

Synchronous cortical gamma-band activity in task-relevant cognition

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Widespread synchronous oscillatory activity, particularly in the gamma ('40 Hz') band, has been postulated to exist in the brain as a mechanism underlying binding. A new method of examining phase synchronicity across multiple electrode sites in specific EEG frequency bands as a function of time was employed, in a conventional cognitive ERP paradigm in 40 normal subjects. A significant late post-stimulus gamma syn-

chronicity response occurred for task-relevant stimuli, whereas for task-irrelevant stimuli no such response was evident. However, an early response was seen for both task-relevant and irrelevant stimuli. This is the first empirical demonstration that widespread synchronous high frequency oscillations occur in humans in relation to cognition. *NeuroReport* 11:669–675 © 2000 Lippincott Williams & Wilkins.

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INTRODUCTION

One of the more fundamental questions in neuroscience is how the brain integrates its disparate network activities (the binding problem). A powerful associative mechanism of brain function has recently come to light. Neural networks activating synchronously at similar frequency and phase, may provide a mechanism underlying the coherence of distributed brain function [1–3]. Gamma (approximately 40 Hz) activity appears to be the most likely frequency range involved in binding synchrony discovered to date [4,5]. Neurophysiologists are uncovering this synchrony in neural networks and proposing that it may represent a way in which the brain encodes information. The evidence from a number of researchers [6,7] shows that action potentials in numerous neurons, simultaneously stimulated in the cortex (and elsewhere in the brain), exhibit synchronous fluctuations of firing rate. These fluctuations occur in the gamma band at around 40 Hz (varying from 30 to 80 Hz in different species). These findings have been recently reviewed by Singer and Gray [1], who show that this synchronous activity also occurs at a larger scale, between concurrently active cortical sites, which show zero time lag between them. They suggest that 'response selection could be achieved by the synchronization of activity among a distributed population of neurons rather than by solely increasing their discharge rate'.

These studies suggest that the 'brain encodes information not just in the firing rates of individual neurons, but also in the patterns in which groups of neurons work together' [8]. These changing patterns of synchrony correlate with a number of other aspects of brain function

including preparation to move, discrimination of odours, shorter reaction times, undertaking a movement, and numerous experiments involving visual processing and binocular rivalry. Stopfer *et al.* [9] recently demonstrated that when picrotoxin (which abolishes the synchronous firing of neurons without altering their firing rates) was given to honey bees that were trained to recognise odours associated with a sugar-water reward, the picrotoxin removed the synchrony and the ability to undertake this task, but the neuron's firing rate remained constant, highlighting the potential significance of synchrony.

In studies at the level of the whole brain, gamma rhythms have been interpreted as 'universal functional building blocks' [5]. Exploration of gamma activity was in fact initiated by Adrian [10] at the whole brain scale, prior to the current resurgence of interest in this index across-scales. In the 1970s and 1980s Freeman [11] showed that a characteristic burst of 40–80 Hz oscillations provided specification for a neural template associated with specific odours. Sheer [12] demonstrated 40 Hz rhythms associated with focused cortical arousal and attention. Basar *et al.* [13] published the first results related to the human auditory 40 Hz response.

Our group has examined peak gamma amplitude in a short interstimulus interval cognitive paradigm [14]. More importantly, we have recently developed a new method to quantify phase synchrony across multiple scalp sites [15], which forms the basis of this study. We have extended this method to enable examination of phase synchrony as a function of time. We then examined the time course of phase synchrony across widespread regions of cortex for

task-relevant and irrelevant stimuli in 40 normal subjects. This is the first empirical study to elucidate the existence and pattern of gamma synchronous activity in a conventional information processing (decision making) cognitive paradigm.

MATERIALS AND METHODS

Subjects and acquisition procedure: This study examined the same data as in our previous study of gamma activity and a full description of the subjects, acquisition procedure and paradigm can be found there [14]. Briefly, data from 40 normal subjects was examined in this study (19 males and 21 females). The males had a mean age of 45.5 ± 15.2 years (s.d.) and the females had a mean age of 45.2 ± 16.5 years. Data were acquired from the Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2 scalp sites with a linked earlobes reference. A continuous acquisition system was employed and data was EOG corrected offline [16]. The sampling rate was 250 Hz.

