Antagonistic Relationship between Gamma Power and Visual Evoked Potentials Revealed in Human Visual Cortex

Eran Privman1, Lior Fisch2, Miri Y. Neufeld3,4, Uri Kramer5,4, Svetlana Kipervasser5,4, Fani Andelman5, Yehezkel Yeshurun1, Itzhak Fried3,5-7 and Rafael Malach2

1Blavatnik School of Computer Science, Tel-Aviv University, Tel-Aviv 69978, Israel, 2Department of Neurobiology, Weizmann Institute of Science, Rehovot 76100, Israel, 3Sackler School of Medicine, Tel-Aviv University, Tel-Aviv 69978, Israel, 4EEG and Epilepsy Unit, Department of Neurology and 5Functional Neurosurgery Unit, Tel Aviv Sourasky Medical Center, Tel Aviv 64239, Israel, 6Department of Neurosurgery, David Geffen School of Medicine and 7Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, CA 90095, USA

Address correspondence to Rafael Malach. Email: rafi.malach@weizmann.ac.il.

Scalp electroencephalography and magnetoencephalography studies have revealed a rapid evoked potential “adaptation” where one visual stimulus suppresses the event-related potential (ERP) of the second stimulus. Here, we investigated a similar effect revealed in subdural intracranial recordings in humans. Our results show that the suppression of the subdural ERP is not associated with a reduction in the gamma frequency power, considered to reflect the underlying neural activity. Furthermore, the evoked potential suppression (EPS) phenomenon was not reflected in recognition behavior of the patients. Rather, the EPS was tightly linked to the level of gamma activity preceding the event, and this effect was independent of the interstimulus time interval. Analyzing other frequency bands failed to reveal a similar link.

Our results thus show a consistent antagonism between subdural ERP and gamma power although both are considered markers for neural activity. We hypothesize that the ERP suppression is due to a desynchronization of neuronal firing resulting from recurrent neural activity. In the vicinity of the freshly stimulated neurons and not an attenuation of the overall neural activity.

Keywords: adaptation, ECoG, gamma-oscillations, intracranial, N170

Introduction

Several electroencephalography (EEG) and magnetoencephalography (MEG) studies in the last 3 decades have investigated adaptation effects of the visual event-related potential (ERP) using the “double pulse” paradigm, where rapid successive presentation of 2 stimuli attenuates the evoked potential (Musselwhite and Jeffreys 1983; Nelson et al. 1984; Noguchi et al. 2004; Kovacs et al. 2006). Recent MEG studies have shown that this phenomenon is short lasting and limited to interstimulus intervals (ISIs) smaller than 600 ms. These studies also found that the effect is category selective (mainly faces compared with other categories) (Harris and Nakayama 2007) and appears to be stronger when the preceding stimulus was perceived as the same individual face (Jacques and Rossion 2006).

This rapid attenuation phenomenon is not limited to higher order visual areas—early cortical areas show similar effects albeit at shorter time intervals (Musselwhite and Jeffreys 1983) and are correlated with performance decrease (Censor 2009). The effect was also shown in the auditory domain and correlated with a performance decrease exhibited by poor readers (Nagarajan et al. 1999).

Another attenuation phenomenon, termed repetition suppression (Desimone 1996) or adaptation, was studied by a number of groups (Miller et al. 1991; Sawamura et al. 2006; McMahon and Olson 2007; De Baene and Vogels 2009) in macaque inferior temporal (IT) cortex, showing decreased firing rate for the adapted stimulus.

Based on the primates’ studies, we have previously proposed that the well-known tendency of cortical neurons to adapt could be employed to examine the invariant properties of human cortical neurons using functional magnetic resonance imaging (fMRI)—a phenomenon termed fMR-adaptation. By examining to what extent the adaptation is sensitive to manipulations of the visual stimulus, one can gain some insight into the invariance of the underlying tuning properties of neurons (Grill-Spector and Malach 2001; Grill-Spector et al. 2006).

