

Corrections

APPLIED BIOLOGICAL SCIENCES. For the article “Tuning genetic control through promoter engineering,” by Hal Alper, Curt Fischer, Elke Nevoigt, and Gregory Stephanopoulos, which appeared in issue 36, September 6, 2005, of *Proc. Natl. Acad. Sci. USA* (102, 12678–12683; first published August 25, 2005; 10.1073/pnas.0504604102), the authors note that Eq. 1 was incorrectly given as

$$P = f_{ss} \left(\mu \left(1 + \frac{\mu}{m} \right) + D \left(2 + \frac{\mu}{m} \right) \right)$$

both in the text and in Fig. 2. The correct equation is as follows:

$$P = f_{ss} \mu \left(1 + \frac{\mu}{m} \right) + f_{ss} D \left(\frac{2\mu}{m} + \frac{D}{m} + 1 \right)$$

The corrected figure and its legend appear below. The error does not affect the conclusions of the article.

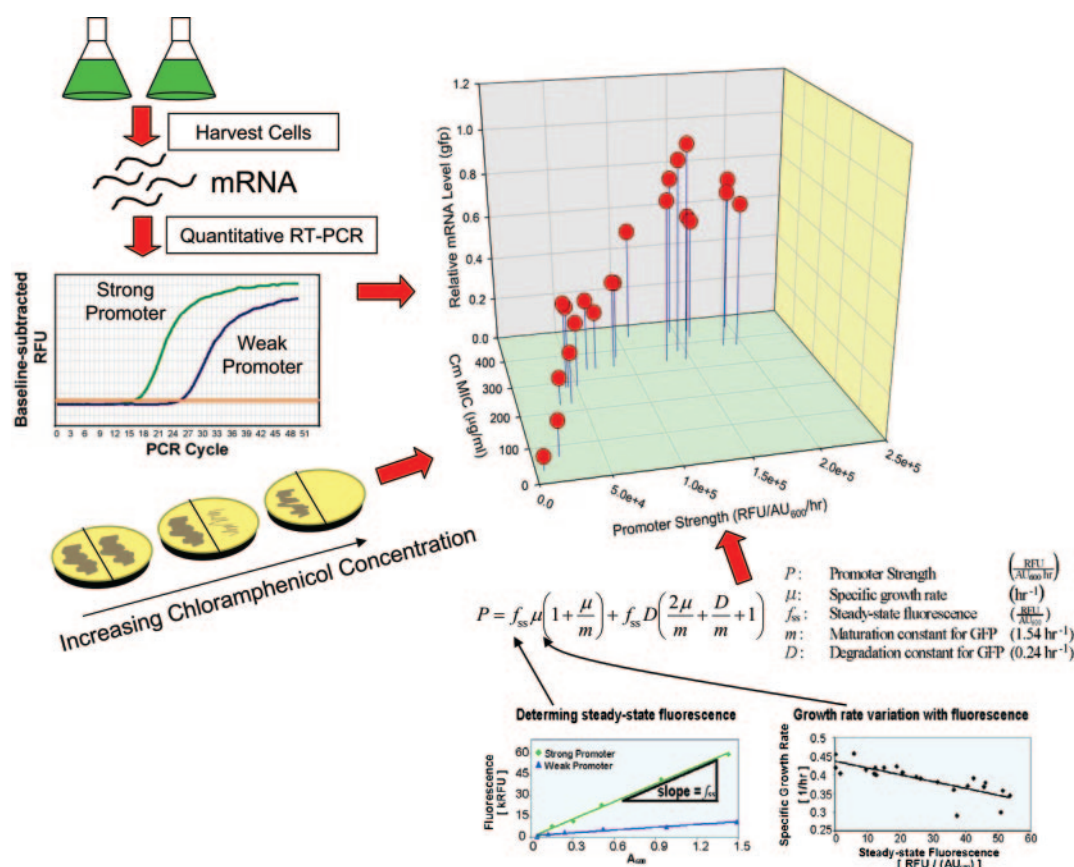


Fig. 2. Comprehensive characterization of the promoter library. Several orthogonal metrics were used to characterize the promoter library and ensure the consistent behavior of all its members for various genes and culturing conditions. We show here three metrics that were chosen for quantifying transcriptional of the promoters: (i) the dynamics of GFP production based on fluorescence, (ii) measurement of the relative mRNA transcript levels in the cultures, and (iii) testing of the MIC for chloramphenicol in an additional library of constructs where the promoter drove the expression of chloramphenicol acetyltransferase. The overall strong correlation between the various metrics suggests a broad-range utility of the promoter library for a variety of genes and conditions.

www.pnas.org/cgi/doi/10.1073/pnas.0511314103

MICROBIOLOGY. For the article “Bovine papillomavirus E7 transformation function correlates with cellular p600 protein binding,” by Joseph DeMasi, Kyung-Won Huh, Yoshihiro Nakatani, Karl Münger, and Peter M. Howley, which appeared in issue 32, August 9, 2005, of *Proc. Natl. Acad. Sci. USA* (**102**, 11486–11491; first published August 4, 2005; 10.1073/pnas.0505322102), the authors note that in Fig. 1B, the panel labeled “E7” appeared incorrectly. The corrected figure and its legend appear below. This error does not affect the conclusions of the article.

