

Functional magnetic resonance imaging: Basic principles of and application to developmental science

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Abstract

Functional magnetic resonance imaging (fMRI) has quickly become the preferred technique for imaging normal brain activity, especially in the typically developing child. This technique takes advantage of specific magnetic properties and physiological processes to generate images of brain activity. These images can be interpreted as a function of group or individual based differences to explore developmental patterns and/or cognitive abilities. In this paper we present an overview of the basic principles of fMRI and a discussion of what is currently known about the physiological bases of the resulting signal. We also report findings from developmental fMRI studies that examine the development of cognitive and neural systems underlying attention and memory. Behavioral performance and age-related neural changes are examined independently in an attempt to disentangle developmental differences from individual variability in performance.

Introduction

One of the most exciting methodologies to evolve toward the end of the twentieth century is that of functional magnetic resonance imaging (fMRI). This methodology began with nuclear magnetic resonance (NMR) and continued with magnetic resonance imaging (MRI) as described by Kennedy *et al.* in this special issue. MRI became especially important to cognitive and developmental psychologists when the functional capabilities were discovered and developed. Whereas MRI is used to produce structural images of subject brains useful for anatomical and morphometric studies the functional component allows an *in vivo* measure of brain activity. The functional methodology measures changes in oxygen levels of the blood in the brain. These changes presumably reflect changes in neural activity that are accompanied by changes in blood flow.

The fMRI method capitalizes on magnetic differences between oxygenated and deoxygenated blood. In short, hemoglobin in the blood 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. Thus, during brain activation, localized increases in blood flow increase blood oxygenation and consequently reduce deoxygenated hemoglobin, causing the

MR signal to increase. It is assumed that these localized increases in blood oxygenation reflect increases in neuronal activity. This method, blood-oxygenation-level-dependent (BOLD) imaging, eliminates the need for exogenous contrast agents, including radioactive isotopes (Kwong, Belliveau, Chesler, Goldberg, Weisskoff, Poncelet, Kennedy, Hoppel, Cohen & Turner, 1992; Ogawa, Lee, Snyder & Raichle, 1990; Turner, Le Bihan, Moonen, Despres & Frank, 1991).

Physiological bases of fMRI

Even with the enormous interest and widespread use of this methodology, the relation between the MR signal and physiological mechanisms underlying this signal are not well understood. BOLD imaging relies on sensitivity to changes in oxygen levels within the circulating blood. The human brain uses roughly 20% of the oxygen needed by the body even though it makes up less than 2% of total body mass. Oxygen is used in breaking down glucose to supply the brain with energy. However, blood flow and glucose consumption far exceed the increases in oxygen consumption. This results in increased amounts of oxygen in the blood that can be detected with fMRI. What is not clear is how blood oxygenation levels relate to neuronal activity.

One model has been put forth in relation to glutamate,

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the primary excitatory neurotransmitter in the brain. Once glutamate has been released and stimulates the postsynaptic receptors it must be removed from the synaptic cleft to prevent continued stimulation (which may lead to excitotoxicity). Glutamate reuptake occurs in non-neuronal cells called astrocytes, where glutamate is converted into glutamine and then returned to the neuron and recycled. The processing of glutamate is the result of glycolysis – breakdown of glucose obtained from the blood (and/or astrocytes) without oxygen. So blood oxygen level is thought to increase after excitatory neurotransmission because of an increase in processing of glutamate in astrocytes (Magistretti, Pellerin, Rothman & Shulman, 1999; Shulman, Hyder & Rothman, 2001). This model appears to work well for glutamate, but it is less clear how the BOLD signal is related to changes in other neurotransmitters, including inhibitory substances like γ -aminobutyric acid (GABA). It is also not clear why or how blood flow increases occur during neuronal activity, although many speculate that it is due to a need for glucose or oxygen (Powers, Hirsch & Cryer, 1996; Mintun, Lundstrom, Snyder, Vlassenko, Shulman & Raichle, 2001).