Although the evoked potential suppression (EPS) created by the double pulse paradigm appears superficially similar to the repetition suppression phenomenon, it is markedly different. The repetition suppression phenomenon is lasting seconds and even lingering for minutes and perhaps even days (Grill-Spector et al. 1999; Grill-Spector 2006; McMahon and Olson 2007). In contrast, the rapid adaptation effect of the EPS is extremely short lived, lasting no more than a few hundred milliseconds at the most.

In the present manuscript, we examined the hypothesis that the “classic” repetition suppression/adaptation effect and the EPS are fundamentally distinct phenomena. While the adaptation effect indeed involves a generalized reduction in neuronal activity, the EPS is a more selective modulation of the evoked response—possibly originating from neuronal desynchronization rather than attenuation.

To test this hypothesis, we examined the double pulse paradigm (Harris and Nakayama 2007) using subdural electrodes implanted in patients during clinical diagnosis for epilepsy. Our results suggest that the subdural EPS is indeed not caused by reduced neuronal activity, since gamma power is unaffected. Rather, it is affected most by gamma activity “preceding” the disrupted event. We propose that the subdural EPS is a neuronal phenomenon that is fundamentally different from the classic repetition suppression/adaptation phenomenon. These results point to the EPS effect as a new kind of attenuation phenomenon that may offer important insights into the nature of the cortical evoked potential.

Materials and Methods

Data Acquisition

Recordings of electrical activity using intracranial subdural electrodes were obtained from 5 patients with medically intractable epilepsy who...
were evaluated for possible surgery (Dewar et al. 1996; Privman et al. 2007). Electrode location was based solely on clinical criteria. Each patient was implanted with subdural electrode arrays containing 40-80 contact electrodes (Ad-tech Medical Instrument Corporation). Electrodes were arranged in 1D strips or in 2D grids placed directly on the cortical surface. Each electrode was 2 mm in diameter, with 8-mm spacing between adjacent electrodes. Recordings were monopolar and were referenced to an extracranial electrode. The signal was filtered electronically between 1 and 70 Hz and sampled at a rate of 200 Hz (Grass-Telefactor). Stimulus-triggered electrical pulses were recorded along with the electrocorticogram (ECoG) data for precise synchronization of the stimuli with the electrical response.

All sessions were conducted at the patients’ quiet bedside while the patient was sitting upright in bed, after periods of at least 3 h without any identifiable seizures. Stimuli were presented via a standard laptop screen, and keyboard responses were recorded for measurement of behavioral performance.

Patients provided written informed consent to participate in the experiment. The experimental protocol was approved by the Tel Aviv Sourasky Medical Center Committee for Activities Involving Human Subjects.

Electrode Localization and Classification

Computed tomography scans following electrode implantation were coregistered to the preoperative magnetic resonance imaging (MRI) using iPlan Stereotaxy software (BrainLAB) to determine electrode positions. The 3D brain image thus mounted with electrode locations was normalized to Talairach coordinate space (Talairach and Tournoux 1988) and rendered in BrainVoyager software in 2 dimensions as a surface mesh, enabling precise localization of the electrodes both with relation to the subject’s anatomical MRI scans and in standard coordinate space. For joint presentation of all subjects’ electrodes and to aid comparison with previous fMRI mapping performed in our laboratory (see below), electrode locations were projected onto a cortical reconstruction of a single healthy subject, which is routinely used to visualize results in our mapping studies (Fig. 2).

The spatial coverage of the recording electrodes varied among the subjects but typically included temporal, parietal, occipital, and frontal lobes.

