Short-latency median-nerve somatosensory-evoked potentials and induced gamma-oscillations in humans

Miho Fukuda,1 Masaaki Nishida,1 Csaba Juhász,1,2 Otto Muzik,1,3 Sandeep Sood,4 Harry T. Chugani1,2,3 and Eishi Asano1,2,5

1Department of Pediatrics, 2Department of Neurology, 3Department of Radiology, 4Department of Neurosurgery and 5Department of Electroneurodiagnostics, Children’s Hospital of Michigan, Wayne State University, Detroit Medical Center, Detroit, MI 48201, USA

Correspondence to: Eishi Asano, MD, PhD, MS (CRDSA), Division of Pediatric Neurology, Children’s Hospital of Michigan, Wayne State University, 3901 Beaubien St., Detroit, MI, 48201, USA
E-mail: eishi@pet.wayne.edu

Recent studies have suggested that cortical gamma-oscillations are tightly linked with various forms of physiological activity. In the present study, the dynamic changes of intracranially recorded median-nerve somatosensory-evoked potentials (SEPs) and somatosensory-induced gamma-oscillations were animated on a three-dimensional MR image, and the temporal and spatial characteristics of these activities were analysed in 10 children being evaluated for epilepsy surgery. Visual and quantitative assessments revealed that short-latency SEPs and somatosensory-induced gamma-oscillations predominantly involved the post-central gyrus and less intensely involved the pre-central gyrus and the anterior parietal lobule. Formation of a dipole of N20 peak with opposite polarities across the central sulcus was well delineated in animation movies. High-frequency (100–250 Hz) somatosensory-induced gamma-oscillations emerged in the post-central gyrus at 13.6–17.5 ms after median-nerve stimulation, gradually slowed down in frequency around and below 100 Hz, and progressively involved the pre-central gyrus and the anterior parietal lobule. Formation of a dipole of N20 peak with opposite polarities across the central sulcus was well delineated in animation movies. The primary motor hand areas proven by cortical stimulation frequently coincided with the sites showing the largest N20 peak and the largest somatosensory-induced gamma oscillations. In vivo animation of SEPs and somatosensory-induced gamma oscillations both may be utilized to localize the primary sensory-motor hand area in pre-surgical evaluation. The dipole on SEPs is consistent with the previously accepted notion that the cortices along the central sulcus are activated. The high-frequency somatosensory-induced gamma-oscillations in the post-central gyrus may represent the initial neural processing for external somatosensory stimuli, whereas the subsequent lower-frequency oscillations might represent the reafferent cortical activity occurring in larger cortical networks.

Keywords: electrical brain stimulation; functional brain mapping; in vivo animation movie; pediatric epilepsy surgery; quantitative sub-dural electroencephalography (EEG) analysis

Abbreviations: ECoG = electrocorticography; FIR = finite impulse response; MEG = magnetoencephalography; SEPs = somatosensory-evoked potentials; TMS = transcranial magnetic stimulation; TSE = temporal spectral evolution


Introduction

Intracranial recording of short-latency somatosensory-evoked potentials (SEPs) evoked by electrical stimulation of the median nerve at the wrist has been used as a standard test to identify the primary somatosensory cortex for the hand in pre-surgical evaluation for brain surgery (Allison et al., 1989). The majority of the published literature has treated SEPs consisting of time-domain signals averaged across somatosensory stimuli; the latency, amplitude and polarity of SEP peaks have been used to identify the primary somatosensory cortex and the central sulcus (Allison et al., 1989; Cedzich et al., 1996). On the other hand, cortical activity on electrocorticography (ECoG) in response to external stimuli can be evaluated using time-frequency domain signal data averaged across stimulus tasks (i.e. event-related spectral analysis; Pfurtscheller and
Lopes da Silva, 1999). Previous studies of event-related spectral analysis on ECoG have suggested that cortical modulation of gamma-range (>30 Hz) oscillations is tightly linked to various forms of physiological activity, including motor (Crone et al., 1998), visual (Niessing et al., 2005; Womelsdorf et al., 2006), auditory (Crone et al., 2001) and language tasks (Sinaï et al., 2005). Yet, few ECoG studies have applied a similar approach to short-latency gamma-oscillations related to passive somatosensory stimuli.

In the present study of children being evaluated for epilepsy surgery, cortical activity related to somatosensory stimulation was recorded using a high sampling ECoG recording system. Based on the hypothesis that sequential animation of ECoG signals facilitates better understanding of functional brain activation, the dynamic changes of intracranially recorded median-nerve SEPs and somatosensory-induced gamma-oscillations were animated on an individual three-dimensional-MR image. We subsequently determined the spatial relationship between the Rolandic cortex, the sites showing SEPs and those showing somatosensory-induced gamma-oscillations. We also described the temporal and phase characteristics of somatosensory-induced gamma-oscillations in these children. In the present study, ‘induced oscillations’ were defined as oscillatory responses consisting of both phase-locked (i.e. a component present after averaging) and non-phase-locked (a component absent after averaging) components.

