Sensorimotor Organization in Double Cortex Syndrome

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Abstract: Subcortical band heterotopia is a diffuse malformation of cortical development related to pharmacologically intractable epilepsy. On magnetic resonance imaging (MRI), patients with “double cortex” syndrome (DCS) present with a band of heterotopic gray matter separated from the overlying cortex by a layer of white matter. The function and connectivity of the subcortical heterotopic band in humans is only partially understood. We studied six DCS patients with bilateral subcortical band heterotopias and six healthy controls using functional MRI (fMRI). In controls, simple motor task elicited contralateral activation of the primary motor cortex (M1) and ipsilateral activation of the cerebellum and left supplementary motor area (SMA). All DCS patients showed task-related contralateral activation of both M1 and the underlying heterotopic band. Ipsilateral motor activation was seen in 4/6 DCS patients. Furthermore, there were additional activations of nonprimary normotopic cortical areas. The sensory stimulus resulted in activation of the contralateral primary sensory cortex (SI) and the thalamus in all healthy subjects. The left sensory task also induced a contralateral activation of the insular cortex. Sensory activation of the contralateral SI was seen in all DCS patients and secondary somatosensory areas in 5/6. The heterotopic band beneath SI became activated in 3/6 DCS patients. Activations were also seen in subcortical structures for both paradigms. In DCS, motor and sensory tasks induce an activation of the subcortical heterotopic band. The recruitment of bilateral primary areas and higher-order association normotopic cortices indicates the need for a widespread network to perform simple tasks. *Hum Brain Mapp* 27:535–543, 2006. © 2006 Wiley-Liss, Inc.

Key words: functional MRI; malformations of cortical development; epilepsy; heterotopia

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INTRODUCTION

Malformations of cortical development occurring as a result of neuronal migration defects during the second trimester of fetal development [Palmini, 2000; Rakic, 1988] are a prominent cause of abnormal neurological development and

epilepsy in humans. Subcortical band heterotopia, or so-called “double cortex,” is a diffuse malformation in which patients present frequently with pharmacologically intractable seizures and have cognitive abilities that range from normal to severe mental retardation. Seizure frequency and severity is variable, but often epilepsy begins in childhood, with multiple seizure types that are difficult to control [Guerrini and Carrozzo, 2002]. About one-third of patients with double cortex syndrome (DCS) present with an association of tonic clonic and myoclonic seizures with atypical absences and drop attacks [Palmini et al., 1991], others present with clinical signs suggesting focal partial epilepsy [Bernasconi et al., 2001]. Epileptic abnormalities are usually characterized by generalized spike-and-wave or multifocal

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TABLE I. Demographic, clinical, electrophysiological, neuroimaging and genetic data of six patients with double cortex syndrome

Patient no.	Gender	Age (yr)	Age at seizure onset (yr)	Seizure types	Examination/neuropsychology	EEG	MRI	Genetics
1	F	19	13	SPS, CPS, SG	Normal exam/average IQ	I: temporal, L>; R II: temporal, bil.	Diffuse SBH, L >> R	n.a.
2	M	15	4	CPS, SG	Normal exam/average IQ	I: generalized II: generalized	Posterior quadrant SBH, symmetric	n.a.
3	F	11	8	CPS, SG	Normal exam/mildly-deficient IQ	I: generalized and temporo-parietal, L II: temporo-parietal, L	Diffuse SBH, symmetric	DCX mutation
4	F	50	10	SPS, CPS	Normal exam/mildly-deficient IQ	I: fronto-temporal, R II: fronto-temporal, R	Diffuse SBH, symmetric	DCX mutation
5	F	26	1	SPS, CPS	Normal exam/mildly-deficient IQ	I: generalized II: generalized	Diffuse SBH, symmetric	DCX mutation
6	F	19	14	CPS	Normal exam/average IQ	I: generalized and temporo-parietal L and R II: n.a.	Diffuse SBH, R > L	n.a.

