Structural and functional brain development and its relation to cognitive development

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Abstract

Despite significant gains in the fields of pediatric neuroimaging and developmental neurobiology, surprisingly little is known about the developing human brain or the neural bases of cognitive development. This paper addresses MRI studies of structural and functional changes in the developing human brain and their relation to changes in cognitive processes over the first few decades of human life. Based on post-mortem and pediatric neuroimaging studies published to date, the prefrontal cortex appears to be one of the last brain regions to mature. Given the prolonged physiological development and organization of the prefrontal cortex during childhood, tasks believed to involve this region are ideal for investigating the neural bases of cognitive development. A number of normative pediatric fMRI studies examining prefrontal cortical activity in children during memory and attention tasks are reported. These studies, while largely limited to the domain of prefrontal functioning and its development, lend support for continued development of attention and memory both behaviorally and physiologically throughout childhood and adolescence. Specifically, the magnitude of activity observed in these studies was greater and more diffuse in children relative to adults. These findings are consistent with the view that increasing cognitive capacity during childhood may coincide with a gradual loss rather than formation of new synapses and presumably a strengthening of remaining synaptic connections. It is clear that innovative methods like fMRI together with MRI-based morphometry and nonhuman primate studies will transform our current understanding of human brain development and its relation to behavioral development. © 2000 Elsevier Science B.V. All rights reserved.

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Magnetic resonance imaging (MRI), with its lack of ionizing radiation and capacity to provide exquisite anatomical detail, has revolutionized the study of human brain development. Other imaging modalities such as conventional radiography, computerized tomography, positron emission tomography (PET), and single photon emission computerized tomography (SPECT) use ionizing radiation. While these latter techniques may be used with pediatric patient populations when clinically warranted, the ethics of exposing children to radioactive isotopes for the advancement of science are less clear (Casey and Cohen, 1996; Morton, 1996; Zametkin et al., 1996). The advent of functional MRI has now further extended the utility of MRI to explore the developing human brain as never before. This paper addresses MRI studies of structural and functional changes in the developing human brain and their relation to changes in cognitive processes over the first few decades of human life.

1. Brain development: What do we know?

Despite the significant gains in the fields of pediatric neuroirnaging and developmental neurobiology, surprisingly little is known about the developing human brain. This is particularly the case during early and late childhood — a time when significant leaps in social and cognitive learning take place. In part, this is due to low mortality rates across this age range in addition to the rare occurrence of autopsies on this population. For example, the Yakovlev brain collection in Washington, DC, contains only a dozen or so normal brains from roughly 500 that are from subjects between the ages of 4 and 18 (Haleem, 1990). Nonetheless, pioneering work in both developmental neurobiology and pediatric brain imaging has begun to paint a picture of how the developing human brain unfolds throughout childhood.

Most of the dynamic activity of brain development occurs in utero but changes continue for the first two postnatal years. By this point, the brain has reached close to 80% of its adult weight (Kretschmann et al., 1986). This is also a period of rapid synapse formation that begins well before birth in primates (Rakic, 1972, 1974; Rakic et al., 1988) and results in overproduction of synapses relative to its adult state. This process of synaptogenesis appears to occur concurrently across diverse regions of the non-human primate cerebral cortex (Rakic et al., 1986). However, in humans postmortem data indicates that synaptogenesis does not occur concurrently with synaptic density peaking earlier in the auditory cortex, at three months, and later in the middle frontal gyrus, at 15 months (Huttenlocher, 1997). In both human and non-human primate studies the early synaptic density peaks are followed by a plateau phase that decreases during childhood and into adulthood. The plateau and pruning phases of some cortical regions (e.g. prefrontal cortex) in primates are relatively protracted compared to others (e.g. visual cortex) (Bourgeois et al., 1989, 1994; Huttenlocher, 1990, 1997). These regions of prolonged development are perhaps most interesting when considering the developing child throughout adolescence and into adulthood.

PET studies of glucose metabolism suggest that maturation of local metabolic rates closely parallel the time course of overproduction and subsequent pruning of synapses (Chugani et al., 1987) with the prefrontal cortex showing a prolonged maturation relative to visual cortex. PET studies, although informative, are typically performed with clinical populations thus justifying their use with developmental populations. The use of PET with pediatric patient populations to understand normal brain development raises questions about the generalization of the results to truly healthy children. With the recent advances in MRI comes a whole new era in the study of the normally developing human brain in vivo.

