Summary of the reasoning leading to the prefrontal dopamine hypothesis in treated PKU

For these reasons it seemed plausible that the moderate imbalance in the Phe:tyrosine ratio in the bloodstreams of children treated early and continuously for PKU might well result in deficits in the cognitive abilities dependent on prefrontal cortex (because of the unusual vulnerability of the dopamine projection to prefrontal cortex to a moderate reduction in the amount of available tyrosine) without significantly affecting other brain regions or other cognitive abilities. Hence, we hypothesized that here was a mechanism by which the modest elevation in the Phe:Tyr ratio in the bloodstream of some children treated for PKU, which results in moderate reductions in the level of tyrosine reaching the brain, might selectively affect prefrontal cortex (by modestly decreasing the level of tyrosine reaching the brain).

A 4-Year Longitudinal Study of Children Treated Early and Continuously for PKU

To investigate our prediction that children treated early and continuously for PKU have selective deficits in the cognitive functions dependent on prefrontal cortex we tested 148 children longitudinally and 364 children cross-sectionally (Diamond et al., 1997). Included were children treated early and continuously for PKU, siblings of the PKU children, matched controls, and children from the general population. Children from the general population were tested cross-sectionally; all other groups were tested longitudinally.

If a PKU child starts dietary treatment too late or discontinues it, the very high plasma Phe levels during those off-treatment periods can cause permanent, widespread brain damage. Therefore, we were careful to include in this study only those PKU children who started dietary treatment soon after birth (80 percent began the low-Phe diet within 14 days of age; all had been placed on a low-Phe diet within 1 month of birth) and who had been continuously maintained on the diet thereafter (i.e., children with early- and continuously-treated PKU).

Because no control group is perfect, we included three different control groups. Siblings provide a partial control for family background and genetic make-up. However, they are an imperfect control group because, except for twins, they are not matched on age or birth order, and are often not matched in gender or health status. Therefore, we also studied children unrelated to our PKU participants, but who matched them on a host of background and health variables such as gender, gestational age at birth, birthweight, ethnic background, religion, age at beginning of testing, community of residence, childcare arrangements, number of siblings, birth order, and the age, level of education, and occupational status of each parent. Selecting control subjects by matching on a list of variables is imperfect as well, however, because the children thus selected may not match on other critical variables that one had not considered. Therefore, we complemented the inclusion of siblings and matched controls with a normative sample of children from the general population. With this last group we attempted to get an estimate of the "normal" developmental progression on each of our tasks.

All children studied had normal birthweights, IQs within the normal range, and no known learning disabilities or serious medical problems. Almost all were full-term (100 percent of the children tested cross-sectionally; 96 percent of the children tested longitudinally). PKU is found primarily among Caucasians, so almost all of our participants were Caucasian (95 percent of the children tested cross-sectionally; 93 percent of the children tested longitudinally).

Because of the large age range studied (6 months–7 years), three different batteries of cognitive neuropsychological measures were used – one for infants (6–12 months of age), one for toddlers (15–30 months of age), and one for young children ($3\frac{1}{2}$–7 years old). A total of 19 cognitive neuropsychological measures were administered (see table 22.2). Infants were tested every month, toddlers every 3 months, and young children every 6 months. At each age, each child was tested on multiple tasks linked to prefrontal cortex and on multiple control tasks that were not linked to prefrontal cortex.

Findings

Deficits in the working memory and inhibitory control abilities dependent on DL-PFC in children treated early and continuously for PKU

We found that PKU children who had been on a low-Phe diet since the first month of life, but who had moderately elevated blood Phe levels (levels roughly 3–5 times normal [6–10 mg/dl; 360–600 mmol/L]), were impaired on all 6 tests that require both holding information in mind and overriding or resisting a dominant response, i.e., tasks dependent on DL-PFC. These six tasks were the A-not-B and the object retrieval tasks for infants; A-not-B with invisible displacement for toddlers; the day–night Stroop-like test, the tapping test, and the three pegs test for young children (see figure 22.7). The fact that even *infants* showed these impairments suggests that the dopaminergic innervation to prefrontal cortex is critical for the proper expression of these abilities even during the first year of life.

These deficits in the working memory and inhibitory control abilities dependent on DL-PFC were evident in all age groups (infants, toddlers, and young children), and remained significant even controlling for IQ, gender, health variables, and background characteristics. The deficits were clear whether the PKU children with blood Phe levels 3–5 times normal were compared to (a) other PKU children with lower Phe levels, (b) their own siblings, (c) matched controls, or (d) children from the general population.

One way to summarize the many comparisons across the 3 age groups and 19 tasks is to look at the results on one dependent measure for every task. For each task (the control tasks as well as those that required working memory plus inhibitory control) we selected the dependent measure that yielded the strongest between-group differences on that particular task. This gave each task the best possible opportunity to yield a difference between groups, whether we had predicted a group difference or not. Of the 24 comparisons between PKU children with blood Phe levels 3–5 times above normal and the 4 other groups of children (PKU children with Phe levels closer to normal [$< 3\times$ normal], siblings of PKU children, matched controls, and children from the general population) on the 6 tasks that require

Table 22.2 List of Tasks

TASKS USED WITH INFANTS (AGES 6–12 MONTHS)

Tests of WORKING MEMORY + INHIBITORY CONTROL, dependent on DORSOLATERAL PREFRONTAL CORTEX:

A-not-B: a hiding task requiring working memory & inhibition of a previously rewarded response. Subject sees reward hidden to left or right (2 identical hiding wells); after a delay subject is allowed to search one well. Linked to dorsolateral prefrontal cortex by work with rhesus monkeys (e.g., Diamond & Goldman-Rakic, 1989).

Object Retrieval: a transparent barrier detour task. Subject can see the reward through all sides of a transparent box, but can reach through only the one open side (Diamond, 1981, 1990). Linked to dorsolateral prefrontal cortex by work with rhesus monkeys (e.g., Diamond & Goldman-Rakic, 1985).

Tests that do NOT require WORKING MEMORY + INHIBITORY CONTROL:

Spatial Discrimination: an associative rule-learning & memory task. Hiding done unseen; subject must learn & remember that reward is always hidden to left or right (2 identical hiding places); after delay between trials, subject is allowed to reach. *Not* impaired by lesions to prefrontal cortex (e.g., Goldman & Rosvold, 1970).

Visual Paired Comparison: a recognition memory task where a sample is presented, a delay imposed, & then subject is given a choice of that stimulus or something new. Linked to the medial temporal lobe (Bachevalier, Brickson, & Hagger, 1993, McKee & Squire, 1992).

TASKS USED WITH TODDLERS (AGES 15–30 MONTHS)

Test of WORKING MEMORY + INHIBITORY CONTROL, dependent on DORSOLATERAL PREFRONTAL CORTEX:

A-Invisible Displacement: a hiding task requiring memory of where the container-with-reward was last moved & inhibition of a previously rewarded response. Similar to A for infants, but not independently, directly linked to prefrontal cortex.

