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Special Considerations for Functional Magnetic Resonance Imaging of Pediatric Populations

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Abstract

Functional MRI (fMRI) provides a non-invasive means of studying both typical and atypical brain development in vivo. However, the developmental and clinical status of the populations of interest impact how neuroimaging data should be collected, analyzed, and interpreted. In the present paper, we review methodological and theoretical issues relevant to developmental and clinical neuroimaging research and provide possible approaches for addressing each. These issues include accounting for differences in biological noise, neuroanatomy, motion, and task performance. Finally, we emphasize the importance of a converging methods approach in constraining and supporting interpretations of pediatric imaging results.

Keywords

functional MRI; development; neuroimaging; pediatric populations

A new era in the study of human brain development and behavior has begun with recent advances in the field of noninvasive functional neuroimaging. Although other functional imaging methods have been available for decades, such as positron emission tomography (PET) or single photon emission computed tomography (SPECT), these methods were largely limited to adult participants or clinical populations undergoing treatment due to their invasive nature (e.g., injection or inhalation of ionizing radiation). In contrast, the noninvasive nature of functional magnetic resonance imaging (fMRI) has permitted new and exciting investigations of brain-behavior associations across typical and atypical development.

The use of fMRI in children remains a challenging undertaking due to practical, methodological, and analytical issues that arise when imaging young children. The development of techniques that allow direct comparisons between children and adults, or typically and atypically developing populations, is an important prerequisite for studying the neural bases of cognitive development and developmental disabilities. A number of issues arise when attempting to make such comparisons, including differences in biological noise, neuroanatomy and behavioral performance. All of these issues may impact the magnitude and time course of the hemodynamic response. The present paper outlines several of the practical and conceptual challenges of pediatric imaging and provides potential approaches for managing these challenges.

DEVELOPMENTAL DIFFERENCES IN ANATOMY AND PHYSIOLOGY

The interpretation of functional imaging studies of development is dependent on the sensitivity and accuracy of the imaging method used to detect these changes. As discussed in more detail in other articles in this special issue, fMRI-based measures of brain activity are an indirect measure of neuronal activity, depending on a complex interplay of physiological parameters (1). An assumption of this methodology is that neuronal activity results in increased glucose metabolism, blood flow, and blood volume. With changes in blood flow come changes in the relative concentration of oxygenated and deoxygenated hemoglobin in the brain. The magnetic susceptibility of oxygenated hemoglobin differs from that of deoxygenated hemoglobin in that hemoglobin in the blood becomes strongly paramagnetic in its deoxygenated state. Highly oxygenated brain regions produce a larger MR signal than less oxygenated areas (2,3). Thus, change in blood oxygenation is detectable with magnetic resonance (MR) and referred to as the blood oxygen level dependent (BOLD) response. The association between changes in blood oxygenation and neuronal activity has been supported by nonhuman primate electrophysiological and neuroimaging studies (4–6).

Circulatory and Respiratory Development

As fMRI is based on changes in blood oxygenation in the brain, presumably a number of physiological variables can influence the hemodynamic response including heart rate, heart rate variability, and respiration. As such, circulatory and respiratory development may contribute to differences in the BOLD response between age groups. Heart rate and respiratory rate in children are almost twice those in adults. Furthermore, children's cardiopulmonary cycle is more dynamic, which might introduce greater movement and thus physiological noise in pediatric data (7). However, motion is not the only problem related to differences in heart rate and respiratory rate. The BOLD signal intensity is based on, and affected by, local changes in oxygen tension that in turn are influenced by the intensity of perfusion in microvasculature resulting from the level of neural metabolism (2,3,8).