To identify visual evoked electrodes, we used standard ERP analysis with a threshold of 3 standard deviation (SD) for the evoked magnitude (max-min) of one of the screening categories in the temporal window of 100- to 250-ms poststimulus (in ECoG recording, strong visual electrodes can get to 6 SD). Of the 215 electrodes analyzed, 10 passed this activation threshold and were defined as visually responsive. In order to differentiate which of these visually responsive electrodes were in low-order and which were in high-order cortex, 2 complementary criteria were used. First, the anatomical location of the electrode was compared with the borders of the visual cortical regions obtained using fMRI in healthy subjects (Hasson et al. 2003; Fisch et al. 2009) (Fig. 2). However, given the potential uncertainty in such neuroanatomical localization, particularly in patients’ data, a functional criterion based on electrical stimulation conducted routinely for clinical purposes with these patients was also used. This criterion was based on the perception of phosphene elicited during electrical stimulation. Such phosphene perception has been previously associated with stimulation in areas V1 and V2 of the visual cortex (Brindley and Lewin 1968) and thus served as an independent, complementary verification of electrode location for the 2 electrodes defined as low order in our sample (Fig. 2).

Stimuli and Tasks

Images were presented on a standard laptop display (60-Hz refresh rate). For screening purposes, we used our standard object category experiment of faces, houses, tools, cars, and animals (Privman et al. 2007). Following Nakayama’s paradigm (Harris and Nakayama 2007), the main experiment (Fig. 1) used stationary grayscale images from 2 categories (faces and houses), with a width of approximately 8° (700 pixels). Each image was presented for 200 ms, followed by a blank, gray screen. A small red fixation dot was superimposed on the pictures. The images were presented in random sequence of pairs with several conditions of 50-ms, 200-ms, and 400-ms ISIs. Pairs were composed of pictures from the same category (faces or houses) or mixed categories. The choice of faces was motivated by previous observation (Privman et al. 2007; Fisch et al. 2009) that many of the high-order ECoG electrodes were strongly activated by this category. Furthermore, using faces allowed a more direct comparison with the scalp EEG EPS phenomena that likewise uses faces (Harris and Nakayama 2007).

The interval between pairs was around 1.5 s. The patient’s task was to fixate on the central fixation dot and to perform a one-back memory task by pressing a button, meaning that the patient had to press a button if the 2 pictures in a pair were identical. One patient participated in an experiment without the 50-ms ISI condition, and this data were excluded from the analysis in Figures 5 and 6.

In low-order visual cortex, as the processing timescale is much shorter, and the selectivity of the electrodes is not to object category but to low-level visual features, we used a “low-order” variant of the experiment where the stimulus duration was 50 ms, the pairs were composed of either the same picture or different pictures, and the patient’s task was to identify a target picture of a flower.

Data Analysis

In the preprocessing stage, potential 50-Hz electrical interference was removed from the raw signals using a linear-phase notch finite impulse response (FIR) filter. To reduce noise in the gamma-band frequencies, each electrode was dereferenced by subtraction of the averaged signal of all the electrodes, thus discarding nonneuronal contributions from the extracranial reference electrode (Miller et al. 2007; Privman et al. 2007).

Time-frequency spectr um decomposition was based on Fourier transform amplitude spectrum, calculated per trial, and averaged across trials (Lachaux et al. 2005). For calculation of band-limited power (BLP) modulations in a given frequency band, the signal was first bandpassed in this frequency range using a linear-phase FIR filter, and the BLP modulation extracted by taking the absolute value of the Hilbert transform (Le Van Quyen et al. 2001). For the BLP plots in Figures 3 and 4, we applied temporal Gaussian smoothing with sigma of 40 ms and then averaged over trials. Note that the BLP of a specific frequency band is equivalent to the average of the spectrogram’s corresponding frequency rows. For the gamma-band analysis, we used the frequency band of 50-70 Hz, analyzing only the gamma power above 50 Hz following several studies which have shown that the higher gamma bands are more closely correlated to the magnitude of the neural activity (Miller et al. 2007). The upper band limit of 70 Hz was imposed.
by the clinical recording system. For the theta/alpha/beta bands, we used the following frequency bands: 4–8 Hz/8–13 Hz/13–30 Hz.

The use of power spectrograms and BLP rather than the more conventional ERP analysis was performed following Lachaux et al. (2005) and Crone et al. (2006). The power spectrogram and the BLP provide a clearer view of the different components of the intracranial EEG signal and a more quantitative measure compared with the conventional ERP analysis.

