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MS Graziano, *et al.*

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nervation of the target muscle through neuronal cell death, axon retraction, or reduced release, increased degradation, or increased re-uptake of neurotransmitter; (ii) altered amounts or function of a neurotransmitter receptor; or (iii) the impairment of central equilibrating mechanisms.

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L.F.M.S., and the provision of laboratory space by the Beth Israel Hospital. H.P. and D.D. were supported in part by grants from NIH, the Alzheimer's Association, and the Freudenberg family. We thank Applied Science Laboratories for engineering support and for the loan of laboratory equipment. We are grateful to J. Guinsey for neuropsychological testing of subjects.

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## Coding of Visual Space by Premotor Neurons

Michael S. A. Graziano,\* Gregory S. Yap, Charles G. Gross

In primates, the premotor cortex is involved in the sensory guidance of movement. Many neurons in ventral premotor cortex respond to visual stimuli in the space adjacent to the hand or arm. These visual receptive fields were found to move when the arm moved but not when the eye moved; that is, they are in arm-centered, not retinocentric, coordinates. Thus, they provide a representation of space near the body that may be useful for the visual control of reaching.

Premotor cortex is involved in the preparation and guidance of movement (1). In monkeys, many premotor neurons are active when the animal moves. In ventral premotor cortex, neurons also respond to visual stimuli and may play a role in the visual guidance of movement. Most of these visual neurons also respond to tactile stimuli; they have tactile receptive fields (RFs) on the face or arms, and corresponding visual RFs extend outward from the tactile fields into the space surrounding the body (Fig. 1) (2, 3). The tactile RFs are somatotopically organized (4), and therefore the corresponding visual RFs provide a map of the visual space near the body (5). Although the visual RFs are large, each one giving only crude information about spatial location, a population of these cells could specify the location of targets for limb and body movements.

In most other regions of the brain, visual RFs are retinocentric. That is, when the eyes move, the visual RFs move with them, thereby remaining at the same retinal site. Such cells form a spatial coordinate system that can measure the position of a stimulus with respect to the eye. However, some investigators have suggested that a more stable coordinate system attached to the head or trunk might better serve visuospatial function (6). We studied the visual responses in ventral premotor cortex (ventral area 6) to determine how they encode the space near the body. Are the RFs of these cells retinocentric, or are they expressed in a coordinate system attached to the head, trunk, or some other part of the

body? We concentrated on studying the bimodal cells with tactile RFs on the arm and tested the effect of varying the angle of gaze and the position of the arm on their visual responses. We found that most of these cells code space in arm-centered coordinates.

Single neuron responses in ventral premotor cortex (Fig. 1A) (7) were studied in two tame male *Macaca fascicularis* (6.0 and 7.0 kg). For one monkey, weekly recording sessions were conducted while the animal was anesthetized with nitrous oxide and oxygen and immobilized with pancuronium bromide. For the second monkey, daily recording sessions were conducted while the animal was unanesthetized and trained to fixate. The animal's head was fixed in place, and the arm contralateral to the recording electrode was restrained. Eye posi-

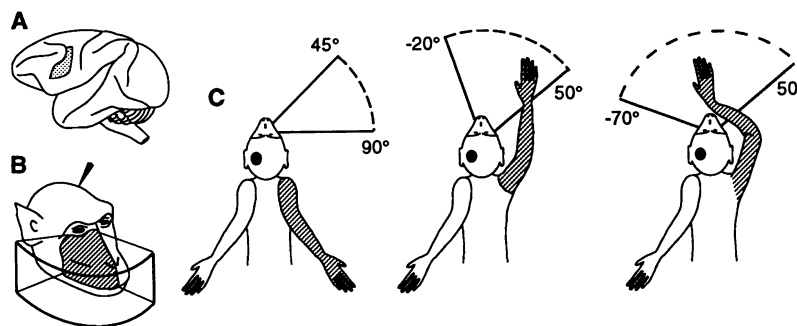
tion was monitored with a scleral search coil (8).