These physiological differences between children and adults are a concern in pediatric studies in that they can introduce greater noise in echo planar and spiral imaging due to movement of lungs and diaphragm (18). Thomason and colleagues (19) recently investigated the impact of changes in breathing on the BOLD signal in more than thirty school-aged children and adults. BOLD signal time series in activated volumes were noisier in children than adults during breath holding, even though there were no differences in overall motion between groups. Greater physiological noise in the children's data resulted in reduced activation levels when compared to adults. These differences may have been due to differences in the underlying physiology or to aspects of the measurement. Differences in noise between age groups during breath holding may suggest that direct comparisons made between adults and children using fMRI need to measure both noise and signal in both groups to determine equivalence of variance. Greater overall noise in children relative to adults would suggest that children would have reduced activation levels across imaging studies reported in the literature. However, several groups have reported greater regional volumes of activity in children relative to adults in language and cognitive control paradigms (20,21). Nonetheless, since test statistics for between-group differences in variance generally assume equal variance between groups, basal metabolism and physiological noise should be considered. Increasing the number of participants in pediatric studies can reduce the variability due to physiological noise, but comparative statistical analysis would still need to account for differences in noise between groups (19).

What are the clinical implications of developmental differences in physiological noise? First, and perhaps most obvious, is that patient populations suffering from asthma and other respiratory disorders may have different physiological noise than other children. Similarly,

as the hemodynamic response may be decreased by hyperventilation, children with anxiety disorders such as panic disorder may show differences in physiological noise during panic attacks with irregular breathing during scanning. Thus, between-group differences in variance due to basal metabolism and physiological noise should be considered when performing pediatric imaging studies. A number of approaches may be taken to minimize this problem including collection of heart rate and respiration data simultaneously with the imaging data, in order to detrend the data for specific biological noise prior to analysis.

Differences in Head Circumference, Neck Length and Skull Thickness

A concern for pediatric fMRI studies is that children are generally anatomically smaller than adults (e.g., head circumference, neck, etc.). The head circumference for a 5 year old may be 6 to 10% smaller than that of an adult. Head circumference, neck length, and width of shoulders can affect MR signal with respect to placement of the child into the scanner and positioning of surface or head coils. Acquisition of high-quality fMRI data requires the placement of the head into the center of the bore and head coil. Children's shorter necks may result in their shoulders preventing their heads from being placed in the center of the head coil. A shorter coil or reconfiguration of coil holders may be necessary to accommodate children. Also children may require padding underneath their heads to lift them into the center of the coil (7).

Thinner skulls in children relative to adults may result in surface coils being closer to brain tissue and enhanced signal detection (13). A similar problem exists for EEG with spatial diffusion of current by the skull, with thicker skulls resulting in greater diffusion of the underlying electrical signal (14). The most rapid increase in skull thickness occurs across the first year of life (15–17). EEG studies comparing volume conduction between 6 to 11 year-old children and adults found skull anatomy and conduction to be similar between these age groups (18–20). One approach that groups have taken with fMRI studies is to move away from surface coils in studies involving different age groups (21) and instead rely on head coils that provide homogeneity in MR signal across the brain (22,23). Such an approach is also relevant for clinical populations with smaller head circumference (e.g., children born prematurely with low birth weight).

Neuroanatomical and Neurophysiological Development

MR images of the developing brain appear adult like in basic structural development by approximately the second year of life, with all major fiber tracts being observed by three years of age (24,25). Overall the grey-to-white matter ratio approximates adult levels by 7 years of age (26). This biological maturation is marked by an initial overabundance of synapses in the first year of life, with later neuronal pruning and cortical organization over the next 16 years. Between the ages of 16 and 72, synaptic density remains relatively stable and then slightly decreases. At seven years of age the average synaptic density in the frontal cortex is approximately 1.4 times that of the adult, even though the size and weight of the brain is almost identical between children and adults (27). The time course of initial abundance and later reduction of synapses is accompanied by changes in local cerebral metabolic rates for glucose (28).

The differences reported among age groups in metabolism and regional and total brain volume may all have an impact on pediatric imaging studies. For example, the BOLD response is based on assumptions of glucose metabolism and thus may be sensitive to developmental changes in metabolism. Differences in regional and overall brain size may have a significant impact on how imaging data is preprocessed and aligned. This concern is relevant for imaging studies of typically developing children and for atypically developing children with known regional volumetric differences in the brain. Spatial normalization or

the use of a common stereotactic space for both children and adults, or typically and atypically developing children, has been questionable.

