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Somatosensory-related gamma-, beta- and alpha-augmentation precedes alpha- and beta-attenuation in humans

Miho Fukuda¹, Csaba Juhász^{1,2}, Karsten Hoechstetter⁵, Sandeep Sood³, and Eishi Asano^{1,2,4,*}

¹ Department of Pediatrics, Children's Hospital of Michigan, Wayne State University, Detroit Medical Center, Detroit, Michigan, 48201, USA

² Department of Neurology, Children's Hospital of Michigan, Wayne State University, Detroit Medical Center, Detroit, Michigan, 48201, USA

³ Department of Neurosurgery, Children's Hospital of Michigan, Wayne State University, Detroit Medical Center, Detroit, Michigan, 48201, USA

⁴ Department of Electroneurodiagnostics, Children's Hospital of Michigan, Wayne State University, Detroit Medical Center, Detroit, Michigan, 48201, USA

⁵ MEGIS Software GmbH, Munich, Germany

Abstract

Objective—A number of human studies have demonstrated that the amplitudes of cortical oscillations are altered by various sensorimotor and cognitive tasks. Event-related augmentation of gamma-oscillations and attenuation of alpha- and beta-oscillations have been often used as surrogate markers of cortical activation elicited by tasks especially in presurgical identification of eloquent cortices. In the present study, we addressed a question whether somatosensory-related gamma-augmentation ‘*precedes*’ or ‘*co-occurs with*’ somatosensory-related attenuation of alpha-beta oscillations.

Methods—We studied 10 patients who underwent intracranial electrocorticography for epilepsy surgery, and determined the temporal and spatial characteristics of median-nerve somatosensory-related amplitude changes at gamma- (30–100 Hz), beta- (14–28 Hz) and alpha-band (8–12 Hz) oscillations.

Results—We found that somatosensory-related gamma-augmentation involving the post- and pre-central gyri evolved into beta- and alpha-augmentation, which was subsequently followed by beta- and alpha-attenuation involving the post- and pre-central gyri.

Conclusions—These observations support the hypothesis that somatosensory-related gamma-augmentation but not alpha-beta attenuation represents the *initial* cortical processing for external somatosensory stimuli. Somatosensory-related alpha-beta attenuation appears to represent a temporally distinct stage of somatosensory processing.

Significance—The present study has increased our understanding of event-related gamma-augmentation and alpha-beta attenuation seen on electrocorticography.

*Corresponding Author: 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. Phone: 313-745-5547; FAX: 313-745-0955; eishi@pet.wayne.edu.

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Keywords

ECoG; *in-vivo* animation movie; pediatric epilepsy surgery; event-related potentials; and functional brain mapping

INTRODUCTION

Previous human studies using scalp electroencephalography (EEG), intracranial electrocorticography (ECoG) and magnetoencephalography (MEG) have demonstrated that the amplitudes of cortical oscillations are altered by various sensorimotor and cognitive tasks (reviewed in Pfurtscheller and Lopes da Silva, 1999; Tallon-Baudry and Bertrand, 1999; Engel et al., 2005). Event-related gamma-augmentation and alpha-beta attenuation have been often used as a surrogate marker of cortical activation elicited by tasks in presurgical identification of eloquent cortices (Crone et al., 1998a; 1998b; Ohara et al., 2000; Pfurtscheller et al., 2003; Szurhaj et al., 2005; Miller et al., 2007; Schalk et al., 2008). Unanswered questions regarding the human sensorimotor system include: whether somatosensory-related gamma-augmentation *precedes* or *co-occurs with* somatosensory-related alpha-beta augmentation or attenuation. Observation of ‘the temporal relationship of two types of oscillations’ is useful to judge the causal significance of an association of two oscillations.

Our recent human study using *in-vivo* ECoG recording demonstrated that median-nerve somatosensory-stimuli augmented gamma-oscillations at 100–250 Hz in the contralateral post-central gyrus within 20 msec after stimuli and such augmented gamma-oscillations gradually slowed down in frequency at 30–100 Hz (Fukuda et al., 2008). Scalp EEG and MEG studies have shown that somatosensory stimuli to the upper extremity elicited beta-augmentation (Cassim et al., 2001; Neuper and Pfurtscheller, 2001; Houdayer et al., 2006) as well as alpha- and beta-attenuation (Pfurtscheller, 1989; Nikouline et al., 2000; Della Penna et al., 2004; Palva et al., 2005; Dockstader et al., 2008; Tecchio et al., 2008) in the contralateral Rolandic area. Yet, the sequential order of somatosensory-related amplitude modulations involving alpha, beta and gamma-bands has not been statistically determined in the same experimental setting in humans, partly because scalp recording may not allow us to satisfactorily measure short-latency somatosensory-related gamma-oscillations free of artifacts.

In the present human study using ECoG recording in patients who underwent presurgical evaluation for intractable epilepsy, we determined the temporal and spatial characteristics of median-nerve somatosensory-related amplitude changes at gamma-, beta- and alpha-band oscillations. Here, benefits of ECoG recording include: (i) a better signal-to-noise ratio compared to MEG (Gaetz et al., 2008; Dalal et al., 2009) and scalp EEG (Pfurtscheller and Cooper, 1975), and (ii) less artifacts from cranial muscles (Crone et al., 1998b). In the present study, ‘related’ oscillations were defined as oscillatory responses consisting of both phase-locked (i.e.: a component present after averaging; also often known as ‘evoked’ oscillations) and non-phase-locked (i.e.: a component absent after averaging; also often known as ‘induced’ oscillations) components, as defined consistently with previous studies (Kalcher and Pfurtscheller, 1995; Pfurtscheller and Lopes da Silva, 1999; Crone et al., 2001).

