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Cortical Responses to Input From Distant Areas are Modulated by Local Spontaneous Alpha/Beta Oscillations

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Abstract

Any given area in human cortex may receive input from multiple, functionally heterogeneous areas, potentially representing different processing threads. Alpha (8–13 Hz) and beta oscillations (13–20 Hz) have been hypothesized by other investigators to gate local cortical processing, but their influence on cortical responses to input from other cortical areas is unknown. To study this, we measured the effect of local oscillatory power and phase on cortical responses elicited by single-pulse electrical stimulation (SPES) at distant cortical sites, in awake human subjects implanted with intracranial electrodes for epilepsy surgery. In 4 out of 5 subjects, the amplitudes of corticocortical evoked potentials (CCEPs) elicited by distant SPES were reproducibly modulated by the power, but not the phase, of local oscillations in alpha and beta frequencies. Specifically, CCEP amplitudes were higher when average oscillatory power just before distant SPES (–110 to –10 ms) was high. This effect was observed in only a subset (0–33%) of sites with CCEPs and, like the CCEPs themselves, varied with stimulation at different distant sites. Our results suggest that although alpha and beta oscillations may gate local processing, they may also enhance the responsiveness of cortex to input from distant cortical sites.

Key words: alpha, beta, CCEP, high gamma, single-pulse electrical stimulation

Introduction

The human cerebral cortex consists of a large-scale network with nodes that are functionally segregated and interconnected so that each node can receive inputs in the form of postsynaptic potentials (PSPs) from, potentially, many other nodes during wakeful behavior. The ease with which activity in one node is elicited or modified by activity in structurally connected nodes, however, is not homogenous across the network and likely depends on

synaptic weights that have been tuned by phylogeny and ontology. These factors are believed to collectively determine the effective connectivity of large-scale cortical networks (Friston 2011), which in turn constrains the dynamics by which activity propagates across these networks during normal (Collard et al. 2016) and abnormal (Korzeniewska et al. 2011) brain states. However, the degree to which the local activity of a node can modify its effective connectivity with other nodes has not been studied in detail.

Oscillations in the alpha-band (8–13 Hz) and low beta-band (13–20 Hz) have been observed nearly everywhere in human cortex, including occipital lobe, sensorimotor cortex, and temporal lobe (Hughes and Crunelli 2005), and have been hypothesized to reflect cortical idling in the absence of task-relevant processing (Pfurtscheller et al. 1996) and/or a gating mechanism that actively inhibits task-irrelevant local cortical processing (Klimesch et al. 2007; Jensen and Mazaheri 2010; Sadaghiani and Kleinschmidt 2016). While task-relevant local cortical processing is accompanied by suppression of alpha/beta oscillations, alpha/beta oscillations are enhanced in task-irrelevant cortical regions. Moreover, modulation of these oscillations by attention, presumably through top-down influences, is correlated with task performance (Thut et al. 2006; Keil et al. 2012; van Diepen et al. 2015). Converging evidence also supports a correlation between alpha-band power suppression and high gamma-band power augmentation, the latter of which is tightly linked with increases in neuronal firing rate and/or synchrony (Ray et al. 2008; Buzsáki and Wang 2012). Indeed, firing rates increase with a decrease in alpha-power or at the trough of the alpha cycle in humans (Haegens et al. 2011; Spaak et al. 2012; Bahramisharif et al. 2013; de Pesters et al. 2016) and in monkeys (Haegens et al. 2015). The phase of alpha and/or beta oscillations can also modulate perceptual processing (Busch et al. 2009; Mathewson et al. 2009; Dugue et al. 2011; Ng et al. 2012), and some investigators have speculated that each cycle of an alpha oscillation encodes the output of an individual perceptual sample or quantum (Baumgarten et al. 2015). However, it is unknown whether the amplitude or phase of local alpha/beta oscillations regulate the effective connectivity of inputs from other nodes in the cortical network.

To investigate these issues, we used the direct application of single-pulse electrical stimulation (SPES) through epi-pial electrode pairs to elicit corticocortical evoked potentials (CCEPs) and corticocortical spectral responses (CCSRs). This technique can only be used in patients undergoing surgical treatment for intractable partial epilepsy (Greenlee et al. 2004; Matsumoto et al. 2004; Lacruz et al. 2007; Entz et al. 2014). CCEPs and CCSRs provide a direct and spatiotemporally precise electrophysiological readout of the PSPs and firing rate changes, respectively, that are elicited by stimulation in nearby or remote cortices via direct and indirect corticocortical connections (David et al. 2010; Matsumoto et al. 2017). CCEPs have been observed to dynamically change according to different physical or pathological states such as vigilance. Moreover, CCSRs in gamma frequencies (>30 Hz), including high-gamma frequencies (>60 Hz), may similarly change (Pigorini et al. 2015; Usami et al. 2015).

