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Saccade-Related Spread of Activity Across Superior Colliculus May Arise From Asymmetry of Internal Connections

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1Laboratory for Mathematical Neuroscience and for Integrated Theoretical Neuroscience, RIKEN Brain Science Institute, Saitama; 2Institute of Industrial Science, University of Tokyo, Tokyo, Japan; and 3Laboratory of Sensorimotor Research, National Eye Institute, National Institutes of Health, Bethesda, Maryland

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Nakahara, Hiroyuki, Kenji Morita, Robert H. Wurtz, and Lance M. Optican. Saccade-related spread of activity across superior colliculus may arise from asymmetry of internal connections. J Neurophysiol 96: 765–774, 2006; doi:10.1152/jn.01372.2005. The superior colliculus (SC) receives a retinotopic projection of the contralateral visual field in which the representation of the central field is expanded with respect to the peripheral field. The visual projection forms a nonlinear, approximately logarithmic, map on the SC. Models of the SC commonly assume that the function defining the strength of neuronal connections within this map (the kernel) depends only on the distance between two neurons, and is thus isotropic and homogeneous. However, if the connection strength is based on the distance between two stimuli in sensory space, the kernel will be asymmetric because of the nonlinear projection onto the brain map. We show, using a model of the SC, that one consequence of these asymmetric intrinsic connections is that activity initiated at one point spreads across the map. We compare this simulated spread with the spread observed experimentally around the time of saccadic eye movements with respect to direction of spread, differing effects of local and global inhibition, and the consequences of localized inactivation on the SC map. Early studies suggested that the SC spread was caused by feedback to change the distribution of activity on a control, calculating motor error, could be accomplished simply by using feedback to change the distribution of activity on a dynamic brain map.

Targets close to the center of the visual field are represented rostrally in the SC (black circle in Fig. 1B) and targets in the periphery are represented caudally (black triangle).

The deeper SC layers contain several different types of neurons that in one classification scheme (Munoz and Wurtz 1995a) are known as buildup and burst neurons. Both types usually have a high-frequency burst of activity (about 800 spikes/s) at the time of the saccade, but the buildup neurons also have a slowly increasing activity (up to nearly 100 spikes/s) before the saccade. A striking but controversial aspect of neuronal activity in the SC intermediate layers is that the low level of activity on the buildup neurons sometimes spreads from caudal to rostral in the SC around the time of a saccade. It is important to emphasize that the activity that spreads is the low buildup of activity, and not the burst that remains centered at the retinotopic location of the target. This intriguing observation, first made in the cat (Munoz et al. 1991a,b), was described as a “moving hill” of activity traveling from caudal to rostral across the map. Similar activity was later found in the monkey SC visual motor neurons (Munoz and Wurtz 1995b), although it was better described as a spread of activity rather than a moving hill because there was little caudal-to-rostral movement of the peak of activity. The spread in the monkey has been confirmed in other experiments; a small spread in both lateral and rostral–caudal directions was found by Anderson et al. (1998), and a spread was observed with the use of two recording electrodes at different rostral–caudal locations (Port et al. 2000).

The initial reports of the moving hill (in the cat) and the spread of activity (in the monkey) led to the hypothesis that it played a functional role in controlling the duration of eye movements (Guitton et al. 1990; Wurtz and Optican 1994). This hypothesis assumed, first, that the spread of activity was driven by information about the movement feedback back to the SC and, second, that the distribution of activity on the map represented the distance the eye still had to go to reach the target (i.e., the instantaneous, or dynamic, motor error). The allure of this hypothesis was that a critical function in motor control, calculating motor error, could be accomplished simply by using feedback to change the distribution of activity on a dynamic brain map.

