Effects of Neural Synchrony on Surface EEG

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It has long been assumed that the surface electroencephalography (EEG) signal depends on both the amplitude and spatial synchronization of underlying neural activity, though isolating their respective contribution remains elusive. To address this, we made simultaneous surface EEG measurements along with intracortical recordings of local field potentials (LFPs) in the primary visual cortex of behaving nonhuman primates. We found that trial-by-trial fluctuations in EEG power could be explained by a linear combination of LFP power and interelectrode temporal synchronization. This effect was observed in both stimulus and stimulus-free conditions and was particularly strong in the gamma range (30–100 Hz). Subsequently, we used pharmacological manipulations to show that neural synchrony can produce a positively modulated EEG signal even when the LFP signal is negatively modulated. Taken together, our results demonstrate that neural synchrony can modulate EEG signals independently of amplitude changes in neural activity. This finding has strong implications for the interpretation of EEG in basic and clinical research, and helps reconcile EEG response discrepancies observed in different modalities (e.g., EEG vs. functional magnetic resonance imaging) and different spatial scales (e.g., EEG vs. intracranial EEG).

Keywords: EEG, LFP, MUA, lidocaine, synchrony

Introduction

Electroencephalography (EEG) is one of the most commonly used methods to measure brain activity in humans. However, despite its widespread use, we still lack a clear understanding of how EEG signals are related to the spatiotemporal organization of underlying neuronal activity. The dominant theory is that a surface electrode provides an aggregate measure of the synaptic potentials of cortical neurons in an open-field arrangement, such as the pyramidal cells that are oriented perpendicularly to the cortical surface and form current dipoles (Nunez 2006). In addition, it has been shown that the surface EEG may also be related to the activity of stellate cells in cortical layer 4C, which receive sensory input from the thalamus (Steinschneider et al. 1992; Tenke et al. 1993). Regardless of its biological origin, it is of particular importance to note that the amplitude of a surface EEG measure is not only dependent on the magnitude of individual current dipoles (Whittingstall and Logothetis 2009), but also on the degree of their temporal synchronization across space (Gloor 1985; Makeig et al. 2002; Nunez 2006). That is, transient increases in neural activity need to be synchronous over a relatively large patch of cortex (Cooper et al. 1965; Nunez 2006) to produce a detectable EEG response. This is due to the superposition principle, where the net sum of temporally coherent dipole sources is larger than that of their individual source magnitudes (Murakami and Okada 2006). It is therefore theoretically possible that increase in cortical neural synchrony alone can enhance surface EEG signals without concomitant changes in the amplitude of cortical activity (Nunez 2006; Cosandier-Rimele et al. 2008; Telenczuk et al. 2010). However, experimental confirmation of this hypothesis remains elusive, partly due to the difficulty in reliably separating intracortical measures of signal amplitude and spatial synchrony. In this study, we made simultaneous intracortical recordings of local field potentials (LFPs) and surface EEG measurements in the primary visual cortex (V1) of 2 behaving nonhuman primates (Macaca mulatta) during visual stimulation. Our aim was to assess how unique changes in intracortical activity—defined by LFP amplitude and synchronization over space—affect the surface EEG. We found that trial-by-trial fluctuations in EEG power not only reflected changes in neural activity but also the degree of temporal synchrony between LFP electrode pairs (spatial coherence or SC). To confirm this finding, we used a pharmacological manipulation (local injections of lidocaine) to dissociate EEG and LFP amplitude. Here, we found that opposing changes in EEG and LFP power could be explained by SC. Our results show that neural synchrony alone can modulate EEG signals in the absence of changes in the amplitude of local neural activity, thus explaining differences often observed between EEG and LFP measurements.