In order to compare the gamma power generated by the first and the second stimuli in a pair, we averaged the gamma BLP in the window of 125- to 250-ms poststimulus onset, per electrode, and ISI condition.

To measure the magnitudes of the EPS and the immediately preceding gamma power as presented in Figures 5 and 6, we calculated the BLP in the corresponding frequency bands (gamma response: 50–70 Hz; evoked response: 8–13 Hz) in the related temporal windows (gamma power immediately preceding the response to the second stimulus: 0–75 ms after second stimulus onset; evoked potential response to the second stimulus: 125–250 ms after second stimulus onset). These results were then averaged across all the face–face trials per ISI, per electrode, and per experiment. To combine the scatter plots of the different electrodes into one plot (Fig. 5), we normalized each electrode by subtracting from each trial (i.e., presentation of a pair of face images) the average of all the face–face trials of this electrode. With the first patient, we did not obtain all the ISI conditions (only 200 ms and 400 ms), so these data were excluded from the analysis of Figures 5 and 6.

Data processing was carried out using MATLAB. For power spectrograms, we used EEGLAB (Delorme and Makeig 2004) code.

Statistical Analysis
Two-tail heteroscedastic $t$-test was used to test for significant differences between EPS of trials preceded by low gamma power and trials preceded by high gamma and for differences between the patients’ reaction time in the 200- to 400-ms ISI conditions.

To validate that the EPS is significantly affected by the gamma power immediately preceding the second stimulus and independently from the ISI, we used analysis of covariance (www.SAS.com, JMP 7.0.2) for evoked response power values, using ISI as categorical factor and gamma power as covariate.

To further confirm the significance of the correlation between EPS and the preceding gamma power independently from the ISI, we used a permutation test according to the following procedure: data were shuffled within ISI condition, we then calculated the $R$ value for each permutation and found the percentile of the $R$ value from the unshuffled data in the $R$ values distribution of the shuffled data.

Error bars, where present, denote standard error of the mean between trials (Figs 3 and 4).

fMRI Mapping of Visual Areas
For comparison of known low- and high-order visual areas, we used maps obtained from previous fMRI experiments using face, man-made object and house images for outlining category-selective regions, and low-order visual stimuli (vertical and horizontal meridian stimulations) for delineating the borders of early visual areas (Hasson et al. 2003).

Results
Our study was based on subdural intracranial EEG (also termed ECoG) recordings obtained from 10 electrodes showing significant visual responses in 5 patients (for selection criteria, see Materials and Methods). The experimental paradigm is presented in Figure 1. Pairs of still pictures of faces and houses were presented to the patients at several ISIs; pairs were composed of pictures from the same or mixed categories (for further details, see Materials and Methods). Stimulus duration was 200 ms, and ISI varied between 50 and 400 ms. The patients had to perform a one-back memory task; responses were collected through button presses.

The visual stimuli elicited reliable responses (see Materials and Methods) in 10 electrodes from 5 patients. In agreement with previous studies, the visually responsive electrodes were located mainly in occipitotemporal visual areas. The locations of the electrodes are depicted in Figure 2 relative to boundaries of well-known human visual areas estimated from fMRI maps in healthy subjects. As can be seen, 8 of the responsive electrodes were located in high-order visual cortex (vicinity of fusiform face area) and 2 were in low-order visual regions (estimated V1–V3); 5 of the high-order electrodes were face selective. As the definition of early visual cortex borders in the patients differed from inherent ambiguity, additional functional criteria were used for validation (see Materials and Methods).

Eys
The main characteristics of the subdural Eys effect from one example electrode are presented in Figure 3 in which the response to a pair of face pictures at 200-ms ISI is compared with a pair of face pictures at 400-ms ISI. The effect is depicted in a spectrogram showing the dynamic changes for each frequency band (top) and in a plot of the evoked responses, measured both as averaged local field potential (LFP) and as power changes in the alpha frequency band (8–13 Hz), and gamma power (frequency band 50–70 Hz) (for more details, see Materials and Methods).

