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FULL-LENGTH ORIGINAL RESEARCH

Presurgical language mapping in children with epilepsy: Clinical usefulness of functional magnetic resonance imaging for the planning of cortical stimulation

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Summary

Purpose: Presurgical language mapping in dominant hemisphere epilepsy to evaluate the risk of postoperative deficit is particularly difficult in children. Extraoperative invasive cortical stimulation can show some areas critical to language, but not all of them, due to scarce sampling, poor cooperation, cortical immaturity, or network reorganization, whereas functional magnetic resonance imaging (fMRI) displays entire networks involved in, but not necessarily critical to, language. In a homogeneous series of children with epilepsy, we compared the contributions of language fMRI and depth electrode stimulations to optimize language mapping.

Methods: Eight children (7.5–15.5 years) with left frontal or temporal epilepsy underwent language fMRI and language stimulation with depth electrodes as part of their comprehensive presurgical workup. fMRI data collected during sentence generation were analyzed using statistical parametric mapping (SPM2) (false discovery rate [FDR] $p < 0.05$). Bipolar stimulations were performed during language production tasks. By coregistering fMRI and postimplantation computed tomography (CT) images, we were able to directly compare the cortical areas identified by both investigations.

Key Findings: fMRI during sentence generation robustly showed activation in the whole perisylvian regions with little reorganization (left hemisphere dominant in 7). Of the 184 electrode contacts tested for language, only 8 were positive (language disruption) in three of the seven patients with periictal language impairment and left language dominance. All of the positive contacts colocalized with an fMRI activated cluster, that is, fMRI did not miss any region critical to language (sensitivity = 100%). However, 54 of the 176 negative contacts were within activated clusters (low specificity).

Significance: In children with epilepsy, the sensitivity of fMRI during sentence generation allows for the detection of all critical regions displayed by cortical stimulation within the large perisylvian language network, but with a low specificity. It is, therefore, useful to optimize the placement of intracranial electrodes when language mapping is necessary. Systematic planning of the electrode placement according to language fMRI maps should increase the yield of extraoperative cortical stimulation, which appears rather low in children when compared to adults.

KEY WORDS: Epilepsy, Pediatric, Functional magnetic resonance imaging, Depth electrode stimulation, Language.

Because of the progress in both presurgical investigations and surgical techniques, epilepsy surgery is more often performed for pharmacoresistant focal epilepsies in children, where seizure control leads to better cognitive development (Lendt et al., 2002; Sinclair et al., 2003). The goal of surgery is to achieve complete resection of the epileptogenic zone while preserving cortical function and avoiding any postsurgery deficit. Focal brain pathology may lead to reorganization of language networks through multifactorial age-dependent cerebral plasticity. Atypical language representation (right-sided or bilateral) is more frequent in adult patients with left hemisphere epilepsy than in the control population (Springer et al., 1999). Intrahemispheric reorganization of language cortex has been demonstrated in adults (Ojemann, 1979), and in children (Duchowny et al., 1996;

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Ojemann et al., 2003; Yuan et al., 2006). Some authors suggest a pattern whereby developmental lesions and early onset seizures do not always displace language cortex from prenatally determined sites (Duchowny et al., 1996; Anderson et al., 2006), whereas others have shown different language patterns in patients with epilepsy (Saltzman et al., 2002; Ojemann et al., 2003; Yuan et al., 2006). However, he potential for language relocalization decreases after the age of 5 years (Vargha-Khadem et al., 1985). Therefore, the perilesional localization of language in patients with dysembryoplastic neuroepithelial tumor (DNET)/focal dysplasias remains a controversy in refractory epilepsy.

Current techniques for localizing eloquent cortex, however, have specific limitations in children, making precise cortical mapping a challenge in this population.

Intracarotid sodium amobarbital, or WADA, testing with selective intracarotid amobarbital injection has been used to assess language, but its localizing power is limited to the determination of hemispheric dominance (Hajek et al., 1998). Cortical stimulations have been used in the past to map eloquent cortices (Penfield & Rasmussen, 1950). Although intraoperative cortical stimulation has been restricted to cooperative patients who were able to cope with awake surgery, subdural grids or depth electrodes have enabled cortical mapping outside the operating room, especially in children (Duchowny et al., 1996; Kurjak et al., 2007). Such preoperative cortical stimulation is currently considered the reference technique for language mapping because of its high specificity: It shows areas that are *critical* for speech (Stanojevic et al., 2002). The choice between depth and subdural electrodes is based on the surgeon's preference, since both techniques are associated with different risks and benefits. Many factors, however, make language cortical stimulation a challenge in children, such as developmental delay and insufficient attention or cooperation. In addition, incomplete myelination is known to decrease the sensitivity of stimulation techniques and requires age-adapted stimulation protocols (Alvarez & Jayakar, 1990; Jayakar et al., 1992).

Single proton emission computed tomography (SPECT) and positron emission tomography (PET) have also been used to map language or motor areas (Vinas et al., 1997; Tatlidil et al., 2000; Borbely et al., 2003). However, these modalities lack both spatial and temporal resolution, and radiation exposure is a concern in children. Functional magnetic resonance imaging (fMRI) has now replaced these techniques thanks to its noninvasiveness and better spatial and temporal resolution.

Language fMRI has demonstrated excellent correlation with the WADA test (Binder et al., 1996; Hertz-Pannier et al., 1997; Lehericy et al., 2000; Balsamo & Gaillard, 2002; Sabsevitz et al., 2003; Woermann et al., 2003), which validates its use for the assessment of hemispheric language dominance in adults as in children. However, fMRI shows the activation of all networks involved in a given task, not just those areas critical to language functions. Therefore, it cannot currently delineate language cortex during surgery.

Although stimulations and fMRI do not directly assess the same process, they both help in the quest for effective language mapping. Clinically relevant issues for children undergoing operation include the following: (1) whether an area is implicated in language function and (2) whether its removal might affect the child's capacity to speak and understand speech. However, the yield of stimulations is highly dependent upon the placement of electrodes, which is currently mostly driven by hypotheses on the epileptogenic zone, rather than on language cortex. Although both issues can be tested in cases of overlap between both cortices, electrodes only minimally misplaced may miss eloquent cortex abutting the epileptogenic zone.

Comparison between cortical stimulations and fMRI has been attempted in both isolated cases and case series (FitzGerald et al., 1997; Ruge et al., 1999; Rutten et al., 2002; Roux et al., 2003) in adults, with a fair concordance of localization of the eloquent regions, but not in children.

The aim of this clinical report was to describe the concordance/complementarity of both techniques in a small series of epilepsy children, using a precise colocalization method of the relevant cortical areas. More specifically, we aimed at questioning the clinical usefulness of language fMRI mapping beyond the establishment of language dominance in children with epilepsy: (1) to assess the sensitivity of language fMRI in detecting critical areas revealed by electrical stimulation, and (2) to question the role of fMRI in the optimization of electrode placement for cortical stimulation.

Patients and Methods

Patients

Among the children operated on at our epilepsy surgery institution (~120 per year), we included all children who had been investigated during three consecutive years for intractable left frontal or temporal lobe epilepsy and who had undergone language mapping with both fMRI and depth electrode stimulation (Table 1 and Fig. 1). This patient population is scarce and particularly difficult to study.