Materials and Methods

Patients

The inclusion criteria of the present study consisted of: (i) age ranging from 5 months to 20 years; (ii) a two-stage epilepsy surgery using chronic sub-dural ECoG recording in Children’s Hospital of Michigan, Detroit, between October 2006 and July 2007; (iii) functional cortical mapping for the primary somatosensory hand area by measurement of median-nerve SEPs and somatosensory-induced gamma-oscillations; (iv) functional cortical mapping for the primary motor hand area using electrical stimulation and (v) sub-dural electrodes chronically implanted on both the pre- and post-central gyri at least 4 cm above the Sylvian fissure (Haseeb et al., 2007). The exclusion criteria consisted of: (i) the presence of massive brain malformations (such as large porencephaly, perisylvian polymicrogyria or hemimegalencephaly) which are known to confound the anatomical landmarks for the central sulcus; (ii) history of previous brain surgery and (iii) the presence of epilepsy partialis continua involving the hand. A total of 13 patients met the inclusion criteria, but three of these 13 patients were excluded due to the history of previous brain surgery. Thus, we studied a consecutive series of 10 children with a diagnosis of medically uncontrolled focal seizures (age: 4–17 years; 7 girls) who satisfied the inclusion and exclusion criteria (Table 1). The study has been approved by the Institutional Review Board at Wayne State University, and written informed consent was obtained from the parents or guardians of all subjects.

Sub-dural electrode placement

For chronic sub-dural ECoG recording and subsequent functional cortical mapping, platinum grid electrodes (10 mm intercontact distance, 4 mm diameter; Ad-tech, Racine, WI) were surgically implanted as previously described (Figs 1A, S1A and S2A; Asano et al., 2005). The total number of electrode contacts in each subject ranged from 74 to 130. The placement of intracranial electrodes was guided by the results of scalp video-EEG recording, MRI and interictal glucose metabolism on positron emission tomography. All electrode plates were stitched to adjacent plates and/or the edge of dura mater, to avoid movement of sub-dural electrodes after placement. In addition, intraoperative pictures were taken with a digital camera before dural closure, to confirm the spatial accuracy of electrode display on the three-dimensional brain surface reconstructed from MRI (Asano et al., 2005).

Co-registration of sub-dural electrodes on the individual three-dimensional MRI

MRI including a T1-weighted spoiled gradient echo image as well as fluid-attenuated inversion recovery image was obtained preoperatively. Planar X-ray images (lateral and anteroposterior) were acquired with the sub-dural electrodes in place for electrode localization on the brain surface; three metallic fiducial markers were placed at anatomically well-defined locations on the patient’s head for co-registration of the X-ray image with the MRI. A three-dimensional surface image was created with the location of electrodes directly defined on the brain surface, as previously described (von Stockhausen et al., 1997; Juhasz et al., 2000; Muzik et al., 2007). The accuracy of this procedure was reported previously as 1.24 ± 0.66 mm with a maximal misregistration of 2.7 mm (von Stockhausen et al., 1997).

Identification of the central sulcus, pre-central gyrus and post-central gyrus

The central sulcus was determined by the consensus of two investigators according to the anatomical MRI landmarks which have been previously validated (Haseeb et al., 2007). The criteria defining the central sulcus included the omega-shaped sulcus at 4–5 cm above the Sylvian fissure on the horizontal plane (Yousry et al., 1997). If there were potentially two sulci showing the omega shape, the sulcus just posterior to the pre-central sulcus which has a junction with the superior frontal sulcus was defined as the central sulcus (Berger et al., 1990; Lehérisy et al., 2000; Sunaert, 2006). The sulcus meeting the above criteria was determined on the 3D Tool Software package (Max-Planck-Institut, Cologne, Germany; von Stockhausen et al., 1997). Once the central sulcus was determined, the gyrus just anterior to the central sulcus was determined as the pre-central gyrus, and the one just posterior to the central sulcus was determined as the post-central gyrus (Haseeb et al., 2007).

If the margin of sub-dural electrode involved the central sulcus but >90% of its recording contact was overlaid on the pre-central gyrus, the sub-dural electrode was considered to belong to the pre-central gyrus. Similarly, if >90% of sub-dural electrode contact was overlaid on the post-central gyrus, the electrode was treated as recording from the post-central gyrus. Otherwise, a sub-dural electrode overlying on the central sulcus was treated as one recording ECoG activities derived from both pre- and post-central gyri.
Extra-operative video-ECoG recording

Extra-operative video-ECoG recordings were obtained using a 192-channel Nihon Kohden Neurofax 1100A Digital System (Nihon Kohden America Inc, Foothill Ranch, CA, USA), which has an input impedance of 200 MΩ, a common mode rejection ratio >110 dB, an A/D conversion of 16 bits, and a sampling frequency selectable from 200 to 10 000 Hz. For evaluation of interictal and ictal epileptiform discharges, the sampling rate was set at 1000 Hz with the amplifier band pass at 0.08–300 Hz for 3 to 5 days. The averaged voltage of ECoG signals derived from the fifth and sixth electrodes (system reference potential) was used as the original reference. ECoG signals were then re-montaged to an average reference, to obtain reference-free topographic maps (Sinai et al., 2005; Nishida et al., 2007). Channels contaminated with large interictal epileptiform discharges or artifacts were excluded from the average reference. No notch filter was used for further analysis in any subjects. Antiepileptic medications were discontinued or reduced during ECoG monitoring until a sufficient number of habitual seizures were captured. Seizure onset zones were identified as previously described (Asano et al., 2003).

SEP's protocol

SEP's were recorded during the interictal state using a method similar to those described previously (Allison et al., 1989; American Clinical Neurophysiology Society, 2006; Haseeb et al., 2007). None of the patients had a seizure within 2 h prior to the recording. Five patients were awake (Patients 2, 3, 4, 7 and 10), whereas the remaining five patients were asleep during the recording; none of the patients were sedated.