Materials and Methods

Data Acquisition

Electrophysiological recordings from 2 awake, behaving monkeys (M. mulatta) are included in the present study. All animal experiments were approved by the local authorities (Regierungspräsidium Tübingen) and are in full compliance with the guidelines of the European Community (EUVD 86/609/EEC) for the care and use of laboratory animals. Surface EEG recordings were made using an Ag/AgCl ring electrode positioned over the visual cortex. Electrode impedance was kept below 20 kΩ. The EEG ring electrode was placed at the base of a recording chamber made from polyetheretherketone (Ensinger Inc., Nufringen, Germany), which was secured to the skull with custom-made ceramic screws. The EEG ring electrode rested on the skull, and a small craniotomy was made to place electrodes for intracortical recording. In monkey A03, the resected patch was ∼2 mm diameter, whereas in monkey D02, ~5 mm of bone were removed. Surgical procedures are described elsewhere together with hardware details of the recording setup (Sheinberg and Logothetis 2001). Three tungsten microelectrodes (FFC, Bowdoinham, and ME) in a triangular orientation were lowered through the center of the EEG ring electrode (diameter = 1 cm) into the cortex (Supplementary Fig. S1A). Electrode tips were typically positioned in the upper or middle cortical layers of V1 and distance between electrodes was 1.8 mm. The impedance of the electrodes varied from 300 to 900 kΩ. All signals were amplified and filtered into a band of 2–8000 Hz (Alpha Omega Engineering, Nazareth, Israel) and then digitized at 20.833 kHz with 16-bit resolution.
(National Instruments, Austin, TX, USA), ensuring sufficient resolution to record both LFPs and spiking activity. All signals were referenced to a nearby wire. Prior to analysis, we re-referenced both the LFP and EEG to a frontal electrode placed on the scalp by subtracting the signal measured in the frontal electrode from the occipital EEG/LFP recording electrodes. This was done to ensure compatibility with typical visual EEG studies in humans and did not make a significant qualitative difference to the spectral estimates of LFP (see Results section). Trials in both passive fixation and movie stimulation conditions exhibiting transients above 6 standard deviations of the mean were excluded from all subsequent analysis as they were most likely due to movement artifacts (e.g., jaw movements). This was the case for ~28% of all trials.

**Visual Stimulation**

Visual stimuli were delivered via a computer screen (refresh rate 90 Hz) placed at eye level, 190 cm in front of the monkey. Eye movements were continuously monitored with an infrared camera (RealEye, Avotec, Stuart, FL, USA) with eye tracking software (iView, Sensomotoric Instruments GmbH, Teltow, Germany). Each trial began with a small fixation point (dot size: 0.4°) on black background. After 1 s of fixation, a 5-s movie segment (full field, 20.13 × 15.19 visual degrees) proceeded, followed by 1 s of poststimulus fixation, resulting in trials totaling 7 s of fixation (Supplementary Fig. S1B). In trials where fixation was held throughout, the monkey received a juice reward, whereas trials where the monkey broke fixation were immediately aborted. Each behavioral block consisted of 20 successful fixations. The movie was a fast-moving clip (no soundtrack) from a commercially available movie (Whittingstall and Logothetis 2009). Tasks (including movie onset/offset times) were controlled by computers running a real-time operating system (QNX, Ottawa, Canada) (Sheinberg and Logothetis 2001).

**Pharmacological Injections**

Each experiment (n = 16 over the 2 animals) consisted of neural recordings in 20 successful movie trials in 3 separate conditions: "baseline," "control," and "drug." The baseline condition consisted of no cortical injections, whereas the drug condition consisted of local injections of lidocaine hydrochloride 2% in artificial cerebrospinal fluid (ACSF). Lidocaine is a local anesthetic that mainly acts through sodium channel blockade and thus reduces LFP and multiunit spiking activity (MUA) (Fozzard et al. 2005), though paradoxically increases the surface EEG (Detsch et al. 1997). It is also fast acting and reversible (Boehnke and Fozzard 2005), though paradoxically increases the surface EEG and ACSF injections, the pH was adjusted with NaOH to 7.25. Lidocaine and ACSF solutions, the pH was adjusted with NaOH to 7.25. ACSF was made of NaCl: 148.19 mM, KCl: 3.0 mM, CaCl2: 1.40 mM, MgCl2: 0.80 mM, Na2HPO4: 0.80 mM, NaH2PO4: 0.20 mM. All chemicals were purchased from Sigma-Aldrich (Schnell, Germany). Lidocaine and ACSF were applied by a custom-made injector, consisting of a triple-barrel glass tube which contained 3 sharpened injection lines (outer diameter = 150 μm, inner diameter = 20 μm) for a better distribution in cortex. The free shaft length of the injection lines was 3.5 mm, which gave sufficient stability to penetrate dura and reach the visual cortex at the same depth as the intracortical sharp electrodes. The distance from the injection tips to the electrodes was held constant at ~2 mm. All 3 lines branched from the same feed line that was driven by a custom-made application device using compressed helium. Flow and volume of applied lidocaine/ACSF were monitored by a high precision flowmeter (Sensiron, Switzerland). Injections were delivered at 0.6 μL/min per line for a total duration of 20 min.

