Electromagnetic function of polymicrogyric cortex in congenital bilateral perisylvian syndrome

R Paetau, J Saranneva, O Salonen, L Valanne, J Ignatius, S Salenius

Background: Congenital bilateral perisylvian syndrome (CBPS) is characterised by bilateral perisylvian polymicrogyria and suprabulbar paresis. Mild tetraparesis, cognitive impairment, and epilepsy are frequently associated. Sensory deficits are surprisingly rare, even though polymicrogyria often extends to auditory and sensorimotor cortex.

Objectives: To study the sensorimotor and auditory cortex function and location in CBPS patients.

Methods: We mapped the sensory and motor cortex function onto brain magnetic resonance images in six CBPS patients and seven control subjects using sources of somatosensory and auditory evoked magnetic fields, and of rhythmic magnetoencephalographic (MEG) activity phase-locked to surface electromyogram (EMG) during voluntary hand muscle contraction.

Results: MEG-EMG coherence in CBPS patients varied from normal (if normal central sulcus anatomy) to absent, and could occur at abnormally low frequency. Coherent MEG activity was generated at the central sulcus or in the polymicrogyric frontoparietal cortex. Somatosensory and auditory evoked responses were preserved and also originated within the polymicrogyric cortex, but the locations of some source components could be grossly shifted.

Conclusion: Plastic changes of sensory and motor cortex location suggest disturbed cortex organisation in CBPS patients. Because the polymicrogyric cortex of CBPS patients may embed normal functions in unexpected locations, functional mapping should be considered before brain surgery.

METHODS

Subjects
Six cooperative CBPS patients (table 1), and seven healthy right handed control subjects gave their informed consent to participate in this study. The study was approved by the ethical committee of the Hospital for Children and Adolescents, University of Helsinki. To optimise signal quality, we included only subjects with normal hearing and a head circumference of 50 cm or more. Patients P1, P4, and P5 came from large CBPS families, P3 from another CBPS family, and P2 and P6 had CBPS of unknown aetiology. The control subjects (a sibling of P2, a son of a deceased CBPS patient from the large CBPS family, three students, and two children of the laboratory personnel) had normal head MRIs and lacked signs and symptoms suggestive of perisylvian cortex dysfunction. All patients were dysarthric and had multiple motor disabilities (table 1). In spite of poor fine motor skills, the patients perceived light touch, pain and joint position normally, even in the facial area.

Two neuroradiologists (OS, LV), independently determined the extent of malformation in all MRIs (table 1, figs 2 and 4). Malformed cortex was defined by nodular white-grey border and surface of the cortex as well as abnormal gyration patterns with deep frontoparietal clefts. None of the subjects had heterotopia. The lesions were symmetric in all patients except P6, whose left hemisphere lesion was limited to the frontoparietal operculum sparing the hand area and temporal

Abbreviations: CBPS, congenital bilateral perisylvian syndrome; ECD, equivalent current dipoles; EMG, electromyogram; HPI, head position indicator; MEG, magnetoencephalography; MRI, magnetic resonance imaging; PMG, polymicrogyria; PPC, posterior parietal cortex; SEF, somatosensory evoked fields; S/N, signal-to-noise; SI cortex, primary somatosensory cortex; SII cortex, second somatosensory cortex.
Table 1 Characteristics of the six patients with congenital bilateral perisylvian syndrome

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>Epilepsy onset-offset age (years)</th>
<th>Tongue lateral movements right/left</th>
<th>Lip movements right/left</th>
<th>Finger movements right/left</th>
<th>Gross motor skills right/left</th>
<th>Intellectual capacity</th>
<th>PMG location on MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>68</td>
<td>F</td>
<td>no</td>
<td>w/w</td>
<td>c/c</td>
<td>+/+</td>
<td>±</td>
<td>bi FP, bi Syl</td>
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</tr>
<tr>
<td>10</td>
<td>M</td>
<td>no</td>
<td>w/w</td>
<td>c/c</td>
<td>+/+</td>
<td>+</td>
<td>bi FP, bi Syl</td>
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<tr>
<td>14</td>
<td>M</td>
<td>no</td>
<td>w/w</td>
<td>c/c</td>
<td>+/+</td>
<td>+</td>
<td>bi FP, bi Syl</td>
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<td>10, 1 sz</td>
<td>M</td>
<td>no</td>
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<td>+/+</td>
<td>+</td>
<td>bi FP, bi Syl</td>
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<tr>
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<td>w/w</td>
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<td>bi FP, bi Syl</td>
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<td>3–12</td>
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<td>–/–</td>
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<td>–/–</td>
<td>–/–</td>
<td>bi Syl</td>
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</tr>
</tbody>
</table>

F, female; M, male; +, normal; –, absent; ±, borderline; (–), mild disability; c, clumsy; w, weak; PMG, polymicrogyria; MRI, magnetic resonance imaging; bi, bilateral; Fop, frontal opercular; FP, frontoparietal; Syl, perisylvian.

