treated with CP-690,550, there were no metabolic abnormalities detected (increases in blood lipids or glucose levels) and no evidence of hypertension nor cases of posttransplant lymphoproliferative disease (*7*). CP-690,550 treatment, however, was associated with dose-related anemia, presumably related to a level of JAK2 inhibition. This was largely restricted to the four animals with the highest drug exposure, who experienced sustained declines in hemoglobin levels. In contrast, the eight animals with ~fourfold lower drug exposure experienced only minor decreases in hemoglobin levels, with animals surviving 90 days recovering to baseline values (Fig. 3C).

The development of safe and effective inhibitors of tyrosine kinases gained validation with imatinib (Gleevec, Novartis, Basel, Switzerland), which dramatically illustrated the feasibility of this approach for chronic myelogenous leukemia (*24*). Although a number of studies have described other compounds that inhibit JAK3 (*11–13*), none have shown efficacy in NHPs. More importantly, they do not exhibit the potency and selectivity of CP-690,550 (table S1). Our findings, however, establish that an orally available JAK3 inhibitor produces sufficient immune suppression by itself to prevent organ transplant rejection without inducing many of the side effects observed with current therapies. At a well-tolerated dose of CP-690,550 (Fig. 3, A to C), we have shown 3-month survival of kidney allografts in NHP at drug exposures consistent with in vitro cellular potency and complete recovery of hemoglobin levels. Ongoing further dose reductions in this model, as well as testing in combination with mechanistically distinct immunosuppressive drugs, will suggest an optimal therapeutic strategy for profiling in humans. Immunosuppression as demonstrated here with CP-690,550, without the adverse events observed with current transplant therapy, may represent a major advance in the prevention and treatment of transplant rejection and possibly other immunological conditions.

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Flexible Retinotopy: Motion-Dependent Position Coding in the Visual Cortex

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Although the visual cortex is organized retinotopically, it is not clear whether the cortical representation of position necessarily reflects perceived position. Using functional magnetic resonance imaging (fMRI), we show that the retinotopic representation of a stationary object in the cortex was systematically shifted when visual motion was present in the scene. Whereas the object could appear shifted in the direction of the visual motion, the representation of the object in the visual cortex was always shifted in the opposite direction. The results show that the representation of position in the primary visual cortex, as revealed by fMRI, can be dissociated from perceived location.

When a stationary window or envelope is filled with a moving pattern, the position of the envelope can appear shifted in the direction of the internal motion (*1*, *2*). The magnitude of the illusion is shown in Fig. 1 (*3–6*). Figure 1, A and C, shows two stimulus conditions presented in an fMRI experiment to determine whether the perceived position of an object is reflected by activity in the visual cortex. In each condition there were four patterns, which were always in the same physical location at all times. The patterns contained motion toward (Fig. 1A) or away from (Fig. 1C) the fovea, causing the patterns to appear shifted toward (Fig. 1B) or away from (Fig. 1D) the fovea, respectively. In two additional conditions (*7*), the four patterns were flickering or stationary, providing a baseline (*8*).

Figure 2A shows the regions in the right hemisphere of one subject that were activated by the patterns containing inward versus outward motion. (Figure 2B shows an expanded view.) Because the patterns and the motion-defined edges (*9*, *10*) in the two conditions (Fig. 1, A and C; Fig. 2, C and D) were in precisely the same retinal (physical) locations at all times, the activation should have been retinotopically identical for both conditions. However, there was a displacement in the activation for each condition; the inward and outward motion conditions produced two distinct regions of activation. When the two conditions were subtracted (inward minus outward) (Fig. 2C), there was significant peripheral activation. Subtracting the two conditions in the opposite order (Fig. 2D) produced activation that was closer to the occipital pole.

The pattern of activation in Fig. 2B is counterintuitive. Patterns that contained inward motion were perceived to be closer to the fovea, yet the peak activity in the visual cortex for this condition was more eccentric (orange activity in Fig. 2B). This result seems impossible at first sight. A stimulus that appears more eccentric should be, and normally is (*11–14*), represented in a more anterior location in the cortex. We thus conducted a control experiment in which flickering (nondirectional motion) patches were presented at locations corresponding to the perceived locations of the stimuli in experiment 1. In two separate conditions, we presented flickering patterns at two different eccentricities and then compared activation for those two states (Fig. 2E). When the flickering patterns were located closer to the fovea, the peak activation was closer to the occipital pole; when the flick-

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ering patterns were located more eccentrically, the peak activation was located in a more anterior position (Fig. 2E and fig. S2). The pattern of activation shown in the first experiment (Fig. 2B) is therefore a nearly perfect reversal of retinotopy: Each subject perceived the patterns in one position, but their visual cortex represented the patterns as being in a different location.