**Multiunit Activity Analysis**

The MUA band, used for assessing the effect of lidocaine, was extracted between 1000 and 4000 Hz using bidirectional operation of a FFT filter. Differences in MUA power during lidocaine and ACSF injections were used to dissociate pharmacological effects from general changes that occurred because of the injection itself. To compute interelectrode spike correlations (MUA synchrony), we used a publicly available spike-sorting algorithm for semiautomatic detection of spike times (Quiroga et al. 2004). The algorithm uses an amplitude threshold of 4 standard deviations of the mean amplitude for spike detection. Only spikes occurring within at least 1.5 ms of one another were kept for analysis. No subsequent spike sorting (e.g., principal component analysis) was applied. The spike timings were binned into 10-ms windows, and the resulting spike rate was compared with the neighboring electrodes by computing the Pearson correlation coefficient.

**Spectral Analysis**

EEG and LFP signals were downsampled to 1000 Hz. For power analysis, we computed the power spectral density for each trial using the Welch method with a 512-ms window length and 50% overlap. SC was obtained using the magnitude squared coherence estimate $C_{xy}$, from the input signals $x$ and $y$ in our case, LFP signals from 2 neighboring sharp electrodes in cortex—with the spectral density $P_{xx}$, $P_{yy}$, and the cross power spectral density $P_{xy}$.

$$C_{xy}(f) = \frac{|P_{xy}(f)|^2}{P_{xx}(f)P_{yy}(f)}$$

In each trial, we computed the average interelectrode coherence (SC) between the LFP in a single microelectrode and its 2 neighbors.

Subsequently, individual frequencies of EEG/LFP power and SC were averaged across traditional EEG frequency bands: delta (2–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), low gamma (30–60 Hz) and high gamma (60–100 Hz). In the baseline condition, we divided the LFP and EEG power in each trial by their respective trial-average. For SC, we subtracted the trial-average from each single-trial measure and reported it as a difference (rather than a percent change for LFP and EEG). This approach minimizes the biases (e.g., due to window size) introduced when using absolute rather than relative coherence values for analysis (see also Supplementary Fig. S7 and [Gerloff et al. 1998; Hummel and Gerloff 2005]). In the drug and control condition, we divided the EEG and LFP power in each trial by the average over all trials in the baseline condition. For SC, we subtracted the trial-average SC in the baseline from each trial in the drug and control condition. For each condition, we label these trial-by-trial changes as ∆EEG, ∆LFP, and ∆SC. These data were then pooled across all experiments and monkeys. Note, that from each trial, we extracted 3 individual combinations of EEG/LFP power and SC: one value for LFP power and SC from each of the 3 microelectrodes, paired with the EEG power measured by the surface electrode. The number of datapoints used for subsequent analysis therefore consisted of 3 times the number of all non-rejected trials. An alternate approach, at which LFP power and SC was averaged over all microelectrodes (thereby keeping the amount of EEG, LFP, and SC values equal) yielded similar results (Supplementary Fig. S6C,D).

**Statistical Analysis**

Prior to statistical analysis, we performed a Lilliefors test on each dataset to ensure it followed a normal distribution. In cases where we performed statistical analysis over all frequency bands (n = 6), we applied Bonferroni correction to correct for the multiple comparisons. Thus, all $P$ values below 0.05/6 = 0.008 were deemed statistically significant. Trial-to-trial correlations were computed using the Pearson correlation coefficient r. Partial correlation between 2 variables A and B while controlling for variable C was computed as:

$$r_{ABC} = \frac{r_{AB} - r_{AC}r_{BC}}{\sqrt{(1 - r_{AC}^2)(1 - r_{BC}^2)}}$$

with the EEGLab analysis toolbox (Delorme and Makeig 2004) as described below.
To evaluate the contribution of SC into the EEG, we first used ΔSC and ΔLFP as regressors in a general linear model (GLM):

\[ Y = \beta_1 X_1 + \beta_2 X_2 + \epsilon \]

where \( Y, X_1, \) and \( X_2 \) are the measured ΔEEG, ΔLFP, and ΔSC, respectively; \( \beta_1 \) and \( \beta_2 \) are weights of ΔLFP and ΔSC, respectively; and \( \epsilon \) is the error term. Measures of ΔEEG, ΔLFP, and ΔSC were normalized by their standard deviation prior to GM analysis. This GLM (Full model) was then compared with a reduced GLM with only ΔLFP as a regressor by computing the F-statistic between the 2 GLMs. This allowed us to investigate whether SC provides significant information on EEG, beyond what could be achieved when using LFP alone. More sophisticated, nonlinear models that may capture additional (albeit moderate) information regarding the contribution of SC and LFP are left for further study (Mazzoni et al. 2010). To assess the relative contribution of either ΔLFP or ΔSC to ΔEEG, we computed the root-mean-square error (RMSE) of the modeled ΔEEG as the following:

\[ \text{RMSE} = \sqrt{\frac{1}{n} \sum_{i=1}^{n} [\Delta \text{EEG}(i) - \Delta \text{EEG}_{\text{modeled}}(i)]^2} \]

where \( n \) is the number of data points. Note that, due to normalization, the RMSE is in standard deviation units. Comparison between the beta weights in the baseline and drug condition was performed using Fisher’s Z-test.