Pioneering work by Logothetis and colleagues (2001) has taken us a step forward in understanding the relationship between the BOLD signal and neuronal activity (also see Raichle, 2001; Bandettini & Ungerleider, 2001). Logothetis recorded electrical activity of neurons in the visual cortex of the monkey in conjunction with fMRI. The results showed a spatially restricted increase in the BOLD signal that corresponded with an increase in neural activity, suggesting a fairly direct relationship between neural activity and fMRI signal. This relationship had only been inferred up to this point but these results provide important confirmation of the fMRI technique. The BOLD signal does indeed reflect neuronal activity (Logothetis, Pauls, Augath, Trinath & Oeltermann, 2001).

To extend this work further, Logothetis and colleagues tried to determine whether the fMRI signal changes shown were related more to neuronal input or output. This was done by examining the BOLD signal changes both in terms of (1) action potentials – firing rates of neurons that occur immediately after stimulus onset and reflect neuronal output; and (2) local field potentials that are slower electrical potentials reflecting predominantly input to neurons. They showed that the BOLD signal changes were more strongly correlated to changes in the local field potentials than to the action potentials. These graded potentials are most likely occurring in the dendrites of the post-synaptic neurons and suggest that activation of a brain area as measured by fMRI reflects input to rather than output from that brain area

(Logothetis *et al.*, 2001). However, this is somewhat of an oversimplification as action potentials can contribute to local field potentials as well. A second note of caution concerns the signal-to-noise ratios for these different techniques. In short, the signal-to-noise ratio for the electrophysiology is far greater than for fMRI signals. So the lack of any detected change in fMRI signal in a given brain region does not mean a lack of information processing in that area (Raichle, 2001). Refer to commentaries and reviews by Rosen, Buckner and Dale (1998), Raichle (1998, 2001) and Bandettini and Ungerleider (2001) for a more in-depth overview of this work and historical perspective of this methodology.

Temporal and spatial characteristics of fMRI

fMRI has particular spatial and temporal advantages over other imaging modalities. The spatial resolution of BOLD and other fMRI methods is typically on the order of 3 to 4 mm in-plane, which is better than most functional imaging methods such as positron emission tomography (PET) and single photon emission computerized tomography (SPECT) described by de Volder in this issue. However, some researchers have pushed the methodology to produce resolution of less than a millimeter, enabling visualization of ocular dominance columns in primary visual cortex (Menon, Ogawa, Hu, Strupp, Anderson & Ugurbil, 1995; Hu, Le & Ugurbil, 1997). These high resolution studies have focused on the transient BOLD effects obtained 1 to 2 seconds after stimulation when an initial negative BOLD signal change is observed. This pre-undershoot has been assumed to be more spatially specific to increased neuronal activity but the effect is much smaller and more difficult to measure with conventional 1.5 T scanners.

To date most studies have relied on the more phasic changes in the BOLD signal to indicate neural activation. These changes occur over several seconds. Following the presentation of a stimulus, the fMRI signal begins to increase after a few seconds and does not peak for approximately 5 to 6 seconds. Subsequently, when the stimulus is turned off, or activity ends, the signal takes approximately 10 to 12 seconds to return to baseline. Rather than settling directly back to baseline the BOLD signal decreases below baseline for a short period, referred to as the post-undershoot (Buxton, Wong & Frank, 1998). This relatively long hemodynamic response was originally considered a limiting factor for the temporal resolution of fMRI studies. However, with the development of event-related designs and selective trial averaging, it is now possible to measure activation over events just 2 seconds apart (Dale

& Buckner, 1997). These event-related designs have greatly increased the versatility of this technique and expanded the possibilities for experimental questions. These designs will be discussed in more detail in the sections that follow.