Using the Grass S88 constant-current stimulator (Astro-Med, Inc, West Warwick, RI, USA), the median nerve contralateral to the presumed epileptogenic foci were stimulated at the wrist with a frequency of 1.0 Hz (with an inter-stimulus interval of 1000 m), a square wave electric impulse of 300 ms, and a current intensity between 5 and 10 mA. The current intensity was adjusted slightly above the motor threshold, and persistent twitching of the thenar muscle was documented throughout the testing as recommended in the standard protocol (American Clinical Neurophysiology Society, 2006). All ECoG recordings were performed using Nihon Kohden Neurofax 1100A Digital System synchronized with the Grass S88 constant-current stimulator. During two sets of 100 stimuli given to the median nerve, ECoG was recorded from 32-channel subdural

Table 1 Summary of clinical data

<table>
<thead>
<tr>
<th>Patients</th>
<th>Gender</th>
<th>Age (year)</th>
<th>Antiepileptic medications</th>
<th>Seizure semiology</th>
<th>Interictal spikes on scalp EEG</th>
<th>Ictal EEG onset on scalp EEG</th>
<th>Electrode placement</th>
<th>Seizure onset zones determined on ECoG</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>4</td>
<td>ZNS</td>
<td>Focal Sz + Spasms</td>
<td>Lt CFPT</td>
<td>Lt CT</td>
<td>Lt TOPF</td>
<td>Lt TOPF</td>
<td>Dysplasia and Gliosis</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>5</td>
<td>TPM</td>
<td>Focal Sz + sGTC</td>
<td>Not captured</td>
<td>Not captured but CSWS was noted.</td>
<td>Rt POTF</td>
<td>Not captured but CSWS involving Rt POT was noted.</td>
<td>Dysplasia</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>7</td>
<td>OXC, ZNS</td>
<td>Focal Sz + sGTC</td>
<td>Lt POTC with SBS</td>
<td>Lt POT</td>
<td>Lt POTF</td>
<td>Lt T; Lt F</td>
<td>Gliosis</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>9</td>
<td>VGB, PHT</td>
<td>Focal Sz</td>
<td>Lt F; Lt T; Rt F</td>
<td>Lt F</td>
<td>Lt PT</td>
<td>Lt F</td>
<td>Cortical Tubers</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>10</td>
<td>LEV, TPM, OXC, LEV</td>
<td>Focal Sz + sGTC</td>
<td>Not captured</td>
<td>Lt F</td>
<td>Lt FPOT</td>
<td>Lt F</td>
<td>Tumor</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>14</td>
<td>OXC, TPM, LEV</td>
<td>Focal Sz + Spasms + sGTC</td>
<td>Not captured</td>
<td>Rt CPT</td>
<td>Rt PFOT</td>
<td>Rt PT</td>
<td>Tumor</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>15</td>
<td>OXC</td>
<td>Focal Sz + sGTC</td>
<td>Not captured</td>
<td>Not captured</td>
<td>Lt F</td>
<td>Not captured but frequent interictal spikes were noted in Rt P.</td>
<td>Tumor</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>15</td>
<td>OXC</td>
<td>Focal Sz + sGTC</td>
<td>Not captured</td>
<td>Not captured</td>
<td>Lt TOPF</td>
<td>Lt T; Lt TO; Lt T</td>
<td>Not applicable</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>16</td>
<td>ZNS, TPM</td>
<td>Focal Sz + sGTC</td>
<td>Generalized</td>
<td>Rt T</td>
<td>Rt TOPF; Lt T</td>
<td>Not applicable</td>
<td>Gliosis</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>17</td>
<td>LEV, OXC, CZP</td>
<td>Focal Sz + sGTC</td>
<td>Rt OPT with SBS; Generalized</td>
<td>Rt OPT</td>
<td>Rt OPTF</td>
<td>Rt O</td>
<td>Dysplasia</td>
</tr>
</tbody>
</table>

Patient 9 did not undergo resective surgery but implantation of vagus nerve stimulator, since independent bilateral epileptogenic foci were indicated by subdural electrocorticography recording. F = female; M = male; ZNS = Zonisamide; TPM = Topiramate; OXC = Oxcarbazepine; VGB = Vigabatrin; PHT = Phenytoin; LEV = Levetiracetam; CZP = Clonazepam; Sz = Seizures; sGTC = secondarily generalized tonic clonic seizures; F = Frontal; C = Central; P = Parietal; O = Occipital; T = Temporal; SBS = secondary bilateral synchrony; CSWS = Continuous spike-and-waves during slow-wave sleep.
electrodes over the frontal-parietal areas involving the Rolandic cortex. The sampling rate was set at 5000 Hz with the amplifier band pass at 0.08–1200 Hz. A total of 200 somatosensory-evoked responses were averaged using BESA® EEG V.5.1.8 software (MEGIS Software GmbH, Gräfelfing, Germany), while ECoG traces affected by movement artefacts were excluded from averaging.

Measurement of N20 peak on the averaged SEP trace

Averaged SEP traces were re-filtered using a low-frequency filter of 30 Hz to minimize the baseline fluctuation (American Clinical Neurophysiology Society, 2006). An N20 peak, defined as a reproducible negative peak between +17 and +22 ms followed...
Somatosensory-induced gamma-oscillations by frequency

Previous human studies using scalp EEG recording reported that an averaged median-nerve SEP trace contained oscillatory components ranging 30–100 Hz (Chen and Herrmann, 2001), 100–250 Hz (Buchner et al., 1995) and above (Curio et al., 1994). In the present study, therefore, we defined oscillations at 30–100 Hz as ‘low-frequency gamma-oscillations’, those at 100–250 Hz as ‘high-frequency gamma-oscillations’ and those above 250 Hz as ‘very-high-frequency gamma-oscillations’.