This error computation hypothesis was controversial (Anderson et al. 1998; Guitton et al. 1993; Sparks 1993), and several subsequent experimental observations in the monkey

INTRODUCTION

The superior colliculus (SC) is a layered, midbrain structure related to rapid (saccadic) eye movements. The superficial layers (related to vision) and the intermediate and deep layers (related to movement) contain a nonlinearly compressed map of retinotopically projection (Fig. 1, A and B) (Cynader and Berman 1972; Robinson 1972). The central visual field is represented in more detail than the periphery and consequently covers a larger proportion of the SC map than does the periphery (Fig. 1B); thus the map is compressed toward the peripheral edge along the rostral–caudal axis. The map is approximately logarithmic (McIlwain 1975; Ottes et al. 1986) and the maps in the different SC layers are aligned (Mohler and Wurtz 1976; Schiller and Stryker 1972; also see review by Sparks 1989).
The spread moves laterally on the SC map as well as caudal to rostral (Anderson et al. 1998) and is difficult to see near the rostral pole (where small errors would have to be prominently represented) (Anderson et al. 1998; Port et al. 2000), both of which are hard to reconcile with the error model. [The spread of activity is so slight that it has not been detected by functional imaging that is sensitive enough to detect the presaccadic burst of activity (Moschovakis et al. 2001).] The motor error idea is also inconsistent with the observed timing of the spread, which reaches the rostral pole either too early (Quaiia et al. 1999) or too late (Soetedjo et al. 2002) to indicate that motor error is zero and that the saccade should be ended. Probably the most compelling reason for rejecting the error computation hypothesis is the result of muscimol inactivation of the SC (Aizawa and Wurtz 1998; Quaiia et al. 1998). One of the strongest predictions of the error computation model is that interrupting the caudal-to-rostral spread with muscimol should delay its arrival at the rostral SC, thereby producing a longer saccade. However, in those lesion experiments saccade length did not increase. Taken together, these experiments show two things: 1) sometimes a low level of activity spreads through the SC buildup neurons at around the time of a saccade, but 2) that spread is not well correlated with the motor control of the saccade. These results cast considerable doubt on the hypothesis that the spread in the SC results from a feedback signal and is computing the remaining error of the ongoing saccade. However, it is still possible that the SC receives input signals that are saccade related, but are not used to compute saccadic error. For example, the end of the SC burst is tightly correlated with the end of the saccade (waitzman et al. 1991) and interruption of a saccade by stimulation of the brain stem omnipause neurons leads to a pause in SC burst neurons (keller and edelman 1994); both of these SC activity changes would require feedback about when the saccade ends.

If the spread across the SC buildup neurons is not caused by an external, feedback signal, then what is its origin? Here we consider the possibility that the spread of activity arises as a consequence of the connections within the SC. We first assume, as have other models (arai and keller 2005; arai et al. 1994; droulez and berthoz 1991; lefèvre et al. 1998; optican 1995; ottes et al. 1986; trappenberg et al. 2001), that neurons within the SC are uniformly distributed, i.e., the neural density, or the number of cells per square millimeter, is the same.

FIG. 1. Asymmetries produced by mapping between the visual field and superior colliculus (SC). A: logarithmic transform between horizontal meridian of the visual field (in degrees of visual angle) and SC (in mm) (ottes et al. 1986; robinson 1972). B: topographic mapping between visual hemifield and contralateral SC. Thick red and thin green lines show horizontal and vertical meridians, respectively, and lighter red curves show increased eccentricity. C: visual-asymmetric and SC-symmetric connection field. Symmetry of yellow spokes on SC map indicates the connection field is isotopic, and asymmetry of the spokes on the visual map emphasizes anisotropy of the visual field. Density of red shading indicates strength of connections. D: visual-symmetric and SC-asymmetric connection fields. In both C and D, the center of the connection fields is the same, (R, θ) = (20°, 30°). E and F: shape of the visual and SC connection fields for the maps in C and D just above. Abscissa is the distance along the θ = 30° line used for the example field shown in C and D with zero as the center of the field. Because of the nonlinear projection of the visual field onto the SC map, the fields can be symmetric on one map or the other, but not both.
everywhere on the map. Second, the spatial distribution and strength of the connections of one SC neuron with its neighbors defines a function, or kernel. All saccade models necessarily contain a kernel, but our model differs in our assumptions about the shape of this kernel.

Many previous SC models (e.g., Arai et al. 1994; Droulez and Berthoz 1991; Gancarz and Grossberg 1999; Lefèvre and Galiana 1992; Optican 1995; Short and Enderle 2001; Trappenberg et al. 2001) assumed that the kernel is determined by the distance between two neurons; i.e., if the distance is the same, the connection strength is the same, between any pair of neurons. Such a kernel is circularly symmetric on the SC (e.g., a Gaussian function). Figure 1C illustrates this symmetry by showing one sample neuron (in yellow; not to scale) on the SC. It also shows that the projection of this kernel back onto the visual field is not symmetric because of the logarithmic projection of the visual field onto the SC (Fig. 1A).