Tests that do NOT require WORKING MEMORY + INHIBITORY CONTROL:

Three Boxes (boxes scrambled after each reach): a memory task where subjects are to try to open all boxes without repeating a choice; a delay is imposed between reaches. S must remember color/shape of the boxes; spatial location is irrelevant. Linked to dorsolateral prefrontal cortex by work with rhesus monkeys (Petrides, 1995).

Three Boxes (stationary): Here, uncovering the boxes in spatial order will suffice. Similar to a condition *not* impaired by damage to dorsolateral prefrontal cortex (Petrides & Milner, 1982).

Delayed Nonmatching to Sample: a recognition memory task where one is rewarded for reaching to the stimulus not matching the sample that was presented shortly before. Linked to the medial temporal lobe by work with rhesus monkeys & amnesic patients (e.g., Murray, Bachevalier, & Mishkin, 1989; Zola-Morgan, Squire, & Amaral, 1989; Squire, Zola-Morgan, & Chen, 1988).

Global–Local (preferential looking procedure): a visual–spatial attention task. Assesses attention to the global and the local features of composite stimuli (e.g., an H made up of S's). Similar to a task linked to parietal cortex by work with brain-damaged patients (e.g., Lamb, Robertson, & Knight, 1989; Robertson, Lamb, & Knight, 1988) and to a task linked to parietal cortex through functional magnetic imaging (fMRI) of neural activity in normal adults.

TASKS USED WITH YOUNG CHILDREN (AGES 3–7 YEARS)

Tests of WORKING MEMORY + INHIBITORY CONTROL, dependent on DORSOLATERAL PREFRONTAL CORTEX:

Day–Night Stroop-like Test: requires holding 2 rules in mind & exercising inhibitory control. S must say "night" when shown a white-sun card, and say "day" when shown a black-moon card. Hypothesized to require the functions of dorsolateral prefrontal cortex, but it has yet to be studied in relation to brain function.

Tapping: a conflict test requiring memory of 2 rules & inhibitory control. When E taps once, S must tap 2×; when E taps 2×, S must tap once. Linked to prefrontal cortex by work with brain-damaged patients (Luria, 1973).

Three Pegs: S is shown a board containing 3 colored pegs arranged in the order: red, yellow, green. S is instructed to tap the pegs in the order: red, GREEN, yellow. This requires remembering the instructed sequence & inhibiting the tendency to tap the pegs in their spatial order. It has yet to be studied in relation to brain function.

Tests that do NOT require WORKING MEMORY + INHIBITORY CONTROL:

Corsi–Milner Test of Temporal Order Memory: Subject is shown a series of stimuli one at a time, & is periodically shown 2 previously presented stimuli & asked, "Which of these two pictures did you see last?" Linked to prefrontal cortex by work with brain-damaged patients (Milner, Corsi, & Leonard, 1991).

Six Boxes (boxes scrambled after each reach): a memory task where S must try to open all boxes without repeating a choice; a delay is imposed between reaches. Similar to tasks linked to prefrontal cortex in rhesus monkeys (Petrides, 1995) & in brain-damaged human adults (Petrides & Milner, 1982).

Stroop control condition: requires learning & remembering 2 rules (as does Stroop above), but requires no inhibition (unlike Stroop above) – 2 arbitrary patterns used; to one, S must say "day," to other, S must say "night".

Corsi–Milner Test of Recognition Memory: S is shown a series of pictures and periodically asked, "Among the pictures I've shown you, which of these two have you already seen?" Linked to medical temporal lobe by work with brain-damaged patients (Milner, 1982; Milner et al.,1991).

Six Boxes (stationary): Here, uncovering the boxes in spatial order will suffice. Similar to a condition *not* impaired by damage to dorsolateral prefrontal cortex (Petrides & Milner 1982).

Global–Local (forced choice procedure): a visual–spatial attention task. Assesses attention to the global and the local features of composite stimuli (e.g., an H made up of S's). Linked to parietal cortex by work with brain-damaged patients (e.g., Lamb et al., 1989; Robertson et al., 1988) and by functional magnetic imaging (fMRI) of neural activity in normal adults.

Line Bisection: a spatial perception task. Subject is asked to indicate the middle of each line. Linked to parietal cortex by work with brain-damaged patients (e.g., Benton, 1969).

working memory + inhibitory control (6 tasks × 4 comparisons per task), PKU children with higher Phe levels performed significantly worse than the comparison groups on 79 percent of these comparisons using the stringent criterion of $p \leq .005$ for each test to correct for multiple comparisons (see table 22.3). This pattern of 19 out of 24 comparisons in the predicted direction would be very unlikely to occur by chance ($p < .004$ [binomial distribution]). In short, the impairment of the PKU children whose blood Phe levels were 3–5 times above normal, on the tasks that require the working memory and inhibitory control functions dependent on DL-PFC, was clear and consistent.

This finding of deficits in the working memory and inhibitory control abilities dependent on DL-PFC in PKU children whose blood Phe levels are mildly elevated (3–5× normal) is consistent with the results of a number of other studies. The most relevant are those by Welsh et al. (1990) and Smith et al. (1996), as these investigators used cognitive tasks tailored to the functions of DL-PFC.

The cognitive deficits documented in many studies of children treated for PKU could be explained away by saying that (a) the blood Phe levels of many of the children were outside the "safe" range (i.e., > 5 times normal), (b) even if current Phe levels were not excessively elevated, earlier Phe levels had been (during the years the children had been off diet), and/or (c) the low-Phe diet had been started too late to avert early brain damage. Those disclaimers are not applicable to the Diamond et al. (1997) study.

A linear relationship between Phe level and performance

The higher a PKU child's current Phe level (the higher a child's Phe:tyrosine ratio), the worse that child's performance on the tasks that required the working memory and inhibitory control functions dependent on DL-PFC. PKU children whose blood Phe levels had been maintained between 2–6 mg/dl performed comparably to all control groups on our tasks. Thus, at least in this subgroup of PKU children, deficits in the ability to simultaneously exercise working memory and inhibitory control did not appear to be a necessary, unavoidable consequence of being born with PKU. The effect of elevated Phe