As can be seen, the ERP of the second stimulus at 200-ms ISI was almost completely suppressed, while at the 400-ms ISI condition, the ERP of the second stimulus remained similar to the ERP produced by the first stimulus. This Eys effect was found in all 8 high-order electrodes. In sharp contrast to the suppression of the Eys at short ISIs, the gamma response remained largely unaffected regardless of the ISI duration. Overall, we found no significant difference between the gamma power generated by the 2 stimuli ($P = 0.5$, $t$-test, $N = 420$, Fig. 3). Similar to the unaffected gamma response to the second stimulus, there was no degradation in behavioral performance; neither accuracy nor reaction times were significantly different in trials with 200-ms ISI compared with 400-ms ISI. For the 5 patients, the accuracy of the one-back response in both ISI conditions was $>90$%; the average reaction time was 393 ms for an ISI of 200 ms and 408 ms for an ISI of 400 ms; no significant difference was found between the 2 conditions ($P = 0.8$, $t$-test, $N = 65$).
Inspection of the response spectrograms and plots shows that at the 200-ms ISI condition, the gamma power immediately preceding the second visual stimulus was of substantially higher amplitude than that found following the 400-ms ISI condition (Fig. 3, green arrows). Given this observation, a possible cause for the abolishment of the ERP may have been the high level of gamma power produced by the first visual stimulus, which persisted during the appearance of the second stimulus.

EPS as a Function of Preceding Gamma Power
As mentioned above, in examining the possible sources of the EPS effect, it appeared that the EPS was most profound when high-gamma activity preceded the stimulus response. This can be seen in Figures 3 and 4, where the green arrows on the gamma plots indicate the gamma power at the onset of the second stimulus. To examine this phenomenon more quantitatively, we analyzed all the trials with pairs of face stimuli and

Figure 3. The EPS effect at different ISIs. Signal recorded from a high-order visual electrode. Left panels (a, c, e, g, red): a pair of different faces presented at 200-ms ISI. Right panels (b, d, f, h, blue): a pair of faces presented at 400-ms ISI. Second stimulus onset at time zero. (a, b) Spectrograms, red -7 dB, blue -7 dB (see Materials and Methods). (c, d) BLP of the evoked potential frequency band (8-13 Hz), gray background—stimulus on. (e, f) BLP of the gamma band (50-70 Hz), green arrows point to the gamma power at the onset of the second stimulus. (g, h) Conventional ERP plots of the same conditions, ellipses highlight the initial ERP. N = 60 trials per condition. Note in c, the striking suppression of evoked potential to the second stimulus that occurred at 200-ms ISI but not at 400-ms ISI (d), this phenomenon is also evident in a and b (arrows). Note also in e that the gamma power of the second stimulus was not affected.

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plotted the evoked response power of the second stimulus as a function of the gamma power that preceded the stimulus arrival. Note that in order to avoid possible confounds due to different category-related responses (Fig. 4 and Supplementary Fig. S5), this analysis included only pairs derived from the same category (faces).

The BLP of all trials was averaged per electrode, per experiment, and per ISI condition (see Materials and Methods). The results of this analysis are presented in a scatter plot in Figure 5. As can be seen, there was a highly significant correlation between the immediately preceding gamma power and the depth of suppression of the evoked potential ($R = 0.9$, $P < 0.001$, Pearson’s correlation coefficient).

Since the gamma power following the first stimulus declined with time, it could be argued that the apparent negative correlation between gamma power and the evoked potential of the second stimulus was an indirect consequence of the longer time interval between the 2 stimuli (which affected both the gamma and the EPS). To examine this possibility, we analyzed the gamma effect independently from the ISI duration by...
examining only the trials with pairs of 2 faces having the same 200-ms ISI. These trials were then sorted into 4 bins according to the amplitude of gamma power immediately preceding the second stimulus. The results, depicted in Figure 6, show the average evoked response of the second stimulus per bin. As can be seen, within the same ISI duration, trials preceded by high gamma showed a strong EPS, while trials preceded by weak gamma had weak EPS. The differences between neighboring bins were significant ($P < 0.05$, $t$-test). Note that in this analysis both the stimulus categories and the ISI were kept constant, thus specifically isolating the non-ISI related component of the gamma modulation. Figure 6, thus, shows that the "antagonistic" effect remains even given these identical parameters.