Figure 3B shows the event-related averages of seven subjects for the orange patches of activation, where the inward motion response was dominant. Figure 3C shows the event-related averages for the blue patches of activation, where the outward motion response was dominant. Figure S1 shows individual subjects' results.

To ensure that there is no systematic bias in the response to inward compared with outward motion, Fig. 3E shows the event-related average of all seven subjects for the condition in which the patterns were flickering rather than containing motion in any direction (Fig. 3D and fig. S3). Because the event-related averages (Fig. 3E) for each of the stimulus conditions were virtually identical, there was no bias in the response to inward or outward motion over the region as a whole. This is consistent with the fact that sensitivity to motion direction does not systematically vary as a function of eccentricity (*15*–*17*).

If the eye, head, or body moves, the retinotopic location of a stimulus can be altered. The difference in activation found in the first experiment (e.g., Fig. 2B), however, cannot be due to these movements. The stimuli in the first experiment were stationary patterns that contained inward or outward motion and generated activation that was shifted either toward or away from the occipital pole [systematically in both hemispheres (*8*)]. Because the activation shifted only in eccentricity, and the eye cannot expand or contract, the results cannot be due to eye movements. Also, the head was immobilized in the experiment, and no motion artifacts were found in the data. Another benefit of using a moving pattern enveloped by a stationary window is that the envelope—the stimulus as a whole—never changes position; it is physically stationary. Therefore, activation that differs between the two experimental conditions (e.g., Fig. 2B) cannot be due to temporal differences in the fMRI blood oxygen level–dependent (BOLD) signal.

Spatially localized attention (*18*, *19*) might be responsible for the above results. However, this is unlikely. The pattern containing inward motion, for example, appeared more foveal and would, if anything, lead observers to attend more centrally. Yet, the activation produced in this condition was predominantly more eccentric, opposite that expected if spatially selective attention had generated the results.

Another possibility is that subjects attended to the origin of motion within the patterns. If for some reason the onset or origin of motion were of more interest or salience, subjects might selectively attend to this region of the visual field. In a control experiment, subjects contin-

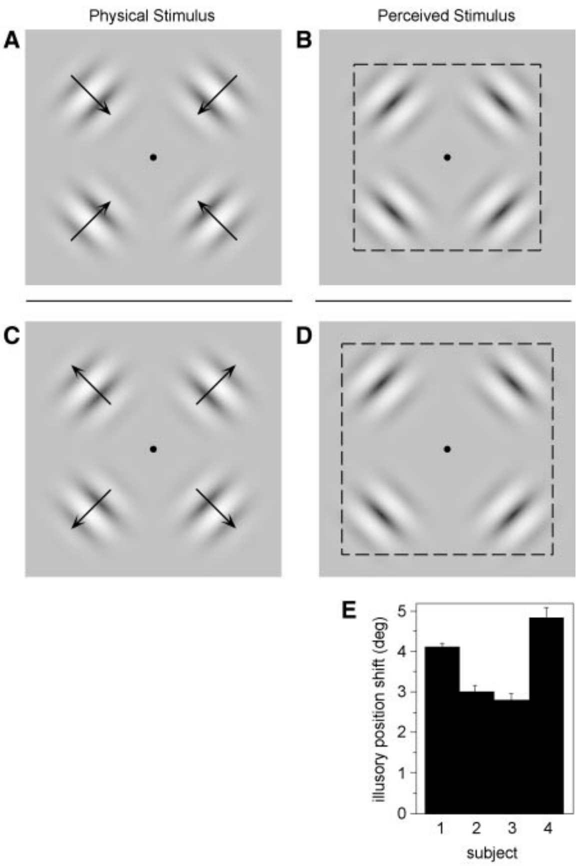

Fig. 1. Stimulus and percept. (**A**) In one stimulus condition, four stationary patterns contained inward moving elements, i.e., the patterns as a whole were stationary but the texture contained within the patterns moved toward the fovea. (**B**) The perceived position of the patterns in (A) is shifted in the direction of the moving texture. The dashed lines, not present in the stimulus, indicate the perceived eccentricity of the patterns. (**C**) In a second condition, the four patterns contained outward motion. (**D**) Outward motion caused the patterns to appear shifted more peripherally. The dashed lines, not present in the stimulus, indicate the perceived eccentricity of the patterns. (**E**) The psychophysically measured magnitude of the illusion, which was consistent with previous studies (*1*, *2*). Error bars, ±1 SEM.