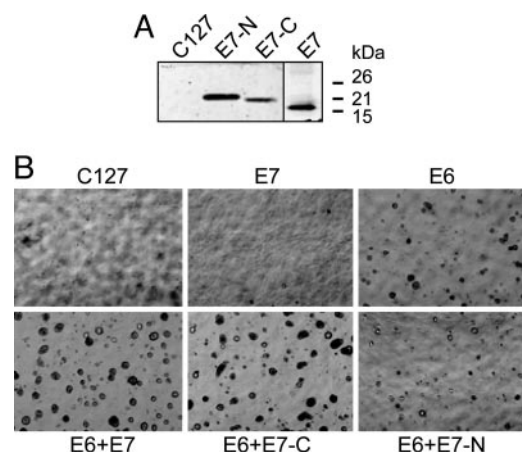


Fig. 1. Transformation assay of FLAG/HA-tagged and untagged BPV-1 E7. (A) Mouse C127 cells were transduced with retrovirus expressing BPV-1 E7 with a FLAG/HA epitope tag at either the C terminus (E7-C) or N terminus (E7-N), or with no tag (E7). Cells were lysed, and proteins were immunoprecipitated by using either an anti-FLAG antibody (Left) or an anti-BPV-1 E7 antibody (Right). Proteins were resolved by SDS/PAGE on a 15% polyacrylamide gel and probed by immunoblotting using the anti-E7 antibody. (B) Cells were assayed for anchorage-independent growth with transduced BPV-1 oncogenes: C127 control cells, cells expressing BPV-1 E7 alone, BPV-1 E6 alone, E6 and E7, E6 and C-terminal FLAG/HA-tagged E7 (E7-C), and E6 and N-terminal FLAG/HA-tagged E7 (E7-N). Cells were suspended in 0.3% Noble agar, DMEM, and 10% FBS and grown for 14 days. Representative fields are shown at $\times 10$ magnification. For further details, see Table 1.

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MEDICAL SCIENCES. For the article “Cell membrane-specific epitopes on CD30: Potentially superior targets for immunotherapy,” by Satoshi Nagata, Tomoko Ise, Masanori Onda, Kazuyasu Nakamura, Mitchell Ho, Andrew Raubitschek, and Ira H. Pastan, which appeared in issue 22, May 31, 2005, of *Proc. Natl. Acad. Sci. USA* (**102**, 7946–7951; first published May 19, 2005; 10.1073/pnas.0502975102), the authors note that on page 7947, in the last sentence of the right column, “(Laboratory of Proteomics and Analytical Technologies, National Institutes of Health)” should read: “(Laboratory of Proteomics and Analytical Technologies, SAIC-Frederick, Inc.).” This error does not affect the conclusions of the article.

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NEUROSCIENCE. For the article “Top-down facilitation of visual recognition,” by M. Bar, K. S. Kassam, A. S. Ghuman, J. Boshyan, A. M. Schmidt, A. M. Dale, M. S. Hämmäläinen, K. Marinkovic, D. L. Schacter, B. R. Rosen, and E. Halgren, which appeared in issue 2, January 10, 2006, of *Proc. Natl. Acad. Sci. USA* (**103**, 449–454; first published January 3, 2006; 10.1073/pnas.0507062103), the author name A. M. Schmidt should have appeared as A. M. Schmid. The online version has been corrected. The corrected author line appears below.

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Top-down facilitation of visual recognition

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Cortical analysis related to visual object recognition is traditionally thought to propagate serially along a bottom-up hierarchy of ventral areas. Recent proposals gradually promote the role of top-down processing in recognition, but how such facilitation is triggered remains a puzzle. We tested a specific model, proposing that low spatial frequencies facilitate visual object recognition by initiating top-down processes projected from orbitofrontal to visual cortex. The present study combined magnetoencephalography, which has superior temporal resolution, functional magnetic resonance imaging, and a behavioral task that yields successful recognition with stimulus repetitions. Object recognition elicited differential activity that developed in the left orbitofrontal cortex 50 ms earlier than it did in recognition-related areas in the temporal cortex. This early orbitofrontal activity was directly modulated by the presence of low spatial frequencies in the image. Taken together, the dynamics we revealed provide strong support for the proposal of how top-down facilitation of object recognition is initiated, and our observations are used to derive predictions for future research.

feedback | object recognition | orbitofrontal cortex | visual cortex | low spatial frequency

The functional architecture of the visual cortex has helped shape the traditional view that visual input is processed serially, in a bottom-up cascade of cortical regions that analyze increasingly complex information. This view has been challenged by models proposing a simultaneous bottom-up and top-down flow of information in the cortex (1–6). Recent findings support those proposals by showing that top-down mechanisms might play an important role in visual processing (7–10), but it remains puzzling how such processing would be initiated. Indeed, the existence of top-down processes that facilitate perception implies that high-level information is activated earlier than some lower-level information. We examine here a specific proposal for the triggering of such top-down facilitation in visual object recognition (11). The gist of this proposal is that a partially analyzed version of the input image (i.e., a blurred image), comprised of the low spatial frequency (LSF) components is projected rapidly from early visual areas directly to the prefrontal cortex, possibly by using the dorsal magnocellular pathway. This coarse representation is subsequently used to activate predictions about the most likely interpretations of the input image in recognition-related regions within the temporal cortex. Combining this top-down “initial guess” with the bottom-up systematic analysis facilitates recognition by substantially limiting the number of object representations that need to be considered (Fig. 1).