We selected the nine children in whom a postimplantation computed tomography (CT) scan was available in a digital format, a mandatory condition for the imaging process of the present study. A 9-year-old girl was excluded from the series because her fMRI was inconclusive (no activated clusters). Among the remaining eight children (seven boys; 8–16 years, median age 11.25 years, seven right-handed), seven had clinical evidence of left language dominance as demonstrated by language impairment during or after seizures (see Table 1). One patient (Patient 4, right-handed) did not exhibit any language impairment either ictally or interictally.

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Table 1. Individual epileptic characteristics

Patient (sex)	Age at fMRI (years)	Seizures: age at onset (years)	Seizures: frequency	Seizures: semiology Periictal language deficit	Neuropsychology	Epilepsy location	Etiology
1 (m)	12	3.2	1/day–1/week	Abdominal aura, pallor, continues his activity but hypotonic, postictal aphasia	Global deficit, FSIQ 61 Visuospatial difficulties	Left IFG + opercula	FCD (neuronal heterotopia)
2 (f)	10.5	3	>1/day	2 types: eye deviation to the right, loss of contact, +/– speech impairment (up to 40 min)	VIQ 86 → 60 FSIQ 76 → 72 Progressive language deficit (fluency, vocabulary, naming)	Left frontal and temporal	Cryptogenic
3 (m)	14	8	1/day–1/week	Generalized or eye and head deviation to the right, visual aura, loss of contact, postictal naming deficit (15 min)	VIQ 66 PIQ 83 Deficit in naming, verbal memory, comprehension, vocabulary	Left posterior temporoparietal	FCD[a]
4 (m)	7.5	3	1/day–1/week	Morpheic, laughs then spasms	Normal language Graphism difficulties	Left MFG	FCD
5 (m)	15.5	10	1/day	No loss of contact, vocalization with hypertonia of RUL, short language postictal deficit	Global delay No specific language deficit	Left IFG	FCD
6 (m)	9.5	5 (1 at age 1.4)	1/day	Morpheic: wakes up, screams, ocular clonia touches his left jaw and whines One seizure with postictal aphasia (several minutes)	VIQ 78 FSIQ 84 No language deficit	Left temporal lateral (T1)	FCD[a]
7 (m)	8	6	>1/day	As if would vomit, opens mouth Repetition difficulties, short post ictal language deficit	VIQ 122 FSIQ 117	Left opercula + IFG + motor strip	DNET[a]
8 (m)	13	9	1/2 weeks	Loss of contact, chewing, some 2GTC Postictal language deficit	VIQ 105 FSIQ 110 No language deficit	Left temporal	DNET

RUL, right upper limb; VIQ, verbal IQ; FSIQ, full-scale IQ; PIQ, performance IQ; IFG, inferior frontal gyrus; FCD, focal cortical dysplasia; m, male; f, female.
[a]No surgery.

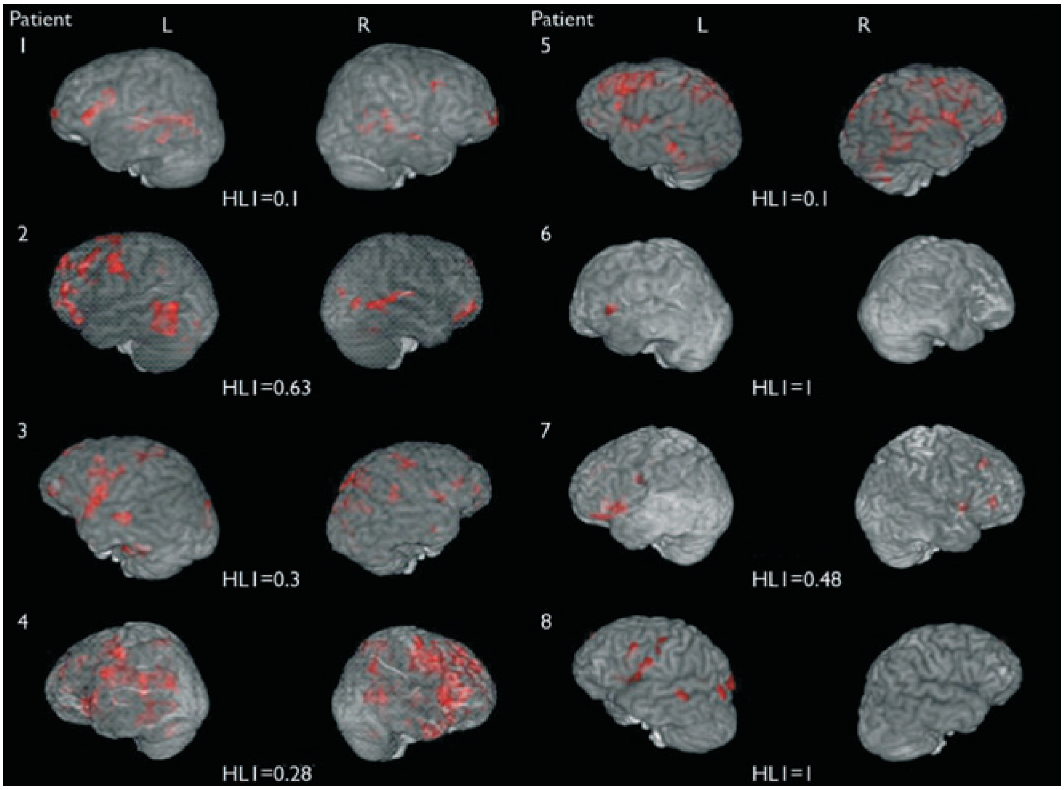

Figure 1.
Surface rendering of fMRI during sentence generation ($p < 0.05$ per cluster) in the patients. Robust activation in the prefrontal regions is seen in all patients. Temporal activation is detected in six patients. Numbers on the left indicating the patient number. HLI, hemispheric laterality index. *In Patient 1, word repetition was used because the child failed the sentence generation task.
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Methods

fMRI paradigm

After having obtained parental consent and child assent, according to our institutional review board approval, language fMRI was performed on a 3-Tesla research magnet (Bruker, Erlangen, Germany) using a modified gradient-echo echo-planar sequence (22 axial slices, resolution $3.7 \times 3.7 \times 5$ mm^3, TR = 5 s). Children were especially trained before testing to optimize comprehension and performance, after careful explanation was given about the covert condition that they would perform during fMRI using the same timing and paradigm as in MRI, but in overt condition and with different words. Among the four expressive and receptive tasks performed in our local procedure (Hertz-Pannier et al., 2001), the candidate task for the present study consisted of generation of sentences, performed covertly to minimize the risk of head and facial movements. In our experience, this expressive language task, close to the widely used verb generation task, and strongly lateralizing, has several major advantages in children, although no control of performance can be obtained during scanning: it is amenable to children with IQs down to 50, does not require much in the way of attentional resources or heavy working memory load, and optimizes the yield of fMRI in terms of assessment of hemispheric dominance, when compared to other language paradigms. In this series, our pragmatic goal with fMRI was to screen the entire language network (as well as its lateralization), rather than to find specific language areas. Patients were presented with a concrete word via headphones every 5 s. They were then asked to silently generate a simple sentence (subject-verb-object) using the presented word. Subjects were instructed not to vocalize their sentences in order to minimize artifacts from face movements. They were given five nouns in each activation block, and activation blocks alternated with blocks of rest of the same duration (total 3 min 35 s). To ensure good comprehension of the auditory stimuli, these were presented during the silent interval formed by the grouping of the slice acquisition gradients (loud beeps) over 1.4 s within each TR of 5 s. During rest, patients were asked to stop thinking of words and to listen to the magnet noise.

