Prefrontal Cortex Development and Development of Cognitive Functions

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Abstract

Even as early as the first year of life, developmental changes are found in prefrontal cortex and in the cognitive abilities dependent on prefrontal cortex. However, prefrontal cortex, and the cognitive abilities that depend on it, continue to develop until early adulthood. The ages of roughly 12 months, 6-7 years, and 10-11 years appear to be watersheds in the development of prefrontal cognitive abilities. Prefrontal cortex is required when concerted concentration is needed, exactly those times when going on "automatic pilot" is not possible or would lead to error. This entry focuses on two of the abilities dependent on prefrontal cortex, working memory and inhibitory control, the abilities needed to hold in mind what you should do and to resist doing what you should not. For each age period (0-1, 1-3, 3-7, and 7-22), advances in these abilities are discussed and then changes in prefrontal anatomy and biochemistry during that age period are discussed.

Prefrontal cortex (PFC) is by far the largest cortical area in the human brain (see entry 4.3/61). It appears to be required when a task is novel or complicated and thus requires concentration. An example would be when you need to guide your actions by information you are holding in mind, and must pay attention so that you act according to that information and not your natural inclination. Its period of maturation is particularly protracted. PFC shows significant developmental changes as early as the first year of life, but does not reach full maturity in humans until young adulthood. In this entry, developmental periods are broken up into 0-1, 1-3, 3-7, and 7-22 years. For each period, changes in cognitive abilities thought to depend on PFC are briefly described, as is evidence of maturational changes in PFC.

Behavioral evidence of improvements in the cognitive functions that depend on PFC during the first year of life: Piaget's "A-not-B" task has been widely used to study infant cognitive development (Wellman *et al.*, 1987). Under the name "delayed response," the almost-identical task has been widely used to study the functions of a subregion of PFC in rhesus monkeys (Goldman-Rakic, 1987). The subregion is dorsolateral PFC (DL-PFC). A participant watches as a reward is hidden to the left or right in one of two identical hiding places. A few seconds later the participant is encouraged to find the hidden treat. The participant must hold in mind over those few seconds where the treat was hidden, and over trials, must update his or her mental record to reflect where the treat was hidden last. The participant is rewarded for reaching correctly by being allowed to retrieve the treat. In this way, the behavior of reaching to that location is reinforced and hence the tendency to make 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 hidden last. Hence, this task requires an aspect of working memory (holding information in mind) plus inhibition of a prepotent action tendency (the tendency to repeat a positively reinforced response).

By roughly 7½-8 months of age, infants reach correctly to the first hiding location with delays as long as 2-3 sec (Diamond, 1985). 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"). Infants show marked improvements in their performance of the A-not-B/delayed response task between 7½-12 months of age. For example, each month they can withstand delays approximately 2 sec longer, so that by 12 months of age delays of roughly 10 sec or longer are needed to see the A-not-B error (Diamond, 1985).

In a transparent barrier detour task called "object retrieval" (Diamond, 1991) a toy is placed within easy reach in a small, clear box, open on one side. There is a very strong pull to reach straight for the toy through the side one is looking, which must be inhibited when an infant is looking through a closed side of the box. At 6-8 months of age, 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. By 11-12 months of age, infants do not need to look along the line of reach at all. Infants progress through a well-demarcated series of 5 stages in performance of this task between 6-12 months of age (Diamond, 1991).

Although the A-not-B/delayed response and object retrieval tasks share few surface similarities, human infants improve on these tasks during the same age period (6-12 months) and so do infant rhesus monkeys (1½-4 months; Diamond). Despite wide individual differences in the rate at which infants improve on 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, 1991).

There is no behavioral task more firmly linked to DL-PFC than the A-not-B/delayed response task (reviews: Goldman-Rakic, 1987; Fuster, 1989). This is one of the strongest brain-behavior relations in all of cognitive neuroscience. DL-PFC lesions in the monkey also disrupt performance on the object retrieval task (Diamond, 1991). MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) injections, which reduce the level of dopamine in PFC, also produce deficits on the task (e.g., Taylor *et al.*, 1990; Schneider & 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].)