There is no evidence, however, that SC kernels are a symmetric function of the distance between two neurons. We therefore explore an alternative possibility: that the kernel is defined by the separation in visual space between two stimuli. The logarithmic projection (see METHODS and RESULTS) of the visual space onto the SC makes this kernel asymmetric (Fig. 1D). Here, we study the consequences of having either symmetric or asymmetric kernels. We show that asymmetric connections within the SC can cause activity to spread across the SC during the movement without any exogenous inputs (if inhibition is low enough). Furthermore, we show that the spread caused by an asymmetric kernel is consistent with recent experimental findings, including those inconsistent with the spread acting as a motor error signal. Thus we propose that an asymmetric connection kernel causes the spread of activity on the SC, and thus external feedback is not a prerequisite for the spread. This raises the possibility that symmetry in connection kernels may be an important factor in the distribution of brain activity in other areas that have nonlinear brain maps.

METHODS

We used computer simulations of an SC model with either a symmetric or asymmetric kernel (see following text). The kernel defines the strength and distribution of the connections among SC neurons and thereby governs the behavior of the SC model. Here we explain qualitatively the background and methods used in the present study. Quantitative details can be found in the APPENDIX.

Logarithmic mapping from visual field to SC

The nonlinear mapping between the visual hemifield and the contralateral SC found in monkeys by Robinson (1972) was fit by Ottes et al. (1986) with the equations

\[
\begin{align*}
x &= B_x \log \left[ \frac{R^2 + 2AR \cos(\theta) + A^2}{A} \right] \\
y &= B_y \arctan \left[ \frac{R \sin(\theta)}{R \cos(\theta) + A} \right]
\end{align*}
\]

where \((x, y)\) represents Cartesian coordinates on the SC topographic map (in mm) and \((R, \theta)\) represents polar coordinates in degrees in the visual field \((A = 3.0^\circ, B_x = 1.4 \text{ mm}, \text{ and } B_y = 1.8 \text{ mm})\).

Connection symmetry

First, we assumed that neurons within the SC are uniformly distributed (same number of cells per square millimeter everywhere on the map), as was assumed in previous studies. Second, we assumed that connection strength was determined by the distance measured on either the SC map (the SC-symmetric kernel) or in the visual field (the visually symmetric, also called the SC-asymmetric kernel; see following text). Here the symmetry, either SC or visual space, refers to being isotropic (the same in all directions) as well as homogeneous (the same for neurons everywhere) in the space (see RESULTS for details).

The present study notes that the connection kernel cannot be symmetric in both visual space and SC space (Fig. 1) because of the logarithmic mapping. We therefore must decide how to define the "distance" between any two neurons, i.e., how to define the kernel. Simply defining distance as the physical separation between the two cells on the collicular map results in the SC-symmetric kernel (Fig. 1C), which was assumed in most previous SC models (Arai et al. 1994; Droulez and Berthoz 1991; Gancarz and Grossberg 1999; Lefèvre and Galiana 1992; Optican 1995; Short and Enderle 2001; Trappenberg et al. 2001). In this kernel, equally distant neurons have the same connection strength.

Alternatively, we could define distance as the separation in visual space between the two points that map to those neurons, i.e., neurons receiving equally separated inputs in visual space have the same connection strength. The separation in space can lead to a visually symmetric kernel simply by Hebb's postulate (Hebb 1949) that "cells that fire together, wire together." Two separate stimuli will be unlikely to appear together consistently because natural visual stimuli appear everywhere relative to the fovea with equal probability. Thus the probability that two neurons fire together will depend on whether a single stimulus excites them both, which will be more likely to happen if the receptive fields of those neurons are close together in visual space. This postulate leads to a visually symmetric kernel. In fact, symmetry in the visual space, but not on the brain map, has been demonstrated in V1 (Angelucci et al. 2002). As shown below, the visually symmetric kernel, once projected back to the SC, becomes asymmetric (Fig. 1D).

The shape of both kernels can be appreciated by looking at a slice along the horizontal meridian. The asymmetry of a kernel in a space shows up as a skewed curve in that space (Fig. 1, E and F; Fig. 2, C and D).

