

Long-range neural coupling through synchronization with attention

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Abstract: In a crowded visual scene, we typically employ attention to select stimuli that are behaviorally relevant. Two likely cortical sources of top-down attentional feedback to cortical visual areas are the prefrontal (PFC) and posterior parietal (PPC) cortices. Recent neurophysiological studies show that areas in PFC and PPC process signals about the locus of attention earlier than in extrastriate visual areas and are therefore likely to mediate attentional selection. Moreover, attentional selection appears to be mediated in part by neural synchrony between neurons in PFC/PPC and early visual areas, with phase relationships that seem optimal for increasing the impact of the top-down inputs to the visual cortex.

Keywords: attention; frontal eye field; area V4; synchrony; top-down; lateral intraparietal area

Introduction

When exploring the world around us, our visual system is confronted with more objects than it can process at any given moment. As a result, we are only aware of a limited number of objects, typically those that are a subject of our attention. Research on the neural mechanisms of visual attention in the last two decades has provided new insights into how neural systems allow us to monitor selectively particular objects or locations while blocking out all distracting information. Attention limits visual processing to objects or

locations that are relevant to behavior by selectively enhancing their representation. In electrophysiological studies this is typically seen in enhanced visual responses or increased sensitivity of individual neurons to locations or objects of interest at the expense of distracting stimuli (Luck et al., 1997; McAdams and Maunsell, 2000; Moran and Desimone, 1985; Motter, 1994; Reynolds et al., 1999; Treue and Maunsell, 1996). We originally proposed that top-down attentional feedback biased the competition between multiple stimulus representations in the cortex (Desimone and Duncan, 1995). More recent neurophysiological and modeling studies have formalized and quantified this “biased competition” idea and suggest that the competition between stimulus representations is more generally a form of contrast normalization in the cortex (Lee and

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Maunsell, 2009; Reynolds et al., 1999; Reynolds and Heeger, 2009).

In addition to enhanced firing rates with attention, recent studies have found that attention can also change the relative timing of spikes in populations of neurons (Bichot et al., 2005; Fries et al., 2001; Saalmann et al., 2007; Steinmetz et al., 2000). Cells with receptive fields (RFs) at the attended location (Fries et al., 2001) as well as cells selective for the attended feature (Bichot et al., 2005) synchronize their activity in the gamma-frequency range (above 30 Hz). Given that cells have short integration times, even small increases in synchrony in a given population can result in pronounced firing rate changes in downstream neurons (Börgers and Kopell, 2008; Murthy and Fetz, 1994; Salinas and Sejnowski, 2000). Consequently, synchrony can act as another potential amplifier of behaviorally relevant signals. Indeed, recent modeling studies show how synchronized activity for attended stimuli could result in the filtering of responses to distracters (Börgers et al., 2008; Tiesinga et al., 2008; Zeitler et al., 2008).

Although both synchrony and firing rates have been shown to be modulated by attention in the visual cortex the exact mechanisms and sources of this modulation in the brain are less clear. Two likely sources of top-down feedback are the prefrontal cortex (PFC) and posterior parietal cortex (PPC) (Corbetta and Shulman, 2002; Desimone and Duncan, 1995; Gottlieb et al., 1998; Miller and Cohen, 2001; Thompson and Bichot, 2005; Thompson and Schall, 2000). Here, we review recent physiological evidence coming from simultaneous recordings in different cortical areas that support the role of PFC and PPC in enhancing and synchronizing visual cortex responses with attention. More generally, the results suggest that phase-coupled gamma-frequency oscillations play an important role in communication across brain regions.

Interactions between PFC and area V4 in attention

Object recognition in monkeys depends on the “ventral stream” visual areas, which includes the

pathway from V1 through V2 and V4 to inferior temporal cortex. Cells in area V4 are selective for features such as color, orientation, and shape (Desimone and Schein, 1987; Desimone et al., 1985; Gallant et al., 1993, 1996; Pasupathy and Connor, 1999; Schein and Desimone, 1990) and they modulate their activity with attention to spatial locations as well as to specific visual features (Connor et al., 1996; Luck et al., 1997; McAdams and Maunsell, 1999, 2000; Mehta et al., 2000; Moran and Desimone, 1985; Motter, 1994; Reynolds et al., 1999; Williford and Maunsell, 2006). Moreover, recent reports have shown that attention increases neuronal synchronization in area V4 (Bichot et al., 2005; Fries et al., 2001, 2008).

