Differential Infraslow (<0.1 Hz) Cortical Activations in the Affected and Unaffected Hemispheres From Patients With Subacute Stroke Demonstrated by Noninvasive DC-Magnetoencephalography

Stefanie Leistner, MD; Tilmann Sander, PhD; Michaela Wachs, MD; Martin Burghoff, PhD; Gabriel Curio, MD; Lutz Trahms, PhD; Bruno-Marcel Mackert, MD

Background and Purpose—Sustained mass depolarization of neurons, termed cortical spreading depolarization, is one electrophysiological correlate of the ischemic injury of neurons. Cortical spreading depolarizations spread in the gray matter at a rate of approximately 3 mm/min and are associated with large infraslow extracellular potential changes (<0.05 Hz). Moreover, smaller infraslow potential changes accompany functional activation and might help to assess neuronal repair after stroke. The objective of the present pilot study was to investigate whether it is feasible to apply noninvasive near-DC-magnetoencephalography to detect and monitor infraslow field changes in patients with acute stroke.

Methods—A simple motor condition was used to induce physiological cortical infraslow field changes. Five patients in a subacute state after ischemic stroke performed self-paced simple finger movements (30-second periods of finger movements, always separated by 30-second periods of rest, for a total of 15 minutes). Near-DC-magnetoencephalography signals were recorded over the contralateral primary motor cortex for the affected and unaffected hemisphere, respectively.

Results—In all patients, the time courses of the contralateral cortical field amplitudes in the infraslow frequency range followed closely the motor task cycles revealing statistically significant differences between finger movement and rest periods. In 4 of 5 patients, infraslow field amplitudes were significantly stronger over the unaffected hemisphere compared with the affected hemisphere.

Conclusions—This study demonstrates that cortical infraslow activity can be recorded noninvasively in patients in the subacute state after ischemic stroke. It is suggested that near-DC-magnetoencephalography is a promising tool to also detect cortical spreading depolarization noninvasively. (Stroke. 2009;40:1683-1686.)

Key Words: infraslow (<0.1 Hz) potentials ■ MEG ■ stroke

It has been shown in two recent clinical studies using subdural electrode strips that clusters of recurrent prolonged cortical spreading depolarizations (CSDs) are associated with the development of delayed ischemic stroke after aneurysmal subarachnoid hemorrhage and with malignant ischemic stroke due to embolic or thrombotic arterial occlusion.1–3 In animals, CSDs have been found to recruit tissue at risk into necrosis.4,5 Thus, clusters of recurrent CSDs mark the period of progressive ischemic damage and it has been suggested that the monitoring of CSDs helps to determine the transition from injury into repair in patients with stroke.1 Unfortunately, noninvasive technology is unavailable yet to monitor CSDs in those patients with stroke in whom no neurosurgical intervention is indicated that would allow placement of a subdural electrode strip.

CSD is characterized by a mass depolarization of neurons that is accompanied by a large infraslow potential change (approximately <0.05 Hz) and a spreading depression of high-frequency neuronal activity (approximately >0.05 Hz). The intracortical recording of this infraslow potential change with microelectrodes in fact represents the gold standard to measure CSD in animals.

Magnetoencephalography (MEG) has been found capable to record infraslow activity in healthy subjects noninvasively. Infraslow potentials are also interesting for the assessment of functional activity and might help to characterize the repair...
after neuronal injury. Functional restitution after stroke is governed by several factors such as lesion localization, adaptive and compensatory processes, and local reorganization. Little is known about if and how neurovascular mechanisms after stroke are modified. In particular, longitudinal studies after stroke are missing. The longitudinal poststroke assessment of infraslow neuronal changes using near-DC-MEG could allow deriving possible prognostic factors.

The present feasibility study examined if near-DC-MEG can be performed and cortical field changes in the infraslow frequency range can be recorded also in patients with stroke. The feasibility to qualitatively and quantitatively analyze infraslow cortical signals in patients with stroke would open up the avenue to further develop the technology for the monitoring of CSDs in patients with stroke and to assess the progress of repair in rehabilitation studies.