In this study we tested whether the amplitude and phase of local alpha/beta oscillations have an effect on the CCEPs and CCSRs that are elicited locally but are due to SPES delivered to nearby or distant cortical nodes.

Materials and Methods

Patients and Clinical Settings

Five patients with drug-resistant partial epilepsy underwent intracranial electrode implantation to localize their seizure onset zone and identify eloquent cortex for surgical planning (Table 1). The implanted electrodes consisted of arrays of macroelectrodes (platinum, 2.3 mm exposed diameter, 1.0 cm spacing, or 2.0 mm exposed diameter, 0.5 cm spacing, or depth electrodes [Ad-tech, Racine, WI, USA], or 4 × 4 arrays of microelectrodes [75 μm

Table 1 Clinical data of the subjects

Subject	Age	Gender	Epileptogenic region	Target lobe for CCEP
1	37	F	Left middle temporal	Temporal
2	43	F	Right temporal	Occipital
3	25	M	Left inferior frontal	Temporal
4	43	F	Left occipital	Temporal
5	15	M	Left superior frontal	Sensorimotor

exposed diameter, 0.9 mm spacing, PMT Corp., Chanhassen, USA)). In all patients, the anatomical placement of macroelectrodes and depth electrodes was chosen based on clinical need. All patients provided written informed consent for the use of cortical recording and stimulation, and for the use of microelectrode arrays in some patients, to supplement standard clinical procedures under research protocols approved by the Institutional Review Board of the Johns Hopkins Medical Institutions. The locations of these electrodes relative to the subject's anatomy were determined by co-registering a postoperative computed tomography scan with a preoperative magnetic resonance imaging (MRI) scan using the BiImage suite (Duncan et al. 2004).

Data Acquisition

In 3 patients (subjects 1–3), electrocorticograms (ECoGs) were referenced to an subdural electrode facing the dura mater remote from subdural grids/strips, and were recorded with a NeuroPort System (BlackRock Microsystems: Salt Lake City, UT, USA), which amplified and sampled the data at 1 kHz with an analog third-order Butterworth anti-aliasing filter. In 2 patients (subjects 4 and 5), ECoGs were recorded with a 256-channel EEG-1100 system (Nihon Kohden America, Irvine, CA, USA), which amplified and sampled the data at 2 kHz. Among the participants, subject 4 was implanted with electrodes twice because the first implantation failed to adequately sample the ictal onset zone. In all subjects, channels with excessive noise were identified visually by a clinical neurophysiologist and excluded from further analysis. All the data were streamed and stored separately for analysis.

Corticocortical Evoked Potentials

The CCEP methodology is described in detail elsewhere (Matsumoto et al. 2004, 2007). Direct electrical stimulation was applied in a bipolar manner to a pair of adjacently placed subdural electrodes using a constant-current stimulator (Grass S12 stimulator, Astro-Med, Inc., West Warwick, RI, USA). In each implantation we selected 1–3 stimulation sites where alpha/beta-band oscillations were observed in the raw ECoG. Single-pulse electrical stimuli (biphasic wave pulse: 0.3-ms duration) were delivered at jittered interstimulus intervals of 3.0–3.6 s (Fig. 1A). Stimulation was monitored by a physician experienced in ECoG interpretation and electrocortical stimulation mapping. One set of trials for each stimulation site comprised 70–200 stimuli, depending on clinical circumstances and the time available for testing. During the recording, we asked the patients to recline comfortably awake on the bed and to continue their usual activities. We titrated stimulation intensity in increments of 0.5–1 mA, making sure that no afterdischarges were induced, up to a maximum of 5 mA for electrode arrays with 0.5 cm spacing or 10 mA for arrays with 1.0 cm spacing. More current was used for electrodes with larger surface area and interelectrode distances to achieve similar current densities. Because stimulation of sensorimotor or visual cortices can