We recognized that accurate measurement of early ‘very-high-frequency gamma-modulations’ using the above-mentioned time-frequency bins was not tenable in the present study; ECoG traces at some electrodes were variably affected by stimulus artefacts at the onset of median-nerve stimulation, and very large stimulus artefacts resulted in un-negligible false amplitude augmentation above 250 Hz up to +15 ms relative to the median-nerve stimulation at some electrodes. Thus, further quantitative analyses using the above-mentioned time-frequency bins focused on high-frequency and low-frequency gamma-oscillations. The site showing the largest increase of ECoG amplitude at high-frequency gamma-oscillations (averaged across 100–250 Hz bands) at +20 ms as well as that for low-frequency gamma-oscillations was identified in each subject, to determine the spatial relationship between the Rolandic cortex and the sites showing the largest N20 peak and gamma-oscillations (Fig. 2).

In vivo animation of the dynamic change of ECoG measures on three-dimensional MRI

The dynamic change of signal voltage on the time-domain SEP recording was delineated every 0.2 ms on the individual three-dimensional MRI (Videos S1–S3), using a method similar to that previously described (Asano et al., 2005). Similarly, ‘high-frequency gamma amplitude’ (defined as the amplitude averaged across 100–250 Hz frequency bands’ normalized to that of the baseline) was sequentially delineated every 5 ms (Videos S4–S6), in order to animate ‘when’, ‘where’ and ‘how many fold’ high-frequency somatosensory-induced gamma-oscillations were increased compared to the baseline. In short, ‘SEP voltage’ and ‘high-frequency gamma amplitude’ for each electrode channel at each epoch was registered into the SurGe Interpolation Software 1.2 (web site: http://mujweb.cz/www/SurGe/surgemain.htm), and the interpolated topography map of each ECoG measure was

Table 2 Spatial and temporal characteristics of N20 peak

<table>
<thead>
<tr>
<th>Patients</th>
<th>State during the test</th>
<th>Location of the largest N20 peak</th>
<th>Latency of the largest N20 peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Awake</td>
<td>Post-central Gyrus</td>
<td>17.6 ms</td>
</tr>
<tr>
<td>2</td>
<td>Awake</td>
<td>Post-central Gyrus</td>
<td>17.4 ms</td>
</tr>
<tr>
<td>3</td>
<td>Awake</td>
<td>Post-central Gyrus</td>
<td>17.0 ms</td>
</tr>
<tr>
<td>4</td>
<td>Awake</td>
<td>Post-central Gyrus</td>
<td>17.8 ms</td>
</tr>
<tr>
<td>5</td>
<td>Awake</td>
<td>Post-central Gyrus</td>
<td>18.2 ms</td>
</tr>
<tr>
<td>6</td>
<td>Awake</td>
<td>Post-central Gyrus</td>
<td>20.2 ms</td>
</tr>
<tr>
<td>7</td>
<td>Awake</td>
<td>Post-central Gyrus</td>
<td>20.0 ms</td>
</tr>
<tr>
<td>8</td>
<td>Awake</td>
<td>Central Sulcus</td>
<td>19.4 ms</td>
</tr>
<tr>
<td>9</td>
<td>Awake</td>
<td>Post-central Gyrus</td>
<td>19.0 ms</td>
</tr>
<tr>
<td>10</td>
<td>Awake</td>
<td>Post-central Gyrus</td>
<td>17.6 ms</td>
</tr>
</tbody>
</table>

by a large positive deflection, was visually identified by the consensus of two investigators (Figs 1B, S1B and S2B). The N20 amplitude was measured on each electrode, where the N20 amplitude was defined as the height between the highest peak of N20 and the preceding trough peak (Haseeb et al., 2007). The brain region underlying the electrode showing the largest N20 amplitude was identified to estimate the location of ‘the primary somatosensory area for the hand’ (Table 2 and Fig. 2).

Somatosensory-induced gamma-oscillations protocol

Somatosensory-induced gamma-oscillations were evaluated using the ECoG traces used for the assessment of SEPs. Each ECoG trial was transformed into the time-frequency domain using complex demodulation technique as featured in the BESA software (Hochstetter et al., 2004; Fan et al., 2007). In that technique, the time-frequency transform was obtained by multiplication of the time-domain signal with a complex exponential, followed by a low-pass finite impulse response (FIR) filter of Gaussian shape. Details on the complex demodulation technique for time-frequency transformation are described elsewhere (Papp and Ktonas, 1977; Hochstetter et al., 2004). This is equivalent to a wavelet transformation with constant wavelet width across frequencies. As a result of this transformation, the signal was assigned a specific amplitude and phase as a function of frequency and time (relative to the median nerve stimulation). In the present study, the amplitude averaged across all trials was used for further analysis. Time-frequency transformation was performed for frequencies between 30 and 400 Hz, with a latency of 100 ms and 900 ms relative to the median nerve stimulation, in steps of 10 Hz and 5 ms. This corresponded to a time-frequency resolution of ±14.2 Hz and ±7.9 ms (50% power drop of the FIR filter).