The cortical regions most often associated with visual object recognition are situated in the temporal cortex (12, 13) and in humans include in particular the fusiform gyrus and the lateral occipital cortex (14–17). However, recent studies indicate that the prefrontal cortex might also play an active role in the cortical network that mediates visual object recognition. In particular, Bar *et al.* (14) compared the functional (fMRI) activity elicited by trials in which objects were successfully recognized with the activity elicited by the same pictures when they were not recognized under

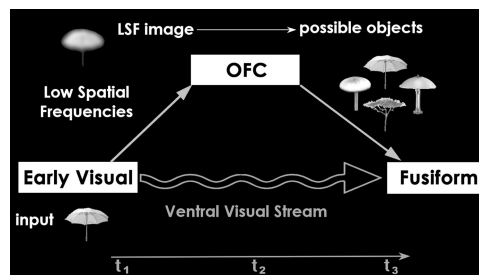


Fig. 1. An illustration of the proposed model. A LSF representation of the input image is projected rapidly, possibly via the dorsal magnocellular pathway, from early visual cortex to the OFC, in parallel to the systematic and relatively slower propagation of information along the ventral visual pathway. This coarse representation is sufficient for activating a minimal set of the most probable interpretations of the input, which are then integrated with the bottom-up stream of analysis to facilitate recognition.

identical conditions (Fig. 2A). In addition to the temporal regions typically associated with object recognition, a prefrontal site, in the orbitofrontal cortex (OFC), was also differentially active in this comparison (Fig. 2B).

How should this OFC activity be interpreted with respect to object recognition? Given that various prefrontal regions have been implicated in semantic analysis (18–20) (although not the orbital section in particular), it would be reasonable to interpret prefrontal activity observed during recognition of everyday objects as reflecting postrecognition semantic processing. According to this view, the OFC activity is not related to the processes required for object recognition *per se*, but rather is a manifestation of related semantic processes taking place after the object has been recognized. An alternative account, however, is that the network that mediates object recognition includes regions beyond the traditionally defined visual cortex and, specifically, that this OFC activation represents the cortical source of top-down facilitation in visual object recognition (11). This alternative is our focus here.

To facilitate recognition, top-down processing would have to start before recognition has been accomplished. Consequently, for the OFC site to be critical for early top-down facilitation, recognition-related activity must develop at that site earlier than it does in temporal regions associated with recognition. Given the brief amount of time that is sufficient for typical recognition to be accomplished, it was critical to use a neuroimaging method with superior temporal resolution to test this alternative account. We therefore combined milliseconds-resolution magnetoencephalog-

Conflict of interest statement: No conflicts declared.

This paper was submitted directly (Track II) to the PNAS office.

Abbreviations: HSF, high spatial frequency; LSF, low spatial frequency; OFC orbitofrontal cortex; MEG, magnetoencephalography; fMRI, functional MRI; ROI, region of interest; RT, reaction time.

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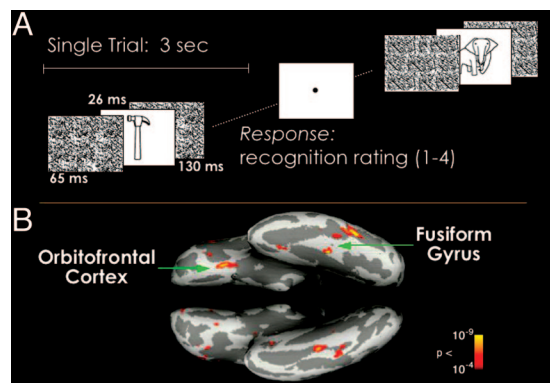


Fig. 2. Recognized vs. not-recognized trials in fMRI. (A) The experimental design. (B) A statistical activation map, illustrating the comparison between successful and unsuccessful recognition of the same objects under identical conditions (adapted from ref. 14). Activity in the anterior fusiform gyrus and collateral sulcus increased linearly with increasing recognition success. In addition, the left posterior OFC was more active for successful than for unsuccessful recognition attempts. Here, we test the hypothesis that this focus is the origin of top-down facilitation in visual object recognition

raphy (MEG) recordings with a behavioral task where the recognition of initially unrecognizable objects became possible with stimulus repetitions (Fig. 2A). The similar paradigm that was previously run with fMRI (14) provided not only the theoretical motivation for the present study, but also qualitatively improved spatial information for interpreting the present MEG findings. In addition, we used phase-synchrony analysis to determine trial-by-trial covariance between visual and orbitofrontal regions and, subsequently, to draw inferences about how these regions interact.