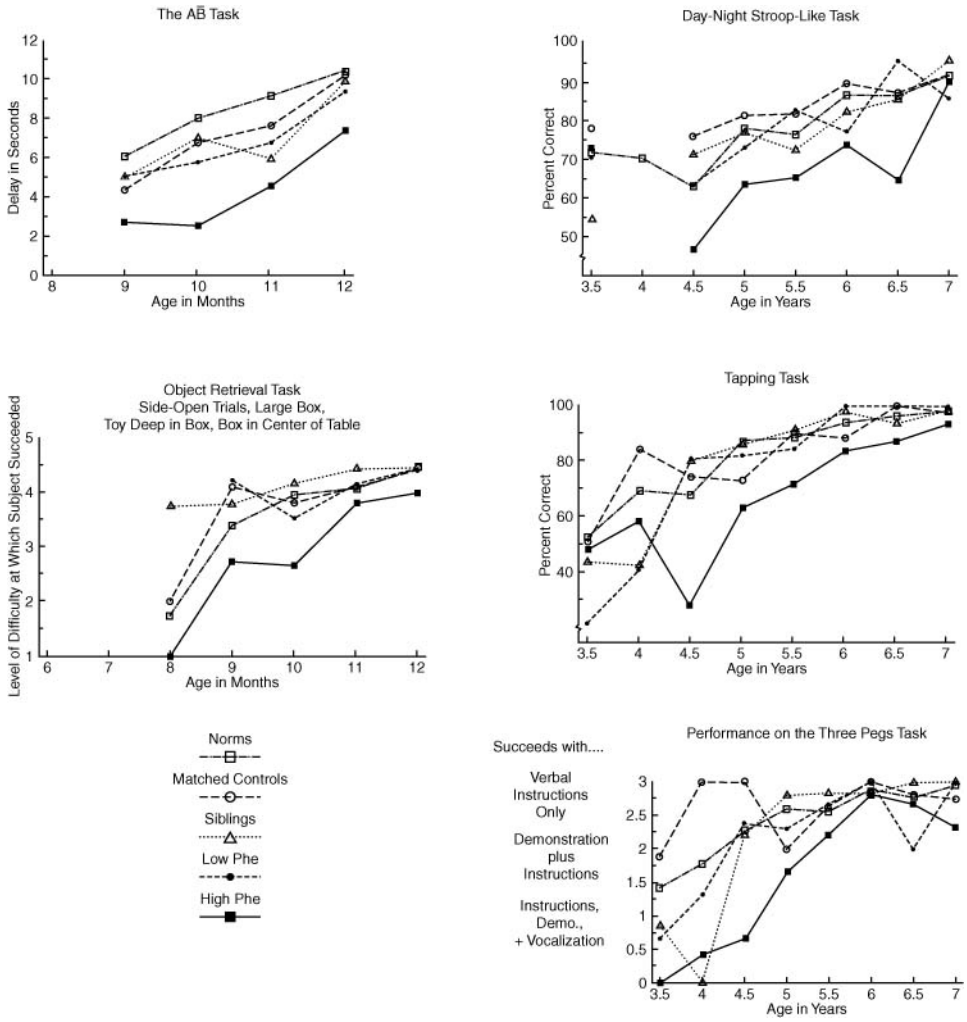


Figure 22.7 Performance of PKU children whose blood Phe levels are 6–10 mg/dl (3–5 times normal) on tasks requiring both working memory and inhibitory control. Note that they are significantly impaired compared to each comparison group: other PKU children with Phe levels closer to normal, siblings of the PKU children, control children matched to the PKU children on a large number of variables, and children from the general population. Note also that they are significantly impaired in the youngest age range investigated (as infants they are impaired on the A-not-B/delayed response and object retrieval tasks) and in the oldest age range investigated (as young children on the day–night, tapping, and three pegs tasks).

levels appeared to be acute, rather than chronic: Performance on these tasks was most strongly and consistently related to *current* blood Phe levels, rather than to mean Phe levels over a wide age range, during the first year of life, or during the first month of life. As current Phe levels varied so too, inversely, did behavioral performance on 5 of the 6 tasks that required acting counter to one's initial tendency on the basis of information held in

Table 22.3 Pairwise Comparisons between Subject Groups Significant at $p \leq .005$

	The 6 tasks that required the working memory & inhibitory control abilities dependent on dorsolateral prefrontal cortex	The 10 control tasks that did are not dependent on prefrontal cortex
PKU children whose plasma Phe levels were 3–5× normals performed significantly worse than the other groups of children on...	19 out of 24 comparisons (79%)	4 out of 40 comparisons (10%)
The other groups of children performed significantly differently from one another on...	2 out of 36 comparisons (5%)	3 out of 60 comparisons (5%)

The .005 significance level was chosen to correct for multiple comparisons. This is similar to what a Bonferroni correction would do.

mind (the exception being A-not-B with invisible displacement). Indeed, over time, changes in blood Phe levels *within the same child* were accompanied by concomitant, inverse changes in performance on these cognitive tasks.

The findings that performance is most closely tied to current blood Phe levels (rather than to Phe levels earlier in life) and that performance covaries with a child's current blood Phe levels is consistent with the biological mechanism outlined above concerning the cause of the cognitive deficits. That is, these findings are consistent with an effect of reduced dopamine on prefrontal cortex function, which would vary directly with changes in the Phe:Tyr ratio in the bloodstream, as opposed to structural, neuroanatomical changes, which might be more fixed.

Like us, Welsh et al. (1990) and Smith et al. (1996) found that performance on measures of DL-PFC function was significantly and negatively correlated with concurrent Phe levels and less so with lifetime Phe levels. Brunner et al. (1983) found that cognitive neuropsychological performance was significantly correlated with concurrent Phe levels but not with Phe levels during infancy. Using IQ and school achievement as the outcome measures, Dobson et al. (1976) also found a significant, negative correlation with concurrent blood Phe levels, and a much weaker association with Phe levels earlier in life. Like us, Stemerdink et al. (1995) found that when blood Phe levels were kept below 3 times normal from birth to the present, PKU children showed no cognitive deficits. The only contrary finding is the report of Sonneville et al. (1990) that Phe levels during the 2 years preceding cognitive testing were a better predictor of speed of responding on a continuous performance test than were concurrent Phe levels.

The relationship found between blood Phe level and performance in Diamond et al. (1997), Welsh et al. (1990), and Smith and Beasley (1989) is particularly impressive considering the truncated range of Phe levels; all PKU children in those studies were on a dietary regimen and their Phe levels were generally within the "acceptable" range. Because participants in Diamond et al. (1997) were followed longitudinally, we are able to present evidence for the first time that performance on tasks requiring the working

memory and inhibitory control functions of DL-PFC covaried inversely with Phe levels in the same child over time. Because of the evidence of cognitive deficits in PKU children whose blood Phe levels are 6–10 mg/dl, the national guidelines for the treatment of PKU have been changed in the United Kingdom, the Netherlands, and Denmark to say that Phe levels higher than 6 mg/dl are no longer considered acceptable, and several clinics in the United States have similarly revised their guidelines.

A developmental delay or absolute, lasting deficits?

Are the cognitive deficits in treated PKU children indicative of a developmental delay or of lasting deficits? On the one hand, all children, even PKU children with Phe levels 3–5 times above normal, improved over time on our tasks. On the other hand, the impression that PKU children may "catch up" to other children is probably misleading. In almost all cases this "catch up" was due to ceiling effects because the same tasks were administered over a wide age range, and these tasks were often too easy for children at the upper end of an age range. We have repeatedly found that the between-group differences reappeared on the next battery of tasks for the next age group. The impairment of the PKU children with higher Phe levels in simultaneously holding information in mind and inhibiting a prepotent response was as evident in our oldest age range (3Ω–7 year olds) as it was in our youngest age range (6–12 month olds). The deficit showed no evidence of subsiding within the age range we studied (6 months – 7 years).