We tested the following hypotheses regarding the sequential order of somatosensory-related amplitude modulations. We hypothesized that somatosensory-related gamma-augmentation represents the initial cortical processing for external somatosensory stimuli in humans, based on the above-mentioned observations in our previous study (Fukuda et al., 2008). We also hypothesized that somatosensory-related gamma-augmentation is subsequently followed by beta-augmentation and alpha-augmentation, according to the observations in previous studies of *in-vitro* preparations of rat somatosensory cortex (Roopun et al., 2006; Kramer et al.,

2008). We further hypothesized that such beta- and alpha-augmentation is eventually followed by beta-attenuation and alpha-attenuation, according to the latencies of alpha-beta attenuation reported in previous human studies using *in-vivo* scalp EEG and MEG recordings (Palva et al., 2005; Bauer et al., 2006; Fan et al., 2007).

MATERIALS and METHODS

Patients

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. We studied a consecutive series of 10 young patients with a diagnosis of medically-uncontrolled focal seizures (age: 4–17 years; 7 females; Table 1) who satisfied the inclusion and exclusion criteria described in our previous study (Fukuda et al., 2008); all subjects analyzed in the present study were included in that study.

Subdural electrode placement

For chronic subdural ECoG recording and subsequent functional cortical mapping, platinum grid electrodes (10 mm intercontact distance, 4 mm diameter; Ad-tech, Racine, WI) were surgically implanted. The total number of electrode contacts in each subject ranged from 74 to 130. All electrode plates were stitched to adjacent plates and/or the edge of dura mater, to avoid movement of subdural 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.

Coregistration of subdural electrodes on the individual three-dimensional MRI

MRI including a T1-weighted volumetric spoiled gradient echo image as well as fluid-attenuated inversion recovery image was obtained preoperatively. The spoiled gradient sequence generates 164 contiguous 1.2 mm sections of the entire head, performed in the sagittal plane, using a (TR/TE/TI) = 5/3/450 ms pulse sequence, flip angle of 12 degrees, matrix size of 256 × 256, and field of view of 220 × 220 mm.

Planar x-ray images (lateral and anteroposterior) were acquired with the subdural 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; 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). The central sulcus, the pre-central gyrus and post-central gyrus were identified according to the anatomical MRI landmarks (Berger et al., 1990; Yousry et al., 1997); the detailed methods to identify the central sulcus were previously described (Fukuda et al., 2008).

Extraoperative video-ECoG recording

Extraoperative 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 Megaohm, a common mode rejection ratio greater than 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 1,000 Hz with the amplifier band pass at 0.08–300 Hz for three to five 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 a common average

reference, as previously described (Hart et al., 1998; Miller et al., 2007; Brown et al., 2008). Channels contaminated with large interictal epileptiform discharges or artifacts were excluded from the average reference (Fukuda et al., 2008). Advantage and limitation of usage of a common average reference for measurement of event-related gamma-oscillations were previously discussed (Crone et al., 2001; Asano et al., 2009). 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. Locations of seizure onset zones or interictal epileptiform activity are described in Table 1.

Median-nerve somatosensory stimulation protocol

Repetitive electrical stimulation of the median nerve was performed during the interictal state using a method described previously (Fukuda et al., 2008). None of the patients had a seizure within two hours prior to the median-nerve stimuli. 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 was stimulated at the wrist with a frequency of 1.0 Hz (with an inter-stimulus interval of 1,000 msec), a square wave electric impulse of 300 μ sec, and a current intensity between 5 mA 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 electrodes over the frontal-parietal areas involving the Rolandic cortex. The sampling rate was set at 5,000 Hz with the amplifier band pass at 0.08–1,200 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 artifacts were excluded from averaging.

Measurement of amplitude changes elicited by somatosensory stimuli

Amplitude changes elicited by passive median-nerve somatosensory stimuli were measured using a method similar to that described previously (Fukuda et al., 2008). Each ECoG trial was transformed into the time-frequency domain using complex demodulation technique as featured in the BESA software (Hoechstetter 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 filter. Details on the complex demodulation technique for time-frequency transformation are described elsewhere (Papp and Ktonas, 1977; Hoechstetter et al., 2004). 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). The low-pass filter used here was a finite impulse response (FIR) filter of Gaussian shape, making the complex demodulation effectively equivalent to a Gabor transform. The filter had a full width at half maximum (FWHM) of 110.8 msec, corresponding to a -6dB attenuation in the frequency domain at 4.0 Hz. Thus, the applied time-frequency transformation had a resolution (defined by the 50% amplitude drop) in the time domain of ± 55.4 msec and in the frequency domain of ± 4.0 Hz; the amplitude measure was sampled in steps of 2 Hz and 25 msec (Tables 2–3 as well as Supplementary Table S1). As a *secondary* analysis in the present study, we also repeated the analysis using a narrower FIR filter corresponding to time-frequency resolution of ± 19.9 Hz and ± 11.1 msec; thereby, the amplitude measure was sampled in steps of 10 Hz and 5 msec. The results are provided in the Supplementary Table S2; the poor frequency resolution in that case did not allow to separate alpha- and beta-band oscillations.