In one child who failed the sentence generation (Patient 1), word repetition was used instead, with the presentation of concrete words through the headphones in the magnet.

Two words were presented in each activation block, and activation blocks alternated with blocks of rest of the same duration. The patient was asked to silently repeat the words immediately after hearing them. During rest, he was to remain quiet and listen to the magnet noise.

Each child underwent a three-dimensional (3D) inversion recovery (IR)-prepped T1 acquisition for anatomic localization of activated clusters.

Electrodes implantation and stimulation

Depth electrode implantation had been planned for seizure monitoring after careful review of video–electroencephalography (EEG) and MRI, and was performed within a mean interval of 6 months around the fMRI. As all but one child had periictal language impairment, we expected a proximity between critical language cortex and the epileptogenic zone. We slightly modified the implantation design in the last child included in the series (Patient 2) to place some electrodes within the fMRI activated clusters, surrounding the hypothetical epileptogenic zone. Depth electrodes were implanted using a frameless stereotactic robotic system (NeuroMate; Schaerer-Mayfield, Venissieux, France) combined with an imaging workstation for trajectory planning and electrode positioning (Voxim software; IVS Solutions, Chemnitz, Germany). Following the implantation, all children underwent a CT scan to confirm each electrode's exact position.

The electrodes were stimulated using the Jayakar protocol during 1 week of EEG-recording (Jayakar et al., 1992). Square pulses of current were applied either to two adjacent contacts or to two contacts separated by a third one (bipolar stimulation). The stimulations began at an intensity of 1 mA, a high frequency of 50 Hz, a 0.3 ms pulse of alternating polarity and a train duration of 3–5 s. Stimulation intensity was increased by steps of 1 mA until either poststimulation discharges were seen on EEG, a clinical response with speech arrest occurred, or a seizure was triggered.

In the children who also had electrodes in either the motor cortex or the sensorimotor area (SMA; n = 3, 8–16 years), a positive response was obtained at an average of 2 mA. Poststimulation discharges were observed with intensities varying from 1.6–10 mA. Therefore, the maximal stimulation intensity was 10 mA.

The language tasks used for stimulations all involved ''ecologic'' language production, and consisted of counting, reading a book aloud, or spontaneously generating speech, depending on child's abilities and the site of stimulation, to keep an acceptable length of the procedure. A response was considered positive when the child displayed a clear and transient arrest in language activity during stimulation.

Fusion of fMRI and CT scan images

To obtain the same reference space for depth electrodes and fMRI, the postimplantation CT scan was aligned with the anatomic MRI data and resliced using MRIcro (Version 1.39) (Rorden & Brett, 2000) and SPM2.

Fusion of CT and fMRI images was performed using two different softwares: Anatomist (CEA, Orsay, France, http://brainvisa.info) and MRIcro (Version 1.39). Fusion with both software packages was similar, as well as the number of electrode contacts either within or outside of activated areas.

Analysis

All stimulation data were reviewed and grouped as positive or negative.

The fMRI data were analyzed using SPM2 (Wellcome Institute for Cognitive Neuroscience, University College, London, United Kingdom). The first three images of each run were discarded to allow stabilization of the longitudinal magnetization. The remaining nonnormalized images were realigned to the first image to correct for head motion during acquisition, coregistered to the anatomic image, resliced, and smoothed (full width at half maximum [FWHM] of 5 mm). Images were then analyzed using pixel-wise thresholds of $p < 0.05$ and $p < 0.01$ (FDR), corrected at a cluster-level of $p < 0.05$. The obtained clusters were then saved as a 3D image.

In an additional analysis to assess hemispheric language dominance, hemispheric laterality indices were calculated by automatically summing all activated clusters in the left and right hemispheres (excluding basal ganglia, occipital cortex, and midline pixels) after linear normalization, and computing Left − Right/Left + Right ratios (Binder et al., 1996).

Sensibility and specificity of the fMRI were calculated using the stimulation results as the reference.

Results

Language representation at fMRI

fMRI during sentence generation elicited consistent activation in the usual perisylvian network in all patients, confirming the robustness of both the task and the analysis threshold, albeit with considerable interindividual variation, as expected in this population (Fig. 1). Activation of the prefrontal cortex (left inferior frontal gyrus) was found in all subjects, whereas posterior temporal activation was seen in six of them.

In the seven patients with periictal language impairment, fMRI confirmed the clinically suspected left hemisphere language dominance with positive hemispheric laterality index (HLI) (between 0.1 and 1; Fig. 1). In Patient 1 where word repetition was used, temporal activation was rather bilateral, contrasting with a clearly left lateralized activation in Broca's area, resulting in an laterality index (LI) of 0.1. In the right-handed child without periictal language manifestations (Patient 4), the dominance side was atypical with a right-sided lateralization (HLI −0.28).

Language stimulation using depth electrodes

Among the 184 depth electrodes contacts stimulated in total, 8 disclosed a positive result, that is, with a language disruption during the stimulation between 2 and 5 mA (Table 2). That corresponded to three of the seven patients with both periictal language deficits and left language dominance on fMRI (Table 3), interestingly including Patient 2 in which the electrode placement had been slightly modified to place contacts within the fMRI activated clusters. Patient 1 stopped counting (repeated in two stimulations) while stimulating two contacts in the pars opercularis at a threshold of 2 mA. Patient 2 stopped counting (first stimulation) and generating nouns (second stimulation) while stimulating two contacts of a single frontal electrode at 4 and 5 mA. In Patient 3, a 2-mA stimulation of two contacts of two different posterior temporal electrodes produced comprehension impairment and reading arrest, followed by a seizure. No language disturbance was obtained in the other four patients.

Table 2. Comparison between language depth electrode stimulation and fMRI activation

	Stimulation +	Stimulation –
SPM analysis: FDR, $p < 0.05$; $\chi^2 = 16.46$ ($p < 0.01$)		
fMRI +	8	54
fMRI –	0	122
SPM analysis: FDR, $p < 0.01$; $\chi^2 = 16.36$ ($p < 0.01$)		
fMRI +	7	41
fMRI –	1	135