The ERP data were collected using a standard auditory oddball paradigm. Stereo headphones conveyed regular tones of 1000 Hz at an interval of 1.3 s to both ears. The subjects were instructed to ignore these tones (task-irrelevant). A second target (task-relevant) tone of 1500 Hz was presented, randomly intermixed with the lower tone, the only constraint being that two high tones were never presented in succession. Eighty-five percent of the tones were task-irrelevant and 15% were targets. The subjects were instructed to respond to the target tones by pressing two reaction-time buttons as fast and accurately as possible with the middle finger of each hand (to counterbalance motor effects). Only correctly identified target epochs for which a button press response was obtained within 1 s of the target tone were analyzed. The recording session was continued until 40 correctly identified target epochs were acquired. Each subject had its eyes open and was instructed to look at a coloured dot in the centre of a screen, in order to minimize eye movements.

Gamma analysis: Narrow band gamma activity (37–41 Hz) was examined, as this encompasses the key frequency of 40 Hz and was also the specific frequency bin which our previous study showed contained the cognitive induced gamma response [14]. Before any further analysis, all single-trials had any linear trend removed by subtracting the line of best fit over 512 samples centred at the stimulus presentation. Following this, for each single-trial epoch, from each recording site, a 64 sample Welch window was moved along sample by sample, starting with the centre of the Welch window at 500 ms prior to the stimulus (–500 ms) and ending with the centre of the Welch window at 750 ms after the stimulus. At each sample position, the phase of the gamma frequency component was computed by means of FFT. This gave a time series of gamma phase from each of the electrode sites.

For each epoch, the phase synchronicity was then estimated at each time point. Phase synchronicity was computed by taking the phase estimates from the various sites at a given time, and computing the circular variance of these phase estimates [15]. This yielded a singular estimate of the extent of phase-locking across these sites, for each point in time. The result was a time series of

gamma phase synchronicity across the sites in question. Seven such waveforms were derived for each epoch, one for global (all sites) synchronicity, and six regional synchronicity waveforms. There were three regional waveforms to examine gradient, these being frontal (Fp1, Fp2, Fz, F3, F4, F7 and F8), centro-temporal (Cz, C3, C4, T3, T4, T5 and T6) and parieto-occipital (Pz, P3, P4, O1 and O2), and three regional waveforms to examine lateralization, these being left hemisphere (Fp1, F3, F7, C3, T3, T5, P3 and O1), midline (Fz, Cz and Pz), and right hemisphere (Fp2, F4, F8, C4, T4, T6, P4 and O2). Phase synchronicity can be thought of as very similar to coherence estimates, except that instead of being derived only from site pairings as with coherence, it is derived across many electrode sites.

For each region, this resulted in a 1.25 s time series of gamma phase synchronicity from –500 ms to 750 ms for each stimulus presentation, sampled at 250 Hz. Following this, the 40 target and their preceding 40 background ERP epochs in each subject were averaged in the same manner as for conventional ERPs. This yielded an average target gamma phase synchronicity waveform and an average background gamma phase synchronicity waveform for each of the seven regions in each subject. Each average waveform was smoothed with a 15 sample running average in order to reduce noise. For ease of interpretation, all the synchronicity waveforms were inverted.

The next stage of the analysis involved testing for the presence of a phase-locking response in relation to the stimulus in the waveforms. From the averages it appeared that there were two such responses, an early response which was maximally evident within the latency window –100 to 100 ms in both targets and backgrounds, and a late post-stimulus response which was evident only in targets and which was maximal in the latency window 250–450 ms. In order to test this, we formed the area under the curve in these two latency windows for each waveform, and compared it with the area under the curve in a pre-stimulus baseline window from –400 ms to –200 ms. If the area under the curve in the response latency window was significantly greater than the area under the curve in the baseline this would demonstrate a significant increase in phase synchronicity and a genuine phase-locking response.