In the present study, the amplitude averaged across all trials was used for further analysis. Time-frequency transformation was performed for frequencies between 4- and 100-Hz, latencies between -100 msec and +900 msec relative to the median nerve stimulation. Gamma-oscillations at 100–250 Hz were not included into the time-frequency analyses in the present study, since our previous study already reported that somatosensory-related gamma-oscillations at 100–250 Hz preceded gamma-oscillations at 30–100 Hz (Fukuda et al., 2008). Thus, the observation of gamma-augmentation at 30–100 Hz preceding beta-augmentation, if demonstrated in the present study, would indicate that gamma-augmentation at 100–250 Hz also preceded beta-augmentation.

At each time-frequency bin, we analyzed the percentage change in amplitude (averaged across trials) relative to the mean amplitude in a reference period between -100 msec and -50 msec relative to the median nerve stimulation, with this reference period treated as stationary (Fukuda et al., 2008); thus, a total number of time-frequency bins in the reference period was 29,400 per subject. This parameter is commonly termed “event-related synchronization and desynchronization” (Pfurtscheller, 1977) or “temporal spectral evolution” (TSE) (Salmelin and Hari, 1994). In all figures, red color indicates a significant increase of amplitude and blue color a significant decrease in the corresponding time-frequency bin relative to the reference period.

To test for statistical significance for each obtained TSE value, two-step statistics was performed using the BESA software: First, statistics based on bootstrapping approach (Davidson and Hinkley, 1999) was applied to obtain an uncorrected p-value at each time-frequency bin. In a second step, correction for multiple testing was performed since each electrode was analyzed at 1,862 time-frequency bins, with TSE values at neighboring bins being partially dependent. A modification of the correction developed by Simes (1986) was used as suggested for time-frequency analysis by Auranen (2002): p values of one frequency bin and channel were sorted in ascending order (p_i , $i=1, \dots, N$), and the maximum index m in the sorted array for which $p_i < \alpha \cdot i/N$ was determined. All uncorrected p-values with $i \leq m$ were accepted as significant. The corrected significance level α was set to 0.05. This approach is less conservative than the classic Bonferroni correction and is specifically suited for partially dependent multiple testing (Simes, 1986; Auranen, 2002).

An additional correction for testing in multiple electrodes was employed using a method similar to that previously described (Brown et al., 2008), since each patient had as many as 32 channels to be measured. TSE values in a given electrode were declared to be *significant* only if a minimum of 6 bins were arranged in a continuous array spanning: (i) at least 3 bins in frequency and (ii) at least 2 bins in duration. Such correction provides a very small probability of Type-I error in determining whether a significant amplitude modulation was truly elicited by the somatosensory task or simply a chance finding. We recognize that this analytic approach may potentially underestimate amplitude modulation with a restricted frequency band (involving 4-Hz width or smaller) or that with a short duration (lasting 25-msec or shorter).

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

In-vivo animation of the dynamic change of ECoG amplitude measures was performed using the method previously described (Brown et al., 2008; Fukuda et al., 2008; Figure 1). In the present study, we defined oscillations at 30–100 Hz as ‘gamma-oscillations’ (Fukuda et al., 2008), those at 14–28 Hz as ‘beta oscillations’ (Palva et al., 2005) and those at 8–12 Hz as ‘alpha oscillations’ (Laufs et al., 2003; Figure 2). Subsequently, ‘gamma amplitude’ (defined as ‘the amplitude averaged across 30–100 Hz frequency bands’ normalized to that of the baseline) was sequentially delineated every 25 msec on the individual three-dimensional MRI surface, in order to animate ‘when’, ‘where’ and ‘how many fold’ somatosensory-related gamma-oscillations were altered compared to the baseline (Figure 1). In short, ‘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 amplitude measure was accurately superimposed to the individual three-dimensional MRI. 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 amplitude measure. Similarly to 'gamma amplitude', 'beta amplitude' and 'alpha amplitude' were sequentially delineated every 25 msec on the three-dimensional MRI.

Determination of the sequential order of amplitude modulations involving gamma-, beta- and alpha-bands

The latencies of epochs showing the largest gamma-augmentation, beta-augmentation, alpha-augmentation, beta-attenuation and alpha-attenuation were determined. The Friedman test (a non-parametric equivalent of the repeated-measures ANOVA) was applied, in order to determine whether any of these latencies differed from others. If the p-value was less than 0.05 on the Friedman test, the Wilcoxon Signed Rank test was applied as a post-hoc test to compare the pairwise latencies (gamma-augmentation vs. beta-augmentation; beta-augmentation vs. alpha-augmentation; alpha-augmentation vs. beta-attenuation; beta-attenuation vs. alpha-attenuation). Using this statistical approach validated previously (Helal et al., 2000; Potschka and Löscher, 2001; Koh et al., 2002), we tested our hypothesis that gamma-augmentation was followed by beta-augmentation, alpha-augmentation, beta-attenuation and finally by alpha-attenuation. The Friedman test and the Wilcoxon Signed Rank test were performed using the computer software SPSS 11.5 (SPSS Inc, Chicago, IL, USA).