The other key prediction that stems from the tested model is that because the projection of LSF to OFC is essential for initiating the top-down facilitation, LSF and high spatial frequency (HSF) in an image are processed differently in the specific OFC site. Consequently, in a second experiment, conducted both in fMRI (experiment 2A) and MEG (experiment 2B), we compared between the activation patterns elicited by images of objects filtered to contain predominantly LSF and by images filtered to contain primarily HSF. This experiment is additionally interesting because, despite previous findings (21), the prefrontal cortex is not typically perceived as selective to specific physical properties of input stimuli.

These three experiments resulted in rich data sets, and we had to constrain our scope here only to those aspects of the data that directly pertain to the tested model and its specific predictions.

Results

Recognition-Related Activity in the OFC Precedes the Corresponding Activity in the Temporal Cortex (Experiment 1). Participants were required to recognize pictures of familiar objects that were presented briefly and interposed between two masks (Fig. 2A). The same pictures were presented repeatedly up to five times in random order, intermixed with the presentations of other objects. It has been shown that objects that are not recognized on a given brief presentation can nonetheless be recognized in a later, identical presentation (22). Therefore, by presenting the same objects repeatedly, participants had several opportunities for successful recognition of those objects. To evaluate the cortical dynamics associated with relatively easy object recognition, some of the stimuli appeared again for a sixth presentation, without a mask and for considerably longer exposure duration (198 ms).

To answer the critical question of whether differential activity would develop in the OFC earlier than in recognition-related regions within the temporal cortex, we compared the MEG signal elicited by trials in which the objects were successfully recognized

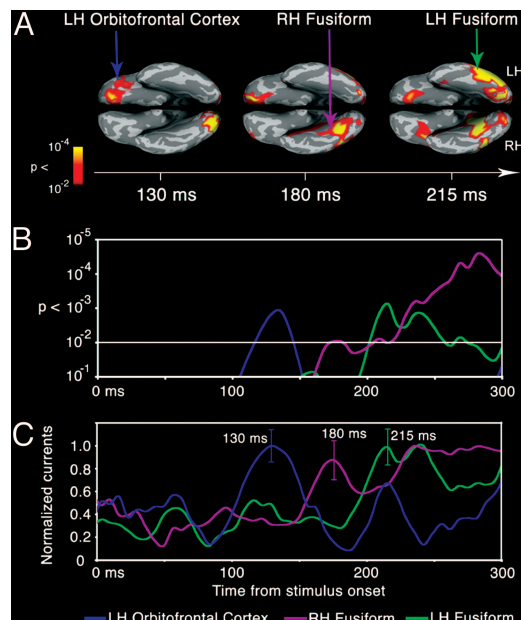
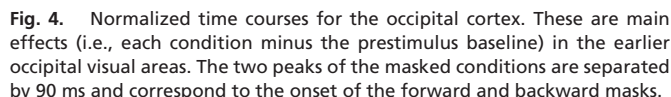


Fig. 3. The cortical chain of events leading to object recognition reveals OFC activity that precedes the temporal cortex activity. (A) Anatomically (MRI) constrained statistical parametric maps calculated from MEG, representing the contrast between trials in which the masked objects were recognized successfully and trials in which the same masked objects could not be recognized. The estimated cortical activation is illustrated here at different latencies from stimulus onset and is averaged across all nine subjects. Differential activation (recognized vs. not recognized) peaked in the left OFC 130 ms from stimulus onset, 50 ms before it peaked in recognition-related regions in the temporal cortex. See Fig. 9, which is published as supporting information on the PNAS web site, for lateral views. These lateral views show early dorsal differential activity, supporting the proposal that early projection relies on magnocellular, dorsal projection and also suggests early frontal-eye-field differential activity. Taken together, these lateral activations provide a reasonable starting point for future studies aimed at characterizing the exact neural pathway mediating the rapid projection of LSF from early visual cortex to the OFC. (B) Corresponding time courses of the development of the differential activation in the OFC and temporal cortex regions of interest (ROIs), depicting p values of the difference between recognized and not-recognized trials as a function of time from stimulus onset. The p values are averaged within the ROI and, thus, do not perfectly correspond to the higher levels of significance depicted in the statistical maps above. (C) Corresponding time courses for normalized current values. Current and statistical values are presented in absolute, unsigned units.