Intracollicular connections

The kernel used in these simulations was defined as the difference between an excitatory function \((E)\) and an inhibitory function \((I)\). For the function \(E\), we considered a Gaussian function either on SC (an SC-symmetric kernel) or in the visual field (an SC-asymmetric kernel). For the function \(I\), a Gaussian function defined "local" inhibition, and a saturating function of the sum of all SC activities defined "global" inhibition (see the APPENDIX). The two different forms of inhibition represent the short-distance, local effects of inhibitory connections within the SC and the long-distance, more global effects of inhibition from outside the SC (e.g., from the substantia nigra (Hikosaka and Wurtz 1983)). Using either kernel (SC-symmetric or -asymmetric) and either inhibition (local or global), the temporal evolution of the SC neural population activity was simulated by solving a partial differential equation (Eq. A5 in the APPENDIX).

RESULTS

Overview of SC-symmetric and -asymmetric kernels

The SC-symmetric and -asymmetric kernels define two different models. Because of the nonlinear map from the visual to the SC, the kernel can be symmetric in only one space or the
between two neurons, the connection kernel is symmetric in the model is determined by the distance in both spaces, but those cases are outside the scope of this paper.

Figure 1 shows the correspondence between the kernels for the visual field and for the SC map. When the connection kernel in the model is determined by the distance on the SC between two neurons, the connection kernel is SC-symmetric (Fig. 1C, right). Here, symmetry means that the kernel is both isotropic (the same in all directions) and homogeneous (the same for neurons everywhere) in the space. The kernel is asymmetric in visual space when it is projected back through the nonlinear map from the SC into visual space (Fig. 1C, left), severely distorting the distances. The fact that the kernel is anisotropic in visual space is illustrated by cross sections through them in Fig. 1E. It is also inhomogeneous on visual space (Fig. 2A). The distortion in the visual field is greater for sites near the center of the field (Fig. 2, A and C) as a result of the logarithmic transformation between visual field and SC map (Fig. 1A).

In contrast, the visually symmetric kernel (Fig. 1D, left) is asymmetric when it is projected onto the SC (Fig. 1D, right). Straight lines near the center of the visual field become more curved on the SC map than lines in the periphery. This kernel is anisotropic on the SC (e.g., Fig. 1F). The kernel is also inhomogeneous on the SC (Fig. 2, B and D). The distortion in the SC is greater for sites more rostral on the SC map, which correspond to sites nearer the center of the visual field. Thus the kernel is called SC-asymmetric.

In simulation studies below, we focused on the effects of different kernels on neurons that show a buildup or small prelude of activity before the saccadic burst, such as buildup neurons in the SC. Because burst neurons have no such activity, they cannot participate in the spread of the prelude. We assume that the main difference between buildup and burst neurons is the amount of inhibition they receive, with burst neurons receiving so much inhibition before saccades that they show no buildup (Quaia et al. 1999).

**Difference in spread in SC-symmetric and -asymmetric kernels**

We first determined the consequences of providing a localized input at one point on the SC map with the two kernels. With an SC-symmetric kernel, activity evoked around the location of the initial input waxes and wanes, but remains centered at the initial site, with no spread being evident (Fig. 3A). In contrast, with an SC-asymmetric kernel (Fig. 3B), the activity does not remain at the input site but spreads toward the rostral SC. This autonomous spread occurs because of the asymmetry of the kernel, i.e., the rostral–caudal difference in strength (cf. Droulez 1991). Figure 4 shows the difference more clearly by showing a section through both asymmetric

**FIG. 2.** Homogeneity of connection fields. A: SC-symmetric connection field is homogeneous (i.e., the same for neurons at all locations) in the SC space, but not in the visual space. B: visual-symmetric connection field is homogeneous in the visual space, but not in the SC space. In A and B, 2 connection fields are shown, having their centers at \((R, \theta) = (10^\circ, 30^\circ)\) (orange) and \((40^\circ, 30^\circ)\) (green). C and D: shape of each of the 2 connection fields for the 4 maps in A and B. Same formats as Fig. 1, E and F. Two connection fields for each map are superimposed by aligning their centers and indicated by their corresponding colors (orange and green). In C the shapes of the 2 connection fields are the same at different locations on the SC map but different on the visual field map, whereas in D they are different on SC but the same on the visual field.