Statistical analysis: For a given region and a given response component (that is, either –100 to 100 ms or 250–450 ms), the area under the curve for the response was compared with the area under the curve for the pre-stimulus baseline across the 40 subjects using a paired Student's *t*-test. Since there were seven different regions to analyze and two response components in both targets and backgrounds, this involved performing 28 distinct tests of significance. Therefore a Bonferroni correction was employed and a significance level of $p < 0.0018$ was required. Prior to performing the statistical tests, outliers were removed from the data. Values > 1.5 times the interquartile range above the upper or below the lower quartiles were considered to be outliers. However, the number of outliers never exceeded three out of the 40 subjects for any of the comparisons, and when the comparisons were repeated with outliers included, in each case the result in terms of whether the finding was significant was never different from the result with outliers excluded.

Control analyses: In order to ensure that any findings were not due to EMG contamination, two different control analyses were performed, in each case on target epochs only. Firstly, the global (all sites) synchronicity waveforms from adjacent frequency bands were examined using exactly the same methodology as for the 37–41 Hz band. As discussed in our previous study [14], EMG is broad spectrum in character, so any synchronicity due to this source would be expected to be present across frequency bands. Initially, the lower adjacent band (33–37 Hz) and the upper adjacent band (41–45 Hz) were examined. If a response was found in either of these bands, then the next lower or higher adjacent band was also examined. Secondly, the global synchronicity waveforms were recomputed omitting temporal and prefrontal sites, where EMG would be expected to be most prominent, and the rest of the analysis repeated.

RESULTS

Conventional ERPs: The group average conventional ERPs for targets and backgrounds are shown in Fig. 1.

Global (all sites) synchronicity: For global (all sites) synchronicity in the latency window –100 to 100 ms, both targets and backgrounds showed a highly significant increase in gamma phase synchronicity compared to baseline (for targets $p < 0.00001$, $t = 5.13$, $df = 39$, no outliers; for backgrounds $p < 0.0007$, $t = 3.73$, $df = 39$, no outliers). This global response can be seen in Fig. 2, which shows the group averages of the global phase synchronicity waveforms for targets and backgrounds. Both targets and back-

grounds show a similar prominent early phase-locking response in this latency window.

In the latency window 250–450 ms, however, targets showed a highly significant increase in phase synchronicity ($p < 0.00006$, $t = 4.52$, $df = 38$, one outlier), whereas backgrounds showed no significant response. This demonstrated a late post-stimulus gamma phase-locking response present only in targets. This can also be seen in Fig. 2.

Gradient regional analysis: In the gradient regional analysis, as for all other regions, targets and backgrounds showed similar findings for the –100 to 100 ms latency window. In the frontal region and the parieto-occipital region, neither targets nor backgrounds showed any significant response. However, in the centro-temporal region, both targets ($p < 0.0001$, $t = 4.34$, $df = 39$, no outliers) and backgrounds ($p < 0.0008$, $t = 3.64$, $df = 39$, no outliers) showed a significant increase in phase-locking. This can be seen in Fig. 3, which shows the group average waveforms of phase synchronicity for these three regions for both targets and backgrounds. The early response can be seen to be prominent in the centro-temporal region, but much less prominent in the other two regions.

For the 250–450 ms latency window, as for all other regions, backgrounds did not show any significant response. However, targets showed a significant phase-locking response in both the frontal region ($p < 0.0002$, $t = 4.16$, $df = 36$, three outliers), and the centro-temporal region ($p < 0.0007$, $t = 3.74$, $df = 38$, one outlier), but not the parieto-occipital region. Again this can be seen in Fig. 3.