Figure 1. Outline of experiment. Subdural grids and microelectrode arrays (MIC) implanted on the left hemisphere in one subject (subject 1, stimulation site 1) is shown as an example. (A) Single-pulse electrical stimulation (SPES) was applied with a biphasic wave of 0.3 ms and randomly jittered interstimulus interval (ISI) of 3.0–3.6 s across the 2 yellow electrodes (bipolar). A few trials at 1 electrode (asterisk in the brain) are shown. We used a stimulation intensity of 5 or 10 mA, to avoid evoking symptoms that would redirect attention to the stimulus. 70–200 trials were recorded and ECoGs were averaged in the time domain relative to onset of SPES (analysis window: –500 to +1500 ms). We excluded electrodes within 1.5 cm from stimulated electrodes, over lesions, ictal onset zones, or contaminated with artifacts (small black dots). Electrodes (shown in white disks) were considered to have effective connectivity with the stimulated site if their averaged waveform (CCEP) exceeded z-scores of 6 relative to baseline (–500 to –10 ms) at least 10 ms after stimulation for 30 ms succession. These electrodes were selected for further analysis. The spectrograms of the window from –500 to –5 ms of stimulation were averaged across all trials without artifacts in selected electrodes and individual alpha/beta-bands with 4 Hz width were selected (8–12 Hz in this case). (B) At each electrode with a CCEP, trials were separately sorted by the average of alpha/beta power from –110 to –10 ms (gray-shaded area; upper 1/3 vs. lower 1/3) or a phase value at the timing of stimulation inferred from –10 ms of stimulation ($< \pi/3$ vs. $> 2\pi/3$). (C) Comparison of CCEPs at the electrode with asterisk (in A) of trials with high versus low power and of trials with up versus down phase in alpha/beta frequencies (high power/up phase: magenta, low power/down phase: green). Shaded areas show one standard deviation from the mean at each time point. Black bars along the x-axis (time) indicate periods of significant differences (Welch's t-test, corrected by false discovery rate [FDR] = 0.05 through the analysis period). To investigate power effects on CCEPs irrespective of phase, we picked only electrodes that showed no phase difference between 2 groups, which were calculated the same way as in C or vice versa. Finally, we investigated whether the electrodes that had significant differences between 2 groups at each electrode had real significance after multiple comparisons were corrected by a nonparametric permutation test.

sometimes evoke symptoms at low intensities (i.e., movement or subjective sensory sensation of a part of the body, and phosphenes), which could cause patients to attend to the stimulus and modify their low-frequency oscillations, we sometimes used 5 mA even for arrays with 1.0 cm spacing and confirmed that stimulation produced no symptom.

Selection of Electrodes and Frequency Band of Alpha/Beta Oscillations

We excluded electrodes (small black dots in Fig. 1A) that were located over a lesion or over the ictal onset zone, electrodes that were contaminated with artifacts according to a clinical neurophysiologist, and all electrodes within 1.5 cm of the stimulated channels, to avoid excessive stimulation artifacts (Keller et al. 2014). In addition, we excluded electrodes that were in a lobe or region separate from that of the stimulating electrodes because the dominant alpha/beta oscillations had different peak frequencies. In the remaining electrodes, ECoGs were averaged in the time domain relative to stimulus onset (analysis window: –500 to +1500 ms) to estimate the CCEP. We calculated the z-score of the amplitude of the resulting waveform in reference to the prestimulus baseline (–500 to –10 ms). If it exceeded 6 (Keller et al.

2011), beginning at least 10 ms after stimulation and lasting for at least 30 milliseconds, the recording site was considered to have significant effective connectivity with the stimulated site, and was included in further analyses. We excluded CCEP components within 10 ms of stimulus onset to avoid stimulus artifacts (Kobayashi et al. 2015). CCEPs usually consist of an early, brief negative component called N1 (10–50 ms) and a later slow negative component called N2 (50–300 ms). In some cases the polarity can be opposite, or only the second negative component is seen without a clear first sharp component (Matsumoto et al. 2017). We also investigated the relationship between the latencies of typical CCEP components (i.e., we could only differentiate N1 and N2) and the approximate distance from stimulation site to recording sites in selected electrodes by aforementioned criteria. Using a partial correlation analysis, we confirmed in some cases that latency was correlated with distance and that amplitude was anti-correlated with distance, both of which corroborated the notion that CCEPs reflect corticocortical connections (see Supplementary Discussion about CCEP latency, and Supplementary Fig. S1). Furthermore, amplitude was correlated with latency when the effect of distance was removed.

We estimated the frequency band of alpha/beta oscillations at the time of stimulation by first computing a spectrogram

from a Fourier transform with a window of -500 to -5 ms relative to stimulation. This spectrogram was then averaged across all trials without artifacts, in all previously chosen electrodes, resulting in a grand average spectrogram of the prestimulus time interval for each individual patient (Fig. 1A). The frequency range of the alpha/beta-band used in subsequent analyses consisted of a band with fixed 4 Hz width (center frequency ± 2 Hz) that was chosen by visual inspection of the grand average spectrogram such that the band was centered on the most prominent power within the alpha/beta frequency range (8–20 Hz). We confirmed that these were compatible with frequencies observed in the raw ECoG signals. This band was used for sorting trials for further analysis.

