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MINISYMPOSIUM

Functional MRI in children: clinical and research applications

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Abstract Functional MRI has become a critical research tool for evaluating brain function and developmental trajectories in children. Its clinical use in children is becoming more common. This presentation will review the basic underlying physiologic and technical aspects of fMRI, review research applications that have direct clinical relevance, and outline the current clinical uses of this technology.

Keywords Functional MRI · Children · MRI

Introduction

Functional MRI (fMRI) is a non-invasive technique to assess brain function using statistical mapping of blood oxygen level-dependent (BOLD) contrast changes during neuronal activity. The technique has undergone extensive development during the last decade and remains an important tool for research investigations in pediatric neuroscience and brain development [1–3]. Clinical use is becoming commonplace in most large pediatric medical centers, primarily neurosurgical applications. This article will review the basic underlying physiologic and technical aspects of fMRI, typical clinical applications in children, and recent clinically relevant research in this area.

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Physiologic aspects

fMRI is based upon the BOLD contrast effect and the concept of neuronal activity—cerebrovascular flow coupling. First recognized by Ogawa et al. [4] in 1990 and applied in humans by Kwong et al. [5], the BOLD effect is secondary to the differing magnetic properties of hemoglobin oxygenation states within the cerebral vascular bed and its detection by MRI. Oxygenated blood (oxyhemoglobin) is diamagnetic, producing little susceptibility-related dephasing effect on MR signal. Deoxyhemoglobin is paramagnetic and elicits a more prominent effect on local field homogeneity and phase coherence (resulting in signal loss). Changes in the relative concentrations of oxy- and deoxyhemoglobin in the vascular bed can therefore result in changes in local detected MR signal.

Cerebral neuronal activity (for example, elicited during an fMRI stimulus condition) is coupled to an increase in regional glucose metabolism and local cerebral blood flow. This increase in cerebral blood flow exceeds demand and results in relative increase in oxyhemoglobin concentration in the cerebrovascular bed. This results in a relative increase in MR signal that is most pronounced in the venous capillaries, venules, and surrounding brain parenchyma [6]. A delay in the hemodynamic response (and detectable BOLD signal) after neuronal activity of 4–6 s is noted, thus fMRI is an indirect and temporally delayed assessor of neuronal activity [7]. Although recent labora-

tory research has documented a relationship between neuronal activity and the BOLD response, the exact mechanisms of the BOLD effect, the underlying vascular response, and neuronal correlates are a subject of ongoing research [8].

The small changes in MR signal resulting from the BOLD effect (1–5% at 1.5 T) are typically detected by echoplanar (EPI) T2*-sensitive GRE (gradient recalled echo) techniques. Modern EPI-GRE T2* sequences allow rapid imaging of the whole brain (30 or more slices) during a single TR period (typically 2,000 to 3,000 ms), with spatial resolution of 2– to 3–mm voxel size. Maximum T2* contrast is achieved with these sequences using echo times of 30–50 msec at field strengths from 1.5 to 3.0 tesla [9]. An advantage of higher field strengths (3.0 T) for fMRI is the linear increase in signal-to-noise and concomitant increase in BOLD contrast compared with 1.5 T. Unfortunately, inherent thermal noise and bothersome susceptibility effects (skull base, sinuses) are also greater [10], increasingly negating these theoretical gains at field strengths above 3 T. This effect coupled with the current FDA guidelines recommending field strengths not to exceed 4 T for clinical MRI or for research in infants and children [11] make 3 T the optimal magnetic field strength for fMRI studies in children in 2009.

Functional MRI paradigms

Because of the small signal changes inherent to the BOLD effect, a sequence using repeated sampling of the brain (one brain volume scan during each TR) while the subject alternates between active cognitive and control tasks is performed (the fMRI paradigm) in order to improve detection, and assess differences in brain activity, during different sensorimotor or cognitive states. Typical fMRI paradigms require 3–7 min of imaging time for acquisition of 100 or more image volumes during 3–5 cycles of alternating behavior. For clinical fMRI, this is most commonly performed in a blocked-periodic design in which blocks of task and control (baseline) conditions are sequentially administered [12]. The other major fMRI paradigm design is event-related, in which discrete short-duration stimuli (events) are distributed in a regular or randomized way [13, 14]. These are more common in research applications but are finding increasing clinical use [15, 16].

The fMRI paradigm used will ideally result in activation of brain regions involved with the sensory, motor, or cognitive task presented, without activation in other regions. The choice of control and task conditions is critical to allowing this distinction. Task and control conditions must be carefully matched in order to elicit a detectable BOLD signal and isolate the function of interest with appropriate neuropsychological considerations in mind [1, 3, 17, 18]. For successful performance of fMRI examinations in children, utilization of age and developmentally appropriate paradigms is critical [2, 19, 20]. Even for a specific neurocognitive domain such as language, it has been shown that not all paradigm designs will generate the same activation patterns [17]. Therefore, a comprehensive battery of fMRI paradigms administered within the time constraints of the MRI exam is often the most effective approach [21–23].

Imaging processing and statistical analysis

After acquisition of T2*-weighted images during the fMRI paradigm, the images must be processed in order to diminish EPI artefacts, to attempt to correct for susceptibility-related distortions, to limit effects from patient movement during the paradigm, to align and transform the T2* EPI images to a higher-resolution anatomic dataset, and to statistically analyze the images for BOLD signal changes between the task conditions on a voxel-by-voxel basis (the statistical map) [7]. These preprocessing and statistical analysis steps define fMRI activation areas as regions of statistically significant task-related increased signal, mapped to higher-resolution anatomic images for clinical use. The processing tools for these types of analyses have traditionally been developed for research applications but are increasingly being offered on clinical MR consoles and by third-party vendors. Open source shareware applications for fMRI analysis and other applications are also now widely available (http://www.nitrc.org/).

The statistical test and threshold selected for processing raw fMRI data will influence the appearance of BOLD-fMRI brain activation maps. The most common statistical tests used for clinical fMRI are the general linear model (GLM) [24] and the cross-correlation method [12]. Cross-correlation and GLM analyses allow modeling of the hemodynamic response function, while the GLM allows incorporation of additional, potentially explanatory, variables (such as motion, respiratory, and cardiac dynamics) in the analysis [7]. Statistical thresholding is typically determined mathematically (in clinical practice typically with a hypothesis-driven approach) to avoid significant false-positive activations. Typically, a threshold for defining a voxel as active is selected such that the probability of false-positive activation is less than 5% (P value<0.05) after applying corrections for the fact that many voxels are being analyzed for signal associations with the same task behavior. Voxel clustering methods [25] and region-of-interest-based methods can be used to limit the severity of the corrections that must be applied and increase sensitivity to activation in expected areas of the brain. Recently, fMRI

researchers are revisiting the question of selecting the best threshold for presentation of BOLD activation maps based on the method of false discovery rates [22, 23].

Determination of the optimum statistical threshold for use in individual clinical patients is a complex problem that has not been resolved [7, 26, 27]. In addition to field strength, inherent noise in the fMRI-BOLD data, fMRI paradigm used, and statistical analysis procedures, a large number of physiologic, developmental, performance-related, and pathologic factors can influence BOLD-fMRI signal changes in individual patients. Currently, the decision about thresholds for presentation of clinical BOLD-fMRI activation maps from individual patients relies heavily on the clinical and technical judgment of the radiologist and other medical personnel involved in the care of the patient.

BOLD signal changes during development

Many anatomic and physiologic changes occur during brain development that can alter the BOLD response in children compared with adults. Developmental anatomic changes are regionally variable and include synaptogenesis and pruning, myelination, alterations in gray matter thickness, as well as increases in overall brain volume [2, 26]. These dynamic structural changes during development are related to higher cerebral metabolism in children (peaking at 3 to 4 years) [28]. Blood hemoglobin content increases with age in childhood [29] and could increase the BOLD effect [30]. Blood pressure increases and heart rate decreases with age [31], and children exhibit a more dynamic cardio-respiratory cycle [26]. Although cerebral perfusion is tightly regulated, increased physiologic noise in children might affect detection of the BOLD response [26].

Despite these physiologic differences, there is evidence that the basic BOLD response in children is similar to that of adults [26, 32], with some task-related differences [33]. Neonates and infants might exhibit significantly different BOLD responses from those of older children and adults, however. Neonates and infants not uncommonly exhibit a negative or inverse signal BOLD response with sensorimotor and visual stimulation paradigms [34–36]. In a recent study of pre-term infants studied with unilateral sensorimotor stimulation fMRI at term-equivalent age, Heep et al. [34] found predominately negative and bilateral BOLD responses in the sensorimotor cortex, contrasting with the primarily contralateral and positive BOLD response seen in older children and adults. Born et al. [36] demonstrated negative BOLD responses to visual stimulation in sedated children up to 44 months of age compared with positive BOLD responses with the same paradigm in adults. These responses were correlated with a CBF decrease (children) and increase (adults) as assessed by FAIR (flow-sensitive alternating inversion recovery) perfusion methods [36]. Although potentially related in part to sleep and sedation effects, rapid increases in synaptic density and higher metabolic rates, as well as altered CBF responses in these areas during early childhood development, might contribute [34, 36].