The oldest children tested by Diamond et al. (1997) were 7 years old. One cannot tell from our study whether sometime after 7 years PKU children whose Phe levels remain only moderately elevated might no longer show the kinds of cognitive deficits we have documented. Many studies of elementary school-age PKU children on the low-Phe diet have found cognitive deficits (e.g., Smith and Beasley, 1988; Welsh et al., 1990; Weglage et al., 1995). Recent studies by Ris et al. (1994) and Smith et al. (1996) report deficits in the cognitive abilities dependent on prefrontal cortex in young adults with PKU. However, dietary compliance tends to become progressively more lax after children enter school so that these studies have included participants whose blood Phe levels were higher than 10 mg/dl. What would happen if blood Phe levels were maintained at 3–5 times normal; would the cognitive deficits eventually disappear? The data do not presently exist to answer that question. Amino acid uptake across the blood–brain barrier changes during development, offering more protection against blood Phe elevations as children get older (Greengard and Brass, 1984; Lajtha et al., 1987). Thus, it is quite possible that the blood Phe levels we found to be detrimental during infancy and early childhood might be more benign in later childhood or adolescence.

Early cognitive deficits or developmental delays – especially when they extend over a long period (such as the 6-year period we have documented) – are likely to have profound and enduring effects, even if the cognitive deficits themselves are subsequently resolved. They affect children's perceptions of, and expectations for, themselves and the perceptions and expectations of others for the children. Such perceptions and expectations can be inordinately difficult to change and can have major effects in shaping development and behavior.

Selective, rather than global, cognitive deficits

The same children, who were impaired on all 6 working memory + inhibitory control tasks, performed well on the 10 control tasks, which required other cognitive abilities dependent on other neural systems such as parietal cortex or the medial temporal lobe. Performance on

the control tasks, moreover, was not related to current blood Phe levels. For each of the 10 control tasks, we compared the performance of PKU children with higher blood Phe levels (6–10 mg/dl; 3–5× normal) to that of the 4 comparison groups: other PKU children with lower blood Phe levels, siblings of the PKU children, matched controls, and children from the general population. This yielded a total of 40 pairwise comparisons (10 tasks × 4 comparisons per task). PKU children with higher Phe levels performed worse on only 10 percent of these comparisons (see table 22.3 above). This pattern of 36 out of 40 comparisons in the predicted direction would be extremely unlikely to occur by chance ($p < .001$ [z distribution]). The consistency of the deficits of the PKU children with Phe levels 3–5 times normal on the working-memory-plus-inhibitory-control tasks and the paucity of deficits on the control tasks is quite striking (55 out of 64 comparisons in the predicted direction [86 percent], $p < .0001$, z distribution).

Thus, the cognitive deficits in children treated early and continuously for PKU, whose blood Phe levels are 3–5 times normal, appear to be selective. The functions of parietal cortex and of the medial temporal lobe appear to be spared, even if the children's Phe levels go up to 6–10 mg/dl. This is consistent with reports by Welsh et al. (1990) and Smith et al. (1996) who found (a) greater impairments on tasks dependent on prefrontal cortex than on tasks dependent on parietal cortex or the medial temporal lobe in those treated early and continuously for PKU, and (b) an inverse relationship between Phe levels and performance on tasks dependent on prefrontal cortex function but no such relationship for tasks dependent on parietal cortex or the medial temporal lobe. This is an example of a very specific, selective effect resulting from a global insult (a moderate elevation in Phe and moderate reduction in tyrosine in the bloodstream that feeds the entire body, and moderately too little tyrosine in the entire brain). The reason for the specificity is the differential, unique sensitivity of prefrontally-projecting dopamine neurons to a mild reduction in the dopamine precursor, tyrosine.

This finding of a deficit in the working memory and inhibitory control functions of DL-PFC, but not in the cognitive functions dependent on other neural systems, is consistent with the mechanism I have hypothesized as the cause of the cognitive deficits: A moderate imbalance in the Phe:tyrosine ratio in blood (as when Phe levels are 3–5 times normal in PKU children) adversely affects the dopamine concentration in prefrontal cortex but not other dopamine systems in the brain because of the special properties of the prefrontally-projecting dopamine neurons, which makes them unusually vulnerable to modest reductions in the level of tyrosine reaching the brain. The specificity of the deficits observed suggests that the cause of those deficits is probably too little tyrosine reaching the brain, rather than too much Phe reaching the brain, because all neural regions would be equally vulnerable to the negative effects of too much Phe; the functions of DL-PFC would not be disproportionately affected. That is, if the cause of the cognitive deficits were too much Phe in the brain, the cognitive deficits should be global, rather than limited to the prefrontal neural system.

Findings we had NOT predicted: Preserved performance on self-ordered pointing and temporal order memory Tasks

The mechanism I have proposed to explain the cause of the cognitive deficits in children treated early and continuously for PKU whose Phe levels are 3–5 times normal, rests on the special properties of the dopamine neurons that project to prefrontal cortex. I had not hypothesized that only certain cognitive functions dependent on DL-PFC would be affected. I was surprised, therefore, that we found that PKU children with Phe levels

3–5 times normal performed normally on 3 tasks dependent on DL-PFC: the three- and six-boxes tasks ([boxes scrambled after each reach], which are adaptations of the Petrides and Milner self-ordered pointing task) and the Corsi–Milner test of temporal order memory. These tasks require working memory (remembering what choices one has already made or remembering the order in which stimuli have been presented) but not inhibitory control. Thus, the treated PKU children with moderately elevated Phe levels were only impaired on the subclass of prefrontal cortex tasks that required *both* working memory and resisting a prepotent action tendency.

These findings were puzzling since there had been nothing in my hypothesis to lead one to predict that certain cognitive functions dependent on dorsolateral PFC should be affected but not others. Although I have emphasized the conjunction of working memory plus inhibitory control as the hallmark of tasks dependent on DL-PFC, I had no explanation at the time for why performance on only certain cognitive tasks that require the functions of prefrontal cortex should be affected in PKU children. The evidence linking self-ordered pointing and temporal order memory to DL-PFC is strong, with converging evidence from lesion studies in rhesus macaques, human adult patients with damage to DL-PFC, and neuroimaging studies in normal human adults (e.g., Petrides and Milner, 1982; Milner et al., 1991; Petrides et al., 1993; Petrides, 1995a) – it was extremely unlikely that the failure to find a deficit on these tasks was due to their not requiring DL-PFC.