At each time-frequency bin we analysed the percentage change in amplitude (averaged across trials) relative to the mean amplitude in a reference period between –100 and –50 ms relative to the median nerve stimulation. The 50-ms reference period was treated as a stationary period. This parameter is commonly termed ‘event-related synchronization and desynchronization’ (Pfurtscheller, 1977), whereas a less suggestive terminology is ‘temporal spectral evolution’ (TSE) (Salmelin and Hari, 1994). In all figures, red colour indicated a significant increase of amplitude, blue colour a significant decrease in the corresponding time-frequency bin relative to the reference period (Figs 1C, S1C and S2C).
accurately superimposed to the individual three-dimensional MRI, as previously described (Asano et al., 2005). Finally, all interpolated topography maps were sequentially registered to the Microsoft Windows Movie Maker 5.1 (Microsoft Corporation, Redmond, WA, USA), and this procedure yielded a movie file showing sequential alteration of each ECoG measure.

**Measurement of the onset latency of high-frequency somatosensory-induced gamma-augmentation**

The onset latency of high-frequency somatosensory-induced gamma-augmentation was determined by visual assessment of raw ECoG traces with a low-frequency filter of 100 Hz and a high-frequency filter of 1200 Hz. Visual assessment was applied, since the temporal resolution of time-frequency bin was not dense enough to determine the exact onset of very early induced gamma-augmentation. The onset of high-frequency somatosensory-induced gamma-augmentation was defined as the peak of sustained high-frequency gamma-range waves initially exceeding the range of baseline fluctuation. The mean and 95% CI of the onset latency of high-frequency somatosensory-induced gamma-augmentation across the 200 trials were computed for each subject (Table 3).

**Estimation of the proportion of a non-phase-locked component in the overall somatosensory-induced gamma-augmentation**

In the present study, ‘somatosensory-induced gamma-oscillations’ consisted of both phase-locked and non-phase-locked components. We determined how the proportion of non-phase-locked component in the overall induced gamma-augmentation changed over time. This analysis was employed at the site showing the largest induced gamma augmentation at +20 ms in each subject. The averaged SEP signal (i.e. a phase-locked component) was first

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*Fig. 2* Spatial relationship between the sites showing the largest N20 peak, somatosensory-induced gamma-augmentation and the primary motor hand areas.
Somatosensory-induced gamma-oscillations

Results

N20 peak on SEPs

SEP traces for three subjects are shown in Figs 1B, and S1B and 2B. SEP voltage mappings for the same three subjects are shown in animation movies (Videos S1–S3). Visual assessment of averaged SEP traces revealed that large and complex deflections were mostly noted in the electrode overlying the post-central gyrus and the central sulcus, and smaller and less complex deflections were noted in the surrounding areas including the pre-central gyrus and the anterior parietal lobule. The largest N20 amplitude was noted in the electrode overlying the post-central gyrus in nine patients and that on the central sulcus in the remaining one patient (Table 2). The mean peak latency of the largest N20 peak across all 10 patients was 18.4 ms (SD: 1.1 ms; 95% CI: 17.6–19.2 ms). As shown in Fig. S1B, two patients (Patients 6 and 8) had a prominent P25 peak preceded by a much smaller N20 peak. The N20 peak exhibited a dipole with opposite polarities across the central sulcus in all patients. The dynamic formation and deformation of such a dipole across the central sulcus was best appreciated in the animation movies (Videos S1–S3).

Visual assessment of somatosensory-induced gamma-oscillations on raw ECoG traces

Individual ECoG traces with different low-frequency filters for three subjects are shown in Figs 1DEFG, S1DEFG.

Table 3 Results of Somatosensory-induced gamma oscillations

<table>
<thead>
<tr>
<th>Patients</th>
<th>Mean onset latency (95% CI)</th>
<th>Site showing the largest gamma augmentation</th>
<th>Magnitude of increase in gamma amplitude at +20 ms (%)</th>
<th>Site showing the largest gamma augmentation</th>
<th>Magnitude of increase in gamma amplitude at +20 ms (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15.2 (15.1–15.4)</td>
<td>Post-central Gyrus</td>
<td>542</td>
<td>Post-central Gyrus</td>
<td>277</td>
</tr>
<tr>
<td>2</td>
<td>15.3 (15.2–15.5)</td>
<td>Post-central Gyrus</td>
<td>469</td>
<td>Post-central Gyrus</td>
<td>224</td>
</tr>
<tr>
<td>3</td>
<td>13.6 (13.5–13.7)</td>
<td>Post-central Gyrus</td>
<td>825</td>
<td>Post-central Gyrus</td>
<td>469</td>
</tr>
<tr>
<td>4</td>
<td>15.0 (15.0–15.3)</td>
<td>Post-central Gyrus</td>
<td>1151</td>
<td>Pre-central Gyrus</td>
<td>320</td>
</tr>
<tr>
<td>5</td>
<td>16.0 (15.8–16.1)</td>
<td>Post-central Gyrus</td>
<td>769</td>
<td>Central Sulcus</td>
<td>246</td>
</tr>
<tr>
<td>6</td>
<td>17.4 (17.2–17.6)</td>
<td>Post-central Gyrus</td>
<td>597</td>
<td>Central Sulcus</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>15.5 (15.3–15.6)</td>
<td>Post-central Gyrus</td>
<td>128</td>
<td>Post-central Gyrus</td>
<td>79</td>
</tr>
<tr>
<td>8</td>
<td>17.5 (17.4–17.6)</td>
<td>Central Sulcus</td>
<td>929</td>
<td>Pre-central Gyrus</td>
<td>192</td>
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<tr>
<td>9</td>
<td>15.9 (15.8–16.1)</td>
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<td>710</td>
<td>Post-central Gyrus</td>
<td>116</td>
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<tr>
<td>10</td>
<td>15.2 (15.1–15.3)</td>
<td>Post-central Gyrus</td>
<td>1032</td>
<td>Post-central Gyrus</td>
<td>533</td>
</tr>
</tbody>
</table>