Table 3. Individual results of depth electrode stimulations

Patient	Location of epilepsy	Depth electrodes: number of stimulated contacts and location	Maximal parameters of language stimulations	Positive contacts for language: number, location, impact, intensity	Maximal parameters of motor stimulations	Surgery
1 (m)	Left opercular	22 left frontal and temporal	2 mA 50 Hz 0.3 ms	Yes, two contacts on one electrode, inferior frontal gyrus, pars opercularis stop counting + seizure	ND	IFG (pars orbitalis) anterior insula, MSPT on the pars opercularis Engel IIa (1 year)
2 (f)	Left frontal	4 left frontotemporal	2–6 mA 50 Hz 0.3 ms	Yes, two contacts on one electrode*, inferior frontal gyrus stop counting and noun generation, 5 mA	ND	Denied
3 (m)	Left posterior temporoparietal	12 left frontotemporoparietal	2–5 mA 50 Hz 0.3 ms	Yes, four contacts on two electrodes, temporoparietal reading arrest, decreased comprehension	ND	Pending
4 (m)	Left frontal	38 left frontal	2–7 mA 50 Hz 0.3 ms	No	Motor stimulation 3 mA	MFG, precentral, very focal Engel I (6 months)
5 (m)	Left frontal	29 left frontal	5 mA 50 Hz 0.3–5 ms	No (discharges)	Sensory stimulation + seizure: 5 mA	Focal IFG lesionectomy, sparing the foot of F3 Engel I (3 years)
6 (m)	Left temporal ext post and ant	30 left temporal	2–6 mA 50 Hz 0.3 ms	No	ND	Denied
7 (m)	Left opercula + IFG + motor	18 left frontal	2–6 mA 0.3 ms	No (postdischarge, seizure aura)	Motor: 2 mA Sensory: 3 mA	Denied
8 (m)	Left temporal	31 left temporal	2–3 mA	No (hearing decreased near Heschl gyrus)	ND	Lesionectomy T1, with left posterior T1 intact, postop deafness, Engel Ia (1 year)

m, male; f, female; ND, not done; mA, milliamperes; Hz, hertz; ms, milliseconds; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; T1, superior temporal gyrus.

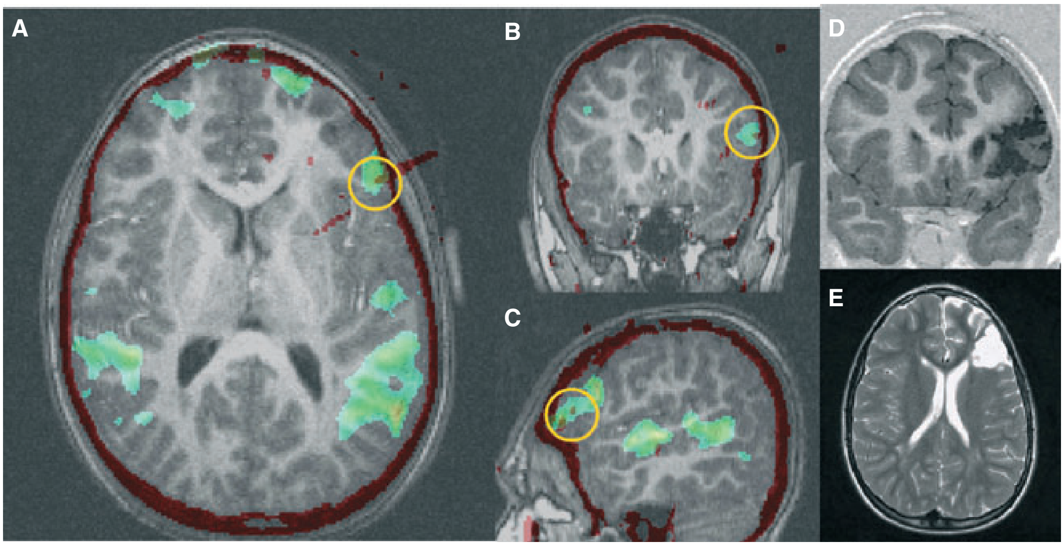

Figure 2.
Excellent colocalization of fMRI activation and positive electrode contact (Patient 1). (**A**–**C**) Axial, coronal, and sagittal views of the CT–fMRI fusion showing positive contacts located in an activated cluster in the pars opercularis of the left inferior frontal gyrus. (**D**–**E**) Postoperative CT scan showing the resection with the pars opercularis left in place. No postoperative language deficit and Engel I at 12 months follow-up.
Epilepsia © ILAE

Colocalization of depth electrodes and fMRI

At the individual level, the colocalization of each positive contact with fMRI-activated clusters was excellent (pars opercularis of the left inferior frontal gyrus in Patient 1 (Fig. 2A–C); inferior frontal gyrus in Patient 2; temporoparietal junction in Patient 3; Table 2).

Although, as expected, a large number of negative contacts were outside activated areas, some were within or at the border of activated clusters [superior temporal sulcus in Patient 1; posterior portion of the middle temporal gyrus in Patients 3 and 6; inferior and middle frontal gyri, precentral gyrus, and SMA in Patients 4, 5, and 7; and superior

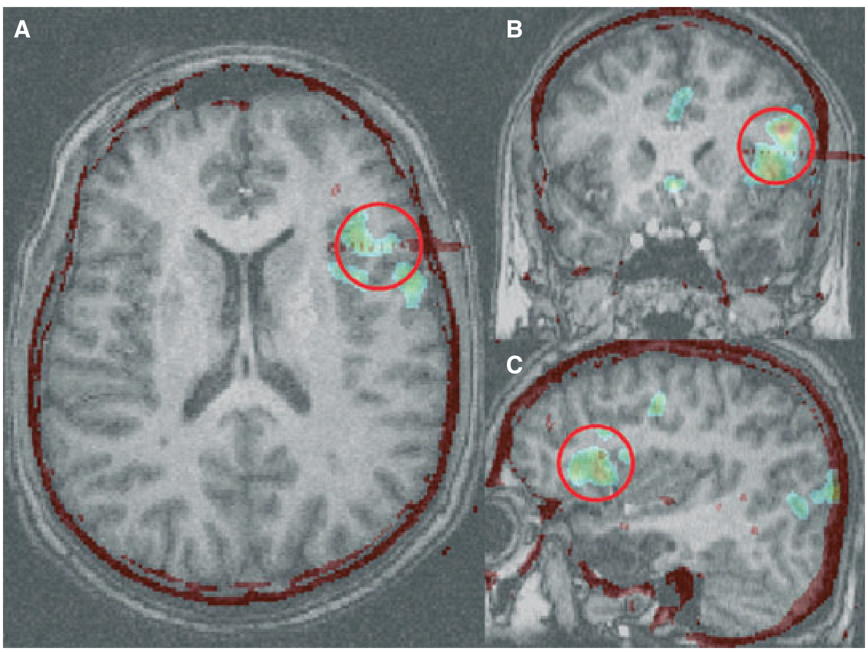

Figure 3.
Low specificity of fMRI activation (Patient 8). (**A**–**C**) Axial, coronal, and sagittal views of the CT-fMRI fusion, where the electrodes within the activated areas were negative to stimulations. Frontal depth electrodes were decided because of the rapid spread of the seizures to the frontal area on the scalp EEG to exclude the possibility of the inferior frontal gyrus being part of the epileptogenic zone. Left temporal dysembryoplastic neuroepithelial tumor resected (lesionectomy). One year after surgery the patient is seizure free.
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temporal gyrus and inferior frontal gyrus in Patient 8 (Fig. 3A–C)].

In the whole series, all eight positive contacts were located within an fMRI cluster activated during sentence generation at the widely used threshold of $p < 0.05$ (FDR). Among the 176 negative contacts, 54 were located within an active fMRI cluster and 122 were not ($\chi^2 = 16.46$, $p < 0.01$, Table 2). At a more stringent threshold (FDR $p < 0.01$), only seven of the eight positive contacts were within an activated cluster (global results $\chi^2 = 16.36$, $p < 0.01$, Table 2, Fig. 4A,B).

