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Functional MRI in Patients with Band Heterotopia

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Functional activation associated with a motor task (fist movements) was studied in three patients with band heterotopias by fMRI. In two patients, additional visual fMRI studies were performed using a flickering checkerboard stimulus. In all patients activation of the outer cortex and of the inner neuronal band could be found during performance of the motor task. Visual stimulation elicited a normal activation pattern without activation of the ectopic neuronal layer in one patient; in another patient activation extended toward the ventricular wall, i.e., along the route of embryonic neuronal migration. The potential participation of ectopic neuronal tissue in physiologic cerebral functions is of clinical impact in patients with neuronal heterotopias suffering from medically intractable seizures prior to epilepsy surgery. © 2001 Academic Press

Key Words: **fMRI; double cortex; laminar heterotopia.**

INTRODUCTION

Laminar or band heterotopias, also called "double cortex syndrome", represent a rare neuronal migration disorder characterized by bilateral ribbons of subcortical gray matter separated from the cortex and from the ventricular walls by white matter (Friede, 1989; Palmini *et al.*, 1991; Barkovich *et al.*, 1989). This developmental anomaly was first described by Matell in 1893 (Matell, 1893). Clinically, patients with band heterotopias present with epileptic seizures, variable degrees of mental retardation, and usually mild neurological signs and symptoms (Palmini *et al.*, 1991; Barkovich *et al.*, 1994).

Little is known about the connectivity and function of the heterotopic neurons. By depth electrode recordings nerve cells within band heterotopias have been shown to exhibit electrogenic patterns similar to those observed in normal cortex (Morell *et al.*, 1992). Metabolic studies with positron emission tomography (PET) revealed normal or even higher glucose utilization in band heterotopias compared to normal cortex (de Volder *et al.*, 1994). However, no activation of periventricular laminar heterotopias during motor and visual tasks was found in a PET activation study by Richardson *et al.* (1998). In contrast, only recently Pinard *et al.* (2000) could demonstrate fMRI activation associated with fingertapping in the subcortical band and the overlying frontal cortex in a single patient with double cortex syndrome.

Patients with disorders of neuronal migration frequently suffer from seizures, which may be medically intractable. Some of these patients may profit from a surgical resection of epileptogenic heterotopias. Therefore knowledge of participation of ectopic neuronal tissue in physiologic cerebral functions is of potential clinical impact.

In the present study brain activation associated with a motor task and visual stimulation was studied in three patients with band heterotopias by functional MRI to further elucidate the function of the cortical and subcortical neuronal tissue.

PATIENTS AND METHODS

Two female patients and one male patient were studied. All patients were informed about the general aims of the study and only participated after giving their informed consent. All patients suffered from seizures since late childhood. Anticonvulsive drugs can affect neuronal activity and cerebral blood flow and thus could influence the results. The clinical data of the patients and the anticonvulsants used during the period of examination are listed in Table 1.

In all patients structural MRI was performed on a 1.5 T scanner (Magnetom Vision) with T1-weighted (TR 650 ms, TE 15 ms, matrix 256 × 256) and T2-weighted (TR 5000 ms, TE 120 ms, matrix 512 × 512) spinecho sequences and T1-weighted inversion recovery sequences (TR 9994 ms, TE 60 ms, T1 350 ms, matrix 256 × 256) in two planes (slice thickness 6 mm, interslice gap 0.6 mm, FoV 230 mm). The fMRI studies were performed in a second session with multislice gradient-echo echoplanar imaging (EPI) sequences (TE 66 ms; TR 5 s for the motor paradigm, 4 s for the visual paradigms; matrix 128 × 128, FoV 256 mm). For anatomic correlation a T1-weighted 3-D magnetization

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TABLE 1

Summary of Clinical Data and MRI Findings

	Patient 1 (B.O.)	Patient 2 (A.M.)	Patient 3 (K.H.)
Age/Sex	19 years, female	25 years, female	42 years, male
Age at seizure onset	9 years	13 years	9 years
Neurological/neuro-ophthalmological findings	Normal	Increased reflexes on the right, strabismus, amblyopia (right eye)	Pendular nystagmus, mild ataxia
Handedness (EI)	Relearned from left to right	Definitely right	Definitely right
IQ	79	76–79	76
Family history	No neuropsychiatric disorders	No neuropsychiatric disorders	No neuropsychiatric disorders
MRI	Asymmetric band heterotopia (1 > r), normal gyral pattern	Asymmetric band heterotopia (1 > r), mild pachygyria, pronounced on the left	Symmetric band heterotopia, symmetric severe pachygyria
Seizure type	GTCS, CPS, SPS, ATS	GTCS, CPS, PMS	GTCS, CPS, TS, MS
Interictal surface EEG	Background activity 8–9/s; generalized theta-waves; paroxysms of slow waves with spiky discharges	Background activity 5/s; bisynchronous paroxysms of sharp and sharp slow waves	Background activity 6/s; bisynchronous paroxysms of slow waves; multifocal spikes and sharp waves
Anticonvulsive drugs	LTG, CBZ	PB, CBZ, VPA	GP, CBZ, CLZ