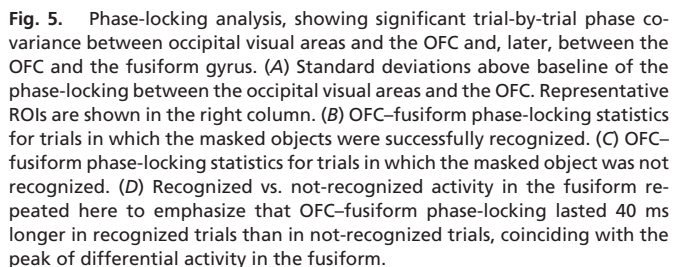
with the signal elicited by similar trials in which the same objects were not recognized. Differential activation in the OFC was found 50 ms earlier than in regions of the temporal cortex previously implicated as being directly involved in object recognition (Fig. 3). In other words, OFC activity was diagnostic of successful recognition earlier than activity in the visual cortex, supporting the critical prediction that stems from the proposed model. This early activity peaked in the left posterior orbital gyrus at 130 ms from stimulus (object) onset and remained statistically significant for about 40 ms. This result of earlier differential OFC activity (recognized vs. not recognized) was significant for each individual subject ($P < 0.01$).

As seen in Fig. 3, the sequence of recognition-related differential activity developed first in the left OFC (Talairach coordinates: $-36, 23, -14$), followed by the right fusiform gyrus (at 180 ms; $34, -53, -14$), followed by the left fusiform gyrus (at 215 ms; $-38, -52, -12$). The OFC activity developed significantly earlier than the right fusiform activity ($t_8 = 2.95$; $P < 0.01$) and the left fusiform activity ($t_8 = 3.26$; $P < 0.01$); and the right fusiform activity developed significantly earlier than the left fusiform activity ($t_8 = 1.92$; $P < 0.05$).



In addition to the OFC focus of interest, occipital visual regions also showed early activity in the masked recognized vs. masked not-recognized contrast, which started as early as 67 ms from stimulus onset. Note that masks were selected randomly and, thus, did not differ systematically between any of the conditions. Unlike the recognized > not-recognized pattern we found in the OFC, this activity in the occipital visual cortex was stronger for not-recognized trials compared with recognized trials ($t_8 = -2.89$; $P = 0.01$). Furthermore, the early occipital activity showed two peaks, separated by 90 ms, perfectly aligned with the temporal onset of the forward and backward masks (Fig. 4). This pattern was absent in the recognized, nonmasked trials. These early visual areas are known to analyze basic visual properties, such as lines at different orientations. Given that the masks consisted of such features and thus were ideal for activating early visual regions, we suggest that this early occipital activity reflects response to the masks. Consequently, we hypothesize that at least one reason why not-recognized items were not recognized is that the cortical analysis in the occipital regions in those trials concentrated on the masks rather than on the objects.

Finally, can these data inform us about a specific “aha” moment of recognition? Peak activity associated with the conscious com-



In summary, this experiment demonstrated that recognition-related activity developed significantly earlier in the OFC than in object areas in the visual cortex. In the subsequent study, we tested the second critical hypothesis: that this early OFC activity is driven by LSF in the image.

The Early Recognition-Related Activity in the OFC Depends on Spatial Frequencies in the Image (Experiment 2). In the model tested here, it was proposed that a LSF representation of the input image is projected directly to the OFC (11), possibly through the dorsal magnocellular pathway. This early and rudimentary projection then activates information in the OFC that subsequently sensitizes the representation of the most likely candidate objects in the temporal cortex as a predictive “initial guess.” Indeed, physiological findings indicate that the magnocellular pathway conveys LSF information early and rapidly (26–28). Anatomical studies regarding direct connections between early visual areas and the prefrontal cortex that will support such a bypass projection are lacking in humans (29)

and so far have been shown between temporal cortex and prefrontal cortex only in monkeys (30). Nevertheless, psychophysical and physiological experiments indicate that LSFs are processed first and fast (31–33), as would be required to produce a top-down initial guess. Taken together, these findings imply the existence and use of the infrastructure required for the theoretically proposed mechanism for triggering top-down facilitation, although future anatomical studies of the exact neural pathways will be highly informative.

Because this model relies on the proposal that a projection of LSF to the OFC initiates the top-down facilitation of object recognition, we predicted that LSF and HSF filtered images would have different effects on activity in the specific OFC site. General differences in spatial-frequency processing have been reported, primarily in the context of early visual processing, size tuning mechanisms, and hemispheric lateralization (34, 35). Here, however, differential sensitivity to LSF and HSF images was used as a test of the proposed mechanism for triggering fast top-down facilitation in object recognition. Consequently, we used both fMRI and MEG to compare the OFC activation pattern elicited by filtered images of objects containing predominantly LSF with the activation elicited by filtered images containing predominantly HSF.

Across all subjects, HSF images were correctly recognized as real or nonreal objects in 90% of the trials, on average, and the LSF on 71% of all trials. The mean reaction times for correct trials were $668 \text{ ms} \pm 50 \text{ ms}$ for HSF images, $723 \text{ ms} \pm 88 \text{ ms}$ for LSF images, and $607 \text{ ms} \pm 52 \text{ ms}$ for the intact images (t tests: LSF vs. HSF, $t_8 = 2.34$, $P < 0.05$; intact vs. LSF, $t_8 = -6.67$, $P < 0.001$; intact vs. HSF, $t_8 = -4.22$, $P < 0.005$). To ensure that there was no significant RT difference between the two main conditions, we selected, post hoc, a subset of trials with the same mean reaction time (LSF = 700 ms; HSF = 700 ms; LSF vs. HSF, $t_8 = -0.05$). This matched-RT subset of trials consisted of 90% of the correct LSF and 78% of the correct HSF trials and was used in the analyses presented here.