Stimulus characteristics and fMRI

The type of stimulus presentation, its duration and frequency can influence the BOLD signal. Initial fMRI studies (e.g. Belliveau, Kennedy, McKinstry, Buchbinder, Weisskoff, Cohen, Vevea, Brady & Rosen, 1991; Blamire, Ogawa, Ugurbil, Rothman, McCarthy, Ellerman, Hyder, Rattner & Shulman, 1992) examining activation of the primary visual cortex used stimulus presentation rates of 8 Hz based on earlier O^{15} positron emission tomography (PET) findings (Fox & Raichle, 1986) showing optimal activity levels with this frequency. Belliveau *et al.* (1991) and Kwong *et al.* (1992) reproduced the PET results of Fox and Raichle (1985) showing a linear increase in MR signal change with flashing visual stimuli at rates of 1, 4 and 8 Hz, followed by a slow drop off in signal over rates of 16 and 32 Hz.

Although the visual stimulation frequency appears to peak at 8 Hz, rarely do psychological events occur at this speed. Schneider, Casey and Noll (1994) examined the effects of stimulus type and presentation rate on cortical activation. fMRI was used to record activation in the visual cortex during single character visual search and reversing checkerboard stimulation at 1, 4 and 8 Hz rates. For the character search, the BOLD signal increased from 2 to 3% as stimulus rate increased from 1 to 8 Hz, independent of the region of processing (refer to Figure 1). In contrast, the reversing checkerboard produced higher magnitudes (from 4.5 to 5%) of activation in primary visual cortex and lower magnitudes in other regions of the visual cortex. The observed activation to the slowest frequency rate of 1 Hz and to the characters was important given that complex, meaningful stimuli (e.g. words and sentences) require slower presentation rates.

Stimulus duration also affects the size of the BOLD response. Savoy and colleagues (1995) demonstrated that visual stimulation as brief as 34 msec in duration could elicit small, but detectable signal changes. They showed that the amplitude and peak time of the BOLD response decreased as stimulus duration decreased from 1,000 to 34 msec in the visual cortex (see Figure 2). More recent studies on amygdala activation following emotional stimuli have used stimulus durations of less than 34 msec (e.g. subliminal masked presentations) and observed BOLD signal changes in subcortical regions like the

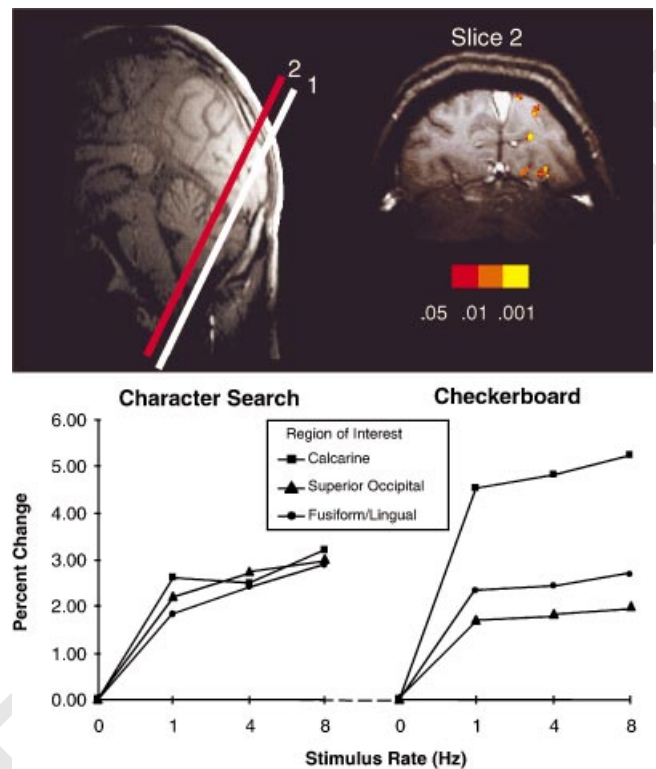


Figure 1 BOLD signal increases in visual cortex as a function of stimulus rate, stimulus type and brain region (adapted from Schneider, Casey & Noll, 1994).