Therefore, if we were to take the depth electrode simulation as gold standard, the fMRI would have a sensitivity of 1 and a specificity of 0.69 when analyzed at $p < 0.05$; and a sensitivity of 0.88 and a specificity of 0.77 when analyzed at $p < 0.01$.

Five children were operated on and none had postoperative deficit. These children have remained seizure-free for a mean follow-up of 16 months (range 6 months–3 years). Three children were denied surgery on the basis of bilateral epileptogenic foci or a high risk of postoperative language deficit (Table 3).

All surgeries spared the areas that were positive during stimulation. In addition, planned resections also spared areas that were activated during fMRI despite their negative response at stimulation (in the Broca or Wernicke area). Therefore, we have no feedback whether those areas were indeed necessary for language.

Discussion

We report the first description of combined language mapping in pediatrics, using coregistered fMRI maps and depth electrode stimulation. Despite its limited sample size, collecting these data in such a series of fairly homogeneous epileptic children with stringent inclusion criteria was a challenge, given the many limitations inherent to a pediatric population. In this series, fMRI during a broad language task amenable to deficient children (sentence generation, FDR < 0.05) showed a large perisylvian network in which it did not miss any critical language areas demonstrated by cortical stimulation (sensitivity = 100%). However, the yield of depth electrode language stimulation was low (8 of 184 contacts; 3 of 7 patients). Notably, one of the three patients with positive contacts had the electrode placement modified according to the fMRI map, to place contacts within the activated clusters. Not surprisingly, fMRI also showed many more activated clusters, either colocalized with negative contacts (30% of them) or outside of any contact (low specificity).

We propose that, beyond the establishment of hemispheric dominance, language fMRI be *systematically* performed in the planning of cortical stimulation, using broad tasks including expressive and receptive processing that activate the whole perisylvian network, in order to plan the implantation scheme according to language maps and increase the yield of cortical stimulation that is highly dependent on appropriate electrode placement.

fMRI

The ability of fMRI to reliably demonstrate language dominance has led to a decline in the use of the WADA test. However, even though fMRI is now everyday practice in adults for that purpose (Binder et al., 1996; Springer et al., 1999; Lehericy et al., 2000), it is not yet fully accepted as a standard of care in pediatric epilepsy because of the limited number of published studies (Hertz-Pannier et al., 1997, 2002; Balsamo & Gaillard, 2002; Wilke et al., 2003, 2006; Szaflarski et al., 2006; Yuan et al., 2006). Expressive tasks such as word fluency or verb generation are the most lateralized tasks and provide better correlation with invasive methods like the WADA test than receptive tasks (Lehericy et al., 2000). Generation of sentences, an easy task largely amenable to impaired children, activates a large left perisylvian network, comprising both expressive and receptive language areas (Broca and Wernicke) as well as the usual cortical areas found to be coactivated in various language tasks (Muller et al., 1997; Vigneau et al., 2006). In this series, seven of the eight children showed clear left dominance. These children had little reorganization despite early left perisylvian epilepsy, as it was found in other studies (Duchowny et al., 1996; Liegeois et al., 2004), unlike some

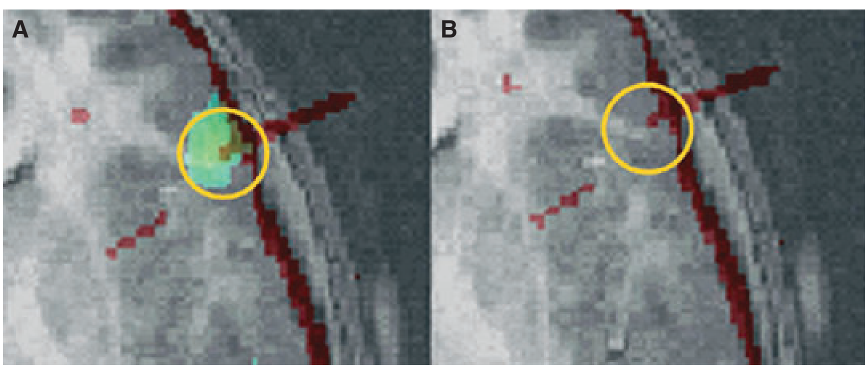

Figure 4.
Threshold effect. (**A**) At FDR $p < 0.05$, the electrode contacts that are positive to stimulation are within an activated area. (**B**) At FDR $p < 0.01$, the activated area around the electrode contacts is no longer detected.
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reported cases, which showed more reorganization with early seizure onset (Gaillard et al., 2000; Sachs & Gaillard, 2003; Wood et al., 2004; Wilke et al., 2006).

Although fMRI activations show all neuronal networks involved in a specific task, they do not indicate the hierarchy between participating regions. Therefore, an activated region may not be functionally critical to the language task being studied (i.e., it could be resected without inducing permanent language deficit, low specificity). However, the use of a "nonspecific" task such as sentence generation showing the whole left perisylvian language network (high sensitivity) seems useful to constrain and refine the planning of cortical stimulation to successfully map language cortex representation, providing we can demonstrate it does not miss any critical area.

In this study, our goal was not to test the specificity of fMRI during either expressive or receptive language, but rather to investigate a clinically meaningful, highly sensitive way of optimizing the electrode placement. Sentence generation showed lateralized frontal activation in all, and temporal activation in six of them, reflecting the findings in our large experience of >250 children with epilepsy over >12 years. Our comprehensive protocol also includes receptive tasks, such as listening to sentences, which exhibits robust bilateral activation in the superior temporal gyrus, with a mild degree of leftward asymmetry in the posterior temporal cortex (Wernicke's area), and a significant overlap with the activation found during sentence generation. Although it might be interesting in some instances to add a receptive task to map larger temporal areas, it would, however, not have increased the yield of fMRI in this study, as all positive contacts were located in sentence generation activation clusters.

Depth electrode stimulation

In this study, we could obtain a language disruption in only three patients. These disruptions included a total of eight electrode contacts of the 184 tested, which is a low yield. Insufficient stimulation intensity is unlikely, because stimulation was terminated in the negative cases due to afterdischarge or seizure-induction. This termination occurred at intensities up to 10 mA, whereas positive responses were obtained at intensities between 2 and 5 mA.

Direct intraoperative cortical stimulation is commonly being considered the gold standard for revealing regions critical to language function in adults (Kral et al., 2006). However, this technique is not feasible in most children. More recently, perioperative stimulations using subdural grids or depth electrodes have been challenged because of their insufficient sensitivity in children (Jayakar et al., 1994; Ojemann et al., 2002, 2003). Using grids, Schevon et al. (2007) showed that children younger than 10 have a lower response rate to cortical stimulation than older children or adults. The following different variables may account for these negative language findings and apply to both grids and depth electrodes:

1 While left language specialization has been shown as early as 3 months in healthy infants (Dehaene-Lambertz et al., 2002, 2010), language representation is still more bilateral in healthy toddlers than later on (Redcay et al., 2008), with increasing specialization of left perisylvian networks until at least 18 years of age (Holland et al., 2001; Schapiro et al., 2004; Brown et al., 2005; Szaflarski et al., 2006; Yuan et al., 2006). This might reduce the possibility of cortical areas whose unilateral left stimulation would induce a speech disturbance.