To date, MRI-based anatomical studies have revealed some interesting maturational changes in brain structure. The most informative studies to date are those based on carefully quantified volumetric measures and large sample sizes of 50 or more subjects (e.g. Giedd et al., 1996a,b; Reiss et al., 1996). The most consistent findings across these studies include: (1) a lack of any significant change in cerebral volume after five years of age (Giedd et al., 1996a; Giedd, et al., 1996b; Reiss, et al., 1996); (2) a significant decrease in cortical gray matter after 12 years (Giedd et al., 1999); and (3) an increase in cerebral white matter throughout childhood and young adulthood (Jernigan et al., 1991; Pfefferbaum et al., 1994; Caviness et al., 1996; Rajapakse et al., 1996; Reiss et al., 1996). Specifically, subcortical gray regions (e.g. basal ganglia) decrease during childhood, particularly in males (Giedd et al., 1996a; Rajapakse et al., 1996; Reiss et al., 1996) while cortical gray matter in the frontal and parietal cortices does not appear to decrease until roughly puberty (Giedd et al., 1999). White matter volume appears to increase throughout childhood and well into adulthood (Caviness et al., 1996; Rajapakse et al., 1996). These increases appear to be regional in nature. For example, there appears to be an increase in white matter in dorsal prefrontal cortex, but not in more ventral prefrontal regions (i.e. orbitofrontal cortex) (Reiss et al., 1996). Total temporal lobe volume appears relatively stable across the age range of 4 to 18 years, while hippocampal formation volume increases with age for females and amygdala volume increases with age for males (Giedd et al., 1996b). This latter finding may be consistent with the distribution of sex hormone receptors for these structures, with the amygdala having a predominance of androgen receptors (Clark et al., 1988; Sholl and Kim, 1989) and the hippocampus having a predominance of estrogen receptors (Morse et al., 1986).

Taken as a whole, these neuroimaging and post-mortem studies seem to suggest that some age-related changes are regional. One such brain region is the prefrontal cortex. Based on the nonhuman and human primate post-mortem studies and pediatric neuroimaging studies published to date, the prefrontal cortex appears to be one of the last brain regions to mature, particularly the dorsolateral prefrontal cortex.

Are the last brain regions to mature the first 'to go'? If so, is the prefrontal cortex region more susceptible to the aging process than other cortical regions? There is neuropsychological evidence to suggest that prefrontal function is sensitive to changes with age (Daigneault et al., 1992; Daigneault and Braun, 1993). This impairment is paralleled by a disproportionate degeneration of the prefrontal cortex

relative to temporal cortex or sensorimotor cortex (Coffey et al., 1992; Cowell et al., 1994; Raz et al., 1997). It appears that prefrontal white matter rather than gray matter may be most susceptible to normal aging as measured with MRI (Svennerholm et al., 1994; Peters et al., 1996; Salat et al., 1999). This pattern of degeneration is different from that observed in individuals with Alzheimer disease (Stout et al., 1996; Salat et al., 1999). If this is indeed the case, then why might the last area to mature be the first to go? One possibility is that brain regions that are most plastic over prolonged periods of development are more sensitive or susceptible to environmental factors (e.g. stressors, toxins) and thus more prone to insult or injury from such environmental influences. Related issues are addressed in Grady's paper in this issue.

2. What is the relation of brain development to cognitive development?

To date, little is known regarding the neural bases of cognition in normally developing children. In order to address the neural circuits underlying cognitive development, a means of assessing, in vivo, the developmental physiological course of the behavior is needed. With the advent of blood oxygenation level dependent (BOLD) imaging (Kwong et al., 1992; Ogawa et al., 1990; Turner et al., 1991), the field of magnetic resonance imaging has been opened to address developmentally driven questions of brain and behavior. This methodology capitalizes on the fact that hemoglobin becomes strongly paramagnetic in its deoxygenated state. Deoxygenated hemoglobin can therefore be used as a naturally occurring contrast agent, with highly oxygenated brain regions producing a larger magnetic resonance (MR) signal than less oxygenated areas. This method eliminates the need for exogenous contrast agents, including radioactive isotopes.