PFC plays an important role in executive function, including the control of attention (Duncan, 1986; Miller and Cohen, 2001; Rossi et al., 2009; Stoet and Snyder, 2009). Lesions or deactivation of areas within the PFC impair attentional selection (Wardak et al., 2006) as well as the ability to switch attention in a flexible manner (Rossi et al., 2007) and have been reported to induce neglect in human patients (Heilman and Valenstein, 1972). One area in particular within the PFC, the frontal eye field (FEF), has been implicated in the control of spatial orienting not only via saccades (Bruce and Goldberg, 1985; Hanes and Schall, 1996; Schall, 1991) but also via covert deployment of attention (Thompson et al., 1997, 2005). FEF has direct reciprocal connections with visual cortical areas including area V4 (Barbas and Mesulam, 1981; Barone et al., 2000; Schall et al., 1995; Stanton et al., 1995; Ungerleider et al., 2008) and it is thus well suited to influence visual processing in the context of attention. Indeed, it has been shown that electrical stimulation of FEF can improve detection thresholds in an attention task and increases responses of V4 neurons to a stimulus in their RF (Moore and Armstrong, 2003; Moore and Fallah, 2001) mimicking the effects of spatial attention on behavior and neuronal responses in V4.

To test whether the FEF might be responsible for the effects of attention on neuronal responses and synchrony in V4, we recorded simultaneously from the two areas while monkeys were performing a covert attention task (Gregoriou et al.,

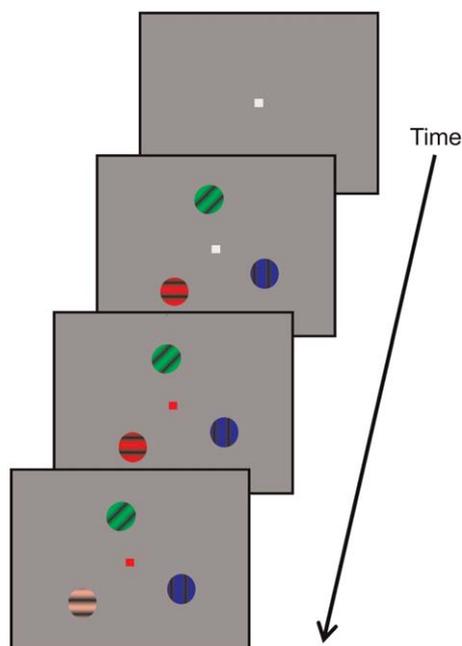


Fig. 1. Behavioral task. The monkeys had to hold a bar to initiate the trial and subsequently fixate the white fixation spot at the center of the screen. After successful fixation three sinusoidal drifting gratings (red, blue, and green) appeared on the screen, at positions distributed radially around the fixation spot at 120° intervals. The fixation spot was subsequently replaced by a small square cue that matched the color of one of the gratings indicating the color of the stimulus to be attended. The monkeys were required to shift their attention to the target stimulus while maintaining fixation of the cue and monitor the target for a color change. The animals were rewarded with a drop of juice for releasing the bar when the target changed color. On any given trial one or both of the distracter stimuli could also change color before the target but the monkeys were trained to ignore the distracters' change. If the monkeys released the bar to the distracter change, failed to maintain fixation, or did not respond to the target color change within 600 ms, the trial was aborted. (See Color Plate 3.1 in color plate section.)

2009). In the task, three colored gratings appeared in the visual field, and one of the gratings was in the joint RF of the cells in V4 and FEF (Fig. 1). A short time after the gratings appeared, a central cue instructed the monkey about which colored grating to attend (the target). The monkey was rewarded for releasing a bar when the target stimulus changed color, ignoring similar changes in the distracters.

