# Frontal Lobe Function and Dysfunction

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# 18
# Guidelines for the Study of Brain-Behavior Relationships During Development

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One way to study the relationship of brain maturation to the elaboration of cognitive abilities during development is to use a two-pronged approach: (1) Study the developmental progression of children's performance on behavioral tasks, and (2) link successful performance on those tasks uniquely to specific neural systems. I would like to suggest a set of guidelines for the conduct and evaluation of such research. I will use the work of myself and others on the development of cognitive abilities linked to dorsolateral prefrontal cortex to illustrate these guiding principles.

### A Brief Overview of the Anatomical Connections and Functions of Dorsolateral Prefrontal Cortex

Dorsolateral prefrontal cortex is located between the frontal pole and the arcuate sulcus in the monkey brain (see Fig. 18–4). It is centered around the principal sulcus (Walker's area 46) and is immediately anterior to the supplementary motor area (SMA) and premotor cortex. SMA and premotor cortex, like dorsolateral prefrontal cortex, are among the subregions of frontal cortex. Dorsolateral prefrontal cortex is defined anatomically, in part, by its reciprocal connections with the **parvocellular portion of the mediodorsal nucleus of the thalamus** (Rose and Woolsey, 1948; Johnson et al., 1968; Leonard, 1969). It also has strong reciprocal connections with **parietal cortex,** and the dorsolateral prefrontal and parietal cortices appear to be coupled in their projections throughout the brain (Pandya and Kuypers, 1969; Goldman and Nauta, 1977; Goldman-Rakic and Schwartz, 1982; Schwartz and Goldman-Rakic, 1984; Selemon and Goldman-Rakic, 1985a,b; 1988; Johnson et al., 1989). The same may be true of the dorsolateral prefrontal and **premotor** cortices to a lesser extent (Pandya and Vignolo, 1969; 1971; Haaxma and Kuypers, 1975; Pandya and Kuypers, 1969; Goldman and Nauta, 1977; Kunzle, 1978). One of the major output structures

of dorsolateral prefrontal cortex is the **caudate nucleus** (Nauta, 1964; Johnson et al., 1968; Kemp and Powell, 1970; Goldman and Nauta, 1977). Other output sites include the **superior colliculus** (Goldman and Nauta, 1976; Kunzle, 1978) and the **cingulate gyrus** (Johnson et al., 1968; Pandya and Vignolo, 1969; Goldman and Nauta, 1977; Kunzle, 1978).

Frontal cortex is the largest area of cortex in the human brain; it has increased the most in size (and in the proportion of brain mass devoted to it) over the course of evolution; and it has an unusually protracted period of maturation (probably only reaching full maturity during puberty). There is general agreement that the most anterior regions of frontal cortex (i.e., prefrontal cortex) subserve our highest cognitive abilities. Dorsolateral prefrontal cortex has been most closely associated with functions of memory and inhibitory control (see discussion of the critical abilities thought to be dependent on dorsolateral prefrontal cortex toward the close of this paper). The role of dorsolateral prefrontal cortex in helping us relate information separated in time or space, and in helping us gain control over our actions so we can choose what we want to do and not simply react, makes this area of the brain of great importance for complex cognitive operations.

The classic test for dorsolateral prefrontal cortex function in nonhuman primates is the delayed response task (Jacobsen, 1935; 1936; for reviews: Nauta, 1971; Warren and Akert, 1964; Rosvold, 1972; Markowitsch and Pritzel, 1977; Diamond, 1991a). This hiding task requires both memory and the ability to inhibit merely repeating the last rewarded response. The classic test for dorsolateral prefrontal cortex function in human adults is the Wisconsin Card Sorting Test (Milner, 1963; 1964). Here, as in delayed response, the subject must flexibly switch to a new response after having been rewarded for a particular response. The subject must remember which sorting criteria were most recently tried and found incorrect, and which sorting criterion is now correct.

The guiding principles I would like to suggest for research on brain-behavior relations in development are as follows:

## 1. Convergent Validity. Use *more than one task* linked to a given neural circuit and on which performance improves during a given period of development

It is important to look for converging evidence from diverse tests all linked to the same neural system. An impairment, or an improvement, on one test might be due to diverse causes; converging evidence from diverse tests is more convincing. These converging results are more powerful the more dissimilar the tasks.

Thus, in our work on the developmental progression during infancy of abilities dependent on dorsolateral prefrontal cortex, for example, we have used two hiding tasks (A$\overline{B}$ and delayed response), which require subjects to keep track of where the reward has been hidden in the absence of visible cues, and a transparent barrier detour task (object retrieval), where nothing is hidden and the reward is always visible, but a circuitous route to the goal is required (see e.g., Diamond,

1988; 1991a). A$\overline{\text{B}}$ and delayed response are almost identical tasks. They were chosen because delayed response has been so firmly and convincingly linked specifically to dorsolateral prefrontal cortex, and because A$\overline{\text{B}}$ has been repeatedly shown to be a clear marker of developmental change during infancy (e.g., Gratch, 1975; Wellman et al., 1987). The object retrieval task was chosen because it is very different from A$\overline{\text{B}}$ and delayed response, and yet work by Moll and Kuypers (1977) has linked it, too, to frontal cortex.

In the A$\overline{\text{B}}$ and delayed response tasks, the subject is centered between two identical hiding wells, one to the left and one to the right. The experimenter holds up an object of keen interest to the subject, and *as the subject looks on* the experimenter places this object in one of the two hiding wells. The experimenter then covers both hiding wells simultaneously with identical covers and a brief delay of 0–10 seconds is imposed during which the subject is prevented from looking at, or moving or straining toward, the correct well. After the delay, the subject is allowed to reach. In these details the A$\overline{\text{B}}$ and delayed response tasks are identical. The tasks differ solely in the rule for deciding where the reward is to be hidden. In A$\overline{\text{B}}$, the reward is hidden in the same well until the subject is correct to a specified criterion (typically, two consecutively correct responses), then the reward is hidden in the other well and the procedure repeated.[1] In delayed response, the hiding location of the reward is varied randomly by a predetermined schedule.

For the object retrieval task, a plexiglass box open on one side is used. A reward is placed in the box; the subject's task is to retrieve the reward. There is no delay nor time limit; a trial ends when the subject retrieves the reward or stops trying. Experimental variables include (1) which side of the box is open (front, top, left, or right), (2) distance of the reward from the opening (ranging from partially outside the box to deep inside the box), and (3) position of the box on the testing surface (near the front edge of the table or far; far to the left, at the midline, or far to the right). The reward is always visible when the box is transparent, but the experimental variables jointly determine whether the reward is seen through a closed side of the box or through the opening. (For greater detail see Diamond, submitted.) Object retrieval requires inhibition of the strong pull to reach straight to the visible reward (rather than detouring around the barrier), and like delayed response, A$\overline{\text{B}}$, and the Wisconsin Card Sorting Test, it requires the subject to remember which responses were most recently tried and found incorrect (in this case, which sides of the box were tried and found closed) and to flexibly switch to a new response.

The converging evidence one would like from the different tasks is that (1) they are all linked to the same neural circuit, and (2) developmental improvements in performance on the tasks occur during the same age period. It is important to be as precise as possible here. For example, different regions of frontal cortex (even different regions within prefrontal cortex) participate in different neural circuits (e.g., Goldman and Rosvold, 1970; Bachevalier and Mishkin, 1986). It is not sufficient, then, to use tasks linked simply to frontal cortex, nor even all linked to prefrontal cortex; they must be linked to the same functional region.

The work by Moll and Kuypers (1977), upon which our choice of the object
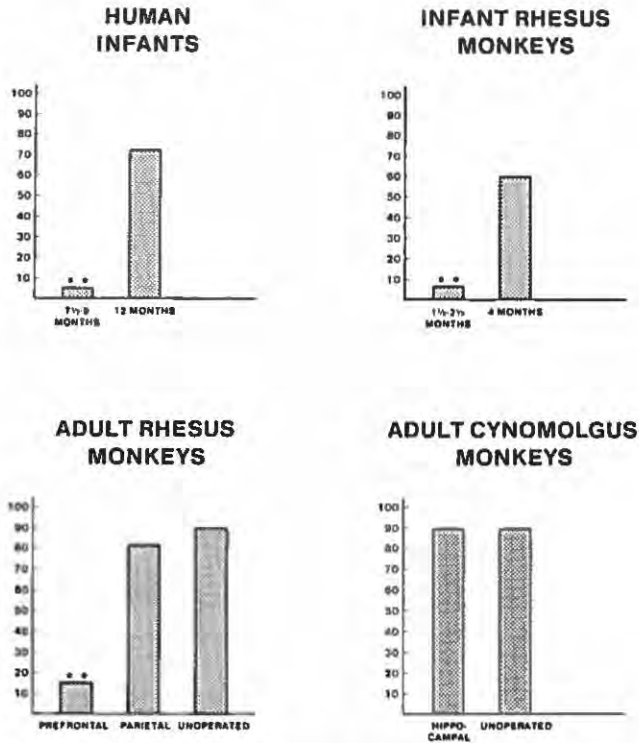
**Figure 18-1** Percentage of trials during object retrieval testing where subjects reached to the box opening without ever having looked into the opening on that trial. Human infants of 7½–9 months, adult monkeys with lesions of dorsolateral prefrontal cortex, and infant monkeys of 1½–2½ months almost never reach to the opening unless they have looked into the opening on that trial. On the other hand, 12-month-old human infants, 4-month-old infant monkeys, unoperated adult monkeys, and adult monkeys with lesions of parietal cortex or the hippocampus often reach to the opening without ever having looked into the opening on that trial. (This figure summarizes work from Diamond 1990b; submitted; Diamond and Goldman-Rakic, 1985; 1986; and Diamond et al., 1989b.)

retrieval task was based, had relied on very large lesions, spanning the supplementary motor, premotor, and dorsolateral prefrontal regions of frontal cortex. Our work, however, has shown that lesions restricted specifically to dorsolateral prefrontal cortex disrupt performance on the object retrieval task (Diamond and Goldman-Rakic, 1985) (Fig. 18-1).[2] Previous work had linked delayed response to dorsolateral prefrontal cortex; our work confirmed this (Diamond and Goldman-Rakic, 1989). Given the marked similarity between A$\overline{B}$ and delayed response it seemed likely that success on A$\overline{B}$, too, would depend on involvement of dorsolateral prefrontal cortex. Our work confirmed this suspicion; lesions restricted to dorsolateral prefrontal cortex disrupt performance on the A$\overline{B}$ task (Diamond and Goldman-Rakic, 1989) (Table 18-1).