Note. Abbreviations: EI, Edinburgh Inventory (Oldfield, 1973); IQ, Intelligence quotient (WAIS). Seizure types: ATS, atonic seizures; CPS, complex partial seizures; GTCS, generalized tonic clonic seizures; MS, myoclonic seizures; SPS, simple partial seizures; PMS, partial motor seizures; TS, tonic seizures. Anticonvulsive drugs: LTG, Lamotrigine; CBZ, Carbamazepine; PB, Phenobarbital; VPA, Sodium valproate; GP, Gabapentin; CLZ, Clonanzepam.

prepared rapid acquisition gradient echo (MP-RAGE) sequence (TR 9, 7 ms, TE 4 ms, TI 300 ms, flip angle 12°) with isotropic 1-mm^3 voxels was acquired.

All three patients performed a motor paradigm consisting of bilateral fist movements versus rest as a control condition. The beginning of every epoch was marked by the acoustically given command start or stop. In two patients additionally the visual system was examined using a flickering checkerboard stimulus.[1] The paradigms were arranged as block designs with four (motor task) or five (visual task) alternating task and control conditions. Every block consisted of four (motor task) or eight (visual task) measurements. The motor paradigm was explained and trained outside the scanner room prior to the examination.

The functional data were transferred to a PC and evaluated using Brain Voyager software (Göbel *et al.*, 1998). The functional 2-D slices were transformed into functional 3-D volumes by interpolating the original voxels to isotropic 1-mm^3 voxels. After 3-D motion correction, temporal smoothing and elimination of linear drifts a correlation analysis with a boxcar reference was performed. The functional maps ($r > 0.5$) were superimposed onto the anatomical data sets and resliced in orthogonal planes. Activation of the inner band was determined by visual inspection in different planes and by analysis of the time series in activated areas.

[1] The third patient was not studied by visual stimulation, because at the time of his examination we did not have a visual stimulation device. All three patients live in different parts of Germany. They came to our institution (Epilepsy center) for short-term evaluation of anticonvulsant therapy. Unfortunately the patient did not agree to return to Freiburg for a further examination.

RESULTS

Imaging revealed circumferential broad layers of ectopic neurons in the white matter of the cerebral hemispheres. In the male patient the ectopic neuronal bands were broad and nearly symmetric in both hemispheres. In the two female patients the double cortex was pronounced on the left side. The overlying cerebral cortex showed generalized severe pachygyric deformation in the male patient. In one of the female patients there was mild pachygyria pronounced in the left hemisphere. In this patient the ectopic band was broader than in the third patient, who had a normal gyral pattern (Figs. 1a–1c).

The motor task resulted in focal cortical activation in both hemispheres in all three patients. The activation in the two female patients was localized in the cortical sensorimotor area around the central sulcus. In the male patient the central sulcus could not be identified morphologically due to the pachygyria. The cortical activation in this subject was localized in an equivalent area in the frontoparietal borderzone. In all three patients additional foci of activation were found in the heterotopic neuronal layer medial and caudal to the activated overlying cortical areas (Figs. 2–4).

Visual stimulation with the flickering checkerboard elicited widespread activation of the cortical visual areas V1 to V5 in both patients studied. In the patient with the smallest ectopic layer, activation was re-