Human infants of 7½-9 months, infant monkeys of 1½-2½ months, adult monkeys in whom DL-PFC has been removed, infant monkeys of 5 months in whom DL-PFC was removed at 4 months, and adult monkeys 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 (Diamond, 1991). In human infants, changes in the pattern of electrical activity detected by electroencephalogram (EEG) over frontal cortex and in the coherence of electrical activity detected by EEG over frontal cortex and parietal cortex (*re: A-not-B*: Bell & Fox, 1992; *re: object retrieval*: Fox, personal communication) correlate closely with developmental improvements on the A-not-B/delayed response and object retrieval tasks. This does not prove that developmental improvements on these tasks rely in part on maturational changes in DL-PFC, but it is consistent with that hypothesis.

Anatomical and biochemical evidence of maturational changes in PFC during the first year of life: Nerve cells consist of axons, dendrites, and a cell body. Dendrites, which branch off from the cell body, represent the largest part of the receptive surface of a neuron. The period of marked growth in humans of the length and extent of the dendritic branches of pyramidal neurons in layer III of DL-PFC is 7½-12 months (Koenderink *et al.*, 1994), exactly coinciding with the period when human infants are improving on the A-not-B/delayed response and object retrieval tasks. Pyramidal neurons of this PFC region have a relatively short dendritic extent in 7½-month-old infants. By 12 months of age, they have reached their full mature extension. The surface of the cell bodies of these neurons also increases between 7½-12 months (Koenderink *et al.*, 1994). The level of glucose metabolism in DL-PFC increases during this period as well, and comes to approximate adult levels by 1 year of age (Chugani *et al.*, 1987).

Dopamine is an important neurotransmitter in PFC. During the period that infant rhesus monkeys are improving on the A-not-B/delayed response and object retrieval tasks (1½-4 months), the level of dopamine is increasing in their brain (Brown & Goldman, 1977), the density of dopamine receptors in their PFC is increasing (Lidow & Rakic, 1992), and the distribution within their DL-PFC of axons containing the rate-limiting enzyme (tyrosine hydroxylase) for the production of dopamine is markedly changing (Rosenberg & Lewis, 1994).

Acetylcholinesterase (AChE) is an enzyme essential for metabolizing another neurotransmitter, acetylcholine. In humans, the pattern of AChE staining in DL-PFC changes dramatically during the first year of life (Kostovic *et al.*, 1988).

Behavioral evidence of improvements in the cognitive functions that depend on PFC between 1-3 years of age: This is the period for which we know least about changes in PFC anatomy or in cognitive functions dependent on PFC. Kochanska *et al.* (2000) report that the ability to inhibit a prepotent response in order to perform a modulated or different response improves markedly from 22-33 months of age and that the consistency across their various measures of inhibition also increased between 22-33 months.

To use a lazy susan to bring a toy within reach requires relating the lazy susan and its movement to the toy and its movement. It also requires inhibition of trying to reach on a direct line of sight (as the younger children try to do) and inhibition of the tendency to push the lazy susan in the direction you want the toy to go (you must push left to get the toy to approach on the right). Children improve in their ability to do this between 12-24 months (Koslowski and Bruner, 1972). Case (1992) similarly reports marked improvements on a simple balance beam problem between 1½ and 2½ years.

Evidence of maturational changes in PFC between 1-3 years: Almost nothing is known about changes in prefrontal cortex during this period. AChE reactivity of layer III pyramidal neurons begins to develop during this period (Kostovic *et al.*, 1988), but that is surely not the only change in prefrontal cortex between 1-3 years of age.