Lateralization regional analysis: The results for the –100 to 100 ms latency window were again very similar for targets and backgrounds. Both targets and backgrounds showed a significant gamma phase-locking response for the left hemisphere (for targets, $p < 0.000001$, $t = 5.96$, $df = 39$, no outliers; for backgrounds $p < 0.0005$, $t = 3.89$, $df = 36$, three outliers). However, no significant response was found within either the midline region, or the right hemisphere. At first sight this appears somewhat at odds with the group average waveforms in Fig. 4, which show no response for the midline region, but appear to show a response in both the right and left hemispheres. However, when the response is compared in each case to the pre-stimulus baseline in the waveforms, it is evident that the response is larger in the left than the right hemisphere. The response in the right hemisphere was not sufficiently large to be significant in either targets or backgrounds (that is, given the Bonferroni correction we employed; in both cases the right hemisphere response was significant to $p < 0.05$).

In the 250–450 ms latency window, again there were no significant findings in the backgrounds. However, in the targets there was a significant phase-locking response in both the left and right hemispheres, but not in the midline region (left hemisphere: $p < 0.00001$, $t = 5.35$, $df = 37$, two outliers; right hemisphere: $p < 0.0015$, $t = 3.44$, $df = 38$, one outlier). These findings can also be seen in Fig. 4, with a prominent late post-stimulus response in both hemispheres in targets. A smaller response is also seen in the midline region in the figure, but this was not significant with the Bonferroni correction we employed, although it was again significant for $p < 0.05$.

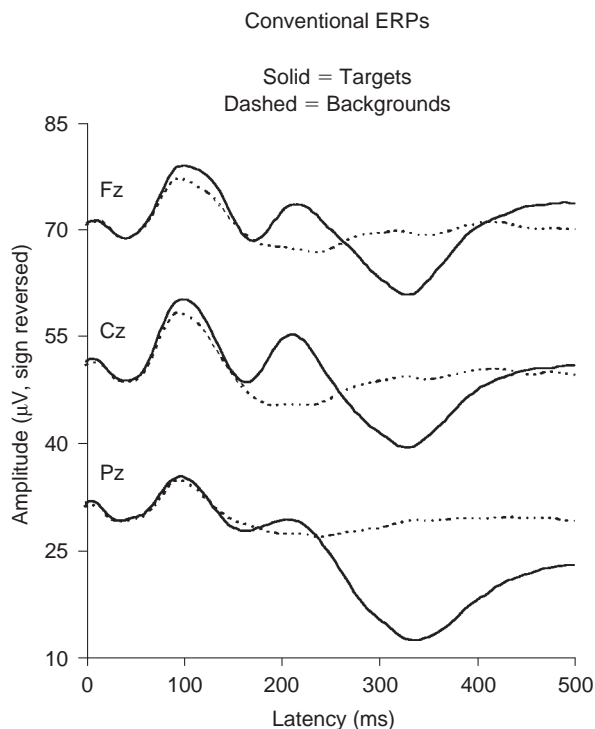


Fig. 1. Conventional grand average ERPs for sites Fz, Cz and Pz in targets and backgrounds.