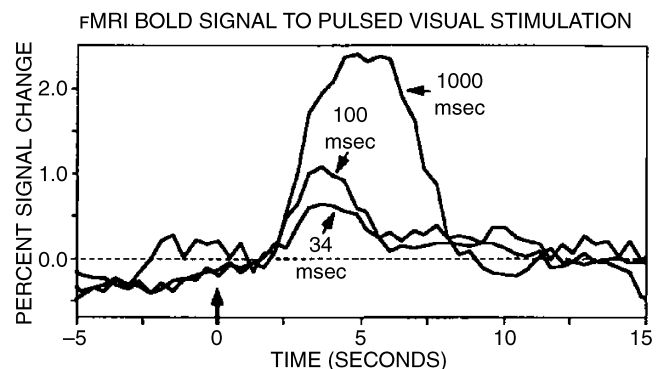


Figure 2 Amplitude and peak time of the BOLD response as a function of visual stimulus duration decreasing from 1,000 to 34 msec in the visual cortex (adapted from Rosen, Buckner & Dale, 1998).

amygdala (Whalen, Rauch, Etchoff, McInerney, Lee & Jenike, 1998). Thus, the BOLD response varies as a function of the duration and type of stimulus as well as the specific brain region activated.

Boynton, Engel, Glover and Heeger (1996) showed not only that brief stimuli could be detected with fMRI, but that the BOLD response over several trials appeared

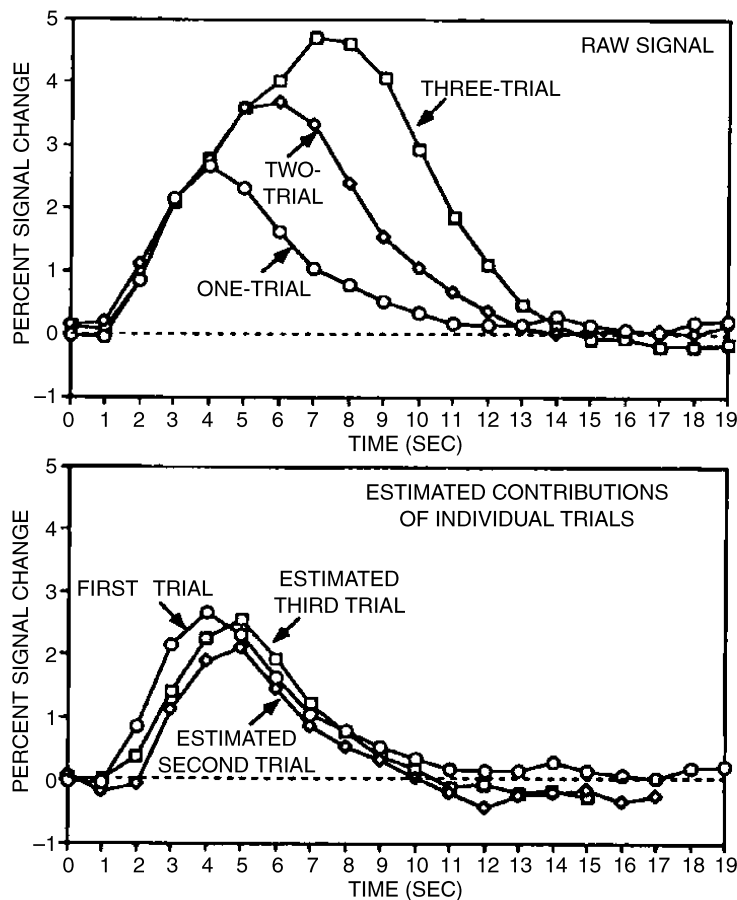


Figure 3 Depiction of the raw BOLD signal evoked when one, two or three stimuli are presented. The contribution of each individual trial can then be determined by subtracting the one-trial condition from the two-trial condition, and the two-trial condition from the three-trial condition and so on. The three estimated trials are roughly similar although subtle but clear departures from linearity can be observed (adapted from Rosen et al., 1998).

to approximate linear summation. To date, several direct tests of the linearity of the BOLD response have observed that the response sums roughly linear over trials for simple visual stimulation (Boyton *et al.*, 1996; Hykin, Bowtell, Glover, Coxon, Blumhardt & Mansfield, 1995; Dale & Buckner, 1997). However, this is only a rough approximation as some departures in linearity occurred across almost all of these studies. The discovery of approximate linear summation of the BOLD response is an important consideration in the development of event-related designs.