2 Reorganization of language distribution has been shown more frequently in subjects with early brain lesions and epilepsy, with a trend toward more bilateral language (Hertz-Pannier et al., 1997; Springer et al., 1999; Liegeois et al., 2004; Yuan et al., 2006). This, however, was not clearly the case in our series, where all children but one showed some degree of left specialization. This relative lack of reorganization may relate to the high rate of developmental lesions that are known to keep language networks in their predetermined sites. Indeed, in Duchowny et al., 1996. most children with developmental lesions had positive language sites that directly overlapped or did lay adjacent to the epileptogenic zone (six of six in the temporal lobe, and 10 of 11 in the frontal region).

3 Alternatively, developmental delay in children with epilepsy, especially in language performance and attentional resources, may limit their capacity for language testing.

4 A fourth hypothesis is that the developing brain has a higher stimulation threshold, due to higher amount of small fibers and lack of complete myelination (Jayakar et al., 1992, 1994; Chitoku et al., 2001). Comparably, Alvarez and Jayakar (1990) showed a progressive increase in afterdischarge and sensorimotor response thresholds with age, which might be related to more complete myelination, more mature neurons, and a shorter chronaxis. These observations raise questions about the safety of the high currents needed to elicit a response in young children (up to 20 mA) (Berger et al., 1989; Alvarez & Jayakar, 1990; Jayakar et al., 1992; Chitoku et al., 2001, 2003; Ojemann et al., 2003; Schevon et al., 2007).

The detection of language cortical areas is also highly dependent on the appropriate placement of grids or depth electrodes because these areas are only 1–2 cm^2 (Ojemann et al., 2002). Placement is currently mostly based on clinical and electrophysiologic hypotheses on the epileptogenic network, as it is impossible to infer the precise cortical organization of language from anatomic data alone. Geometric differences between grids and depth electrodes (grids: 3–5 mm in diameter, separated by 1 cm; depth electrodes: 2 mm in diameter, separated by 1.5 mm) also influence the stimulated volume. Although subdural grids allow stimulation of the cortical surface, depth electrodes induce transcortical stimulation. In adults, bipolar stimulation applied to stereoencephalography (SEEG) got better responses when high frequency stimulation was applied (Ostrowsky et al., 2000). No such studies have been reported in children.

Even when eliciting a response, stimulation can occasionally be misleading, since a case of falsely positive stimulation was recently published (Seeck et al., 2006). In that case, no language deficit occurred after surgical removal of an area where cortical stimulation had induced a speech arrest.

Finally, some authors have recently suggested the need for alternative, more sensitive, and complementary techniques such as fMRI or magnetoencephalography (MEG) (Schevon et al., 2007) in addition to specific cortical stimulation.

Colocalization of stimulation contacts and fMRI clusters

A few studies have compared intraoperative stimulations and fMRI in short series of adults. In 1997, FitzGerald et al. (1997) superimposed an intraoperative photograph of a stimulation map onto functional maps merged with an MR angiogram. Later, Ruge et al. (1999), Rutten et al. (2002), and Roux et al. (2003) compared the responses of intraoperative stimulation (either bipolar or monopolar) to fMRI maps (for verb generation, picture naming, verbal fluency, and sentence comprehension) using neuronavigation or video/photographic recordings. Although Ruge found no fMRI false negatives in 426 stimulation sites in 14 patients, Roux found at least 9 cortical areas that were positive to stimulation but not activated on fMRI, depending upon the type of language task. Overall, in these studies the sensitivity of fMRI, considered within the group of areas involved by the electrodes, varied from 38–100%, and the specificity from 65–97%. Our data are the first currently available in children.

The challenge in presurgical mapping is to maintain high sensitivity to lower the risk of postoperative deficits while preserving reasonable specificity. The statistical threshold substantially influences the extent of activated areas and the possible limits of resection. To provide a framework for clinical use, we kept the same threshold for all patients. We used a threshold of FDR $p < 0.05$, which is commonly used in pediatric and adult studies. This threshold has shown convincing results, usually favoring sensitivity over specificity in the analysis (Wilke & Lidzba, 2007). In this presurgical series, where our goal was indeed to favor fMRI sensitivity, it proved appropriate to display all the critical areas demonstrated by cortical stimulations. When we used a more stringent threshold (FDR $p < 0.01$) to ensure that the method was reasonably robust, only one positive contact was located just outside the corresponding activated cluster. Therefore, we suggest that a threshold such as FDR ($p < 0.05$) be used to ensure that all essential areas are included.

If cortical stimulation was considered as the reference to display critical regions in this pediatric series, in the absence of any other possible gold standard, the sensitivity of fMRI would reach 100% at a threshold of 0.05, that is, fMRI did not miss any critical region (sensitivity remained high, at 88%, when using a more stringent threshold of 0.01), and the specificity for both thresholds would be, respectively, 0.69 and 0.77. However, those values might not reflect entirely the reality, since the stimulation itself is neither sensitive nor specific at 100%. In addition, sensitivity/specificity results observed in this short series cannot be easily generalized. Indeed, both depend heavily on the study design, which includes many variables (type of language tasks in both fMRI and stimulation, performance of the patients, size of the population, parameters of stimulation, and so on). However, this preliminary study demonstrates the possibility to achieve good sensitivity of fMRI, and paves the way for larger studies that will progressively refine the yield of fMRI for the planning of electrode placement. Currently, the trajectory of the electrodes is decided solely according to the scalp EEG in conjunction with the semiology of the seizures and an eventual lesion. Their exact trajectory is then planned by looking at the MRI of the patient and might be slightly modified to avoid cortical vessels. Because the clinical and EEG information enable the surgical team to decide on an approximate location, within a few millimeters, if there is an fMRI activated area in that vicinity, then a modification of the trajectory by a few millimeters will not affect the quality of the recording from an epileptology point of view (to find the epileptogenic zone), but might enable testing of language in that precise location.

In the child where electrode placement was slightly modified according to the fMRI results by place contacts within an activated cluster in the left frontal operculum (Patient 2), the stimulations elicited a positive response. This further suggests that appropriate placement of electrodes according to fMRI may increase the yield of stimulations.

Of course, not all fMRI activated areas could be correlated with stimulations, due to the restricted number of implanted electrodes. In addition, our goal was not to compare between both modalities the localizations of regions specific to a particular language component, but to highlight the whole language network in which electrodes should be placed to successfully map language. Indeed, the fMRI task used here includes numerous oral language processes (comprehension, phonology, semantics, syntax, and so on) and activates the entire perisylvian network, when compared to simple rest. This procedure maximized our chances of detecting all regions involved in "real-life" language ability. In addition, testing each electrode with specific language tasks would considerably lengthen the procedure considering the attentional control of our pediatric population. Because we could demonstrate the high sensitivity of fMRI in this study, it is thus not surprising to find numerous regions activated at fMRI that are not critical to language (low specificity).

Finally, the only ''gold standard'' for testing the function of a specific cortical area would be an unexpected postoperative deficit. This fortunately is rare and did not occur in this series.