Moreover, our work has shown that performance on all three tasks improves during the same period of development in both human infants and

Table 18-1 Percentage Correct on the AB̄ Task by Delay and by
Experimental Group

| Experimental groups | Delay (in seconds) | | |
|---|---|---|---|
| | 2 | 5 | 10 |
| Adult rhesus monkeys with lesions of dorsolateral prefrontal cortex | | | |
| F1 | 45 | | |
| F2 | 71 | 63 | 58 |
| F3 | 67 | 67 | 64 |
| F4 | 67 | 63 | 59 |
| Mean | 63 | 64 | 60 |
| Adult rhesus monkeys with lesions of parietal cortex | | | |
| P1 | 97 | 94 | 92 |
| P2 | 100 | 100 | 99 |
| P3 | 98 | 99 | 98 |
| Mean | 98 | 98 | 96 |
| Unoperated adult rhesus monkeys | | | |
| U1 | 99 | 98 | 98 |
| U2 | 96 | 98 | 96 |
| U3 | 99 | 96 | 97 |
| Mean | 98 | 97 | 97 |
| Adult cynomolgus monkeys with lesions of the hippocampal formation | | | |
| H1 | 98 | 93 | 87 |
| H2 | 100 | 88 | 86 |
| H3 | 95 | 95 | 80 |
| Mean | 98 | 92 | 84 |
| Unoperated adult cynomolgus monkeys | | | |
| C1 | 92 | 96 | 95 |
| C2 | 99 | 91 | 91 |
| C3 | 87 | 95 | 85 |
| Mean | 92 | 92 | 90 |
| 5-month-old infant rhesus monkeys with lesions of dorsolateral prefrontal cortex at 4 months | | | |
| I1 | 81 | 75 | 65 |
| I2 | 75 | 73 | 71 |
| Mean | 78 | 74 | 68 |
| Unoperated 5-month-old infant rhesus monkey | | | |
| I3 | 97 | 97 | 97 |

infant monkeys. In human infants, performance improves on AB̄, delayed response, and object retrieval between 7½ and 12 months of age (Diamond, 1985; Diamond and Doar, 1989; Diamond, submitted) (Figs. 18–2 and 18–3). In infant monkeys, performance improves on all three of these tasks between 1½ and 4 months of age (Diamond and Goldman-Rakic, 1986) (see Fig. 18–1 and Table 18–1).

## 2. Divergent Validity, 1: Study the role of *other neural regions* in performance of these tasks

To determine that the tasks of interest are linked specifically to one neural circuit it is important to demonstrate that the functioning of other neural regions is not also related to performance of these tasks.[3] For example, is improved perfor-
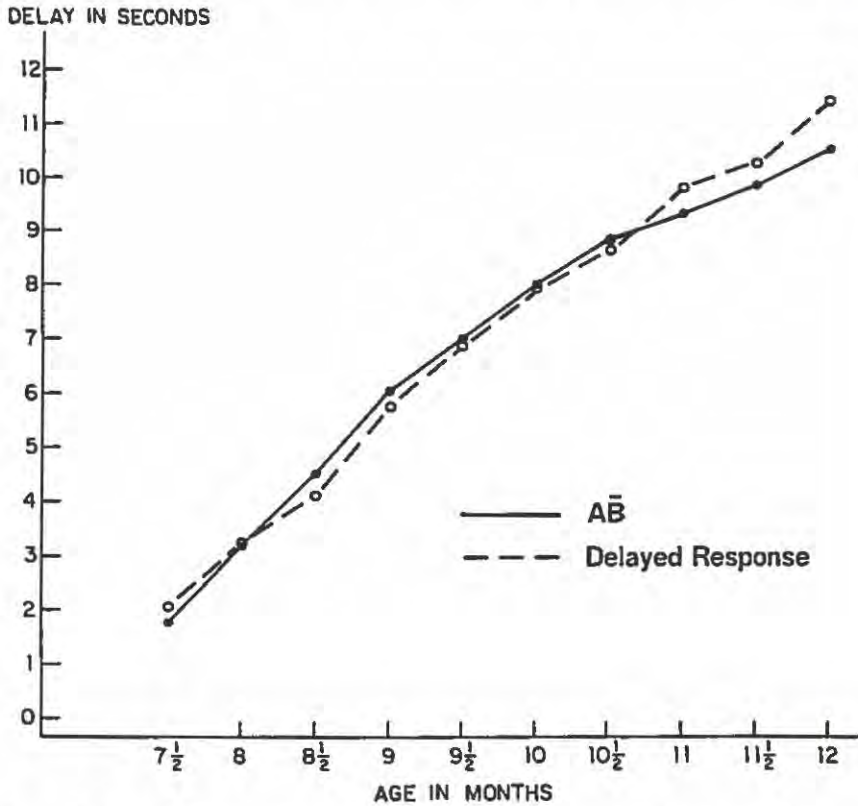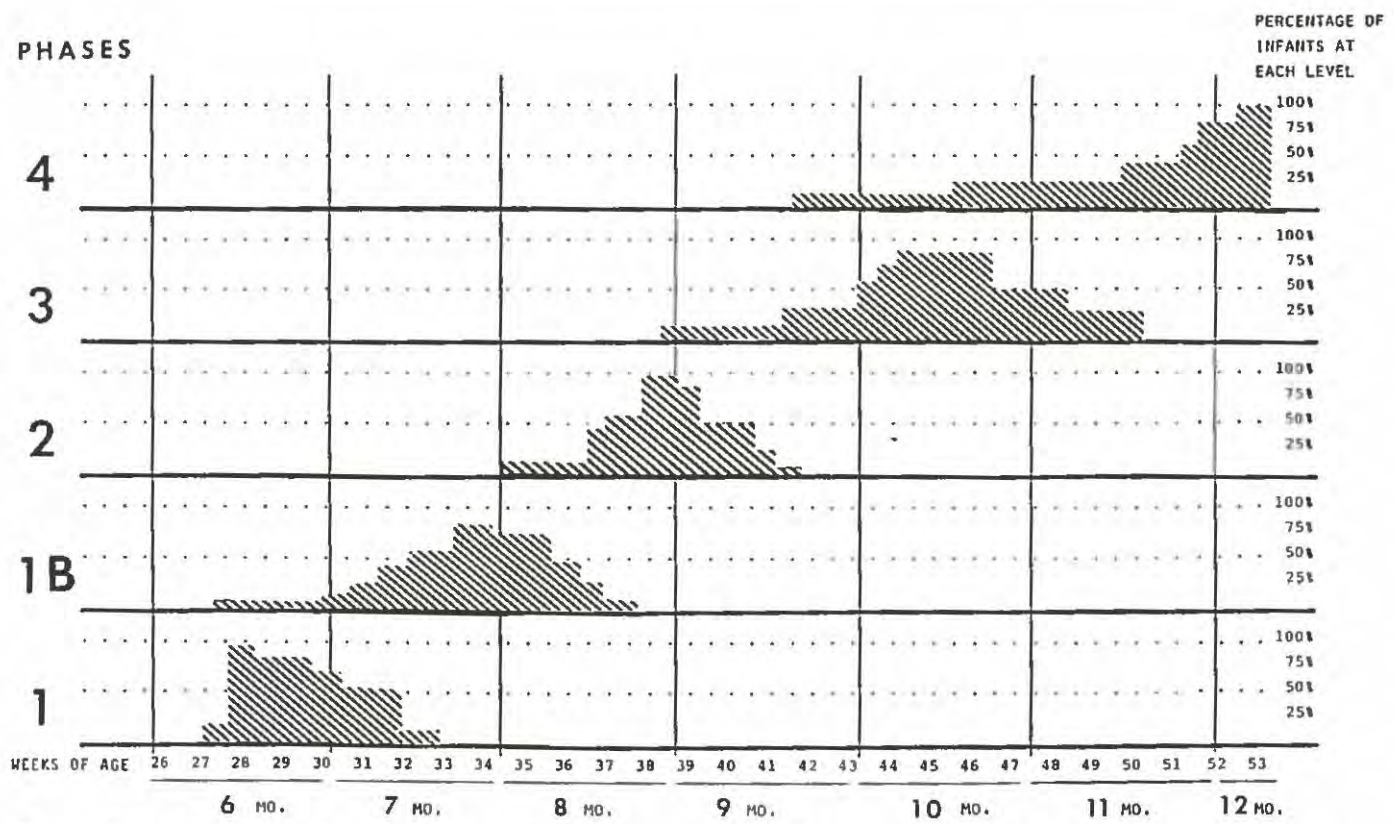
Figure 18–2  Developmental progression in the delay human infants can tolerate on the AB̄ and delayed response tasks. AB̄ results are usually reported in term of the age at which the AB̄ *error* occurs. In an attempt to use a comparable measure for the delayed response task, results are plotted here in terms of the delay at which errors occurred (i.e., the delay at which performance was below the criterion of 88% correct). The AB̄ results are shown by the solid line and are based on the infants studied longitudinally in Cambridge, MA by Diamond (1985). The delayed response results are shown by the dashed line and are based on the infants studied longitudinally in St. Louis, MO by Diamond and Doar (1989). (From Diamond and Doar, 1989, with permission. © John Wiley & Sons, Inc., 1989.)

mance simply due to general brain development? Is impaired performance a sequela that follows damage anywhere in the brain?

To address these kinds of questions, Diamond and Goldman-Rakic investigated the role of parietal cortex in performance of the AB̄, delayed response, and object retrieval tasks. Parietal cortex is involved in the processing of spatial information and the programming of movements in space (see, e.g., LaMotte and Acuna, 1978; Van Essen, 1979; Andersen, 1988). These abilities would appear to be relevant to all three tasks: In AB̄ and delayed response the hiding wells differ only in spatial location, and in object retrieval the subject must reach around a spatial barrier. Removing all of inferior parietal cortex (Brodmann's

**Figure 18-3** Developmental progression of the performance of human infants on the object retrieval task with transparent barrier, showing histograms for the age distribution of each phase. (From Diamond, submitted.)

area 7), however, had no observable effect on performance of A$\overline{B}$ and delayed response, and while the monkeys with lesions of parietal cortex showed some initial misreaching errors in aiming their hand to clear the box opening on object retrieval, they showed none of the errors on the task characteristic of monkeys with lesions of dorsolateral prefrontal cortex, infant monkeys, or human infants (Diamond and Goldman-Rakic, 1985; 1986; 1989) (see Table 18-1 and Fig. 18-1).