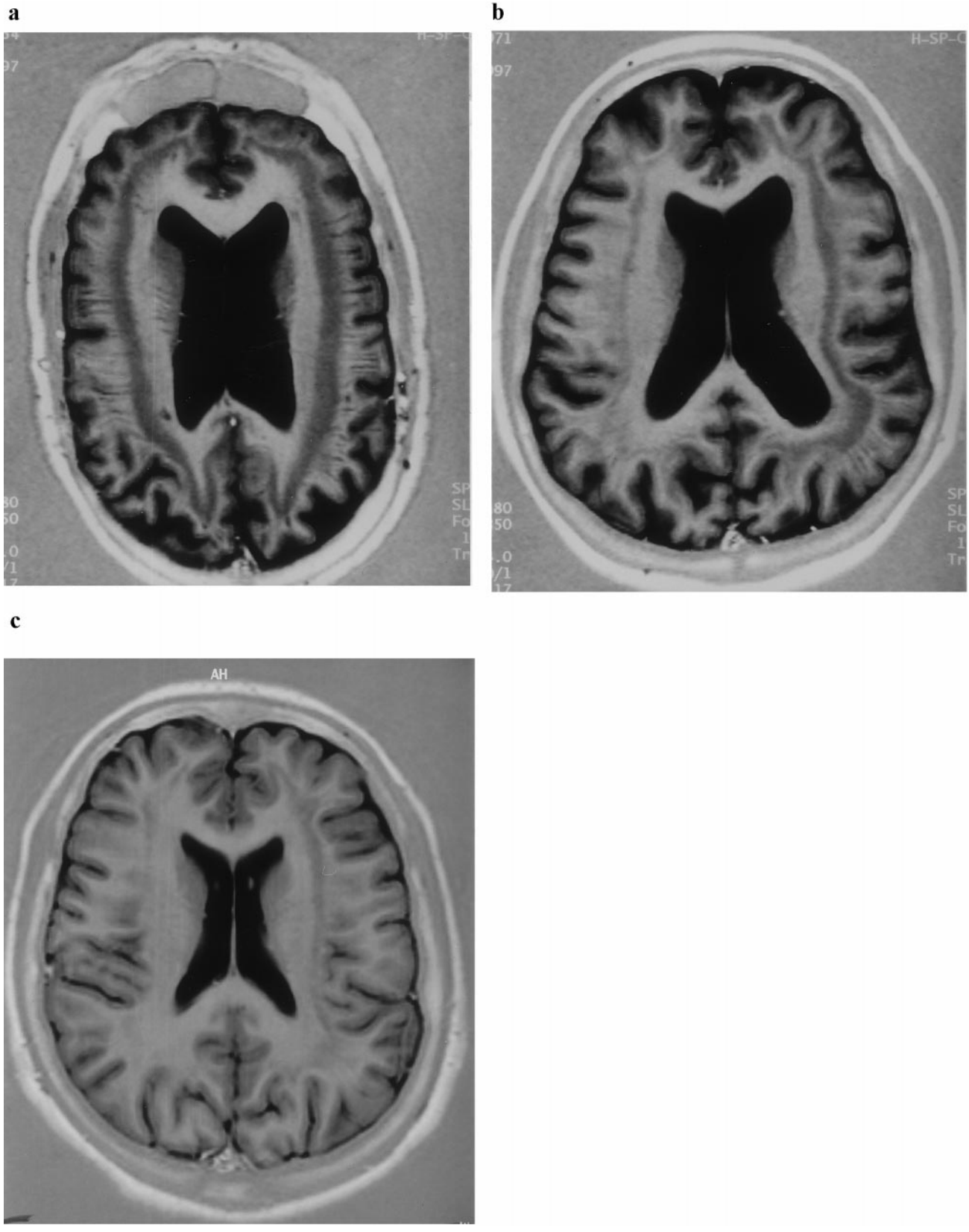