Most importantly in the present context, LSF object images elicited a significantly higher fMRI signal than the HSF images in the OFC, in the same region where we found early recognition-related activity in experiment 1 ($t_7 = 2.65$, $P < 0.033$) (-21 , 21 , -19). Correspondingly, there was a significant difference between the MEG current amplitudes estimated from the LSF and HSF conditions within the same OFC region (-24 , 25 , -12) ($t_8 = 3.56$, $P < 0.008$). The polarity of the MEG source signal is associated with the direction of the current with respect to the cortex (inwards or outwards), and it is not straightforward to relate this direction unambiguously to activation or inactivation, both because of the complex structure of the cortical neurons and the spatial smoothness of our minimum-norm solution. However, from the fMRI study, it seems that the OFC signals are all negative compared with fixation (i.e., “deactivations”). We therefore also used negative polarity for the MEG signal (Fig. 6). Although there is currently no clear understanding of the ubiquitous deactivations that are often obtained in neuroimaging studies (36), the critical aspect here is that the OFC region clearly responds differentially to LSF and HSF images. The MEG data indicate that this LSF–HSF differential activity peaked $\approx 115 \text{ ms}$ from stimulus onset.

The OFC activity was highly similar for the LSF and intact conditions and significantly different from that elicited by the HSF images, which is particularly relevant. The model tested here predicts that a lack of LSF information will diminish the contribution of top-down processes and will therefore result in relatively slower recognition performance. By selecting HSF and LSF images with equal RT (i.e., equalized recognition level), we used HSF images that were recognized as quickly but, presumably, without top-down contribution. That recognition in both LSF and HSF conditions was significantly slower than performance with intact images (93-ms difference in average performance level) emphasizes the idea that optimal recognition relies on both types of information: Whereas LSF information promotes the generation of initial

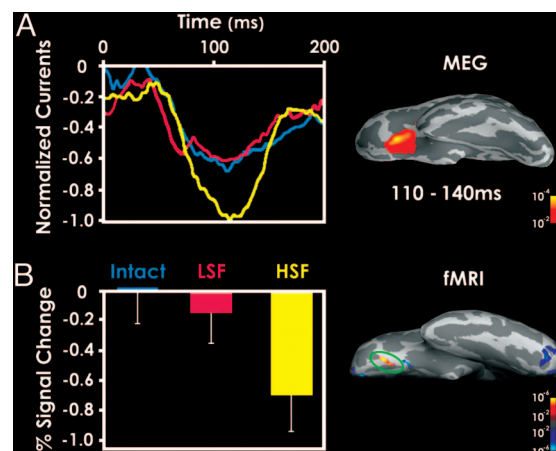


Fig. 6. Comparison of the cortical signal elicited by LSF and HSF during recognition. ROI analysis of the left medial OFC for both MEG and fMRI. (A) MEG data. Normalized currents illustrate the main effects of spatial frequency content on OFC activity during the first 200-ms interval from stimulus onset. Note that OFC activity peaked here $\approx 115 \text{ ms}$ and started to develop even earlier, whereas, in experiment 1, it peaked $\approx 130 \text{ ms}$ from stimulus onset. Here, this peak signifies the arrival of information to the OFC, which presumably initiates the top-down facilitation, whereas the 130-ms peak in the previous study distinguishes recognized from not-recognized trials. Therefore, it might be possible that this onset difference indicates the time interval that it takes to generate successful predictions about the input, after the LSF information has reached the OFC. A peak of activity in the occipital cortex was seen at 100 ms, which did not differ between LSF and HSF responses. In fact, differential activity in the occipital cortex did not appear until 160 ms after stimulus onset. (B) fMRI data. Comparison of percent signal change within the OFC ROI elicited by intact, LSF, and HSF images (see *Methods*).

predictions in OFC, HSF information is required for converging to a single identity in the visual cortex. In other words, neither LSF nor HSF images were recognized in the same manner as intact images are in reality, but the similarity between the response to intact and LSF images in the OFC shows that the OFC part of recognition is identical as long as LSF information is present, and it is independent of HSF information.

We conducted a trial-by-trial covariance analysis to test whether the presumably feed-forward and feedback projections (Fig. 5) are more synchronized (and thus better functionally connected) for LSF images compared with HSF images. Indeed, there was a clear interaction between the occipital visual regions and the OFC and between the OFC and the fusiform gyrus for both LSF and intact images, as suggested by this synchrony analysis (Fig. 7) but significantly less synchrony between these regions for the HSF stimuli. Furthermore, as would be predicted from the tested model, the synchrony in MEG signal between early visual areas and the OFC, which presumably mediates the early feed-forward projection of LSF, precedes the synchronized activity between the OFC and the fusiform, which presumably subserves the feedback activation of candidate interpretations based on the LSF content. Finally, the phase-lock pattern indicates that here, too, LSF images, but not HSF images, result in similar dynamics as intact images.