Bil., bilateral; CPS, complex partial seizures; DCX, doublecortin gene; I, interictal epileptic abnormalities; II, seizure onset; L, left; n.a., not available; R, right; SBH, subcortical band heterotopia; SG, secondary generalized seizures; SPS, simple partial seizures.

spiking [Palmini et al., 1991]. Electrophysiological studies using intracerebral recordings [Bernasconi et al., 2001; Morrell et al., 1992] and magnetoencephalographic studies [Toulouse et al., 2003] done in patients with DCS have shown that both the heterotopic and normotopic cortices are involved in the genesis of interictal epileptic spikes. On MRI, DCS is characterized by a band of subcortical heterotopic gray matter separated from the overlying (normotopic) cortex by a layer of white matter. The heterotopic band is sometimes asymmetrical and of variable thickness and is generally most obvious in fronto-centro-parietal regions [Barkovich et al., 1994]. Histologically, the subcortical band consists of clusters of unlaminated ganglion cells with a variable degree of columnar organization [Harding, 1996]. Mutations in the doublecortin gene, or more rarely the LIS1 gene, are important in the pathogenesis of DCS [Gleeson, 2000].

The function and connectivity of the subcortical heterotopic band is only partially understood. Tracer studies that examined the thalamocortical connections in the somatosensory system of the *tish* mutant rat model of “double cortex” have shown that both neurons in the normotopic cortex and those in the heterotopic band establish topographically organized bidirectional connections with the thalamus [Schottler et al., 1998], suggesting that primary sensorimotor information is represented in a parallel manner in both cortices. In this model, mechanical stimulation of a single whisker elicited enhanced uptake of (14-C) 2-deoxyglucose in appropriate barrel columns of both normotopic and heterotopic gray matter [Schottler et al., 2001].

Functional imaging studies in humans have been sparse and have provided conflicting results. A study using magnetoencephalography showed that the heterotopic neurons participate in processing somatosensory and auditory stim-

uli [Toulouse et al., 2003]. Functional magnetic resonance imaging (fMRI) studies have shown motor activation of the heterotopic band underneath the primary motor cortex in a few DCS cases [Draganski et al., 2004; Iannetti et al., 2001; Pinard et al., 2000; Spreer et al., 2001]. On the other hand, a [¹⁵O] H₂O positron emission tomography (PET) study of complex cognitive and motor learning tasks [Richardson et al., 1998] in two DCS patients and a visual fMRI study [Spreer et al., 2001] failed to show significant activation of the heterotopic band. To date there have been no fMRI studies specifically dedicated to the evaluation of the somatosensory function in DCS patients. Moreover, it is unclear whether sensorimotor organization of the normotopic cortex in DCS involves only primary areas or a more widespread network.

The aim of the present study was to investigate the motor and somatosensory function in patients with DCS using fMRI.

SUBJECTS AND METHODS

Subjects

We studied six right-handed patients with DCS (5 females; mean age 23 years) and six right-handed healthy control subjects (4 females; mean age 25 years). Four patients were investigated at the Montreal Neurological Institute (MNI) and two at the Istituto Nazionale Neurologico Carlo Besta in Milan, Italy. All had been seizure-free for at least 48 hours prior to the MRI experiments. The ethics committee of both institutions approved the study and written informed consent was obtained from each patient prior to the fMRI.

Demographic, clinical, electrophysiological, and neuroimaging data of the patients are summarized in Table I. All patients had intractable epilepsy with multiple seizure types

except for Patient 6, whose seizures were more easily controlled with medication. Three patients had mild to moderate cognitive deficits, while the others had a normal neuropsychological evaluation. All patients had otherwise normal neurological examinations. Genetic testing showed that three individuals had the doublecortin mutation, while three others declined testing.

All patients had routine scalp EEG recordings and video-EEG telemetry was performed in all, except Patient 6. Interictal epileptic discharges were generalized in Patients 2, 3, 5, and 6. Patients 1, 3, 4, and 6 also had lobar or multilobar abnormalities. Focal seizure onset was seen in Patients 3 and 4, and more diffuse changes at seizure onset were present in the others.

Experimental Design

The motor task consisted of active, acoustically cued fingers-to-thumb opposition. Brief training was given outside the scanner before the fMRI experiment to verify the compliance of the patient and the absence of mirror movements. During scanning, the task was paced by a metronome at 1.5 Hz to control for differences in movement repetition rate and type of pacing stimuli that may influence the BOLD signal [Jancke et al., 1998, 2000]. This pace was also chosen because all patients could perform it efficiently. Compliance during scanning was monitored visually by an observer standing next to the patient throughout the fMRI exam to further ensure accurate task performance and the absence of head or any other movements. We did not observe any mirror movement during the performance of the motor task in any patient.

The sensory stimulus consisted of light manual brushing at approximately 2 Hz using a 4-cm wide soft brush moving back and forth in a proximal-distal direction over the skin of the palm and fingers. For each subject the sensory stimulus was practiced in a preliminary session prior to scanning to ascertain that brush stimuli did not induce a painful sensation.