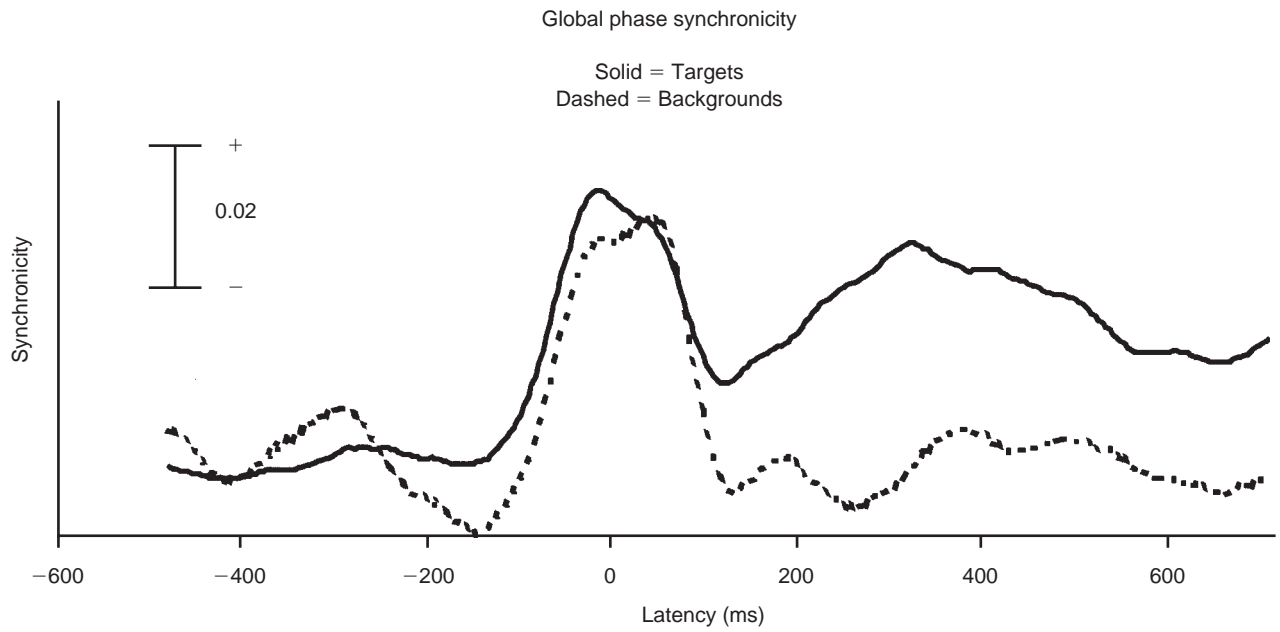


Fig. 2. Grand average global gamma phase synchronicity waveforms in targets and backgrounds.