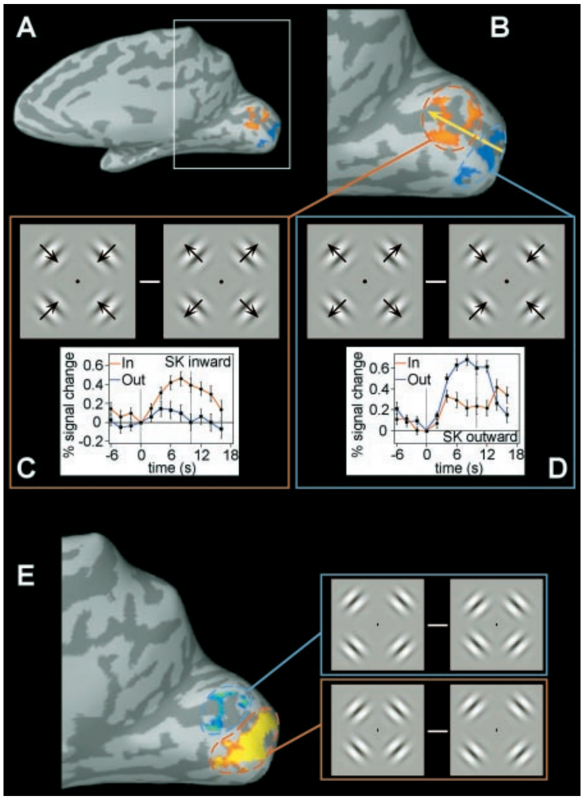

Fig. 2. Results of the first experiments for one subject (*8*). (**A**) The cortical surface of the right hemisphere, showing the occipital region. (**B**) A closeup view of the same surface. Increasing eccentricity in the visual field is indicated by the direction of the yellow arrow. (**C**) When the two experimental conditions were subtracted (inward motion minus outward motion), there was a significant resulting activation (orange). The plot in the lower panel of (C) shows the event-related average for inward and outward motion for the voxels that were significantly activated [orange activity in (B)] by this subtraction. (**D**) When the two conditions were subtracted in the opposite direction (outward minus inward), there was significant activation (blue). The plot in the lower panel of (D) shows the event-related averages for the voxels that were significantly activated by this subtraction [blue activity in (B)]. (**E**) The results of an experiment in which flickering patterns (similar to Fig. 1, except with no net motion signal) were physically displaced in position by an amount comparable to the magnitude of the visual illusion (from Fig. 1E). When flickering patterns were closer to the fovea, activation was more posterior. Flickering patterns located more eccentrically produced activation that was more anterior. The cortical separation between the inner and outer patches of activation (orange and blue, respectively) is comparable to the separation between the patches shown in (B). Error bars, ±1 SEM.

uously performed a difficult task at the fixation point (fig. S7). Although the task was difficult (average accuracy ~73%), the pattern of activation in this experiment was identical to that in the first: Peak fMRI activity occurred not where the patterns were retinotopically located, but closer to the trailing edges of the moving patterns. Spatially localized attention therefore fails to explain the results.

Perhaps subjects attentionally tracked (*20*, *21*) one of the moving bars as it passed through the stationary envelope of the pattern. In this case, observers may have attended to the origin of the moving pattern to choose a moving bar to track. We thus conducted a control experiment in which the patterns contained gratings that moved at ~10 Hz (*8*). Attentional tracking is impossible at such high temporal frequencies (*22*), yet the pattern of activation in the visual cortex remained the same.