At least two different groups (29,30) have examined how age-related structural differences might impact the ability to localize brain activity within a common stereotactic space as that used with adults. Burgund and colleagues (30) examined the shape and variability of brain regions in children 7 and 8 years of age, relative to adults 18 to 30. Transformation of whole brain volumes into a common stereotactic space showed that anatomical differences between these children and adults were small relative to the resolution of the fMRI data. This finding has been replicated and further verified by developmental activation studies examining time courses (BOLD responses) and locations of functional activation foci in children and adults in response to visual stimulation. Time courses were similar between children and adults, and peak amplitudes of time courses were comparable in all sensorimotor loci. There were negligible between-group differences in location of all foci. Variability in the location of activity was statistically similar in the two groups. Voxelwise comparisons of the two groups showed minimal differences between children and adults in visual and motor cortex regions. The small differences in time courses and locations of activation foci between child and adult brains validate the feasibility of direct statistical comparison of these groups within a common space (31). These findings do not generalize to children of younger ages, however.

Muzik and colleagues (29) compared the contour of brain images between healthy adults and two children groups with intractable epilepsy (a younger group ranging between 2 and 6 years of age, and an older group between 7 and 14 years of age). Their results indicated greater differences between the contours of younger children and adults, than between the older children and the adults. The authors argue that the error associated with spatial normalization of the younger children's brains to an adult template precludes the application of statistical parametric mapping (SPM) in this age group. In addition, although the error in the spatial normalization procedure for the older children is higher than in adults, this error did not result in artifacts in the SPM analysis. Thus, the quality of spatial normalization of a pediatric brain relative to an adult template is age-dependent, with a more pronounced difference in children less than 6 years of age than in older pediatric populations.

Another issue of importance is the stability in shape of the hemodynamic response function across development. Although, the hemodynamic response in school-aged children appears to be similar to the adult response (32,33), data from fMRI studies in infants have been mixed. Some studies report a similar peak in the hemodynamic response as that shown in adults (34–36), but others report a decrease in the hemodynamic response that is inverted relative to the adult response, but similar in overall time course (37–40). Many of these studies have imaged infants while sedated (38,40,41) or sleeping (38,39) and only a few have imaged awake infants (e.g., 34). There has been a suggestion that sedative agents such as Phenobarbital induce a negative BOLD response by reducing blood perfusion. However, data from a study performed on a large infant population (42) found no reliable correlation between the BOLD response and the type of sedation used. Further, a negative BOLD response was reported in a study performed on non-sedated infants (39). Taken collectively, these studies suggest that sedation alone cannot fully explain BOLD signal changes observed in young infants. However, the largest study to date with unsedated infants as young as 3 months old (34) showed a response strikingly similar to that of the adult.

At least two studies have examined the BOLD hemodynamic response in children (32,33). Richter and Richter (32) measured changes in the BOLD response time course with age (7 to 61 years) as a continuous variable. The main finding was an age-dependent effect on the shape of the hemodynamic response function, most pronounced in the decay part of the response. Accordingly, if hemodynamic response functions differ across ages, it may be

better to use parameters such as the latency of the leading edge or the peak intensity, rather than the area under the peak or latency of the trailing edge. This finding is qualified by earlier work (33) showing that similar-aged children and adults produced similar hemodynamic responses when behavioral performance was equated. Thus, the importance of examining performance differences when comparing different age groups is underscored, as differences in the BOLD response could potentially be explained by longer reaction times or poorer performance for the younger subjects.

Methodological studies such as those described above have contributed significantly to pediatric research as they validate comparing imaging data obtained from typically developing school-aged children and adults. Spatial normalization procedures may be more challenging with younger children and infants (24,25) or clinical groups that show consistent neuroanatomical differences (43). For example, hemispherectomies early in development for severe epilepsy and/or strokes and brain trauma that result in large brain lesions in one or both hemispheres would not lend themselves to a common stereotactic space with typically developing children (44). As such functional mapping within individual subjects, rather than stereotactic localization across subjects may be justified. A functional mapping approach would entail identification of brain regions using specific behavioral assays (e.g., visual stimuli known to activate primary visual cortex, or word generation known to activate language areas) for each individual subject. This approach has been used by several groups in mapping visual cortices in healthy adults (e.g., 45) and an approach used prior to surgical removal of tissue in cases of severe epilepsy, tumors, etc. (46).