Effect of Alpha/Beta Oscillations on CCEPs

To examine the local effect of alpha/beta-band power and phase as accurately as possible, the data were analyzed at each electrode separately. A Hilbert transform was applied to the period from -500 to -5 ms after high- and low-pass filtering with fixed Butterworth filters of order 4 in each trial. Trials were sorted (Fig. 1B) by the average of alpha/beta power from -110 to -10 ms (power spectrum density: PSD [$\mu\text{V}^2/\text{Hz}$]), or by their phase value ($-\pi$ to π) at the timing of stimulation, which was inferred from the phase of the filtered ECoG 10 ms prior to stimulation, estimated from the center frequency and the latency to stimulation. To avoid the inherent edge effects of the Hilbert transform (Aru et al. 2015), we did not use the data from -10 to -5 ms relative to stimulation for sorting of CCEPs. From trials (n) sorted by power, we chose a subset of trials with the upper 1/3 and lower 1/3 of alpha/beta power (almost $n/3$ in each group) and defined these as high/low power trials, respectively. For trials sorted by phase, trials satisfying phase $< \pi/3$ and $> 2\pi/3$ were considered as up/down phase trials (each group accounting for $n/3$ trials), respectively. Because the effect of oscillation phase on cognition has been reported to depend on power (Mathewson et al. 2009), we also examined the effect of phase after selecting trials with alpha/beta power in the upper 1/2 of all trials.

SPES-induced responses typically lasted for several hundred milliseconds, and not more than 1.0 s (see the representative waveform in Fig. 1A). Therefore, we used a long period (2.3 s on average) before stimulation for estimating a surrogate of background baseline shifts accompanying dynamic changes in alpha/beta power (Nikulin et al. 2007; Schalk 2015). Randomly choosing an integer (x) from -10 to -210 , surrogate trials from $x-2000$ to x ms of stimulation were sampled from each trial in n trials, and 2 average waveforms from high/low power (up/down phase) trials were computed the same way that real trials were computed. The procedure was repeated 1000 times and average waveforms from the same group were further averaged to estimate the baseline at each time point for each group (high/low power trials). Each trial in each group was subtracted by the corresponding surrogate and statistically compared. The null hypothesis was that the 2 groups were the same at any time point. For every time point within the analysis window the 2 groups were compared by Welch's t -test, and multiple comparisons were corrected for using the Benjamini-Hochberg procedure (Benjamini and Hochberg 1995) with a false discovery rate cutoff of $q < 0.05$ across the analysis period in each electrode. The typical waveform of CCEPs could usually be clearly seen within 300 ms after stimulation. So, we considered power/phase effects to be significant if we found differences in CCEP amplitudes within from $+10$ to $+500$ ms of stimulation, without a significant difference during the baseline period (-500 to -10 ms relative to stimulation) (Fig. 1C).

Furthermore, to investigate the effect of alpha/beta power on CCEPs irrespective of phase, we removed electrodes that showed significant phase differences between 2 groups ($P < 0.05$) by the Mardia-Watson-Wheeler test. On the other hand, when we investigated the effect of alpha/beta phase on CCEPs irrespective of power, we removed electrodes that showed significant power differences between 2 groups by Welch's t -test.

To solve the multiple comparison problems arising from multiple recording sites, we also applied nonparametric statistical testing (Maris and Oostenveld 2007). At each electrode where we found significance based on the aforementioned criteria, we selected all the samples where the t -value satisfied $q < 0.05$ from $+10$ to $+500$ ms of stimulation. Then we calculated the sum of them and made cluster-level statistics. When investigating the effect of alpha/beta power on CCEPs, 2 groups that consisted of $1/3 n$ trials respectively were randomly taken after sorting all the trials (consisting of n trials) by power. Also, corresponding background shifts in the 2 groups were calculated and subtracted from each trial in both groups. Both groups were compared and cluster-level statistics were calculated. Then only the highest statistic from all the recording electrodes was taken. This procedure was repeated 1000 times (the highest cluster statistics in each permutation were rounded up to the nearest integer for efficient computing) and the null distribution of the maximum cluster-level statistics was compared with the original cluster-level statistics. When investigating the effect of alpha/beta phase on CCEPs, random phases taken from von Mises distribution were added to the phase of each trial after sorting all the trials by phase, and 2 groups were selected by the aforementioned criteria (phase added by random phase $< \pi/3$ or $> 2\pi/3$). Background shifts were corrected as well. A P -value threshold was defined < 0.05 .

Effect of Alpha/Beta Oscillations on CCSRs

To investigate the effect of SPES on neuronal firing rates, we calculated SPES-induced changes in high gamma power (70–110 Hz) (CCSR^{HG}: high gamma corticocortical spectral response). We selected electrodes for analysis and frequency band of alpha/beta oscillations the same way we did for CCEPs. Artifacts were present at 60 and 100 Hz throughout the recording with the Blackrock system or 60 Hz with NihonKohden system. Therefore, we band-passed raw data from high/low power trials at 70–95 Hz for Blackrock data or at 70–110 Hz for NihonKohden data with a Butterworth filter of order 6 in each trial before the Hilbert transform. We applied filtering in the backward direction from $+1500$ to $+5$ ms because stimulation artifacts around 0 ms were so large that it interfered with analysis. In the electrodes that showed significant alpha/beta-band effects on CCEPs, we compared the difference between CCSR^{HG} in trials with high versus low alpha/beta power the same way we compared the CCEPs. The nonparametric test was also applied for the electrodes of significance.