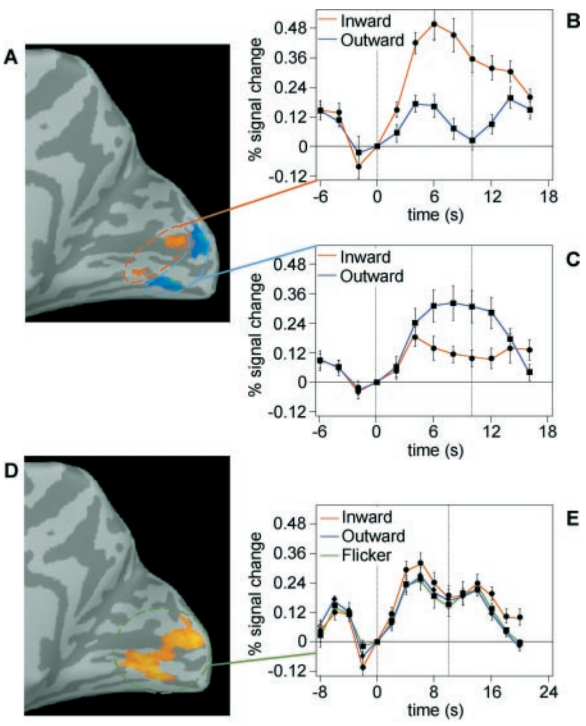

Fig. 3. Results of the first experiment for seven subjects, averaged. (**A**) Surface map of one subject [different from the subject in Fig. 2B (*8*)]. (**B**) Event-related averages for the regions that produced significantly greater activation for inward compared with outward motion (orange activity on representative surface map). There was a significant difference at each of the sampling times during which the stimulus was present (least significant difference was at 2 s, $P < 0.01$). (**C**) Event-related averages for the regions that produced significantly greater activation for outward compared with inward motion (blue activity on representative surface map). The overall difference was significant ($P < 0.0001$). (**D**) Activation produced by the flickering patterns alone. The activity in (A) overlapped the activity produced in the flickering condition. (**E**) Event-related average for the entire region of interest [orange in (D)]. There is no difference in the event-related activity for the three conditions (inward motion, outward motion, and flickering, $P > 0.05$) for this region of interest as a whole. Error bars, ±1 SEM.

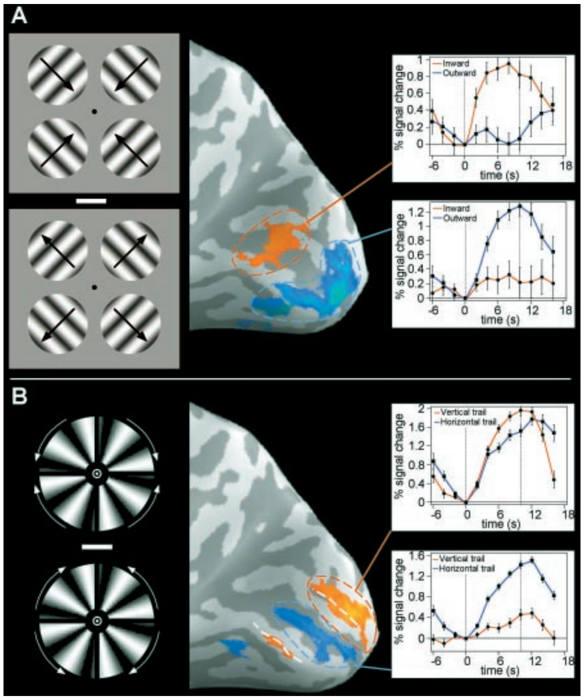

Fig. 4. Results of two additional experiments for one subject. (**A**) In one control experiment, the four patterns containing motion had sharply defined borders. Although there is no illusory position shift in this condition, the same pattern of activation was observed (middle panel) . (**B**) In a second control experiment, the patterns did not contain any clear optic flow. The motion within the patterns originated from either the vertical or the horizontal meridian. When the two conditions were subtracted (motion originating from the vertical meridian minus motion originating from the horizontal meridian), the pattern of activation (middle panel) was consistent with the first experiment. Motion originating at the horizontal and vertical meridians produced selective activation at the representations of the horizontal (blue) and vertical (red) meridians, respectively. The white dashed lines indicate the borders of V1. Error bars, ±1 SEM.

Why does an object that appears shifted toward the fovea generate activity that is more eccentric? Why did the activity we found correlate precisely with what subjects did not perceive? Clearly, the location that is assigned to an object in the visual cortex is not simply shifted in the direction of its motion, despite the existence of mechanisms, at least in the retina, that subserve this role (*23*).

The peak activation that we found occurred at the trailing edge or origin of motion in the patterns. Because it is known that there are mechanisms that operate selectively at such trailing edges (*24*–*28*)—to deblur (*29*) or suppress visual responses, for example—an intriguing possibility is that the activity we measured is the result of a related process, perhaps akin to deblurring, masking, or persistence reduction, that operates more strongly on the trailing edges of moving objects.

If the increased activation that we measured is the product of a mechanism that operates more strongly on the trailing edge of the pattern, then we might expect a reduction in the visibility of the trailing edge. This should cause a compression in the apparent size of the pattern as a whole, as well as a distortion in the apparent luminance distribution of the pattern. In two additional experiments, we measured the perceived position and contrast of both the trailing and leading edges of the patterns containing motion (figs. S4 and S5). The trailing edge of the pattern was perceptually shifted (or compressed) in the direction of motion more dramatically than was the leading edge. The apparent contrast was also reduced more strongly at the trailing edge than at the leading edge of the pattern. These results are consistent with some visual illusions (*25*, *30*, *31*). They also partially explain why the perceived positions of the patterns in our first experiment appeared to be shifted in the direction of motion: Because the contrast of the trailing edge is perceptually reduced, the midpoint of the pattern as a whole appears displaced toward the leading edge.