We plotted somatosensory RFs by manipulating the joints and stroking the skin. Visual RFs were plotted with objects presented on a wand. To distinguish a visual response from a tactile response, we also tested the cells with the animal's eyes covered. Visual responses were tested quantitatively with stimuli presented by a motorized track.

In the anesthetized preparation, 141 neurons were studied, of which 42% ( $n = 59$ ) were somatosensory, 1% ( $n = 2$ ) were visual, 27% ( $n = 38$ ) were bimodal visual-somatosensory, and 30% ( $n = 42$ ) were unresponsive to our stimuli. In the awake preparation, 211 neurons were studied, of which 36% ( $n = 75$ ) were somatosensory, motor, or both (9); 8% ( $n = 17$ ) were visual; 31% ( $n = 65$ ) were bimodal; and 25% ( $n = 54$ ) were unresponsive. Of the visual and bimodal cells, only nine showed any response during overt movements of the animal.

A typical example of a bimodal cell studied in the anesthetized preparation is shown in Fig. 1B. When a visual stimulus was moved within 10 cm of the tactile RF on the face, the cell responded. By approaching the face from various angles, we measured the extent of the visual RF in three dimensions. Figure 1C shows another cell studied under the same condition. It had a tactile RF on the contralateral arm. When the arm was moved toward the ipsilateral side, the visual RF was dragged across the midline and into the ipsilateral field of view, even though the eyes remained fixed; that is, the visual RF was not retinocentric; rather, it was arm-centered.

In the awake preparation, we studied the effects of changing the position of both the animal's arm and gaze. Figure



**Fig. 1.** (A) Ventral premotor cortex (shaded). (B and C) Two examples of RFs of bimodal, visual-tactile neurons studied in the anesthetized preparation. In (B), the tactile RF (stippled) and the visual RF (boxed) correspond in location. The arrowhead indicates the hemisphere recorded from. In (C), the lateral borders of the visual RF are shown by solid lines. As indicated by the dashed line, the RF extended more than 1 m from the animal. The black dot on the head indicates the hemisphere recorded from. When the arm was out of view (left), the visual RF extended from 90° to 45° contralateral. When the arm was moved forward (center), the visual RF moved to the front of the animal. When the arm was bent toward the ipsilateral side (right), the visual RF moved with it.

Department of Psychology, Princeton University, Princeton, NJ 08544, USA.

\*To whom correspondence should be addressed.

(top) shows the experimental paradigm. Each trial began with the illumination of one of three lights, A, B, or C, spaced  $20^\circ$  apart along the horizontal meridian. The monkey was required to maintain fixation throughout the trial for a juice reward; 300 to 600 ms after fixation began, the stimulus (a 10-cm-diameter white ball) was advanced toward the monkey for 700 ms at

14.5 cm per second along one of the four trajectories shown (I through IV). The ball was moved into its next starting position during the 5-s intertrial interval. The three possible eye positions and four possible stimulus positions yielded 12 conditions, which were presented interleaved, usually 10 trials per condition. We studied the effect of arm position by running a block of