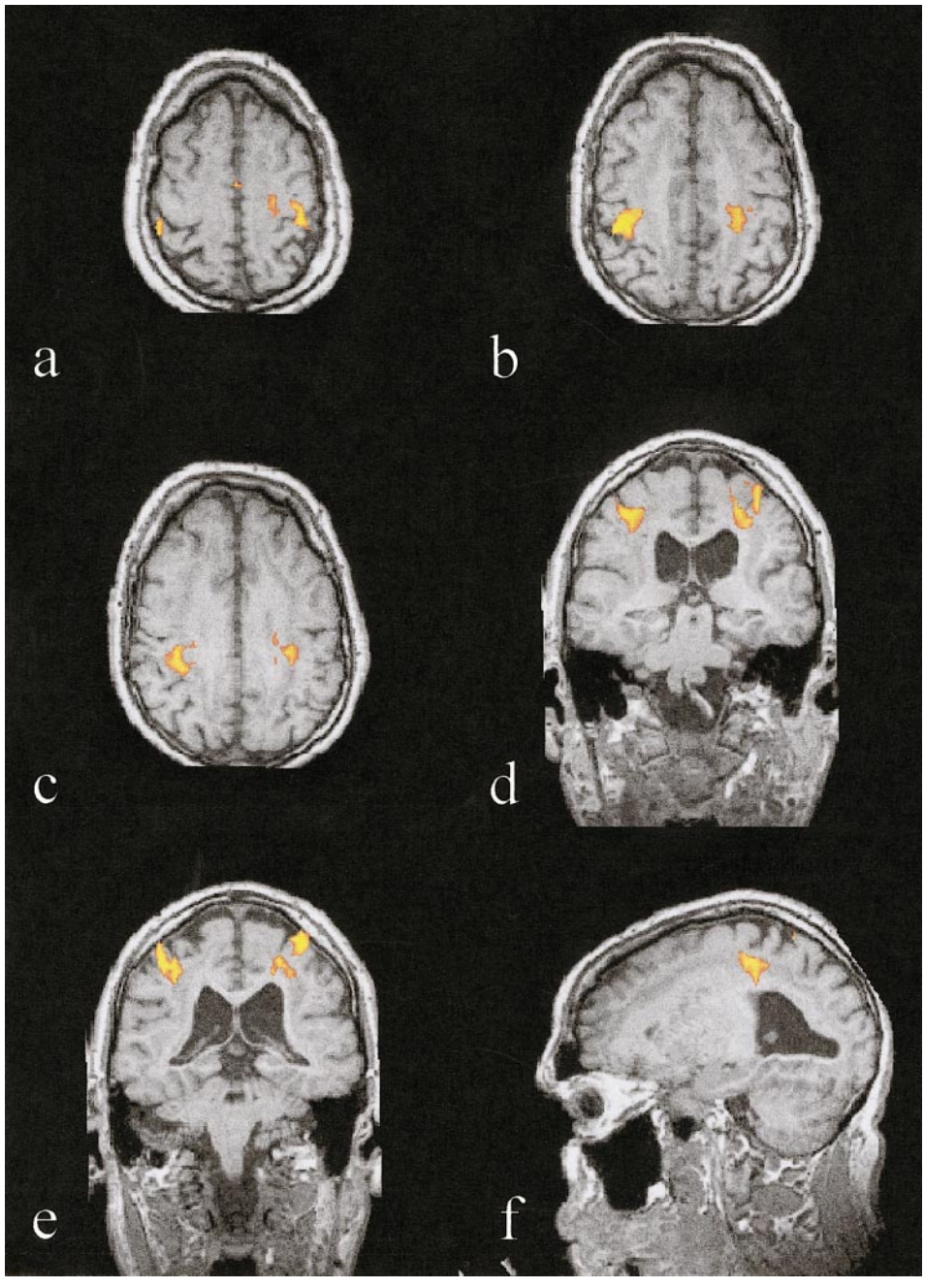


