Functional MRI in Patients with Band Heterotopia

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Received October 12, 2000; published online May 30, 2001

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.

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) spin echo 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 echo planar 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
prepared rapid acquisition gradient echo (MP-RAGE) sequence (TR 9, 7 ms, TE 4 ms, TI 300 ms, flip angle 12°) with isotropic 1-mm³ 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.

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-mm³ 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.

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).

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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 there were 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).

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.
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
(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
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).

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-
trod recordings from ectopic cell populations in sub-
cortical heterotopias that revealed electrogenic pat-
terns 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 lam-
inar heterotopias (Miura et al., 1993; Lee et al., 1994;
de Volder et al., 1994; Morioka et al., 1999). In a recent
H₂(15)O PET activation study patients with band het-
erotopias 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 pa-
tients with nodular heterotopias task related activa-
tion could be detected (Richardson et al., 1998; Cala-
br ese et al., 1995). Only recently, Pinar d et al. (2000)
were the first to describe activation of the ectopic neu-
ronal band and the overlying cortex during finger-tap-
ing in a patient with double cortex syndrome by fMRI.

In our fMRI study activation of the heterotopic neu-
ronal tissue adjacent to the hand area in sensorimotor
cortex could be found in all three patients while per-
foming bilateral fist movements.

In both patients who were studied by visual stimu-
lation 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 extra-
cortical activation pattern resembles the route of the
embryologic neuronal migration. Thus, it could be spe-
culated 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 affect-
ing neuronal migration have shown differences in neu-
ronal 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 tar-
gets (Stanfield et al., 1979; Nowakowski, 1987). Nor-
mal information processing of these connections has
been shown in the visual cortex (Dräger, 1976; Lem-
mon and Pearlman, 1981; Simmons et al., 1983; Nowa-
kowski, 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 oth-
ers do not.

In the present study, only motor and sensory para-
digms were applied. Further studies are mandatory to
elucidate whether the ectopic layer in patients with
band heterotopias also participates in “higher” cogni-
tive 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.
FMRl is a promising tool to study the function of the
malformed regions and thus may help to avoid postop-
erative deficits.

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