Conclusion

This study confirms the high sensitivity of fMRI for detecting all the areas critical for language in children when an appropriate ''broad'' task is chosen. This makes fMRI an exquisite tool to be used systematically for preoperative mapping, even in patients with cognitive deficits, whereas depth electrode stimulations retain the ability to test the critical contribution of each cortical area in language function, and to tailor the resection when the epileptogenic zone lays within or in close vicinity to eloquent cortex. Considering, however, that the sensitivity of cortical stimulation techniques is limited in pediatrics not only by the number of electrodes but also by many practical constraints and by the immaturity of the brain, fMRI provides a useful complementary method for optimizing language mapping in the epilepsy surgery workup. We believe that in order to increase the yield of cortical stimulations, an ideal approach would be to plan the trajectory of the electrodes according to fMRI activation maps, in addition to the hypotheses on the epileptogenic zone. This would allow surgeons to more efficiently combine epilepsy mapping and language mapping, which is especially relevant when the epileptogenic zone is close to language cortex. Modifying the trajectory by a few millimeters would enable the cortical stimulation to confirm cortical function. This step, along with the optimization of both stimulation parameters and task paradigms in children, would provide better language mapping for planning resective surgery. It would also allow better assessment of the concordance of electrode stimulation and fMRI activation.

Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

Alvarez L, Jayakar P. (1990) Cortical stimulation with subdural electrodes: special considerations in infancy and childhood. *J Epilepsy* 3:125–130.

Anderson DP, Harvey AS, Saling MM, Anderson V, Kean M, Abbott DF, Wellard RM, Jackson GD. (2006) FMRI lateralization of expressive language in children with cerebral lesions. *Epilepsia* 47:998–1008.

Balsamo LM, Gaillard WD. (2002) The utility of functional magnetic resonance imaging in epilepsy and language. *Curr Neurol Neurosci Rep* 2:142–149.

Berger M, Kincaid J, Ojemann GA, Lettich E. (1989) Brain mapping techniques to maximize resection, safety, and seizure control in children with brain tumors. *Neurosurgery* 25:786–792.

Binder JR, Swanson SJ, Hammeke TA, Morris GL, Mueller WM, Fischer M, Benbadis S, Frost JA, Rao SM, Haughton VM. (1996) Determination of language dominance using functional MRI: a comparison with the Wada test. *Neurology* 46:978–984.

Borbely K, Gjedde A, Nyary I, Czirjak S, Donauer N, Buck A. (2003) Speech activation of language dominant hemisphere: a single-photon emission computed tomography study. *NeuroImage* 20:987–994.

Brown TT, Lugar HM, Coalson RS, Miezin FM, Petersen SE, Schlaggar BL. (2005) Developmental changes in human cerebral functional organization for word generation. *Cereb Cortex* 15:275–290.

Chitoku S, Otsubo H, Harada Y, Jay V, Rutka JT, Weiss SK, Abdoll M, Snead OC III. (2001) Extraoperative cortical stimulation of motor function in children. *Pediatr Neurol* 24:344–350.

Chitoku S, Otsubo H, Harada Y, Jay V, Rutka JT, Weiss SK, Elliott I, Ochi A, Kitayama M, Snead OC III. (2003) Characteristics of prolonged after discharges in children with malformations of cortical development. *J Child Neurol* 18:247–253.

Dehaene-Lambertz G, Dehaene S, Hertz-Pannier L. (2002) Functional neuroimaging of speech perception in infants. *Science* 298:2013–2015.

Dehaene-Lambertz G, Montavont A, Jobert A, Allirol L, Dubois J, Hertz-Pannier L, Dehaene S. (2010) Language or music, mother or Mozart? Structural and environmental influences on infants' language networks. *Brain Lang* 114:53–65.

Duchowny M, Jayakar P, Harvey AS, Resnick T, Alvarez L, Dean P, Levin B. (1996) Language cortex representation: effects of developmental versus acquired pathology. *Ann Neurol* 40:31–38.

FitzGerald DB, Cosgrove GR, Ronner S, Jiang H, Buchbinder BR, Belliveau JW, Rosen BR, Benson RR. (1997) Location of language in the cortex: a comparison between functional MR imaging and electrocortical stimulation. *AJNR Am J Neuroradiol* 18:1529–1539.

Gaillard WD, Hertz-Pannier L, Mott SH, Barnett AS, LeBihan D, Theodore WH. (2000) Functional anatomy of cognitive development: fMRI of verbal fluency in children and adults. *Neurology* 54:180–185.

Hajek M, Valavanis A, Yonekawa Y, Schiess R, Buck A, Wieser HG. (1998) Selective amobarbital test for the determination of language function in patients with epilepsy with frontal and posterior temporal brain lesions. *Epilepsia* 39:389–398.

Hertz-Pannier L, Gaillard WD, Mott SH, Cuenod CA, Bookheimer SY, Weinstein S, Conry J, Papero PH, Schiff SJ, Le Bihan D, Theodore WH. (1997) Noninvasive assessment of language dominance in children and adolescents with functional MRI: a preliminary study. *Neurology* 48:1003–1012.

Hertz-Pannier L, Chiron C, Vera P, Van de Morteele PF, Kaminska A, Bourgeois M, Hollo A, Ville D, Cieuta C, Dulac O, Brunelle F, LeBihan D. (2001) Functional imaging in the work-up of childhood epilepsy. *Childs Nerv Syst* 17:223–228.

Hertz-Pannier L, Chiron C, Jambaque I, Renaux-Kieffer V, Van de Moortele PF, Delalande O, Fohlen M, Brunelle F, Le Bihan D. (2002) Late plasticity for language in a child's non-dominant hemisphere: a pre- and post-surgery fMRI study. *Brain* 125:361–372.

Holland SK, Plante E, Weber Byars A, Strawsburg RH, Schmithorst VJ, Ball WS Jr. (2001) Normal fMRI brain activation patterns in children performing a verb generation task. *NeuroImage* 14:837–843.

Jayakar P, Alvarez LA, Duchowny MS, Resnick TJ. (1992) A safe and effective paradigm to functionally map the cortex in childhood. *J Clin Neurophysiol* 9:288–293.

Jayakar P, Duchowny M, Resnick T. (1994) Subdural monitoring in the evaluation of children for epilepsy surgery. *J Child Neurol* 9:61–66.

Kral T, Kurthen M, Schramm J, Urbach H, Meyer B. (2006) Stimulation mapping via implanted grid electrodes prior to surgery for gliomas in highly eloquent cortex. *Neurosurgery* 58:ONS36–ONS43; discussion ONS36–43.

Kurjak A, Miskovic B, Andonotopo W, Stanojevic M, Azumendi G, Vrcic H. (2007) How useful is 3D and 4D ultrasound in perinatal medicine? *J Perinat Med* 35:10–27.

Lehericy S, Cohen L, Bazin B, Samson S, Giacomini E, Rougetet R, Hertz-Pannier L, Le Bihan D, Marsault C, Baulac M. (2000) Functional MR evaluation of temporal and frontal language dominance compared with the Wada test. *Neurology* 54:1625–1633.

Lendt M, Gleissner U, Helmstaedter C, Sassen R, Clusmann H, Elger CE. (2002) Neuropsychological outcome in children after frontal lobe epilepsy surgery. *Epilepsy Behav* 3:51–59.