Data Acquisition

Blood oxygen level-dependent (BOLD) fMRI images were obtained on a 1.5 T Siemens Vision scanner using a T_2^* -weighted gradient echo-planar imaging sequence (TR = 3 s, TE = 50 ms, matrix = 64×64 mm, FOV = 320 mm, for 20×5 mm slices positioned along the AC/PC line and covering the whole brain). Two runs of 100 volumes each were obtained sequentially for right and left motor tasks and sensory stimuli. Each run was performed using a block design, in which the task was alternated with rest periods in 30-s blocks.

High-resolution T_1 -weighted anatomical scans were acquired for all patients in the same session using a T_1 -fast field echo sequence (TR = 18 ms, TE = 10 ms, one acquisition average pulse sequence, flip angle = 30° , matrix = 256×256 , FOV = 256, thickness = $1 \times 1 \times 1$ mm).

For immobilization of the head, we used a vacuum bag (50 $\times$ 70 cm, 10-L fill) filled with small polystyrene beads (S&S X-ray Products, Brooklyn, NY).

Motion Correction

Before generating the activation maps, motion correction was performed using in-house software to realign images. A Gaussian filter of 6 mm full width at half maximum (FWHM) was applied to the data and each frame was registered to the third frame in the respective run.

To assess potential movements during the fMRI, we checked the log file produced by the motion correction algorithm in all subjects. In general, frames for which translations and rotations were ≥ 1 –2 mm were excluded from the analysis. In our analysis, translations and rotations in x-, y-, and z-axes ranged from 0.3–0.5 mm, indicating that the subjects were still during the exam.

Data Analysis

Image processing and statistical analysis were done using fMRISTAT-MULTISTAT software developed at the MNI [Worsley et al., 2002]. Statistical analysis was based on a linear model with correlated errors [Worsley et al., 2002]. For each run the design matrix of the linear model was first convolved with a gamma hemodynamic response function with a mean lag of 6 s and a standard deviation of 3 s [Lange and Zeger, 1997]. It has been recently shown that, even though fMRI in single trials may have low reproducibility, the fMRI reproducibility can indeed be improved by averaging the result over a number of trials [Liu et al., 2004]. We checked each single run in each subject and found that the location of activation areas were consistent within subjects. The runs were then combined using another linear model for the run effects, weighted inversely by the square of their standard errors. A hierarchical random effects analysis was then performed by multiplying the fixed effects variance by a regularized estimate of the ratio of random and fixed effects. For healthy controls, the results were combined yielding the group statistical maps for each contrast. The resulting *t*-statistic images were thresholded using the minimum given by a Bonferroni correction and random field theory [Worsley et al., 2002]. For an exploratory search involving all peaks within the gray matter covered by the slices, the threshold for reporting a peak as significant ($P < 0.05$) was at $t = 4.7$.

RESULTS

Anatomical MRI

MRI showed bilateral diffuse and symmetric subcortical band heterotopia in Patients 3, 4, and 5, and a diffuse asymmetric band in Patients 1 and 6. In Patient 2, a symmetric subcortical heterotopic band was visible in the posterior head quadrant (Fig. 1). The band was thick in Patients 2, 3, 4, and 5, and thin in Patients 1 and 6. No area of pachygyria of the normotopic cortex was seen in any patient.

Motor Task

In healthy controls, simple motor task elicited contralateral activation of the primary motor cortex (M1) and ipsilateral

Figure 1.

Representative T_1 -weighted axial MRI showing the subcortical heterotopic band in Patients 1–6 (right is right on the image). The arrowheads point to the band.

eral activation of the cerebellum and left supplementary motor area (SMA) activation.

Details of motor activations in DCS patients are listed in Table II. All patients showed task-related activations in the contralateral normotopic M1. All had significant activation within the subcortical heterotopic band underlying the left M1 for right-sided motor testing. All cases except for Patient 1 also showed involvement of the right heterotopic band for left-sided motor task. Other areas of normotopic cortex activations included the ipsilateral M1 in Patients 2, 3, 4, and 6, the SMA in all patients, the premotor area in Patients 1, 3, and 4, and the secondary somatosensory area (SII) in Patient 6. Subcortical activations were found in the contralateral putamen in Patients 1 and 3 and the ipsilateral cerebellum in all patients. Motor activations are illustrated in Figure 2.