Behavioral evidence of improvements in the cognitive functions that depend on PFC between 3-7 years of age: Clear improvements in tasks that require holding information in mind plus inhibition are seen between 3-7 years of age. Three-year-olds make an error reminiscent of infants' A-not-B error, but with a more difficult task. On this task, 3-year-olds sort cards correctly by the first criterion (whether it is color or shape: Zelazo *et al.*, 1996), just as infants and prefrontally-lesioned monkeys are correct at the first hiding place, and just as adults with PFC damage sort cards correctly according to the first criterion (Wisconsin Card Sort test: Milner, 1964; Stuss *et al.*, 2000). Three-year-olds err when they must switch to a new sorting criterion, e.g., when cards previously sorted by color must now be sorted by shape, just as infants of 7½-9 months and prefrontally-lesioned monkeys err when required to switch and search for the reward at the other location, and just as adults with PFC damage err when required to switch to a new sorting criterion. Although 3-year-old children fail to sort by the new sorting criterion, they can correctly state the new criterion (Zelazo *et al.*, 1996), as is sometimes seen with adult patients who sustained damage to PFC (Luria & Homskaya, 1964; Milner, 1964). Infants, too, sometimes indicate that they know the correct answer on the A-not-B task, by looking at the correct well, although they reach back incorrectly to the well that was previously correct (Hofstadter & Reznick, 1996).

Another example of apparently knowing the correct answer, but not being able to act in accord with it is provided by work with "go/no-go" tasks (Tikhomirov, 1978; Livesey & Morgan, 1991). Here, the participant is to respond to one stimulus but do nothing when shown another. Children 3-4 years old repeat the instructions correctly, but they cannot get themselves to act accordingly; they respond even to the "no-go" stimulus. By 5 years, they perform well on the card sort and go/no-go tasks.

The problem on the card sort task appears to be in (a) integrating two dimensions of a single stimulus (e.g., if children are used to focusing on whether stimuli are red or blue, they have trouble re-focusing and concentrating instead on whether the same stimuli are trucks or stars) and (b) inhibiting the tendency to repeat their previously correct response. Similarly, children of 3 years have difficulty with "appearance-reality" tasks (e.g., Flavell, 1986) where, for example, they are presented with a sponge that looks like a rock. Three-year-olds typically report that it looks like a rock and really is a rock, whereas children of 4-5 years correctly answer that it looks like a rock but really is a sponge. The problem for the younger children is in relating two conflicting identities of the same object (e.g., Rice *et al.*, 1997) and in inhibiting the response that matches their perception. Manipulations that reduce perceptual salience, by removing the object during questioning, enable children of 3-4 years to perform much better [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 the impulse to give the veridical answer. Here, as well, manipulations that reduce the perceptual salience of the true state of affairs aid children of 3-4 years (e.g., Zaitchik, 1991). Carlson *et al.* (1998) reasoned that pointing veridically 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 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.

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 reflect the development of the ability to hold more than one thing in mind and to inhibit the strongest response tendency of the moment. For example, children of 3 or 4 years fail tests of liquid conservation (they do not attend to both height and width, attending only to the most perceptually salient of the two dimensions) and they fail tests of perspective-taking where they must mentally manipulate a scene to indicate what it would look like from another perspective and must inhibit the tendency to give the most salient response (i.e., their current perspective). By 5 or 6 years, they can do these things. Since part of the difficulty posed by Piaget's liquid conservation task is the salience of the visual perception that the tall, thin container contains more liquid, placing an opaque screen between the child and the containers before the child answers enables younger children to perform better (Bruner, 1964).

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 better able to wait for the preferred reward (Mischel & Mischel, 1983).

Between 4 and 5 years of age children show improvement on several tests in the CANTAB battery that are designed to assess frontal lobe function (Luciana & Nelson, 1998). For example, their improved ability to retain temporal order information in memory is demonstrated by better performance at 5 years on (a) a test of spatial memory span that is similar to the children's game, Simon, or the Corsi block task (the child must touch boxes displayed on a computer screen in the order in which he or she just saw them change color) and on (b) a spatial self-ordered pointing task where the child must keep track of which squares he or she has already touched.

The "day-night" task (Gerstadt *et al.*, 1994) requires that children hold two rules in mind and inhibit the tendency to say what the stimuli really represent; instead they must say the opposite ("Say 'night' when shown a white card with a picture of the sun, and say 'day' when shown a black card with a picture of the moon and stars"). Children of 3½-4½ years find the task very difficult; by 6-7 years it is trivially easy. If abstract designs are used as the stimuli, even children of 3½ have no difficulty correctly saying 'day' to one and 'night' to the other (Gerstadt *et al.*, 1994). Hence, the need to learn and remember two rules is not in itself sufficient to account for the poor performance of young children on the task.