The abilities most generally considered essential for A$\overline{B}$ and delayed response are memory and inhibition; the latter is also thought essential for object
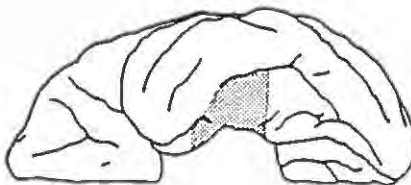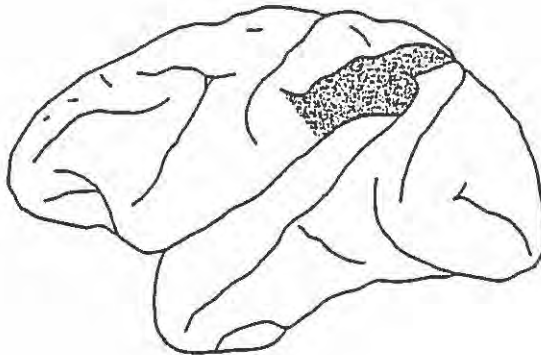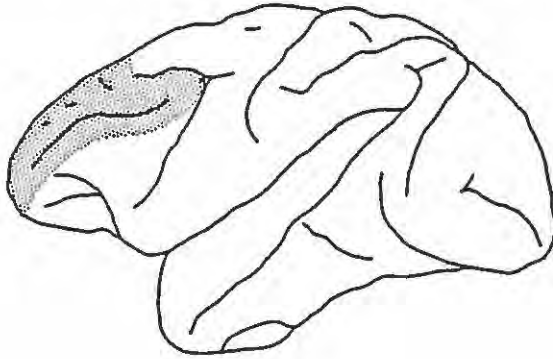
retrieval (see, e.g., Diamond, 1985; 1988; 1991a). These abilities are frequently associated with the hippocampus (see, e.g., Squire and Zola-Morgan, 1983; Douglas, 1967). Therefore, Diamond and colleagues (1989b) went on to investigate the role of the hippocampus in performance of these tasks. As was found with parietal cortex, however, the presence or absence of the hippocampus appeared to have no effect on performance of $A\overline{B}$ or delayed response at the brief delays at which monkeys with lesions of dorsolateral prefrontal cortex, infant monkeys, or human infants fail, and no effect on object retrieval performance (see Table 18–1 and Fig. 18–1). This was true even though (1) the lesions of the hippocampus included not only the hippocampus proper (Ammon's horn) but also the dentate gyrus, subiculum, 90% of the parahippocampal gyrus (area TF-TH of von Bonin and Bailey, 1947), and the posterior half of the entorhinal cortex (Fig. 18–4); and (2) the monkeys with these hippocampal lesions were profoundly impaired on delayed nonmatching to sample, a classic memory test closely linked to hippocampal function.

Delayed alternation bears some resemblance to delayed response, and performance on it, too, is impaired following lesions of dorsolateral prefrontal cortex. It was not chosen for study, however, because of questions of divergent validity—for delayed alternation is sensitive to damage to diverse regions of the brain (e.g., performance is impaired by lesions of the hippocampus or by lesions of dorsolateral prefrontal cortex). On this task, the reward is hidden (out of sight,

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Figure 18–4 Sites of the brain lesions. From top to bottom: dorsolateral prefrontal cortex lesion, inferior parietal cortex lesion, and hippocampal formation lesion (including the subiculum and posterior portion of the entorhinal cortex). The prefrontal and parietal lesions are shown on lateral views of the brain. The hippocampus is a deep structure that cannot be seen from the brain's surface. In the ventral view of the brain, the shaded area indicates the cortex that was removed in the hippocampal formation lesion. The hippocampus itself is buried deep beneath this region of cortex.

The dorsolateral prefrontal cortex lesions included cortex in both banks of the principal sulcus, the anterior bank of the arcuate sulcus, and all tissue on the dorsolateral surface rostral to the arcuate sulcus. This area corresponds most closely to area 46 of Walker, including Walker's areas 8 and 9 as well. In the terminology of Brodmann's map of the macaque brain, it corresponds to most of Brodmann's area 9, area 8, and some of area 10.

The parietal cortex lesions included the posterior bank of the intraparietal sulcus, the posterior bank of the superior temporal sulcus for about 10 mm, and all cortex between the two sulci including roughly 4 mm of the Sylvian fissure (i.e., most of Brodmann's area 7).

The hippocampal formation lesions included fields CA1–4 of the hippocampus proper, the dentate gyrus, the subiculum, 90% of the parahippocampal gyrus (area TF-TH of von Bonin and Bailey), and the posterior half of the entorhinal cortex. Inadvertent damage to area TE of von Bonin and Bailey also occurred. The caudate nuclei, lateral geniculate nuclei, amygdaloid nuclei, and the temporal stem were undamaged in all animals. There was some shrinkage and gliosis in the mammillary bodies, and extensive gliosis bilaterally throughout the fornix.

All lesions were bilateral, symmetric, and performed in one stage.

during a brief delay of 5 seconds or so) in the well to which the subject did not reach last time. Note that if a subject reaches perseveratively to one well, the reward will continue to be hidden in the other well, and the subject will continue to be wrong on one trial after another. Perseveration is a frequent consequence of damage to diverse areas of the brain. Any subject who tends to perseverate will tend to do poorly on delayed alternation. However, subjects can perseverate because of diverse reasons and the delayed alternation task tends not to discriminate between these different etiologies.

**3. Demonstrate that success on the tasks in question depends specifically on a given neural circuit in the *infant,* as it does in the adult**

*3A. Damage to a mature system may produce different effects than damage to a developing, or immature, system*
There are three issues here. One, it is possible that different neural systems may subserve similar functions at different ages. It has been suggested that lower areas of the brain might mediate infants' performance on a task, even though performance of that task by adults is mediated by a later maturing area of the brain. Thus, if a neural region is late maturing, lesions of that region may produce deficits in the adult, but not in the infant (for examples see Divac et al., 1967; Goldman, 1971; 1974).

Although successful performance on $A\overline{B}$, delayed response, and object retrieval depends on dorsolateral prefrontal cortex in the adult, this would not necessarily have to be true in the infant. For this reason it is important to investigate directly the effects of lesions in infant monkeys, and not only in mature animals. Diamond and Goldman-Rakic (1986) investigated this for the $A\overline{B}$ and delayed-response tasks, and found the same impairment in infant monkeys operated at 4 months and tested at 5 months as is found in adult monkeys following lesions of dorsolateral prefrontal cortex (see Table 18–1). This was true despite extensive preoperative training on the tasks given to the infant monkeys, and despite their excellent performance even at long delays prior to surgery. The effect of lesions of dorsolateral prefrontal cortex on object retrieval performance in infant monkeys has yet to be investigated, but it is important that this be tested as well.

Table 18–2 summarizes this body of work looking at the performance of human infants, infant monkeys, and monkeys with selective brain lesions on three behavioral tasks ($A\overline{B}$, delayed response, and object retrieval):

*3B. The effects of destruction, or the characteristics of breakdown, are not necessarily a mirror-image of the characteristics of maturation*
The second issue is that deficits following destruction or breakdown of a system are by no means an infallible guide to what happens during maturation of that system. Lesion studies, even in the infant, are not sufficient. First, impairments that result from the improper functioning, or lack of functioning, of a part do not necessarily tell you the functions of that part. In addition, of course, deficits may not even be due to damage to that part but might be due to damage to fibers

**Table 18-2**  Studies of the Developmental Progression of Human Infants, the Developmental Progression of Infant Monkeys, and the Effects of Lesions in Infant and Adult Monkeys on the Same Three Behavioral Tasks.

| | A$\overline{B}$ | Delayed response | Object retrieval |
|---|---|---|---|
| Human infants show a clear developmental progression from 7½ to 12 months. | Diamond, 1985 | Diamond & Doar, 1989 | Diamond, submitted |
| Adult monkeys with lesions of frontal 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 hippocampus succeed. | Diamond, Zola-Morgan, & Squire, 1989 | Squire & Zola-Morgan, 1983 | Diamond, Zola-Morgan, & Squire, 1989 |
| Infant monkeys show a clear developmental progression from 1½ to 4 months. | Diamond & Goldman-Rakic, 1986 | Diamond & Goldman-Rakic, 1986 | Diamond & Goldman-Rakic, 1986 |
| 5-month-old infant monkeys, who received lesions of frontal cortex at 4 mo, fail. | Diamond & Goldman-Rakic, 1986 | Diamond & Goldman-Rakic, 1986 | |

of passage or to overlying cortex (in the case of a deep structure such as the hippocampus). Second, the way a system deteriorates from damage or old age is by no means necessarily the reverse of how that system is built up during development, although there are often parallels. For example, the last abilities to develop are often the first to deteriorate, but the order of development is not always exactly the opposite of the order of deterioration. Research must be done on functioning in the intact brain of infants (both monkey and human), and linking maturational changes in the neural circuit in question to improved performance on the behavioral measures.

For this reason, the kind of work being done in the laboratories of investigators such as Fox and Chugani is of great importance. In a longitudinal study of A$\overline{B}$ and object retrieval performance, Fox and Bell (in press) found increased frontal electroencephalogram (EEG) activity in individual infants at the time that each infant was improving on the tasks. The relation between increased frontal cortex activity and improved performance was significant for each task. Using 2-deoxy-2[$^{18}$F]fluoro-D-glucose and positron emission tomography (PET), Chugani and associates (1987) have been able to measure metabolic rates for glucose uptake in localized regions of the brain in healthy, awake infants at rest, as young as 5 days of age. The more active a neural region, the more glucose it will need to use. Chugani and coworkers (1987) found that beginning around

8 months, glucose utilization increases specifically in frontal cortex (i.e., activity in frontal cortex appears to increase just before and during the period when infants are improving on the A$\overline{\text{B}}$, delayed response, and object retrieval tasks).

Much work remains to be done, however, especially on the role that specific maturational changes in dorsolateral prefrontal cortex play in the age-related changes in performance of A$\overline{\text{B}}$, delayed response, and object retrieval. What exactly is changing in the prefrontal neural system over these months that permits the system to subserve functions it had earlier been incapable of supporting?

One likely maturational change is increasing levels of dopamine in the prefrontal neural system. Dopamine is a particularly important neurotransmitter in prefrontal cortex, where its concentrations are higher than in any other cortical region (Brown et al., 1979). There are two main dopaminergic systems in the brain. One originates in the ventral tegmental area and projects heavily to prefrontal cortex (Divac et al., 1978; Porrino and Goldman-Rakic, 1982). The other originates in the substantia nigra and projects heavily to the caudate nucleus (Anden et al., 1964). The caudate is a major output structure of dorsolateral prefrontal cortex (Selemon and Goldman-Rakic, 1985a). Thus, both cortical and subcortical components of the prefrontal system receive strong dopaminergic input.

High levels of dopamine in dorsolateral prefrontal cortex are essential for proper functioning: (1) If dorsolateral prefrontal cortex is selectively depleted of dopamine by local injection of 6-OHDA, monkeys show impairments on delayed response as large as those found after dorsolateral prefrontal removal (Brozoski et al., 1979). (2) Monkeys treated with MPTP (1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine) show deficits on object retrieval similar to those seen following dorsolateral prefrontal cortex lesions and similar to those seen in young infants (Taylor et al., 1990; Saint-Cyr et al., 1988). MPTP injection results in reduced levels of dopamine in the substantia nigra and in the frontal-striatal system (Elsworth et al., 1987; Mitchel et al., 1986) and is thought to produce behavioral deficits similar to those seen in patients with Parkinson's disease (Burns et al., 1983; Stern and Langston, 1985). Here, depletion of dopamine in the neural circuit appears to produce the same deficits on object retrieval as do lesions to the circuit.