Materials and Methods

The study was approved by the local ethics committee and performed in accordance with the recommendations of the Helsinki Declaration. Baseline characteristics of the patients cohort are given in the Table. The patients were mildly to moderately disabled (mean National Institutes of Health Stroke Scale 4.2; mean grade of hand pareses 3). Their handedness, side of the infarct, etiology, and methodical details and data analysis, see Mackert et al.6

Infraslow MEG signals were recorded over the affected and unaffected hemisphere in a randomized order. As exemplary physiological activation modality, an established motor paradigm was chosen, which is simply practicable.6,8 Patients performed self-paced simple finger movements, which were trained before the recording session. Patients were instructed to bend the fingers only slightly without great muscular effort. For a total of 15 minutes recording time, 30-second periods of finger movements following a prerecorded spoken instruction were monitored above the contralateral hemisphere by MEG. Each movement period was followed by a 30-second rest period. In total, 30 minutes recording time was performed (affected and unaffected hemisphere). To assess reliably the movement onset time, the surface electromyogram was recorded from forearm muscles.

For the recording of infraslow magnetic fields, a modulation-based MEG technique was used inside a conventional magnetically shielded room. Patients were lying in a supine position on a sinusoidally horizontally moving bed with a multichannel planar 49-channel SQUID device positioned tangentially over the pericentral motor cortex representing the hand area. The bed head modulation transposed cranial infraslow fields to the modulation frequency of 0.4 Hz, in which the magnetic noise is much lower than<0.1 Hz. Magnetic fields were recorded with a bandpass from 0.016 to 64 Hz with a sampling rate of 250 Hz. The infraslow field values were calculated by demodulation and reconstruction using an extended current source. Experimental setup, data acquisition, and analysis were performed according to previous study protocols (for technical and methodical details and data analysis, see Mackert et al,6 Wübber et al,6 Mackert et al,10 and Sander et al.11

Results

Five patients with clinically symptomatic subacute stroke were investigated: Patient 1 with right sensorimotor hemiparesis, Patient 2 with left facial and sensorimotor hemiparesis, Patient 3 with right facial and sensorimotor hemiparesis, Patient 4 with left motor arm paresis, and Patient 5 with left motor hand paresis (Table).

In all data sets, finger movements were accompanied by motor-related infraslow magnetic field changes over the contralateral motor cortex, which were clearly above noise level. These infraslow field changes were characterized by a fast increase of field strength at the beginning of activation, sustained field amplitudes during the 30-second activation, and a slower decrease after the end of the finger movement (Figure 1).

In 2 patients (S1 and S2), motor output (using electromyography) and heart rate were monitored. In patient S1, electromyographic activity was approximately 60% stronger on the healthy compared with the affected side, but muscle action was clearly visible on both sides. Heart rate was approximately 80 beats/min for both sides. In patient S2, electromyographic strength was similar on the healthy and

### Table. Clinical and CT Morphological Baseline Characteristics and Strength of Motor-Related MEG Amplitudes (B/ft±SD) of the Patient Cohort

<table>
<thead>
<tr>
<th>S</th>
<th>Age, F/M</th>
<th>Sex</th>
<th>Infarct Side</th>
<th>Infarct Territory</th>
<th>Infarct Size, mm</th>
<th>Infarct Localization</th>
<th>Infarct Sub-/Cortical</th>
<th>Infarct Location</th>
<th>Infarct Etiology</th>
<th>Stroke, Days</th>
<th>BMRC Arm</th>
<th>NIHSS</th>
<th>mRS</th>
<th>BI</th>
<th>UH</th>
<th>FT±SD</th>
<th>AH</th>
<th>FT±SD</th>
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<tr>
<td>1</td>
<td>60</td>
<td>M</td>
<td>Left</td>
<td>MCA</td>
<td>10×20</td>
<td>Cortical</td>
<td>MCA territory</td>
<td>Large artery</td>
<td>11</td>
<td>4-</td>
<td>3</td>
<td>2</td>
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<td>Right</td>
<td>MCA</td>
<td>20×20</td>
<td>Sub-/cortical</td>
<td>MCA territory</td>
<td>Large artery</td>
<td>6</td>
<td>3-</td>
<td>7</td>
<td>3</td>
<td>70</td>
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<td>Per-insular</td>
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<td>10</td>
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<td>Subcortical</td>
<td>Internal capsule</td>
<td>Lacunar</td>
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<td>70</td>
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</table>