Visual assessment of individual ECoG traces of low-frequency filter of 100 Hz revealed that high-frequency (100–250 Hz) somatosensory-induced gamma-oscillations emerged in the post-central gyrus at 1.3 ± 0.5 ms after median-nerve stimulation. The magnitudes of the 'high-frequency gamma-amplitude' and 'low-frequency gamma-amplitude' were computed at sites showing the largest measures among each individual.
and S2DEFG. Visual assessment of raw ECoG traces with a
low-frequency filter of 100 Hz revealed that somatosensory-
induced gamma augmentation initially ranging from 100
to 250 Hz emerged in two to five electrodes overlying the
post-central gyrus or the central sulcus 4–6 cm above the
Sylvian fissure (Figs 1F, S1F and S2F). The mean latency of
onset of high-frequency induced gamma-augmentation
across all 10 subjects was 15.7 ms (SD: 1.1 ms; 95% CI:
14.9–16.5 ms). Such induced gamma-oscillations gradually
slowed down in frequency around and below 100 Hz,
progressively involved the neighbouring areas predomi-
nantly in the post-central gyrus and less intensely in the
pre-central gyrus as well as the anterior parietal lobule.

Visual assessment of averaged ECoG traces with a
low-frequency filter of 500 Hz revealed the presence
of very-high-frequency somatosensory-induced gamma-
augmentation above 500 Hz (Figs 1G, S1G and S2G),
which emerged about simultaneously with high-frequency
induced gamma-augmentation in all 10 patients. Visual
assessment also revealed that very-high-frequency gamma-
augmentation predominantly involved the post-central
gyrus, as did high-frequency gamma-augmentation.

Such very-high-frequency gamma-augmentation was pre-
ceded by prominent artifacts induced by median-nerve
stimulation. By counting the number of waveforms con-
tained in a 10-ms cursor, we estimated that phase-locked
very-high-frequency gamma-augmentation with a frequency
of 500–700 Hz was present in all patients.

Assessment of somatosensory-induced
gamma-oscillations using time-frequency
plot matrixes

Time-frequency plot matrixes showing the sequential
change of ECoG amplitude for given channels for three
patients are presented in Figs 1C, S1C and S2C. The
mean increase of ‘high-frequency gamma-amplitude’ at
+20 ms compared to the reference period across 10 patients
was 715% (SD: 298%; 95% CI: 14.9–16.5 ms). The magnitude of high-frequency
and low-frequency gamma-augmentation reached
statistical significance in all subjects (Simes corrected
$P<0.05$). The magnitude of gamma-augmentation at

Fig. 3 Proportion of a non-phase-locked component in the overall somatosensory-induced gamma-augmentation. (A) The magnitude of
increase in high-frequency gamma-amplitude fell below 10% of the baseline amplitude at +70 ms in Patients 6 and 7. Thus, the proportion
of non-phase-locked component in the overall high-frequency induced gamma-augmentation was not plotted at +70 ms and afterwards in
these two patients. (B) The magnitude of increase in low-frequency gamma-amplitude fell below 10% of the baseline amplitude at +55 ms
in Patient 6, at +70 ms in Patient 7, at +85 ms in Patient 4 and +95 ms in Patient 10. Similarly, the plotting was terminated before +100 ms
in these four patients.
+20 ms was greater in the high-frequency band as compared to that of the low-frequency band ($P<0.001$ by the paired $t$-test). The sequential change of 'high-frequency gamma-amplitude' is delineated in animation movies (Videos S4–S6). The maximum increase of 'high-frequency gamma-amplitude' at +20 ms was noted on the electrode overlying the post-central gyrus in nine patients and overlying the central sulcus in the remaining patient (Table 3). The sites showing increase of 'low-frequency gamma-amplitude' were, to a large extent, spatially overlapped with those showing increase of 'high-frequency gamma-amplitude'. The maximum increase of 'low-frequency gamma-amplitude' at +20 ms was noted on the electrode overlying the post-central gyrus in seven patients, the pre-central gyrus in two patients and overlying the central sulcus in the remaining patient (Table 3).

**Proportion of a non-phase-locked component in the overall somatosensory-induced gamma-augmentation**

The proportion of non-phase-locked component in the overall high-frequency induced gamma-augmentation was 40% on average (range: 10–68% across the 10 subjects) at +15 ms, slowly increased over time until +35 ms (mean rate: +0.5%/ms; 95% CI: +0.2 to +0.8%/ms), then rapidly increased between +35 and +50 ms (mean rate: +2.9%/ms; 95% CI: +2.0 to +3.8%/ms), and reached 98% on average (range: 94–100%) at +55 ms. The vast majority of high-frequency gamma-augmentation consisted of non-phase-locked component after +55 ms. Thereby, the increase rate of the proportion of non-phase-locked component was greater between +35 and +50 ms compared to that between +15 and +35 ms ($P<0.001$ by the paired $t$-test; Fig. 3A).