Estimation of the proportion of non-phase-locked component in the overall somatosensory-related oscillatory-augmentation

In the present study, 'somatosensory-related gamma-oscillations' consisted of both phase-locked (i.e.: somatosensory-evoked potentials [Papakostopoulos et al., 1975; Desmedt et al., 1987; Bast et al., 2007]) and non-phase-locked components. We determined the proportion of non-phase-locked component in the overall somatosensory-related oscillatory-augmentation at the site showing the largest gamma-augmentation in each subject. The averaged somatosensory-evoked signal (i.e.: a phase-locked component) was first removed from the single trial time series, as performed in previous studies (Tallon-Baudry et al., 1996; Crone et al., 2001; Trautner et al., 2006; Fukuda et al., 2008). Then, the percentage change in non-phase-locked amplitude relative to the mean amplitude in the reference period was computed at each time-frequency bin. Finally, this procedure yielded the proportion of non-phase-locked component in the overall somatosensory-related gamma, beta, and alpha-augmentation.

RESULTS

Temporal and spatial characteristics of somatosensory-related augmentation of gamma-, beta- and alpha-oscillations

The latency of largest augmentation of each frequency band and the magnitude of amplitude/power augmentation of each frequency band are summarized in Tables 2–3 as well as Supplementary Table S1. Significant gamma-augmentation (30–100 Hz) was noted in all 10 subjects (Figure 2), and the largest augmentation of gamma-oscillations was noted at 25 msec after median-nerve stimulation in all subjects. The number of sites showing significant gamma-augmentation was 11.7 on average (95% confidence interval [95%CI]: 7.2 to 16.2). The offset of significant gamma-augmentation occurred at 140 msec on average across 10 subjects (95% confidence interval [95%CI]: 107 – 173 msec). The maximal increase of 'gamma-amplitude' compared to the reference period was 131% on average across all 10 subjects (95%CI: 87 – 175%). No correlation was found between the age and the maximal increase of 'gamma-amplitude' ($p=0.9$ on Spearman's correlation; $N=10$). There was no association between sleep

state and the maximal increase of 'gamma-amplitude' ($p=0.3$ on Mann-Whitney test; $N=10$). The largest increase of 'gamma-amplitude' was noted in the electrode overlying the post-central gyrus in eight subjects and pre-central gyrus in the remaining two subjects (patients 5 and 8).

Significant beta augmentation was noted in nine subjects (except for patient 6). The largest increase of 'beta-amplitude' was noted at 42 msec on average (95% CI: 32 – 51 msec). The number of sites showing significant beta-augmentation was 8.2 on average (95% CI: 4.5 to 11.9). The offset of significant beta-augmentation occurred at 122 msec on average (95% CI: 77 – 168 msec). The maximal increase of 'beta-amplitude' was 76% on average across the nine subjects (95% CI: 56 – 95%). No correlation was found between the age and the maximal increase of 'beta-amplitude' ($p=0.2$ on Spearman's correlation; $N=9$). There was no association between sleep state and the maximal increase of 'beta-amplitude' ($p=0.5$ on Mann-Whitney test; $N=9$). The largest increase of 'beta-amplitude' was noted in the electrode overlying the post-central gyrus in six subjects and pre-central gyrus in the remaining three subjects (patients 3, 5 and 8).

Significant alpha augmentation was noted in eight subjects (except for patients 4 and 6). The largest increase of 'alpha-amplitude' was noted at 97 msec on average (95% CI: 71 – 123 msec). The number of sites showing significant alpha-augmentation was 5.5 on average (95% CI: 1.0 to 10.0). The offset of significant alpha-augmentation occurred at 169 msec on average (95% CI: 123 – 214 msec). The maximal increase of 'alpha-amplitude' was 95% on average across the eight subjects (95% CI: 39 – 152%). No correlation was found between the age and the maximal increase of 'alpha-amplitude' ($p=0.3$ on Spearman's correlation; $N=8$). There was no association between sleep state and the maximal increase of 'alpha-amplitude' ($p=0.8$ on Mann-Whitney test; $N=8$). The largest increase of 'alpha-amplitude' was noted in the electrode overlying the post-central gyrus in six subjects and pre-central gyrus in the remaining two subjects (patients 5 and 8).

Proportion of non-phase-locked component in the overall somatosensory-related oscillatory-augmentation

In short, we found that somatosensory-related gamma-, beta- and alpha-augmentation contained both phase-locked and non-phase-locked components. The proportion of non-phase-locked component in the overall gamma-augmentation was 35% on average (95% CI: 23% – 46%) at +25 msec. The proportion of non-phase-locked component in the overall beta-augmentation was 28% on average (95% CI: 16% – 40%) at the epoch when beta-augmentation reached the maximum. Similarly, the proportion of non-phase-locked component in the overall alpha-augmentation was 28% on average (95% CI: 9% – 47%) at the epoch when beta-augmentation reached the maximum.

Temporal and spatial characteristics of somatosensory-related attenuation of beta- and alpha-oscillations

The latency of largest attenuation of each frequency band and the magnitude of amplitude/power attenuation of each frequency band are summarized in Tables 2–3 as well as Supplementary Table S1. Significant beta-attenuation was noted in six subjects (patients 2, 4, 5, 8, 9, and 10). The magnitude of beta-attenuation reached significance at 146 msec on average (95% CI: 87 – 204 msec). The largest attenuation of 'beta-amplitude' was noted at 208 msec on average (95% CI: 157 – 260 msec). The number of sites showing significant beta-attenuation was 3.6 on average (95% CI: 0.1 to 7.1). The offset of significant beta-attenuation occurred at 350 msec on average (95% CI: 258 – 442 msec). The maximal decrease of 'beta-amplitude' was 31% on average across the six subjects (95% CI: 12 – 49%). No correlation was found between the age and the maximal decrease of 'beta-amplitude' ($p=0.2$ on Spearman's

correlation; $N=6$). The maximal attenuation of 'beta-amplitude' was noted in the electrode overlying the post-central gyrus in four subjects (patients 2, 4, 5 and 9) and the central sulcus in the remaining two subjects (patients 8 and 10).