Results

Local Alpha/Beta Power Reproducibly Affects CCEP, But its Phase Does Not

Among 5 patients, we applied SPES to a total of 14 sites near electrodes with alpha/beta-band oscillations (Table 1). For each stimulation site, we investigated local alpha/beta power/phase effects at each electrode that showed significant CCEPs, implying effective connectivity with the stimulation site (Fig. 1). We found significant CCEPs in 7–100% of the electrodes we included for analysis (Table 2). For 7 out of 14 stimulation sites, we observed

alpha/beta power effects at 2–33% of the sites that showed significant CCEPs (Table 2 and Fig. 2). All the statistical data are presented in Supplementary Table S2. On the other hand, we only observed an effect of phase on CCEP amplitude in one electrode with 1 out of 14 stimulation sites. When we only investigated phase effects in trials with the highest alpha/beta power prior to stimulation (upper 50th percentile), an effect of phase on CCEP disappeared. Six stimulation sites without a significant effect are presented in Supplementary Figure S2.

Alpha/Beta Power Modulates CCEPs

To further investigate the effect of alpha/beta power on CCEPs, we measured the amplitude of the peak or trough of the CCEP waveform closest to the minimum *P*-value (Fig. 3). These CCEP amplitudes were always higher in trials with high alpha/beta power (upper third of trials) than in trials with low power. Alpha power effects were most frequently observed at a center frequency of 10 Hz (19 sites). Among all sites with significant power effects, we investigated whether higher alpha power was associated with higher CCEP amplitude. First, we calculated the logarithm of the ratio of the average baseline alpha power in high (magenta trials in Fig. 1C) versus low (green trials in Fig. 1C) power trials, and we calculated the ratio of the CCEP amplitudes (closest to the minimum *P*-value) in high versus low power trials (as in Fig. 1C). Finally, we tested the correlation between these 2 ratios. We found a significant correlation ($r = 0.69$, $P = 0.003$; Pearson correlation analysis).

When we analyzed the effect of alpha/beta oscillations on CCEP latency, we observed a significant power effect on CCEP N2 latency in 2 out of 14 cases, which indicated that alpha oscillations with high power were associated with longer latency (see Supplementary Discussion about Alpha/beta oscillation effect on CCEP latency, and Supplementary Fig. S3). On the other hand, the effect of phase on CCEP latency was not reproducible (Supplementary Figs S4 and S5).

Alpha/Beta Power Rarely Affects High-Gamma CCSR

We also investigated the effect of alpha/beta power on CCSR^{HG}. Using the same criteria we used for CCEPs, we observed significant

CCSR^{HG} in only 0–21% of the analyzed electrodes (Supplementary Table S1, Fig. 2, and Supplementary Fig. S2). Among the electrodes that showed significant alpha/beta-band effects on CCSR^{HG}, we compared CCSR^{HG} in trials with high versus low alpha/beta power. We observed a power effect on CCSR^{HG} in only 2 electrodes across all patients. In both cases, trials with high alpha/beta power were associated with greater CCSR^{HG} after ~200 ms (Fig. 4A). A small phase effect on CCSR^{HG} was also found in 2 electrodes across all patients, and stimulation at up-phase might have made high-gamma activity slightly increased (Fig. 4B).

Discussion

Oscillations at alpha and beta frequencies are prominent features of the human electroencephalogram, whether recorded at the scalp or with intracranial electrodes. They are observed most consistently over primary and secondary sensory cortices, with beta frequencies perhaps more prominent over motor cortex (Hughes and Crunelli 2005), possibly reflecting greater synchronization of their generators in regions with more homogenous function and/or thalamocortical inputs. The mechanisms generating alpha/beta oscillations are not well understood, but may depend on both local cortical circuitry and thalamocortical inputs to cortical circuits (Lopes da Silva et al. 1980; Steriade et al. 1987; Hawasli et al. 2016). Models focusing on the hippocampus or local cortical circuitry have suggested interlaminar interactions and the interaction of several inhibitory dynamics as potential mechanisms for slow-band oscillations (Rotstein et al. 2005; Lee et al. 2013). On the other hand, thalamocortical generators may also contribute to these oscillations via inputs to deep layers of cortex from thalamocortical relay (TCR) neurons that are firing in a phasic pattern, in turn controlled by inhibitory neurons in the thalamic reticular nucleus (TRN) (Sherman and Guillery 1996). During these oscillations, local cortical activity is inhibited, or “gated.” When TRN neurons receive suprathreshold ascending inputs from the periphery (in first order thalamic nuclei such as the lateral geniculate nucleus or ventral posterolateral nucleus) or from other cortical regions (in higher order thalamic nuclei, e.g., pulvinar), their firing pattern shifts from the burst mode to a tonic mode that supports thalamocortical transfer of input from the