Given the prolonged physiological development and organization of the prefrontal cortex during childhood, tasks believed to involve this region are ideal for investigating development with this methodology. Cognitive processes that have been attributed to the prefrontal cortex include working memory, response inhibition and attention allocation (Goldman-Rakic, 1987; Diamond, 1988; Fuster, 1989). Memory, inhibition, and attention are often treated as three distinct psychological constructs. However, aspects of these cognitive processes may be part of a single construct or common underlying circuitry. For example, memory and inhibition are both involved in maintenance of information in that when relevant information is represented and maintained in memory, competing representations or memories are subsequently suppressed or inhibited. Likewise, selective attention and inhibition are part of a similar construct in that when we attend to a relevant event, other salient and competing, but nonetheless irrelevant events are suppressed or inhibited in favor of the relevant event. Similarly, selective attention and memory may represent a single construct in that the classic description of working memory (Baddeley, 1986) includes a component referred to as a central executive that allocates attentional resources to relevant events. Therefore, memory can be defined in part as the selective allocation of attention to relevant events or representations.

This component of working memory does not significantly differ from selective attention.

Perhaps the common component of overlap in the three previous examples of the psychological constructs of attention, memory, and inhibition, is the presumed presence of interfering or competing information. In the case of attention, the interference may be from simultaneous input or output. In the case of memory, interference may be due to competing memories/representations. If there is no interference, then inhibitory processes are seemingly not necessary and the constructs of attention and memory may be more easily distinguished. One distinguishing component is within the temporal domain with attention predominantly involving present information and memory involving past information. When there is interference from competing sources then the definitions of attention and memory are less discrete in that they can be defined as the ability to represent relevant events in the presence of salient, competing, and compelling, yet otherwise irrelevant events. How do we ignore and select from competing sources of information (stimulus selection), or from competing response alternatives (response selection), or for that matter, ignore or inhibit a behavior or response altogether (response execution)? This question suggests that inhibition can occur at different stages of attentional processing (i.e. during stimulus selection, during response selection, or during response execution) and likewise during memory of different types of information (e.g. stimulus sets, behavioral sets). So, both attention and memory appear to involve inhibitory processes when there is interference from competing sources.

Developmentally, inhibitory processes of this nature are of interest because they appear to be involved in both cognitive and social learning throughout childhood and adolescence. Often, the terms 'inhibitory control' and 'behavioral regulation' are used to describe inhibitory processes in cognitive and social development (Posner and Rothbart, 1998; Casey, in press). Clinically, inhibitory processes are important because they appear to be disrupted in a number of developmental disorders that have as a core deficit a problem inhibiting inappropriate behaviors and thoughts (e.g. Attention Deficit-Hyperactivity Disorder, Obsessive Compulsive Disorder, and Tourette syndrome). Interestingly, the prefrontal cortex and related circuitry have been implicated in these developmental disorders.

How does prefrontal circuitry relate to the normal development of inhibitory processes? Here, emphasis may well be placed on the role of the prefrontal cortex in supporting different types of information (e.g. verbal, spatial, motor, emotional) against interference over time and/or from competing sources (Goldman-Rakic, 1987; Cohen and Servan-Schreiber, 1992). A number of classic developmental studies have demonstrated that these memory and attention related processes develop throughout childhood and adolescence (Flavell et al., 1966; Pascual-Leone, 1970; Case, 1972; Keating and Bobbitt, 1978). Further, the converging evidence of prolonged development and organization of prefrontal cortex throughout childhood and adolescence (Huttenlocher, 1979; Chugani et al., 1987; Diamond, 1988, 1991, 1996; Bourgeois et al., 1994; Rakic et al., 1994) may suggest an important parallel between brain development and cognitive development. The most impor-

tant difference between the development of the prefrontal cortex relative to other cortical regions (e.g. visual cortex) is in the plateau and gradual decrease in synapses into young adulthood (Bourgeois et al., 1994). This decrease in synaptic density is gradual during late childhood and adolescence and coincides with the continued development of cognitive capacities. Accordingly, increasing cognitive capacity during childhood may coincide with a gradual loss rather than formation of new synapses and presumably a strengthening of remaining synaptic connections. These processes may represent the behavioral, and ultimately, the physiological suppression of competing, irrelevant behaviors. One can imagine that a response to a particular event in the environment will be speeded with repeated exposure and subsequent strengthening of the relation between that event and response. At a physiological level, this may be reflected in the observation that 'neurons that fire together wire together'. Simultaneously, competing, but less frequent behaviors are presumably weakened. With concurrent myelination of connecting fibers, one can begin to understand factors that may contribute to the change in speed of information processing that is observed throughout childhood and adolescence.