Luria's "tapping" test (Luria, 1966) also requires (a) remembering two rules and (b) inhibiting a prepotent response, 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. Adults with large frontal lobe lesions fail this task (Luria, 1966). Children improve on the task over the same age range they improve on the day-night task (Diamond & Taylor, 1996). Moreover, performance on the two tasks is correlated so that children whose performance on the day-night task is delayed or accelerated show a corresponding delay or acceleration in their performance on the tapping task (Diamond *et al.*, 1997; Diamond, 2001).

The "counting span" and "spatial span" tasks of Case (1972) require finding target stimuli, counting them or remembering their locations, holding that information in mind while finding target stimuli in new arrays, and keeping track of the answers computed on each trial so that they can be repeated back in order at the end. Thus, these tasks require temporal order memory and resisting interference from prior and interpolated activity. A meta-analysis of 12 cross-sectional studies revealed strong linear improvements on both tasks between 4½-6½ years (Case, 1992). Performance on these tasks is highly correlated with performance on Piaget's "balance beam" task, "Raven's matrices," and "concept acquisition." On the balance beam and Raven's matrices tests, 4-year-olds tend to answer accordingly to what is perceptually salient. By 7-8 years of age, they are able to take two dimensions, or two perspectives, into account and relate one to the other. They can mentally manipulate, combine, re-combine, order, and re-order information.

Anatomical evidence of maturational changes in PFC between 3-7 years: The density of neurons in human DL-PFC is highest at birth and declines thereafter. At 2 years of age, it is 55% above the adult mean, but by 7 years it is only 10% above adult levels (Huttenlocher, 1990). Thus there is a dramatic change in neuronal density in DL-PFC between 2-7 years. The synaptic density of layer III pyramidal cells in DL-PFC increases after birth and reaches its maximum at about 1 year of age; by 7 years of age the decrease in synaptic density is significant, though not yet down to adult level (Huttenlocher, 1979). Another change during this period is a marked expansion in the dendritic trees of layer III pyramidal cells in human DL-PFC between 2-5 years of age (Mrzljak *et al.*, 1990). In addition, the density of neuropeptide Y-immunoreactive neurons in human DL-PFC increases between ages of 2-4 years and 6-7 years (DeLalle *et al.*, 1997).

Behavioral evidence of improvements in the cognitive functions that depend on PFC between 7 years of age and adulthood: Some abilities dependent on DL-PFC appear to reach their adult levels by about 11 years of age. The Wisconsin Card Sort test is one of the classic tests for studying PFC function in adults (Milner, 1964; Stuss *et al.* 2000). Here, the participant must deduce the rule for sorting cards, which can be sorted by color, shape, or number. Children do not begin to reach adult levels of performance on this task until they are about 11 years old (Chelune & Baer, 1986). Continuous, marked improvement is seen on the counting and spatial span tasks through age 8, and then improvement is less steep until performance asymptotes around 10-11 years of age (Case, 1972, 1992). Pascual-Leone's tasks (the compound stimulus visual information and the digit placement tests) show similar developmental progressions (Pascual-Leone, 1970; Case, 1972). Hale *et al.* (1997) report that resistance to interference improves from 8 to 10 years, when it approximates adult levels.

Other abilities dependent on PFC continue to show improvement into adulthood. Zald & Iacono (1998) report that spatial working memory improves from 14-20 years of age. They found that 20-year-olds were significantly more accurate than 14-year-olds at indicating the location of an object in space using memory even after brief delays of only 0.5 sec. (There was no age difference in the ability to accurately indicate an object's location using visual feedback.) The improvement with age was in the ability to accurately get the information into working memory, not in the ability to hold it in mind for a longer period. Indeed, they found little difference over age in the rate of degradation of the memory.