DEVELOPMENTAL AND CLINICAL DIFFERENCES IN ABILITY

A challenge for pediatric imaging studies that has received a significant amount of attention recently is in the experimental design and analysis used to compare groups (e.g. adults versus children, typically versus atypically developing populations) of differing ability. Specifically, performance differences between groups make it challenging to determine if differences in brain activation reflect biological differences (e.g., biological maturation) or individual differences in ability. Increased difficulty or practice may alter both the magnitude of blood flow and the regional pattern of activation (47,48). In other words, when comparing two age groups, it is important that both groups find the task similarly challenging. Otherwise, the observed brain activation may differ for reasons that are not necessarily related to the underlying question at hand. This challenge in equating task difficulty has been tackled by a number of groups using different approaches (49 for review)

Parametric Manipulations of Task Difficulty

A design that has been used with success in a number of laboratories (49 for review) addresses performance differences by parametrically manipulating task difficulty (i.e., varying difficulty levels within the same task). Parametric designs typically titrate task difficulty by increasing the task demands (50). For example, increasing response competition (51), memory load (52) and/or stimulus degradation (53,54) are all manipulations that have been used in developmental imaging studies. An additional benefit of the parametric approach is that incremental changes in activity with the parametric manipulation are highly convincing evidence of utilization of a neural area by the process being manipulated in the study design. This approach provides different difficulty levels of a task on which groups can be compared (see Figure 1). Thus comparisons are made either for identical levels of the task that may lead to different performance across groups (condition-matched) or for different levels of the task that lead to similar performance across groups (performance-matched). Such an approach is important when comparing clinical groups of different abilities (e.g., ADHD, 55).

Not all tasks lend themselves to parametric designs as performance on a behavioral task may not correspond to a monotonic function of task difficulty. As such, different cognitive processes would be required at each level of difficulty as opposed to more of the same cognitive process.

Post-hoc Matching of Groups by Performance

An alternative strategy used to address differences in ability across groups, is to assign participants to subgroups based on their behavioral performance post hoc. Analyses are then completed on groups who are similar or different in performance across age groups (33). The main advantage of this post-hoc matching analysis is the ability to distinguish between patterns of activity that are: performance-related, age/group-related or independent of performance and age/group. In other words, this methodology allows one to dissociate brain activity related to age, from that related to behavioral performance. However valuable this analytic approach may be, there are some limitations. This technique would not be appropriate if there were insufficient overlap in the behavioral performance of the two groups. Moreover, statistical power is greatly reduced due to the division of the sample and thus large sample sizes are required. Finally, there remains the question of whether children who perform at adult levels, and adults who perform at levels comparable to children, are indeed performing the tasks similarly and/or are different in unique ways from their corresponding age group.

Correlating and Co-varying Age and Performance

A third approach used to address performance differences when comparing patterns of brain activity between age groups is to examine the association between ability and activation, while co-varying age, and vice versa. This approach dissociates brain activity related to age from that related to behavioral performance, without the constraint of reduction in power due to the subdivision of the sample into performance-based subgroups. However, to avoid violations in important statistical assumptions, this approach would require overlap in the distribution of performance and linearity in the measures. Correlational analyses of this sort have been used for several years to address questions regarding age versus performance-driven differences in patterns of brain activity (21,49,52,56).

Regardless of the approach that is used to compare imaging data from developmental or clinical population, it is important to address differences in ability or trait when interpreting results. For clinical and developmental studies, often the differences in ability are at the very heart of the question. For example, when delineating neural processes underlying anxiety in children, how well the child can regulate emotions is important and thus differences on this measure would be of interest. For example, children with anxiety and depression, who report higher levels of everyday anxiety, show enhanced activity of limbic regions (e.g., amygdala) implicated in affect-related processing (57) (See Figure 2). Thus, using the correlational approach provides insight as to the extent to which a brain region (e.g., amygdala) is related to the underlying symptoms of a disorder (e.g., a child's own rating of everyday anxiety).