Ultimately, the exact contributions of the complex anatomic and physiologic changes that occur in childhood on the BOLD response are incompletely understood and are the basis for ongoing research [2, 26].

Procedures for the pediatric fMRI examination

The general requirements for fMRI performance include: an MRI scanner with gradient hardware capable of performing fMRI useable EPI T2* sequences (currently readily available on most clinical scanners), stimulation/paradigm presentation hardware and software (audio and visual) linked to the scanner to allow for precise synchronization of stimuli and MR sequence performance, and hardware and software for documenting patient responses during the fMRI paradigm. As described above, 3-T scanners are preferred for fMRI studies [9, 10].

Performance of useful clinical fMRI examinations in children requires special preparation and resources. Prior to the scheduled exam, the child is assessed for fMRI based on the underlying neurologic deficits, developmental level, and ability to complete the fMRI exam. At our institution this assessment is done by the radiologist and referring neurologist in consultation with a neuropsychologist and others directly involved in the care of the child. Explanation of the MR procedure, fMRI paradigms, and exam indications to the patient and parents in a calm, child-centered environment is crucial. Practicing the fMRI paradigms is important to maximize performance and to adapt the tasks for the child's clinical and developmental level. Centers performing routine clinical fMRI in children have adopted a wide range of techniques for preparation for the MRI examination, including video presentations and mock scanners for habituation [1, 2, 19, 37]. Patient comfort is maximized during positioning in the scanner, with special care to assess comfort of applied headphones and goggles, as well as the child's head in the RF coil. Patient discomfort produces compliance issues that can limit fMRI paradigm performance, patient attentiveness, and the length of time available for fMRI performance.

Patient motion significantly limits fMRI performance in children [19, 20, 38]. Despite the ability to retrospectively correct for head motion during data analysis, gross head movement typically results in unusable fMRI data. Use of head coil bite bars, inflatable head cushions, and forehead

and chin straps can be used to limit head movement but are difficult to implement in children. Yuan et al. [38] recently performed a detailed analysis of head movement in a large cohort of healthy children ages 5 to 18 years performing a variety of language tasks. In this study head motion was more pronounced in younger children and boys. fMRI paradigms using active responses and multi-sensory stimulation (i.e. auditory and visual) were less susceptible to head motion. Use of a visual component to the paradigms might be particularly important to limit excessive head movement, especially in young boys.

Success rates for fMRI studies in children are likewise age- and gender-related. Older children and girls have a higher rate of successfully completed exams. Byars et al. [19] report a success rate of 43% in healthy 5-year-olds increasing to 100% for healthy children older than 15 in a research study of normal language development. Other investigators report that reliable and useful fMRI data can be obtained in 95% of typically developing children age 8 and older and 80% of those 4 to 5 years of age [2]. Subjects with cognitive impairment or neuropsychiatric disorders have a lower rate of fMRI success. In our institution during the last 2 years, 78% of children presenting for clinical fMRI studies, with a wide range of underlying pathologies and neurologic deficits, were able to complete fMRI exams with multiple administered paradigms. The more routine application of real-time fMRI processing on most clinical systems allows for immediate assessment of study success and will likely diminish the number of inadequate studies. Real-time fMRI analysis can provide results similar to those of more time-intensive research software analysis in children [39].

Research applications

fMRI has been used extensively to answer basic questions in neuroscience during the last 15 years. Applications in children have been less common but are growing as larger cross-sectional and longitudinal studies are performed. The primary basic research applications of fMRI in children have been in the areas of language development and specialization [18], neurobehavioral and cognitive disorders [40, 41] and visual spatial processing [42, 43]. Of these applications, the assessment of language development and organization has the most relevance to current clinical fMRI applications and will be briefly reviewed.

Clinical evaluations of language organization have been aided by detailed lesion and deficit analyses, primarily in adults [44]. Although extremely useful for outlining areas of the brain important for various aspects of language function, they provide more limited data on how language is processed and the normal developmental trajectories of these language networks. These investigations as well as other anatomic and functional studies have established a left-hemispheric dominance for semantic and phonological language functions in most individuals. This lateralization is supported by normal structural asymmetries in frontal and temporal parietal brain regions identified by structural analysis [45–47]. These asymmetries are present during early childhood and even prenatally [48] and have been shown to correlate with direct clinical assessments of language laterality [49]. Although these anatomic asymmetries might produce a developmental bias toward left-hemispheric language dominance, the true developmental trajectory for functional organization within the brain has only recently been investigated, primarily with functional MRI techniques [18].

Left-hemispheric language dominance has been demonstrated in infants [50] and potentially fetuses as early as 33 weeks' gestation [51]. Hemispheric language dominance has also been shown to be related to handedness. Recent fMRI studies in adults have shown that approximately 95% of right-handed subjects are left-hemispheric dominant for language while 20–27% of non-right-handed subjects (ambidextrous and left-handed) exhibit atypical (bilateral or right-side) hemispheric language dominance [52]. Despite the clear role of the left hemisphere for language function, data from language assessments of unilaterally brain-injured children generally demonstrate that most children with early left-hemisphere damage go on to acquire language abilities in the normal range (with some variability) [53]. This demonstrates the remarkable plasticity of the developing brain compared with that of adults. Most research points to a critical period for language development in early childhood (to 6 years of age) with more limited capacity for development beyond this time period [2, 53, 54].

Identifying the normal developmental course of language lateralization and location within the brain has been a major area of research utilizing fMRI techniques and has aided in our understanding of brain plasticity. Most fMRI studies of language lateralization in children have shown similar patterns of activation compared with adults [3], supporting the establishment of language networks by early childhood. Although the general patterns of activation are similar for most tasks, a growing body of evidence demonstrates that there are changes in functional organization with development.

Holland et al. [55], in an initial study of 17 children (7–18 years old) performing a verb-generation task adapted from earlier PET studies [56], demonstrated similar left-hemisphere-dominant activation patterns as in adults [57, 58]. A statistically significant association of the degree of left lateralization with age was noted, most pronounced in the left inferior frontal gyrus. These findings were confirmed in a much larger cross-sectional study in which 332

healthy children (ages 5–18 years) performed a verb-generation task. BOLD signal changes were found to increase with age in specific task-related regions of the brain, suggesting the effect was related to differential maturation of the brain rather than performance-related issues [18, 59]. An additional longitudinal study of 30 children (ages 5–7), scanned once per year performing the same verb-generation task, also demonstrated this effect, with increasing activation with age in the left inferior frontal, middle temporal, and angular gyri [60]. In addition, areas of diminishing activation with age were noted in the left posterior insula, left superior frontal, and right anterior cingulate regions, suggesting both progressive and regressive changes during maturation (Fig. 1).

Additional studies using word generation and reading tasks have also demonstrated age-related changes in BOLD localization with greater and more widespread activation in children compared with adults [61–63]. These age-related organizational effects are primarily noted in language skills acquired during a longer period of time (e.g., vocabulary and semantic knowledge, sentences with complex syntactic load) [18, 61, 64] versus those designed to assess early acquired language skills (such as word-picture matching) [65]. Application of more advanced data-driven statistical analysis techniques such as independent component analysis (ICA), and Bayesian connectivity analysis are beginning to allow probing of multiple task-related networks during language processing and their changes with development [65–69].

Clinical applications

The clinical use of fMRI in children is primarily presurgical. In our institution there are two major clinical scenarios: (1) preoperative assessment of language and memory function prior to surgery for intractable epilepsy, and (2) presurgical evaluation of potentially eloquent cortex in patients with brain lesions (tumors, cavernous malformations). Other indications for evaluation include preoperative assessment of auditory cortex in children being assessed for cochlear implantation [16] and EEG-fMRI for detection of epileptogenic brain regions [70]. As the most common role of clinical fMRI is in the evaluation of surgical patients regarding sensorimotor and language systems, these areas are the focus of this review. Unfortunately, the literature on validation of fMRI techniques by direct cortical stimulation or other intraoperative techniques is primarily related to adults. Although some studies have addressed the role of fMRI in the surgical decision-making process in children [1, 71], no prospective trials outlining the clinical benefit of fMRI in terms of reducing morbidity and mortality in pediatric neurosurgical patients have been performed.