Table 2 Alpha/beta-band effect on CCEPs

Subject-# of stimulation site	# of trials	Stimulus Intensity [mA]	# of sites with significant CCEPs (percentage of analyzed electrodes)	Target center frequency [Hz]	# of effect on CCEP (percentage of the sites with significant CCEPs)		
					Power	Phase	Phase (upper 50th percentile)
1-1	146	5	60 (62)	10	12 (20)	0 (0)	0 (0)
1-2	162	5	58 (60)	10	3 (5)	0 (0)	0 (0)
1-3	72	5	64 (64)	10	1 (2)	0 (0)	0 (0)
2-1	184	10	9 (64)	10	3 (33)	0 (0)	0 (0)
2-2	183	10	2 (11)	10	0 (0)	0 (0)	0 (0)
2-3	177	10	7 (50)	9	0 (0)	0 (0)	0 (0)
3-1	125	10	20 (100)	9	0 (0)	0 (0)	0 (0)
4-1	148	10	8 (73)	9	1 (13)	0 (0)	0 (0)
4-2	134	10	13 (100)	8	1 (8)	0 (0)	0 (0)
4-3	128	5	14 (26)	9	0 (0)	0 (0)	0 (0)
4-4	147	5	4 (7)	9	0 (0)	0 (0)	0 (0)
5-1	127	5	22 (52)	13	2 (9)	0 (0)	0 (0)
5-2	100	5	24 (56)	13	0 (0)	1 (4)	0 (0)
5-3	99	5	32 (76)	13	0 (0)	0 (0)	0 (0)

Subject 4 was investigated twice. 4-1 and 4-2 were done in the first implantation, and 4-3 and 4-4 were done in the second implantation.

Figure 2. Alpha/beta power effects on CCEP. Red circles show all the electrodes that had significant alpha/beta power effect (only the stimulation sets that had any numbers of significant channels were shown). Spectrogram of the baseline in each stimulation set is shown in its inset. All microelectrodes (4×4 electrodes in subject 1 [MIC: microelectrodes]) and depth electrodes (colored electrodes in subject 5) were shown but excluded by the aforementioned selection criteria. Representative averaged waveforms from 2 groups (high power/up phase: magenta, low power/down phase: green) at one electrode are shown in each stimulation sets. Scales and black bars are the same as for Figure 1. The electrodes that showed significant CCSR^{HG} are accentuated with a bright ring. a, b, of Subj.1-1 and 5-1: See Figure 4 about these 4 electrodes.

Figure 3. Scatter plot shows the relationship between baseline alpha or beta powers of high/low power trials and the corresponding CCEP amplitudes of the peak or trough closest to the timing with minimum P-value in all red electrodes. Note that the ratio of the CCEP amplitude between high and low power trials (y-axis) is always more than 1.0, regardless of the ratio of baseline alpha/beta power between high and low power trials (x-axis), which means high alpha/beta power makes CCEP large (logarithmic transformation was applied for the latter ratios). H, high power trials; L, low power trials.

periphery or from other cortical regions. Recent modeling work has also emphasized a cortical effect on the generators of thalamic oscillations (Destexhe 2009; Willis et al. 2015) and its effect on changes in firing patterns (Barardi et al. 2016) in a more quantitative manner. The shift from burst to tonic firing modes is accompanied by a suppression of alpha/beta oscillations. This model is consistent with human EEG studies that have consistently associated the suppression of alpha/beta oscillations with local cortical. Conversely, enhancement of alpha/beta oscillations has been associated with local cortical inactivity or “idling” (Pfurtscheller et al. 1996).

In recent years SPES has been used by a growing number of investigators (Greenlee et al. 2004; Matsumoto et al. 2004; Lacruz et al. 2007; Entz et al. 2014) to probe the functional connectivity of cortical networks sampled by electrode arrays implanted for diagnostic purposes in patients undergoing epilepsy surgery. The CCEPs that arise from SPES are believed to represent summed PSPs elicited by orthodromic or antidromic action potentials originating either directly from the distant cortical SPES, or via indirect pathways that may involve first order or higher order thalamic nuclei (Matsumoto et al. 2017). CCEPs appear to be robust electrophysiological markers for functional connectivity between different cortical sites, but their constituent PSPs may or may not have an impact on the