We quantitatively validated that the EPS was significantly affected by the gamma power preceding the second stimulus and independently from the ISI. To that end, we used analysis of covariance for evoked potential values, for the whole data set of face-face pairs (including 50/200/400-ms ISIs). In the analysis, we used ISI as categorical factor and gamma as covariate. We found that the level of evoked potential decreased significantly as gamma increased ($P = 0.7 \times 10^{-10}$), with the same rate of decrease for all ISIs ($P = 0.81$). To further confirm the significance of the correlation between EPS and the preceding gamma power independently from the ISI, a permutation test was performed ($P < 0.001$, see Statistical Analysis).

To summarize, we found a strong correlation between the suppression of the evoked potential and the gamma power immediately preceding it.

Several other electrophysiological parameters that could potentially contribute to the EPS effect were examined. First, we looked at the offset activity of the first stimulus or any other late component that could potentially cancel out the ERP of the second stimulus. To examine this possibility, we duplicated a single stimulus ERP (from the object category experiment) and linearly added the 2 duplicates while shifting them in time relative to each other using the same ISIs (200 and 400 ms). The results of this simulation (Supplementary Fig. S1) showed no cancellation effect.

Second, we analyzed the amplitude and phase of other frequency bands, specifically, theta (4–8 Hz), alpha (8–13 Hz), and beta (13–30 Hz). We could not find any significant correlation to the EPS phenomenon in the theta and alpha bands in the period preceding the second stimulus. The only additional frequency band that showed a significant correlation to the EPS effect was the beta band ($R = 0.81$, $P < 0.001$). This correlation could be produced by the well-known low-frequency event related desynchronization (ERD) effect (Crone et al. 1998; Mukamel et al. 2005). Closer examination of trials with a fixed...
ISI of 200 ms revealed that the correlation to the beta power showed a positive trend, although not reaching significance \((R = 0.48, P < 0.08)\), compared with the correlation to the gamma power in fixed ISI of 200 ms \((R = 0.75, P < 0.003)\, \text{Supplementary Fig. S4}\).

Could the EPS effect be specific to the one-back memory task? To examine this possibility, we analyzed the same phenomenon during a different target identification task (see Materials and Methods). We found that the EPS effect was still present during this task (see also Discussion).

**Category Selectivity of the Suppression Effect**

To gain insight into the stimulus selectivity of the EPS effect, we examined to what extent it depended on the attributes of the visual stimulus. Figure 4 shows an example of the EPS effect in one category selective electrode when mixing preferred and nonpreferred stimuli. As can be seen, when the first stimulus belonged to a nonpreferred category, which did not produce a strong gamma response, the EPS was absent. This was reflected in the second ERP having a similar magnitude to that produced by the first stimulus. The complementary sequence, with a preferred stimulus followed by a nonpreferred one, is presented for reference in Supplementary Figure S5.

The EPS phenomenon showed strong exemplar invariance. Electrodes that were object category selective demonstrated a strong EPS effect for any combination of exemplars as long as they were from the preferred category (Fig. 4). Comparing the EPS strength between identical pictures and pairs of different exemplars from the same category showed a weak trend for a deeper EPS for identical exemplars, but this effect did not achieve significance \((P = 0.22, \text{t-test}, \text{and Supplementary Fig. S3})\).

We searched for the EPS phenomenon in low-order visual areas (2 of the 10 electrodes). In contrast to the high-order electrodes, here we have not observed EPS even at a short ISI of 50 ms, possibly due to shorter “life times” of the processing in early visual areas (Uusi-tilo et al. 1996), and the corresponding rapid decay of the gamma response following the termination of the visual stimulation (Supplementary Fig. S2).