The proportion of non-phase-locked component in the overall low-frequency gamma-augmentation was 30% on average (range: 6–53%) at +15 ms, gradually increase over time until +35 to +45 ms, then gradually decreased until +55 to +65 ms, again increased over time and reached 88% at +100 ms. Thereby, the increase rate of the proportion of non-phase-locked component was somewhat greater between +15 and +45 ms (mean rate: +1.1%/ms; 95% CI: +0.4 to +1.7%/ms) compared to that between +45 to +65 ms (mean rate: −1.0%/ms; 95% CI: −2.1 to +0.8%/ms), although the difference did not reach statistical significance ($P=0.06$ by the paired $t$-test; Fig. 3B).

**Electrical brain stimulation**

The primary motor hand area involved the pre-central gyrus in eight patients, the electrode overlying the central sulcus in seven patients, and the post-central gyrus in nine patients (Fig. 2). The primary motor hand area involved the site showing the largest N20 peak in eight patients, that showing the largest 'high-frequency gamma-amplitude' in eight patients, and that showing the largest 'low-frequency gamma-amplitude' in nine patients. The site showing the largest N20 peak was more frequently classified as the primary motor hand area compared to the remaining sites (mean frequency: 0.80 versus 0.16; $P=0.01$ by the Wilcoxon signed rank test). Similarly, the site showing the largest 'high-frequency gamma-amplitude' (mean frequency: 0.80 versus 0.16; $P=0.01$) and that showing the largest 'low-frequency gamma-amplitude' (mean frequency: 0.90 versus 0.16; $P=0.006$) were more frequently classified as the primary motor hand area compared to the remaining sites.

**Discussion**

The major findings in the present study can be summarized in five points: (i) recording of SEPs revealed that neuronal activation represented as N20 peak most predominantly involved the post-central gyrus, and formation of a dipole of N20 peak with opposite polarities across the central sulcus was well delineated on animation movies; (ii) recording of somatosensory-induced gamma-oscillations revealed that neuronal activation represented as gamma-augmentation initially and predominantly involved the post-central gyrus and subsequently and less intensely involved the pre-central gyrus and the anterior parietal lobule; (iii) the frequency of most predominant somatosensory-induced gamma-augmentation was initially 100–250 Hz range and gradually slowed down to around 100 Hz and below; (iv) a substantial proportion of somatosensory-induced gamma-augmentation was initially phase-locked, and the proportion of a non-phase-locked component gradually increased over time and (v) The primary motor hand areas proven by electrical brain stimulation frequently coincided with the sites showing the largest N20 peak as well as the largest somatosensory-induced gamma-augmentation.

**Significance of in vivo animation of SEPs and somatosensory-induced gamma-oscillations**

Combination of visual assessment of raw ECoG traces and in vivo animation of ECoG summary measures on the individual three-dimensional MRI facilitated better recognition of the temporal and spatial characteristics of cortical activations induced by median-nerve stimuli in the present study. Each raw ECoG trace had abundant information on electro-physiological responses to somatosensory stimuli. Visual assessment of ECoG traces revealed reproducible gamma-oscillations associated with somatosensory stimuli most predominantly in the post-central gyrus. Visual assessment of ECoG traces with a low-frequency filter of 100 Hz was especially helpful in recognition of the gradual slow down in the frequency of somatosensory-induced gamma augmentation in each electrode (Figs 1F, S1F and S2F). Although raw ECoG traces may not be sufficient to express the summary observations in a form of explicit
knowledge, sequential animation of ‘time-locked ECoG voltage’ and ‘gamma-amplitude’ was able to delineate: ‘where’, ‘when’ and ‘how much’ electro-physiological changes were induced by contralateral median-nerve stimulation.

Initial cortical activation associated with the median-nerve stimulation

In the present study, initial cortical activation was thoroughly investigated using measurement of N20 peak and early high-frequency somatosensory-induced gamma-augmentation. Formation and deformation of a dipole of N20 peak with opposite polarities across the central sulcus was well delineated on animation movies in all patients (Videos S1–S3), and this observation was consistent with that of a previous study (Allison et al., 1989). It has been speculated that the generator of N20 may be located in Brodmann Area 3b (= the anterior bank of the post-central gyrus facing the central sulcus) and that its volume conduction to the cortical surface can be variable (Allison et al., 1989; Balzamo et al., 2004). It has been also speculated that P25 may arise from the crown of the post-central gyrus with surface positivity and that its volume conduction to the cortical surface may be larger compared to that of N20 (Allison et al., 1989; Buchner et al., 1995; Balzamo et al., 2004; Haueisen et al., 2007).

Visual assessment of ECoG traces as well as quantitative time-frequency analyses in the present study revealed that high-frequency somatosensory-induced gamma-augmentation emerged at 15.7 ms on average and that such induced high-frequency gamma-augmentation was not confined to the electrodes overlying the central sulcus at 15–20 ms after stimuli, but extensively involved the post-central gyrus including the middle (Brodmann Area 1) and posterior portion (Brodmann Area 2) of it. A previous study of SEPs using depth electrode recording showed an N20 peak with a widespread field involving the lateral surface and deeply situated anterior bank of the post-central gyrus (Balzamo et al., 2004). Taken together, early high-frequency gamma-augmentation observed in the present study may represent initial neural processing for external somatosensory stimuli in widespread neural networks in the post-central gyrus.