Significant alpha-attenuation was noted in six subjects (patients 2, 4, 5, 8, 9, and 10). The magnitude of alpha-attenuation reached significance at 221 msec on average (95% CI: 137 – 304 msec). The largest attenuation of 'alpha-amplitude' was noted at 292 msec on average (95% CI: 201 – 382 msec). The number of sites showing significant alpha-attenuation was 3.3 on average (95% CI: -0.4 to 7.0). The offset of significant alpha-attenuation occurred at 500 msec on average (95% CI: 306 – 693 msec). The maximum offset latency of alpha-attenuation was 825 msec (patient 2). The maximal decrease of 'alpha-amplitude' was 39% on average (95% CI: 22 – 56%). No correlation was found between the age and the maximal decrease of 'alpha-amplitude' ($p=0.7$ on Spearman's correlation; $N=6$). The maximal attenuation of 'alpha-amplitude' was noted in the electrode overlying the post-central gyrus in three subjects (patients 2, 4 and 9), the central sulcus in two subjects (patients 8 and 10) and the pre-central gyrus in the remaining one subject (patient 5).

The sequential order of amplitude modulations involving gamma-, beta- and alpha-bands

The Friedman test, applied to ECoG data analyzed using a time-frequency sampling of 2 Hz and 25 msec, demonstrated that at least one of the latencies of epochs showing the largest gamma-augmentation, beta-augmentation, alpha-augmentation, beta-attenuation and alpha-attenuation differed from others ($p=0.001$). The post-hoc test suggested that the latency of largest gamma-augmentation was smaller than that of beta-augmentation ($p=0.01$), the latency of largest beta-augmentation was smaller than that of alpha-augmentation ($p=0.02$), the latency of largest alpha-augmentation was smaller than that of largest beta-attenuation ($p=0.04$), and the latency of largest beta-attenuation was smaller than that of alpha-attenuation ($p=0.04$). Additional analysis using a time-frequency sampling of 10 Hz and 5 msec also suggested that the latency of largest augmentation of oscillations at 40–100 Hz was smaller than that at 20–30 Hz ($p=0.007$ on Wilcoxon Signed Rank test). Furthermore, we compared the pairwise onset-latencies of gamma-augmentation, beta-augmentation, alpha-augmentation, beta-attenuation and alpha-attenuation. We found that the onset-latency of gamma-augmentation was smaller than that of beta-augmentation ($p=0.01$), the onset-latency of beta-augmentation was smaller than that of alpha-augmentation ($p=0.02$), the onset-latency of alpha-augmentation was smaller than that of beta-attenuation ($p=0.04$), and the onset-latency of beta-attenuation was smaller than that of alpha-attenuation ($p=0.04$). The sequential order of amplitude modulations involving gamma-, beta- and alpha-bands is well visualized in Figures 1 and 2 as well as Video S1.

DISCUSSION

Mechanism of somatosensory-related gamma-oscillations followed by beta- and alpha-oscillations

Our previous study showed that high-frequency (100–250 Hz) somatosensory-related gamma-oscillations emerged in the post-central gyrus at 13.6 to 17.5 msec after median-nerve stimulation and gradually slowed down in frequency at 30 – 100 Hz (Fukuda et al., 2008). The present study of ECoG recording in humans demonstrated that median-nerve somatosensory-stimuli elicited gamma-augmentation (30 – 100 Hz; maximally at 25 msec on average) in the contralateral Rolandic area; such gamma-augmentation gradually slowed down in frequency and evolved into beta-augmentation (14 – 28 Hz; maximally at 42 msec on average) and alpha-augmentation (8 – 12 Hz; maximally at 97 msec on average) in the majority of subjects.

The mechanism of such fast-to-slow transition of neural oscillations has been debated. The observation of gamma-band augmentation followed by beta-band augmentation has been reported in previous studies of *in-vitro* rat somatosensory cortex (Roopun et al., 2006; Kramer et al., 2008), and *in-vitro* rat hippocampus (Whittington et al., 1997; Traub et al., 1999; Kopell et al., 2000; Bibbig et al., 2001). It was demonstrated that *in-vitro* kainate application to the rat somatosensory cortex augmented gamma-oscillations at 30 – 70 Hz in the superficial cortical layers II-III, beta-oscillations at 20 – 30 Hz in the deep cortical layer V, and subsequently slower beta-oscillations at 13 – 17 Hz in the all cortical layers (Roopun et al., 2006; Kramer et al., 2008). Such *in-vitro* gamma-oscillations at 30 – 70 Hz were suppressed by a blockage of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors mediating fast synaptic transmission or a blockade of GABA(A) receptors (Roopun et al., 2006). On the other hand, such *in-vitro* beta-oscillations at 20 – 30 Hz were blocked by reducing gap junction conductance with carbenoxolone but were not affected by blockage of synaptic transmission; the period of such beta-oscillations at 20 – 30 Hz was set by an outward potassium current in the cortical layer V (Roopun et al., 2006). Subsequently-appearing *in-vitro* slower beta-oscillations at 13 – 17 Hz are facilitated upon reduction of glutamatergic excitation using an AMPA receptor antagonist (Kramer et al., 2008).