ACCLIMATION TO, AND MODIFICATION OF, THE IMAGING ENVIRONMENT FOR PEDIATRIC POPULATIONS

Many aspects of participating in an fMRI experiment can be challenging for children (e.g., assessment in a medical environment, large and noisy equipment, and confinement in a small space). Discomfort with the scanning procedure may affect performance and neural activation through decreased attention to instructions, decreased task performance, and engagement of emotional and stress-related systems during the procedure. Explanation of,

and acclimation to, the scanning environment prior to the actual fMRI data acquisition, is key to avoiding these problems.

Acclimation to the Imaging Environment

Meeting with the child and guardian before the MRI, either on an earlier day or prior to scanning on the same day, may help to alleviate anxiety about the procedure. Allowing the child to become familiar with the staff, to be trained on the task, and to gain experience with the scanner environment will increase the child's comfort and compliance. Minimizing the medical nature of this first appointment by foregoing lab coats or the presence of hospital equipment, may also help keep the anxiety level low for children or clinical populations who may have had prior negative medical experiences.

Simulation of the scanner experience allows the experimenter to acclimate the child to the future scanning procedure, assess the child's ability to remain still, and determine the child's ability to successfully complete a scan. This procedure can be achieved with presentation of pictures or a video of the scanner environment or through the child practicing at being still in a pretend magnet, while scanner sounds are played. Some sites have actual replicas of the scanner environment including bore, moving bed, and stimulus/response system in which they simulate the scanning procedure for participants (see Figure 3). Although these devices may seem costly, the time and money invested in simulation may reduce time and costs of MR staff and equipment related to unusable data due to excessive motion or early termination of the scan due to discomfort.

Simulators provide a unique opportunity for the subject to see and hear the scanner environment and to train on motion compliance, an essential element of the collection of usable fMRI data from child clinical populations such as those with hyperactivity (58). Recently a number of research groups have begun combining these mock scanners with automated motion training systems, which track children's head movement as they watch a video. If the head movement is larger than a predetermined threshold, the automatic system interrupts the video to alert the child that he/she has moved. Motion compliance training shapes the child's behavior by incrementally decreasing the movement threshold to within an acceptable range (e.g., less than 2 mm). See

<http://www.sacklerinstitute.org/cornell/assaysandtools/> for additional information on automated head-tracking systems.

Modifying the scanning environment for pediatric participants

The actual scanner environment itself may present problems for children. For example, pediatric populations may differ in their perception and tolerance of loud sounds made by the scanner (59). While all subjects are required to wear some form of sound attenuation and hearing protection, additional efforts may improve the individual's comfort and performance, especially for patient populations sensitive to loud or unfamiliar noises. Standard ear protection, earplugs, and circumaural earphones will reduce the sound levels to below these distracting volumes. However, adult-size earplugs that push out of the ear or loosely fitting earphones may not offer substantial protection. Pediatric earplugs are available from vendors and at most scanning facilities on request.

Many imaging studies require the recording of manual responses such as finger or hand movements during performance of a behavioral task. Response collection devices in the scanner may need to be adjusted for children. Button response devices should be comfortable and securely fit on children's hands so that the children are not tempted to move to readjust their hands on the buttons. Poorly fitted button response devices may result in children having their fingers misaligned on the buttons and registering incorrect responses

when they intend to register correct ones. A number of sites use Velcro straps that help keep the response collection device in place to avoid having subjects wiggling to see where the device is relative to their hand.

A number of approaches can be used to make the scanner environment more child-friendly. For example, showing the child a favorite video as they are moved into the bore of the magnet can reduce anticipatory anxiety. Once the child is comfortably placed in the scanner bore, there are a number of ways to decrease the children's anxiety during the data collection. These approaches take into account differences between the simulator and scanning experience. First, the actual scanning procedure is longer than the simulation as localizing and structural scans are gathered prior to beginning the functional scans. One way to minimize boredom is to keep the child occupied, without interruption, through the experiment by showing a video through the structural and localization scans. Second, the scanning experience is different from the simulator experience in that the child is usually alone in the magnet room behind a heavy door. The sense of isolation can be decreased by having the experimenter or parent interact with the child between runs using a camera system incorporated into some stimulus presentation systems. Alternatively, in cases where the child is particularly anxious, the parent may be pre-screened for metal, given ear protection, and allowed to stay in the scanning room with the child.