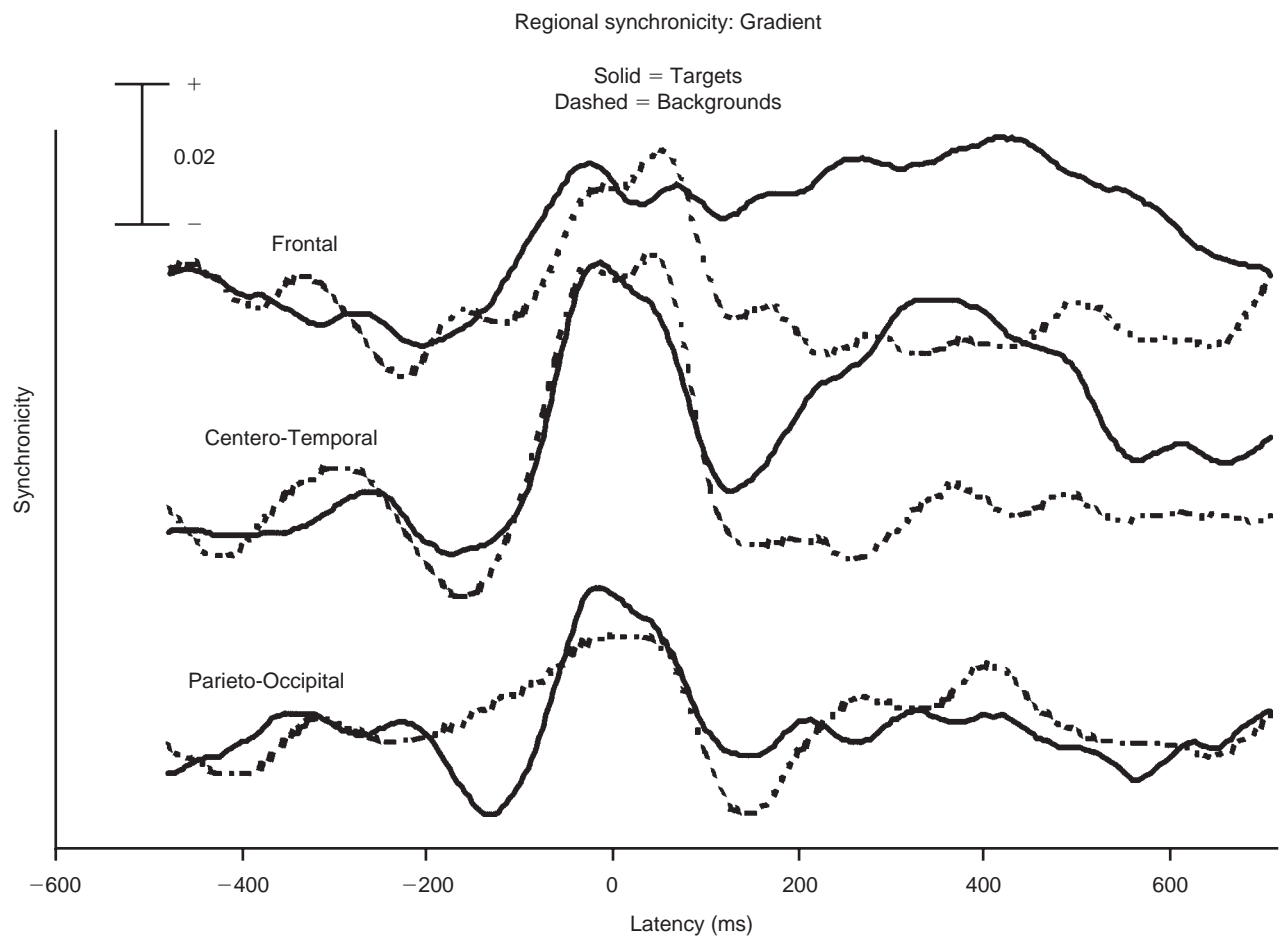


Fig. 3. Grand average regional gamma phase synchronicity waveforms for the frontal, centro-temporal and parieto-occipital regions in targets and backgrounds.