The present study demonstrated that somatosensory-related gamma-, beta- and alpha-augmentation contained both phase-locked and non-phase-locked components. A previous human study showed that somatosensory-evoked potentials recorded on averaged ECoG included phase-locked negative-positive-negative peaks at +20, +30 and +45 msec (Allison et al., 1989). These phase-locked peaks formed a gamma-range frequency oscillation and may have contributed to a proportion of somatosensory-related gamma-augmentation observed in the present study. Similarly, phase-locked peaks at +30, +45 and +80 msec as well as those at +45, +80 and +180 msec on somatosensory-evoked potentials may have contributed to the proportions of somatosensory-related beta-augmentation and alpha-augmentation, respectively.

Previous human studies using *in-vivo* scalp EEG recording as well as ECoG recording have reported the presence of gamma-to-beta transition in response to novel auditory stimuli (Haenschel et al., 2000) and the presence of gamma-to-beta transition associated with visual short-term memory task (Tallon-Baudry et al., 1999; 2001). In the present study, gamma-to-beta-transition was elicited by repetitive somatosensory-stimuli in children regardless of wakefulness or sleep. Thus, significance of gamma-to-beta transition in the present study might be different from that in the above-mentioned cognitive studies by Haenschel et al., 2000 or Tallon-Baudry et al., 1999; 2001. Further studies using different stimuli would be needed to determine the significance of gamma- followed by beta-oscillations observed in the present study. The somatosensory stimuli used in the present study retained several parameters such as intensity, frequency, duration, and emotional content.

Mechanism of somatosensory-related beta- and alpha-attenuation preceded by gamma-, beta- and alpha-augmentation

The present study demonstrated that median-nerve somatosensory-stimuli elicited beta-attenuation (14 – 28 Hz; maximally at 208 msec on average) and alpha-attenuation (8 – 12 Hz; maximally at 292 msec on average) in a substantial proportion of subjects; such attenuation of alpha- and beta-band oscillations followed augmentation of gamma-, beta- and alpha-band oscillations. This temporal course of amplitude alteration supports our hypothesis that somatosensory-related gamma-augmentation but not alpha-beta attenuation represents the *initial* cortical processing for external somatosensory stimuli. We also speculate that somatosensory-related alpha-beta attenuation represents a distinct somatosensory processing occurring *after* the cortical processing represented by gamma-augmentation.

The mechanism of such beta- and alpha-attenuation still remains hypothetical, but some studies have shown association between greater beta-alpha attenuation and greater awareness or attention to sensory stimuli (Palva et al., 2005; Bauer et al., 2006; Fan et al., 2007). Previous studies of healthy adults using MEG showed that tactile stimuli to the finger elicited attenuation of alpha- and beta-oscillations in the contralateral central area as well as concurrent augmentation of gamma-oscillations (30 – 100 Hz); thereby, the magnitude of alpha-beta attenuation as well as gamma-augmentation was larger when subjects perceived or attended stimuli compared to when they did not (Palva et al., 2005; Bauer et al., 2006). Another study of healthy adults using MEG showed that painful stimuli to the index and middle finger elicited attenuation of beta-oscillations (20 Hz) in both central areas at 150 – 350 msec after stimuli; thereby, the magnitude of beta-attenuation was larger in the contralateral side compared to the ipsilateral side but there was no difference in the magnitude of beta-attenuation between high-intensity and low-intensity stimuli or between rare-target (i.e.: more attention) and frequent-target stimuli (Hauck et al., 2007). A study of healthy adults using high-density scalp EEG recording demonstrated attenuation of alpha- and beta-oscillations at 200 – 450 msec after a warning signal during the attention network test (Fan et al., 2007). The present study was not designed to compare the magnitudes of alpha-beta attenuation between awake and sleep state on an intra-individual basis and failed to determine whether the magnitude of alpha-beta attenuation was associated with awareness or attention to somatosensory stimuli.

On the contrary to our observation that passive somatosensory-related gamma-augmentation preceded beta-alpha attenuation, previous ECoG studies of motor-induced amplitude alteration commonly demonstrated that visually-cued as well as self-paced motor-tasks elicited alpha-beta attenuation prior to gamma-augmentation (30–100 Hz) in the pre- and post-central gyri (Crone et al., 1998a; 1998b; Ohara et al., 2000; Pfurtscheller et al., 2003). Thereby, analyses of ECoG signals time-locked to movement onset revealed that brief gamma-augmentation temporally corresponded to movement onset, whereas alpha-beta attenuation was observed before movement onset, persisted during the movement, and lasted after gamma-augmentation subsided (Ohara et al., 2000; Pfurtscheller et al., 2003). Possible explanations for motor-induced alpha-beta attenuation occurring prior to movement onset include that (i) baseline alpha-beta oscillations reflect idling or inhibition of cortical areas and that (ii) attention or preparation toward movement induced alpha-beta attenuation prior to the actual execution of movement which then induces gamma-augmentation (Neuper et al., 2006; Klimesch et al., 2007; Palva and Palva, 2007).

Methodological issues

Factors which may affect the findings of cortical mapping using somatosensory-induced amplitude alteration include antiepileptic 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 somatosensory evoked potentials but no significant changes in somatosensory-evoked gamma-oscillations were noted after a single oral administration of lorazepam (Restuccia et al., 2002). A previous study of healthy adults demonstrated that phenytoin, one of the sodium channel blockers, elevated motor thresholds to transcranial magnetic stimulation (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 somatosensory-induced amplitude alteration.