PROCESSING AND ANALYSIS OF PEDIATRIC IMAGING DATA

Most adult functional neuroimaging studies typically involve single-group designs that compare two or more experimental conditions, rather than two or more groups of participants. By contrast, developmental and clinical neuroimaging studies involve multi-group designs and comparisons. Typically group differences require an explicit test of interactions between groups on specific task conditions (11,23,33,56) using an analysis of variance (ANOVA) or a general linear model (GLM). However, when assumptions of these statistical tests are violated then such methods should be reconsidered. For example, unequal variance between groups as discussed with regard to differences in biological noise between age groups may prevent such a statistical approach (10). Similarly, when the group comparison involves a group that cannot be registered within the same stereotactic space easily (e.g., patients with hemispherectomies), then a pooled analysis across groups would be prohibited (60).

A number of fMRI studies on memory, attention, and auditory processing in typically and atypically developing populations have been completed (see 61,62 for reviews). Across such studies, groups can differ in a number of ways including: 1) which brain regions (localization) are involved during performance on a given task; 2) the magnitude of activity (percent change in volume) within each brain region; and 3) the spatial extent of activation (number of voxels) within these regions. Based on cross sectional (12) and longitudinal studies (63), the pattern of activity within brain regions central to task performance (i.e., regions that correlate with reaction time and accuracy) appears to become more focal or fine-tuned with age with enhanced activity. In contrast, regional activity not correlated with task performance appears to become attenuated with age. This pattern of activity, observed across a variety of paradigms, has been suggested to reflect development within, and refinement of, projections to and from brain regions with development (12,21,49,56,64). This pattern of cortical recruitment across development underscores the importance of examining spatial extent (volume) and magnitude (percent change in MR signal) of activity in pediatric imaging studies.

CROSS-SECTIONAL VERSUS LONGITUDINAL DESIGNS IN PEDIATRIC IMAGING

Behavioral change over the course of development is no doubt a reflection of complex changes and interactions between genes and experiences. These differences in genes and experience, in combination with large individual variability in brain structure, introduce significant noise in cross-sectional developmental neuroimaging studies. Recent longitudinal imaging studies have shown that tracking development within individuals is more sensitive to subtle developmental changes than cross-sectional comparisons (63). Precision in defining developmental trajectories for cognitive and neural processes is critical for characterizing their disruption in developmental disabilities (65). A number of behaviors may be completely appropriate at one age, but inappropriate at another age. Clinical disorders may reflect exaggerated and/or residual behaviors and neural processes that do not necessarily diminish or change with maturity. These behaviors are typically examined in terms of either developmental delays or deficiencies. Understanding normal progressions in behavioral and neural systems will have a significant impact in determining the biological substrates of clinical disorders and targeting effective treatments and interventions.

Future research will no doubt take advantage of the ability to image children multiple times over the course of learning with fMRI, to delineate developmental and experience-based processes in cortical activity (63). To determine whether the immature brain engages in the same neural processes as the mature one, one would need to compare brain activity in the mature system with brain activity in the immature system, both before and after training (49). Investigators are already beginning to take advantage of this approach in investigating the impact of behavioral and cognitive interventions in developmental disorders like dyslexia (66,67) and attention deficit-hyperactivity disorder (52).

IMPORTANCE OF A CONVERGING METHODS APPROACH

Functional neuroimaging is on the cusp of offering new and substantial information about the brain-behavior relationships underlying typical and atypical development. However, combining empirical evidence from other imaging modalities on how brain structure and function change with development, or are altered in disorders, may further constrain theories of typical and atypical cognitive development (68,69).