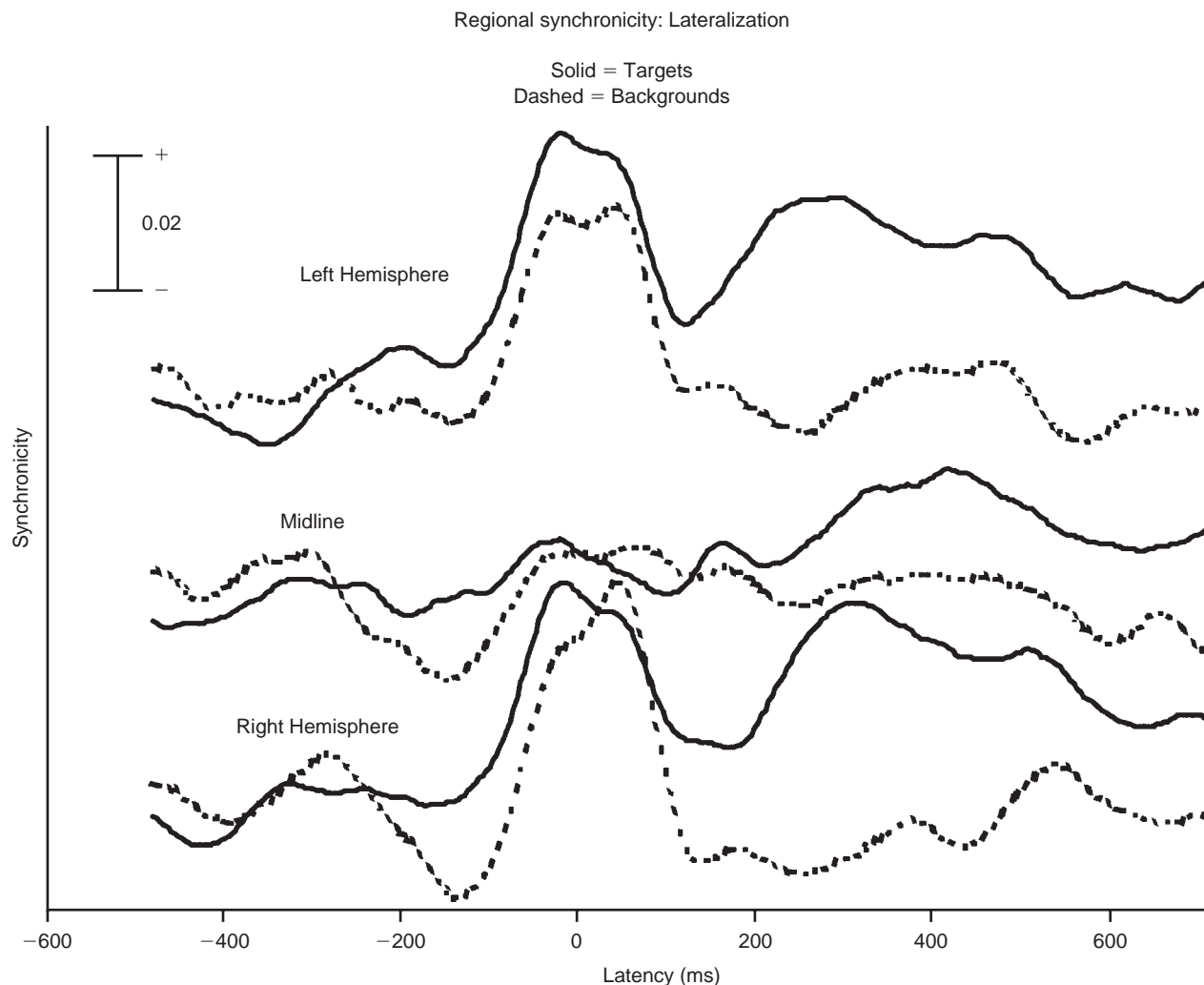


Fig. 4. Grand average regional gamma phase synchronicity waveforms for the left hemisphere, midline and right hemisphere regions in targets and backgrounds.

Control analyses: The 33–37 Hz bandwidth showed no significant global synchronicity response in targets in either the –100 to 100 ms or 250–450 ms latency windows. The 41–45 Hz bandwidth, however, did show a significant response in targets in both the –100 to 100 ms ($p < 0.00001$, $t = 8.09$, $df = 36$, three outliers) and 250–450 ms ($p < 0.00001$, $t = 6.43$, $df = 38$, one outlier) latency windows. In light of this the 45–49 Hz bandwidth was analyzed. However, this bandwidth showed no significant increase in synchronicity in either latency window.

The global synchronicity waveforms recomputed to exclude temporal and prefrontal sites still showed a significant response in targets in both the –100 to 100 ms ($p < 0.00001$, $t = 5.52$, $df = 37$, two outliers) and 250–450 ms ($p < 0.00005$, $t = 4.63$, $df = 36$, three outliers) latency windows.

DISCUSSION

This study demonstrated for the first time in humans the presence of widespread gamma phase-locking in response to task-relevant and irrelevant stimuli. Two different

phase-locking response components were observed. The first, an early response found in the latency window –100 to 100 ms, was present similarly in both targets and backgrounds, and was seen in the global (all-sites) analysis, and in the centro-temporal region and left hemisphere. The second, a late post-stimulus response in the latency window 250–450 ms, was found only in targets, and was seen in the global (all-sites) analysis, in the frontal and centro-temporal regions, and in both the left and right hemispheres. Both responses were relatively narrow band, being confined to the 37–45 Hz frequency range.

We have previously found a late post-stimulus gamma amplitude response in targets at a single-trial level of about the same latency as the late synchronicity response seen in this study (mean peak latency 357.6 ms) [14]. This gamma amplitude response, however, had slightly different frequency characteristics to the phase synchronicity response observed here. The amplitude response was confined almost entirely to the 37–41 Hz bandwidth, with a slight presence in the 33–37 Hz range, and was not seen in either the 29–33 Hz or 41–45 Hz frequency ranges. The

synchronicity response seen in this study was present in the 37–41 Hz and 41–45 Hz bands. Thus the frequency range of the phase synchronicity response extended somewhat higher than that of the amplitude response, although they overlap. Despite this minor difference, these two responses are likely to be closely related.