There are some critical concepts to bear in mind when performing and interpreting fMRI studies in clinical patients [72].

fMRI activation regions might not be functionally specific. Complex cognitive tasks recruit multiple areas,

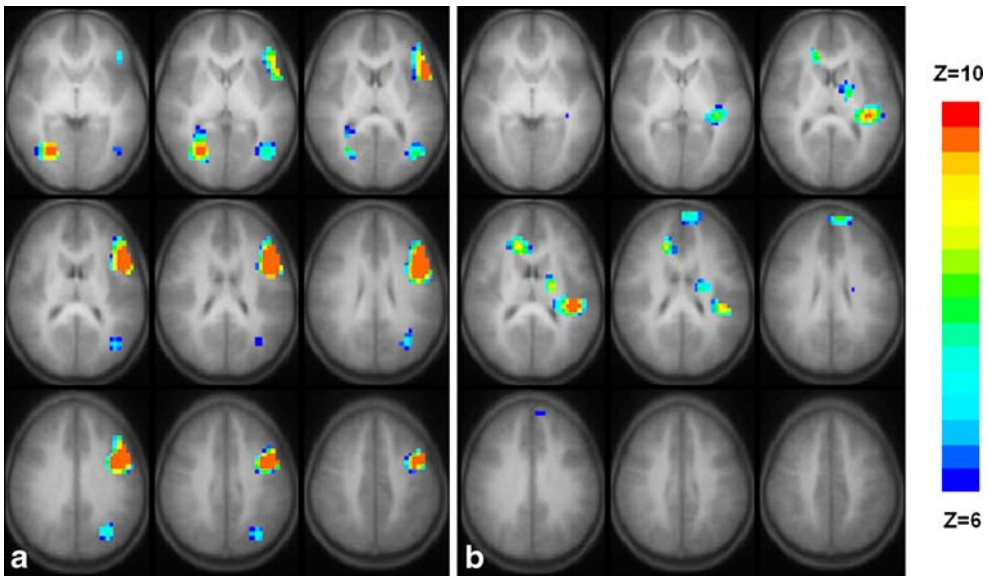

Fig. 1 Brain regions with significant BOLD signal changes with subject age for normal children performing the task of covert verb generation (*group analysis*) (images used with permission from [60]). **a** Regions with statistically significant BOLD signal increases with age were found in right lingual and inferior temporal gyri, left medial temporal gyrus, left inferior/medial frontal gyrus (*Broca's area*), and left angular gyrus. **b** Several cortical and subcortical areas (*left posterior insula*, *left superior frontal gyrus*, *left thalamus*, and *right anterior cingulate gyrus*) show decreases in BOLD signal associated with age

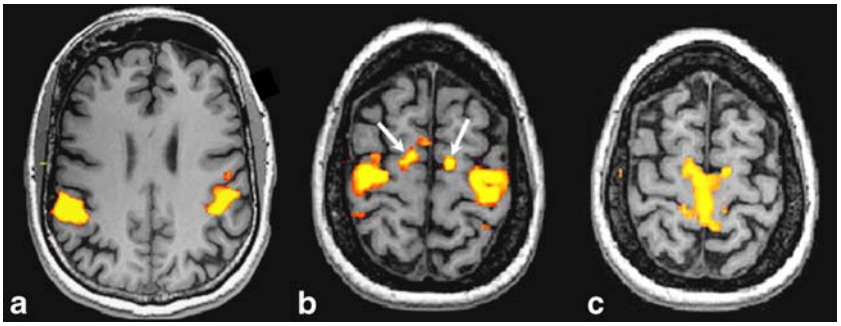

Fig. 2 Images from active motor fMRI in a normal volunteer. **a** Tongue movement, **b** bilateral sequential finger tap, **c** bilateral foot flexion and extension. Note the somatotopic distribution of activation with face motor is more caudal along the central sulcus, and foot motor more craniad and medial in location. Supplementary motor region activation identified on the finger-tapping image (*arrows*, **b**)

the resection of which could result in no obvious clinical deficit. On the contrary, lack of activation in a brain region does not indicate lack of critical brain function.

fMRI is an indirect evaluation of neuronal function and relies on statistical mapping techniques that are not clinically standardized.

fMRI examinations are constructed to assess specific neuronal functions that are chosen by the examiner and might not assess all areas that could result in patient deficit after surgery.

The BOLD effect can be directly altered by pathologic states in which there are changes in cerebrovascular autoregulation and neurovascular coupling [73]. These include vascular steno-occlusion, tumors with neovascularity, and arteriovenous malformations [73–75]. In these scenarios caution should be used in interpreting clinical fMRI examinations, particularly the significance of lack of fMRI activation. Application of additional studies to assess cerebral hemodynamics in these cases can be helpful in accurately interpreting results.

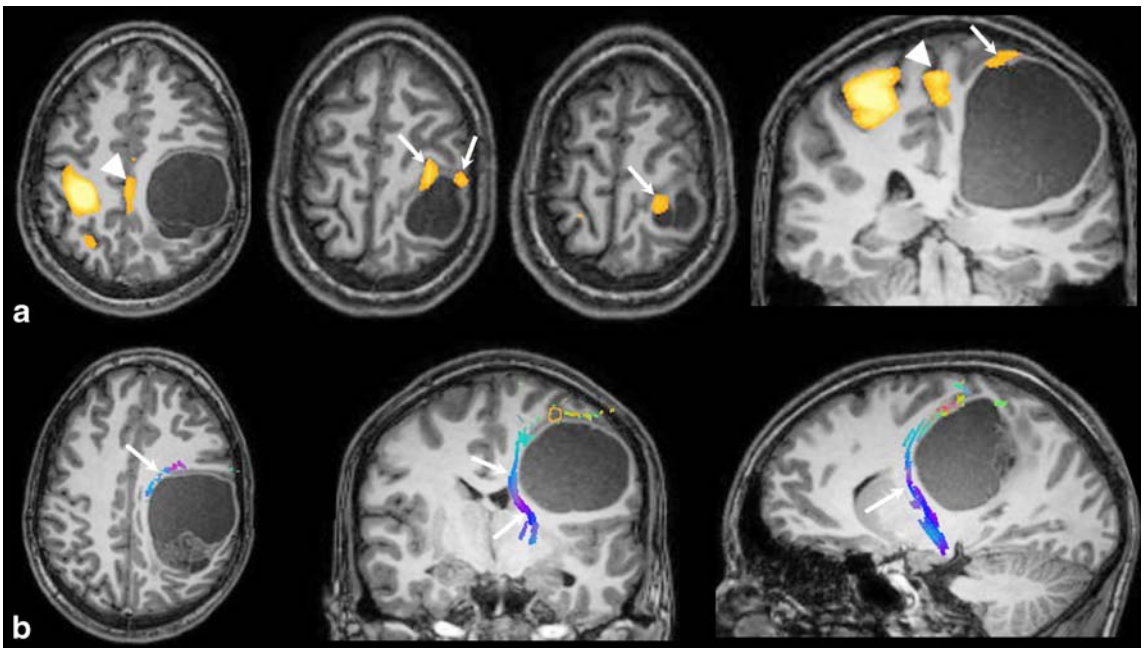

Fig. 3 Sensorimotor fMRI in a 15-year-old right-handed boy with a 1-week history of right arm and leg weakness and right facial droop. Large left perirolandic cystic and solid mass. There was significant distortion of the central sulcus, making assessment difficult. **a** Bilateral sequential finger-tapping fMRI demonstrates activation along the anterior superior aspect of the cystic mass along a very distorted central sulcus (*arrows*). Activation is also noted in the supplementary motor area (*arrowheads*). Note larger area of activation along the right central sulcus in the expected hand motor region. **b** Tractography of the corticospinal tract. Tractography of the left corticospinal tract performed using fMRI activation areas and brainstem regions of interest. The tract streamlines are displaced medially and anteriorly by the mass lesion (*arrows*). fMRI and tractography data were incorporated into operative neuronavigation for resection. Outcome: No new postoperative deficits noted after complete resection. Pathology showed anaplastic ependymoma (WHO grade III)

Associations developed based upon group analyses of many subjects might not translate well to an individual clinical patient, although such a framework is needed for contextual interpretation of individual maps from a specific paradigm.

Defining eloquent sensorimotor systems

A simple, reproducible, and highly useful application of fMRI is identification of components of the sensorimotor system for presurgical mapping [3, 76]. The sensorimotor system has been extensively evaluated by fMRI, and paradigms for assessment are tolerated by most patients, including children. Identification of the central sulcus and its orientation in patients with space-occupying lesions or distortions from prior surgery can be difficult, although it is usually readily identifiable by anatomic criteria in normal subjects. fMRI use in these patients can improve preoperative identification of eloquent sensorimotor cortex [77].

Paradigms can be active or passive in nature, auditory or visually cued, unilateral or bilateral, and can be easily modified according to the patient's ability. Typically performed paradigms include sequential finger thumb opposition, hand grasping, wrist flexion and extension, foot flexion and extension, lip puckering, and tongue movement for motor strip assessment, and tactile stimulation with brushes or air puffs for sensory component evaluation [72]. fMRI activation areas are somatotopically arranged along the central sulcus. Secondary regions including the supplementary motor area and premotor cortex are commonly identified (Figs. 2 and 3). A study using a sequential finger-tapping task in a cohort of healthy children ages 5–18 years demonstrated increases in BOLD signal in these typical areas that correlated with age [59].

Passive motor tasks have been found to elicit similar BOLD responses to active tasks in children [78]. Repetitive tactile stimulation, passive movement paradigms, or median or tibial nerve electrical stimulation can be used in sedated patients to identify somatosensory areas [78–83]. In patients with tumor- or lesion-related paresis, tactile stimulation can be used with good results [84, 85]. Although block paradigms of sequential left-side, right-side movement or mixed paradigms with sequential movements of different body parts might allow for a more rapid assessment of multiple regions, secondary sensorimotor areas will not be visible as they are potentially common to each experimental condition. Paradigms with movements of a single part of the body alternating with rest are suggested for presurgical evaluation in order to fully outline these motor systems [72].