Discussion

This study was designed to test a proposed mechanism for the activation of top-down facilitation during object recognition (11). Our results demonstrate that (i) differential activity unique to successful recognition developed in the OFC 50 ms before it developed in fusiform regions previously implicated in object recognition; (ii) this early OFC activity is differentially sensitive to spatial frequencies, and it is similar for intact images and images that contain only LSF; (iii) phase synchrony among the OFC, fusiform, and early visual areas suggest that these regions interact

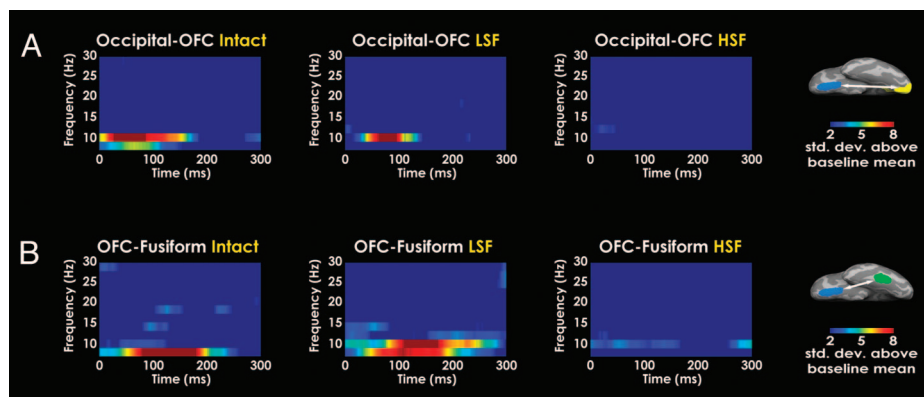


Fig. 7. Phase-locking analysis, implying that cortical interactions between the occipital visual areas and the OFC and, relatively later, between the OFC and the fusiform gyrus require LSF. (A) Phase-locking between the occipital visual areas and the OFC. No significant occipital–OFC phase-locking was found for HSF images. (B) OFC–fusiform phase-locking peaked from 80 to 190 ms from stimulus onset for intact and LSF images, ≈ 50 ms later than occipital–OFC phase-locking. No significant OFC–fusiform phase-locking was found for HSF images.

during object recognition in a manner predicted by the tested model; and (iv) this functional connectivity is significantly stronger for images that contain LSF compared with images that contain primarily HSF. Naturally, a direct test of causal relations between these regions in the future, using lesion studies, for example, will be helpful. Finally, the OFC is not a region that is traditionally considered a visual area, in that it is not generally expected to respond differentially based on the physical properties of the input. Here, we show that the OFC does respond differentially and in a manner that supports the tested model.

Recent models have promoted the role of top-down analysis in cortical processing (1–3, 5, 6, 37, 38). Until now, however, it was not clear whether top-down facilitation is part of the dynamics that lead to visual object recognition and, if it is, when and where a top-down cortical signal would be initiated. Our results suggest that this stream propagates from the OFC, ≈ 130 ms from stimulus onset, and it is directly related to recognition success.

The role of the OFC has generally been discussed in the context of emotional processing, reward, and decision-making (39, 40) (though generally in various subregions posterior to the OFC region observed here). However, the OFC has also been shown to be involved in the analysis of visual information and in visual memory (21, 41–45). Furthermore, the OFC is the prefrontal region with the strongest connections to the inferior temporal cortex (46); and there is evidence for LSF (i.e., magnocellular) projection from visual cortex to various regions within the prefrontal cortex (39). Finally, activity in the OFC has been associated with guessing and hypothesis-testing, as well as with the generation of expectations (44, 47, 48), all of which are in agreement with the role attributed here to this region as a source of top-down predictions. It is possible that the OFC serves as a rapid detector and predictor of potential content based on coarse aspects of the input (i.e., gist). This information would naturally be highly valuable in dangerous situations (49), when shared with the amygdala, for example. But the same information can, in parallel, facilitate object recognition also in nondangerous situations (11). Indeed, the OFC is located optimally for subserving such a role, being part of an orbitofrontal–amygdala–inferior temporal reciprocal triad (50). More generally, the capability to derive a great deal about the most likely identity of the input image based on its LSF appearance might have developed through survival-related considerations; it is obviously advantageous for an organism to recognize items in the periphery, (where visual acuity is low, and the image is thus analogous to a LSF representation) as soon as possible. Once these mechanisms have evolved, they could be used also to facilitate foveal visual recognition based on the rapidly available LSF information.