How does knowing where a function (e.g. attention or memory) resides in the brain better our understanding of behavior? One contribution of knowing where in the brain a particular function 'resides' is that it helps constrain our theories and models of behavior. What we know about the anatomy, physiology and connective circuitry of a particular region can provide insight into the behavior or construct of interest. To what extent psychological constructs are unique or overlapping (e.g. memory and inhibition) may in part be determined by whether these functions have overlapping or unique regions of brain activity.

A number of normative pediatric fMRI studies have examined prefrontal cortical activity in children during memory and attention tasks (Casey et al., 1995, 1997). In fact, the first published pediatric fMRI study examined prefrontal cortical activation in children performing a working memory task (Casey et al., 1995). One of the central themes of this paper is the importance of examining the functional development of the prefrontal cortex and related circuitry in the context of cognitive development, particularly with regard to memory and attention. This is important for a number of reasons. First, as stated earlier, there is considerable development and organization of the prefrontal cortex throughout childhood and adolescence. Second, cognitive processes such as memory and attention that have been attributed to the prefrontal cortex appear to develop during this period. Third, the prefrontal cortex and related circuitry have been implicated in a number of developmental disorders that involve disruption of attention and memory in the context of interference (e.g. Attention Deficit-Hyperactivity Disorder, Autism).

2.1. Memory and inhibition

As mentioned previously, the first published pediatric fMRI study examined prefrontal activation in children performing a working memory task (Casey et al., 1995). The purpose of this study, at the time, was to determine the feasibility of using fMRI with children to examine higher level cognitive processing in children.

Six children between the ages of 9 and 11 years were scanned while performing a working memory task used previously in adults with fMRI (Cohen et al., 1994). The study included two task conditions: a memory condition and a comparison/control condition. The memory condition required children to observe sequentially presented letters and to respond whenever the current letter was the same as the letter occurring two trials back ('2-back memory task'). In other words, children responded to repeats of letters with a single intervening (interfering) letter. In the comparison condition, subjects monitored similar sequences of letters for any occurrence of a single, pre-specified letter. Both the memory and comparison conditions required subjects to monitor sequences of letters presented visually one at a time, encode each letter, evaluate its identity, and respond to a target by pressing a button. The conditions differed in that the memory task required the subject to keep in mind the two previous letters rather than just a single target letter, and to continuously update this mental record over time. These latter cognitive operations are central to the concept of working memory (Baddeley, 1986) and consistent with our view of prefrontal involvement in the representation of information over time against interference from competing sources.

Echo planar images were acquired on a 1.5 T GE scanner using 5 inch surface coils while the children performed the memory and comparison conditions. Eight 5 mm coronal slices covering the frontal poles were acquired. Images were registered to a reference image to correct for movement using a modified version of Woods et al., 1992 3-D automated image registration (AIR) algorithm. Movement did not correlate with the experimental manipulation, but rather appeared to increase as a function of time on task and was minimal. The average movement across the entire study was less than .5 mm with .34 mm of movement in the x-direction, and 0.47 mm in the y-direction. Areas of significant activation were identified, by performing pixel-wise t-tests, comparing the memory and comparison conditions.
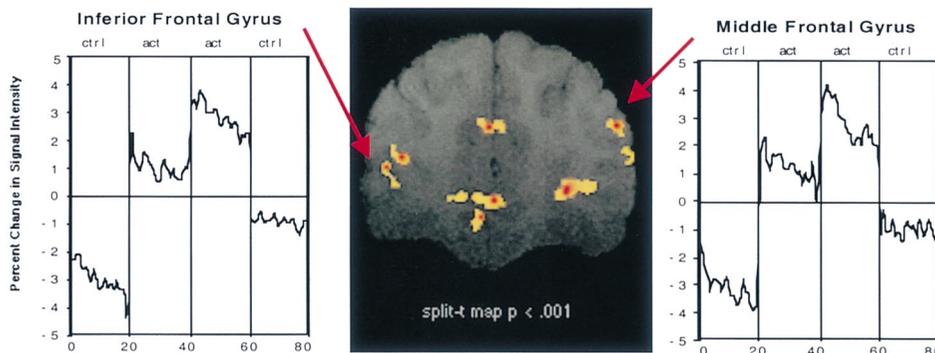