An excellent recent study by Collins et al. (1998) begins to make sense of what we found. They compared the effect of lesioning prefrontal cortex to the effect of depleting prefrontal cortex of dopamine. Their anatomical lesions were excitotoxic, which is a technique that destroys the cell bodies in the target region, but not the fibers of passage, so that one can have more confidence than with traditional lesioning methods that the observed effect is due to damage to the target region specifically. They depleted prefrontal cortex of dopamine by injecting it with 6-hydroxydopamine (6-OHDA). The concentrations of norepinephrine and serotonin in prefrontal cortex were not similarly reduced because the investigators pre-injected prefrontal cortex with a norepinephrine antagonist (talsupram) and a serotonin antagonist (citalopram). Although their work is in the marmoset, they replicated the findings of others in the rhesus macaque, plus they added one important new finding.

Replicating the work of others (e.g., Butters et al., 1969; Goldman and Rosvold, 1970; Diamond and Goldman-Rakic, 1989), Collins et al. (1998) found that their lesions of prefrontal cortex impaired performance on the delayed response task. Similarly, like others (e.g., Petrides and Milner, 1982; Petrides, 1995a) they found that their lesions of prefrontal cortex impaired performance on the self-ordered pointing task, and to the same degree as the same lesions impaired performance on delayed response. Finally, as others had reported (e.g., Sawaguchi and Goldman-Rakic, 1991), they found that depleting prefrontal cortex of dopamine impaired performance on delayed response. No one before had ever looked at the effect of dopamine depletion on self-ordered pointing. However, Collins et al. (1998) found that, when they depleted the same region of prefrontal cortex of dopamine, performance on the self-ordered pointing task was *not impaired*. (See table 22.4 for a summary of this set of results.)

Thus, even though prefrontal cortex is necessary for successful performance on self-ordered pointing (as can be seen from the lesion results), the dopamine innervation of prefrontal cortex is not necessary for successful performance of the task. Luciana and Collins (1997) found a dissociation that is perhaps similar in that performance on one of their working memory tasks appeared to rely critically on dopamine while performance of

Table 22.4 Summary of the results of the 1998 study by Collins, Roberts, Dias, Everitt, and Robbins

	Behavioral Task	
	Delayed Response	*Self-Ordered Pointing*
Type of Lesion to Frontal Cortex:	requires working memory + inhibition	requires working memory
Excitotoxic (cell bodies destroyed)	Performance IMPAIRED	Performance IMPAIRED
6-OHDA (dopamine depleted)	Performance IMPAIRED	Performance ***SPARED***

the other working memory task did not. They found that a dopamine agonist (bromocriptine) improved performance on delayed response and a dopamine antagonist (haloperidol) impaired performance on delayed response, but neither affected performance on a non-spatial working memory task. Unfortunately, though, there is no evidence that Luciana and Collins' non-spatial working memory task requires DL-PFC.

The effects we documented in children treated with PKU whose blood Phe levels were 6–10 mg/dl, is (we contend) due to reduced dopamine in prefrontal cortex. Consistent with the results that Collins et al. (1998) obtained after our study was completed, we found that these treated PKU children were impaired on our delayed response task (A-not-B) but not on our self-ordered pointing tasks (three- and six-boxes [boxes scrambled after each reach]). The results that had seemed puzzling at the time end up providing additional support for our hypothesis. It appears that the dopamine content of prefrontal cortex is critical for certain cognitive functions dependent on prefrontal cortex (working memory + inhibition) but not for others (when working memory is taxed alone). We still do not understand, however, why that is the case. Luciana and Collins (1997) suggested that dopamine might be critical when the information that must be held in mind is spatial. Such an explanation cannot account for our results, however, because not only were the prefrontal tasks on which we found sparing non-spatial, but we found impairments on the day–night and tapping tasks (neither of which require attending to, or holding in mind, spatial information).

An Animal Model of Mild, Chronic Plasma Phe Elevations

With children it was possible only to measure blood levels of Phe and tyrosine and cognitive performance. To more directly investigate the biological mechanism underlying the cognitive deficits of children treated for PKU, we developed and characterized the first animal model of treated PKU (Diamond et al., 1994b) and subsequently worked with the genetic mouse model of PKU (Zagreda et al., 1999). The animal model enabled us to study the effect of moderate, chronic plasma Phe elevations on neurotransmitter and metabolite levels in specific brain regions. Thus, we could directly investigate our hypothesis that the cognitive deficits associated with moderately elevated plasma Phe levels are produced by a selective reduction in dopamine synthesis in prefrontal cortex.

Building on work modeling the untreated PKU condition (Greengard et al., 1976; Brass and Greengard, 1982), Diamond et al. (1994) administered a phenylalanine hydroxylase inhibitor (a-methylphenylalanine) plus a small supplement of Phe to mildly and chronically elevate the blood Phe levels in rat pups. (The Phe supplement was needed because a-methylphenylalanine does not inhibit phenylalanine hydroxylase completely.) There were 2 experimental groups: (a) pups whose blood Phe levels were elevated postnatally, and (b) pups whose blood Phe levels were elevated pre- and postnatally. Control animals came from the same litters as the first group and received daily control injections of saline.

All were tested on delayed alteration, a task sensitive to prefrontal cortex dysfunction (e.g., Bättig et al., 1960; Kubota and Niki, 1971; Wikmark et al., 1973; Larsen and Divac, 1978; Bubser and Schmidt, 1990). Testers were blind to the group assignment of their animals. Each of the testers was assigned 4 animals in each group and the order of testing was randomized across experimental condition. Blood samples were collected at multiple time points to determine the animals' Phe levels. High performance liquid chromatographic (HPLC) analyses of the brain tissue assessed the distributions and concentrations of dopamine, serotonin, norepinephrine, and their metabolites in various brain regions (prefrontal cortex, caudate-putamen, and nucleus accumbens).[1]

The most dramatic neurochemical effects of the moderate elevation in blood Phe levels was the reduction in dopamine and in the dopamine metabolite, HVA, in prefrontal cortex in each of the PKU-model animals. There was almost no overlap between HVA levels in the prefrontal cortex of controls and that of either PKU-model group: All control animals but one had higher HVA levels in prefrontal cortex than *any* animal in either experimental group. In contrast, as predicted, the levels of dopamine and dopamine metabolites were not reduced elsewhere in the brain, and norepinephrine levels were not reduced elsewhere in the brain or in prefrontal cortex. We had predicted that norepinephrine levels would be unaffected (even though norepinephrine is made from dopamine) because previous work had shown that norepinephrine levels are relatively insensitive to alterations in precursor (Irie and Wurtman, 1987).

The PKU-model animals were impaired on delayed alternation in the same ways and under the same conditions as are animals with prefrontal cortex lesions. On the delayed alternation task, the animal is rewarded only for alternating goal arms (i.e., for selecting the goal arm *not* selected on the previous trial). Thus, the animal must remember which goal arm was last entered over the delay between trials and must inhibit repeating that response. The hallmark of performance after prefrontal cortex is removed is that subjects fail when a delay is imposed between trials, although they are unimpaired at learning the alternation rule or in performing the task when no delay is imposed (*in rats*: e.g., Wikmark et al., 1973; Larsen and Divac, 1978; Bubser and Schmidt, 1990; *in monkeys*: e.g., Jacobsen and Nissen, 1937; Bättig et al., 1960; Kubota and Niki, 1971). We found that the animals with moderately elevated plasma Phe levels learned the delayed alternation task normally and performed well when there was no delay, but failed when a delay was imposed between trials (see figure 22.8), just as do prefrontally-lesioned animals.