**FIG. 3.** In the model simulation the spatiotemporal evolution of neuronal activity depends on the symmetry of SC connections. A: SC-symmetric connection field gives stationary locus of activity after persistent input at one point [black cross at \((R, \theta) = (15^\circ, 30^\circ)\)]. B: SC-asymmetric connection field causes initial locus of activity to expand and move rostrally. SC maps show frames of spatiotemporal activity moving from left to right (early to late) after the start of input. Yellow asterisk indicates the shift of the center of gravity of simulated activity. Model produces a spread of activity only on the map with asymmetric connections on the SC.
(Fig. 4B) and symmetric (Fig. 4D) kernels. The net effect of the kernel is to create an input for all the SC neurons. The asymmetric kernel gives rise to an input field that is skewed rostrally (Fig. 4C), which causes the neural activity to spread. The symmetric kernel creates an input field that is trapped locally by balanced excitation and inhibition (Fig. 4E), so there is no spread. In Fig. 3, the center of gravity of the activity (COA) is shown to indicate the spread. The COA shown here moves more than that reported in the monkey (Anderson et al. 1998; Munoz and Wurtz 1995b) because the COAs reported by those authors include both the spread and the stationary burst. The burst is an order of magnitude greater than the spread, whereas the COA here is computed using only the prelude activity on buildup neurons.

Permutations of these simulations show that the autonomous spread is robust; the spread occurs with a wide range of parameters, as long as the connection kernel is SC-asymmetric. It made no difference whether the input was sustained as in the example in Fig. 3B or transient as in Fig. 5A. The relative strength of excitation and inhibition could be varied over substantial ranges without disrupting the spread; halving the strength of the excitatory connections (Fig. 5B) or doubling the strength of the inhibitory connections (Fig. 5C) did not substantially change the magnitude of the spread. [Of course, the inhibition must be less than the excitation, e.g., quadrupling the strength of inhibition eliminated the spread (Fig. 5D).]

We next varied the nature of the inhibition. The commonly used symmetric kernel has a center-surround shape, with a small excitatory center superimposed on a larger inhibitory surround (a “Mexican hat” function). It is well known, however, that there is another major source of inhibition in the SC other than that resulting from local connections; projections from the substantia nigra pars reticulata of the basal ganglia (Hikosaka and Wurtz 1985) provide a more global inhibition throughout the SC map. We therefore compared the effects of the two types of inhibition tested separately: local inhibition as used in the previous simulations (Fig. 6A) and global inhibition in the absence of any local inhibition (Fig. 6B). There was a spread of activity with global inhibition just as there was with local inhibition, but the characteristics of the spreads were different; the COA stays near the location of the initial input longer in the case of global inhibition.

Simulations of abnormal conditions

We also tested the model under two abnormal conditions to show the robustness of the spread in our model. The first shows the effect of inactivating a part of the SC, a common experimental procedure (e.g., Aizawa and Wurtz 1998). With the SC-asymmetric model, inactivation at a spot on the map does not halt the spread of activity because the intrinsic connections provide many paths around the lesion (Fig. 7). Under the old hypothesis—that the spread is indicating motor error—it would represent a vector (with both magnitude and direction) and always point along a streamline (lines of isoevoked activity in Fig. 1B) toward zero, which is in the rostral SC (fixation zone) (Optican 1995). Thus if the spread is motor error, purely driven by feedback signals, and if there is a lesion on the streamline between the initial site of activation and the fixation zone, the spread would “fall into the lesion” and disappear. Feedback could not generate a perpendicular component that would drive the activity around the lesion and then toward the rostral pole. Thus the results of the inactivation experiment disprove the error computation hypothesis (Aizawa and Wurtz 1998; Quaia et al. 1998). In contrast, we have now demonstrated by the
SC-asymmetric model that the spread can continue by getting around the lesion because of the asymmetry of the intrinsic connections.

In the second experiment two stimuli were presented at once, another common experimental procedure (e.g., Edelman and Keller 1998; Robinson 1972). In these experiments, monkeys usually made a saccade toward one stimulus or the other, but sometimes made a saccade to a point between the two. The observed SC activity stayed at both locations throughout the movements (Edelman and Keller 1998). For the SC-asymmetric model, two initial inputs were provided and the spread from each of the activated SC sites was followed (Fig. 8). In the case of local inhibition, one spot always prevailed and spread toward the rostral SC whereas the other died out (Fig. 8A).