**Results**

Our main goal was to investigate how changes in LFP synchrony modulate surface EEG recordings. For this, we first computed the correlation between trial-by-trial fluctuations in LFP power (ΔLFP), SC (ΔSC), and EEG power (ΔEEG) in the drug-free baseline condition. As shown in Table 1, both ΔLFP and ΔSC were significantly correlated to ΔEEG in all frequency bands (P < 0.01), with the highest correlations observed in the high-gamma range (60–100 Hz). In addition, they also shared a strong correlation with one another (ΔLFP,SC). This is illustrated in Figure 1A, showing a scatter plot of high-gamma ΔEEG, ΔLFP, and ΔSC. We therefore computed the partial correlation coefficient between ΔSC and ΔEEG while correcting for ΔLFP (Table 1). Partial correlations remained significant (except for \( p_{EEG,SC} \) in the alpha range), thus demonstrating that ΔSC and ΔLFP are both independently related to ΔEEG.

When only analyzing data where ΔLFP is negatively modulated and ΔSC positively modulated relative to their respective trial-average (\( n = 141 \), upper left quadrant of Fig. 1A), we found that ΔEEG was significantly positively modulated (4.75%, 2-sided t-test, \( P < 0.01 \)). In the opposite case—when ΔLFP was positive but ΔSC negative (\( n = 98 \), bottom right quadrant of Fig. 1A)—the average ΔEEG was negatively modulated (−3.51%, \( P < 0.01 \)). This indicates that dissociations between ΔLFP and ΔEEG (i.e., ΔLFP ≠ ΔEEG) may be explained by ΔSC. Indeed, we found that the average ΔSC was higher when ΔEEG was greater than ΔLFP (ΔSC_{ΔEEG > ΔLFP} = 0.02, \( n = 390 \), \( P < 0.01 \)) compared with cases where ΔEEG was less than ΔLFP (ΔSC_{ΔEEG < ΔLFP} = −0.03, \( n = 306 \), \( P < 0.01 \)). To compute the extent of this EEG-LFP dissociation, we subsequently subtracted LFP from EEG power in each data-pair (ΔEEG-LFP). ΔEEG-LFP was positively correlated to ΔSC (Fig. 1B, \( r = 0.34, P < 0.01 \)). A similar result was obtained when comparing ΔEEG-LFP and interelectrode MUA synchrony (Supplementary Fig. S2A). In contrast, correlations between ΔEEG-LFP and firing rates were slightly negative (Supplementary Fig. S2B). This demonstrates that EEG exceeded LFP power when MUA synchrony was high, whereas LFP power was stronger than EEG in cases of increased MUA power.

Given the strong linear relation between ΔSC/ΔLFP and ΔEEG, we used a GLM to investigate the relative contributions of ΔSC and ΔLFP to ΔEEG. This is illustrated in Figure 1C for a subset of trial-by-trial measures of ΔEEG (red), ΔSC (black), and ΔLFP (blue) as well as modeled ΔEEG (dashed red line). For visual purposes only, all values are normalized to their maximum value. The difference between ΔEEG and ΔLFP varies considerably, indicating that ΔLFP alone cannot fully explain ΔEEG. For example, in the transition from trial 3 to 4, ΔLFP decreases while ΔEEG and ΔSC increase. However, when combining ΔLFP and ΔSC, the modeled ΔEEG (dashed red line) better resembles the measured ΔEEG values. In order to quantify the individual contribution of LFP and SC, we carried out 3 separate analyses: First, we calculated the F-statistic by comparing the full GLM containing both ΔLFP and ΔSC as regressors, against a null model consisting of only the ΔLFP regressor (Fig. 1D). For all frequency bands but the alpha range, the F-statistic was significant (\( P < 0.01 \)), confirming that ΔSC explains a component of the ΔEEG that cannot be explained by ΔLFP. Second, we computed the RMSE between the measured and modeled ΔEEG (Fig. 1E) when either using ΔLFP, ΔSC, or both to model ΔEEG. In all frequency bands, the combination of both ΔLFP and ΔSC produced the smallest RMSE. A similar effect was seen when performing the same analysis on data obtained during the fixation period prior to visual stimulation (i.e., no visual stimulus, Supplementary Fig. S3A,B), thus confirming that our results are largely invariant to external stimulation. Lastly, we directly compared the ΔLFP and ΔSC beta weights from the GLM (Table 2). Across all frequency bands, the ΔSC beta weight was slightly smaller, representing an average contribution of 38 ± 8%. The average ΔLFP contribution was 62 ± 8%. Taken together, the main findings from these analyses is that LFP and SC contribute separately to the EEG with SC (−40%) contributing slightly less than LFP (−60%).