Based on Boyton's findings, Dale and Buckner (1997) demonstrated that stimuli could be presented as rapidly as every 2 seconds (i.e. event-related design) by using methods similar to those applied in evoked potential studies. Trials were selectively averaged to reveal predicted patterns of visual cortex activation with alternating checkerboard stimulation. This design is based on the assumption of linear summation depicted in Figure 3.

The figure depicts the raw BOLD signal evoked when either one, two or three stimuli are presented. In this study, the stimulus duration and inter-stimulus interval were each 1 second (i.e. 2-sec trials). The response both increases and is prolonged with increasing trials, suggesting no saturation in the response with repetitive stimulation. The contribution of each individual trial can then be determined by subtracting the one-trial condition from the two-trial condition, and the two-trial condition from the three-trial condition and so on. The three estimated trials are roughly similar although subtle but clear departures from linearity can be observed. This finding demonstrates that the BOLD response can be shown to add linearly over trials and allows for event-related designs with intervals much shorter than the hemodynamic response (see also Buckner & Braver, 1999).

In sum, there are several characteristics of the BOLD fMRI signal that affect the design of imaging studies

and the interpretation of their results. These include stimulus characteristics such as duration (e.g. 33 vs 1,000 msec), presentation rate (e.g. 1 vs 8 Hz) and stimulus intensity (e.g. flashing checkerboard vs letter). Most importantly, these effects vary as a function of the stimulus type (e.g. visual vs affective) and brain region of interest (e.g. visual cortex vs amygdala).

Application of fMRI to developmental science

Perhaps the most exciting application of the previously described methodology is its application to developmental science. However, each special population brings with it different issues that must be addressed when examined with new methodologies. Children are no different in this regard. For example, given their smaller capillaries, faster heart rate and respiration rate, greater synaptic density, immature myelination, etc., one might expect significant variability in the BOLD response in children relative to adults. However, the BOLD response in children and adolescents appears to be quite similar to that in adults both in terms of time course and peak amplitude, although there is individual variability in the hemodynamic response (for a more detailed review of the pediatric fMRI literature and concerns refer to Thomas & Casey, 1999; Casey, 2000; Casey, Giedd & Thomas, 2000; Casey, Thomas, Welsh, Livnat & Eccard, 2000; Gallaird, Hertz-Pannier, Mott, Barnett, LeBihan & Theodore, 2000). There are other variables that may significantly affect our ability to interpret patterns of brain activity in developing populations. A critical one is related to performance differences across age groups. For this reason, we will provide examples of imaging studies that examine the relation among changes observed in the BOLD response with development and with individual variability in performance. Each of these examples emphasizes developmental studies of prefrontal cortex largely because our own work has focused on prefrontal function and development.

In a typical fMRI experiment subjects are asked to perform behavioral tasks that differ in important ways. Comparisons are then made between levels of activity in particular brain regions during performance of the two tasks or between two task conditions. One approach that has been used in these studies is to perform a subtraction between these conditions to determine which brain regions are more active when performing a particular task or cognitive operation. A second approach, that we emphasize here, is to correlate the level or degree of activation with behavioral performance on the different task conditions. With this approach it is possible to consider age-related and performance-related changes independently

and this can help to distinguish between developmental differences and individual variability in performance.