With global inhibition each point led to a spread of activity that coalesced into one stream of activity (Fig. 8B). Thus the global inhibition model is more consistent with experimental results that show an “averaged” saccade.

DISCUSSION

Consequences of symmetric and asymmetric SC connections

We explored a consequence of the nonlinear mapping of the visual field onto the SC, a two-dimensional structure. The logarithmic projection from visual space to SC means that there are two logically consistent ways to interconnect SC neurons, either with a kernel that is symmetric in SC coordinates (i.e., SC-symmetric) or with a kernel whose image, projected back into the visual field, is symmetric (i.e., necessarily SC-asymmetric). Our model shows a spread of activity only when there is an asymmetry in the connections within the
SC. The logarithmic projection map defines the SC-asymmetric connection (Figs. 1 and 2), although it is the nature of the intrinsic connections—not the nature of the projection map—that gives rise to the spreading of activity.

Simulations with our model demonstrated that an SC map with asymmetric connections produces a spread of activity on the map from caudal to rostral (Fig. 3). This is an autonomous spread in the absence of any external feedback signals. The spread was ubiquitous over a wide range of parameters (Fig. 5) and for both local and global inhibition (Fig. 6). Thus SC-asymmetric connections could underlie the observed perisaccadic spread of activity on the SC, without any saccadic error feedback to the SC. In contrast, simulation of the SC-symmetric connections never led to any such spread of activity (Fig. 3). Therefore a model of SC-symmetric connections requires extrinsic input to produce the spread. Computationally, this is a general phenomenon not only on the SC but in any brain area with symmetric connections (Amari 1977); i.e., symmetric connections lead to so-called neutrally stable attractors (Amari 1977; Seung 1996; Zhang 1996). Indeed, previous SC models with symmetric connections had to add further directional (anisotropic) intrinsic connections or specific extrinsic drives to induce the spreading activity. The same approach is also used in other areas, e.g., to move activity across head-direction cells in hippocampus (Zhang 1996).

Role of inhibition in the SC spread of activity

One of the implications of our model simulations is that the amount and distribution of inhibition are critical in determining network behavior. The level of inhibition set in the model determines whether there is any spread (Fig. 5, C and D). Even when inhibition was set low enough to allow the spread, the nature of the spread differed, depending on whether the inhibition was local or global. With local inhibition, the caudal part of the activity decayed as the rostral part spread, creating a moving hill of activity similar to what Munoz et al. (1991b) found in the cat (cf. Fig. 6A). In contrast, with global inhibition, the caudal part of the activity remained at the initial site, whereas the activity spread rostrally, creating a spread of activity similar to what Munoz and Wurtz (1995b) found in the monkey (cf. Fig. 6B). We do not know whether this similarity is simply coincidental, or indicates a species difference, because the cat and the monkey are the only species studied sufficiently to evaluate the nature of the spread of activity (but see also below).

Is there any evidence at the level of single neurons in the SC for the characteristics assumed in our model? On the key point of inhibition, there is abundant evidence for extensive inhibitory connections within the intermediate layers of the SC where the buildup neurons are located. At an anatomical level, axon terminals that contain the precursor of γ-aminobutyric acid (GABA) are extensive in the cat (Lu et al. 1985) and across species roughly a third of the neurons are GABAergic (Mize 1992). Electrical stimulation of SC intermediate layers in awake monkeys (Munoz and Istvan 1998) and in ferret brain slices (Meredith and Ramoa 1998) produces inhibition both locally and at substantial distances across the intermediate layers. Thus there is ample evidence that there are substantial numbers of neurons intrinsic to the SC that can provide...
intrinsic and extrinsic inhibition. There are also many areas that provide extrinsic GABAergic input to SC, including such oculomotor-relevant areas as substantia nigra pars reticulata, zona incerta, and mesencephalic reticular formation (Appell and Behan 1990). These inputs can cover extensive areas of the SC and could easily be the source of the global inhibition in our model. In addition, it might well be that studies using electrical stimulation within the SC antidromically activated these external inputs, rather than just intrinsic neurons within the SC; this remote effect would then have been included in the assessment of long-range connections within the SC. In any case, it is clear that there is a substrate of neurons supporting both local and global inhibition within the SC.