Sensory Task

All healthy controls showed task-related contralateral activation of the primary sensory cortex (SI) and the thalamus. The left sensory task induced also a contralateral activation of the insular cortex.

Details of locations of sensory activations in DCS patients are listed in Table III. Task-related activations in the contralateral normotopic SI were found in all patients. Contralateral activation of the heterotopic band underlying SI was seen in Patient 5 for sensory stimulation of the right hand and Patients 2 and 3 for left-sided testing. Other areas of normotopic cortex activations included the ipsilateral SI in Patients 2 and 3 and SII in the normotopic cortex in all subjects, except Patient 5. The contralateral thalamus was activated

TABLE II. Functional areas activated during motor task in six patients with double cortex syndrome

Task	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Right hand	M1, L M1-B, L SMA, L PMA, R Putamen, L Cerebellum, R	M1, L M1-B, L SMA, L	M1, L M1-B, L SMA-B, L	M1, bil M1-B, L SMA, R PMA, bil	M1, L M1-B, L SMA, R	M1, bil. M1-B, L SII (sm), L
Left hand	M1, R SMA, L PMA, bil. Putamen, R Cerebellum, L	Cerebellum, R M1, bil. M1-B, R SMA, L Cerebellum, L	Cerebellum, R M1, bil. M1-B, R SMA, L PMA, R Putamen, R Cerebellum, L	Cerebellum, R M1, R M1-B, R SMA, L PMA, R Cerebellum, L	Cerebellum, R M1, R M1-B, R SMA, R Cerebellum, L	Cerebellum, R M1, bil. M1-B, R SMA, L SII (sm), bil. Cerebellum, L

-B, corresponding area in the underlying heterotopic band; bil., bilateral; IC, internal capsule; L, left; M1, primary motor area; PMA, premotor area; R, right; SII, secondary somatosensory area; sm, supramarginal gyrus; SMA, supplementary motor area.

Figure 2.

Examples of motor fMRI maps showing activations in the heterotopic band and the overlying normotopic cortex superimposed on the T_1 -weighted MRI in three patients (A–C). Right is right on the images. **A:** Task-related activations for the right hand in Patient 1 showing the involvement of the subcortical heterotopic band underlying the left M1 (M1-B, L). Activations in the normotopic cortex are seen in the left M1 (M1, L), left SMA (SMA, L), and right PMA (PMA, R). **B:** Activations for the left hand in Patient 2 showing the involvement of the subcortical heterotopic band underlying the right M1 (M1-B, R). Activations in the normotopic cortex are seen bilaterally in M1 (M1, bil) and the left SMA (SMA, L). **C:** Activations for the left hand (upper panels) in Patient 3 showing the involvement of the subcortical heterotopic band underlying the right M1 (M1-B, R). Activations in the normotopic cortex are seen bilaterally in M1 (M1, bil), the left SMA (SMA, L), and the right PMA (PMA, R). Activations for the right hand (lower panels) show the involvement of the in the heterotopic band underlying the left SMA (SMA-B, L) and the left M1 (M1-B, L). Activations in the normotopic cortex were seen bilaterally in M1 (not shown). The arrowheads indicate the subcortical heterotopic band on the anatomical MRI and the arrows show the location of the central sulcus. B, corresponding area in the underlying heterotopic band; bil., bilateral; L, left; M1, primary motor area; PMA, premotor area; R, right; SMA, supplementary motor area.

in Patients 1, 2, and 3. Sensory activations are illustrated in Figure 3.

DISCUSSION

In our DCS patients, simple motor and sensory tasks induced activations in expected regions of the primary motor and somatosensory areas of the normotopic cortex [Boecker et al., 1994; Hlustik et al., 2001; Kim et al., 1993; Puce et al., 1995]. Task-related activations were seen in subcortical structures in half the patients and in the cerebellum in all. The motor task induced a contralateral activation of the heterotopic gray matter underlying M1 in all patients. Activation of the heterotopia underlying SI was less consistent across patients.

Activation in Normotopic Cortex

In agreement with previous studies of patients with DCS that used a motor paradigm comparable to ours, we found a contralateral M1 activation [Draganski et al., 2004; Iannetti et al., 2001; Pinard et al., 2000]. In addition, we found ipsilateral M1 activation, as well as a network including SMA, PMA, and SII as shown in the three examples in Figure 2.