A number of fMRI studies examining prefrontal cortical activity in children during performance of attention and working memory tasks have been published (e.g. Casey, Cohen, Jezzard, Turner, Noll, Trainor, Giedd, Kaysen, Hertz-Pannier & Rapport, 1995; Casey, Trainor, Orendi, Schuber, Nystrom, Giedd, Castellanos, Haxby, Noll, Cohen, Forman, Dahl & Rapoport, 1997; Rubia, Overmeyer, Taylor, Brammer, Williams, Simmons & Bullmore, 1999; Thomas, King, Franzen, Welsh, Berkowitz, Noll, Birmaher & Casey 1999; Nelson, Monk, Lin, Carver, Thomas & Truwit 2000; Klingberg, Forssberg & Wessterberg, 2001). One such study attempted to independently examine the relation between changes in the BOLD signal and individual performance versus changes associated with development. In brief, that study used a Go-NoGo task with fMRI to examine prefrontal activity in 18 individuals 7 to 11 and 18 to 24 years (Casey *et al.*, 1997). Subjects were instructed to respond to any letter but X. Letters were presented at a rate of 1 per 1.5 seconds and 75% of the trials were target trials to build up a compelling tendency to respond. Although several regions in the prefrontal cortex were active during performance of the task, only the regions of the ventral prefrontal and anterior cingulate cortices correlated with behavioral performance, irrespective of age (refer to Figure 4). Those individuals performing well with few errors activated ventral prefrontal regions more than those individuals who made more errors. In contrast, the individuals making the most errors activated the anterior cingulate more, consistent with this region's involvement in monitoring conflict and/or errors (see Posner, Bush & Luu, 2000; Botvinick, Braver, Barch, Carter & Cohen, 2001; Casey, Yeung & Fossella, 2002). Figures 4 and 5 show a child performing a Go-NoGo task in the scanner environment and the representative pattern of brain activity associated with task performance, respectively.

Of particular interest were the developmental findings of this study. We showed greater activity in the dorsolateral prefrontal cortex (superior and middle frontal gyri) in children relative to adults during task performance. There were no significant differences in extent of head movement or variance in MR signal between groups to account for these findings. One explanation for this result then is that the children had greater difficulty with the task (twice as many errors overall) and thus were recruiting more of the prefrontal cortex to perform the task. However, post-hoc analyses revealed that those children performing at adult levels, with few errors, were the children who activated this region more. Thus it appears that children recruit both dorsal and ventral



Figure 4 Illustration of a child in the MRI scanner environment viewing images through a mirror and LCD panel positioned just above the head coil and making responses using a fiber optic response collection device.