The above results demonstrate that LFP synchrony modulates the surface EEG in a manner that is independent of LFP amplitude. A particularly interesting implication of this finding is that, given the remarkably strong contribution of SC, an increase in EEG amplitude may be visible when a decrease in LFP amplitude is observed. To further investigate this in a more robust manner, we analyzed EEG and LFP recordings during the application of lidocaine. Lidocaine has been shown to reduce LFP (Rauch et al. 2008) and MUA (Fozzard et al. 2005; Rauch et al. 2008), though paradoxically increase the surface EEG (Detsch et al. 1997), thus creating a strong dissociation between EEG and LFP power. Given our

**Table 1**

Baseline condition: Pearson (r) and Partial (Pr) correlation coefficients between trial-by-trial fluctuations in EEG, LFP, and SC for all classical EEG frequency bands

<table>
<thead>
<tr>
<th>Frequency band</th>
<th>ΔLFP</th>
<th>ΔEEG</th>
<th>ΔSC</th>
<th>PrEEG</th>
<th>PrEEG</th>
<th>PrSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low γ</td>
<td>0.27*</td>
<td>0.23*</td>
<td>0.19*</td>
<td>0.33*</td>
<td>0.43*</td>
<td>0.62*</td>
</tr>
<tr>
<td>High γ</td>
<td></td>
<td></td>
<td></td>
<td>0.24*</td>
<td>0.19*</td>
<td>0.25*</td>
</tr>
<tr>
<td>Low α</td>
<td>0.35*</td>
<td>0.27*</td>
<td>0.32*</td>
<td>0.12*</td>
<td>0.31*</td>
<td>0.52*</td>
</tr>
<tr>
<td>High α</td>
<td></td>
<td></td>
<td></td>
<td>0.17*</td>
<td>0.32*</td>
<td>0.38*</td>
</tr>
</tbody>
</table>

*P < 0.01.
previous findings, we hypothesized that a lidocaine-induced dissociation between EEG and LFP can be explained by a concomitant change in SC. Indeed, we found that LFP activity during lidocaine application was not only attenuated but also more synchronized. An example of simultaneous EEG–LFP recordings in a single trial is shown in Figure 2. Under

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**Table 2**

GLM beta weights: beta weights ± their 95% confidence interval for different frequency bands

<table>
<thead>
<tr>
<th>Frequency band</th>
<th>$\Delta$</th>
<th>$\theta$</th>
<th>$\alpha$</th>
<th>$\beta$</th>
<th>Low $\gamma$</th>
<th>High $\gamma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta$ LFP-Baseline</td>
<td>0.23 ± 0.080</td>
<td>0.19 ± 0.079</td>
<td>0.15 ± 0.081</td>
<td>0.29 ± 0.076</td>
<td>0.41 ± 0.072</td>
<td>0.49 ± 0.086</td>
</tr>
<tr>
<td>$\Delta$ LFP-Drug</td>
<td>0.14 ± 0.081</td>
<td>0.20 ± 0.079</td>
<td>0.10 ± 0.083</td>
<td>0.16 ± 0.076</td>
<td>0.16 ± 0.072</td>
<td>0.30 ± 0.086</td>
</tr>
<tr>
<td>$\Delta$ SC-Baseline</td>
<td>0.28 ± 0.076</td>
<td>0.22 ± 0.074</td>
<td>0.37 ± 0.070*</td>
<td>0.41 ± 0.063</td>
<td>0.43 ± 0.073</td>
<td>0.56 ± 0.053</td>
</tr>
<tr>
<td>$\Delta$ SC-Drug</td>
<td>0.08 ± 0.070</td>
<td>0.12 ± 0.068</td>
<td>0.02 ± 0.060</td>
<td>0.27 ± 0.060</td>
<td>0.31 ± 0.087*</td>
<td>0.45 ± 0.061*</td>
</tr>
</tbody>
</table>

*Significant difference between beta weight in the baseline and drug condition: $P < 0.01$. 