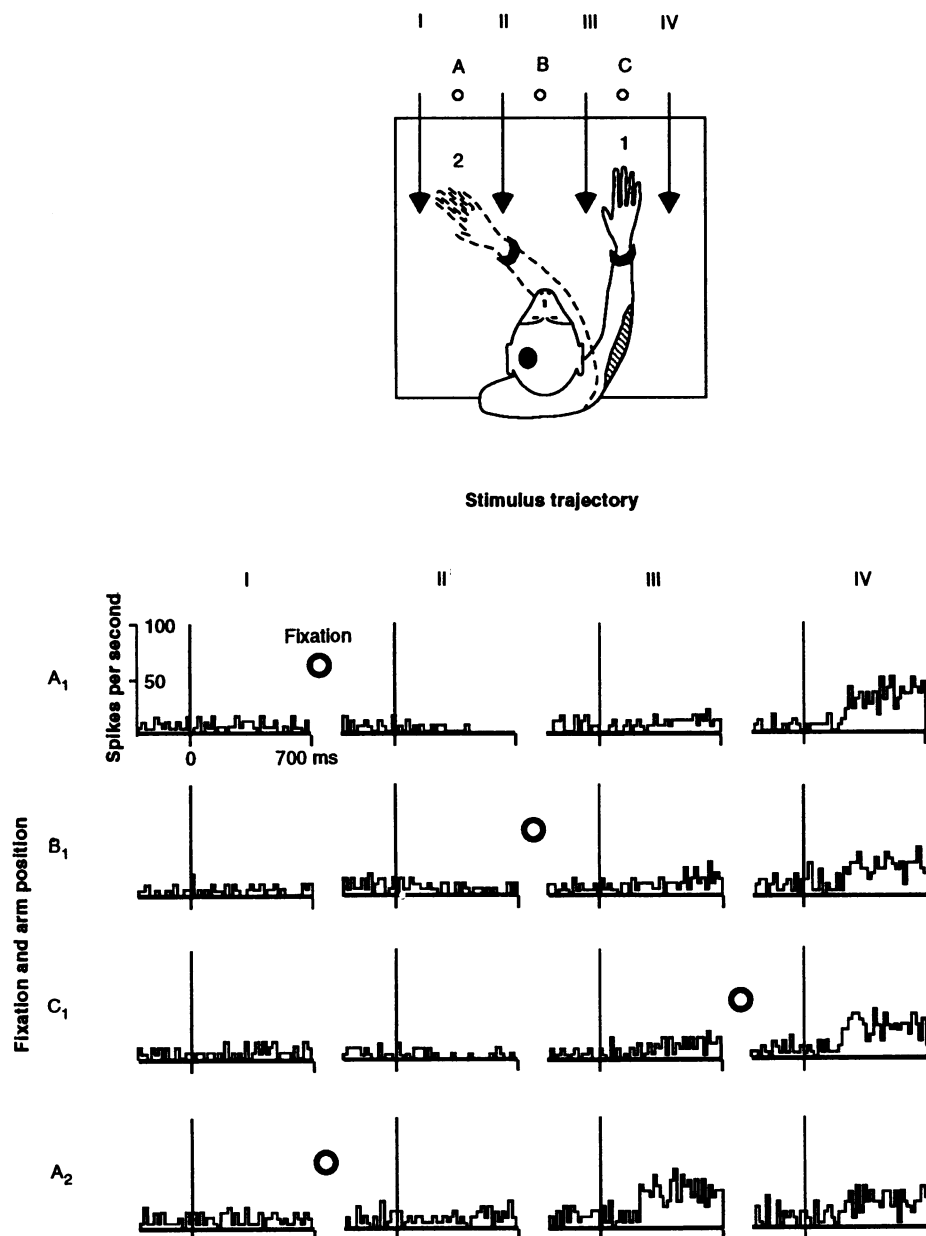
trials while the arm was in one position and then moving the arm to a new position and running a second block.

Figure 2 (bottom) shows the result for one neuron. This cell had a tactile RF on the contralateral arm. Labels  $A_1$ ,  $B_1$ , and  $C_1$  show the visual response when the arm was fixed to the right. The cell gave a significant visual response only when the stimulus was presented on the far right, in position IV ( $P < 0.05$ , paired  $t$  test between pre-stimulus and stimulus period). The visual response remained at position IV, whether the eyes were looking to the left (as in  $A_1$ ), to the center ( $B_1$ ), or to the right ( $C_1$ ). The arm was then bent toward the left, and the cell was retested. As shown in  $A_2$  for one eye position, the visual response moved with the arm. Because of the large size of the visual RF, the cell responded to both locations III and IV; however, the peak response was at location III, shifted to the left. The effect of arm position on the spatial location of the visual response was significant, but the effect of eye position was not (10). Thus, the visual RF was arm-centered, not retinocentric.

Responses from a second neuron in the awake preparation are shown in Fig. 3. Unlike the previous cell, this cell did not have a tactile RF on the arm; instead, it had a bilateral tactile RF on the eyebrow. The corresponding visual RF did not move when the arm moved; it also did not move when the eyes moved (11). This spatial invariance is particularly striking, because the fovea fell to the left of the RF when the monkey fixated light A and fell to the right of the RF when the monkey fixated light C. Although the location of the visual response was independent of eye position, the magnitude of the response was significantly greater when the eyes were deviated to the right (11). Similar modulation by gaze has been reported for other brain areas (6).