The mechanisms generating the synchronous gamma activity observed in this study are difficult to determine. Evaluation of phase synchronicity, like coherence, is complicated by the fact that volume conduction may contribute to the findings [17]. In relation to the late post-stimulus gamma synchronous response in targets, our previous study [14] showed that the late gamma amplitude response was maximal in the midline and parieto-occipital sites. This is the opposite of the synchronicity response which was most evident in frontal and centro-temporal regions, and in the hemispheres but not the midline. Thus the topography of synchronicity was virtually the inverse of the amplitude topography. This indicates that volume conduction from a single site is unlikely as an explanation for these findings, since if this were the case the sites with largest amplitudes would also show the greatest synchronicity [18]. The mechanisms underlying synchronous gamma activity remain contentious. Nevertheless, three strands of research have presently emerged that propose testable mechanisms underlying this activity. The first is that limbic system theta activity acts as the selective process that determines which set of networks will be integrated, and gamma activity is preferentially involved in the integration [19]. A second thrust of research activity proposes that GABA inhibitory activity is involved in the disinhibition of glutamate and the generation of gamma synchrony [20]. The third approach comes from numerical simulations of gamma by our group, which suggest that increased arousal may be associated with widespread synchronous gamma activity [21].

The functional significance of the two gamma phase synchronicity response components is not yet clear, and remains to be resolved in future studies. One possibility in relation to the early response component is that it might relate to the auditory middle latency sequence, which has been shown to have a strong 40 Hz character [22]. Alternatively, early synchrony might be important in priming the brain for subsequent stimulus processing. The late post-stimulus response, being found only in targets, probably reflects aspects of post-discrimination processing, and this together with its latency suggests that it may relate to the N2 and P3 ERP components and reaction time. It may be related to response preparation or to the evaluation and updating of stimulus context, which are associated with the N2 [23] and P3 components [24], respectively.

The regional effects are important to evaluate, but it is worth clarifying an important interpretive issue. The fact that no synchrony response was evident in a given region, does not mean that the sites in that region are not involved in synchronous processing. Rather, it means that they are not synchronous with each other. For example, the midline region consistently failed to show either the early or late synchrony responses. This only demonstrates that the signals at Fz, Cz and Pz are not phase-locked with each other. They may well be phase-locked with other sites, however, and in fact the findings demonstrate that for both

Fz and Cz this is indeed the case. The left hemisphere findings for the early response have one possible explanation. It has been demonstrated that less novel and more "routinized" information processing preferentially engages networks in the left hemisphere [25]. The early response almost certainly precedes evaluation of the relevance (target or background) of the present stimulus, and therefore represents an index of the more routine form of processing activity in this paradigm (which is designed to examine novelty rather than routine processing). Although this would account for the left hemisphere prominence of the early response, it is not clear why it is most prominent in the centro-temporal region. The late response was found more widely within all regions except the midline and parieto-occipital, and might therefore be a more general response. The significance of this topography is not apparent. It is interesting that it reflects a quite different distribution to P3 which is maximal parietally.

The control analyses showed that the results of this study were unlikely to be due to EMG contamination. Firstly, the phase synchronicity responses were confined to the 37–41 and 41–45 Hz bands and were not present above or below this frequency range. Secondly, the findings were still present to about the same extent when temporal and prefrontal electrodes were excluded from the analysis. These results tend to exclude EMG as an explanation for these findings. This confirms the findings of our previous study of gamma amplitude which showed that EMG contamination could not explain the post-stimulus gamma response in this bandwidth [14].

CONCLUSION

Widespread phase synchronization of gamma in response to stimuli has never been previously demonstrated in data from humans at the scale of the whole brain, and the phase-locking responses observed in this study may provide new insights into this level of processing and provide a link to the physiological gamma findings at more microscopic scales. The methodology employed in this study potentially opens a new window on brain function which may also shed light on some of the sources of unexplained variance in other more conventional indices, particularly since it offers further explication with high temporal resolution of gamma activity, in relation to the more conventional slow EEG and late component ERP indices of information processing.

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