Generally, imaging methods can be categorized into those that provide functional information and those that provide structural information about the brain. Magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI) correspond to structural imaging methods that are used to measure brain structure and chemistry. More specifically, MRI is used to measure gross size or volume differences in brain regions, MRS measures the concentration of cerebral metabolites that have been related to neuronal loss or damage, and DTI can be used to measure the regularity and myelination of fiber tracts. DTI holds promise for tracking neuroanatomical changes in the strength and number of neuronal connections with learning and development. This methodology may allow us to determine if developmental changes in separate regions of activation are associated with simultaneous developmental changes in connectivity between those regions (70,71). In addition, MRS may help to determine if areas are recruited differently in atypically developing populations or show evidence of neuronal loss or damage at certain points in development. Although all three of these structural measures (MRI, MRS and DTI) can be correlated with behavior, none of them involves simultaneous collection of behavioral data or the ability of measuring functional changes that accompany trial-by-trial behavior.

In contrast to structural imaging methods, functional imaging methods allow one to measure brain activity associated with simultaneous changes in behavior. Such techniques include fMRI, event related brain potentials (ERPs), magneto-encephalography (MEG), near infrared spectroscopy/optical imaging (NIRS), PET and SPECT. Each of these methods can be distinguished in terms of the relative temporal and spatial resolution, depth of recording (i.e. superficial or deep structure), relative signal-to-noise or contrast-to-noise ratios, degree of invasiveness, and expense or ease in use with developmental or clinical populations. Whereas the BOLD response in fMRI is recorded on a scale of seconds, ERPs and MEG measure neural activity from the scalp and have millisecond temporal resolution, but less spatial resolution. Combining these methods (fMRI with MEG or ERP) may help to distinguish the temporal sequence of neural activation reflected in fMRI activation maps or neural activation too rapid or diffuse to be measured by fMRI (72). Unfortunately, few such studies have been carried out in pediatric populations. Clearly the combined use of these functional methods together with the previously described structural methods will be important in constraining interpretations of pediatric imaging data.

Given the relative variability in brain structure and function across individuals, fMRI has rarely been used as a diagnostic tool for psychiatric disorders. However, this methodology has proven useful in cases of epilepsy and tumors in guiding the removal of tissue while avoiding regions critical for basic sensorimotor and cognitive functions (73,74). This methodology has been shown to be effective in assessing recovery of function following tumor removal (40) and interventions following stroke (75). Clinical uses of BOLD-based fMRI technology will continue to expand with continued developments in this methodology.

CONCLUSIONS

Functional MRI continues to provide a powerful means for addressing developmental questions concerning both typically and atypically developing populations. In the future, the impact of this methodology may be enhanced by combining it with other complementary structural (e.g., DTI, MRS) and functional imaging methods (e.g., ERP and MEG). The combined use of these methods in a longitudinal design will no doubt be most informative in terms of what changes with learning and development, and what aspects of atypical development change with the progression of developmental disabilities and as a function of treatment intervention.

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Figure 1.

Illustration of manipulating task difficulty in a go/nogo task as evidenced by an increasing number of errors for each level of the task. The left panel shows the number of errors made on nogo trials as a function of the number of preceding go trials for children and adults. The middle panel shows the percent change in MR signal to nogo trials as a function of preceding go trials in ventral prefrontal cortex in adults, but not children. The right panel shows location of activity in the inferior frontal gyri (IFG) on an axial image (Adapted from 20).

Figure 2.

Correlation between the child's self-report of everyday anxiety based on the Screen for Child Anxiety Related Emotional Disorders (SCARED) and MR signal change in the right amygdala to fearful face stimuli for anxious (circles), depressed (triangles), and healthy children (squares) and localization of activity on a coronal image (Adapted from 64)

Figure 3.

Pictures of various MR simulators. The top panel shows a scanner simulator that includes a replica of the head coil and stimulus display device just above (courtesy of the Neuroimaging Laboratory, Department of Child and Adolescent Psychiatry, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht). The bottom panels show a 10-year-old male in the scanner simulator, wearing headphones and looking at the video display where, during the simulation, a movie is playing or, during a study, the experimental stimuli are projected (courtesy of the Sackler Institute for Developmental Psychobiology at Weill Medical College of Cornell University).