To examine whether attention modulated neuronal responses we compared responses in trials where the target appeared inside the RF of the recorded neurons and in trials in which the target appeared outside the RF (Fig. 2). Neurons in both FEF and V4 showed enhanced responses with attention inside their RF. However, we found that the effect of attention on firing rate occurred significantly earlier in FEF compared to V4 (at 80 ms after cue onset in the FEF and at 130 ms after cue onset in V4) which is consistent with the idea that FEF is a source of feedback that modulates V4 responses with attention.

In addition to enhanced firing rates with attention, we also found enhanced synchrony in both areas in the gamma-frequency range (30–60 Hz). These results are consistent with previous reports on the effect of attention in area V4 (Fries et al., 2001, 2008) and show that neurons in FEF too show enhanced synchronization in the gamma range with attention. These findings suggest that neurons in FEF and V4 which encode the location of the behaviorally relevant stimulus synchronize their activity and could thus increase their impact on postsynaptic neurons in their target areas.

Increases in firing rate and synchrony within each area, however, do not establish a functional link between the two areas. If FEF and V4 are functionally coupled during attention then activity in the two areas should be correlated and exhibit increased phase locking with attention, as revealed by enhanced inter-area coherence. Using different measures of coherence (spike-field, field-field, and spike-spike) Gregoriou et al. (2009) indeed found that gamma-frequency coherence between V4 and FEF signals increased with attention for sites with overlapping RFs (Fig. 3). Interestingly, this effect of attention on coupled oscillations between the areas was proportionately larger than the one measured within areas. Importantly, there was no effect of attention on inter-area coherence when there was no overlap between the V4 and FEF RFs. This result suggests that the functional coupling between the two areas is spatially selective and in this particular paradigm becomes prominent only between sites with overlapping RFs. Although the design of the task allowed the animal to use both color and

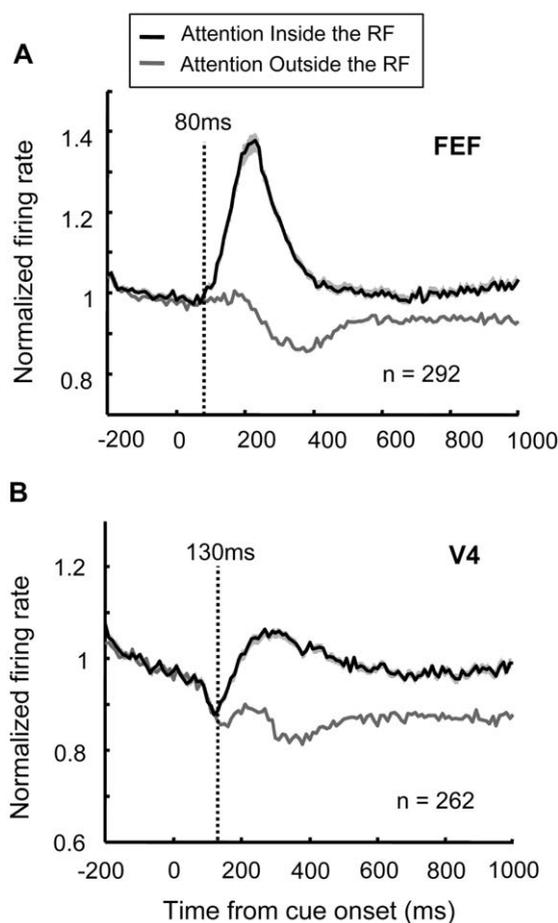


Fig. 2. Attentional effect on firing rate. Normalized firing rate of FEF neurons (A) and V4 neurons (B) averaged over the population of recorded visually responsive cells in each area. Black lines show responses when attention was directed inside the receptive field of the recorded neurons, gray lines show responses when attention was directed outside the receptive field. Shaded area over the lines indicates the standard error of the mean (\pm) at each time point. Dotted vertical lines show the latency of the attentional effect at the population level. Adapted from Gregoriou et al. (2009).

location for selecting the target stimulus, the strong spatial selectivity of the attention effects underlines the importance of spatial location in target selection.