The level of dopamine in the brain increases markedly during the period when performance on A$\overline{\text{B}}$, delayed response, and object retrieval is improving in infant monkeys (Diamond and Goldman-Rakic, 1986; Goldman-Rakic and Brown, 1982).[4] Given the importance of dopamine for dorsolateral prefrontal cortex function and given the increases in brain dopamine levels during the period when tasks dependent on dorsolateral prefrontal cortex are first mastered, it is reasonable that increases in dopamine levels over age may play a causal role in the developmental improvements on these tasks. This remains to be directly demonstrated, however.

### 3C. Although work with animals or adult patients is important, evidence must, at some point, be obtained directly in children

Work with nonhuman primates is useful because the most precise information on brain function comes from invasive procedures that cannot be used with humans. Adult patients enable the investigator to study the effects of brain dam-

age that one would never want, nor would one be allowed, to impose solely for the purposes of research. However, work with animals or adults needs to be complemented by work with children. There is an inescapable inferential leap when drawing conclusions about development in children from studies of animals or adults. At some point, children themselves must be studied.

One way to do this is to study the performance of children with well-localized, verifiable brain damage, much as adult patients are studied. Another valuable approach is to use noninvasive measures of brain function, such as EEG, event related potential (ERP), and magnetoencephalography, to study functioning in intact, healthy children. Yet another approach is to study children with lower levels of dopamine but who appear to have no structural damage to the brain. Children with early-treated phenylketonuria (PKU) may fall in this latter category, as they are thought to have a functional deficit in frontal cortex function due to dopamine depletion with no structural damage. We are now investigating whether these children are impaired specifically on tasks linked to dorsolateral prefrontal cortex function in the face of otherwise preserved cognitive functioning, and whether there is a relationship between their performance and their levels of dopamine.

If PKU is untreated, it results in severe mental retardation (Primrose, 1983; Tourian and Sidbury, 1978). Dietary regulation, begun early and consistently maintained, results in IQs within the normal range and no gross cognitive impairments (Dobson et al., 1977; Holtzman et al., 1986; Hudson et al., 1970; Koch et al., 1984; Williamson et al., 1977). There are reports, however, that even when a special diet is followed, children with PKU may have residual frontal lobe signs (Cowie, 1971; Pennington et al., 1985; Welsh et al., 1990). It would make sense that these children might have such a selective impairment given the tendency of PKU patients, even when they have been maintained on diet from shortly after birth, to have lower dopamine levels (Krause et al., 1985), and given the importance of dopamine for frontal cortex function.

At least for the present, however, studies of children need to be complemented by more precise, invasive procedures with animals. Too often, studies of brain-behavior relationships in children are able to be correlational only. For example, the research with children with early-treated PKU needs to be complemented by work with infant monkeys where the relation between maturational changes in dopamine levels within dorsolateral prefrontal cortex and the emergence of cognitive functions subserved by dorsolateral prefrontal cortex can be studied directly, and where the nature and underlying mechanisms of the causal relation can be explored. Thus, while studies of animals must be complemented by studies of brain-behavior relations in children, so too must studies of children be complemented by studies of brain-behavior relations in animals.

**4. Use *the same tasks* when studying the developmental progression in children and when studying the neural basis in other populations, rather than tasks that are simply similar.**

Tasks that appear to be similar, or appear to require similar abilities, often turn out to depend on quite different neural systems. Small changes in a task, which one might have thought would be inconsequential, often turn out to be critical.

For example, dorsolateral prefrontal cortex is not required if the rule is to reach to a *different* object than the one you just saw, but it apparently *is* required if the rule is to reach to the *same* object you just saw (Mishkin et al., 1962). As the delay increases on A$\overline{B}$ and delayed response, these tasks change from being sensitive selectively to dorsolateral prefrontal cortex function at delays of 2–5 seconds to being sensitive to hippocampal function as well at delays of 15 seconds or more (Diamond et al., 1989b). Patients with frontal lobe damage are selectively impaired in producing as many words as they can think of beginning with a given letter (*F*, *A*, or *S*; e.g., Benton, 1968), but they are not selectively impaired in producing as many words as they can think of belonging to a given category (e.g., animals or clothing). The neuropsychological literature is replete with such fascinating dissociations. Similarly, any ability such as memory, attention, or inhibition can be shown to be present in very young children on one test but absent in much older children on a different test, even though both tests are considered measures of "memory" or "inhibition." The exact manner in which something is assessed is terribly important.

For this reason, in our work with human infants, infant monkeys, and adult monkeys, we have used the same tasks, not simply analogous ones. A$\overline{B}$, delayed response, and object retrieval were administered to all subjects. Accommodations were made for species differences: e.g., toys served as the reward for human infants; peanuts and raisins served as the reward for monkeys. Aside from these small adjustments, however, children and monkeys were tested in the same way on all three tasks.

This guideline raises a problem, however, in studying brain-behavior relations in development during the preschool and early elementary school years. After 1–2 years of age, children need more sophisticated tasks than can be used with monkeys, but not until 8–12 years of age can they succeed on tests of frontal cortex function used with adult patients. With children 3–8 years of age, we have used modifications of the tasks used with adults (e.g., the Wisconsin Card Sorting Test [Diamond and Boyer, 1989] and the Stroop Test [Diamond et al., in prep.]). It is possible, however, that we have modified the tests in ways that we did not realize were crucial, and this is of great concern to us. Evidence directly linking the versions of the tests we have used to frontal cortex function is critically needed.

Two caveats are in order concerning guideline #4. First, sometimes a task must be modified *in order* for it to measure the same ability in a different population. An obvious example would be that a test of memory given in English to English-speaking children should be administered in French to French-speaking children if one is interested in testing memory. Similar modifications are sometimes needed to accommodate age or species differences in subjects. Some of the early work in child development foundered because experimenters tried to use the same tasks with children that had been used with animals without modifying the tasks to make them appropriate for children (for some examples, see Donaldson, 1978). Sometimes a task must be modified in order to keep it equivalent for two different populations.

The second caveat is that sometimes using the same task, even when it appears to be appropriate for each population, is not a guarantee that one is

**Table 18-3** Performance on Delayed Nonmatching to Sample by Age and Delay

| | 5-sec delay | | | 30-sec delay |
|---|---|---|---|---|
| Ages | Mean number of trials to criterion[a] | Percent passing criterion | Percent correct | Percent correct |
| 12 months[b] | 17 | 50 | 66 | 65 (N = 6)[c] |
| 15 months | 16 | 67 | 67 | 65 (N = 8) |
| 18 months | 16 | 67 | 71 | 81 (N = 8) |
| 21 months | 11 | 92 | 80 | 80 (N = 11) |
| 24 months | 9 | 92 | 87 | 86 (N = 11) |
| 27 months | 7 | 100 | 85 | 90 |
| 30 months | 8 | 100 | 84 | 86 |
| 3 years | 6 | 100 | 93 | 96 |
| 4 years | 5 | 100 | 98 | 99 |
| 5 years | 5 | 100 | 94 | 95 |

[a]Criterion = 5 correct responses in a row. For subjects who never reached criterion (6 subjects at 12 months, 4 subjects each at 15 and 18 months, and 1 subject each at 21 and 24 months) the total number of trials they were tested (25) is entered here.

[b]N = 12 for all ages.

[c]Only subjects who passed criterion at 5 sec were tested at 30 sec.

tapping the same ability in two different populations. The delayed nonmatching to sample task[5] is a test of memory sensitive to hippocampal damage in adult monkeys (e.g., Zola-Morgan and Squire, 1986) and sensitive to amnesia in human adults (Squire et al., 1988). It is also a task appropriate for testing young children, and on which they show a developmental progression between 12 and 30 months of age (Diamond, 1990a; Overman, 1990).[6] However, while this task is a measure of memory ability in adult monkeys and human adults, sensitively reflecting damage to neural structures important for memory, the developmental progression of improved performance on delayed nonmatching to sample *in infants* does *not* chart the maturation of this memory function or of the hippocampal neural circuit, even though the same task is used with infants, adults, and monkeys.

Until about 21 months of age, children fail this task even at delays of only 5 seconds (Table 18-3), although it is well established that infants can remember for far longer than 5 seconds well before 21 months (there is evidence of such memory by at least 2-3 months of age: e.g., Werner and Perlmutter, 1979; Rovee-Collier, 1984). Indeed, emerging anatomical and biochemical evidence indicates that the hippocampus develops quite early in humans and monkeys (e.g., Rakic and Nowakowski, 1981; Eckenhoff and Rakic, 1988; Bachevalier et al., 1986; Kretschmann et al., 1986; see Diamond, 1990a). Moreover, in the same session in which children first succeed on delayed nonmatching to sample with a 5-second delay they typically succeed with 30-second delays as well (see Table 18-3). One might expect success at a delay of 30 seconds to come in later if the task were assessing the development of memory. In adult monkeys or humans, in whom other abilities are fully mature, disturbance of the memory

system produces errors on the task—for memory is, indeed, one of the abilities required for success, but it is only one of the required abilities. The slow developmental progression in performance of the delayed nonmatching to sample task is due to the late maturation of some other ability. We tested whether this late-developing ability might be the ability to deduce an abstract rule, the ability to quickly encode visual stimuli (speed of processing), or the ability to tolerate retroactive interference (Diamond, 1990a; Towle and Diamond, 1991). Telling the children the rule or giving them a long time to encode the stimulus only marginally improved performance. However, reducing retroactive interference (by not introducing a reward after subjects displaced the sample when the sample was presented alone during familiarization) had a dramatic effect: It enabled children to succeed almost 12 months earlier (Towle and Diamond, 1991).

Here is a case where a task has been linked specifically to a discrete neural circuit, and where the same task has been used with children and the developmental progression documented, yet it is incorrect to conclude that the developmental progression in children's performance of the task reflects maturation of that neural circuit. Thus, while it is true that success on delayed nonmatching to sample requires hippocampal involvement, and it is true that success on delayed nonmatching to sample appears relatively late in development, it is not true that the late emergence of success on this task is due to late maturation of the hippocampus, or of the memory ability it subserves. This illustrates why caution must be used in drawing conclusions about brain-behavior relations in development. In this case important clues came from two sources: (1) Infant monkeys also show a protracted developmental progression in performance of the task despite evidence of early hippocampal maturation in the monkey (Bachevalier and Mishkin, 1984; Brickson and Bachevalier, 1984; Bachevalier, 1990 and (2) the qualitative aspects of the performance of infant monkeys and human infants on the task are different from those of adult monkeys and human patients (e.g., adult monkeys and humans succeed at the shortest delays and perform progressively more poorly as the delay increases; human infants and infant monkeys perform at chance even at the very shortest delay; their performance does not worsen as delay increases). This leads directly to guideline #5.