MEG recordings

Somatosensory evoked responses were recorded from all subjects, and auditory evoked responses and MEG-EMG coherence were recorded from five patients and five control subjects. One patient and two control subjects were studied before MEG-EMG coherence was included in the protocol. Technical or practical obstacles prevented auditory experiments in two subjects. MEG data were recorded in a magnetically shielded room (Neuromag–122™; Neuromag Ltd, Helsinki, Finland) whole-head gradiometer. The subject sat with the head immobile inside the sensor helmet and watched either silent cartoons during somatosensory and auditory stimulation or his or her active hand during the motor task. Before data acquisition, a head coordinate system was created with help of three fiducial points (both preauricular points and the nasion). Three head position indicator (HPI) coils were attached around the scalp and their positions were determined with a three-dimensional digitiser (Isotrak; Polhemus Navigation Sciences, Colchester, VT, USA). The reference point was fixed on the scalp to compensate for possible head movement during the digitisation procedure.

Head position relative to the sensor helmet was determined every 5–13 minutes at the beginning of each stimulation block by leading current pulses to the HPI coils. The subjects were monitored continuously through a video camera, and all patients and children were accompanied by a member of the research group in the shielded room. From each subject 60–90 minutes of magnetic brain activity was collected during the experiments, and stored for off-line analysis.

Somatosensory and coherence data were sampled at 0.6 kHz and auditory data at 0.3 kHz. The recording pass bands were 0.3–190 Hz and 0.3–90 Hz, respectively.

Somatosensory evoked fields (SEFs) to alternating left and right median nerve electrical stimulation (0.2-ms, constant current pulses triggering motor response) and auditory evoked fields (AEFS) to alternating left and right ear tones (1 kHz, 50-ms sine waves, intensity set individually to comfortable and equally loud perception in each ear) were averaged on-line until satisfactory signal-to-noise (S/N) ratio was achieved at about 100 averages. S/N ratio was judged visually during ongoing stimulation. If no visible responses were discerned, stimulation was continued until 250 averages. Whenever possible, the stimulation procedure was repeated to judge consistency of the responses; thus the final source analysis was based on replicated artefact-free averaged responses to 150–250 stimuli. Large magnetic artefacts >3000 fT/cm or eye blinks >150 uV automatically rejected the concomitant response from the averaging process. A long interstimulus interval of 1.5 s was chosen not to suppress responses of the second somatosensory cortex (SII) or the auditory evoked magnetic 100-ms response (N1m) of the youngest subjects.

EMG was recorded from both the first dorsal interosseous muscles (recording pass band 0.3–190 Hz, sampling frequency 0.6 kHz). The subject was taught to keep the muscle weakly contracted for 4–6 minutes, to produce a rhythmic firing of muscle unit potentials at around 10–40 Hz. To identify the motor cortex, coherence spectra between MEG and rectified EMG signals were averaged over 4–6 minutes of sustained contraction.20

Off-line data analysis

All 122 MEG traces were first screened visually to identify the signal of interest (epileptiform spikes, spontaneous rhythms, evoked responses) and to identify and remove artefacts. Frequency spectra at each sensor were calculated over unfiltered data sets. Mu rhythm was quantified from amplitude spectra calculated during auditory stimulation and during the motor tasks. Next, the MEG data were displayed as magnetic field patterns and evaluated visually for dipolar fields at each data point over the signal of interest. Finally, dipolar fields were modelled with equivalent current dipoles (ECDs) using a least-squares fit and a spherical MRI-guided head model within the Neuromag software. An ECD models the three-dimensional location, orientation, and strength of the current dipole that best explains a measured field pattern and thus represents local cortical activity. If one dipole did not explain all signal components, additional ECDs were found on the basis of differential timing or spatial distribution. Finally, a set of 1–6 dipoles with fixed locations and orientations but freely changing strengths was used to explain the spatiotemporal evolution of all signal components. ECDs were considered adequate if they explained the signal of interest, remained stable in location over a few milliseconds, were physiologically relevant, and if they remained practically unaffected by the other dipoles of a multidipole set.