When the objects were presented for considerably longer durations and not masked, recognition was trivial. In those trials, the early OFC activity was lower than that elicited by the masked recognized trials. This pattern of results indicates that when objects are easily recognizable, the recognition process is so rapid and efficient that it does not benefit as much from early top-down facilitation. These situations are ecologically uncommon, however, because objects around us rarely appear in isolation and as clearly as on a computer screen in the laboratory. Instead, objects' visibility is typically affected by illumination conditions, clutter, occlusion, and so on, and thus object recognition can benefit from top-down facilitation and from other sources (51) not only in brief and masked presentations. In the same context of lack of top-down facilitation during exceptionally easy recognition attempts, it is important to keep in mind that the proposed model does not imply that top-down facilitation from OFC is essential for recognition to be accomplished. If this pathway is eliminated, as in prefrontal patients for example, recognition is predicted to be slower but not impossible.

The phase-locking analysis demonstrated high trial-by-trial synchrony between the occipital region and the OFC (presumably feed-forward) and between the OFC and the fusiform gyrus (presumably feedback). The strength and delay of this phase-locking varied as a function of recognition success. In addition, experiment 2 demonstrated that the same OFC site responds differently to LSF images compared with HSF images, even when recognition difficulty was equated. Therefore, the early OFC activation observed in experiment 1 cannot be explained as a manifestation of increased attentional load due to larger effort. But this early and stimulus-specific OFC response might nevertheless be seen as related to attentional allocation. It has been suggested (52) that top-down attention signals enhance perceptual processing in the sensory cortex. This proposal can be fine-tuned by the model tested here, in conjunction with the data we report, by demonstrating that (i) the top-down signal depends on the particular physical properties of the target image, and (ii) the feedback signal to the visual cortex is specific in that it sensitizes only the representation of the most likely interpretations of the input rather than generally elevating visual sensitivity. This idea is supported by recent studies reporting the involvement of the magnocellular pathway in attention (53, 54).

The other key prediction, that the cortical site where such top-down facilitation originates would be sensitive to spatial frequencies in the input image, was supported by the second study we report here. In a related electrophysiological study in monkeys (55), it was shown that prefrontal representations carry information about properties of object categories, without emphasizing information about the appearance of individual objects. IT activity, on

the other hand, emphasized features of individual objects with less information about categorical membership. These findings are in agreement with our proposal that prefrontal representations are coarser because they rely on LSF and do not include fine detail. In other words, a low-level visual property, such as LSF, might provide the foundation for a high-level cognitive faculty, such as categorization. Indeed, event-related potentials studies (56, 57) have repeatedly shown that humans can distinguish between the category of objects in scenes extremely rapidly, which we argue can be mediated by coarse LSF representations, and that this distinction is first apparent in prefrontal cortex time courses ≈ 150 ms from stimulus onset. That such prefrontal representations subsequently guide the activation of IT representations is supported by fMRI studies in human patients (9, 58) and electrophysiology recordings in monkeys (10).

In conclusion, we were able to demonstrate that differential activation unique to successful recognition attempts develops and peaks in the OFC significantly earlier than it does in regions in the temporal cortex previously implicated in mediating object recognition and that this early activity is driven by LSF in the image. These results provide critical support for the proposed model and demonstrate that the prefrontal cortex plays a more active role in object recognition than previously considered.

Methods

A detailed description of the methods is provided in *Supporting Methods*, which is published as supporting information on the PNAS web site.

Experiment 1. Subjects. Nine healthy volunteers participated in the experiment.

Stimuli. The stimuli were line drawings depicting objects such as tools, furniture, clothes, means of transportation, and animals (see Fig. 8, which is published as supporting information on the PNAS web site).

Experimental design. Stimuli were presented between one and six times. The experimental trials consisted of 420 masked presentations of 154 different objects, and 84 nonmasked presentations of 84 of these objects. Subjects were required to recognize each of the objects and indicate their level of knowledge about the identity of the object. Each stimulus was presented for 63 ms. The first mask,

preceding the object presentation, was presented for 27 ms, and the second mask was presented for 108 ms.

All times are reported with respect to the onset of the stimulus not the onset of the first mask. A sixth, nonmasked presentation was displayed for 198 ms (the total sum duration of a picture and two masks in the other conditions).

Experiment 2A (MEG). Subjects. Nine subjects participated in the experiment.

Stimuli. The images were grayscale photographs of common, everyday objects without background. See *Supporting Methods* for exact details about the spatial filtering used.

Experimental design. This experiment was designed to reveal possibly different functional processing routes for the LSF and HSF contents of visual objects. Each subject saw each object only once, in one of its three possible conditions (i.e., LSF, HSF, or intact), and the sequence of presentation was pseudorandomized across subjects. All images were presented for 750 ms. Subjects were asked to indicate by key press, irrespective of the spatial frequency content, whether the image they saw represented a normal everyday object or an abstract sculpture.

Experiment 2B (fMRI). Subjects. Twelve subjects participated in the experiment. Four of the 12 participants were excluded from the analysis because of an exceptionally low number of “recognized” responses.

Stimuli and design. Stimuli and design were the same as in experiment 2A.

Data acquisition. All MRI scans were acquired on a 3T Siemens Trio whole-body scanner, using gradient-echo echo-planar pulse sequences for the functional and a standard magnetization-prepared rapid-gradient echo for the high-resolution anatomical scans.

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