Validation with direct electrocortical simulation (ECoS), the surgical gold standard, has generally been excellent [86, 87]. In a recent study using 3 T, fMRI activation areas correlated with ECoS (assuming a 10-mm sphere of influence) in 100% of a series of perirolandic glioma patients [76]. Shinoura et al. [88] have suggested that in some cases fMRI outperforms direct cortical stimulation for assessment of eloquent sensorimotor cortex in patients with perirolandic tumors. In another study, lesion to fMRI activation region distance was found to correlate with new postoperative deficit in patients with tumors near the motor cortex. Those patients with a lesion to fMRI activation distance of <5 mm had a higher risk of deficit than those with larger distances between motor fMRI activation regions and the tumor margin [89]. Supplementary motor region activation can also be useful to assess preoperatively, as significant (though usually transient) motor and language deficits can occur with surgery in this area. fMRI can identify these areas and can be used to predict postoperative deficits with planned resections in the medial frontal lobe [90].

A recent study by De Tiège et al. [91] documented a high success rate of motor fMRI (93%) in a group 40 children with simple focal epilepsy undergoing surgery. fMRI contributed significantly to the surgical management in 74% of children in this study.

Defining eloquent language cortex and hemispheric language lateralization

Paradigms for language assessment

Language is a complex cognitive task. A multitude of paradigms have been created to assess different aspects of language function. There is, therefore, tremendous variability in the batteries of paradigms used at different institutions for assessment of language in clinical patients. For clinical patients, it is important to utilize multiple language tasks in order to engage multiple language domains and to more fully define language processing [18, 64, 92, 93]. In children, multiple language tasks might be even more important to assess language reorganization and plasticity effects from varied neuropathology [64]. The use of multiple tasks reduces the likelihood of non-diagnostic findings, improves inter-rater reliability, and helps in the confirmation of language laterality [93]. The following is a brief description of the standard language tasks used clinically in children at our institution (Fig. 4).

(1) Verb generation (sequential finger-tapping control) [55, 56]

The verb generation (VG) task involves the auditory presentation of a series of concrete nouns every 5 s. The patient is instructed to covertly (silently) generate as many verbs associated with the noun as possible. The control task is

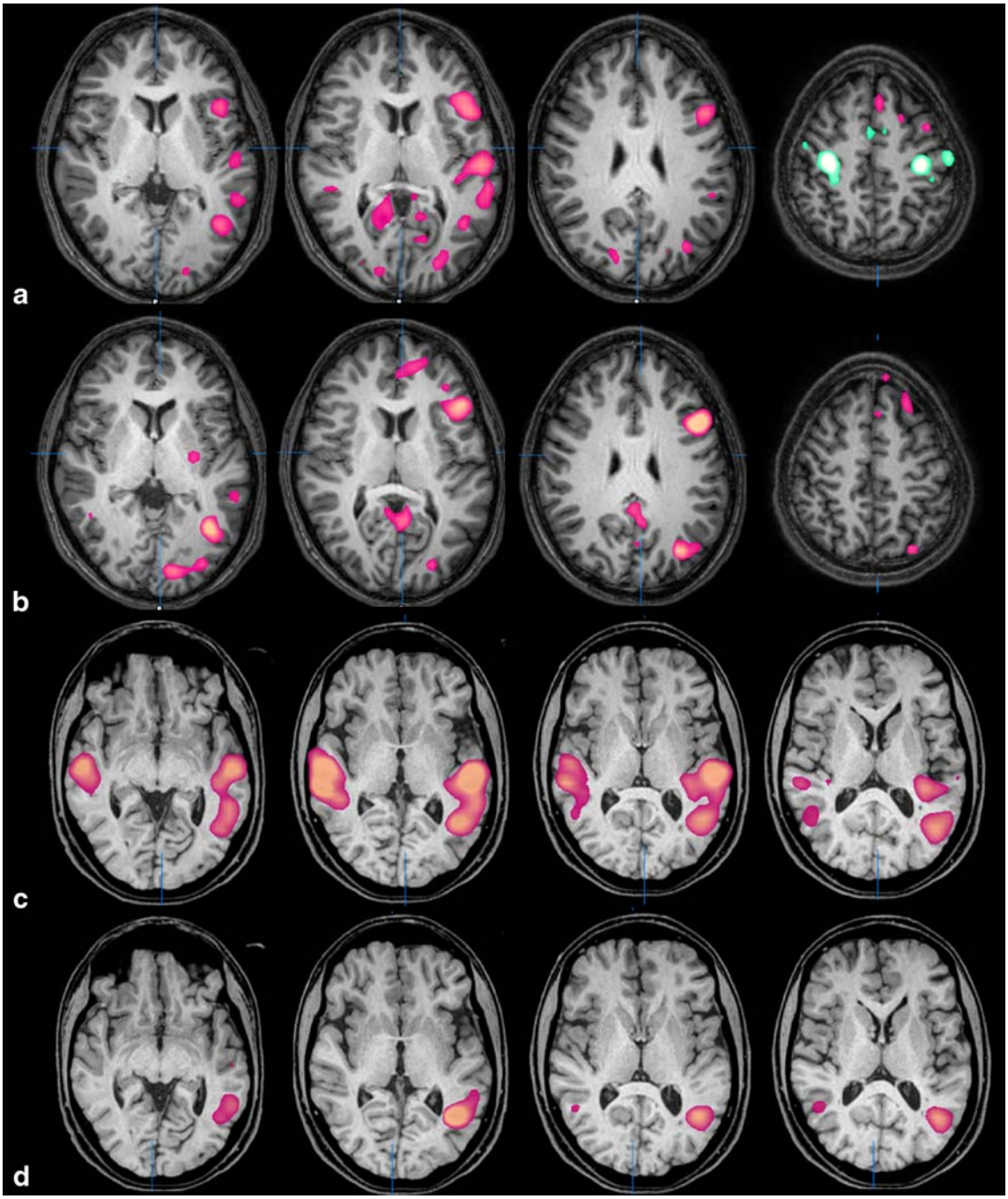

Fig. 4 Language fMRI. Examples of typical activation distributions with multiple language tasks in a 14-year-old child. Images are in radiological convention (*left of image is the right side of the patient*). **a** Verb generation (*bilateral sequential finger-tapping control*), **b** semantic decision (*tone-discrimination control*), **c** story processing (*tone control*), **d** story processing (*backward story control*). With the verb-generation task (**a**), activation is predominately left-side, in the inferior frontal gyrus, middle frontal gyrus, and left temporal parietal region. Activation regions during the control state (*green regions*) are noted along the central sulcus bilaterally (*hand motor regions*) and in the supplementary motor area. Similar task-related activation is noted with the semantic decision task (**b**). With the story processing (*tone control*) paradigm (**c**), bilateral activation is noted along the posterior sylvian region and superior temporal gyri bilaterally. Asymmetric activation is noted along the more posterior superior temporal sulcus on the left. With the story processing (*backward speech control*) paradigm (**d**), activation is noted along the left superior temporal sulcus extending into the left temporal parietal region

bilateral sequential finger thumb opposition (finger tapping) cued by a target tone played every 5 s. The finger-tapping component allows a control for the auditory stimulation present in the verb generation task, distracts the subject from language processing during the control period, and allows a method for assessing patient compliance with the paradigm.

Activation patterns with VG have been extensively studied in a wide age-range of children [55, 59, 94]. Typical activation is left lateralizing within the inferior frontal gyrus, middle frontal gyrus, dorsolateral prefrontal regions, superior temporal lobe, temporal parietal junction, and medial frontal lobe (Fig. 4). Smaller homologous regions in the right frontal and temporal parietal regions are typically seen. Temporal parietal activation is more variable with this task in individual patients.

(2) Semantic decision (tone-discrimination control) [64, 95]

The semantic decision (SD) task used at our institution is modified for children and involves the auditory presentation of single words (animal names). The child then makes a button press if the animal fits a target semantic property (does the animal walk on four legs?). In the control condition the child listens to a series of tones for a specific tonal sequence and then answers via a button press if it is present. Activation patterns are similar to those seen in adults with this paradigm and are predominantly in the left middle and inferior frontal gyri and left middle and inferior temporal gyri (Fig. 4) [64, 96]. Frontal activation with SD is broadly similar to VG, with slightly more anterior IFG activation [3]. There is more inferior temporal gyrus activation with SD versus VG in most studies, with similar middle temporal gyrus activation [55, 95]. The SD task provides an additional assessment of frontal language areas and has the added capability of allowing direct assessment of patient performance.