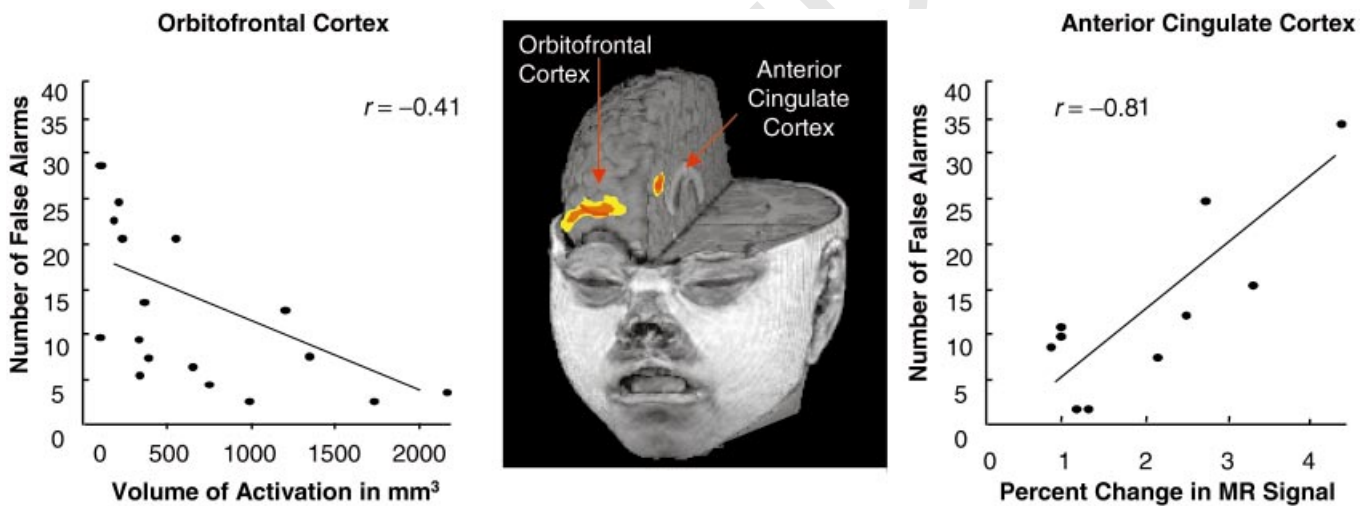


Figure 5 Magnitude and volume of brain activity as a function of number of errors (false alarms) on the Go-No-Go task for the anterior cingulate and orbitofrontal cortex (adapted from Casey et al., 1997).

prefrontal cortex while adults recruit predominantly ventral prefrontal regions – those that correlate with task performance. This finding suggests a refinement in the organization and/or efficiency in recruitment of prefrontal cortex, particularly within the dorsolateral prefrontal cortex with age.

At least five different studies have been published on healthy children, between the ages of 8 years and adulthood, using working memory tasks that involve maintenance of verbal or visuospatial information (Casey et al., 1995; Thomas et al., 1999; Nelson et al., 2000; Luna, Thulborn, Munoz, Merriam, Garver, Minshew,

Keshavan, Genovese, Eddy & Sweeney, 2001; Klingberg et al., 2001). Three of the studies used versions of the n-back task in which subjects had to remember the identity or location of a stimulus either 1, 2 or 3 trials back. Only one of those three studies included adults (Thomas et al., 1999). In that study, even though attempts were made to equate behavioral performance between children and adults by using different memory loads (1-back for children versus 2-back for adults), children did more poorly as a function of time on task. Nonetheless, across all three studies, dorsolateral regions of prefrontal cortex including superior and middle frontal gyri and also

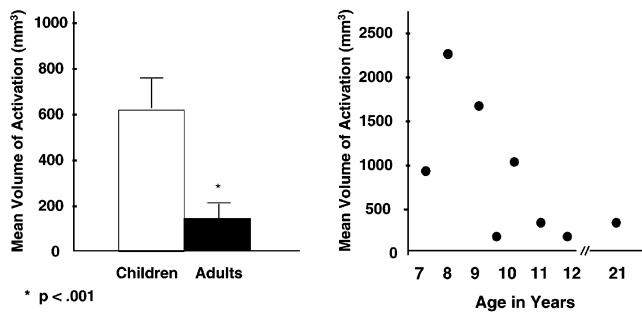


Figure 6 Volume of brain activity in the superior and middle frontal gyri for children and adults during the performance of a Go-No-Go task (adapted from Casey et al., 1997).

parietal cortex were the most reliably activated regions, similar to the adult imaging literature (e.g. Braver, Cohen, Nystrom, Jonides, Smith & Noll, 1997; Cohen, Forman, Braver, Casey, Servan-Schreiber & Noll, 1994; Cohen, Perlstein, Braver, Nystrom, Noll, Jonides & Smith, 1997; Casey, Cohen, O'Craven, Davidson, Irwin, Nelson, Noll, Hu, Lowe, Rosen, Truwitt & Turski, 1998).

In a more recent study by Klingberg and his colleagues, they scanned individuals 9 to 18 years of age on a slightly different version of a working memory task. In this task, subjects were required to remember the location of either 3 or 5 targets presented in a 4×4 grid. After a 1,500 msec delay, a probe stimulus was presented and subjects responded whether the probe was in one of the target locations. Older children showed greater activation in superior frontal and parietal cortices than younger children. Further analysis showed that individual working memory capacity correlated with activity in these same regions as illustrated in Figure 5. These results suggest that the amplitude of the BOLD signal is enhanced as a function of brain maturation and that this change reflects enhanced memory capacity or efficiency.