If there is a mechanism that operates more strongly near the trailing edges of patterns that contain motion, then, in addition to a reduction in the perceived contrast, we might also expect a difference in the nature of the perceived motion that occurs at the trailing and leading edges. We examined this possibility by presenting flickering (directionally ambiguous) gratings at the trailing and leading edges of the patterns containing motion (fig. S8). Although there was no net motion in the flickering stimuli, observers perceived the flickering gratings to move in a direction opposite that of the coherent motion within the pattern. This illusory motion was stronger near the trailing edge of the moving pattern, revealing an imbalance in motion processing at the trailing and leading edges.

In the first experiment, the patterns containing motion were blurry (Fig. 1). However, if there is a mechanism that operates more strongly at the trailing edge or origin of motion in these patterns, it should operate whether or not the patterns are blurry. We thus conducted an experiment identical to the first, except that the patterns were given a hard aperture rather than a blurry luminance profile (Fig. 4A). The illusory position shift is reduced or eliminated in these sharp-edged patterns (*1*, *2*). The pattern of activation, however, was identical to that in the first experiment (Fig. 4A). Therefore, the pattern of activation is not specific to a visual illusion, but to the trailing edges or origin of the motion.

If there is a mechanism that selectively operates on the trailing edges of moving patterns, it should operate irrespective of whether a shift in the position of the pattern is perceived: This is precisely what we found. The bias in the retinotopic representation of the pattern is consistent in both this experiment and the first one. The peak activity always occurred near the trailing edge, no matter where the patterns were perceived (compare Figs. 2 and 4). Clearly, activity in the visual cortex, as revealed by fMRI, does not necessarily correlate with shifts in perceived position.

All of the stimuli described thus far have been symmetrically moving patterns—either toward or away from the fovea. Is it possible that the optic flow in these stimuli was responsible for the results? In an additional experiment, using stimuli that did not contain expanding or contracting optic flow, we presented segments of a windmill pattern that moved either toward or away from each other (Fig. 4B and fig. S6). Although there is no clear optic flow in this stimulus, the pattern of activation was identical to that in the previous experiments: Peak activation always occurred near the trailing edge of the moving patterns.

The experiments presented here clearly demonstrate that the representation of position, even in early visual cortical areas such as V1, depends on motion signals that are present in a scene. The imaging and psychophysical results revealed a mechanism that operates selectively on the trailing edges of moving stimuli. More important, the results demonstrated a clear dissociation: fMRI activation did not correlate with what subjects perceived, showing that the BOLD response is not a necessary correlate of perception.

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Optical Imaging of a Tactile Illusion in Area 3b of the Primary Somatosensory Cortex

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In the tactile funneling illusion, the simultaneous presentation of brief stimuli at multiple points on the skin produces a single focal sensation at the center of the stimulus pattern even when no physical stimulus occurs at that site. Consistent with the funneling percept, we show with optical imaging in area 3b of the primary somatosensory cortex (SI) that simultaneous stimulation of two fingertips produces a single focal cortical activation between the single fingertip activation regions. Thus, in contrast to traditional views of the body map, topographic representation in the SI reflects the perceived rather than the physical location of peripheral stimulation.

The key aspect of the tactile funneling illusion is the illusory perception of skin stimulation at a single site central to an actual line of multiple stimulation sites (*1*–*5*). Inputs at lateral sites are "funneled" centrally so that the perceived intensity at the central site is greater than that perceived to stimulation at the middle site alone. With two-point stimulation, a funneled sensation is produced at a central location that is not directly stimulated (*1*, *3*, *4*). This illusion has been reported on the forearm, palm, and fingers. Thus, the funneling illusion is characterized by a perception of spatial mislocalization and increased tactile intensity.

How is a mislocalized sensation encoded in the brain? Previous studies have shown that the funneling illusion is encoded in the primary somatosensory cortex (SI) and not peripherally at the skin (*2*). The responses of SI neurons to three-point skin stimulation have demonstrated that a broad distribution of cortical neurons are recruited (*6*, *7*). However, it is unknown which of the SI areas (areas 3a, 3b, 1, or 2) are involved in funneling and at what stage the funneling is first encoded. Furthermore, the SI is topographically organized, but it is unknown whether the somatotopy is founded on a physical map or a perceptual map. The funneling illusion may provide an answer to whether cortical activation corresponds to the actual or perceived site of peripheral stimulation.

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