(3) Story processing (tone listening or backward story control) [64, 67, 97]

The story processing task involves the auditory presentation of five simple stories, each composed of ten

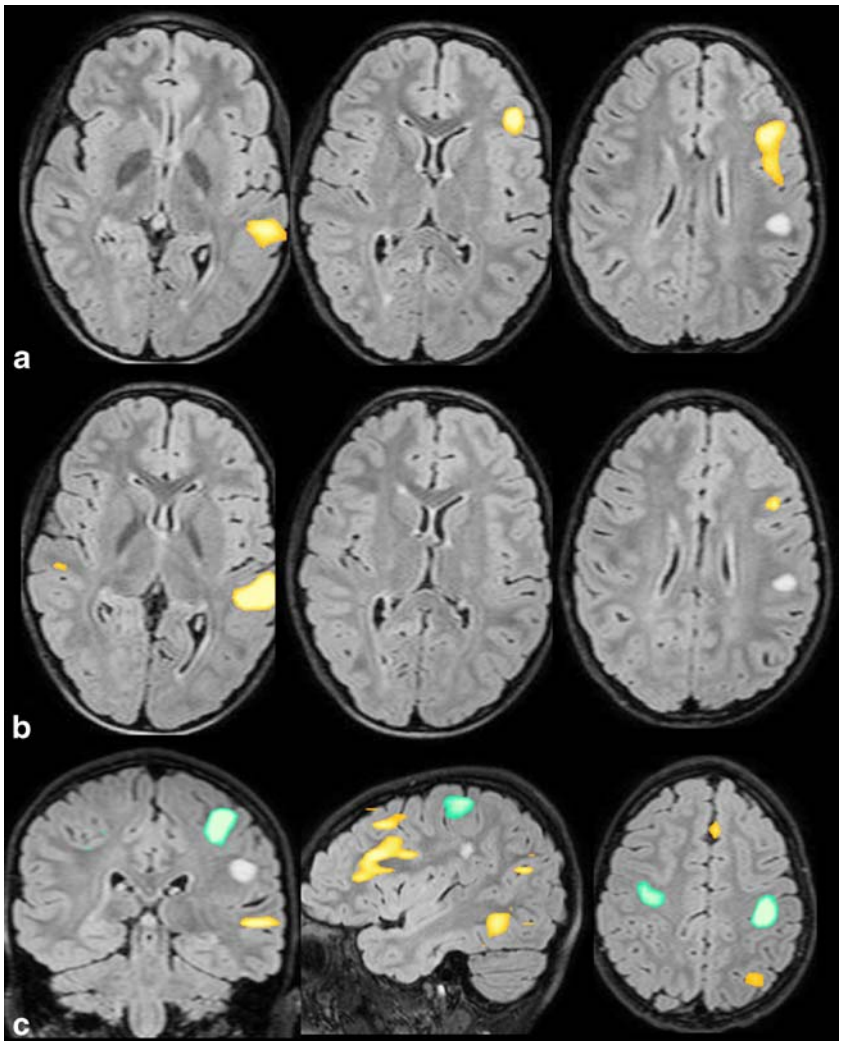

Fig. 5 Typical language lateralization pattern in an 11-year-old right-handed boy with a left inferior parietal (*post central gyrus*) subcortical signal abnormality and seizures. He was being evaluated for surgery. fMRI was obtained to document speech lateralization and motor mapping. **a** Verb generation (*sequential finger-tap control*), **b** story processing (*backward story control*), and **c** verb generation (*sequential finger-tap control*) show activation during control task. Left hemispheric lateralization is noted with verb generation (**a**) in a typical distribution. Lateralization index (*LI*) is: 0.97 (*frontal ROI*), and 0.96 (*temporal parietal ROI*). Left-hemispheric lateralization is also noted with story listening in both the left posterior temporal and temporal parietal regions and in a smaller region in the left frontal lobe. Overlaying the finger-tap component, activation with finger tapping is noted just above and anterior to the lesion [green regions (**c**)]. Tractography (*not shown*) outlined the arcuate fasciculus adjacent to the medial aspect of the lesion

sentences with specifically formulated and complex syntactic constructions that engage multiple brain regions. The control tasks are listening to various tonal sequences [67] or to identical periods of temporally reversed speech [97]. Activation regions identified when contrasted with tonal groups are bilateral in distribution, involving the primary auditory cortex, bilateral superior temporal gyrus, and left inferior frontal gyrus more variably. With the backward story control, activation is much more lateralized and less extensive. Activation is typically limited to the left middle and superior temporal gyri along the posterior superior temporal sulcus (Fig. 4). Variable activation in the left inferior frontal gyrus can also be seen. The advantage of the tone discrimination control is that it activates bilateral brain regions and might be sensitive to shifts in language lateralization contralateral to the injured hemisphere [64]. The advantage of the backward story control is that it allows assessment of dominant-hemisphere temporal parietal language areas, regions that are more variably activated by verb generation or semantic decision tasks.

Other paradigms

An additional paradigm that may find increasing clinical use is determination of linguistic prosody (identifying a statement versus a question). In this task the patient decides whether a delivered audiovisual sentence is a statement or a question based upon prosody alone. In a pediatric version of this task [64] there is predominantly right-hemispheric lateralization of activation. Use of this task might allow the assessment of non-semantic language components that could be related to right-hemispheric injury. Other tasks such as read-response naming and auditory and reading sentence comprehension have also been used for clinical language assessments [3, 98, 99].

Clinical exam interpretation

Given the variable regions activated and the multiple tasks needed for comprehensive fMRI evaluation of language in

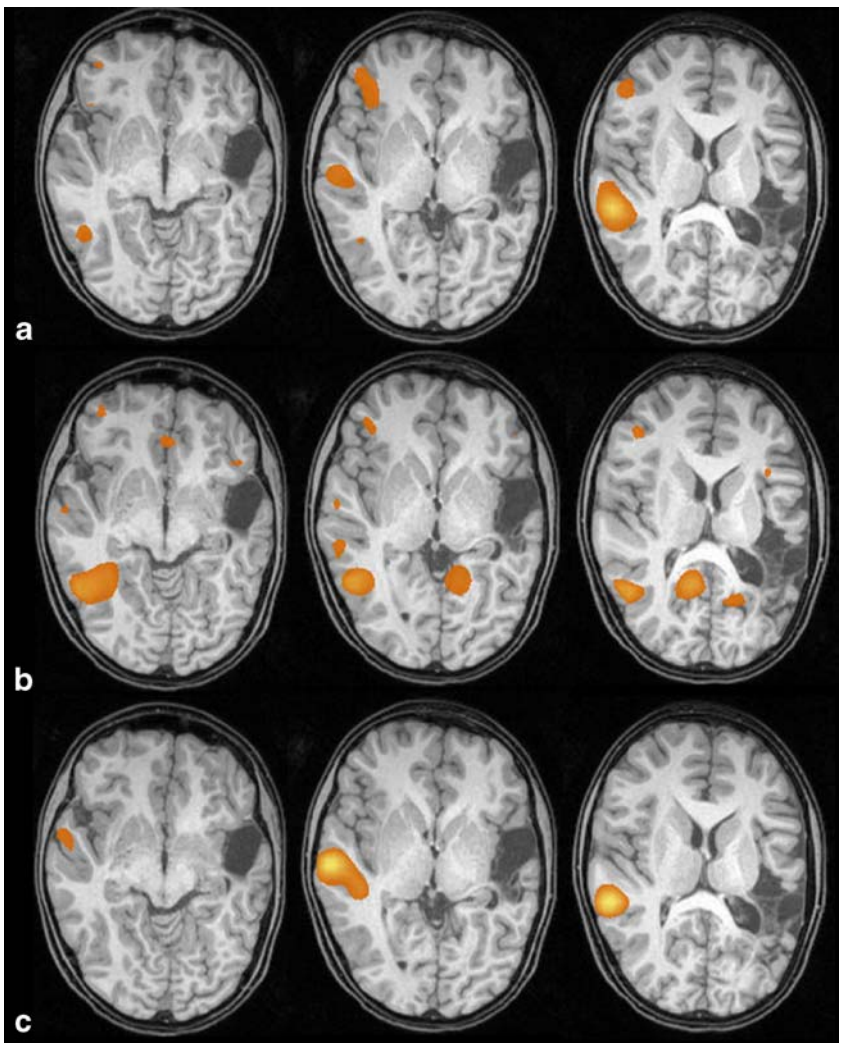

Fig. 6 Atypical language lateralization (*right-hemispheric lateralization*). **a** Verb generation (*sequential finger-tap control*), **b** semantic decision (*tone-discrimination control*), **c** story processing (*backward speech control*). An 11-year-old left-handed boy with history of left-hemispheric perinatal infarct with areas of encephalomalacia in the left temporal lobe, insula, and temporal parietal junction. Activation pattern is right-side with all paradigms, localized to homologous regions in the right hemisphere. The child underwent the intracarotid amobarbital procedure (*IAP*), with the finding of right hemispheric language lateralization

children, interpretation can be complex. Interactive visual assessment of activation patterns at multiple statistical thresholds is imperative. Descriptions of language laterality and hemispheric dominance in clinical and research contexts have typically been described on the basis of a region-of-interest (ROI) laterality, or asymmetry, index (LI) [3, 18, 72]. Using this technique, the number of activated voxels in a left-side ROI is compared with that in an identical right-side ROI via this equation: $LI = (L - R)/(L + R)$. Left-side-only activation would give an LI of +1. Activation of the right hemisphere only would give an LI of −1. Cutoff values for lateralization categorization are typically 0.1–0.25 [100]. For example using a cutoff value of 0.2, LI of >0.2 are considered indicative of left lateralization, while those <−0.2 are consistent with right lateralization. Between −0.2 and 0.2 indicates bilateral language representation [3]. LI calculations are dependent on the statistical technique and threshold used for calculating activated voxels, ROI used, and fMRI task [3, 100, 101]. LI calculations are more robust when a combined task approach (conjunction analysis) and a priori ROIs (to typical language areas instead of the whole hemisphere) are used [102, 103]. An approach using ROIs derived from group normative data and setting the threshold related to the mean *t*-value of the pixels within the ROI has been used in some studies with good success, although smaller LI thresholds are used for categorization (0.1) [91, 101]. Threshold-independent techniques for computing LI as well as boot-strapping techniques for estimating the optimum threshold for LI have been proposed [105]. It seems prudent to use LIs calculated with varying thresholds, ROIs, and multiple tasks in individual patients in order to more completely assess language laterality [100]. Interestingly, visual assessment of lateralization in individual patients might be as good as ROI-based LI calculations in determining lateralization, with excellent agreement when directly compared [99, 106].