FIG. 1. Structural MRIs of the three patients with laminar heterotopias (T1-w. inversion recovery sequence, for technical parameters see text) show bands of ectopic neuronal tissue in the white matter of the cerebral hemispheres which are broader on the left in the both female patients (b, c). Note additional severe generalized pachygyria in the male patient (a) and mild pachygyric deformation in one of the female patients (b); in the third patient (c) the gyral pattern is normal.

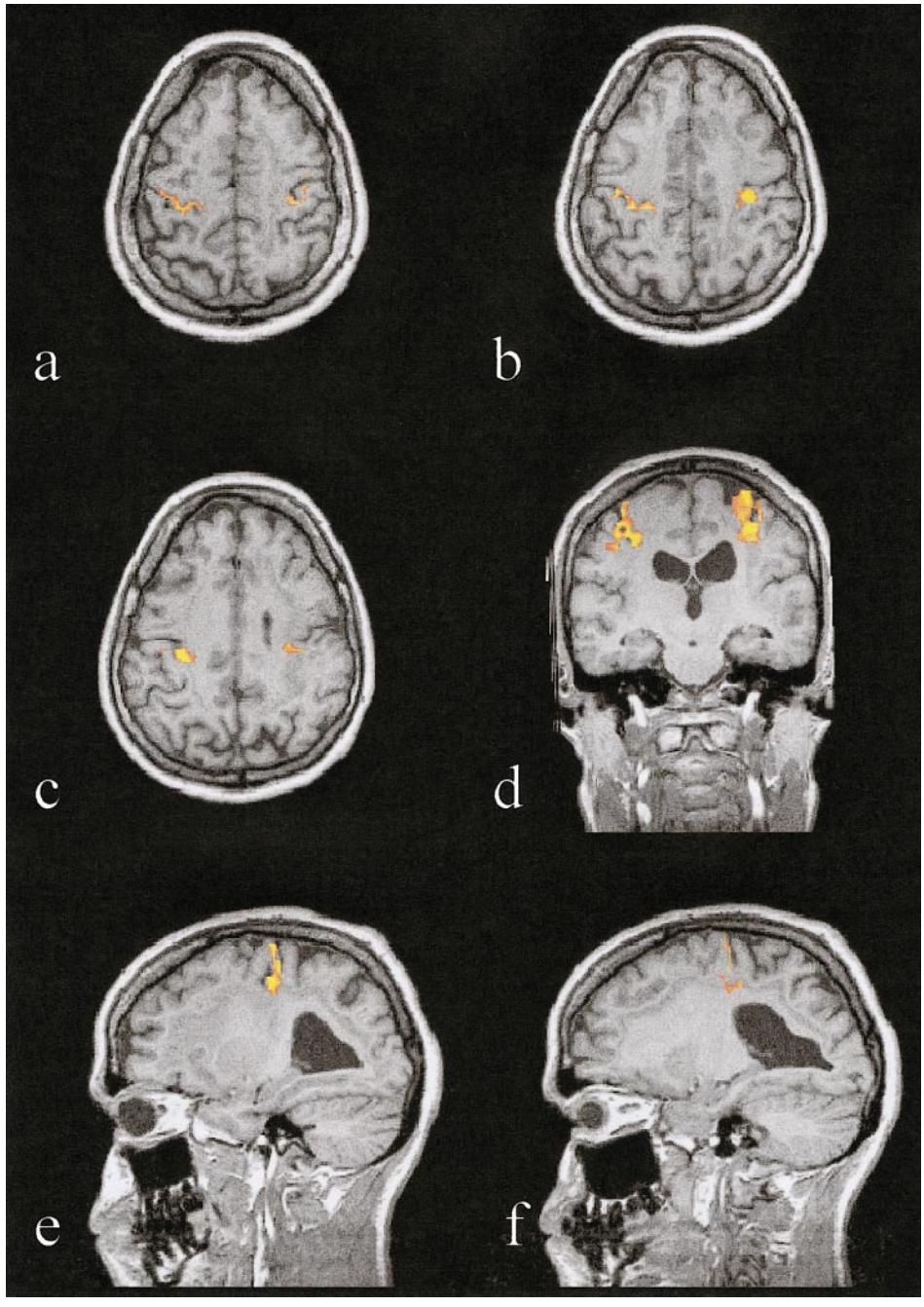


FIGS. 2–4. FMRI activation induced by bilateral fist movements. In all patients the outer primary sensorimotor cortex is activated and additional activation foci are seen in the inner neuronal band. Results are shown from Pat. 1 (Figs. 2a–f), Pat.2 (Figs. 3a–f) and Pat. 3 (Figs. 4a–f). In Figs. 4g and 4h time courses of activation in the areas marked by yellow squares in Figs. 4a and 4c are shown.

stricted to the outer cortex. In the other patient, activation extended from the outer cortex through the white matter toward the wall of the occipital horns (Fig. 5). However, since the ectopic neuronal band faded out, leaving only the outer cortex toward the occipital poles, the two layers in this region were not clearly distinguishable even in the anatomical images. No ectopic neuronal tissue could be identified between the outer cortex and the ventricle, nor were there nodular heterotopias in the ventricular wall. In the periventricular "activations" the level of significance was lower and the time-course series less regular than in the outer cortex (Figs. 5i and 5j).