In total, we tested 33 of the 82 visual and bimodal cells in the awake animal by varying the direction of gaze. Of these, 23 had somatosensory responses on the arm, 4 had somatosensory responses on the face, and 6 were purely visual. For 32 cells (97%), the visual RF remained at the same location in space, despite the  $40^\circ$  shift in eye position. Only one cell, with a tactile response on the chin, had a visual RF that moved with the eye in a retinocentric fashion. For 21 cells (64%), the magnitude of the response was significantly modulated by eye position.

We tested 43 of the 74 "arm" bimodal cells by varying the position of the arm. For 37 cells (86%), moving the arm caused a shift in the location of the visual RF (12). Of these 37 cells, 22 were tested with multiple eye positions, and in all cases the visual RF remained near the arm, indepen-



**Fig. 2. (Top)** Experimental paradigm for the awake preparation. On each trial, the animal fixated one of three lights  $20^\circ$  apart (A, B, or C), and the stimulus was advanced along one of four trajectories (I through IV). The arm was fixed in one of two positions. The stippling shows the tactile RF of the cell illustrated beneath. The trajectories and the monkey are drawn to the same scale. **(Bottom)** Histograms of neuronal activity, summed over 10 trials, as a function of eye position (A, B, and C), stimulus position (I through IV), and arm position (to the right in  $A_1$ ,  $B_1$ , and  $C_1$  and to the left in  $A_2$ ). The vertical lines indicate stimulus onset. The circles indicate the location of the fixation light. When the arm was fixed to the right, the neuron responded best to the rightmost stimulus trajectory (IV), whether the eye looked to the left (as in  $A_1$ ), to the center (as in  $B_1$ ), or to the right (as in  $C_1$ ). However, when the arm was fixed to the left ( $A_2$ ), the neuron responded best to stimulus trajectory III; that is, the visual RF moved toward the left with the tactile RF. Results for conditions  $B_2$  and  $C_2$  were similar.

dent of the position of the eyes. Six cells were tested while the monkey's view of his arm was occluded, and for five of these the visual RF moved with the arm, implying that the effect of arm position is mediated at least partly through proprioception.

These results show that the visual RFs in ventral premotor cortex are not retinocentric. Rather, almost all remain at the same location, regardless of the direction of gaze. For most bimodal cells with tactile responses on the arm or hand, the visual RF is anchored to the arm and moves with it. These cells appear to measure the location of the stimulus with respect to the arm. This type of arm-centered coordinate system would be useful for hand-eye coordination, such as guiding the arm toward or away from visual targets, particularly because premotor cells that fire during arm movement are also programmed in arm-centered coordinates (13).

Premotor cortex contains a crude somatotopic map of the body (4). Although we have studied primarily the arm portion of the map, other portions of the map may have similar visuospatial properties. For example, bimodal cells with tactile responses on the face might have head-centered visual RFs, which would move as the head is rotated. Because these cells would measure the location of an object with respect to the

head, they would be particularly useful for reaching with the mouth toward food or other animals.