**Discussion**

**Relevance to the Nature of the ERP**

Our results provide a number of new insights regarding the nature of subdural ERP signals. To the extent that these signals contribute to the scalp ERP, they could potentially illuminate this noninvasive signal as well. Concerning the nature of the subdural ERP, our results suggest that a reduction in ERP amplitude does not necessarily imply a reduction in overall neuronal activity. The basis for this claim is the observation that even in cases where we find a complete elimination of the ERP, the gamma power response remained essentially unchanged (see Results and Figs 3 and 4).

It has previously been shown that in sensory cortex, broadband gamma power reflects the overall firing rate of the local neuronal population (Nir et al. 2007; Xing et al. 2009). Furthermore, a strong link between firing rate and gamma power was found in adaptation studies of macaque IT cortex (De Baene and Vogels 2009). These results can be interpreted under the likely (although unproven) assumption that the local field potential and ECoG reflect similar neuronal phenomena. Thus, the results can be viewed as showing a clear dissociation between the evoked LFP response (ERP) proper and the firing activity of the neuronal population. Under certain temporal stimulus dynamics, the former can be completely eliminated while the latter remains relatively unchanged. It should be noted that the ERP did not reflect the perceptual state or the behavioral performance of the patients. Neither error rates nor reaction times in the one-back memory task showed a significant difference between the 200- and 400-ms ISI conditions where a significant EPS difference was observed.

In contrast to the observed mismatch between the ERP suppression and patients' behavior, the gamma power response matched the behavioral performance in the 2 ISI conditions. This link is compatible with a number of previous studies (Tallon-Baudry 2003; Fries et al. 2007; Fisch et al. 2009) showing a tight link between perceptual awareness and gamma power as well as single-unit activity (Quiroga et al. 2008).

Finally, an important additional outcome of the present study is the demonstration that under certain circumstances 2 different markers of neuronal activity—the subdural evoked potential and gamma power—actually show an antagonistic relationship.

**Possible Origins of EPS Effect**

Could the finding of a tight negative correlation between ERP amplitude and gamma power immediately preceding the stimulus-evoked response be due to additional factors? One obvious parameter that may have contributed to the EPS effect is the ISI duration. Indeed, both the gamma power and the reduction in low frequency power (the ERD) were affected by the ISI simply because at long intervals their sustained level was diminished. However, by examining the impact of these frequencies while maintaining the ISI duration fixed, we could identify the source of the EPS effect. Thus, our results clearly demonstrate that the EPS effect was related to gamma power (Fig. 6), while the link between the ERD and EPS when equating ISI duration did not reach significance \((P < 0.08, \text{Supplementary Fig. S4})\).

We cannot rule out the possibility that modulations in ERD, similar but of opposite sign to the gamma power changes, had an impact on the EPS as well. However, the fact that under constant ISI, this effect was largely diminished suggests that the correlation between the beta power preceding the second stimulus and the EPS effect was mainly a direct consequence of ISI timing.

Another possibility to consider is that the EPS effect was simply due to a linear voltage summation of the ERP from the first stimulus with that of the second one. If the ERP contains a later negative potential, then simply summing the first and second ERPs at short intervals may cause the 2 waveforms to cancel out. We examined this possibility by summing 2 individual ERPs at various intervals but failed to create an EPS-like phenomenon using this approach (Supplementary Fig. S1).

Finally, it could be argued that the EPS effect was specific to the one-back memory task, which may have enhanced the sustained gamma activity preceding the second stimulus. However, in a few cases, we used a different task (target recognition) and yet the EPS effect remained unaffected.

It should be noted that EPS-like effects were described using scalp EEG and MEG under a variety of tasks, such as letters classification (Noguchi et al. 2004), gender discrimination (Kovacs et al. 2006), and target face identification (Harris and...
Nakayama 2007). The extension of our results to scalp EEG should be made with caution since important differences exist between scalp and intracranial recordings. For example, the ECoG signal is clearly far more local compared with the scalp-recorded EEG. Nevertheless, it should be noted that specifically with regards to the EPS effect, our results are similar to the findings of Harris and Nakayama (2007) with MEG recordings, with the only difference being in the gamma power results.