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Figure 1. EEG-LFP dissociations are explained by SC. (A) Scatter plot of trial-by-trial modulation in the high-gamma range (60–100 Hz) for LFP ($\Delta$LFP), EEG ($\Delta$EEG), and SC ($\Delta$SC) across all monkeys. $\Delta$LFP and $\Delta$EEG represent the percent change from the trial-average, whereas $\Delta$SC is computed as difference (see Materials and Methods section). Statistical analysis shows that $\Delta$SC is significantly higher when $\Delta$EEG is greater than $\Delta$LFP (see Results section). (B) Scatter plot of trial-by-trial differences between $\Delta$EEG and $\Delta$LFP ($\Delta$EEG-LFP) versus $\Delta$SC. $\Delta$EEG-LFP is positively correlated to $\Delta$SC ($P < 0.05$), indicating a relation between SC and the dissociation of EEG and LFP power. (C) An example trace of trial-by-trial fluctuations of LFP (blue), SC (black), and EEG (red). Dashed red line with open circles is the modeled EEG ($\text{EEG}_{\text{modeled}}$) using LFP and SC as regressors in a GLM. For visual purposes only, all measures were normalized to their maximum change (normalized change). (D) F-statistics obtained when comparing $F$ values of the full GLM to a reduced GLM (using $\Delta$LFP as a single regressor) for all frequency bands. Asterisk indicates that adding $\Delta$SC as a regressor in the GLM explained a significant amount of $\Delta$EEG variance ($P < 0.01$) which could not be explained by $\Delta$LFP alone (see Materials and Methods section). (E) When only using only $\Delta$SC or $\Delta$LFP to model $\Delta$EEG (reduced models, blue and green bars, respectively), the root-mean squared error (RMSE) was consistently higher than when combining both regressor in a GLM (full model, red bars).
lidocaine, LFP signals are reduced in amplitude, though more temporally synchronized (Fig. 2A,B) while the surface EEG amplitude slightly increases (Fig. 2C). Figure 3 shows the average lidocaine-triggered change in EEG and LFP power and SC across all trials. As expected, the LFP exhibited a significant broadband decrease in power (Fig. 3A). MUA was also suppressed, though this reduction was moderate with spiking activity resembling that observed during spontaneous neural activity without lidocaine application (Supplementary Fig. S4A). On the other hand, EEG power increased with lidocaine, particularly in the high-frequency range. These LFP and EEG findings are in line with previous studies of lidocaine application/injection in monkeys and humans (Detsch et al. 1997; Rauch et al. 2008). Aside from changes in amplitude, we found that SC significantly increased with lidocaine application (Fig. 3B). Statistical analysis (2-sided paired t-test) revealed that lidocaine-triggered changes in LFP and SC were significant across all frequency bands (P<0.01, Fig. 3C), while increases in the EEG were only statistically significant in the high gamma range (P<0.01, Fig. 3C). None of these effects were observed during control injections of ACSF (Supplementary Fig. S4).

The above result demonstrates a clear dissociation between LFP and EEG signal power during local application of lidocaine. A possible explanation is that the observed increase in SC reflects enhanced temporal synchrony of neural sources, which—due to the superposition principle—causes the observed increase in EEG. Alternatively, the application of lidocaine may simply enhance the volume-conducted or “far-field” component of the LFP, which is common to all penetrating electrodes, and thus cause a spurious increase in SC. Such a scenario could arise from the presence of noise in the frontal reference electrode. To address this, we compared the SC results obtained using a frontal reference electrode (Fig. 3C) to that obtained when using a local referencing scheme (see Materials and Methods section). In both cases, the results were similar (Supplementary Fig. S5A), indicating that the choice of electrical reference cannot explain the lidocaine-triggered increase in SC. In addition, we found that trial-to-trial changes in ΔSC and ΔLFP were reduced but remained positively correlated in the drug condition (Table 3), indicating that SC values are not spuriously high due to low LFP signal strength.