Figure 4. Alpha/beta power/phase effect on $CCSR^{HG}$. We observed the significant power effect in 2 channels (a, b of Subj. 5-1 in Fig. 2), both of which showed high gamma increase in high power trials around the transition of CCEP deflection, after ~200 ms. We observed a significant phase effect in 2 channels (a, b of Subj. 1-1 in Fig. 2). In the process of calculating $CCSR^{HG}$, both ends of each analysis window were contaminated with artifacts. So data <250 ms from each end of the data were removed from $CCSR^{HG}$ (also <250 ms from the start in CCEP data removed to align time window with $CCSR^{HG}$) for presentation. The other conventions are the same as for Figure 1.

firing behavior of local neuronal populations. SPES can also elicit $CCSR$'s in a variety of frequency ranges, including the high gamma (60–150 Hz) range. Because high gamma power modulation is an excellent index of changes in the aggregate firing rates of local neuronal populations (Ray et al. 2008; Lachaux et al. 2012), $CCSR^{HG}$ may provide additional information of the downstream effects of SPES on the firing behavior of local neuronal populations where CCEPs may also be observed.

Our results suggest that during wakefulness, larger alpha or beta oscillations allow input from connected areas to elicit a larger CCEP, regardless of the phase of the oscillations. Our

correlation analysis provided additional support for this finding, especially at sites with more prominent alpha/beta oscillations. Based on current models of the generators for CCEPs, our findings have interesting implications for the neurophysiological mechanisms that govern human cortical networks.

The mechanisms generating CCEPs are not well established, but it is believed that the early (<50 ms) sharp component of the CCEP represents PSPs generated via a direct corticocortical pathway with axons that terminate in layer II/III in cortex (Lorente de No 1949; Kobayashi et al. 2015). In contrast, the later (>50 ms), slow component of the CCEP is likely a multisynaptic

response with generators that include a corticothalamocortical pathway (Matsumoto et al. 2017). This transthalamic pathway most likely passes through higher order thalamic nuclei (Sherman 2005) before it reaches cortical neurons, although it is not well established which layer receives the afferents (axons from pulvinar have been reported to terminate in layer I) and what kinds of neurons are affected.

The neurophysiological mechanisms and functional significance of alpha and beta oscillations remain controversial. Based on early observations (Pfurtscheller et al. 1996) it was hypothesized that alpha and beta oscillations are generated by cortical areas that are not activated by a stimulus or task, and correspond to an awake but “idling” state of cortical and thalamocortical circuits. Conversely, based on recent observations that these oscillations are enhanced in task-irrelevant regions and that this enhancement correlates with task performance (Worden et al. 2000; Thut et al. 2006; Händel et al. 2011), investigators have hypothesized that they reflect an active process of local cortical inhibition (Klimesch et al. 2007; Jensen and Mazaheri 2010; Sadaghiani and Kleinschmidt 2016) that reduces interference with task-relevant processing in other cortical areas. Notwithstanding these differences, there is general agreement that alpha and beta oscillations are locally suppressed in cortical areas that are activated by a task and that this suppression is greater when attention is focused on the task. This so-called “event-related desynchronization,” or ERD, is associated with greater local activity and excitability. The latter is reflected by higher motor evoked potentials when TMS is applied directly to motor cortex during ERD (Takemi et al. 2013; Schulz et al. 2014). Thus, the relative power of alpha/beta oscillations may reflect the degree of local activity in cortical and thalamocortical circuits at any given time. Instead of testing the effect of these oscillations on the local activation state of cortex, however, we tested their impact on the functional connectivity between local and distant cortical areas, estimated by the amplitude of CCEPs and CCSR^{HG}s elicited locally from stimulation at distant sites with anatomical and functional connectivity.

It may seem counterintuitive that cortex would be more receptive to input from distant cortical sites when it is in a state of lower local excitability. However, local excitability may only pertain to the likelihood of output from this region and not to its responsiveness to external inputs from distant, but connected sites. It is possible that higher power alpha/beta oscillations are generated by a larger and more synchronous population of local neurons, especially inhibitory interneurons, and that input to these neurons from connected cortical regions results in larger PSPs. An important caveat is that the input from distant regions, in this case, is artificial, and unlike physiological inputs, the action potentials that elicit CCEPs arrive without contextual inputs from other brain regions, for example, without top-down attention-related inputs from frontal lobe. Nevertheless, unexpected input from connected cortical regions may occur under natural circumstances, for example reflecting bottom-up input from a novel stimulus. In the thalamus, the burst mode appears to be a metastable network state that is easily converted to the tonic mode when it receives suprathreshold input (Sherman and Guillery 1996; Barardi et al. 2016). If a similar mechanism is at play in our findings, cortex in a less active state, indexed by higher alpha/beta power, may be more responsive to new inputs, potentially facilitating new processing threads originating elsewhere. It is important to note that although we studied the effect of power in spontaneous alpha/beta oscillations, we did not test the effect of task-related modulations of alpha power or manipulations of attention. Such experimental manipulations may be

useful in future studies. Conversely, lower alpha/beta power may represent a state in which cortex is more active, perhaps already processing previous inputs and/or generating outputs, but is less responsive to additional inputs from connected cortical regions. It is tempting to speculate that this could potentially serve to stabilize existing processing threads.