Fig. 1

Fig. 1. Location of activation in the middle and inferior frontal gyri for a representative subject and the corresponding change in MR signal intensity as a function of task manipulation averaged across subjects.
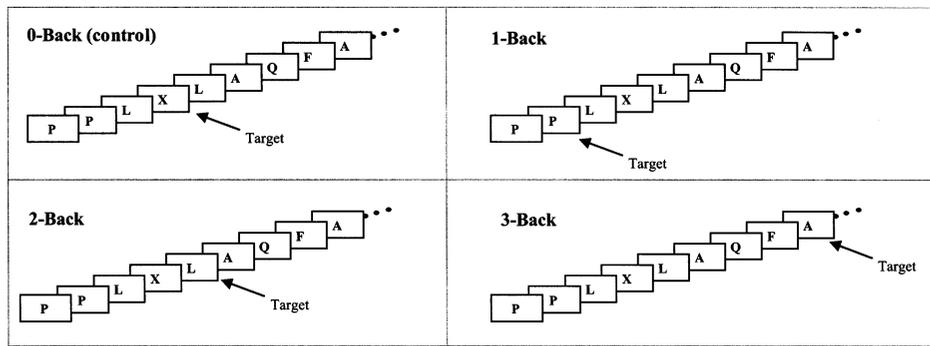
Fig. 2. Illustration of the *n*-back task with memory load varying from 0 to 3.

The results demonstrated reliable activity in the dorsolateral prefrontal cortex in children. Fig. 1 depicts the location of activation and the change in MR signal intensity as a function of scans across time. The increases in activity nicely map onto the experimental manipulation. Reliable activity was observed also in the anterior cingulate cortex. These results replicate an earlier fMRI study with adults showing dorsolateral prefrontal activity using the same paradigm (Cohen et al., 1994) and a more recent event-related fMRI study of working memory (Cohen et al., 1997) showing dorsolateral activation during active maintenance of stimulus information with interference from intervening trials. The similar distribution of activity across frontal gyri for children and adults taken from the Casey et al. (1995) and Cohen et al. (1994) studies are striking. Taken together, these two initial studies suggest a similar distribution of prefrontal cortical activity in children and adults during performance of a working memory task. However, the percent change in signal observed for the children was on average two to three times that observed for the adults in the Cohen et al. study. Based on the behavioral data available, the children had more difficulty with the task. On average, children performed at 70–75% accuracy in the Casey et al. study while adults performed at or above 90% accuracy in the Cohen et al. experiment. This demonstrates the importance of collecting behavioral responses in the scanner, but also raises concerns with regard to the interpretation of the findings given the behavioral differences. Are the differences maturational or strategic in nature or both?

A study that may help address this question is one presented by Braver et al., 1997, and others (Jonides et al., 1997; Rypma et al., 1999), which examined prefrontal cortical activity as a function of increasing memory load in adults. They performed the same sort of memory task as described previously, but varied the memory load from 0 to 3 as can be seen in Fig. 2. The subject monitored a sequential display of single letters and responded only when the current letter was the same as the letter *n* trials before it (e.g. if $n = 2$, then A-F-A or G-B-G, but not A-F-G-A or A-A). Subjects practiced until they reached 90% accuracy on the highest memory load of $n = 3$. The results revealed monotonic increases in percent change in MR signal intensity in prefrontal cortex as depicted in Fig. 3. We

mention this study because it is an elegant example of a task that may be especially well suited for developmental populations. This paradigm allows for the manipulation of memory load (number of trials back the subject must remember) by age and/or ability.

Although the Casey et al. (1995) study demonstrated the use of fMRI in pediatric populations, there was no direct comparison between children and adults since these studies (Cohen et al., 1994; Casey et al. 1995) were performed at different sites and with different scanning parameters. A similar working memory task as described by Braver et al. (1997) was used to perform a more direct comparison of brain activation for children and adults. This study was an extension of a multi-site collaboration whose primary goals were (1) to demonstrate the reproducibility of fMRI results across several US sites; and (2) to determine the feasibility of using fMRI with pediatric populations.