DISCUSSION

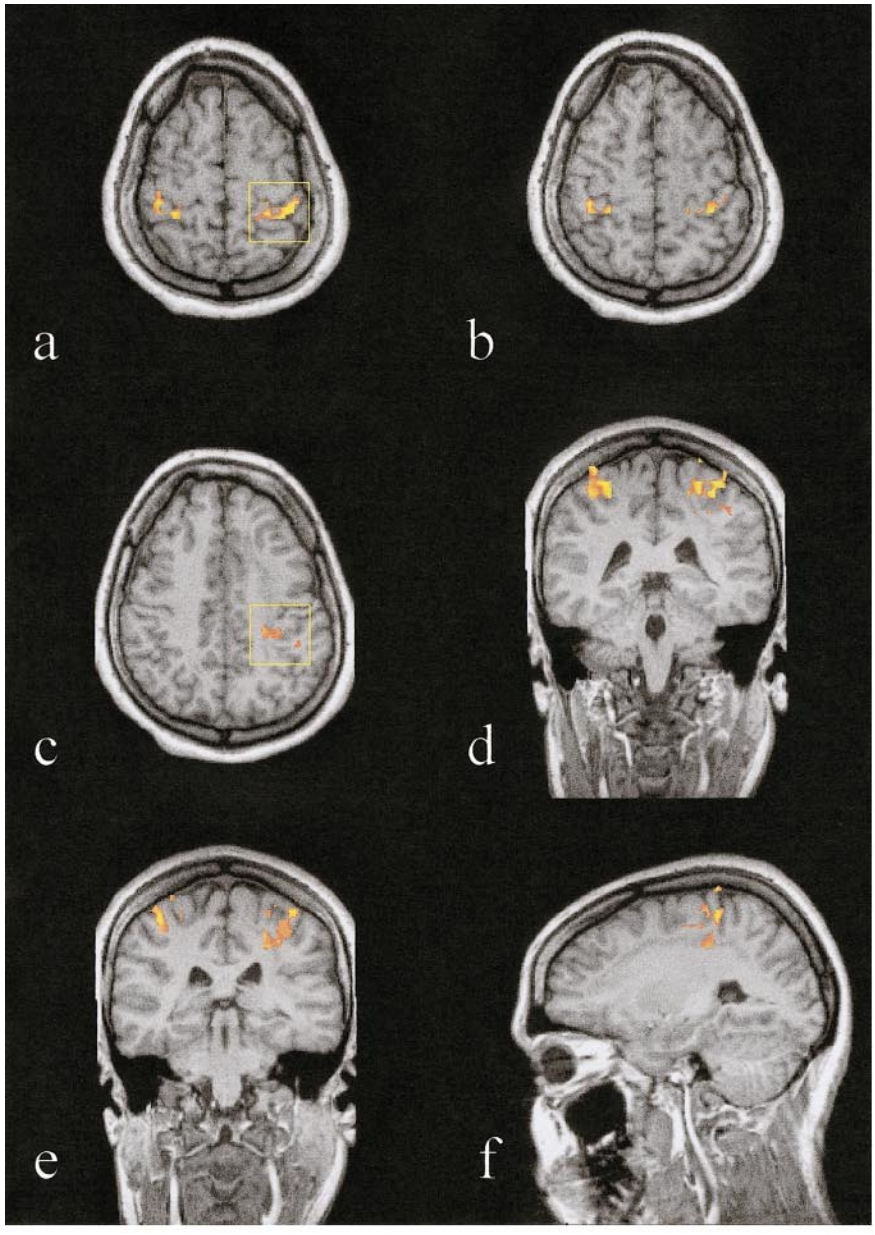
This fMRI study in patients with band heterotopias revealed task related blood oxygen level dependent

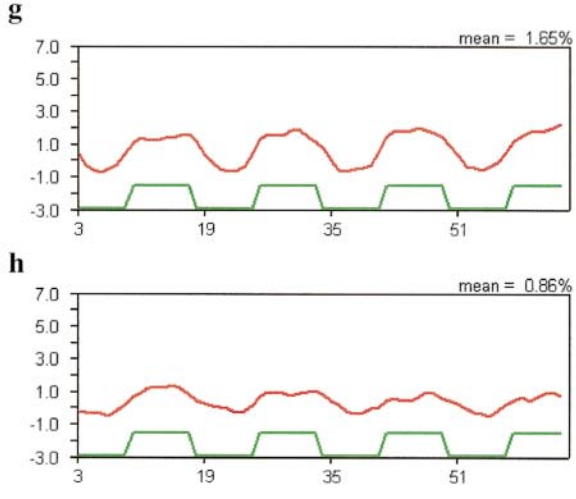


FIGS. 2–4—*Continued*

(BOLD) contrast in cortical areas adjacent to the heterotopic band and additional activation of the inner ectopic gray layer during performance of the motor task in all subjects. In one of the two patients studied with visual stimulation, activation extended from the outer cortex toward the wall of the occipital horns of the lateral ventricles, i.e., along the embryologic route of neuronal migration.

In the developing brain cortical neurons are generated predominantly in the subventricular zone. Guided by specialized radial glial fibers (Gadisseux and Evrard, 1985; Barkovich *et al.*, 1992) the neurons migrate to their cortical destination site to form the six-layered neocortex with a peak incidence during the 8th to 24th week of gestation (Rakic, 1972; Volpe, 1995). Periventricular laminar heterotopias result from a migrational arrest during this critical period of brain development. Histologically, the heterotopic band primarily consists of small pyramidal cells, which are randomly arranged in the outer segment and exhibit a