Moreover, we found that the lower an animal's prefrontal dopamine levels, the worse that animal performed on the delayed alternation task. The neurochemical variable most strongly and consistently related to performance on delayed alternation was the level of HVA in prefrontal cortex. This is consistent with previous work, which has demonstrated that delayed alternation performance is highly dependent on the level of dopamine in

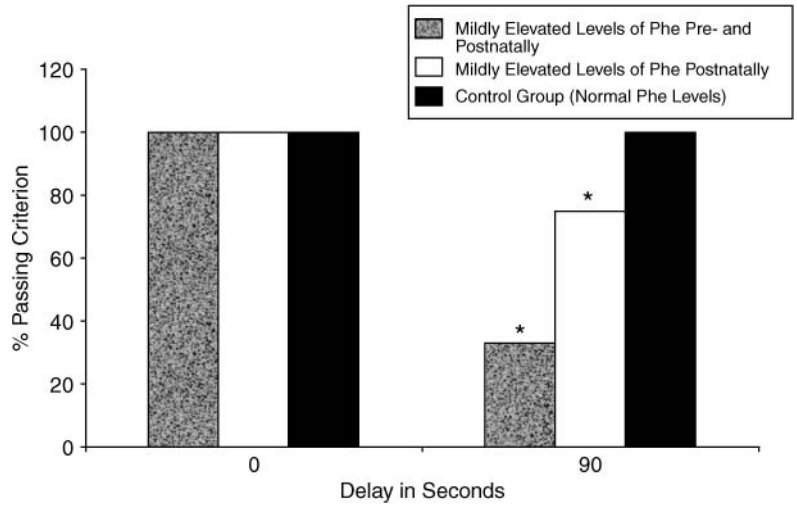


Figure 22.8 Rats with chronic, mild elevations in their blood Phe levels, to create an animal model of early- and continuously-treated PKU, show the same pattern of performance on the delayed alternation task, as do monkeys in whom dorsolateral prefrontal cortex has been lesioned and as do rats in whom the homologue to dorsolateral prefrontal cortex has been lesioned. That is, they can learn the delayed alternation rule and perform well when there is no delay, but are impaired when a delay is introduced.

prefrontal cortex, and is uncorrelated with serotonin or norepinephrine levels (Brozoski et al., 1979; Sahakian et al., 1985; Simon et al., 1980) or with dopamine elsewhere in the brain (Sahakian et al., 1985; Simon et al., 1980).

Thus, Diamond et al. (1994b) found the neurochemical changes (reduced levels dopamine and the dopamine metabolite, HVA, in prefrontal cortex) and the cognitive deficits (impaired performance on a behavioral task dependent on prefrontal cortex [delayed alternation]) predicted by our model in both groups of PKU-model animals with moderately elevated blood Phe levels. The only result that deviated from those predicted was an effect on the serotoninergic system in PKU-model animals. The lack of complete specificity may have been because blood Phe levels were a bit more elevated than intended (6.5× normal, rather than $\leq 5\times$ normal) or because the neurochemical effects of moderately elevated blood Phe levels are not quite as localized as I have hypothesized. We are investigating this further with the genetic mouse model of PKU created by McDonald and colleagues (McDonald et al., 1990; Shedlovsky et al., 1993).

What We Thought was Independent, Confirming Evidence from Visual Psychophysics for the Proposed Causal Mechanism

If it is the special properties of the dopamine neurons that project to prefrontal cortex that make the functions of prefrontal cortex particularly vulnerable to moderate increases in the ratio of Phe to tyrosine in the bloodstream, then any other dopamine neurons that share those special properties should also be affected by moderately elevated blood Phe:tyrosine ratios. It

so happens that the dopamine neurons in the retina share all those same unusual properties. They, too, have unusually rapid firing and dopamine turnover rates (Iuvone et al., 1978; Fernstrom et al., 1986; Iuvone et al., 1989). Moreover, the competition between Phe and tyrosine at the blood–retinal barrier is fully comparable to their competitive uptake at the blood–brain barrier (Rapoport, 1976; Hjelle et al., 1978; Fernstrom et al., 1986; Tornquist and Alm, 1986). Indeed, it has been shown that a small reduction in the level of tyrosine reaching the retina dramatically reduces retinal dopamine synthesis (Fernstrom et al., 1986; Fernstrom and Fernstrom, 1988), mirroring the effect on dopamine synthesis in prefrontal cortex. Therefore, to be consistent, I had to predict that retinal function should also be affected in PKU children who have been on a low-Phe diet since the first month of life, but who have moderately elevated blood Phe levels (levels roughly 3–5 times normal [6–10 mg/dl; 360–600 mmol/L]) – even though no visual deficit had been reported in these children before.

The aspect of retinal function most firmly linked to the level of dopamine in the retina is contrast sensitivity. Contrast sensitivity refers to one's ability to detect differences in luminance (brightness) of adjacent regions in a pattern. Your contrast sensitivity threshold is the limit of how faint items printed in gray can become before you fail to perceive them at all. People with better contrast sensitivity can perceive fainter lines than can people who require more of a luminance difference between foreground and background. Patients with Parkinson's disease, who have greatly reduced levels of dopamine, have impaired contrast sensitivity (Kupersmith et al., 1982; Regan and Neima, 1984; Skrandies and Gottlob, 1986; Bodis-Wollner et al., 1987; Bodis-Wollner, 1990). It is thought that this occurs because dopamine is important for the center-surround organization of retinal receptive fields (Bodis-Wollner and Piccolino, 1988; Bodis-Wollner, 1990).

To investigate contrast sensitivity, we (Diamond and Herzberg, 1996) tested children between the ages of 5.4 and 9.8 years on the Vistech test (Ginsberg, 1984; Rogers et al., 1987; Mäntyjärvi et al., 1989; Tweten et al., 1990; Gilmore and Levy, 1991; Lederer and Bosse, 1992). We found that children treated early and continuously for PKU, whose blood Phe levels were 6–10 mg/dl (3–5× normal), were impaired in their sensitivity to contrast at each of the 5 spatial frequencies tested (1.5–18.0 cycles per degree; see figure 22.9). Even though all children had been tested under conditions of 20/20 acuity, the PKU children were significantly less sensitive to visual contrast than their same-aged peers across the entire range of spatial frequencies. These group differences remained robust even when the two PKU children whose IQs were below 90 were omitted from the analyses. Indeed, at the next to the highest spatial frequency (12 cycles per degree), the "group" variable accounted for 70 percent of the variance, controlling for acuity, gender, age, and testsite. At no spatial frequency was the contrast sensitivity of any PKU child better than that of his or her own sibling. Acuity was normal in the treated PKU children. Standard eye exams had never detected a problem in this population because acuity is normally tested under conditions of high contrast; an impairment in contrast sensitivity was not revealed before because no one had tested for it.