## 5. Compare the *qualitative,* as well as quantitative, aspects of children's performance on the tasks to that of brain-damaged populations

Because someone may fail a task for a variety of reasons, it is important to determine the reasons for failure. The qualitative aspects of performance should be investigated, and not simply rate of success or failure. If one is comparing the performance of children with the performance of animals with selective lesions, then the younger children should fail under the same conditions and in the same ways as do the animals with lesions to the relevant neural system. Changes in task parameters should affect both the young children and the lesioned animals in the same ways. It becomes more likely that the performance of the children and lesioned animals reflects the presence or absence of the same abilities and depends upon the same neural system, the more parameters on which their per-

formance matches and the more identical the circumstances under which these behaviors are elicited.

For example, in comparing human infants and monkeys with lesions of dorsolateral prefrontal cortex we have looked not only at their overall success rates but also at the conditions under which they err and what their errors look like. Figures 18–5 and 18–6 illustrate this. On the A$\overline{B}$ and delayed response tasks, human infants of 7½–9 months fail at delays of only 2–5 seconds. The only group of adult monkeys to fail at such brief delays are those with lesions of dorsolateral prefrontal cortex. Monkeys with lesions of parietal cortex or the hippocampus perform as well as unoperated controls here.

Moreover, at these delays infants show a characteristic pattern of performance: Their errors are confined to trials on which side of hiding is reversed and to the next few trials at that new location. Their performance is excellent when the reward is hidden in the same well as on the previous trial and they were correct on the previous trial (Repeat-following-correct trials; see Fig. 18–5). The only group of adult monkeys to show this pattern of performance are monkeys with lesions of dorsolateral prefrontal cortex (see Fig. 18–5), and they show this pattern at the same delays as do 7½–9-month-old human infants. At long delays monkeys with lesions of the hippocampal formation also fail A$\overline{B}$, but they never show this differential pattern of performance by type of trial. At delays of 15–30 seconds, they have difficulty remembering where the reward has been hidden and their performance declines, but it does not decline selectively for reversal trials. When monkeys with hippocampal lesions reach incorrectly, they show some tendency to repeat that error on the next trial, but where these strings of errors begin is randomly distributed over a testing session (Diamond et al., 1989b).

On the object retrieval task, human infants of 8½–9 months lean all the way over to look in the opening when the left or right side of the box is open. When they do this they reach with the hand contralateral to the opening, which though easier from this position than reaching with the ipsilateral hand, looks very contorted and is therefore termed an "awkward reach." The awkward reach is not the result of a hand preference, as it is seen on both sides of the box (Diamond, submitted; Bruner et al., 1969; Gaiter, 1973; Schonen and Bresson, 1984). One group of adult monkeys also shows this strange awkward reach—monkeys with lesions of dorsolateral prefrontal cortex (Fig. 18–6).

## 6. Divergent Validity, 2: Study performance on *other tasks linked to other neural circuits*

It is also important to establish a second kind of divergent validity by determining that performance on tasks linked to other neural circuits and requiring other abilities (1) does not improve over the same age period as does performance on tasks linked to the neural system of interest, and (2) is not affected by disruption of functioning in the neural system of interest. (The first kind of divergent validity discussed previously was that disruption of functioning in other neural systems should not affect performance on tasks linked to the neural system of inter-

## AB̄ PERFORMANCE WITH DELAY OF 2-5 SEC

### 1 HUMAN INFANTS



### 2 INFANT RHESUS MONKEYS
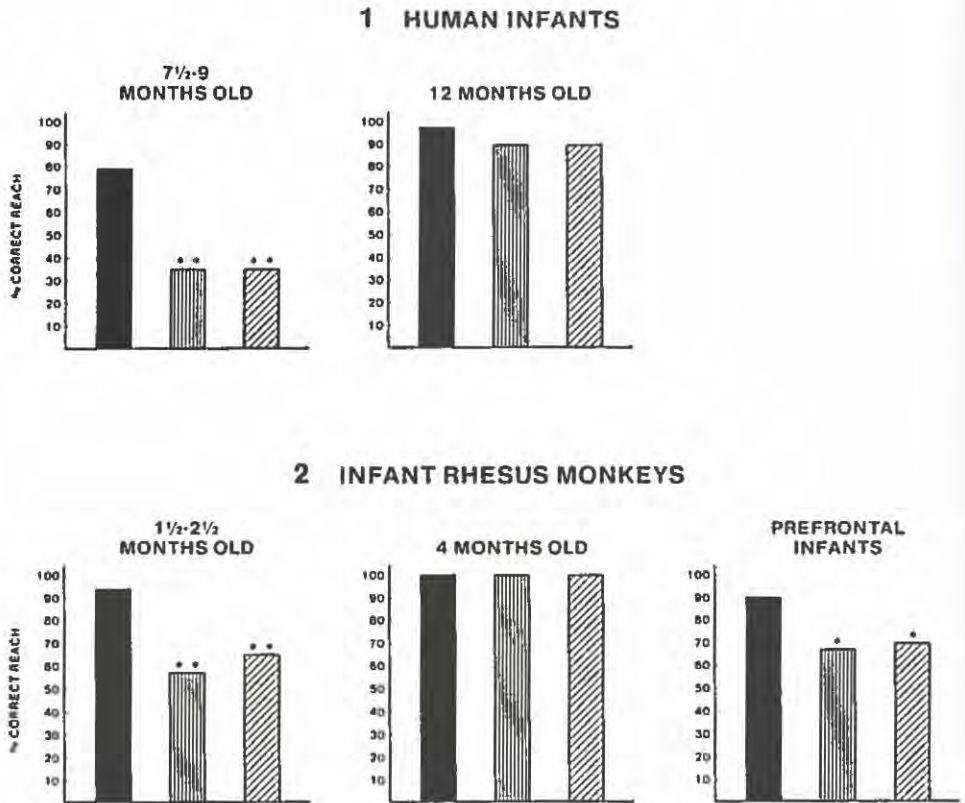


Figure 18-5  Percentage correct by type of trial at delays of 2-5 sec for human infants, infant monkeys, and monkeys with lesions to prefrontal cortex, parietal cortex, and the hippocampal formation. **Row 1**: Human infants of 12 months perform perfectly. Human infants of 7½–9 months perform well on repeat-following-correct trials, but perform significantly worse on reversal trials and on repeat-following-error trials in both the AB̄ task (Diamond, 1985) and the delayed-response task (Diamond and Doar, 1989). **Row 2**: Infant rhesus monkeys of 4 months perform perfectly. Infant monkeys of 1½–2½ months and infant monkeys who have received bilateral lesions of dorsolateral prefrontal cortex at 4 months and were retested at 5 months show a similar pattern of differential performance over trials as do 7½–9-month-old human infants (Diamond and Goldman-Rakic, 1986).

est.) This is important for determining whether improvements, or impairments, are general or specific. For example, are all abilities improving at the same time, at the same rate, or are developmental changes more pronounced in different abilities during different age periods?

For instance, while human infants improve on AB̄, delayed response, and object retrieval (tasks all linked to dorsolateral prefrontal cortex) between 7½ and

## 3 ADULT RHESUS MONKEYS
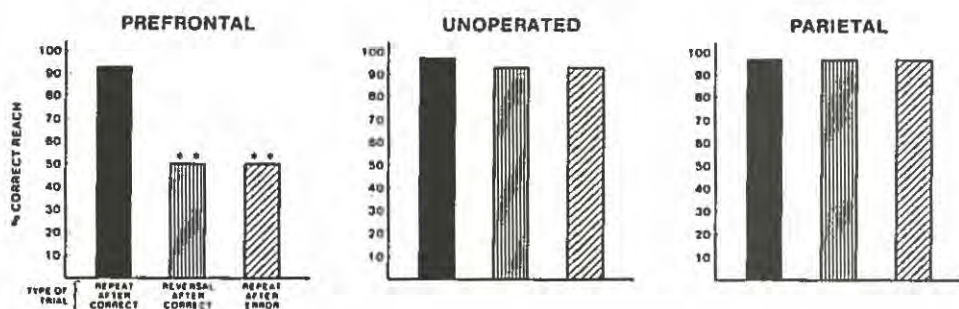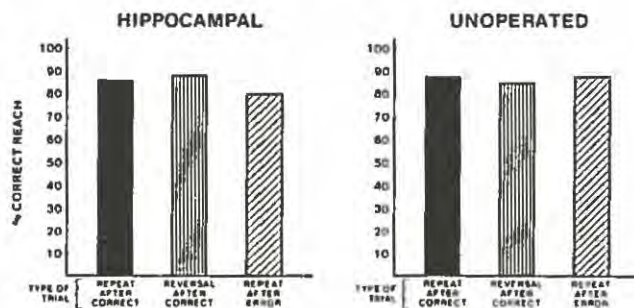


## 4 ADULT CYNOMOLGUS MONKEYS



**Figure 18-5 (continued)** Row 3: Unoperated adult rhesus monkeys and those with bilateral lesions of inferior parietal cortex perform perfectly. Adult rhesus monkeys with bilateral lesions of dorsolateral prefrontal cortex, however, show the same pattern of differential performance over trials as do 7½–9-month-old human infants (Diamond and Goldman-Rakic, 1989). Row 4: Unoperated adult cynomolgus monkeys and those with bilateral lesions of the hippocampal formation perform perfectly at delays of 2–5 sec (Diamond et al., 1989b). (At delays of 15–30 sec hippocampal monkeys no longer perform well on the task, but at these delays they still do not show the pattern of differential performance by type of trial seen in 7½–9-month-old human infants, 1½–2½-month-old rhesus monkeys, and in infant and adult rhesus monkeys following lesions of dorsolateral prefrontal cortex).

12 months of age, they improve on visual paired comparison (a task linked to the hippocampal-amygdala system) (Brickson and Bachevalier, 1984; Saunders, 1989) between 2 and 9 months of age (Diamond, 1990a; Fagan, 1990). In the visual paired comparison task, subjects look at a stimulus for a fixed familiarization period or until habituated, a delay is imposed, and then memory of the sample is tested by pairing the sample with another stimulus. Preferential looking at the new stimulus is taken as evidence of memory of the sample, since infants have a natural preference for novelty (Fagan, 1970; Diamond, 1990a).

**Figure 18–6**   The "awkward reach" in an infant monkey of 2 months, a human infant of 9 months, and an adult monkey with bilateral lesion of dorsolateral prefrontal cortex. **Frame 1:** Subject leans and looks at bait through opening of box. **Frame 2:** Subject reaches in awkwardly with the far hand. **Frame 3:** Opening is on the other side of the box. Performance is the same. Subject leans and looks into the opening. **Frame 4:** Subject reaches in awkwardly with the far hand.

The visual paired comparison task presents some of the same task requirements as do A$\overline{B}$ and delayed response: All require that memory be updated on each trial (to remember where the reward was just hidden or which stimulus was just presented). All present the to-be-remembered information visually and only once. All impose the delay within a trial, as opposed to between trials or between testing sessions. However, the visual paired comparison task also differs considerably from A$\overline{B}$ and delayed response. For example, A$\overline{B}$ and delayed response require a reaching response; visual paired comparison does not. The to-be-remembered information is presented much longer in visual paired comparison. In A$\overline{B}$ and delayed response the same two hiding wells are used throughout, presenting possible problems of proactive interference; in visual paired comparison, on the other hand, new stimuli are used on each trial (rather than using the same two stimuli repeatedly, varying only which is the sample on a given trial). Subjects must remember spatial location information for A$\overline{B}$ and delayed response, but not for visual paired comparison.