Liegeois F, Connelly A, Cross JH, Boyd SG, Gadian DG, Vargha-Khadem F, Baldeweg T. (2004) Language reorganization in children with early-onset lesions of the left hemisphere: an fMRI study. *Brain* 127:1229–1236.

Muller RA, Rothermel RD, Behen ME, Muzik O, Mangner TJ, Chugani HT. (1997) Receptive and expressive language activations for sentences: a PET study. *Neuroreport* 8:3767–3770.

Ojemann GA. (1979) Individual variability in functional localization of language. *J Neurosurg* 50:164.

Ojemann JG, Ojemann GA, Lettich E. (2002) Cortical stimulation mapping of language cortex by using a verb generation task: effects of learning and comparison to mapping based on object naming. *J Neurosurg* 97:33–38.

Ojemann SG, Berger MS, Lettich E, Ojemann GA. (2003) Localization of language function in children: results of electrical stimulation mapping. *J Neurosurg* 98:465–470.

Ostrowsky K, Isnard J, Ryvlin P, Guenot M, Fischer C, Mauguiere F. (2000) Functional mapping of the insular cortex: clinical implication in temporal lobe epilepsy. *Epilepsia* 41:681–686.

Penfield W, Rasmussen T. (1950) *The cerebral cortex of man. A clinical study of localization of function*. Macmillan, New York.

Redcay E, Haist F, Courchesne E. (2008) Functional neuroimaging of speech perception during a pivotal period in language acquisition. *Dev Sci* 11:237–252.

Rorden C, Brett M. (2000) Stereotaxic display of brain lesions. *Behav Neurol* 12:191–200.

Roux FE, Boulanouar K, Lotterie JA, Mejdoubi M, LeSage JP, Berry I. (2003) Language functional magnetic resonance imaging in preoperative assessment of language areas: correlation with direct cortical stimulation. *Neurosurgery* 52:1335–1345; discussion 1345–1337.

Ruge MI, Victor J, Hosain S, Correa DD, Relkin NR, Tabar V, Brennan C, Gutin PH, Hirsch J. (1999) Concordance between functional magnetic resonance imaging and intraoperative language mapping. *Stereotact Funct Neurosurg* 72:95–102.

Rutten GJ, Ramsey NF, van Rijen PC, Noordmans HJ, van Veelen CW. (2002) Development of a functional magnetic resonance imaging protocol for intraoperative localization of critical temporoparietal language areas. *Ann Neurol* 51:350–360.

Sabsevitz DS, Swanson SJ, Hammeke TA, Spanaki MV, Possing ET, Morris GL III, Mueller WM, Binder JR. (2003) Use of preoperative functional neuroimaging to predict language deficits from epilepsy surgery. *Neurology* 60:1788–1792.

Sachs BC, Gaillard WD. (2003) Organization of language networks in children: functional magnetic resonance imaging studies. *Curr Neurol Neurosci Rep* 3:157–162.

Saltzman J, Smith ML, Scott K. (2002) The impact of age at seizure onset on the likelihood of atypical language representation in children with intractable epilepsy. *Brain Cogn* 48:517–520.

Schapiro MB, Schmithorst VJ, Wilke M, Byars AW, Strawsburg RH, Holland SK. (2004) BOLD fMRI signal increases with age in selected brain regions in children. *Neuroreport* 15:2575–2578.

Schevon C, Carlson C, Zaroff C, Weiner H, Doyle W, Miles D, Lajoie J, Kuzniecky R, Pacia S, Vazquez B, Luciano D, Najjar S, Devinsky O. (2007) Pediatric language mapping: sensitivity of neurostimulation and Wada testing in epilepsy surgery. *Epilepsia* 48:539–545.

Seeck M, Pegna AJ, Ortigue S, Spinelli L, Dessibourg CA, Delavelle J, Blanke O, Michel CM, Landis T, Villemure JG. (2006) Speech arrest with stimulation may not reliably predict language deficit after epilepsy surgery. *Neurology* 66:592–594.

Sinclair DB, Aronyk K, Snyder T, McKean J, Wheatley M, Bhargava R, Hoskinson M, Hao C, Colmers W. (2003) Pediatric temporal lobectomy for epilepsy. *Pediatr Neurosurg* 38:195–205.

Springer JA, Binder JR, Hammeke TA, Swanson SJ, Frost JA, Bellgowan PS, Brewer CC, Perry HM, Morris GL, Mueller WM. (1999) Language dominance in neurologically normal and epilepsy subjects: a functional MRI study. *Brain* 122:2033–2046.

Stanojevic M, Hafner T, Kurjak A. (2002) Three-dimensional (3D) ultrasound – a useful imaging technique in the assessment of neonatal brain. *J Perinat Med* 30:74–83.

Szaflarski JP, Holland SK, Schmithorst VJ, Byars AW. (2006) fMRI study of language lateralization in children and adults. *Hum Brain Mapp* 27:202–212.

Tatlidil R, Xiong J, Luther S. (2000) Presurgical lateralization of seizure focus and language dominant hemisphere with O-15 water PET imaging. *Acta Neurol Scand* 102:73–80.

Vargha-Khadem F, O'Gorman AM, Watters GV. (1985) Aphasia and handedness in relation to hemispheric side, age at injury and severity of cerebral lesion during childhood. *Brain* 108:677–696.

Vigneau M, Beaucousin V, Herve PY, Duffau H, Crivello F, Houde O, Mazoyer B, Tzourio-Mazoyer N. (2006) Meta-analyzing left hemisphere language areas: phonology, semantics, and sentence processing. *NeuroImage* 30:1414–1432.

Vinas FC, Zamorano L, Mueller RA, Jiang Z, Chugani H, Fuerst D, Muzik O, Mangner TJ, Diaz FG. (1997) [15O]-water PET and intraoperative brain mapping: a comparison in the localization of eloquent cortex. *Neurol Res* 19:601–608.

Wilke M, Lidzba K. (2007) LI-tool: A new toolbox to assess lateralization in functional MR-data. *J Neurosci Methods* 163:128–136.

Wilke M, Holland SK, Ball WS Jr. (2003) Language processing during natural sleep in a 6-year-old boy, as assessed with functional MR imaging. *AJNR Am J Neuroradiol* 24:42–44.

Wilke M, Lidzba K, Staudt M, Buchenau K, Grodd W, Krageloh-Mann I. (2006) An fMRI task battery for assessing hemispheric language dominance in children. *NeuroImage* 32:400–410.

Woermann FG, Jokeit H, Luerding R, Freitag H, Schulz R, Guertler S, Okujava M, Wolf P, Tuxhorn I, Ebner A. (2003) Language lateralization by Wada test and fMRI in 100 patients with epilepsy. *Neurology* 61:699–701.

Wood AG, Harvey AS, Wellard RM, Abbott DF, Anderson V, Kean M, Saling MM, Jackson GD. (2004) Language cortex activation in normal children. *Neurology* 63:1035–1044.

Yuan W, Szaflarski JP, Schmithorst V, Schapiro M, Byars A, Strawsburg RH, Holland S. (2006) fMRI shows atypical language lateralization in pediatric epilepsy patients. *Epilepsia* 47:593–600.