If a common oscillatory input to the two areas were responsible for causing these coupled oscillations, then gamma synchrony in FEF and V4 would be expected to have a zero phase lag. While we found that the relative phase lag between

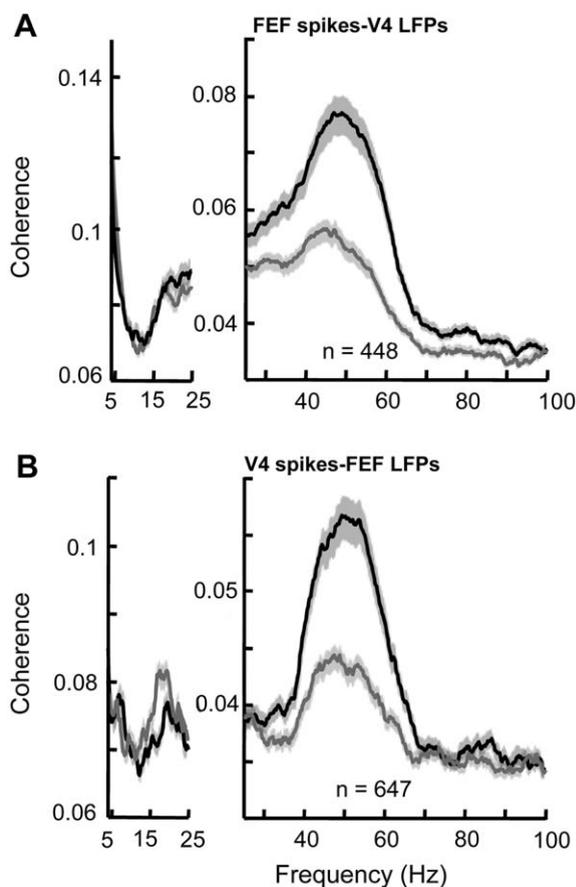


Fig. 3. Enhancement of synchronization with attention across FEF and V4. (A) Spike-field coherence between spikes from FEF and LFPs from V4 averaged across all pairs with overlapping receptive fields. (B) Spike-field coherence between spikes from V4 and LFPs from FEF averaged across all pairs with overlapping receptive fields. Tapers providing smoothing of ± 10 Hz were used for spectral estimation of higher frequencies (right part of each graph, 25–100 Hz) and tapers providing smoothing of ± 3 Hz were used for lower frequencies (left part of each graph, <25 Hz). Conventions as in Fig. 2. Adapted from Gregoriou et al. (2009).

spikes and local field potentials (LFPs) within each area was close to zero for gamma frequencies (40–60 Hz), the relative phase between spikes in one area and the maximum depolarization of the gamma oscillations in the LFPs in the other area showed a shift by about half a gamma cycle (140–150°) (Fig. 4). This phase shift corresponds to a time delay of about 8–13 ms, and examination of frequency bands other than gamma for which

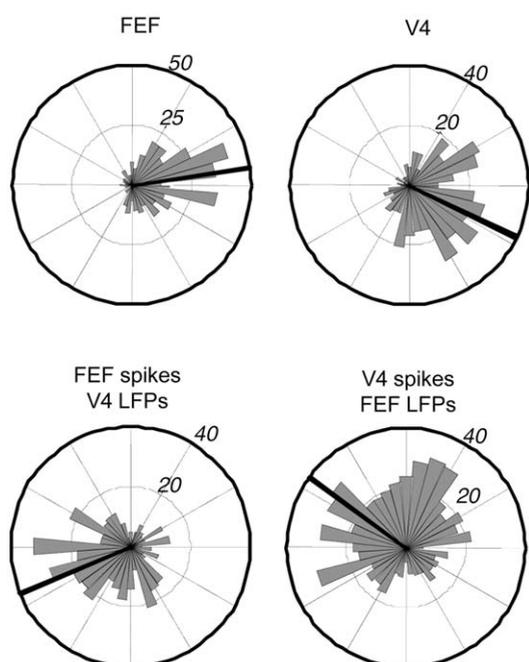


Fig. 4. Distribution of average relative phase (40–60 Hz) across the population of recorded pairs of signals, between FEF spikes and FEF LFPs, V4 spikes and V4 LFPs, FEF spikes and V4 LFPs, and V4 spikes and FEF LFPs. Black solid lines indicate the median of the distribution. Adapted from Gregoriou et al. (2009).