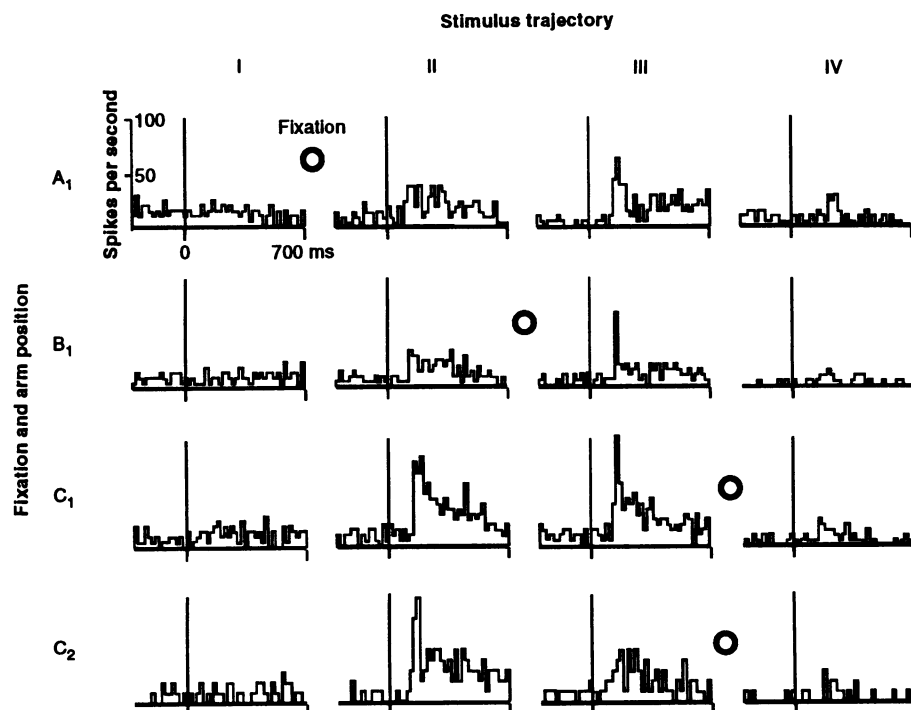
Ventral premotor cortex is not the only brain area that appears to represent space through "body part-centered" coordinates. We have reported similar bimodal responses and arm-centered RFs in the putamen (14). Premotor cortex projects directly to the putamen, and both receive a heavy input from bimodal regions of the posterior parietal lobe, especially from area 7b. These areas appear to form a system for the coding of near extrapersonal space and for guidance of movement within that space (3).

Other brain areas use a similar, body part-centered strategy. Neurons in the frontal eye fields, parietal area LIP (lateral intraparietal area), and the superior colliculus guide saccadic eye movements in retinocentric coordinates and have visual and auditory RFs that move as the eye moves (15, 16). Thus, a general principle of sensory motor control appears to be that the sensory stimulus is located in a coordinate frame centered on the relevant body part (3). Another general principle supported by our results is that space is encoded in different brain structures for different behavioral functions (16). These structures include ventral premotor cortex and the putamen, specialized for visuomotor space, the

frontal eye fields, LIP and the superior colliculus, specialized for oculomotor space, and also mid-dorsolateral prefrontal cortex, specialized for short-term mnemonic space (17), and the hippocampus specialized for navigational space (18). This view of a multiplicity of spatial structures and coordinate systems contrasts with commonly held views that all of visual space is encoded by one master coordinate system, probably centered on the point between the eyes and located in the posterior parietal cortex.