ECoG recording from healthy humans is not feasible, and all of our subjects were patients with focal epilepsy; thus, interpretation and generalization of our observations must be made cautiously. First, we cannot completely rule out the possibility that somatosensory-related amplitude-modulation was altered by the effects of interictal epileptiform discharges, lesions and seizures. A previous study of rats showed that lesioning of the entorhinal cortex resulted in decreased physiological gamma-oscillations in the hippocampus (Bragin et al., 1995). Further studies, preferably with multivariate statistical evaluation on a larger sample, would be required to determine how event-related amplitude modulation is altered by the effects of lesions and epilepsy.

In patients 5 and 8, the pre-central gyrus showed the largest augmentation of gamma-, beta-, and alpha-oscillations, whereas the largest amplitude modulations were noted mainly in the post-central gyrus in the remaining subjects. Neither the epileptogenic lesion nor seizure onset zone involved the Rolandic or parietal region in patients 5 and 8. Previous human studies of somatosensory-evoked potentials using ECoG and magnetic fields using MEG showed that a large peak involved the pre-central gyrus in a subset of subjects, regardless of the location of structural lesions (Kawamura et al., 1996; Haseeb et al., 2007). Thus, it may be difficult to attribute the site showing the largest amplitude-augmentation to the location of the epileptogenic lesion or seizure onset zone in the present study. Studies using extraoperative ECoG recording are always associated with spatial sampling limitations, which probably have influenced our observations. All children had subdural 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 subdural electrodes or the deeply-situated cortex along the central sulcus.

In the present study, the inter-stimulus interval was 1,000 msec, and a period between –100 msec and –50 msec relative to the median nerve stimulation was set as a reference period. To our best knowledge, none of the previous human studies using *in-vivo* scalp EEG and MEG recordings demonstrated that somatosensory-induced alpha-beta attenuation lasted longer than 900 msec; thus, there is no strong evidence violating the assumption that ECoG during the reference period was unaffected by a lingering effect of alpha-beta attenuation.

Figure 2 demonstrates the variability in amplitude modulations across patients; in some cases, gamma augmentation occurred in a wide frequency range at 30 – 100 Hz, whereas in others, gamma augmentation involved a narrower gamma-band range. Such variability cannot be explained by the effect of alternating current artifact at 60 Hz alone; further studies are needed to determine the significance of such variability across patients.

CONCLUSIONS

The observations in the present study support the hypothesis that somatosensory-related gamma-augmentation but not alpha-beta attenuation represents the *initial* cortical processing for external somatosensory stimuli. Somatosensory-related alpha-beta attenuation appears to represent a temporally distinct stage of somatosensory processing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Somatosensory-related amplitude modulation in a 17-year-old girl with uncontrolled occipital lobe epilepsy (patient 10)

Topographic maps of ‘alpha amplitude (left)’, ‘beta amplitude (center)’ and ‘gamma amplitude (right)’ are presented. (A) The largest increase of ‘gamma-amplitude’ (264% compared to the baseline) was noted in the post-central gyrus at 25 msec (red arrow). (B) The largest increase of ‘beta-amplitude’ (60%) was noted in the post-central gyrus at 50 msec (pink arrow). (C) The largest increase of ‘alpha-amplitude’ (38%) was noted in the post-central gyrus at 75 msec (orange arrow). (D) The largest decrease of ‘beta-amplitude’ (63%) was noted in the electrode on the central sulcus at 175 msec. (E) The largest decrease of ‘alpha-amplitude’ (68%) was noted in the electrode on the central sulcus at 225 msec.

Figure 2. Time-frequency plot matrixes showing somatosensory-related amplitude modulation
 Significant gamma-augmentation was noted in all 10 patients. Subsequently, significant beta-augmentation was noted in nine patients (except for patient 6). Subsequently, significant alpha-augmentation was noted in eight patients (except for patients 4 and 6). Subsequently, significant beta-attenuation was noted in six patients (except for patients 1, 3, 6 and 7); subsequently, significant alpha-attenuation was noted in the same six patients.

Table 1

Summary of Clinical Data.

Patient	Gender	Age (yr)	Handedness	Antiepileptic medications	Electrode placement	Seizure onset zones determined on ECoG	Histology
1	F	4	Lt	ZNS	Lt TOPF	Lt TOPF	Dysplasia (Lt F) and Gliosis (Lt F TOP)
2	F	5	Rt	TPM	Rt POTF	Not captured but CSWS involving Rt POT was noted.	Dysplasia (Rt TP)
3	F	7	Lt	OXC, ZNS	Lt TOPF	Lt T; Lt F	Gliosis (Lt TOP)
4	F	9	Rt	VGB, PHT	Lt FPTO	Lt F	Cortical Tubers (Lt F)
5	F	10	Rt	LEV	Lt FPT	Lt F	Tumor (Lt F)
6	M	14	Rt	OXC, TPM, LEV	Rt PFOT	Rt PT	Dysplasia (Rt P)
7	F	15	Rt	OXC	Rt FPT	Not captured but frequent interictal spikes were noted in Rt P.	Tumor (Rt P)
8	M	15	Rt	OXC	Lt TOPF	Not captured but frequent interictal spikes were noted in Lt T.	Tumor (Lt T)
9	M	16	Rt	ZNS, TPM	Rt TOPF; Lt T	Rt T; Rt TO; Lt T	Not applicable
10	F	17	Rt	LEV, OXC, CZP	Rt OPTF	Rt O	Gliosis (Rt O)

Patient 9 did not undergo resective surgery but implantation of vagus nerve stimulator, since independent bilateral epileptogenic foci were identified by subdural electrocorticography recording. F: female. M: male. ZNS: Zonisamide. TPM: Topiramate. OXC: Oxcarbazepine. VGB: Vigabatrin. PHT: Phenytoin. LEV: Levetiracetam. CZP: Clonazepam. Lt: Left. Rt: Right. F: Frontal. C: Central. P: Parietal. O: Occipital. T: Temporal. CSWS: Continuous spike-and-waves during slow-wave sleep.