In healthy subjects, during simple movements of the dominant hand, ipsilateral activation of the motor cortex is not consistently found [Boecker et al., 1994; Kobayashi et al., 2003]. Activation of the ipsilateral M1 may be seen more often in relation to simple finger movements of the non-dominant hand [Alkadhi et al., 2002] and has been shown to be related to task complexity [Baraldi et al., 1999; Lotze et al.,

TABLE III. Functional areas activated during sensory task in six patients with double cortex syndrome

Task	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Right hand	SI, L	SI, bil	SI, bil	SI, L	SI, L SI-B, L	SI, L
	SII (ins), L Thalamus, L	SII (ins), L Thalamus, L	SII (sm), L	SII (sm), L	Frontal-B, L	SII (sm), bil
Left hand	SI, R	SI, bil. SI-B, R	SI, bil. SI-B, R SII (ins)-B, R SII (sm), R	SI, R	SI, R	SI, R
	Thalamus, R	Thalamus, R	Thalamus, R			

-B, corresponding area in the underlying heterotopic band; bil., bilateral; ins, insula; L, left; R, right; sm, supramarginal gyrus; SI, primary somatosensory area; SII, secondary somatosensory areas.

2000; Rao et al., 1993; Sadato et al., 1996; Verstynen et al., 2005; Wexler et al., 1997]. Possible explanations for the ipsilateral M1 activation include descending ipsilateral projections from motor cortex to the spinal cord [Ziemann et al., 1999] and interhemispheric communication from the ipsilateral motor cortex to the contralateral one through inhibitory callosal projections [Chen et al., 2003].

Ipsilateral M1 activation is often seen in patients with various neurological disorders including stroke [Cao et al., 1998; Weiller et al., 1992], brain tumors [Yoshiura et al., 1997], and multiple sclerosis [Lee et al., 2000; Reddy et al., 2000; Rocca et al., 2004]. In these conditions the ipsilateral recruitment has been viewed as a mechanism to compensate for the effects of a lesion causing a motor deficit. In cases of early brain damage such as congenital hemiparesis [Bernasconi et al., 2000; Vandermeeren et al., 2003] or malformations of cortical development presenting with hemiparesis, possible mechanisms for ipsilateral M1 activation include lack of regression of normally transient fetal connections, enhanced development of normally occurring ipsilateral projections, or aberrant ipsilateral projections [Maegaki et al., 1995].

The pathways mediating ipsilateral motor activation in our DCS patients are unclear. Our patients had no evident abnormalities in the normotopic cortex and no apparent clinical motor deficit. Moreover, it is unlikely that the activation of the ipsilateral M1 was related to movements of the nonstimulated hand. Indeed, prior to the fMRI experiment we carefully checked for the absence of mirror movements. In addition, patients were monitored visually throughout the scanning period by an observer. Future studies using transcranial magnetic stimulation of motor cortices may shed light on the origin of descending motor pathways projections and thus allow us to study the likely role of areas activated by movement on fMRI.

The frequent involvement of ipsilateral primary motor cortex during a simple task in our patients might be a reflection of their perception of the task as more difficult, thus leading to the recruitment of pathways that are activated in normal individuals when performing complex tasks [Verstynen et al., 2005]. Although we did not assess quantitatively the task difficulty, all our patients were able to perform the motor task reliably at a low pace. During the training session, however, they could not sustain an increase

in pace for the required period of the fMRI experiment. Therefore, based on this clinical observation, we can assume that our simple motor paradigm at 1.5 Hz was perceived as relatively difficult. This explanation is further supported by the presence of SMA, PMA, and SII activations. Activation of the SMA, which is involved in movement programming and execution [Ohara et al., 2000; Weilleke et al., 2001], and the PMA have been observed during complex [Rao et al., 1993] or imagined movements. SII is considered to function as a higher-order processing area for somatosensory perception [Karhu and Tesche, 1999] and its activation has been related to manual dexterity and coordination [Disbrow et al., 2000].

Other contributors to these distributed areas of activation during a simple task may be an atypical connectivity due to abnormal brain organization, as previously shown in malformations of cortical development [Janszky et al., 2003], and the epileptic state. As epilepsy has been shown to modify brain development [Holmes et al., 1990; Vargha-Khadem et al., 1992], it is conceivable that this condition has impacted brain and functional organization in our DCS patients, considering also that all but one had a longstanding history of severe epilepsy.

The sensory task in our DCS patients induced a pattern of activation that was similar to that seen in healthy individuals [Hansson and Brismar, 1999; Polonara et al., 1999], involving the contralateral SI and SII in all, and ipsilateral SI in three of them.