At the time, we interpreted these results as providing converging evidence in support of the biological mechanism I had proposed. I had predicted the contrast sensitivity deficit for the same reason I had predicted DL-PFC cognitive deficit. Both predictions had been based on the special sensitivity of dopamine neurons that fire rapidly and turn over dopamine rapidly to moderate reductions in the level of available tyrosine. We had found two superficially unrelated behavioral effects, a selective deficit in cognitive functions dependent on DL-PFC and a selective visual defect in contrast sensitivity, both of which had been predicted based on the same underlying hypothesis.

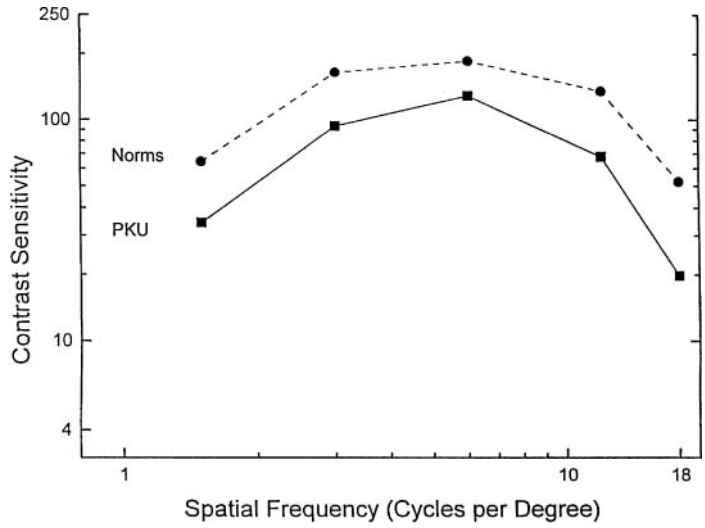


Figure 22.9 PKU children whose blood Phe levels are 6–10 mg/dl were found to be significantly impaired in contrast sensitivity compared to children of the same age at every spatial frequency investigated.

However, I was troubled by one lack of convergence. In the Diamond and Herzberg study (1996), we found that contrast sensitivity performance did not correlate with children's current blood Phe levels, but rather with their Phe levels during the first month of life. Whereas in the Diamond et al. (1997) study, we had found that, on the cognitive tasks that required the working memory and inhibitory control functions dependent on DL-PFC, performance had correlated with children's current blood Phe levels, not their Phe levels during the first month of life.

If contrast sensitivity were poor because the retina was low on "fuel" (i.e., low in dopamine) then contrast sensitivity performance should have covaried with current blood Phe levels. The failure to find such a relationship might have been due simply to the truncated range of concurrent Phe levels in the contrast sensitivity study. Only PKU children whose current Phe levels were 6–10 mg/dl had been included in that study; whereas the cognitive study had included PKU children with lower Phe levels as well as those with Phe levels of 6–10 mg/dl. On the other hand, the range in Phe levels during the first month of life was great and so included sufficient variability to find a relationship with contrast sensitivity performance. The possibility also existed, however, that long-lasting structural damage might occur to the visual system during the first weeks of life, when the visual system is maturing rapidly, and when the Phe levels of PKU infants are dramatically elevated. PKU infants are generally not placed on the low-Phe diet until they are about 2 weeks old; thus for the first 2 weeks of life, their Phe levels can easily reach 20–30 mg/dl. Might those extremely high Phe levels, at a time of very rapid maturation of the visual system, cause irreparable damage to the visual system? (In utero, the fetus's levels of Phe and tyrosine depend upon the mother's levels, so it is believed that the detrimental effects of PKU begin postnatally.)

One way to test for the latter possibility is to study pairs of siblings, both of whom have PKU. Since over 150 different mutations of the phenylalanine hydroxylase gene can cause

PKU, amniocentesis testing for PKU is extremely expensive. Therefore, fetuses are not usually tested for PKU unless there is already one child with PKU in the family. In the US, the older sibling with PKU (in whom it was detected postnatally) usually starts the low-Phe diet at about $1\frac{1}{2}$–2 weeks of age, while the younger sibling (in whom PKU was detected prenatally) usually starts the low-Phe diet by 2 or 3 days of age. For this study we have been flying in pairs of PKU siblings from all over the US and UK (Diamond et al., 1999a). Within each of these families, the earlier-born child (mean age at testing = 13 years, range = 7–16 years) was exposed to extremely high levels of Phe for a mean of 11 days (range = 8–14 days before initiation of diet), while the later-born sibling (mean age at testing = 10 years, range = 6–14 yrs) was exposed to extremely high levels of Phe for a mean of only 3 days (range = 1–5 days). All of the children began the low-Phe diet within the first month of life and have remained on it continuously ever since.

Our preliminary results indicate that the earlier-born PKU siblings show worse contrast sensitivity (as measured by the Regan low contrast letter acuity charts [Regan and Neima, 1983]) than their later-born siblings under conditions of low contrast (4 percent contrast; see figure 22.10). This is striking because contrast sensitivity usually improves with age. For example, among siblings pairs without PKU, older siblings performed significantly

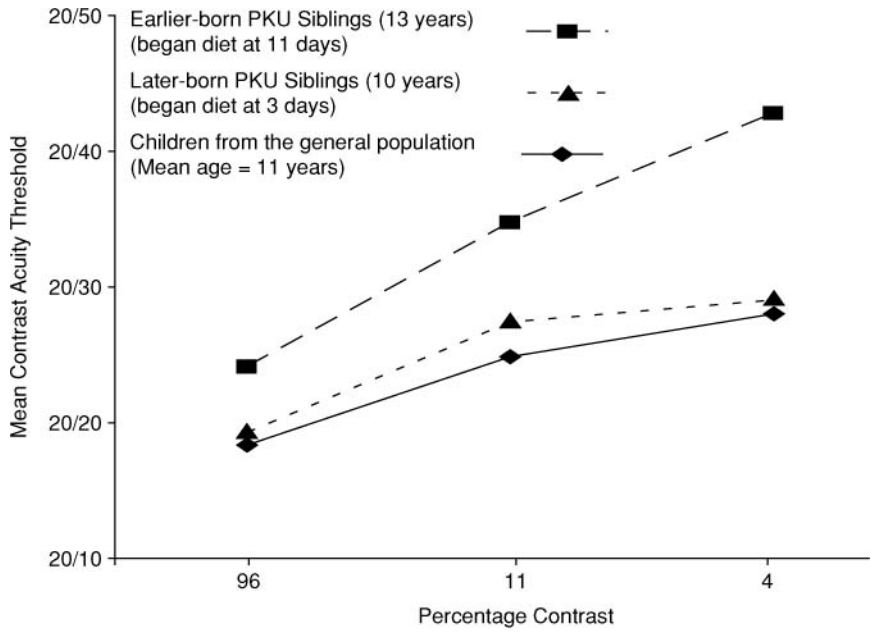


Figure 22.10 Discrimination performance for the PKU sibling pairs and a normal comparison group are shown for the three acuity charts, each chart was presented at a different level of contrast (96%, 11% and 4%). Thresholds were calculated by using the least squares error method to apply a linear curve fit to the obtained data and selecting the 75% correct discrimination value as the threshold. Earlier-born PKU children, who started on dietary treatment at roughly 11 days of age, showed impaired acuities compared to the other children, as can be seen by their elevated line on the graph. Since the charts differed only in contrast, the sharper drop-off in performance of the earlier-born PKU children when tested at lower contrast, indicates that these children have a deficit in contrast sensitivity.

better than their younger siblings, the reverse of the pattern seen in the PKU sibling pairs. The earlier-born PKU siblings (who started diet at $1\frac{1}{2}$–2 weeks of age) also showed worse contrast sensitivity than their same-age peers (see figure 22.10).