above-chance coherence could be measured (beta and theta frequencies) revealed the same consistent time delay. Although one cannot rule out the possibilities that the oscillatory coupling between FEF and V4 is due to a common input that has the necessary delays, or that the true delays include integer multiples of the cycle durations and are mediated by indirect pathways from FEF to V4, a direct functional coupling between the two areas with an 8–13 ms transmission delay would seem the most parsimonious explanation for all the results. Such an interpretation is also supported by previous studies that measured visual response latencies across different visual areas. Visual response latencies in V1 and V2 as well as between other areas in the ventral visual stream that are directly connected have been shown to differ by a similar amount of time (~10 ms) indicating that conduction times and synaptic delays could account for this delay

(Nowak and Bullier, 1997). Taken together, the results raise the tantalizing possibility that the phase of gamma oscillations is time-shifted to allow spikes produced in one area to arrive at the time of maximum depolarization in the other area, accounting for the latency of information transfer between the two areas. This phase relationship was the same in both attention conditions indicating that it reflects more general principles of communication between the two areas under visual stimulation. However, an increase in synchrony with attention of the sort observed in our study would result in enhanced phase locking between activities in the two areas, with more spikes from one area arriving at the right time to have a larger impact on the other area and therefore bias activity for the attended stimulus.

A Granger causality analysis supported the idea that FEF was the initiator of the coupled oscillations across the two areas. Granger causality analysis provides a statistical measure of the relative strength of influences of one area upon another. It does that by essentially testing whether past values of one signal help predict future values of another signal (Geweke, 1982; Granger, 1969). In agreement with the hypothesis that FEF initiates the gamma oscillations, we found that although significant influences with attention were found in both directions (from V4 to FEF and from FEF to V4) for gamma frequencies, the attentional effects on the Granger causality values appeared significantly earlier in the FEF to V4 direction than the reverse direction (Fig. 5). However, later in the trial these effects became significantly larger for the V4 to FEF direction indicating that while the FEF to V4 (top-down) input predominates when attention is directed to the location of interest, enhanced bottom-up input from V4 may sustain activity in FEF later in the trial when attention is maintained on the target and further visual processing is required. An analysis of the relative latencies of attentional effects on firing rates and LFP gamma power in the two areas suggested that firing rate changes in FEF initiated the attentional effects on synchrony within and across areas.

The findings described above extend the results of previous studies which have established the

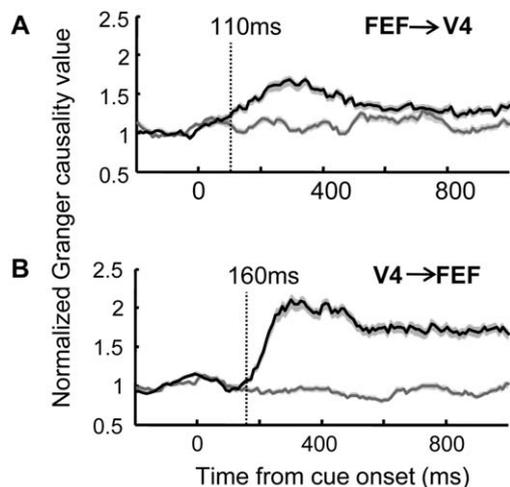


Fig. 5. Directional influences between FEF and V4. Population average of normalized Granger causality values averaged between 40 and 60 Hz across all combinations of FEF-V4 LFPs. Plots for each direction of influence, FEF→V4 (A), V4→FEF (B) are shown. Conventions as in Fig. 2. Adapted from Gregoriou et al. (2009).

role of FEF in attentional selection and have led to the proposal that the FEF holds a saliency map which encodes the behavioral significance of the stimuli (Thompson and Bichot, 2005). Naturally, other brain structures that project to V4 and that have also been implicated in attention, such as the PPC (Andersen et al., 1990; Goldberg et al., 2006; Lewis and Van Essen, 2000), are likely to contribute to the attentional effects on gamma synchrony and firing rates in V4.