Each participating group examined brain activity in both adults and children during performance of a spatial working memory task designed as an analog of the verbal working memory task just described. In this task, subjects monitored a linear array of four boxes for the location of a dot. The dot appeared in a new location every two seconds for 500 ms. Participants maintained fixation on a central crossbar, and received instructions for three different response conditions. In the visual condition, participants made no response. In the motor condition, participants were required to indicate the current spatial location of the dot by pressing the corresponding key on a four-button box. In the memory condition, participants were asked to indicate the location at which the dot had appeared a given number of trials previously. For example, in a 2-back paradigm, subjects responded by indicating the location at which the dot had appeared two trials previously. Therefore, the motor and memory conditions are identical except in the memory demands and extent of interference from preceding trials. Further, the number of intervening stimuli to be remembered could be manipulated, so as to vary memory load. Participants were pre-tested outside of the scanner to assess which memory load was appropriate for each individual. Performance of 75–95% accuracy was required, with the intent of equating task performance across age groups. For some participants this level of performance required a 2-back condition, while others
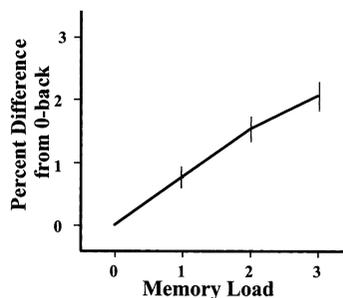

Fig. 3. Monotonic increases in percent change in MR signal in prefrontal cortex as a function of memory load.
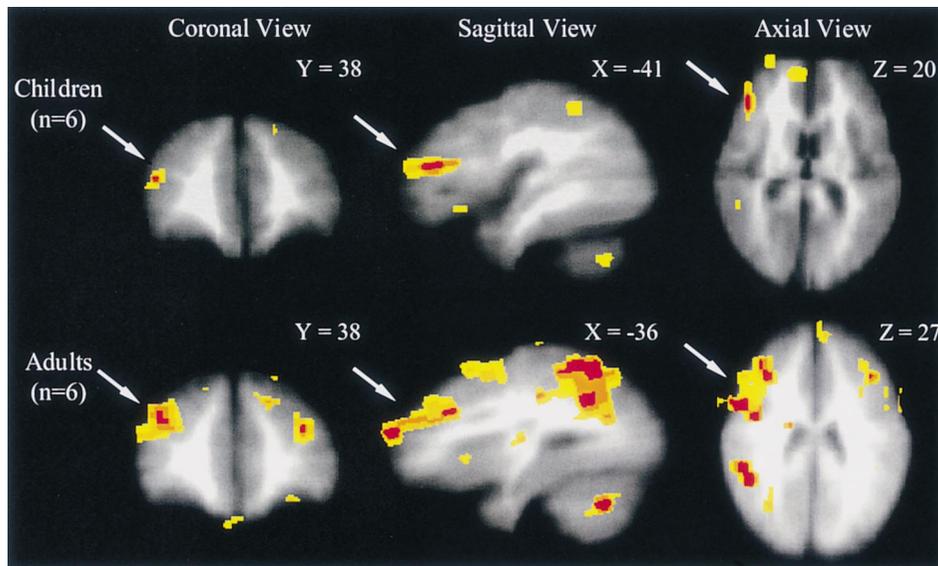
Fig. 4

Fig. 4. Coronal, sagittal, and axial views of brain activity for children and adults during performance of a spatial working memory task.

could achieve this level only in a 1-back condition. A voxelwise multifactorial analysis of variance (ANOVA) was conducted pooling data across subjects. A contiguity threshold of three contiguous pixels and $P < 0.005$ were used as criteria for significant activity.

As reported in Casey et al. (1998), the results for adults were reproducible and reliable across all participating sites. The results, from six children and six adults at the Pittsburgh site (Thomas et al., in press) demonstrated reliable activity in the right dorsolateral prefrontal cortex, right superior parietal cortex, and bilaterally in the inferior parietal cortex during the memory condition, relative to the motor condition (refer to Fig. 4). The activity in prefrontal cortex was lateralized to the right hemisphere, predominantly, and was more anterior and superior than observed in the previously described studies.

In part, these results suggest that spatial working memory tasks activate very similar cortical regions for school-age children and adults. However, despite an attempt to equate performance between age groups by varying memory load as a function of age, children performed worse than adults on both the memory and motor tasks. Adults performed at near ceiling (99%) on the motor and memory tasks compared to the children who performed significantly worse (93% and 69%, respectively). Although children were performing close to ceiling at the beginning of the scan session, by the end of the scan session their performance had significantly deteriorated. Performance by adults continued to improve as a function of time on task. The few regional differences in brain activation (e.g. insular cortex) observed between groups might reflect these performance differences.