These results suggest that a short exposure, of only a couple of weeks, to high concentrations of Phe during the sensitive neonatal period can have long-lasting effects on the visual system, evident 13 years later, even if Phe levels are subsequently lowered and maintained at lower levels. This is significant because it suggests that the current practice of allowing up to 2 weeks to pass before beginning treatment for an infant born with PKU may be ill-advised. Since the blood sample to test for PKU is taken at birth, it would be feasible to start the diet earlier. These results also suggest that although we obtained the results I had predicted for contrast sensitivity in the Diamond and Herzberg (1996) study, we obtained those results for reasons *other* than the ones I had predicted. The deficits in the working memory and inhibitory control abilities dependent on DL-PFC do indeed appear to occur for the reason I had hypothesized (because of reduced levels of dopamine in DL-PFC due to elevated blood ratios of Phe to tyrosine). Those deficits covary with concurrent levels of Phe in the bloodstream. However, the retinal deficit in contrast sensitivity appears to be caused by the inordinately high levels of Phe in the first weeks of life, does not covary with current levels of Phe, and appears to be structural.

Conclusions

DL-PFC is recruited when one must concentrate, such as when one must both hold information in mind and inhibit a prepotent response. DL-PFC begins subserving these cognitive functions even during the first year of life. Even as infants, we are thinking problem-solvers. Prefrontal cortex continues to mature over the next 15–20 years of life, just as the child's cognitive development, while remarkable by 1 year, continues to unfold over the next 15–20 years.

Dopamine is a particularly important neurotransmitter in prefrontal cortex. The level of dopamine increases in the brain of rhesus macaques during the period when infant rhesus macaques are improving on the A-not-B/delayed response and object retrieval tasks, tasks linked to DL-PFC. To begin to look at the role of dopamine in prefrontal cortex function early in life in humans we studied children treated early and continuously for PKU because we predicted that they would have lower levels of dopamine in prefrontal cortex, but otherwise normal brains, a prediction we were able to confirm in an animal model. We predicted this because the children have moderately elevated levels of Phe (3–5 times normal [6–10 mg/dl]) and moderately reduced levels of tyrosine in their bloodstreams. Since Phe and tyrosine compete to cross from blood to brain, and since the transporter proteins have a higher affinity for Phe than for tyrosine, the upshot of a moderate increase in the Phe:tyrosine ratio in the bloodstream is a moderate reduction in the amount of tyrosine reaching the brain. Most dopamine systems in the brain are insensitive to modest decreases in the amount of precursor (i.e., tyrosine). However, the dopamine neurons that project to prefrontal cortex are different. They fire faster and turn over dopamine faster, and are acutely sensitive to even a modest change in the level of tyrosine. Because of the special properties of this dopamine projection, we predicted and found a specific, localized effect (prefrontal cortex affected but not other regions of the brain) even though the insult is global (a mildly increased Phe:tyrosine ratio throughout the bloodstream and mildly reduced tyrosine levels throughout the brain).

Cognitive deficits in children treated early and continuously for PKU whose blood Phe levels are 3–5 times normal went officially unrecognized for years, despite the protestations of parents and teachers that something was wrong, in part because the children performed within the normal range on IQ tests. Their IQ scores were in the 80s and the 90s, just as are the IQ scores of patients in whom prefrontal cortex has been damaged or removed. IQ tests, or any general tests of intellectual functioning, can easily miss specific deficits. The global cognitive measures that had been in use in clinics were too imprecise to detect the children's deficits. Global measures, such as overall IQ score, are poor indices of *specific* cognitive functions and poor indicators of what particular neural system might be affected if there is a problem. Developmental cognitive neuroscientists now have precise measures of specific cognitive functions, sensitive to the functions of particular neural subsystems. These measures can help in the study and treatment of diverse developmental disorders.

The other reason for the lack of official recognition of the cognitive deficits in children treated early and continuously for PKU was the lack of any hypothesized causal mechanism whereby a global insult might produce a selective effect on the functions of only one neural system (prefrontal cortex). The information on such a causal mechanism already existed in neuropharmacology through the work of Anne-Marie Thierry, Robert Roth, Michael Bannon, and colleagues, but the clinicians working on PKU and the neuroscientists working on the properties of the dopamine projection to prefrontal cortex did not know of one another's work.

Young children often fail to inhibit the prepotent response, despite their best intentions and despite knowing what they should do. It would be a shame to mistakenly label such a young child as "bad," "stupid," or "willful." It is not enough to know something or remember it, one must get that knowledge into one's behavior. Infants and young children, in whom prefrontal cortex is not yet mature, sometimes do the wrong thing even though they know what they should do and are trying to do it. Their attention is sometimes so captured by the desired goal object that they either cannot inhibit responding (as in delay of gratification or Go–No Go paradigms) or cannot override the strong tendency to go straight to that goal when an indirect route is required (as in the object retrieval and windows tasks). To sustain focused concentration one needs to be able to resist distraction; to relate multiple ideas to one another one needs to resist focusing exclusively on only one idea; when visual perception is misleading one needs to be able to resist acting in accord with what one sees; and to act in new ways one needs to resist falling back into one's usual way of acting or thinking. That is, one needs inhibitory control, dependent upon prefrontal cortex. The ability to exercise inhibitory control, which prefrontal cortex makes possible, frees us to act according to what we choose to do rather than being simply creatures of habit or immediate perception. The ability to hold information in mind, which also depends upon prefrontal cortex, enables us to remember what we are supposed to do, to consider alternatives, to remember the past and consider the future, and to use what we know and not just what we see to help guide our actions and choices. These abilities make it possible for us to solve new, undreamed-of challenges and make it possible for us to exercise free will and self-determination. This is not to say that it makes it easy, of course, but prefrontal cortex helps make it possible.

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NOTE

1 We had intended to include two regions of frontal cortex (prefrontal cortex and the anterior cingulate). However, it turned out the brain sections we sampled to assess the anterior cingulate were actually from prefrontal cortex.

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