Interactions between PPC and area MT in attention

Despite the compelling evidence that PFC plays an important role in attentional control, unilateral lesions of PFC do not permanently abolish the ability of monkeys to attend to visual stimuli, particularly when attention is maintained on the same stimulus across several trials (Rossi et al., 2007). This suggests that other cortical areas contribute to top-down feedback, with PPC a likely candidate. Electrophysiological studies in monkeys have reported modulation of posterior parietal neuronal responses with attention (Bisley

and Goldberg, 2003; Constantinidis and Steinmetz, 2001; Gottlieb et al., 1998; Lynch et al., 1977; Robinson et al., 1978), and it has been proposed that the lateral intraparietal area (LIP) in PPC holds a saliency map that guides attentional selection, much like the FEF (Gottlieb, 2007). In agreement with this idea it has been shown that inactivation of LIP delays the discrimination of visual targets in the hemifield contralateral to the inactivated site (Wardak et al., 2004), and in humans, PPC lesions cause hemispatial neglect (Mesulam, 1981) and inability to filter out distracters (Friedman-Hill et al., 2003).

Direct evidence supporting the idea that PPC provides top-down feedback to extrastriate cortical areas was found in a study that employed simultaneous recordings in LIP and area MT (Saalmann et al., 2007), two areas which share reciprocal connections. Monkeys performed a delayed match to sample task in which both spatial and feature-based attention were manipulated. The monkeys were required to match the location and the orientation of the sample and the test stimuli. The sample and test stimuli could either appear at the same location inside the common RF (i.e., attention inside the RF) or the sample could appear outside and the test stimulus inside the RF (“attention elsewhere” condition). When both sample and test stimuli occurred at the same position, they could either have different orientations (i.e., spatial attention only) or the same orientation (i.e., both spatial and feature-based attention). Both areas showed significant increases in firing rate when attention was directed inside the RF. Attentional effects in LIP occurred earlier than in MT, consistent with the hypothesis that it is a source of feedback to MT. Moreover, in contrast to MT in which responses were mainly modulated by the spatial locus of attention, LIP responses were modulated by attention to both features and locations. Responses of LIP neurons to the test stimulus with the preferred orientation were enhanced when it matched the orientation of the sample. This is in agreement with the idea of a saliency map which integrates information about features from feature-selective areas and sends topographically organized attentional feedback to visual

cortical areas (Gottlieb, 2007; Itti and Koch, 2001; Thompson and Bichot, 2005).

To test whether neural activity was synchronized across areas, Saalman et al. calculated coherence between LFPs in LIP and MT. Enhanced coherence was found between 20 and 35 Hz for the condition where attention was directed inside the common RF in both “spatial” and “spatial and feature-based” attention compared to the condition where attention was directed outside the RF. Coherence between a subset of spike trains in the two areas was also reported, confirming that spiking activities in the two areas are synchronized. Interestingly, the phase between LIP and MT spike trains indicated that LIP leads MT by 5–7 ms, which could be accounted for conduction and synaptic delays between the two areas. This time lag could ensure that signals from LIP arrive in MT at the depolarizing phase of the local oscillations maximizing the likelihood of spike generation.

Saalman et al. also calculated the percentage of MT spikes preceded by LIP spikes in the different attention conditions. Attention appeared to cause a 10% increase in the number of MT spikes preceded by LIP spikes within 10 ms. This percentage accounted for a considerable amount of the overall increase in the firing rate of MT neurons with attention, a finding which confirms that attention does not simply lead to overall increases in the firing rate but that it has a direct effect on the relative timing of spikes causing more spikes from one area to be phase locked to activity in the other area.