Sources of MEG activity coherent with EMG signals were determined from cross correlograms (inverse Fourier transform of the normalised cross spectrum at each MEG sensor). The time-domain cross correlogram oscillations typically had dipolar fields, which were modelled with single dipoles fitted to a set of 28 MEG channels around the maximum amplitude oscillation. The largest coherence peak and cross correlogram oscillation were required to occur in the same channels.

Evoked response sources repeatedly found in replicated trials were accepted for further analysis. Spatial accuracy for each response was determined from the distance between replicated sources, which did not differ between the patient and control groups (7 mm for the somatosensory 20-ms...
response, N20m, 11 mm for the somatosensory 35-ms response, P35m, and 12 mm for the auditory N1m).

The mean ECD parameters (peak latencies, three-dimensional locations, and dipole strengths) of replicated sources were used to represent a subject’s response in statistical comparisons (Student’s two-tailed t-tests).

MEG sources were mapped onto T1-weighted MRI volumes (Siemens Vision 1.5-T or Magnetom 1.0-T; Siemens, Erlangen, Germany). MRI and MEG data were analysed in the same head coordinate system defined by the three fiducial points (see above).

RESULTS

Somatosensory responses

Somatosensory evoked fields (fig 1) of the control subjects were in line with previous observations: the earliest (17–40 ms) signals peaked around 20 ms and 35 ms after the stimulus and were explained with 1–2 ECDs in the contralateral primary somatosensory (SI) cortex. The contralateral and ipsilateral second somatosensory (SII) cortices in the frontoparietal opercula peaked in 82% of the trials around 102 ms. The posterior parietal cortex (PPC) in the postcentral sulcus and the ipsilateral SI in the central sulcus became active around 36% of the responses.

In CBPS patients, distorted brain anatomy prevented reliable identification of specific somatosensory areas, and SI was defined by sources of the early (17–40 ms) peaks, which occurred at expected latency and slightly reduced amplitude, especially for the right-hemisphere SIIc-35 (p<0.05). SI responses originated at the central sulcus in three hemispheres and within the abnormal contralateral frontoparietal cortex in nine hemispheres out of 12 (see figs 2 and 4). Early ipsilateral SI activity occurred in three patients. P2 had left frontal-lobe activity close to midline at 37 ms and P3 showed ipsilateral parietal 38-ms activity (fig 2, dipole 7). Stimulation of the mildly paretic left hand of P6 elicited simultaneous contralateral and ipsilateral SI activity at 22 ms and 35 ms. The sources of 20-ms and 35-ms responses were more widely separated in patients than in control subjects (mean ± SEM: distance 18 ± 3 mm, range 49 mm ± 7 ± 2 mm; range 32; p<0.005). Also, more dipoles (2.3 ± 0.3 v 1.5 ± 0.1; p<0.05) were needed to explain the patients’ than the control subjects’ SI responses.

All subjects had late 70–90-ms SI/PPC peaks generated at contralateral and/or ipsilateral central sulcus with current orientation perpendicular to the sulcus. Given the localisation inaccuracy of about 1 cm, these late peaks may represent PPC activity as well as true ipsilateral SI responses.

Second somatosensory cortex (SII) activity was defined as any late responses generated lateral and inferior to SI. SII responses occurred less often in patients (38%) than control subjects (82%). When present, patients’ SII source locations varied considerably: some had unusually deep right-hemisphere SII.

Auditory evoked responses

All auditory evoked responses consisted of a contralateral and ipsilateral 100-ms deflection, N1, which was the main target of our interest, as well as of later deflections peaking at 180–250 ms. As expected, N1 sources of control subjects were located in the auditory cortex close to the gyri of Heschl in the supratemporal cortex. A single auditory cortex dipole in each hemisphere explained all auditory responses in three control subjects, while a third source peaked around 125 ms in two control subjects.