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7. Other terms for this site include F4 and F5 (4), and 6Va, PMa, and PMv [references in S. Q. He, R. Dum, P. L. Strick, *J. Neurosci.* **13**, 952 (1993)].
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9. Eleven percent ( $n = 22$ ) responded only to passive somatosensory stimulation; 7% ( $n = 15$ ) responded only during active, voluntary movements; and 18% ( $n = 38$ ) appeared to respond under both conditions. However, in some cases, especially for neurons related to the mouth, it was difficult to distinguish somatosensory response from motor activity. Therefore, this last category probably contains some neurons that were actually purely somatosensory purely motor.
10. Results for this cell were analyzed with a  $4 \times 3$  analysis of variance (ANOVA), and specific comparisons were tested with contrast analyses [see Rosenthal and R. Rosnow, *Contrast Analysis: Focused Comparisons in the Analysis of Variance* (Cambridge Univ. Press, New York, 1985)]. These specific comparisons showed that  $B_1$  and  $C_1$  significantly matched a pattern of weights derived from  $A_1$  and had no significant residual variance (for  $B_1$ ,  $F_{\text{match}} = 52.69$ ,  $P < 0.01$ , and  $F_{\text{residual}} = 1.03$ ,  $P > 0.05$ ; for  $C_1$ ,  $F_{\text{match}} = 177.98$ ,  $P < 0.01$ , and  $F_{\text{residual}} = 2.87$ ,  $P > 0.05$ ). However,  $A_2$  showed a significant residual, and thus its pattern was significantly different from that of  $A_1$  ( $F_{\text{match}} = 31.89$ ,  $P < 0.01$ , and  $F_{\text{residual}} = 50.79$ ,  $P < 0.01$ ).
11. Specific comparisons within the ANOVA (10) showed that  $A_1$ ,  $B_1$ , and  $C_2$  significantly matched a pattern of weights derived from  $C_1$  and had no significant residual variance (for  $A_1$ ,  $F_{\text{match}} = 31.15$ ,  $P < 0.01$ , and  $F_{\text{residual}} = 2.60$ ,  $P > 0.05$ ; for  $B_1$ ,  $F_{\text{match}} = 14.09$ ,  $P < 0.01$ , and  $F_{\text{residual}} = 1.79$ ,  $P > 0.05$ ; for  $C_2$ ,  $F_{\text{match}} = 58.23$ ,  $P < 0.01$ , and  $F_{\text{residual}} = 2.41$ ,  $P > 0.05$ ). The ANOVA also showed a significant main effect of eye position ( $F = 16.33$ ,  $P < 0.01$ ), reflecting the increase in response when the monkey looked to the right.
12. In the anesthetized animal, 12 "arm" bimodal neurons were tested, and for 8 of them (67%) the visual RF moved with the arm. In the awake animal, 31 "arm" bimodal cells were tested, and for 29 of them (94%) the visual RF moved with the arm.
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**Fig. 3.** Response of a bimodal neuron with a tactile RF on the eyebrows. The visual response was best when the stimulus was near the midline (trajectories II and III), matching the location of the tactile RF. The visual RF remained in the same location in space, whether the eyes looked to the left ( $A_1$ ), to the center ( $B_1$ ), or to the right ( $C_1$ ). However, the magnitude of the response varied with eye position; it was greatest at position C. When the arm was fixed to the left ( $C_2$ ), the visual response did not move with the arm, presumably because it was anchored to the tactile field on the head. Results for conditions  $A_2$  and  $B_2$  were similar. (See also the legend to Fig. 2.)



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## Horizontal Propagation of Excitation in Rat Visual Cortical Slices Revealed by Optical Imaging

Manabu Tanifuji,\* Takeshi Sugiyama, Kazuyuki Murase

Optical imaging with high spatial and temporal resolution of neural activity in rat cortical slices was used to investigate the dynamics of signal transmission through neural connections in the visual cortex. When inhibition due to  $\gamma$ -aminobutyric acid was slightly suppressed, horizontal propagation of excitation in both the supra- and infragranular layers became prominent. This propagation was not affected by vertical cuts in either the supra- or infragranular layer, which suggests that excitation is at least partially conveyed horizontally by reciprocal vertical connections between neurons in these layers.

The integration of information from different parts of the visual field is an essential aspect of information processing. In the primary visual cortex (VC), horizontal connections extending along cortical layers and forming clustered terminals on distant but similar functional columns have been proposed to represent such integrations (1–5). Besides those horizontal clustered connections, an analysis of dendritic and axonal arborizations of individual VC cells has revealed that vertical interlaminar connections also have some horizontal spread (2, 4, 6). Thus, horizontal interaction can be based on the vertical interlaminar connections as well as on the horizontal clustered connections, but their relative contributions in sending excitation horizontally have still not been clarified. In order to reveal pathways where excitation is conveyed horizontally, we tried to visualize the propagation of neural activity by using optical imaging techniques and voltage-sensitive dyes (7–9).