Table 2

The sequential order of amplitude modulations involving gamma-, beta- and alpha-bands.

	Epoch Showing the Largest Gamma Augmentation	Epoch Showing the Largest Beta Augmentation	Epoch Showing the Largest Alpha Augmentation	Epoch Showing the Largest Beta Attenuation	Epoch Showing the Largest Alpha Attenuation
Patient 1	25 msec (post-CG)	25 msec (post-CG)	100 msec (post-CG)	Not Applicable	Not Applicable
Patient 2	25 msec (post-CG)	25 msec (post-CG)	150 msec (post-CG)	275 msec (post-CG)	375 msec (post-CG)
Patient 3	25 msec (post-CG)	50 msec (pre-CG)	100 msec (post-CG)	Not Applicable	Not Applicable
Patient 4	25 msec (post-CG)	25 msec (post-CG)	Not Applicable	150 msec (post-CG)	150 msec (post-CG)
Patient 5	25 msec (pre-CG)	50 msec (pre-CG)	50 msec (pre-CG)	175 msec (post-CG)	350 msec (pre-CG)
Patient 6	25 msec (post-CG)	Not Applicable	Not Applicable	Not Applicable	Not Applicable
Patient 7	25 msec (post-CG)	50 msec (post-CG)	75 msec (post-CG)	Not Applicable	Not Applicable
Patient 8	25 msec (pre-CG)	50 msec (pre-CG)	125 msec (pre-CG)	225 msec (CS)	325 msec (CS)
Patient 9	25 msec (post-CG)	50 msec (post-CG)	100 msec (post-CG)	250 msec (post-CG)	325 msec (post-CG)
Patient 10	25 msec (post-CG)	50 msec (post-CG)	75 msec (post-CG)	175 msec (CS)	225 msec (CS)
Mean	25 msec	42 msec	97 msec	208 msec	292 msec
95% CI	Not Applicable	32 – 51 msec	71 – 123 msec	157 – 260 msec	201 – 382 msec
Median	25 msec	50 msec	100 msec	200 msec	325 msec
p = 0.01			p = 0.04		p = 0.04

P-values on the Wilcoxon-Signed Ranks Tests are shown. 95% CI: 95% confidence interval. pre-CG: pre-central gyrus. CS: central sulcus. post-CG: post-central gyrus.

* Two patients showed rebound augmentation of beta-oscillations following attenuation of beta-oscillations. Such rebound augmentation of beta-oscillations occurred in the post-central gyrus and reached significance at 500 – 625 msec with a maximal increase of 14% at 600 msec in patient #9. Similar rebound augmentation of beta-oscillations occurred in the pre-central gyrus and reached significance at 350 – 475 msec with a maximal increase of 38% at 425 msec in patient #10.

Table 3

The magnitude of amplitude modulations involving gamma-, beta- and alpha-bands.

	The Maximum Increase of 'Gamma Amplitude'	The Maximum Increase of 'Beta Amplitude'	The Maximum Increase of 'Alpha Amplitude'	The Maximum Decrease of 'Beta Amplitude'	The Maximum Decrease of 'Alpha Amplitude'
Patient 1	121% (post-CG)	102% (post-CG)	45% (post-CG)	Not Applicable	Not Applicable
Patient 2	98% (post-CG)	98% (post-CG)	234% (post-CG)	16% (post-CG)	27% (post-CG)
Patient 3	197% (post-CG)	92% (pre-CG)	113% (post-CG)	Not Applicable	Not Applicable
Patient 4	134% (post-CG)	37% (post-CG)	Not Applicable	35% (post-CG)	45% (post-CG)
Patient 5	149% (pre-CG)	64% (pre-CG)	86% (pre-CG)	18% (post-CG)	36% (pre-CG)
Patient 6	56% (post-CG)	Not Applicable	Not Applicable	Not Applicable	Not Applicable
Patient 7	87% (post-CG)	78% (post-CG)	30% (post-CG)	Not Applicable	Not Applicable
Patient 8	122% (pre-CG)	106% (pre-CG)	141% (pre-CG)	23% (CS)	34% (CS)
Patient 9	80% (post-CG)	45% (post-CG)	76% (post-CG)	29% (post-CG)	24% (post-CG)
Patient 10	264% (post-CG)	60% (post-CG)	38% (post-CG)	63% (CS)	68% (CS)
Mean	131%	76%	95%	31%	39%
95%CI	87 – 175%	56 – 95%	39 – 152%	12 – 49%	22 – 56%
Median	122%	78%	81%	26%	35%

95% CI: 95% confidence interval. pre-CG: pre-central gyrus. CS: central sulcus. post-CG: post-central gyrus. Regardless of augmentation or attenuation of oscillations, the site showing the largest amplitude changes was always localized in the Rolandic area in all patients. This observation is consistent with the generally-accepted notion that both gamma-augmentation and alpha-beta attenuation can serve as a surrogate marker of eloquent cortex (Pfurtscheller and Lopes da Silva, 1999).