Another task that requires precise spatial memory is the pattern span task (Wilson *et al.*, 1987). On any given trial some of the squares in a grid pattern are filled and some unfilled, after a quick look, the participant is presented with the grid with one change; the participant is to find that change.

Performance on this task improves dramatically between 5-11 years, when it reaches adult levels (Wilson *et al.*. 1987).

Several bodies of work indicate that the ability to inhibit a prepotent response tendency continues to improve until early adulthood. In the "directed forgetting" paradigm, participants are directed to forget some of the words they are shown and to remember others. Even children as old as roughly 11 years show more intrusions of the to-be-forgotten words than do adults (e.g., Harnishfeger & Pope, 1996; Lehman *et al.*, submitted). The "anti-saccade" task requires the participant to suppress the tendency to reflexively look to a visual stimulus in the periphery, and instead look away in the opposite direction. It depends especially on the frontal eye fields, and the supplementary eye fields and DL-PFC (O'Driscoll *et al.*, 1995; Luna *et al., in press*). Performance on the task improves continuously from 8 through 20-25 years of age (Munoz *et al.*, 1998; Luna *et al., in press*). Luna *et al.* (*in press*) report that while activation in the frontal eye fields, supplementary eye fields, and DLPFC increased during anti-saccade performance in participants of all ages, increased activation of the thalamus, striatum, and cerebellum was seen only in adults, suggesting that the circuit connecting PFC with subcortical regions might mature late..

<u>Anatomical evidence that PFC is not fully mature until adolescence or early adulthood</u>: One of the functions of glial cells is to provide an insulating sheath, called myelin, around the axons of neurons, which increases the speed of transmission of communication between neurons and which acts as an electrical insulator, decreasing lateral transmission and interference, thus improving the signal: noise ratio. Myelination of PFC is protracted and does not reach adult levels until adolescence (Huttenlocher, 1970; Giedd *et al.*, 1999). For example, using MRI and following the same children longitudinally, Giedd *et al.* (1999) were able to show that the amount of white matter (i.e., myelinated axons) increased linearly in frontal cortex from 4-13 years of age.

Portions of the neuron that are unmyelinated, such as the cell body, have a gray appearance. In their longitudinal study, Giedd *et al.* (1999) found that gray matter in frontal cortex increased until adolescence, reaching its maximum size at 12 years of age for males and 11 years of age for females. However, in cross-sectional volumetric studies, Jernigan *et al.* (1991) and Sowell *et al.* (1999a) report *reductions* in gray matter volume between childhood and adolescence, with the most dramatic changes occurring in dorsal frontal and parietal cortex. Sowell *et al.* (*2001*) related these gray matter changes to cognitive performance, and found that, between 7-16 years of age, gray matter in frontal cortex (which included in their analyses not only PFC, but motor cortex, and all cortex inbetween) decreased in size and the ability to accurately remember which words had and had not been presented earlier (i.e., the ability to remember which words had been seen in the present context and to discriminate them from other familiar words) improved. Impressively, gray matter thinning in frontal cortex was significantly correlated with this source memory, independent of age. Indeed, while the relation between frontal cortex gray matter thinning and this ability remained significant controlling for age, the relation between age and source memory was no longer significant controlling for frontal gray matter changes.

Synaptogenesis occurs concurrently with myelination. Huttenlocher (1979) reports that the synaptic density of layer III pyramidal cells in DL-PFC increases until about the age of 1 year, and then decreases, finally reaching adult levels at about 16 years of age. Huttenlocher and Dabholkar (1997) report that the formation of synaptic contacts in DL-PFC reaches its maximum after 15 months of age, and synapse elimination occurs late in childhood, extending to mid-adolescence for DL-PFC.

Developmental changes in PFC continue into adulthood. Sowell *et al.* (1999b) report a reduction in the density of gray matter in frontal cortex between adolescence (12-16 years) and adulthood (23-30 years). Kostovic *et al.* (1988) report that acetylcholinesterase (AChE) reactivity of layer III pyramidal cells in DL-PFC, which begins to develop after the first postnatal year, finally reaches its peak intensity in young adults.

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