Conclusion

The results from the two studies reviewed here, reveal similar general principles that govern the interaction of FEF and LIP with early visual areas in attention. Both FEF and LIP are well suited to provide top-down attentional feedback to V4 and MT, respectively, as shown by the earlier onset of attentional effects in parietal and prefrontal activities. This feedback is manifested in the oscillatory coupling of neural activity between the interconnected areas. The results from both studies

showed that the coupled oscillations are shifted in time by 8–13 ms between FEF and V4 and 5–7 ms between LIP and MT, which could reflect the time necessary for spikes from one area to reach the other so that action potentials arrive in each area at its most excitable phase. This could maximize the probability of spike generation in the receiving area and could therefore amplify the impact of inputs corresponding to the attended stimulus over less coherent inputs corresponding to the unattended stimulus (Fig. 6). The difference in the time lag found in the two studies could be explained by the shorter distance between LIP and MT compared to the longer distance FEF-V4 connections and by the relative strength of connections. It should be noted however, that the frequency range within which enhanced phase locking was observed was different in the two cases. Whereas enhanced oscillatory coupling between FEF and V4 was found between 40 and 60 Hz, the same effect was observed in lower frequencies for LIP-MT coupling (20–35 Hz). It is possible that this diversity reflects differences in the tasks employed in the two studies. Early, “evoked” gamma-band activity as well as lower frequency beta-band synchrony has been associated with template matching and working memory processes (Herrmann et al., 2004; Tallon-Baudry et al., 2001), which were present in the task used by Saalman et al. The late, “induced” gamma-band synchrony seen by Gregoriou et al. is more likely to reflect sustained attention to a stimulus (Fries et al., 2008). The degree to which these processes and their underlying mechanisms may differ remains to be elucidated in future studies.

Synchrony in different frequency bands has been suggested to mediate different attentional processes. More specifically, a study undertaken to elucidate the role of PFC and LIP in bottom-up, stimulus-driven and top-down, goal-directed attention showed enhanced coherence between LIP and PFC in frequencies 22–34 Hz in bottom-up attention, whereas with top-down attention, coherence was greater between the two areas in somewhat higher frequencies, 35–55 Hz (Buschman and Miller, 2007). The authors suggested that an extended network of areas participating in top-down processes synchronizes in lower frequencies