An alternative explanation for the augmentation of CCEP amplitudes by high versus low alpha oscillations would be the summation of CCEPs with spontaneous alpha/beta oscillations. However, we would expect this to depend on the phase of these oscillations at the time of SPES, and there would have to be a systematic correlation between the power and phase of these oscillations in the baseline at the time of SPES. We did not observe this in our data.

The mechanisms generating CCSR^{HG}s, including CCSR^{HG}s are also largely unknown, but stimulation studies with single unit recordings or dye imaging have indicated that direct cortical stimulation evokes increased spiking immediately after stimulation, which is then followed by inhibition (Li and Chou 1962; Alarcon et al. 2012; Kozyrev et al. 2014). This is consistent with CCSR studies that have typically observed an increase, followed by a decrease, of high gamma activity, which serves as an index of population neuronal firing rates (Ray et al. 2008).

In our comparison of CCSR^{HG} in the setting of high versus low alpha/beta power or up/down phase, we observed significant differences in a very limited number of electrodes. In monkeys, high gamma generators have been identified in supragranular and granular layers (Maier et al. 2010; Spaak et al. 2012), while the generators for low-frequency oscillations (delta, theta, and alpha) have been localized to deeper layers (Maier et al. 2011). Mejias et al. revealed in their cortical model that input to the deep cortical layer modifies alpha power in that layer, affecting high gamma power in the superficial layer via interlaminar interactions (Mejias et al. 2016). We observed an effect of alpha/beta power on CCSR^{HG} only at longer latencies, suggesting that this effect was more likely mediated through input to deeper layers of cortex via a transthalamic route. Input from the thalamus may have a limited influence on the main generators of CCSR^{HG} in more superficial layers. Additionally, the relative absence of effects on CCSR^{HG}s could have been due to inadequate spatial sampling. CCEPs occur at lower frequencies and are generally more distributed and detectable than the higher frequency activities of CCSR^{HG} (Kajikawa and Schroeder 2011). Since the latter probably reflects downstream changes in firing rates in response to distant SPES, it is perhaps not surprising that this would occur in a smaller subset of sites with CCEPs, which reflect evoked synaptic potentials that may or may not result in firing rate changes.

We did not observe reproducible phase effects on CCEPs, but it is difficult to definitively rule out these effects. The lack of significant phase effects can arise from inadequate temporal precision when estimating the phase at which stimuli were delivered, or temporal jitter in the effect of stimulation on local neuronal activity (Aru et al. 2015). We also failed to detect phase effects on the CCSR^{HG}s, with the exception of a few recording sites (Fig. 4B), where we observed small modulations that were statistically significant at relatively few, noncontiguous time points, far less impressive than the effect of power. Future studies will be needed to verify phase effects on CCEPs and CCSR^{HG}s.

Our results may also have implications for the interpretation of cognitive event-related potentials (ERPs). ERPs may depend not only on a given task, but also on the amplitude or phase of local alpha/beta oscillations when the task occurs

(Stampfer and Basar 1985). Analysis of ERPs after stratification by baseline alpha/beta power might help understand the effects of task-related brain activation.

Our findings may also complement the results from transcranial magnetic stimulation and CCEPs elicited during sleep. In this state, when brain electrical activity is dominated by very low-frequency oscillations (<2 Hz), evoked responses are typically larger than in wakefulness (Massimini et al. 2005, 2007; Pigorini et al. 2015; Usami et al. 2015). Although the oscillations we studied herein were in a higher frequency range and occurred during wakefulness, we found that stimulation-evoked responses are larger when oscillation amplitudes were higher, similar to the effect of very low-frequency oscillations during sleep.

There were a few limitations of our study in addition to those already mentioned. First, the subjects were all patients with intractable partial epilepsy on antiepileptic drugs. These factors may have affected our results. Second, we did not analyze power/phase effects at the site of stimulation because we thought stimulation was high enough, especially around the stimulation site, to maximally affect neuronal output to other areas, regardless of local oscillations. Nevertheless, a previous simulation demonstrated that stimulation during the network depolarization phase of ongoing oscillations at the site of stimulation, elicited a longer period of poststimulus quiescence (Anderson et al. 2009). Third, although a recent TMS study suggested that stimulation can evoke local oscillations (Rosanova et al. 2009), the local modulation of oscillations after stimulation was beyond the scope of our study.

Supplementary Material

Supplementary material is available at *Cerebral Cortex* online.

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Notes

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