Previous studies using scalp recording showed that an averaged SEP trace contained low-amplitude gamma-oscillations at 100–250 Hz (Buchner et al., 1995) and 600 Hz (Curio et al., 1994; Restuccia et al., 2002) in the 15–20 ms range. Yet, the exact origin of such phase-locked gamma-oscillations was not previously clarified. In the present study, we found high-frequency somatosensory-induced gamma-augmentation at the similar time range, and that about 60% of high-frequency gamma-augmentation was phase-locked at 15–20 ms. Thus, one can speculate that a phase-locked component of high-frequency somatosensory-induced gamma-oscillations were observed by Buchner et al. (1995), whereas both phase-locked and non-phase-locked high-frequency induced gamma-oscillations were observed in the present study. We also found that both high-frequency and very-high-frequency induced gamma-oscillations predominantly involved the post-central gyrus in the present study. Thus, we estimate that the origin of such somatosensory-induced gamma-oscillations may be, at least partially, of cortical origin.

Subsequent cortical activation represented as low-frequency gamma-oscillations

The present study showed that somatosensory-induced gamma-oscillations emerging in the post-central gyrus progressively involved the neighbouring areas predominantly in the post-central gyrus and less intensely in the pre-central gyrus and the anterior parietal lobe, and gradually slowed down in frequency around and below 100 Hz and lasted for up to 60 ms upon visual assessment. As best seen in Fig 3A and B, the time course of proportion of non-phase-locked component in the overall responses was quite different between high- and low-frequency induced gamma-oscillations. These observations may indicate that high-frequency gamma-augmentation was not simply a harmonic of low-frequency gamma-augmentation. Possible explanations include that such subsequent low-frequency gamma-augmentation may represent the reafferent cortical activity occurring in larger cortical networks, to allow integration of external somatosensory stimuli rather than recognition of passive movement of the contralateral thumb. A previous study of healthy adults using scalp EEG showed that proprioceptive-induced gamma oscillations at 40 Hz were present at the contralateral Rolandic region at 60 ms after stimuli (Arnfred et al., 2007). Another previous study of adults with focal epilepsy using intracranial ECoG recording and each individual’s brain surface image demonstrated that gamma-band ECoG power (75–100 Hz) was increased in both pre- and post-central gyri about 200–500 ms after the onset of contralateral fist-clenching (Crone et al., 1998).

It is still not certain whether short-latency induced gamma-oscillations represent unperceived cortical processing alone or perceived along with unperceived processing. The present study showed no difference in the magnitude of low- or high-frequency gamma-augmentation between five awake patients and the other five asleep patients (Table 3); no intra-individual comparison of the magnitude of gamma oscillations between different states was performed in the present study. A study of rats using intracranial ECoG showed that phase-locked somatosensory-evoked gamma oscillations at 30–60 Hz band were smaller at 40–100 ms when stimulation was given during slow-wave sleep state compared to during awake state (Shaw and Chew, 2003). Another previous study of healthy adults using magnetoencephalography (MEG) showed that non-phase-locked pain-induced gamma-oscillations at
patients with extratemporal lobe epilepsy suggested that et al. (1992; Werhahn, 1996). In a previous study of young patients with focal epilepsy, 41 of the 50 subjects had the primary motor hand area in the post-central gyrus (Haseeb et al., 1996). In our previous study of young patients with focal epilepsy, 41 of the 50 subjects had the primary motor hand area in the post-central gyrus (Haseeb et al., 2007). Previous studies of healthy adult volunteers using transcranial magnetic stimulation (TMS) demonstrated that the TMS-induced current flowing across the central sulcus in an ‘anterior-to-posterior’ but a ‘posterior-to-anterior’ direction optimally activated the motor cortex (Brasil-Neto et al., 1992; Werhahn et al., 1994). Another human study of patients with extratemporal lobe epilepsy suggested that surgical resection of the post-central gyrus resulted in more pronounced deficits of the contralateral extremities compared to that after resection of the pre-central gyrus (Polkey, 2000).

**Methodological considerations**

Factors which may affect the findings of cortical mapping using SEPs, somatosensory-induced gamma-oscillations and electrical brain stimulation include anti-epileptic drugs, which are generally believed to reduce cortical excitability. A previous study of healthy adults using scalp EEG recording showed that the amplitude of N20 was decreased on SEPs but no significant changes in phase-locked somatosensory-evoked gamma-oscillations at 600 Hz were noted after a single oral administration of lorazepam (Restuccia et al., 2002). A previous study of healthy volunteers demonstrated that phenytoin, one of the sodium channel blockers, elevated motor thresholds to TMS but had no effect on motor-evoked potential amplitudes, silent period duration, or intracortical excitability (Chen et al., 1997). Another study of healthy volunteers demonstrated that vigabatrin, which increases gamma-aminobutyric acid levels, reduced intracortical excitability but had no effect on motor threshold to TMS (Ziemann et al., 1996). In the present study, thus, we cannot rule out a potential effect of chronic use of antiepileptic drugs on the magnitude or latency of N20 peak or somatosensory-induced gamma-oscillations.

Studies using extraoperative ECoG recording are always associated with spatial sampling limitations. All children had sub-dural electrode coverage involving the lateral surface of post- and pre-central gyri in the present study. It is still uncertain whether the maximal cortical response was obtained from one of the active electrodes placed at every 1 cm distance, or the maximal response occurred from the brain region between sub-dural electrodes or the deeply situated cortex along the central sulcus (Balzamo et al., 2004).

**Future direction**

In the present study, no intra-individual analysis of cortical activation between different somatosensory tasks was employed. Thus, somatosensory stimulation during different sleep or attention states may clarify what types of gamma-oscillations represent perceived and unperceived somatosensory processing. Adding another clinically applicable task such as tactile or proprioceptive stimulation to the standard task used in the present study may also increase our understanding of the role of gamma-oscillations in different types of sensory processing.

**Supplementary material**

Supplementary material is available at Brain online.
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