BMRC indicates British Medical Research Council; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; BI, Barthel Index; UH, unaffected hemisphere; AH, affected hemisphere; MCA, middle cerebral artery.
affected sides with muscle action clearly visible. Heart rate was approximately 75 beats/min for both sides.

For the data analysis, averaged signals over 30 periods were used. (The recording technique allows also data analysis on a single trial basis.) The amplitudes of motor-related infraslow field changes were significantly stronger for the unaffected compared with the affected hemisphere in 4 of 5 patients (S1 to S4) and in one case approximately the same (S5; mean amplitude: 496.0 fT ± 70.0 versus 268.5 fT ± 51.3, paired t-test; see Figure 1 and Table). Subjects with cortical infarcts (S1 and S2) showed the clearest difference in the motor-induced field changes.

In 3 patients, the spatial motor-related field patterns of the unaffected hemisphere had a predominantly dipolar structure compared with predominantly distorted patterns over the affected hemisphere (Figure 2). Thereby, the dipolar generator was individually located close to the N20 field pattern.

**Discussion**

The present study proved the feasibility and applicability of DC-MEG in patients with stroke. The application of DC-MEG to patients with stroke presents various difficulties. Patients with stroke cannot keep as still as healthy subjects. Especially, inadvertent head motions or eye movements can alter the MEG signal-to-noise ratio. As a consequence of these constraints, in the present first step, only patients with milder forms of stroke in a subacute stage were investigated.

By analyzing temporal dynamics, strength of amplitude, and field pattern, the physiological stimulus condition revealed stable and clearly separable activation-related infraslow field changes above noise level in all patients. The profiles of infraslow magnetic fields followed the motor activation closely during the 30-minute recording session as known from studies in healthy subjects. A fast increase of the amplitude was recorded at the beginning of
finger movements. Sustained elevated amplitudes were seen during the activation period over 30 seconds. A slower decrease characterized the period after the finger movements.

Beyond revealing stable signal changes, the noninvasive DC-MEG technique allowed to detect intraindividual differences. In 4 of 5 patients, the motor-related activation generated significantly stronger infraslow signals over the unaffected compared with the affected hemispheres. Thereby, the clearest difference was found for subjects with cortical lesions compared with subcortical lesions. Because cortical lesions affect a greater cerebral network, cortical lesions are expected to cause the greater reduction of activation-related amplitudes. However, because functional asymmetry, eg, caused by handedness14 or performance differences due to the degree of individual functional impairment,15,16 could also contribute to the differential results, follow-up studies have to further characterize these findings.

The reconstructed motor-related infraslow magnetic field pattern displayed a predominantly bipolar structure over the unaffected hemisphere, whereas the spatial pattern over the affected hemisphere was not bipolar or showed major distortions.

**Summary**

In this pilot study, a noninvasive modulation-based MEG measuring technique was able to monitor and to localize activation related infraslow activity in a patient sample with subacute ischemic stroke. In the next step, the noninvasive MEG method might allow to investigate also patients with stroke in the acute stage, eg, for monitoring of spontaneous pathological infraslow waves of cortical spreading depolarization occurring during ischemic stroke events. In addition, longitudinal DC-MEG studies of neuronal recovery after stroke could allow optimizing rehabilitation regimes.

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**Disclosures**

None.

**References**


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