There is currently no evidence for or against the other key element in the model, the rostral–caudal asymmetry in the strength of the local connections. There is no evidence of asymmetry in long-distance connections in the intermediate layer in either the cat (Behan and Kime 1996) or the ferret (Meredith and Ramoa 1998). Local connections can be inferred from studies of identified neurons in the cat (for summary see Grantyn and Moschovakis 2004), but the functional extent of connections is most clearly shown by the use of tissue slices that allow precise measures of distances between sites of stimulation and affected neurons. The technique revealed the interaction between excitation and inhibition in SC by showing that a reduction of GABAergic inhibition in rat intermediate layers produces synchronized bursts of activity similar to the burst before saccades (Isa et al. 2004; Saito and Isa 2003). The extent of this excitatory and inhibitory action is shown most exactly by SC slice experiments using photoactivation of caged glutamate (Pettit et al. 1999; also see McIlwain 1982). Such experiments show that strong excitatory responses are elicited by photostimulation $\pm 300 \mu m$ from a recorded neuron’s soma with only weaker responses out to 500 $\mu m$, whereas inhibitory responses were restricted to photostimulation within 150 $\mu m$ (Özen et al. 2004). The picture that emerges is one in which the distances for monosynaptic connections are short and the reach of local inhibition is shorter than that for excitation. The short distances produce no problem for the model, but the apparently shorter range of inhibition than excitation does; the model assumes a more extensive reach of inhibition than excitation. However, the slice results are based on monosynaptic connections and our model does not require these local connections to be monosynaptic. On another key point of rostral–caudal asymmetry of these local connections, we are unaware of any evidence for such asymmetry in the length of connections or their strength. The slice technique, however, should be able to contribute to the answer to this question as well as to the relative reach of excitation and inhibition, once polysynaptic connections are considered.

**Comparison of spread in the model to spread in the SC**

The model can be critical in providing clues as to the nature of the spread in the SC of the low-level buildup or prelude activity, but only if the characteristics of the simulated spread and the experimentally observed spread are similar. We think there are several such similarities. First, the spread of activity in the monkey SC has been shown to extend laterally as well as rostrally (Anderson et al. 1998), which is the case with the simulated spread (Fig. 3B). Second, another characteristic of the spread in the monkey is that it can be variable from trial to trial and from neuron to neuron (Port et al. 2000). In the model such variability is easily produced by varying the strength of inhibition (Fig. 5, C and D). Although it is not obvious that the strength of local inhibitory connections would vary in the brain, variation in global inhibition from the substantia nigra would be reasonable. Third, the activity in the cat is best described as a moving hill of activity (Munoz et al. 1991b), whereas that in the monkey is better described as a spread of activity (Munoz and Wurtz 1995b). As described above for the model, local inhibition produced a moving peak of activity similar to that in the cat, whereas global inhibition produced a spread of activity similar to that in the monkey (Fig. 6). Fourth, simulated inactivation did not stop the spread of activity on the SC map (Fig. 7). Finally, we have shown that if the inhibition is too great, activity cannot spread; thus more inhibition on burst than buildup neurons may explain why burst neurons in the SC do not show a buildup of activity.

**Implications of the SC-asymmetric connection model**

A few generalizations can be made with respect to the SC. First, the spread of activity can occur in the absence of any feedback signal and thus need not be involved in saccadic control. Second, the spread may require a reduction of inhibition from outside (e.g., the substantia nigra pars reticulata). If that reduction occurred around the time of a saccade, it would explain why the spread is always correlated with a saccade, and it predicts that a reduction at other times should also reveal a spread of activity. Third, if the spread is caused by asymmetric intrinsic connections, it may be just an epiphenomenon, with no contribution to movement control. This is not surprising, given its small size relative to the burst of activity that drives the saccade. Fourth, it is possible that the spread may have a function we do not recognize, i.e., in establishing connections during development or as part of a feedforward controller in orienting behavior.