As more tasks are studied, a better understanding emerges of the abilities developing during each age period and depending on the different neural circuits.

## REMAINING QUESTIONS

### What Happens After 12 Months of Age in the Neural Circuit of Interest?

The work on A$\overline{B}$, delayed response, and object retrieval appears to provide a window into dorsolateral prefrontal cortex development between 7½ and 12

months of age. Neither dorsolateral prefrontal cortex, nor the abilities it sub-serves, are fully mature by 12 months of age, however. Indeed, frontal cortex is not thought to be fully mature until puberty. For example, children do not per-form at adult levels on the Wisconsin Card Sorting Test (a criterial test of frontal cortex function in adults [Milner, 1963]) until about 9–10 years of age (Chelune and Baer, 1986). What changes occur in the dorsolateral prefrontal neural cir-cuit, and when, after 12 months? In what ways do the abilities dependent on frontal cortex change and improve over these years? Is the improvement simply quantitative, or is it qualitative as well? Is the improvement gradual, or are there growth spurts and plateaus? When are critical points in the development of fron-tal cortex reached?

We have begun to investigate these questions. In a study of 72 children (12 each at 3, 4, 5, 6, 7, and 8 years of age) we have found a significant improvement from 3–6 years on seven different measures of abilities associated with frontal cortex, with a leveling off from 6–8 years (Diamond et al., in prep.) (Fig. 18–7). On all tests we found this same pattern; there were no exceptions. This suggests that the age of 6 may be something of a watershed; on a host of tests linked to frontal cortex, children either reach ceiling performance by 6 years of age or reach a plateau where they remain for at least the next 2 years. Five of our tests assessed inhibitory control of action, one assessed the ability to execute a sequence of actions, and one assessed the ability to remember sequential infor-mation. The tests of inhibition were: tapping (Luria, 1973), Stroop (Stroop, 1935), three pegs (Wozniack et al., 1987), Simon Says, and simultaneous switch (Luria, 1973). The test of sequential action was flat-fist-edge (Luria, 1973). The memory task was multiple boxes (Petrides & Milner, 1982; Passingham, 1985; Petrides, 1988).

On the tapping task, a subject must tap twice when the experimenter taps once, and then tap only once when the experimenter taps twice. This requires inhibiting the pull to do what the experimenter does. Frontal patients fail because, while they may start out correctly, they shortly begin to mirror the experimenter's behavior, rather than following the rule. Similarly, children under 6 years tend to match what the experimenter does rather than follow the rule. Only by 6 years could children consistently succeed on the task (Fig. 18–7A).

In the adult version of the Stroop test, the names of colors are printed in the ink of another color (e.g., the word "blue" is printed in red ink). Subjects are instructed to report the color of the ink. This requires inhibiting the customary response when reading, which is to ignore the ink and attend instead to the meaning of the word. Frontal patients fail the test, as they tend to recite the words and not the color of the ink (Perret, 1974). In our version of the Stroop test for children we use a deck of cards. The front of half the cards is black with a yellow moon and several stars; the front of the other cards is white with a bright sun. Subjects are to say "day" when the experimenter turns over a black card and "night" when a white card appears. This is similar to a modified Stroop test used by Passler and associates (1985) where plain black and white cards were used. Passler and colleagues found on their version that children were at ceiling by the youngest age they tested (6 years). We found that most children ≥ 6 years
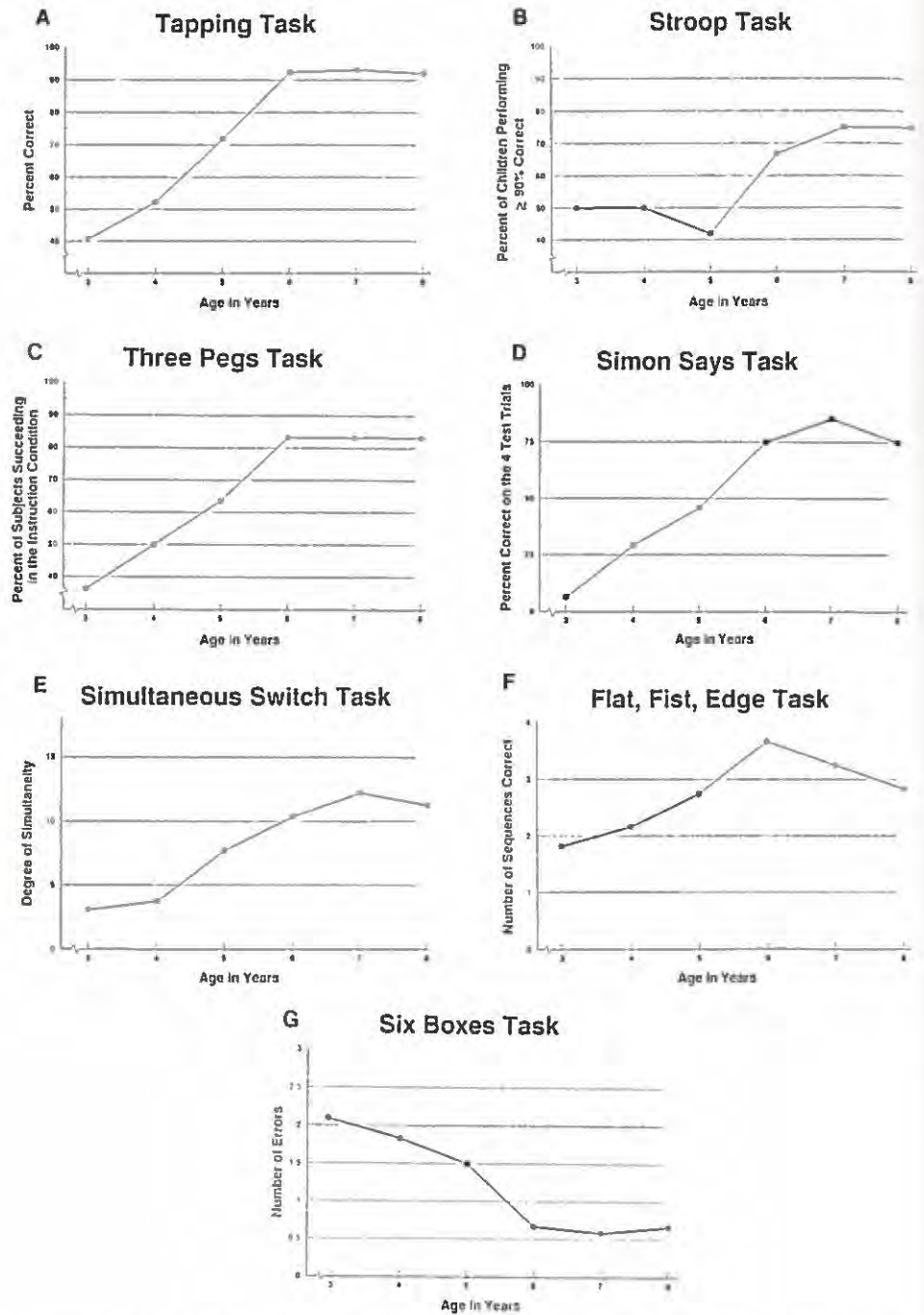
**Figure 18-7** Developmental progression in children aged 3-8 years on eight tests of abilities associated with frontal cortex.

succeeded, but not most children at younger ages. Indeed, there was little change in the number of children succeeding from 3 to 5 or from 6 to 8 years, but there was a dramatic improvement from 5 to 6 years.

On the three pegs test, the subject is to hammer in a row of pegs (red, yellow, and green) in the order: red, green, and then yellow. The subject must inhibit the tendency to hammer the pegs in spatial left-right order, and instead follow the rule. Performance improved steadily from 3–6 years, and remained at ceiling thereafter (Fig. 18–7C).

Simon Says is a common children's game. The trials of interest here are where the experimenter fails to say "Simon Says." On these trials, the child is not supposed to do anything. This requires inhibiting the tendency to carry out the command anyway. On other trials, the child is to touch his or her nose or eyes, for example, as instructed by "Simon." Before 6 years, children are much more likely to act when they should refrain from acting than are children ≥ 6 years.

In the simultaneous switch: fist–flat task, the subject starts with one hand in a fist on the table, and the palm of the other hand flat on the table. The subject is then to switch these hand positions simultaneously back and forth six times. This requires inhibiting one hand from doing what the other is doing. Younger subjects, like frontal patients, tend to err by doing the same thing with both hands or by switching the position of one hand and then the other. We found a marked increase between 4 and 6 years in the degree of simultaneity children showed in switching one hand to one position while simultaneously switching the other hand to the other position. At the 2 extremes of the age range there was little change: Performance did not significantly improve between ages 3 and 4, nor between ages 6 and 8 (Fig. 18–7E).

In the flat–fist–edge task, the subject must change the position of one hand in the following sequence: palm flat on the table, closed fist on the table, and palm at right angles to the table (edge). This sequence is repeated 4 times. Here, the children appeared to reach ceiling at 6 years and thereafter their performance declined slightly.

In the Multiple Boxes task, the subject watches as the experimenter hides a sticker in each of six boxes. All boxes are then closed. The subject is permitted to open one box at a time, in any order he or she chooses. A 10-second delay is imposed between reaches. The goal is to open all the boxes without repeating a choice. The number of reaches needed to open all the boxes progressively decreased until age 6 where it plateaued.This task is selective for dorsolateral prefrontal cortex damage in both monkeys (Passingham, 1985; Petrides, 1988) and human adults (Petrides and Milner, 1982). In short, on all seven of the tasks used, a significant improvement was found up to 6 years. There was little further change from 6–8 years, either because the tests were not sensitive enough to pick up such changes, or because the abilities tapped by these tests remain relatively constant during the 6–8 year age period.

It should be noted, however, that the Stroop test had to be modified for use with children, as those at the younger end of the age range cannot read, and the three pegs test and Simon Says have never been directly linked to frontal cortex function in children or adults. Such evidence, directly linking the modified

Stroop test, the three pegs test, and Simon Says to frontal cortex function, is needed. Moreover, even though there is evidence linking performance on the tapping test, the adult version of the Stroop test, and the simultaneous switch tests to the integrity of frontal cortex, information on the role of localized regions within frontal cortex in supporting performance on these tasks is lacking. Such information is needed.