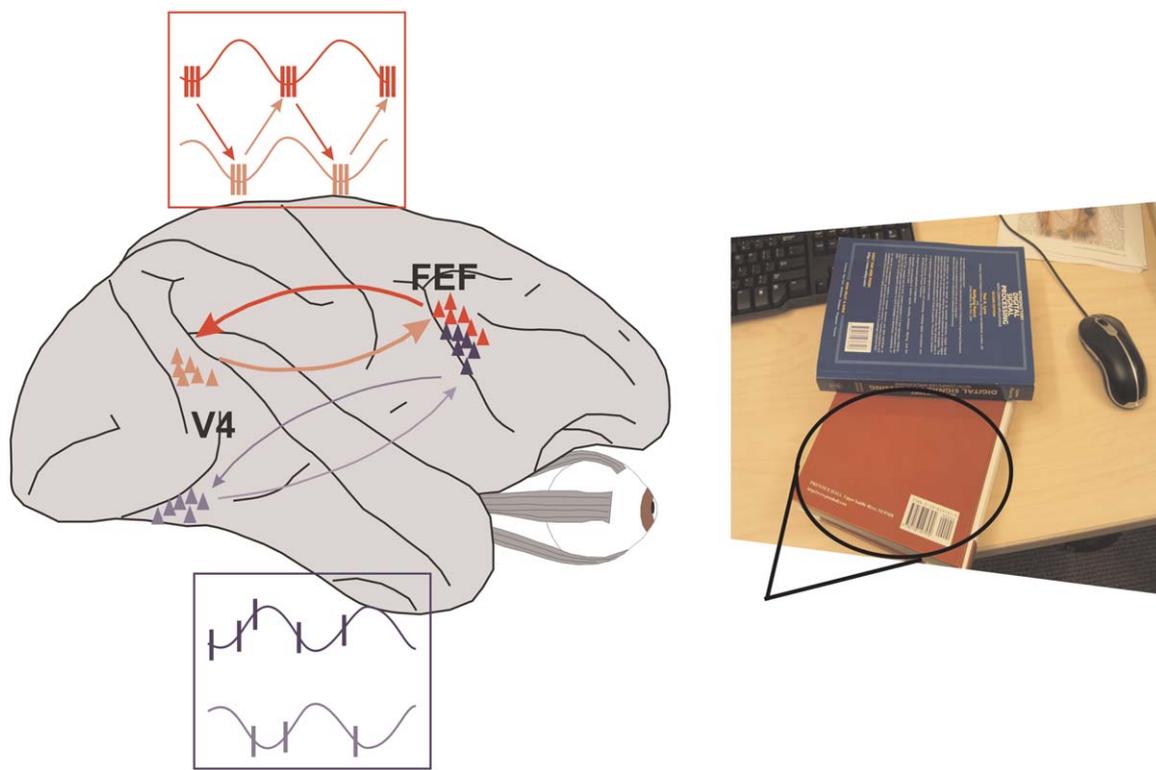


Fig. 6. Schematic illustration of inter-areal neuronal communication in attention. Dark red and light red triangles illustrate neurons in FEF and V4, respectively, encoding the attended stimulus (red book on the right), whereas dark blue and light blue triangles illustrate FEF and V4 neurons, respectively, encoding the unattended stimulus (blue book). The vertical lines in the boxes above and below the schematic brain illustrate action potentials of neurons in the four groups. Arrows indicate propagation of action potentials between areas along the projecting axons. Coherent spikes which arrive at the phase of maximal excitability increase the probability of generating spikes in the receiving area (red box). Note the phase relationship between excitability fluctuations in the two areas which facilitates neuronal communication. Less coherent spikes corresponding to the unattended stimulus (blue box) are less effective in triggering spikes in the receiving area and result in weak communication between the areas and a weaker representation of the unattended stimulus. (See Color Plate 3.6 in color plate section.)

which are more robust to conduction delays and would thus be better suited to mediate long-range or polysynaptic communication in the brain (Engel et al., 2001; Kopell et al., 2000). In contrast, synchrony in higher frequencies, in the gamma range, during bottom-up attention was suggested to reflect local computations underlying the enhancement of sensory representations (Buschman and Miller, 2007; Kopell et al., 2000). A number of studies have found long-range synchronization across distant brain areas in frequencies lower than gamma (Brovelli et al., 2004; Pesaran et al., 2008; Roelfsema et al., 1997; Sirota et al., 2008; von Stein et al., 2000) providing support to this idea. Our results (Gregoriou et al., 2009) which show

synchronization of activity in gamma frequencies within each area and strong coupling between FEF and V4 in the gamma range are in agreement with the proposal that gamma synchronization can be viewed as a local phenomenon observed within an area or across areas that are monosynaptically connected (von Stein et al., 2000).

Top-down inputs (from FEF to V4) are dominant at the onset of attention to a location possibly mediating attentional selection, but the bottom-up inputs (from V4 to FEF) come to predominate later in the trial when further visual processing is required during sustained attention. Indeed, once the relevant stimulus has been selected, the brain needs to insulate its sensory

representation from other inputs competing for effective visual processing. Modeling studies have shown that more coherent inputs which are oscillating in the gamma range can render less coherent inputs ineffective and can thus “lock” the representation of the attended stimulus by filtering out competing inputs (Borgers et al., 2008; Tiesinga et al., 2008; Zeitler et al., 2008).

The dynamic nature of selective interactions across brain areas in the course of attention shows that long-range oscillatory coupling between distant parts of the brain controls the activity in selective neuronal populations by setting the optimal phase difference which will facilitate neuronal communication (Fries, 2005; Womelsdorf and Fries, 2007). In a network of fixed anatomical connections such a mechanism of neuronal communication could provide the basis for the dynamic control of interactions among the subset of neuronal populations that are most relevant to the task at hand. Future studies should aim to elucidate the role of different frequencies in oscillatory coupling and their relevance to behavior.

Acknowledgments

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