FIGS. 2–4—*Continued*

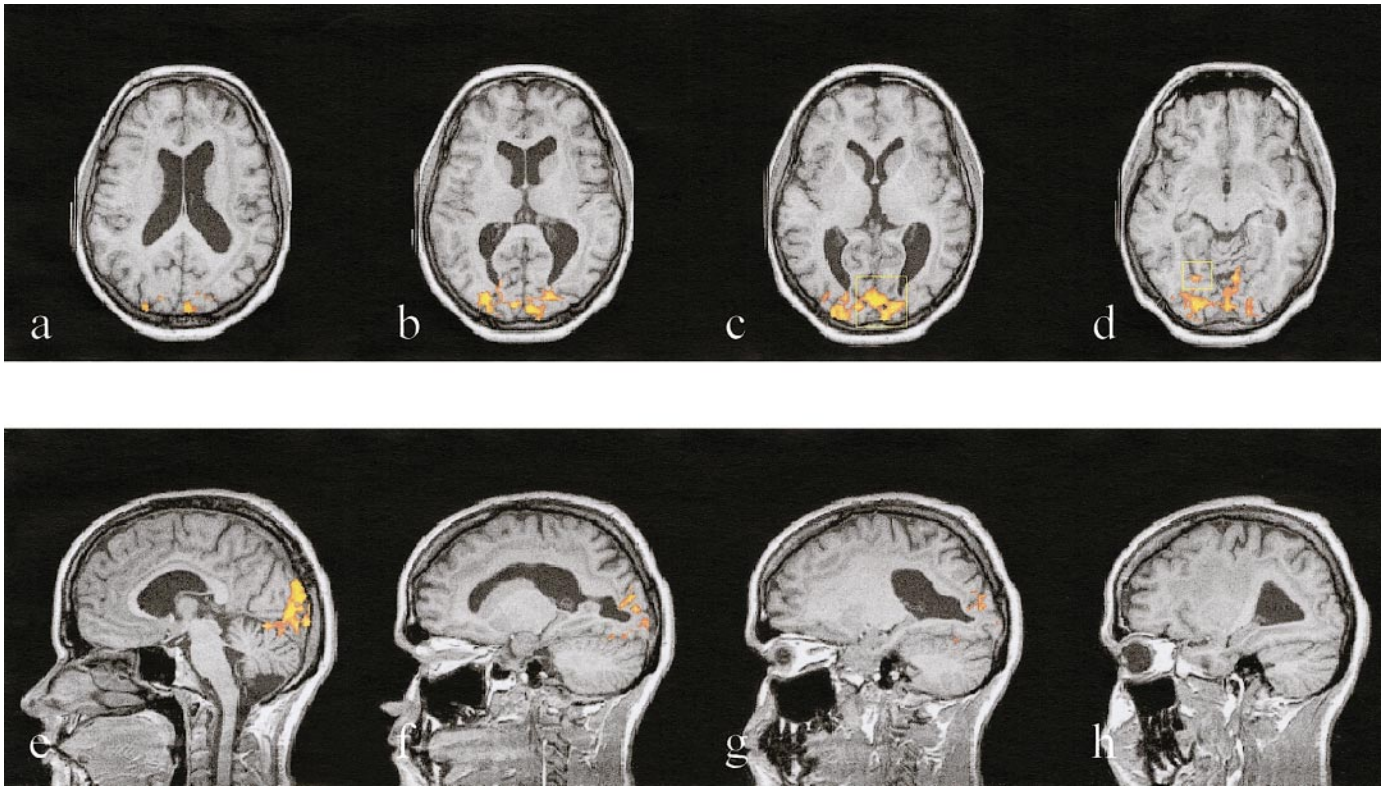


FIG. 5. Axial (a–d) and sagittal (e–h) views of visual activation induced by stimulation with a flickering checkerboard in Pat.2. Some evidence for ectopic activation can be seen in parts of visual cortex. Time courses of activation are shown for the outer cortex (i) and periventricular regions (j).

columnar organization in the inner segment of the band (Harding, 1996). The cortex overlying the heterotopic lamina in most cases has a normal six layered pattern, but an abnormal four layered cortex may be found (Friede, 1989). Macroscopically, it may be normal or exhibit a disturbed gyral pattern (Friede, 1989; Pinard *et al.*, 1994). The distribution and thickness of the heterotopic neuronal band may vary from patient to patient. Frequently it is thickest in the posterior frontal and parietal lobes (Barkovich *et al.*, 1994).