Finally, we reanalyzed the data on a trial-by-trial basis (similar to the drug-free data). A scatter plot of the lidocaine-induced changes in high-gamma ΔEEG, ΔLFP, and ΔSC values (n = 678) is shown in Figure 4A. Note that each value here is compared with the trial-average in the baseline condition. As both SC and EEG increased under lidocaine while ΔLFP decreased, we investigated if the observed dissociation of ΔEEG and ΔLFP (see also Supplementary Fig. S5B,C) could be explained by ΔSC. We first applied the beta weights obtained in the baseline condition (see above) to a GLM and predicted ΔEEG in the lidocaine condition. An example of the predicted ΔEEG for a subset of trials is shown in Supplementary Figure SSD. F-statistics were significant for all but the theta and the alpha band (Fig. 4B). Overall, RMSE values of predicted high-frequency ΔEEG (Fig. 4C, ModelBaseline) were similar to that in the baseline condition (Fig. 1E) and markedly lower than those using single regressor models. Hence, despite the dissociation between ΔLFP and ΔSC, both contributions remain important for explaining EEG. Only a small reduction in RMSE was achieved by using beta weights derived from lidocaine data (ModelDrug). This shows that the general contribution of ΔLFP and ΔSC to ΔEEG is widely invariant to pharmacological manipulation, thus suggesting a more generalized mechanism. This can also be seen when comparing beta weights of baseline and lidocaine data (Table 2). Although high-frequency SC weights were slightly increased, their relative contribution of ~40% to EEG power remained unchanged. In summary, trial-by-trial analysis of data obtained during baseline condition shows that neural synchrony modulates EEG independently of LFP amplitude. By using pharmacological manipulation, we additionally found that if synchrony is sufficiently strong, increases in EEG can be observed along with concomitant decreases in LFP amplitude. Taken together, our results suggest that a significant portion of EEG-LFP dissociations can be explained by neural synchrony.

It is worth noting that although the measure of coherence is often used for measuring the degree of synchrony between neurophysiological signals, one must be cautious in interpreting its results (Guevara and Corsi-Cabrera 1996; Ramírez et al. 2008). We therefore used 2 different measures of interelectrode synchrony and compared the results. First, we band-pass filtered the LFP signals in the traditional EEG frequency bands and computed the Pearson correlation coefficient between them. The results were highly similar to those reported here, and are thus not presented. Second, we summed the raw LFP time series from all 3 intracortical electrodes prior to LFP power analysis, and compared this with the EEG. The summation process minimizes contributions from nonsynchronous activity and thus provides an alternate measure of spatial synchrony. We found that this “raw LFP average” was better correlated to the EEG compared with LFP power, which was averaged over all 3 electrodes after spectral analysis (Supplementary Fig. S6A,B). These results further confirmed that the EEG indeed represents the average of temporally synchronized sources.

Discussion

The findings presented here offer direct experimental evidence for the long hypothesized dependence of EEG amplitude on the synchrony of neuronal sources rather than simply the strength of their activation. More specifically, we demonstrate how neural synchrony “amplifies” the contribution of localized neural activity (LFP) into the EEG, thus explaining the amplitude differences often observed between intracranial and surface measurements of neural activity.

First, we observed that trial-by-trial changes in EEG gamma power (30–100 Hz) were strongly correlated to LFP power, whereas correlations were considerably lower in the alpha (8–12 Hz) range (Table 1). These correlations do not reflect instantaneous, cycle-to-cycle correlations between filtered EEG and LFP signals, but rather shared fluctuations in their trial-by-trial amplitude values. In this respect, our findings are in good agreement with intracortical recordings in humans and awake macaques, who show that very slow (<0.1 Hz) fluctuations in the band-limited power of high-frequency LFP remain strongly correlated across distances exceeding 10 mm (Leopold et al. 2003; Nir et al. 2008), which is within the range of the LFP and EEG electrodes used in this study.
Figure 2. Effects of lidocaine on single-trial EEG and LFP. (A) Simultaneous recordings from 2 intracortical electrodes (LFP1 and LFP2) and a single surface EEG. After lidocaine application, LFP1,2 become more synchronized, though their amplitude is reduced. (B) Spectral power analysis of the single-trial data shown in (A) for the LFP (B) and EEG (C). Note that lidocaine slightly increases EEG power, while LFP power is reduced.