Neuroanatomical Differences

Few of the visual electrodes recorded were localized in early visual areas (see Materials and Methods). Although exhibiting robust gamma and ERP responses, these electrodes failed to show an EPS effect even when ISI was shortened to 50 ms. We cannot rule out the possibility that early visual areas possess different sensitivities to EPS. However, an alternative, parsimonious, interpretation may be that early cortex electrodes are distinguished from the high order ones by the lack of sustained gamma responses. If this interpretation is correct, then the failure to elicit EPS in these electrodes was due to lack of preceding gamma power. Thus, in early cortex electrodes gamma power declined to baseline before the initiation of the next volley of activity produced by the second stimulus, even under the short ISI used.

Possible Neuronal Mechanism Underlying the EPS

We next consider the possible mechanism that may account for the EPS phenomenon, that is, the disruption of the ERP by a prior visual stimulus. Lacking direct single-unit recordings from large neural populations, we can only propose tentative hypotheses. A plausible model that can explain the EPS phenomenon and is compatible with known cortical properties could be as follows: following a quiet period, the background activity of cortical neurons is quite low. However, as a result of a sudden onset of a visual stimulus, a massive, synchronous activation in a large population of stimulus selective neurons is produced in the vicinity of the recording electrode. This synchronous activation is reflected in the typical evoked potential that we observe. Following the first stimulus of the pair and probably due to the dense local recurrent connections (e.g., Amir et al. 1993), the activity in the neuronal populations continues to reverberate, producing the observed sustained high gamma power (Fisch et al. 2009 and see Figs 3 and 4). If, during this high-activity period, a second stimulus is presented, the neurons which remain continuously active following the previous stimulus now disrupt the synchronization of the neuronal population selective to the incoming second stimulus. There are a number of putative mechanisms that may underlie such a desynchronization effect. For example, inhibitory neurons in the vicinity of the reverberating neurons may be transiently activated by these neurons. This activation could in turn generate fast, asynchronous, inhibitory pulses (Cardin et al. 2009) that may disrupt the second stimulus-driven synchronization. Alternatively, if there is a large overlap between the neurons that are activated by the first and second stimuli—the neurons that are already fully activated by the first stimulus will fail to transiently and synchronously reactivate. Thus, the evoked potential that depends on such synchrony will be suppressed. Regardless of the precise mechanism, the consequence of this activity-based disruption is that the evoked potential, which depends on synchronized activity, is eliminated. However, such disruption does not prevent the neurons sensitive to the second stimulus from starting to asynchronously reverberate and thus generate the broadband gamma power increases we observe following the second stimulus.

Could the reduced evoked response be a consequence of attentional modulation? The lack of EPS effect during cross category presentations argues against this possibility since presumably attention was modified in both same and different category presentations. Furthermore, the behavioral performance as measured by accuracy and reaction times during the one-back task did not show any significant link to the suppression condition, which is expected if the EPS is related to attentional mechanisms.

Another visual phenomenon that shows similarity to the EPS is the attentional blink (AB) (Fell et al. 2002; Dehaene et al. 2003). In both the AB and EPS experimental paradigms, pictures follow each other with fairly short ISI. However, there are also substantial differences between the 2 phenomena. Most critically, during EPS, the stimuli are presented in isolated pairs with long intervals between pairs (1.5 s in our paradigm). Previous research has shown that such a presentation sequence prevents the AB (Fell et al. 2002), and indeed, in our study, the patients had no difficulty in perceiving both stimuli in each pair. However, it may well be that the initial neuronal mechanisms that are initiated during the AB as proposed by Dehaene et al. (2003) may partially operate during EPS as well. Additional exploration in which interpair intervals will be manipulated parametrically is needed to examine whether the 2 phenomena can indeed be integrated.

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Supplementary Material

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

Notes

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References