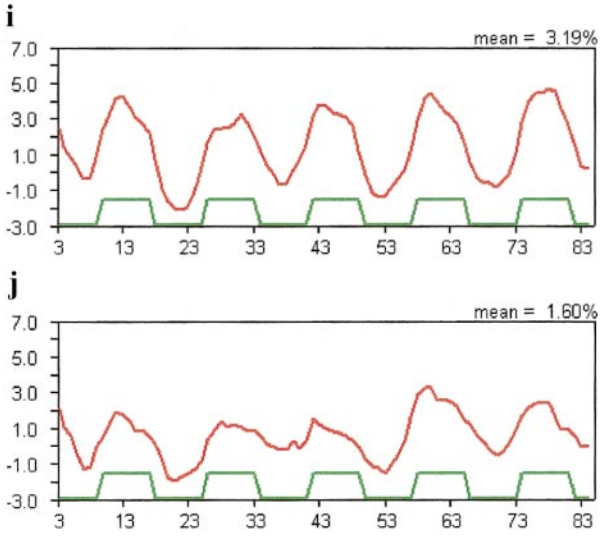


FIG. 5—*Continued*

Neuropathological studies suggest that laminar heterotopias and pachygyria/agyria are related developmental disorders. This assumption is supported by genetic findings indicating that band heterotopias and pachygyria/agyria share the same X-linked dominant gene (Pinard *et al.*, 1994). Des Portes *et al.* (1998) and Gleeson *et al.* (1998) could map this gene to a small region on the short arm of the X-chromosome and called it doublecortin. The doublecortin gene is highly expressed in neurons and their precursors during fetal brain development. Due to the X-linked inheritance males are affected more severely by mutations of this gene and may develop classic lissencephaly while heterozygous females express milder phenotypes of subcortical band heterotopia. Accordingly, in the single male of our patient sample the double cortex was accompanied by a severe generalized pachygyria. One of the female patients had delineated pachygyric foci and the other had a normal gyral pattern.

Several previous studies point to a participation of heterotopic neuronal tissue in physiologic cerebral functions. Morell *et al.* (1992) reported on depth elec-

trode recordings from ectopic cell populations in subcortical heterotopias that revealed electrogenic patterns similar to those observed in the normal cortex in addition to organized epileptiform activity arising from the ectopic gray matter. Several PET studies could demonstrate normal or increased glucose utilization at rest compared with normal cortex in nodular and laminar heterotopias (Miura *et al.*, 1993; Lee *et al.*, 1994; de Volder *et al.*, 1994; Morioka *et al.*, 1999). In a recent $H_2(15)O$ PET activation study patients with band heterotopias showed activation of the cortex overlying the ectopic gray matter, but not of the heterotopic band, while performing visual attention and motor learning tasks (Richardson *et al.*, 1998). However, in some patients with nodular heterotopias task related activation could be detected (Richardson *et al.*, 1998; Calabrese *et al.*, 1995). Only recently, Pinard *et al.* (2000) were the first to describe activation of the ectopic neuronal band and the overlying cortex during finger-tapping in a patient with double cortex syndrome by fMRI.

In our fMRI study activation of the heterotopic neuronal tissue adjacent to the hand area in sensorimotor cortex could be found in all three patients while performing bilateral fist movements.

In both patients who were studied by visual stimulation the double cortex was broadest in frontoparietal regions and smallest in the occipital lobes adjacent to the outer visual cortex. In one of the two patients activation extended from the outer cortex toward the wall of the occipital horns of the lateral ventricles, although in this region in the anatomical images no ectopic neuronal tissue could be depicted. The extracortical activation pattern resembles the route of the embryologic neuronal migration. Thus, it could be speculated that in this case ectopic neurons, scattered within the macroscopically normal white matter and ventricular wall, participated in the visual task.

The results of animal studies with mutations affecting neuronal migration have shown differences in neuronal function and connectivity depending on the type of genetic alteration. In the reeler mouse mutation, that shows a widespread neuronal migration deficit, abnormally positioned neurons find their normal targets (Stanfield *et al.*, 1979; Nowakowski, 1987). Normal information processing of these connections has been shown in the visual cortex (Dräger, 1976; Lemmon and Pearlman, 1981; Simmons *et al.*, 1983; Nowakowski, 1987), but not in other brain regions of the reeler mouse (Devor *et al.*, 1975; Nowakowski, 1987). In other mouse models with disturbances of neuronal migration confined to the hippocampus (Nowakowski and Davis, 1985) or the cerebellum (Nowakowski and Wahlsten, 1985; Nowakowski, 1987) axons of normally positioned neurons do not reach their abnormally seated targets. Thus, the connectivity of heterotopic neurons may differ even within different regions of the same brain. Therefore it seems reasonable that only parts of the ectopic neurons in double cortex syndrome participate in physiologic cerebral functions while others do not.

In the present study, only motor and sensory paradigms were applied. Further studies are mandatory to elucidate whether the ectopic layer in patients with band heterotopias also participates in "higher" cognitive functions such as language.

The potential participation of heterotopic neurons in physiologic cerebral functions is of clinical impact in patients with migrational disorders suffering from medically intractable seizures. Some of these patients may profit from a surgical resection of the heterotopias. FMRI is a promising tool to study the function of the malformed regions and thus may help to avoid postoperative deficits.

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