Figure 3. Effects of lidocaine on EEG, LFP, and spatial coherence (SC). (A) Average lidocaine-induced changes in EEG and LFP power. Results are displayed as percent change from baseline condition. (B) SC spectra before (green) and after (blue) lidocaine application. (C) Lidocaine induced changes (as in A and B), for all classical EEG frequency bands. Asterisk indicates a statistically significant change ($P < 0.01$) of EEG power. Changes in LFP and SC were significant for all frequency bands.
Second, our results demonstrate that modulations in SC explained a significant portion of the EEG, which could not be explained by LFP power alone. These results are in line with the modeling study by Cosandier-Rimele et al. (Cosandier-Rimele et al. 2008), who showed that when the magnitude of neural activity is held constant, increases in the degree of synchronous activity result in increasing scalp EEG. Using a GLM with SC and LFP as predictors, we found that their respective contributions to EEG amplitude were ∼40% and 60%, respectively. Furthermore, these contributions were similar during pharmacological dissociation of EEG and LFP, thus suggesting that they reflect a more generalized mechanism of EEG generation. In fact, when using model weights of the baseline condition during lidocaine application, we could predict changes in EEG power and show that the dissociation of EEG and LFP power can be explained when integrating the impact of neural synchrony. This demonstrates that even when neural activity is suppressed, the relatively strong contribution of synchrony may nonetheless result in strong surface EEG measurements. Overall, we found that the contributions of SC were frequency dependent, being highest in the high-frequency range, (Fig. 1D) while being consistently weaker in the alpha band (Supplementary Fig. S3; Figs. 1D and 4C). The source of this frequency-dependent effect is unclear. It has been shown that the amplitude of alpha oscillations in early visual regions is negatively correlated to that in higher-order regions of the IT cortex (Bollimunta et al. 2008, 2011). The relatively large integration area of the EEG electrode may therefore represent a mixture of these distinct sources, resulting in a low correlation of EEG with SC in V1. Our findings may also have arisen from the differential distribution of alpha sources across different layers. Recent studies using laminar recordings of LFP in awake monkey visual cortex show that alpha-band LFP activity is concentrated in the deep granular and infragranular layers of cortex (Bollimunta et al. 2008; Maier et al. 2010, 2011), while the magnitude of spontaneous fluctuations in the gamma range (30–100 Hz) can be up to twice as large in the superficial layers compared with

<table>
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<tr>
<th>Frequency band</th>
<th>Δ</th>
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<th>β</th>
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</table>

*P < 0.01.

**Figure 4.** Effects of lidocaine on ΔEEG, ΔLFP, and ΔSC. (A) Scatter plot of high-gamma ΔLFP, ΔEEG, and ΔSC in the lidocaine condition. (B) F-statistics for the addition of ΔSC into the GLM analysis in the drug condition (as in Fig. 1D). (C) RMSE values for all frequency bands using ΔSC (blue bars), ΔLFP (green bars) or a combination of both to model ΔEEG (red and orange bars). The red bars (ModelBaseline) illustrate the RMSE when using GLM weights obtained in the baseline condition, whereas the orange bars reflect GLM weights in the lidocaine (drug) condition (ModelDrug). Taken together, these findings show how the combination of SC and LFP is a better predictor of EEG than either of them alone. The relatively small difference in RMSE between ModelDrug and ModelBaseline indicate that the relative contributions of LFP and SC to EEG are widely invariant to pharmacological manipulation.
Our findings have an important implication for basic EEG studies, particularly those combining EEG with other imaging modalities such as functional magnetic resonance imaging (fMRI). We have previously shown that the local application of lidocaine significantly decreases the amplitude of the BOLD signal (Rauch et al. 2008), while we here demonstrate that it triggers an increase in surface EEG amplitude. This highlights the impact of neural synchrony as an important mechanism behind any potential dissociation between EEG and fMRI measurements (Nunez and Silberstein 2000; Meltzer et al. 2009; Yesilyurt et al. 2010). A likely cause of this observation is that synchronization among a large population of neurons is less metabolically demanding (Buzsáki and Draguhn 2004), thus explaining why increases in EEG may appear concurrently with a reduction of the BOLD signal. Should this be the case, dissociations between EEG and BOLD may prove extremely informative in serving as a noninvasive marker for separating the effects of synaptic input (fMRI) versus global synchronization (EEG), and potentially open a new avenue for identifying distinct neural codes used in behavioral tasks.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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References


The lidocaine-induced increase in neural synchrony also raises the question about its origin. One possibility is that lidocaine simply diminishes background neural activity, which could increase the signal-to-noise ratio of stimulus evoked transients and result in spuriously high interelectrode synchrony. However, we found a similar increase in SC during the fixation period, indicating that the increase in synchrony is unrelated to stimulus-selective projection neurons but rather reflects unselective mass activity. As lidocaine more strongly affects neurons with high firing rates (Fozzard et al. 2005), it may particularly suppress fast-spiking interneurons (Tanaka and Yamasaki 1966). Given that active decorrelation has been shown to be a fundamental property of intracortical processing (Cohen and Maunsell 2009; Wiechert et al. 2010), lidocaine infusion may therefore disrupt this process, resulting in the observed overly correlated network activity.