Neural activity evoked by stimulation of white matter (WM) in frontal sections of the rat VC was recorded as an absorption change in a voltage-sensitive dye by optical recording apparatus with high spatial (128 by 128 photodiodes) and temporal (0.6 ms)

resolution (10–14). Stimulation first evoked vertical propagation toward the cortical surface (Fig. 1A); this response was separated spatially into three components: (i) early excitations in layer VI (latency, 2.4 ms) and (ii) in layer IV (4.8 ms), where geniculate axons are known to innervate cortical cells, and (iii) a later excitation in layers II–III (7.2 ms) (8). The vertical propagation was followed by a horizontal spread in supra- and infragranular layers (SGLs and IGLs), especially in layers II–III and V (Fig. 1A) (24 ms). The range of the spread was varied in different slices, but mostly was restricted to a short distance [ $0.886 \pm 0.220$  mm and  $0.976 \pm 0.271$  mm in layers II–III and layer V, respectively ( $n = 5$ )] (15).

Cortical excitation is thought to be limited by the  $\gamma$ -aminobutyric acid (GABA)-mediated inhibitory mechanism, and the difference in the horizontal spread is probably due to the strength of the GABA-mediated inhibition. In fact, the horizontal spread increased after addition of 1  $\mu$ M bicuculline methiodide (BMI), a GABA<sub>A</sub> receptor antagonist (Fig. 1B). The range of the horizontal spread was dose-dependent at  $0.948 \pm 0.224$  mm,  $1.218 \pm 0.361$  mm,  $2.007 \pm 0.379$  mm, and  $2.247 \pm 0.501$  mm at 0.5, 1.0, 2.0, and 5  $\mu$ M BMI, respectively (layers II–III,  $n = 5$ ). Further, the layers showing horizontal spread within this range of BMI concentration were the same as in the control solution (brackets in Fig. 1, A and B, at 24 ms), and no significant change

in the vertical propagation was observed, except for an increase in the signal intensity (Fig. 1, A and B, at 7.2 ms). Thus, the excitatory connections underlying the horizontal propagation in the presence of BMI were probably the same as those in the control solution, at least within this lower range of BMI concentration.

One way to test whether the horizontal propagation is due to the horizontal clustered connections is to examine the effects of a vertical cut in parts of cortical layers. If this were the case, the cut in SGLs, for example, should disrupt propagation in SGLs but not in IGLs. Although the experiment is simple, the results may be doubtful, because a cut may have other effects on a slice. Thus, the effect of a cut on vertical propagation was examined by making a cut just above the stimulation electrode along a line of vertical propagation through layer I to layer IV (16). We found that vertical propagation was separated on the left and right sides of the cut but the overall pattern of propagation was the same as in the control slice (17) ( $n = 4$ ). This result suggests that a cut can be used to disrupt certain parts of neural connections without affecting other properties of slices.

Figure 1C shows the effects of a vertical cut in SGLs on horizontal propagation. Contrary to expectation, in three out of four cases a vertical cut did not interrupt propagation in either SGLs or IGLs (Fig. 1C). In the remaining case, propagation was interrupted in both SGLs and IGLs at the cut. For the former cases, we analyzed the propagation on an expanded time scale around the time when it passed through the cut (Fig. 2). In all of these cases, the neural excitation in SGLs did not propagate directly through the cut in a horizontal direction, but reciprocal connections between SGLs and IGLs allowed horizontal propagation parallel to the lamina to bypass the cut (Fig. 2, 24 ms through 29.4 ms). These vertical propagations seemed to be essential to maintain horizontal propagation crossing over the cut in SGLs as well as in IGLs. As in the latter observation, when the upward vertical propagation from IGLs to SGLs was not evoked sufficiently, horizontal propagations in both layers were interrupted at the cut.

Similarly, when a vertical cut was made in IGLs, horizontal propagations in both IGLs and SGLs were not interrupted by the cut (Fig. 3) ( $n = 3$ ). The stimulation of WM evoked horizontal propagations in both the SGLs and IGLs up to the cut. When the excitation reached the cut (Fig. 3, 36 ms), it propagated vertically from the SGLs down to the IGLs, skipped over the cut (Fig. 3, 48 ms through 84 ms), and then continued to propagate horizontally in both the SGLs and IGLs (Fig. 3, 96 ms).

Department of Information Science, Fukui University, Bunkyo, Fukui 910, Japan. M. Tanifuji is also affiliated with PRESTO Research Development Corporation of Japan.

\*To whom correspondence should be addressed.