An interesting finding across all five normative fMRI studies described above is the implication of regional development of the prefrontal cortex. In the Go-NoGo study children recruited dorsolateral prefrontal regions more than adults even though activity in this region did not correlate with task performance. In the four working memory studies, children recruited predominantly dorsal prefrontal regions but none of the children performed at adult levels. Further, Klingberg's findings suggest that the efficiency in recruitment and amplitude of BOLD signal in prefrontal cortex continues to mature during adolescence. Taken together these findings suggest a refinement in the organization or efficiency of prefrontal cortex with development.

In sum, the available data on human brain development suggest protracted development of dorsolateral

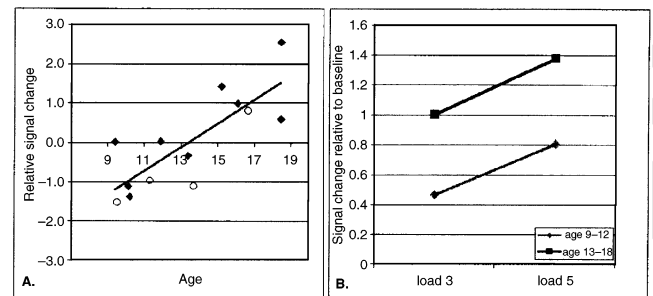


Figure 7 Relative signal change plotted as a function of age and behavioral performance on a working memory task (adapted from Klingberg et al., 2002).

prefrontal cortex. Perhaps not coincidentally, development of cognitive processes presumably subserved by this region appears to parallel this brain development. Clearly the use of functional imaging with cognitive tasks will further our knowledge on links between brain development and cognitive development. Unfortunately, to date, there are still few published studies using fMRI to examine the normal development of cognition (Thomas & Casey, 1999; Casey, Thomas, Welsh, Livnat & Eccard, 2000; Gallaird *et al.*, 2000). The studies that have been published typically are based on small sample sizes of 10 or fewer per group and on wide age ranges of 8 to 18 years. Further, these studies rarely include children younger than 8 years of age, an age when a significant amount of prefrontal development has occurred already. As more laboratories begin to use this method in developmental science, we can begin to take full advantage of the technique in helping us further understand the relation between behavioral and brain development.

Conclusions

This paper has described the basic principles and characteristics of fMRI and illustrated how the technique can be used to map changes in the human brain as a function of development. However, as these methods and others such as pharmacologic MRI and diffusion tensor imaging continue to evolve and are combined there is no end to the possibilities of their use in understanding behavioral and brain development. A number of recent studies with both humans and animals have shown the detection of neurotransmitter activity using pharmacologic MRI that correlates with PET, microdialysis and behavioral data (e.g. Chen, Galpern, Brownell, Matthews, Bogdanov, Isacson, Keltner, Beal, Rosen & Jenkins, 1997). These studies have focused largely on animal work, but more recent studies illustrate

the utility of the method with humans (e.g. Vaidya, Austin, Kirkorian, Ridlehuber, Desmond, Glover & Gabrieli, 1998). This work is described in greater detail in the article by Vaidya in this special issue. Ultimately, pharmacologic MRI studies may be sensitive probes in elucidating brain regions involved in developmental disorders and in successful interventions and may prove extremely useful in addressing neurochemical questions within development. The diffusion tensor imaging technique, described by Uluğ and Li *et al.* in this special issue, provides an opportunity to examine fiber tracts in the developing human brain. This method has the potential for understanding hypothesized developmental delays in ADHD and dyslexia (e.g. Klingberg, Vaidya, Gabrieli, Moseley & Hedehus, 1999) as well as other disorders. Even though many of the imaging methods described in this special issue are in their infancy with regard to applications to developmental science, we predict they will have a significant impact on evolving theories of human development over the next decade.

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