In CBPS patients, N1 originated in the posterior sylvian fissure on areas appearing polymicrogyric on MRI or immediately adjoining such areas. Additional sources occurred in four patients: unusual activity at 95–190 ms was found in the medial parietal cortex of P1, and P2, P3, and P6 showed one or two additional right or left temporal lobe sources at 100–160 ms. Especially the patients’ right hemisphere sources were more numerous, weaker, and a few mm deeper than those of control subjects (table 2). Systematic latency patterns could neither be seen between ipsilateral and contralateral nor between left and right hemisphere responses.

Spontaneous activity

Five patients and five control subjects produced centroparietal mu rhythm suppressed during active and passive movements of the contralateral hand. It was exceptionally abundant and only partially suppressed in the right hemisphere of P4. Control subjects had a slightly higher frequency (9–12 Hz v 7–10 Hz) and larger spectral peaks (22 ± 5 fT/cm v 14 ± 2 fT/cm) than patients, but the differences did not reach statistical significance.

Rare epileptiform transients occurred in three patients. Patient 1 had lambda waves in her normal visual cortex, P3 generated sharp waves in the normal-appearing left inferior temporal cortex (and developed psychomotor epilepsy two years later), and P5, with a single Rolandic seizure, had bilateral spikes generated by his polymicrogyric frontal opercula.
activity was generated close to the motor cortex (MI) in the anterior bank of the central sulcus, within 12±2 mm from the earliest ipsilateral SEF sources. In the patients group sources originated within 20±5 mm from the early SEF sources and localised to MI in P5 and P6, and to abnormal frontal or frontoparietal cortex in P2 and P4 (fig 4). Thus, normal MEG-EMG coherence was associated with normal central sulcus gross anatomy, and abnormal coherence always occurred with abnormal central sulcus anatomy.

**DISCUSSION**

**Study populations**

The clinical symptoms and MRI findings of our patients were similar to those described previously in bilateral perisylvian polymicrogyria, although our patients had less severe epilepsy and may represent a relatively mild part of the disorder spectrum. We observed no systematic difference between patients with familial and unknown aetiology. The small patient and control groups are, however, likely to preclude detection of some subtle differences and emphasise individual variations.

**Origin of MEG signal within PMG cortex**

MEG signals of our patients—especially of the oldest one, P1—were attenuated compared with control subjects, even though the difference was not always statistically significant.

Extended gyral crowns relative to fissures, could reduce the overall MEG amplitudes, because MEG signals mainly originate in the fissural cortex. Excessive convexal cortex would be expected to increase EEG signals, which are dominated by radial currents. Evoked potentials of some of our patients, and previous studies of evoked somatosensory potentials in other PMG patients have shown rather attenuated than enlarged signals, and do not support the hypothesis of relative dominance of radial currents in PMG. Also, the orientation of apical dendrites—that is, orientation of cortical net current may be abnormal in PMG cortex. We found most MEG sources close to big clefts, but the source orientations—for example, dipoles 1, 2, and 5 in fig 2, could be tangential as well as perpendicular to the cortex surface and, in some patients, would agree with currents generated by microgyri.

Nearly normal evoked responses agree with nearly normal glucose metabolism, proton spectroscopy, functional MRI, and visual evoked responses reported in PMG cortex. They also suggest that thalamocortical afferent fibres reach layer I–III neurones without being stopped by an impenetrable glotic scar between layers VI and III, as suggested by Golgi analysis for the classic four layered PMG cortex. Therefore, the four layered PMG may not be valid for our patients, or the macroscopic deformity must embed large cortical areas of normal histology. Little is known about the electromagnetic properties in unlayered or mixed-type PMG, which may be more relevant in familial CBPS.27

**Anomalies of auditory evoked potentials and SEF sources**

PMG areas generated surprisingly normal evoked responses, although some response components originated in unusual locations. The right sylvian fissure—that is, evoked responses of the auditory and of the second somatosensory cortices originated deeper than usual in many patients. Because the corresponding dipoles were relatively weak, such a deep location probably reflects the real anatomy rather than summation of parallel sources over an extended cortical area, mislocalised by the single dipole algorithm. The finding agrees with previous observations, but its mechanism is unknown.

**MEG-EMG coherence and the location of the motor cortex**

MEG of the first dorsal interosseus muscle of all control subjects was coherent with MEG signals recorded over the contralateral hemisphere, although control subjects 2 and 4 showed only weak coherence. Four CBPS hemispheres lacked significant MEG-EMG coherence (fig 3). Maximum coherence amplitudes of control subjects ranged between 0.008 and 0.072, mean±SEM 0.031±0.007, and they were not significantly lower in CBPS patients. However, the coherence peaks were wider in control subjects (11±1 Hz) than patients (5±1 Hz; p<0.001). The main spectral peaks fell in the normal range (15–35 Hz) in all control subjects, and in P4 and P5. P2 showed large coherence peaks at an abnormal 8-Hz frequency and P6 at 38 Hz.