Typically fMRI exams are interpreted in clinical patients as left-hemispheric dominant (typical activation pattern), right-hemispheric dominant (right-hemispheric homologues exhibit greater numbers of active voxels), and bilateral language representation (if not right or left lateralizing). Gaillard [3] has broken down bilateral patterns as either (1) equal activation in homologous regions, (2) frontal-temporal diaschisis (different lateralization for frontal and temporal-parietal regions), or (3) task-related (in which different tasks elicit different lateralization) (Figs. 5, 6, 7, 8 and 9). Bilateral activation patterns can be problematic in evaluation of individual clinical patients, as this fMRI pattern can often not be conclusively interpreted [100]. In such cases, a well chosen battery of fMRI paradigms designed

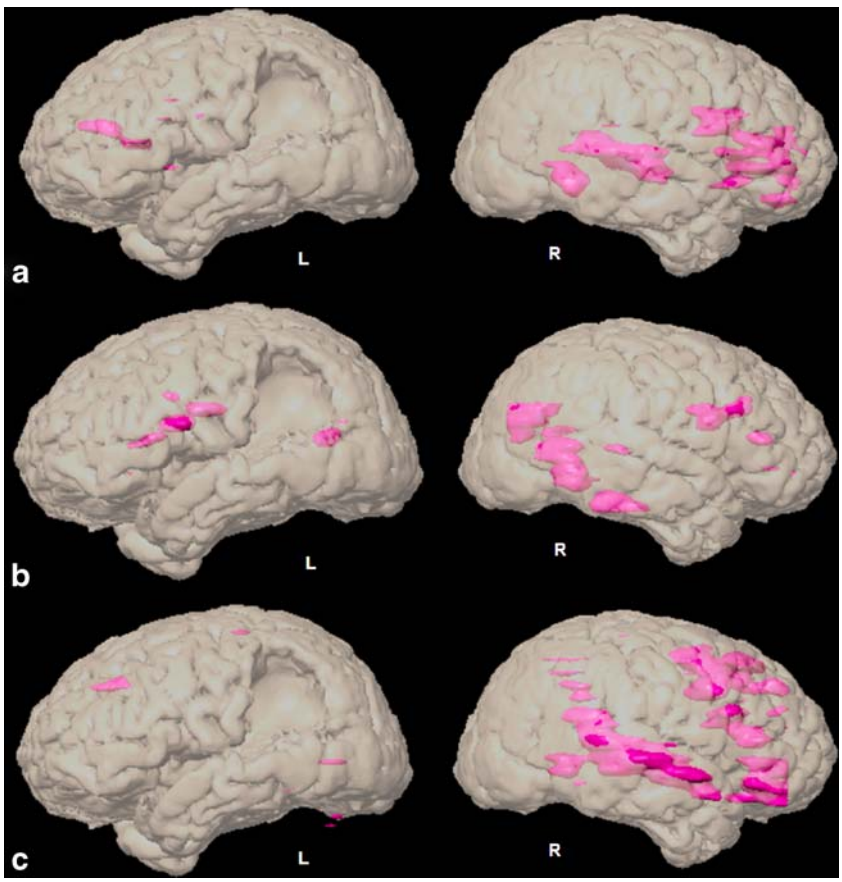

Fig. 7 Same child as in Fig. 6. Volumetric representation of activation areas superimposed on segmented brain surface. **a** Verb generation (*sequential finger-tap control*), **b** semantic decision (*tone-discrimination control*), **c** story processing (*backward speech control*). Activation is strongly right-lateralizing with some small areas of activation along the margins of the region of encephalomalacia and in the right frontal lobe. R- right hemisphere, L - left hemisphere

to activate left-dominant, right-dominant and bilateral language areas can facilitate the most accurate assessment of the patient's redistributed language patterns [64].

Effects of neuropathology

Neuropathology can have a marked effect on language lateralization in children as detected by fMRI. Yuan et al. [104] in a study of 18 children with epilepsy noted atypical language lateralization in 78%, compared with 11% in an age/gender/handedness-matched control group. A significant association between duration of epilepsy and atypical lateralization was noted, suggesting a causal link of seizure activity and language redistribution in this population. Tillema et al. [107] evaluated 10 children with prior perinatal MCA stroke and 10 healthy age-matched controls with a verb-generation task. They found displacement of activation to right inferior frontal homologous regions and more bilateral superior temporal activation when compared with healthy controls. Similar right-hemispheric displacement has been reported in young adults with left-hemisphere periventricular lesions acquired pre- or perinatally [108]. A recent large study of epilepsy patients who had both MRI and bilateral Wada testing demonstrated a high incidence of right-hemispheric lateralization (46%) in left-handed subjects with early acquired left-hemispheric lesions [109]. These studies demonstrate the important effects of early acquired pathologic states on language development and regional specialization.

Validation/comparison with direct assessments of language lateralization and localization

The traditional method for determining language dominance prior to surgery has been the Wada, or intracarotid amobarbital, procedure (IAP). Another method of language mapping is direct electrocortical stimulation (ECoS) either during conscious surgery or by utilizing subdural grid electrodes [110]. Both of these methods induce transient deficits and differ fundamentally to techniques of language mapping used with fMRI. Comparisons between these modalities is of importance, however, as they form the

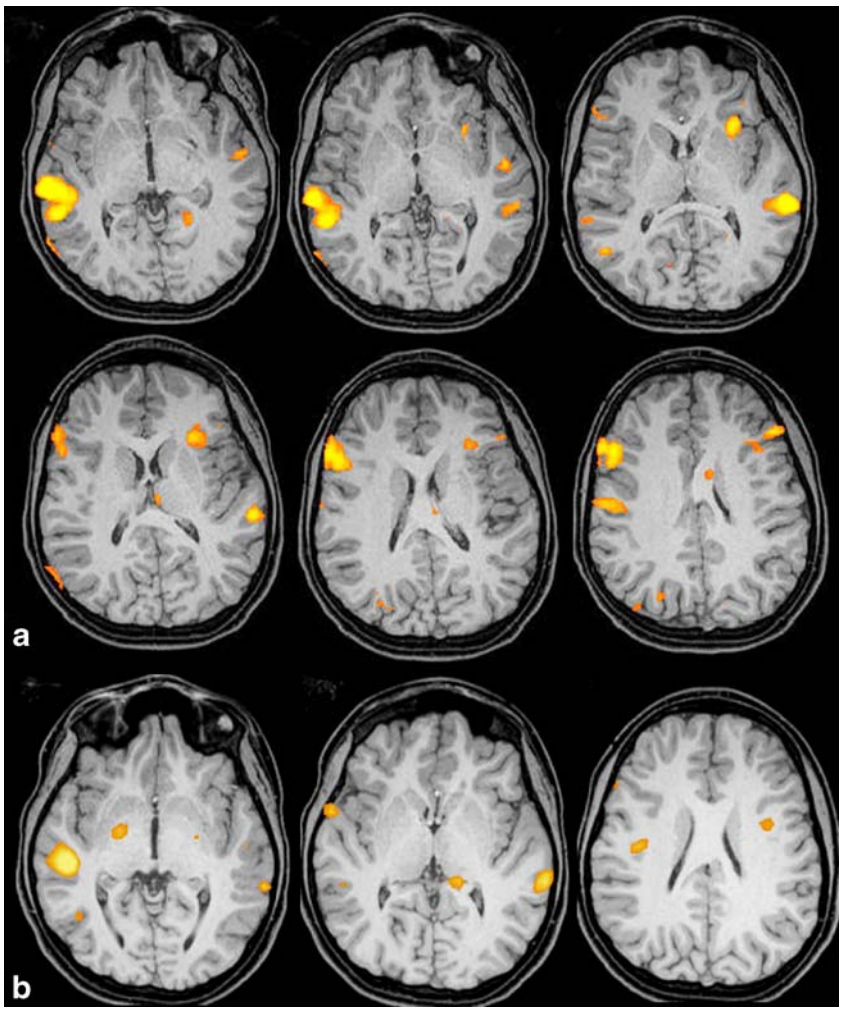

Fig. 8 Atypical language lateralization. A 12-year-old left-handed girl with history of infantile spasms and intractable left frontal lobe origin seizures since age 8. **a** Verb generation. **b** Story processing (backward story control). Verb generation (performed twice) demonstrates a bilateral activation pattern with more pronounced middle frontal gyrus activation regions on the right, bilateral temporal parietal activation (more pronounced on the right), and slightly more pronounced and focal left inferior frontal activation. Using a whole-hemisphere ROI for lateralization, there was right lateralization, with an LI of -0.33. Using a smaller ROI limited to the inferior frontal gyrus, there was mildly leftward lateralization, LI of 0.24. Mild rightward lateralization of temporal parietal activation was noted, with an LI of -0.27. This case demonstrates atypical bilateral activation with frontal temporal diaschisis and outlines the difficulty encountered at times using fMRI for language lateralization in children with chronic epilepsy. In this scenario, evaluation with IAP or ECoS is necessary for accurate language lateralization assessment

clinical gold standards for language lateralization and localization in surgical patients.