Activation in the Subcortical Heterotopic Band

There is evidence from experimental and clinical data suggesting that subcortical heterotopic gray matter may be involved in physiologic brain function in patients with DCS. Histologically, the heterotopic band consists of small pyramidal cells, which are arranged in the outer segment and exhibit a columnar organization in the inner segment of the band. Although the band has a disorganized distribution of pyramidal cells, there is evidence that connectivity with subcortical structures is likely maintained [Harding, 1996; Schottler et al., 1998]. Depth electrodes recordings from the heterotopic band have revealed normal electrophysiological activity, similar to the one observed in the normal cortex, in addition to epileptiform activity [Morrell et al., 1992]. Simi-

Figure 3.

Examples of sensory fMRI activation maps superimposed on the T_1 -weighted MRI in three patients. **A:** Task-related activations for the right hand in Patient 1. Activations in the normotopic cortex are seen in the left SI (SI, L), the left SII in the insular cortex (SII, ins, L) and the left thalamus. **B:** Activations for the left hand in Patient 2 showing the involvement of the subcortical heterotopic band underlying the right SI (SI-B, R). Activations in the normotopic cortex are seen bilaterally in SI (SI, bil) and in the right thalamus. **C:** Activations for the left hand in Patient 3 showing the involvement of the subcortical heterotopic band underlying the

right SI (SI-B, R) and SII at the level of the insular cortex (SII-B, ins, R). Activations in the normotopic cortex are seen bilaterally in SI (SI, R and SI, L), the right SII in the supramarginal gyrus (SII, sm, R) and the right thalamus. The arrowheads indicate the subcortical heterotopic band and the arrow the location of the central sulcus. Right is right on the images. B, corresponding area in the underlying heterotopic band; bil., bilateral; ins, insula; L, left; R, right; sm, supramarginal gyrus; SI, primary somatosensory area; SII, secondary somatosensory areas.

lar results were found in a recent magnetoencephalography (MEG) study, which also showed that sequential information processing could be observed in the normo- and heterotopic cortices. Spatiotemporal analysis of MEG dipole localization resulted in an early activation of the normotopic neurons and in a later activation of neurons in the heterotopic cortex [Toulouse et al., 2003]. In a study using diffusion tractography, similar patterns of connectivity were found in patients with heterotopia and in control subjects [Eriksson et al., 2002]. Moreover, magnetic resonance spectroscopy studies [Iannetti et al., 2001; Munakata et al., 2003] have shown normal amounts of the neuronal marker N-acetyl aspartate in the heterotopic band, and PET studies [De Volder et al., 1994; Miura et al., 1993] demonstrated that the subcortical band has a glucose metabolism comparable to that of the overlying normotopic cortex, suggesting preserved neuronal and axonal integrity.

Although we cannot formally exclude the possibility that common vascular factors are shared between the normo-

and heterotopic cortices, the fact that the band is distant from the sulci and large vessels, as well as the size of activations we found in our patients, are more in keeping with neuronal activation. Indeed, it has been shown that sizeable fMRI activations are related to a high density of neurons rather than to hemodynamic factors [Krings et al., 1997].

Relation Between Normotopic and Heterotopic Cortices

In our study the heterotopic band beneath M1 was consistently activated during the contralateral motor task, and in half of the patients activation of the band below S1 was seen in relation to the contralateral sensory task. The functional relationship between the normotopic cortex and the heterotopic band was not simple, as other regions of heterotopic gray matter were activated in concert with the non-primary areas of the normotopic cortex only in Patient 3.

One hypothesis to explain this regional selectivity is that the heterotopic band is more prominently involved in cortico-subcortical (i.e., vertical) signaling than cortico-cortical (i.e., horizontal) processing. It is perhaps this preserved vertical connectivity between primary normotopic and heterotopic gray matter that explains why our DCS patients do not have focal neurological deficits. In contrast, the developmental delay associated with the condition may result from a disturbance of cortico-cortical connectivity, as seen in animal models of heterotopia [Colacitti et al., 1998] and other brain developmental disorders [Innocenti et al., 2003].

In conclusion, our study showed that to perform a simple voluntary motor task, patients with DCS recruit a widespread network involving bilateral primary areas and higher-order association cortices, suggesting increased attentional demand and motor programming. As more patients with DCS are being examined with fMRI, concepts derived from plasticity mechanisms will allow for a more comprehensive basis for decision-making in epilepsy surgery for these patients [Bernasconi et al., 2001].

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