The largest cross correlogram oscillations peaked at 12 ms (range 22–6 ms) before zero point—that is, MEG signal leading the EMG signal, and had dipolar fields in all control subjects, in P2 and P5 (both hemispheres), and in the left hemisphere of P4 and P6. In control subjects, coherent brain
Some CBPS patients had early ipsilateral somatosensory evoked responses. In contrast to normal ipsilateral activity (~90 ms) mediated by multisynaptic cortico-cortical pathways, the early ipsilateral responses suggest monosynaptic innervation by contralateral thalamocortical axons through the corpus callosum, or by ipsilateral afferent fibres.

Short-latency SI response components could originate in widely separated cortical areas. At least two generators in Brodmann areas 3b and 1 contribute to the early somatosensory evoked responses. Separation of individual generators by several cm in some patients agrees best with plastic changes shifting the sites of thalamocortical synapses to the

<table>
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<tr>
<th>Table 2</th>
<th>Sources of auditory evoked cortical contralateral (N1c) and ipsilateral (N1i) responses to left and right ear tones</th>
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<tr>
<td></td>
<td>Right hemisphere</td>
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<tr>
<td>CBPS patients (n)</td>
<td>5</td>
</tr>
<tr>
<td>Latency (ms)</td>
<td>101 ± 4†</td>
</tr>
<tr>
<td>Strength (nAm)</td>
<td>24 ± 5†</td>
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<tr>
<td></td>
<td>±3*</td>
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<tr>
<td></td>
<td>46 ± 3*</td>
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<td></td>
<td>0 ± 4</td>
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<td>55 ± 8</td>
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<tr>
<td>Control subjects (n)</td>
<td>5</td>
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<tr>
<td>Latency (ms)</td>
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<td>Strength (nAm)</td>
<td>36 ± 6</td>
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<td>±1*</td>
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<td>55 ± 1</td>
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<td>±4</td>
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<td></td>
<td>3 ± 5</td>
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<td>5 ± 3</td>
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</table>

Data expressed as mean ± SEM.

| Sources of somatosensory responses to median nerve stimulation at primary somatosensory cortex (circles) and of coherent activities reflecting motor function (squares) mapped on MRI slices. Normal locations are seen in P5 and in the left hemisphere of P6. The circle in the left hemisphere of P6 represents 20-ms and 35-ms responses to both ipsilateral and contralateral median nerve stimulation; all other circles represent responses to contralateral stimulation.
periphery of a cortical lesion as shown in experimental four layered PMG.27

Cortex–muscle interaction

In contrast to robust sensory responses, abnormal cortex did not produce normal oscillations associated with motor function. MEG-EMG coherence was relatively weak in both our control subjects and our CBPS patients. However, in contrast to CBPS patients with weak or absent coherence, all control hemispheres and those three CBPS hemispheres with normal central sulcus anatomy had normal dipolar correlogram fields explained with dipoles in precentral motor cortex. If the central sulcus anatomy was abnormal no MEG-EMG coherence occurred, or it occurred at abnormal frequency, or it had abnormal source locations in the frontoparietal PMG cortex.

The coherence peaks were within normal frequency range except for P2, whose 8-Hz coherence indicates an abnormal cortex–muscle interaction. Coherence peaks in the 5–12 Hz range are occasionally observed in normal subjects, but, in contrast to P2, these subjects show the strongest coherence in the 15–35 Hz range.25 We thus found a large individual variability both for the strength and frequency of cortical activity coherent with EMG in the CBPS patients. The coherence spectra not only implicate that motor circuitry in many CBPS patients may produce rhythmic activity, resulting in modulation of corticospinal descending commands in the normal 15–35 Hz range, but also that the rhythmic activity may be abnormally slow or absent reflecting abnormal motor cortical or thalamocortical circuitry in patients with frontoparietal PMG.

Practical considerations

Individually organised functional circuitities of CBPS patients may reside, at least in part, within PMG cortex. Although our patients did not have severe epilepsy, we hope that our results would encourage careful functional mapping in CBPS patients under evaluation for epilepsy surgery.

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