2.2. Attention and inhibition

Which prefrontal systems are involved in selective attention when there is interference from competing sources, either during input or output? Two examples of developmental fMRI studies addressing this question are described below.

One classic paradigm for examining selective attention when there is interference during output is the go no-go paradigm. At least one fMRI study using a version of the go no-go paradigm with healthy children and adults has been published to date (Casey et al., 1997). Nine children (7–12 years) and nine young adults (21–24 years) were scanned while performing a version of the task. The task required that the subject simply press a button to all sequentially presented letters except the letter 'X'. Stimulus duration was 500 ms and the interstimulus interval was 1500 ms. The percentage of targets (non-Xs) was maintained at 75% to increase the degree of interference in the output by building a prepotent tendency to respond. Gradient-echo, echo planar images TR = 6000, TE = 40, 128×64 acquisition matrix) were acquired in eight 5 mm contiguous coronal slice locations during three task conditions: (1) inhibitory trials defined by the presence of 50% nontargets (i.e. Xs); (2) control trials consisting of 100% targets (i.e. non Xs); and (3) control trials consisting of 100% targets, but with interstimulus intervals of 3500 ms, resulting in an equal number of motor responses as the inhibitory condition. The two comparison conditions thus controlled for stimulus parameters (number of stimuli and interstimulus interval) and response parameters (number of responses and inter-response interval), respectively.

An analysis of variance with a Bonferroni adjustment showed reliable activation in the anterior cingulate, inferior and middle frontal gyri, and orbitofrontal gyri for both the children and adults. In this investigation, the general location of activation in prefrontal cortex did not differ for children as compared to adults, but overall volume of prefrontal activation, particularly in dorsolateral prefrontal regions, was greater for children than adults (refer to Fig. 5). This difference in volume of dorsolateral prefrontal activity was due to a lack of robust activity in this area for
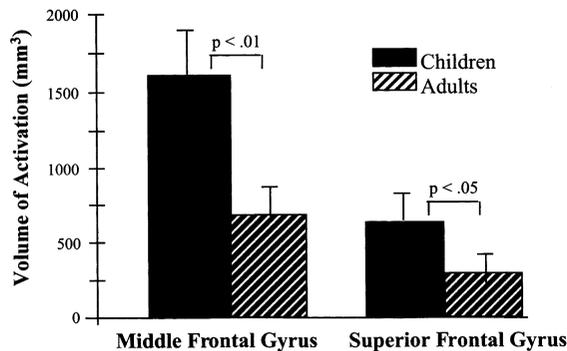

Fig. 5. Volume of brain activation in the superior and middle frontal gyri for children and adults during the performance of a go no-go task.

the adults. Adults showed the most robust activity in more ventral regions of prefrontal cortex. This pattern of greater brain activity in children relative to adults is suggestive of a gradual decrease in the brain tissue required to perform the task. This decrease may parallel the loss rather than formation of new synapses observed in post mortem studies.

Only activity in the orbitofrontal and anterior cingulate cortex in children and adults correlated with behavioral performance on this task such that the greater activity in the orbitofrontal cortex, the better the performance and the greater the activity in the anterior cingulate cortex, the worse the performance. It should be noted that those children with the best performance and the most orbitofrontal activity also had the most dorsolateral prefrontal activity. This observation suggests that children may be less selective in the portions of prefrontal cortex recruited in performance of the task and/or are relying on different strategies to perform the task compared to adults. An event-related design may provide a clearer understanding of the neural mechanisms underlying the performance of this task. In a recent fMRI study by Konishi et al., 1997 using a go no-go paradigm with a mixed trial design, right ventral prefrontal activation discriminated no-go from go trials in healthy adults. This finding is particularly interesting, given that when we grouped our subjects (children and adults) by performance, using a median split on the number of false alarms (i.e. responses to nontarget stimuli), we observed significant differences between groups only in ventral prefrontal cortex (Casey et al., 1996).