The IAP is expensive and invasive and carries with it a small but definite risk of complications [111–113]. It is more difficult to perform in children [110, 111], and its invasive nature limits repeat assessments [114]. Although providing lateralization information, the IAP cannot spatially localize language functions in the brain, an advantage of fMRI. There can be difficulty in accurately performing the IAP or subdural neurostimulation in young children, providing an additional potential role for fMRI or other non-invasive tools for language mapping in this age group [110].

Correlation studies between fMRI and the IAP for language lateralization have fairly consistently shown an 85–90% concordance rate focusing primarily on mixed-age or adult epilepsy populations [3, 17, 112, 113, 115, 116]. In general, there are discrepancies between fMRI and the IAP for language lateralization in about 10% of cases [106, 117]. The best correlations between the IAP and fMRI are obtained with the use of verbal fluency or semantic decision tasks, with less correlation with receptive language tasks [118]. The use of multiple tasks increases the degree of concordance between fMRI and the IAP [3, 102, 103].

Discrepancies are most pronounced in patients who exhibit atypical language lateralization, primarily those with bilateral representation [114, 115, 117]. Discordance between fMRI and the IAP is also more common in patients with neocortical epilepsy (a more common scenario in children than adults) and left temporal lobe seizure origin [106]. A recent careful study of 40 epilepsy patients (primarily adults), all assessed by the IAP and fMRI (using three language paradigms and a conjunction analysis), demonstrated 91% concordance when the IAP was clearly left- or right-hemispheric lateralized [103]. Looking at the subgroup in this study who exhibited bilateral language representation by the IAP, fMRI typically lateralized either left or right. Three of the seven subjects in this group demonstrated different lateralizations depending upon the fMRI task used.

Few studies have specifically evaluated language-based fMRI with the IAP in children. Anderson et al. [114] studied a heterogeneous population of 38 children with frontal and temporal cerebral lesions with a word-generation fMRI paradigm. Thirty of these children had inferior frontal activation (86% success rate) and 15 were compared with IAP, ECoS, or definite lateralizing clinical symptoms. Thirty percent of the children exhibited atypical (right or bilateral) activation patterns. Of the children with corroborating lateralization evidence, fMRI was concordant in 12 (80%), and discordant in 3. Discordant patients exhibited bilateral language representation on visual and quantitative fMRI assessment but were left-dominant on corroborative evaluation. Liégeois et al. [119] assessed eight children with epilepsy with a verb-generation paradigm using a direct-activation magnitude comparison between homologous frontal lobe regions. They demonstrated concordance of fMRI lateralization with IAP in all patients.

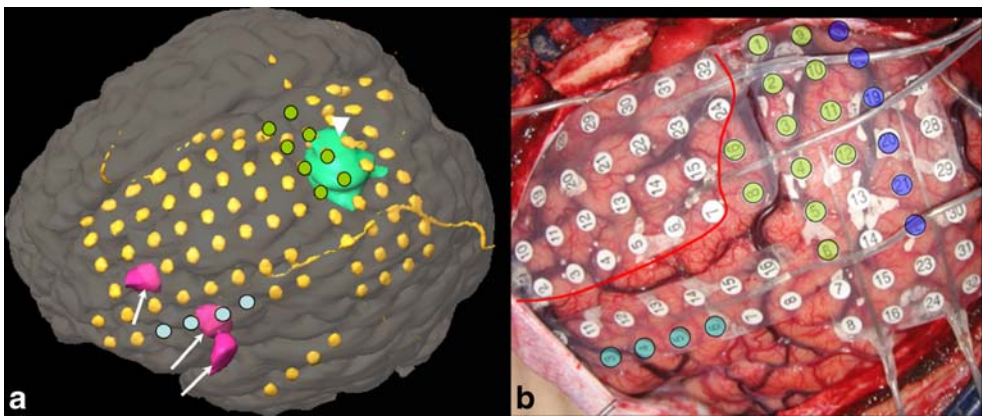

Fig. 9 Same child as in Fig. 8. **a** Volumetric representation of fMRI activation areas, subdural grids, and subdural grid stimulation regions producing patient deficits during preoperative mapping. Images produced in an operative neuronavigation system (BrainLab iPlan 2.6. Munich, Germany). **b** Operative photo during grid placement for cortical mapping and seizure localization (operative image and correlation courtesy K. Lee, MD, and K.D. Holland-Bouley, MD). **a** Frontal areas of activation with verb generation are noted in pink (*arrows*) and activation areas with finger tapping are noted in blue-green (*arrowhead*). Grids are segmented from CT imaging and overlayed in yellow. Areas of grid stimulation producing naming pause or initiation delay are noted in blue, overlying the fMRI activation areas in the left inferior frontal lobe. Areas of grid stimulation producing right arm or hand movement are marked in green, corresponding well with areas of fMRI activation with sequential finger tapping. In the intraoperative image (**b**), areas of most pronounced discharges during electrographic and electroclinical seizures were noted in the left superior frontal lobe and medial frontal region. Area of planned resection is marked in red. Grid locations resulting in sensory symptoms are marked in blue. Surgery: left frontal resection. Pathology: moderate cortical dysplasia with subpial gliosis. Outcome: seizure-free at short-term follow-up, no new deficits

Medina et al. [120] recently performed a Bayesian meta-analysis of the published literature of direct correlations of fMRI and IAP or ECoS [120]. In 240 patients who underwent language fMRI and the IAP, the sensitivity and specificity of fMRI for language lateralization was 92.5%. They demonstrated that the utilization of fMRI increased the final post-test probabilities of hemispheric language dominance in both the epilepsy and non-epilepsy populations.

The roles of fMRI and the IAP in the work-up of presurgical patients have been recently debated [111, 121]. The literature comparing these modalities is variable but converging. Despite the variable techniques used to perform fMRI examinations in the literature, the correlation between fMRI and invasive confirmatory tests of language function has been very good. Although fMRI might not be able to replace the IAP in all circumstances, utilization of routine fMRI can diminish IAP utilization by as much as 80% [3]. Careful application and interpretation of fMRI in children is warranted given the limited pediatric-specific literature, the different neuropathologies encountered in children, as well as the pediatric-specific fMRI performance and developmental language lateralization issues. Standardization of tasks, statistical analysis techniques, and reporting is still needed.

fMRI has also been used in an attempt to guide resections near eloquent language regions. Because fMRI will demonstrate areas of the brain that are associated with but not necessarily essential to a particular task, fMRI will always exhibit a lack of specificity for language mapping in this scenario. The gold standard for language mapping in surgical patients is ECoS during a conscious craniotomy [122, 123]. Direct comparisons between language fMRI and ECoS for regional language mapping have been few, and the results have been variable. The sensitivity of fMRI