## What Happens Before 7½–8 Months of Age in the Neural Circuit of Interest?

Development does not begin at 7½–8 months. Indeed, it is only because of the developmental accomplishments present by 7½–8 months that testing on A$\overline{B}$, delayed response, and object retrieval can begin at roughly those ages. For example, hiding tasks are not possible with younger infants because they will not search for a hidden object. What abilities are developing before 7½–8 months, and what are the neural bases for these accomplishments? What is happening in frontal cortex up until this age? I have suggested (Diamond, 1990b; 1991b) that some of the accomplishments between 5 and 8 months of age may be made possible by maturational changes in the supplementary motor area (an area of frontal cortex immediately posterior, and medial, to dorsolateral prefrontal cortex). The inhibition of the reflexes of the hand (the grasp and avoidance reactions) and the ability to link two action sequences together into a larger means-end sequence (e.g., removing a cloth in order to then retrieve the reward underneath it) may require involvement of the supplementary motor area. More work is needed in testing this hypothesis and in exploring when and where other neural changes are occurring.

## What Abilities Are Dependent on the Neural Circuit of Interest and in What Ways Do These Abilities Change Over Age?

For example, if success on A$\overline{B}$, delayed response, and object retrieval depends on involvement of dorsolateral prefrontal cortex, as it now appears, what ability(s) are required by these tasks that accounts for this dependence?

Many of the tasks dependent on dorsolateral prefrontal cortex and on which infants show a developmental progression between 7½ and 12 months (e.g., A$\overline{B}$ and delayed response) appear to require memory. For instance, monkeys with dorsolateral prefrontal cortex lesions and human infants perform well if there is no delay but fail with a delay, all other conditions being equal. What are the characteristics of this memory ability?

### Spatial Memory
One prominent theory is that the memory ability subserved by dorsolateral prefrontal cortex is memory of spatial information in particular (e.g., Goldman-Rakic, 1987). Evidence for this view includes: Monkeys with lesions of dorsolateral prefrontal cortex are less impaired on some nonspatial memory tasks (e.g., delayed object alternation) than they are on comparable spatial memory

tasks (e.g., delayed spatial alternation) (Mishkin et al., 1969). Monkeys with lesions of the principal sulcus (the "heart" of dorsolateral prefrontal cortex in the monkey) perform well on spatial tasks that do not require memory but fail spatial tasks that require memory (Goldman and Rosvold, 1970). There are cells in dorsolateral prefrontal cortex that increase firing after a cue is presented and maintain that level of activity throughout the delay (i.e., they appear to serve a memory function); moreover, a subset of these cells is direction-selective, i.e., they fire more if the cue was on the right or left (Fuster and Alexander, 1971; Niki, 1974; Funahashi et al., 1989).

In addition, the anatomical connections between dorsolateral prefrontal cortex and inferior parietal cortex (Brodmann's area 7) are particularly strong (e.g., Schwartz and Goldman-Rakic, 1984). Indeed, not only are there heavy reciprocal connections between these two areas, but throughout diverse areas of the brain, wherever dorsolateral prefrontal cortex projects so does inferior parietal cortex, and in each case their projections interdigitate (i.e., columns of cells receiving projections from prefrontal cortex alternate with columns of cells receiving projections from parietal cortex) (e.g., Goldman-Rakic and Schwartz, 1982; Selemon and Goldman-Rakic, 1985; 1988). This is relevant because parietal cortex participates in that portion of the visual system specialized for the perception of motion rather than the perception of form or texture. It is conceivable that through its connections with parietal cortex, dorsolateral prefrontal cortex might specialize in the memory of spatial information rather than memory of object features.

However, lesions of inferior parietal cortex leave $A\overline{B}$ and delayed response performance undisturbed. Subjects are evidently able to succeed at these tasks without the perceptual information processed in parietal cortex. Problematic for the spatial memory view is that infants and prefrontally operated monkeys generally perform well at the first location (well A), even though spatial memory is required here as elsewhere. Errors generally first appear only when the location of the reward changes. Some of the cells in dorsolateral prefrontal cortex (and within the principal sulcus itself) that increase firing after a cue is presented and maintain that level of activity throughout the delay fire selectively depending on the *color* of the cue, just as other cells there fire selectively depending on the location of the cue (Quintana et al., 1988; Wilson and Goldman-Rakic, 1989).

Moreover, most tasks diagnostic of frontal cortex damage in human adults do not appear to have a spatial component. For example, in the Wisconsin Card Sorting Test the sorting criterion (color, shape, or number) changes during testing, and the subject must stay attentive to which criterion is currently correct, but spatial position is irrelevant to the task. Similarly, spatial position is irrelevant on the self-ordered pointing task, which requires subjects to keep track of what stimuli they have already pointed to (Petrides and Milner, 1982). Here, the spatial locations of the stimuli are scrambled after each reach. Indeed, when the stimuli are left stationary, so that the task can be solved by spatial memory, patients with frontal cortex damage perform well. A version of the self-ordered task has recently been used with monkeys, where lesions confined only to the principal sulcus produced severe deficits in performance, even though spatial memory is irrelevant to the task (Petrides, 1988).

### Memory of Temporal Order

Another prominent theory of frontal cortex function is that it is specialized for the memory of temporal order information (e.g., Milner et al., 1985). For example, there is a potential for *proactive interference* from previous trials during A$\overline{B}$ and delayed response testing as the same two hiding places are used throughout. Once the reward has been hidden at well A on at least one trial and at well B on at least one trial, one might consider the task to be one of temporal order memory: "Where was the reward hidden most recently?"

Evidence for this viewpoint includes: When adult patients are shown a series of pictures, patients with frontal cortex damage can tell you which of two pictures they saw before, but not which of the two pictures they saw most recently (Corsi, cited in Milner, 1971). When asked about well-known events from the last several decades, patients with frontal cortex damage are impaired in recalling the order in which the events occurred, yet are unimpaired in their recognition and recall of the events (Shimamura et al., 1990). Indeed, all tasks sensitive to frontal cortex damage in the monkey require temporal discrimination (e.g., "I have seen the reward hidden at A and at B. Where was it hidden most recently?"), although the spatial component has been emphasized in theoretical discussion of these tasks. Monkeys with frontal cortex damage, human infants, and infant monkeys generally perform well at the first location (even though spatial memory is required here as elsewhere); errors appear when the location of the reward changes, i.e., when memory of temporal order is first required.

Most tasks diagnostic of frontal cortex damage in humans appear to require resistance to proactive interference (e.g., the Wisconsin Card Sort: "Which sorting criterion is the correct one now?", and the self-ordered pointing task: "Which stimuli have I already pointed to?").

If dorsolateral prefrontal cortex is specialized solely for the memory of temporal relationships, however, why then are there cells in dorsolateral prefrontal cortex that code the left-right location of stimuli or responses? Why, too, does damage to dorsolateral prefrontal cortex produce more profound deficits on spatial tasks (e.g., delayed spatial alternation) than on nonspatial tasks (e.g., delayed object alternation)?

Tulving and Schacter (e.g., Schacter, 1987; Tulving, 1989) have suggested that frontal cortex is critical for the memory of both space and time, specifically memory of the spatial or temporal context in which information is acquired.

### Relational Memory

Spatial and temporal information (e.g., left, right; earlier, later) are inherently relational. Perhaps memory for relational information in general is dependent on dorsolateral prefrontal cortex and develops between 7½ and 12 months of age in human infants. Evidence consistent with this includes: Patients with frontal cortex damage often do well on typical delayed recall tests but fail delayed comparison tests where they must judge whether a color they saw earlier is the same shade as the color they see now, or whether a tone they just heard is the same pitch as the tone they hear now (Prisko, cited in Milner, 1964). Patients with frontal cortex damage are notoriously poor at relating two pieces of information together (e.g., Barbizet, 1970; Heilman and Valenstein, 1972). Grossman (1982)

administered eight visual and auditory reversal tasks (i.e., tasks that required that subjects appreciate the relation between original and transformed states) mediated by linguistic and nonlinguistic symbol systems to adults with localized brain damage. He found no domain-specific deficits; rather, patients with frontal cortex damage were impaired across the board on the reversal tasks regardless of modality or content. Similarly, memory for space and/or time might not be a unique ability but might be a subset of relational memory in general.

It would make sense if relational memory were more difficult than single item memory, as it requires remembering a relation between two things. Perhaps memory of information that is inherently relative, i.e., that requires relating one thing to another (e.g., left, right; smaller, bigger; softer, louder) matures later and more slowly than memory of individual items (e.g., red, girl, circle). Perhaps, too, memory of any relative information, spatial or not, requires involvement of dorsolateral prefrontal cortex.

The idea that memory of space, time, or relational information in general might have a unique developmental trajectory, appear later (i.e., between 7½ and 12 months), and be sensitive to different experimental parameters[7] than memory for other, nonrelational information (e.g., color or shape) has never been considered by developmental psychologists, although it deserves investigation.[8]

### Memory Plus Inhibition
I have argued that dorsolateral prefrontal cortex is required whenever *any information at all* must be remembered within each trial as long as the task *also* demands inhibition of a prepotent response (Diamond, 1985; 1988). That is, it may not matter whether one must remember temporal, spatial, relational, color, or object information. The critical factor may be whether the task demands *both memory and inhibition of a dominant response.*

Evidence for the role of inhibition is extremely strong: All memory tasks linked to dorsolateral prefrontal cortex in the monkey also impose an inhibitory demand. The *pattern* of error on the A$\overline{B}$ and delayed response tasks (i.e., errors confined to reversal trials and the trials immediately thereafter) shown by infants or by prefrontally operated monkeys cannot be accounted for by forgetting alone, for the delay is equal on all trials but errors are not equally distributed over trials (Diamond, 1985; Diamond and Goldman-Rakic, 1989). Indeed, monkeys with lesions of the hippocampal formation, who have impaired memory, never show this pattern of error on A$\overline{B}$ (Diamond et al., 1989b). Moreover, when a task requires memory, but not inhibitory control, human infants perform well months before they first succeed on A$\overline{B}$ or other tasks dependent on dorsolateral prefrontal cortex (e.g., Baillargeon et al., 1985; Fagan, 1970), and monkeys with lesions of dorsolateral prefrontal cortex also perform well (as on the delayed nonmatching to sample task [e.g., Mishkin et al., 1962; Bachevalier and Mishkin, 1986]).

Note, if dorsolateral prefrontal cortex is necessary whenever a task requires both memory *and* inhibition, then success on delayed *matching* to sample should depend on dorsolateral prefrontal cortex involvement, and this appears to be the case. Monkeys with lesions of lateral frontal cortex fail delayed matching to sample, although they succeed at delayed nonmatching to sample (Mish-

kin et al., 1962). In delayed matching to sample, a sample object is presented, a brief delay is imposed, and then the subject is given the choice of reaching to the object that matches the sample or to a novel object. A reach to the matching object is rewarded. Infants (e.g., Fantz, 1964; Fagan, 1970; Diamond, 1990a) and monkeys (e.g., Brush et al., 1961; Harlow, 1950) have a natural preference for novel stimuli. Therefore, to succeed at delayed matching to sample an infant or monkey must not only remember what he or she has seen but must inhibit the tendency to reach to the new object. (Hence, the importance of using different objects on each trial—for if the objects have been seen on previous trials then neither object will be novel and there will be no response bias to inhibit—and the importance of giving subjects sufficient time with the sample so they begin to get bored with it.)