A second developmental fMRI study (Casey et al., 1998) using a variation of the go no-go task just described involved manipulating the degree of interference at both input and output (i.e. stimulus selection and response execution). In the former task, emphasis was placed on interference during response execution. In this task, the probability of a nontarget (i.e. X) oscillated between 10 and 60% rather than simply using 50 and 100% target probabilities. Each trial was 1 s in duration and the repetition time of the scan was 5 s (i.e. five behavioral trials). In other words, five behavioral trials occurred during a single acquisition. MR signal change was examined scan by scan for sets of five trials that consisted of 0, 1, 2, 3, or 4 nontargets (i.e. X). We hypothesized that increasing the number of responses relative to nonresponses would result in increased interference in response information and an increase in ventral prefrontal activity. Further, we hypothesized that increasing the number of nontargets relative to targets would increase interference in stimulus information (i.e. between the target stimuli and the salient nontarget stimulus) and result in increased dorsolateral prefrontal activity.

As with our previous study, we observed increased dorsolateral prefrontal activity in children and adults when nontarget probability was high (e.g. scans with three or more nontarget Xs). During low nontarget probability (e.g. scans with only two or less Xs) we observed increased ventral prefrontal activity. Anterior cingulate activity increased during both low and high nontarget probability suggesting that interference, regardless of type (input/stimulus or output/response), activates this region. Developmentally, the pattern of activity in dorsolateral prefrontal cortex for children appeared to be different from adults. First, activity was observed in the dorsal prefrontal cortex for both high and low nontarget probability scans for

children and not adults. Second, with adults, increases in dorsal prefrontal cortex occurred only for scans with at least four out of five nontargets (X), whereas with children, increases in dorsal prefrontal cortex occurred for scans with as few as three Xs. These findings suggest perhaps that dorsal prefrontal cortex in children is less specific to type of information and less efficient in representing information relative to adults.

In sum, the two previous sets of memory and attention studies show both common and discrete regions of brain activity. Both sets of studies activated dorsolateral prefrontal cortex. During the go no-go task, this was observed when nontarget probabilities increased (presumably greater interference during input or in stimulus information). For the memory tasks, this was observed when the memory load or number of intervening trials increased. Both of these tasks are examples of situations where the subject has to represent the relevant target stimulus in the face of interfering nontarget stimuli. The results suggest that the dorsolateral prefrontal cortex supports stimulus information from interfering sources regardless of task (attention or memory). A region of nonoverlap was the orbitofrontal cortex. This region was predominantly activated during the go no-go task when target probability was high, in turn making the response compelling and salient. Accordingly, this compelling tendency to respond could interfere with the representation of when not to make a response. Thus the results suggest that ventral prefrontal cortex supports response information (e.g. conditions during which a response should be withheld). Unfortunately, there was no interference in output/response information during the memory tasks to determine whether ventral prefrontal cortex supports response information regardless of task. Finally, it was the case that both versions of the go no-go tasks and the memory tasks activated the anterior cingulate cortex. What the tasks had in common was presumably interference. During the go no-go task, this was observed when nontarget probabilities increased (i.e. greater interference during input or in stimulus information) and when target probabilities increased (i.e. making the response more salient). Accordingly, the anterior cingulate cortex is activated regardless of type of information or stage of attentional processing (stimulus selection versus response selection). In contrast, the areas of prefrontal cortex that are active when there is interference during attention and memory appear to be information specific (stimulus information in dorsal prefrontal and response information in ventral prefrontal cortex).

3. Conclusions

In this paper, MRI-based morphometric and functional neuroimaging studies of human brain development have been described. These studies, while largely limited to the domain of prefrontal functioning and its development lend support for continued development of attention and memory both behaviorally and physiologically throughout childhood and adolescence. Differences were observed in the magnitude of the patterns of activity, both in volume (Casey et al., 1997) and percent signal change (Casey et al., 1995; Cohen et al., 1994).

This paper illustrated how the techniques of MRI and fMRI can be used to map changes in the human brain as a function of development. However, we can push the methodology a step further and investigate changes in the human brain to pharmacologic probes. A number of recent studies with both humans and animals have shown the detection of neurotransmitter activity using pharmacologic MRI (phMRI) that correlates with PET, microdialysis, and behavioral data (e.g. Chen et al., 1997). These studies have focused largely on animal work, but more recent studies illustrate the utility of the method with humans (e.g. Vaidya et al., 1998). Ultimately, pharmacologic MRI studies may be sensitive probes in elucidating brain regions involved in developmental disorders and may prove extremely useful in addressing developmental neurochemical questions. It is clear that innovative methods like fMRI together with MRI-based morphometry and pharmocologic probes will transform our current understanding of human brain development.

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