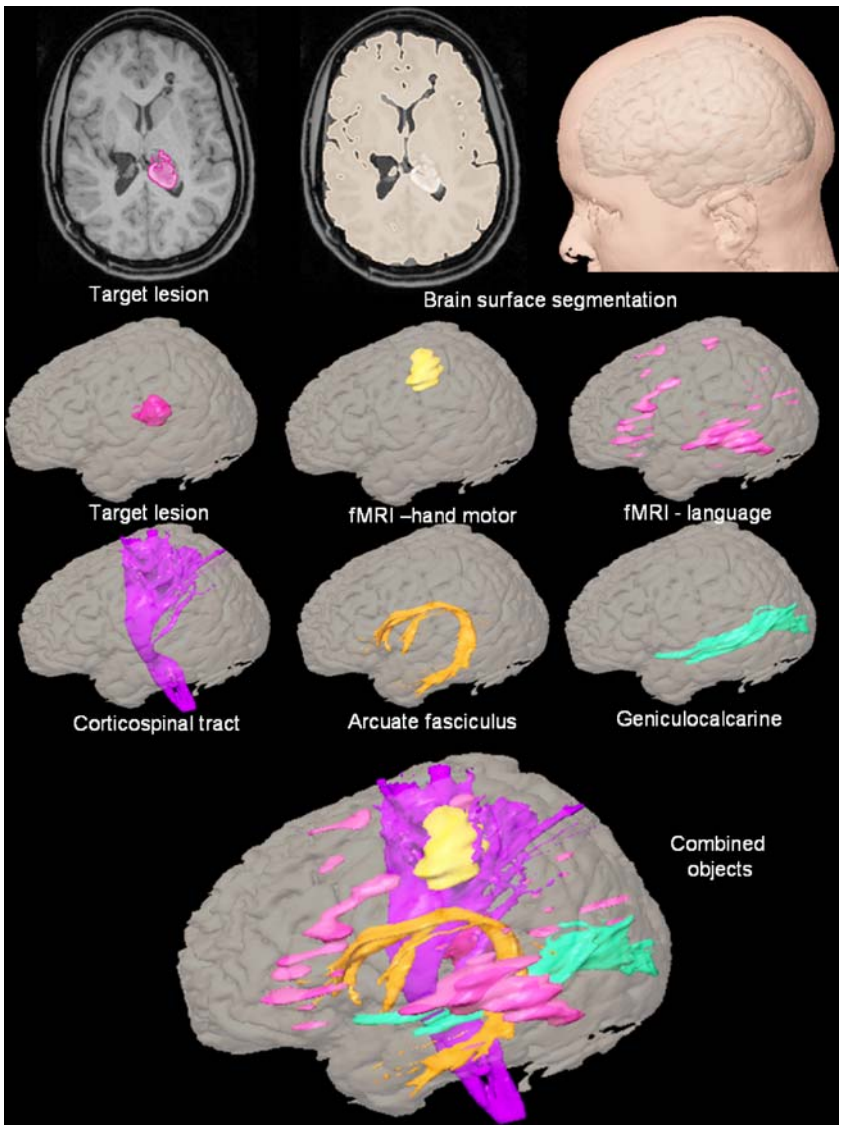

Fig. 10 Operative integration of fMRI and DTI data. A 17-year-old girl with history of multiple cavernous malformations and surgery. She presented with increasing headaches and an enlarging left thalamic hemorrhage (*target image*). fMRI and DTI were performed to identify a safe access route to this deep lesion. Objects were created in the planning system corresponding to the outlines of the fMRI activation regions and DTI-derived streamlines for preoperative planning and operative integration. Target lesion is semi-automatically outlined within the planning system. Brain surface is automatically segmented from an isotropic T1 dataset. The relationships of the fMRI- and DTI-derived functional regions can be viewed three-dimensionally for assessment of safe operative corridors to the deep target lesion

in identifying critical language areas as established by ECoS varies between 22% and 100%, with specificities of between 61% and 100% [124]. This is due in part to the non-specificity of fMRI, variable fMRI language paradigms used, effects of adjacent lesions, and statistical thresholding effects. ECoS procedures typically use an object-naming task, which has shown to be inferior to verb-generation or semantic-decision tasks in activating frontal and temporal language regions by fMRI. When similar tasks are performed during ECoS and fMRI, spatial correlation improves [123].

In a recent detailed study, Bizzi et al. [125] evaluated 34 patients with gliomas in eloquent brain regions using both fMRI (verb-generation task) and ECoS. For essential language areas they found an overall sensitivity of fMRI of 80% and specificity of 78%. Sensitivity diminished from 93% to 65% as tumor grade increased. Although patient performance and mass effect might account for sensitivity decreases, reduced BOLD sensitivity in the vicinity of brain tumors has been found by other authors [126] and is likely related to tumor vascular effects and diminished regional autoregulation [127]. Unfortunately, very few studies have addressed fMRI language mapping compared to ECoS in children. Careful application of fMRI in this context is warranted until larger correlative studies have been performed.

Despite the variable reported correlations, fMRI might be additionally useful to guide intraoperative ECoS procedures, to preoperatively identify regions for grid placement to guide potential cortical stimulation, to identify surgical corridors, and for counseling parents and children for surgery in eloquent areas [39, 123].

Memory

In addition to language lateralization, the assessment of hippocampal integrity to sustain memory after temporal lobe resection is important and also traditionally assessed by the IAP. Assessment of memory by fMRI is possible and has begun to be tested in clinical patients. Utilization of higher-resolution imaging protocols are necessary for optimal assessment [128]. At this time, although there are encouraging clinical research studies correlating fMRI activation patterns with the IAP [128, 129] and postoperative memory after temporal lobe resection in adults [129], routine application in children is not warranted until adequate normative data and more standardized paradigms are available. Assessment of memory by fMRI techniques in children represents an important future research area.

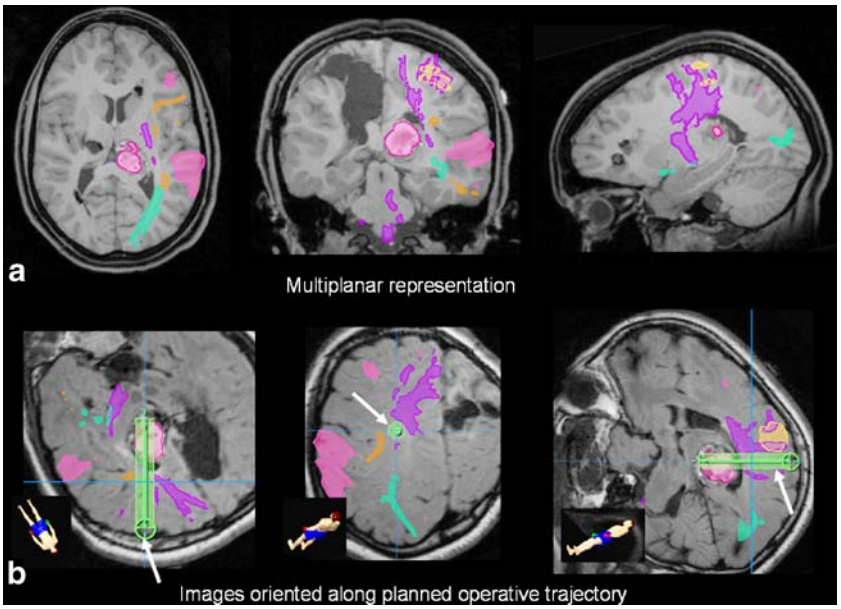

Fig. 11 Same child as in Fig. 10. Intraoperative integration for functional neuronavigation. Using the planning station, coupled with a frameless stereotactic system in the OR, an operative trajectory can be identified (*arrows* in **b**, *green trajectory*), limiting the craniotomy and minimizing the potential for disruption of functionally important areas. **a** Multiplanar reconstruction. **b** Images and functional objects are reoriented perpendicular to the proposed operative tract. A small craniotomy was performed, guided by the neuronavigation system, with balloon dilatation of the planned operative tract performed to minimize adjacent tissue disruption. Outcome: Complete resection of the hemorrhagic cavernous malformation was performed with no patient deficit. (Images produced using BrainLab iPlan 2.6, Munich, Germany. Operative planning performed in conjunction with Todd Maugans, MD, Department of Neurosurgery, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA)

Multimodality functional imaging and functional neuronavigation

Combining fMRI with other modalities such as diffusion tensor imaging (DTI) tractography, magnetoencephalography/magnetic source imaging (MEG), positron emission tomography (PET), and single photon emission computed tomography (SPECT) allows for a more detailed preoperative evaluation of complex neurosurgical patients (multimodality integration) [130] (Figs. 10 and 11). MEG and fMRI can often provide complementary information in clinical patients [131]. Combining functional modalities (fMRI, DTI, MEG) into modern neuronavigation systems allows for guidance of surgical access and resection (functional neuronavigation) [130]. Use of fMRI in conjunction with ECoS and frameless stereotaxy has been found to help facilitate tumor resection in children with a wide variety of lesions near eloquent cortical regions [132].

Reimbursement

In the U.S., clinical billing codes for fMRI examinations became active in January 2007 by the Centers for Medicare and Medicaid services [133]. The accepted clinical indication is for pre-operative neurosurgical planning. The codes can be billed as 70554 or as 70555 and 96020 together. Code 70554 denotes a study performed in an automated fashion by an imaging technologist without need for physician or neuropsychologist patient assessment or paradigm administration. This is typically a simple motor or sensory assessment.

Code numbers 70555 and 90620 should be billed when a physician or neuropsychologist is required and actively participates in patient assessment, paradigm administration, and reporting. This is typically for cognitive functions such as language, memory, or higher-order or more complex movement paradigms. The actual billing will be site-specific. For example, if a radiologist protocols the imaging and interprets the imaging results and a neuropsychologist assesses the patient, administers the paradigm, and provides a clinical assessment, the radiologist would bill 70555, and the neuropsychologist would bill 96020. If the radiologist performs image interpretation, patient assessment, and fMRI paradigm administration and processing, and performs assessment of neurologic function before, during or after the procedure, the radiologist would bill both 70555 and 96020. This testing could include assessment of response during the fMRI procedure. Requirements to bill 96020 are: "The physician or psychologist is responsible for selection and administration of testing of language, memory, cognition, movement, sensation, and other neurological functions when conducted with functional neuroimaging, monitoring of performance of this testing, and determination of validity of neurofunctional testing relative to separately interpreted functional magnetic resonance images" [133].

When billing using the appropriate CPT codes, we are having success with exam pre-authorization and payments based upon our contract terms with third-party payers. Clinical functional MRI reporting should include information regarding patient performance during the study and results of patient assessment that determined the type of cognitive tasks administered in addition to technical and interpretive details of the procedure.

Conclusion

Functional MRI has been used extensively to evaluate cognitive processes and has added greatly to our understanding of basic neuroscience mechanisms. In children, its research use in a number of areas is being performed and has allowed for a greater understanding of brain development, particularly with regard to language lateralization and specialization. Clinical applications are evolving and becoming more widespread. Further research is necessary to standardize methodologies of fMRI performance and interpretation in clinical patients, as well as to validate results with clinical gold standards and patient outcomes.

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