Delayed nonmatching to sample is formally similar to delayed matching to sample (only the rule is different: "Reach to the familiar object" for delayed matching to sample, "reach to the new object" for delayed nonmatching to sample). However, inhibitory control is not required for delayed nonmatching to sample, as the natural preference is to reach to the new object. Hence, delayed nonmatching to sample requires only memory, not inhibitory control. It is dependent on the hippocampal neural circuit, not dorsolateral prefrontal cortex (Mishkin et al., 1962; Zola-Morgan and Squire, 1986; Zola-Morgan et al., 1989). On the other hand, delayed matching to sample requires both memory and inhibitory control; performance here appears to be impaired by lesions to either the hippocampal system or to dorsolateral prefrontal cortex (Mishkin et al., 1962).

### Inhibition

Perhaps memory is not one of the abilities dependent on dorsolateral prefrontal cortex at all, and not one of the abilities developing between 7½ and 12 months. Since the delays at which dorsolateral prefrontal cortex is typically required are so brief (e.g., 2–5 seconds on A$\overline{B}$ and delayed response), perhaps this might better be described as "maintaining attention" than "memory." If one conceives of the ability to span a few seconds' delay as an ability to resist distraction and maintain focused attention, then one might conceive of A$\overline{B}$ and delayed response as requiring, not memory plus inhibition, but two types of inhibition (the ability to resist distraction and to resist repeating a rewarded response). Memory may not be required for the object retrieval task, as the goal object is always visible (although memory of which sides of the box have been tried and found closed is probably still important). It is clear, though, that the object retrieval task imposes a strong demand on inhibitory control: The pull to reach straight to the visible goal must be inhibited if the subject is to detour around the transparent box to the opening. For example, subjects perform significantly better on object retrieval when an opaque box is used; i.e., when they cannot see the goal object through a closed side of the box and so do not have to fight the tendency to reach straight to the object (Diamond, submitted; Taylor et al., 1990b). Inhibition is certainly an ability required by all three tasks on which infants improve between 7½ and 12 months: A$\overline{B}$, delayed response, and object retrieval.

However, just as a memory demand alone does not appear to be sufficient to require dorsolateral prefrontal cortex involvement, neither is a simple inhibitory demand sufficient. For example, even before 7½–12 months, infants are able to inhibit their tendency to reach impulsively for any new object (Fox and Bell, 1990). Infants and prefrontally operated monkeys succeed on $A\overline{B}$ and delayed response if there is no delay (no requirement to hold something in mind), even on reversal trials where the pull to reach back to where they were previously reinforced must be inhibited (e.g., **infants:** Gratch and Landers, 1971; Harris, 1973; Gratch et al., 1974; Fox et al., 1979; **monkeys:** Harlow et al., 1952; Battig et al., 1960; Fuster and Alexander, 1971). Still, it is possible that "memory plus inhibition" is not the best way to characterize the abilities maturing between 7½ and 12 months or the abilities dependent on dorsolateral prefrontal cortex. Fox and Bell (1990), for example, characterize the ability as "inhibition of a response in the presence of distraction." Further work is needed to help us better understand the underlying abilities and choose among these competing hypotheses.

To better understand the abilities subserved by any neural circuit, or developing during any particular period of life, control tasks must be used. Ideally, they should differ in one way only from the tasks of interest. Examples of such pairs of tasks are delayed nonmatching to sample and delayed matching to sample, or delayed response for spatial location and delayed response for color or objects. In this way, hypotheses can be rigorously tested and eliminated.

## What Roles Do Different Regions and Pathways Within the Same Neural Circuit Play in Subserving the Functions of the Circuit?

For example, how do the different regions of frontal cortex, the caudate nucleus, and the cingulate contribute to performance of various tasks? How distinct are the abilities they subserve? How does maturation of these and other related areas affect performance of tasks linked to dorsolateral prefrontal cortex?

The caudate nucleus is a major output structure of dorsolateral prefrontal cortex. Damage to the caudate, as in parkinsonism, appears to result in many frontal cortexlike deficits (Taylor and Saint-Cyr, 1986; see also Lees and Smith, 1983; Stern et al., 1983; Benecke et al., 1987). There has been much suggestion that many of the changes early in life in functions attributed to frontal cortex are due to maturation of the caudate, rather than to maturation of frontal cortex itself (Goldman and Rosvold, 1972; Villablanca et al., 1979; Vicedomini et al., 1982; 1984). It is critical to determine, especially during infancy and early childhood, the extent to which the caudate is important for performance of tasks linked to frontal cortex.

A pathway that may be undergoing important changes even as early as 7½–12 months is the callosal connection between the frontal cortices in each hemisphere. Over this age period infants become able, for the first time, to do one action with one hand while simultaneously doing something else with the other hand, such as raising the object retrieval box and, at the same time, reaching for the toy inside (Diamond, 1990b). This complementary use of the two hands may well be dependent on maturation of the interhemispheric connections via the

corpus callosum between the right and left frontal cortex, especially between the supplementary motor areas.

Human adults (Luria, 1973; Laplane et al., 1977) and monkeys (Brinkman, 1984) with lesions of the supplementary motor area have difficulty with the complementary use of the two hands. Their hands tend to do the same thing, making bimanual coordination difficult. For example, patients with damage to the supplementary motor area have great difficulty making a fist with one hand while simultaneously turning their other hand palm up. They either do the same thing with both hands or execute the movements sequentially. This is very similar to the behavior seen in 7½–9-month-old infants. When they raise the object retrieval box with both hands, for instance, these infants have great difficulty not lowering the second hand when one hand goes down to reach in the box. By 8½– 9 months, infants can solve this sequentially by first raising the box and then reaching in, but not until 9½–10 months can they simultaneously raise the box and reach inside. Simultaneous integration of the movements of the two hands probably requires inhibitory projections via the corpus callosum so that the tendency of one hand to do the same thing as the other hand can be suppressed. Adults who were born without a corpus callosum (congenital acallosals) have difficulty suppressing "associated movements"; i.e., they have difficulty inhibiting one hand from doing what the other is doing (Dennis, 1976), and the inhibitory control of callosal fibers on movement has been well documented (e.g., Asanuma and Okamoto, 1959).

I hope the guidelines presented here may be of some help to those doing research on brain-behavior relations in development. The importance of converging evidence from diverse experimental approaches, of divergent validity, and of looking at the qualitative, as well as quantitative, aspects of performance cannot be overemphasized. It is important not to stop simply with linking a task to a neural system, but to understand what abilities are required by that task and how that neural system functions to subserve one or more of those abilities. Work on humans should be supplemented by work with nonhuman primates, work on one neural region should be supplemented by work on other related and unrelated neural regions, work on one age range by work on older and younger ages, and work with one behavioral task by work with other tasks. Many questions remain to be answered, and there is room for much fruitful collaboration. I am convinced that work in neuroscience will continue to help us better understand how the mind changes as a child grows up, and that work in developmental psychology will continue to help us better understand how the brain makes complex cognitive operations possible.

## NOTES

1. Infants make a characteristic error on the A$\overline{\text{B}}$ task, from which the task derives its name. They typically reach correctly at the first place the reward is hidden, well A, but when the reward is then hidden at well B, infants still search at well A, although they just saw the reward hidden at B moments earlier. That is, they are correct when the reward is

hidden at A but not when it is hidden at B; they reach to A but not to B. Hence, the name of the task "A-not-B."

2. It will be important in future work to determine the contributions of the supplementary motor area and premotor cortex to performance of the object retrieval task, as well as to determine the relative contributions of the subregions of dorsolateral prefrontal cortex (the sulcus principalis and the periarcuate region). Delayed response appears to depend most crucially on sulcus principalis; it will be important to determine whether the same is true for object retrieval.

3. More precisely stated, the functioning of other neural circuits should not be related *in the same ways* to the tasks. See guideline #5. Almost any task is going to require multiple abilities, such as visual processing, memory, and motor programming. More than one neural circuit will then be required for successful performance of the task, but the functioning of each neural circuit will affect task performance in different ways and be sensitive to different task parameters.

4. More precise information about changes in dopamine levels specifically in prefrontal cortex during development, or in human infants as opposed to infant monkeys, is not yet known.

5. The delayed nonmatching to sample task assesses recognition memory for objects: First a sample object is presented at the center of the testing area. In order to insure that the subject has seen the sample, the subject must displace it to retrieve a reward underneath. Then an opaque screen is lowered and a delay typically is imposed. The screen is then raised revealing the familiar sample object and a new object the subject has never seen before (one to the left of midline and the other to the right). If the subject displaces the new object (i.e., the one that does *not* match the object presented before the delay) a hidden reward is revealed for the subject to retrieve. The left-right position of the new and familiar objects is varied randomly over trials.

The testing procedure currently used, with different junk objects on every trial ("trial-unique stimuli"), was independently devised by Gaffan (1974) and by Mishkin and Delacour (1975). Delayed nonmatching to sample is used because monkeys find it difficult to learn delayed *matching* to sample, given their natural preference to reach to the new object (Harlow, 1950; Brush et al., 1961; Mishkin et al., 1962; Gaffan et al., 1984). Young children show this same preference (Diamond, in press, b).

6. Children cannot be tested on delayed nonmatching to sample, using the same procedure as used with monkeys or adult patients, until about 12 months of age.

7. For example, might memory for space and/or time be disrupted by delays of only 2–5 seconds when it first appears, while memory for other information is only disrupted by longer delays of $\geq$ 15–30 seconds from the very outset? When monkeys with lesions of dorsolateral prefrontal cortex fail memory tasks they do so at delays of only 2–5 seconds; if the task is not sensitive to dorsolateral prefrontal cortex damage at those delays, it is unlikely to be sensitive to it at longer delays (e.g., Diamond and Goldman-Rakic, 1989). Monkeys with hippocampal lesions, on the other hand, usually succeed at delays under 15–30 seconds, even on tasks specifically sensitive to hippocampal damage (e.g., Mishkin, 1978; Zola-Morgan et al., 1989).

8. Somewhat distant, though related questions have been investigated using the A$\overline{\text{B}}$ task, where psychologists have shown that 9-month-old infants tend to encode relative position, rather than absolute location or particular body movement (Bremner and Bryant, 1977; Butterworth, 1975); and infants can learn to associate the color of the cover over a hiding place with the toy and so they will reach to that color regardless of where the toy is hidden. (Bremner, 1978; Butterworth et al., 1982, expt. 2).

Piaget (1952 [1936]) characterized much of the change occurring in the latter part of the first year as the development of the ability to "put into relation." Certainly, infants

begin to be able to relate two objects in play (Fenson et al., 1976) and to relate reaching one place and looking another during this period (Millar and Schaffer, 1972; Diamond, submitted). Holding relational information in memory might be part of this general development.

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