**Implications of intrinsic connections**

The spread of activity we have found in the model with asymmetric kernels may be applicable to other maps in the brain because all sensory maps in the brain are nonlinear. Are there, then, signs that activity can spread across such maps when inhibition decreases? One example may be the well-known visual, aural, and tactile hallucinations that can accompany migraine headaches (for review, see Dahlem and Chronicle 2004). Lashley (1941) proposed that because the aura appeared to move, it might be attributed to a spread of activity across the cortex. The mechanism for this spread is not well understood, but has been associated with a wave of depression that spreads across the cortex (spreading depression of Leão 1986) or with changes in network properties (Dahlem et al. 2000; Reggia and Montgomery 1996; Schwartz 1980). Our theoretical study suggests that activity might spread across brain areas that have asymmetric intrinsic connections, simply because inhibition is sufficiently reduced. This idea is consistent with the finding that prophylactic drugs for migraine augment cortical inhibition and is more specific than a mechanism of general “hyperexcitability” (Dahlem and Chronicle 2004). Thus although phenomena (e.g., pathological and ex-
perceptual hallucinations) that arise in other brain maps may have characteristics quite different from the spread of activity we have considered in SC, we suggest that what they may have in common is the consequence of reduced inhibition on maps with asymmetric connections.

**APPENDIX**

**Simulation details**

The excitatory kernel $E(x, x')$ and the inhibitory kernel $I(x, x')$ were represented by a two-dimensional Gaussian function of distance $d(x, x')$

\[
\frac{a_{sc}}{\sqrt{2\pi}s_{sc}} \exp \left[ -\frac{d_{sc}(x, x')^2}{2s_{sc}^2} \right] \quad (A1)
\]

or

\[
\frac{a_{vi}}{\sqrt{2\pi}s_{vi}} \exp \left[ -\frac{d_{vi}(x, x')^2}{2s_{vi}^2} \right] \quad (A2)
\]

for the SC-symmetrical or visually symmetrical kernels, respectively. Thus the shape of the kernel is like a “Mexian hat” [i.e., the difference of the two Gaussian-shaped functions $E(x, x')$ and $I(x, x')$; Fig. 4]. Here $d_{sc}(x, x')$ indicates the distance between $x$ and $x'$ measured in the SC space (in millimeters), whereas $d_{vi}(x, x')$ indicates the distance measured in the visual space (in degrees) between two points in the visual hemifield corresponding to $x$ and $x'$; $a_{sc}$ and $a_{vi}$ scale the magnitude of the connection strength, respectively; $s_{sc}$ and $s_{vi}$ are the respective SDs. The parameters were set to $(a_{sc}, s_{sc})$ values of $(8, 0.1)$ and $(8, 2)$ for the SC-symmetrical lateral excitation and inhibition, respectively, or $(a_{vi}, s_{vi})$ values of $(8, 1.5)$ and $(18, 18)$ for the visually symmetrical lateral excitation and inhibition, respectively, throughout the paper (except for Fig. 5).

When simulating global inhibition, we omitted the term $I(x, x')$ but added the term $G(t)$, given by

\[
G(t) = G_0 + \psi \left[ \int_{x \in \text{SC}} r(x, t) dx \right]
\]

where $G_0$ represents a constant and $\psi(z)$ is a sigmoidal function given by (Naka and Rushton 1966)

\[
\psi(z) = \frac{a z^n}{z_0^n + z^n} \quad (A4)
\]

where $a$ is the saturation value of $\psi(z)$; $z_0$ is a value that gives half the maximum; and $n$ is a constant that determines the maximum slope. Because the shape of the function $\psi(z)$ is sigmoidal, the overall form of $G(t)$ is also sigmoidal and its value is bounded between $G_0$ and $G_0 + a$. All neural activities are summed together by \( \int_{x \in \text{SC}} r(x, t) dx \) and fed into $\psi(i)$, thereby implementing the global feedback inhibition. The parameters were set as follows: $G_0 = 0.05; a = 300; z_0 = 600$; and $n = 8$.

To run the simulation of the dynamics, we adopted the following neural field equation (Amari 1977; Wilson and Cowan 1973)

\[
\tau \frac{d r(x, t)}{d t} = - r(x, t) + \sigma \left[ \int_{x' \in \text{SC}} \left( E(x, x') - I(x, x') \right) r(x', t) dx' + H(x, t) + G(t) \right] \quad (A5)
\]

where $x$ denotes the location in the SC; $t$ is time; $r(x, t)$ is the neuronal activity of the neuron at $x$; $\tau$ is the simulation time constant (see following text); $E(x, x')$ and $I(x, x')$ represent the strength of the lateral excitation and inhibition from the neuron at $x'$ to the neuron at $x$, respectively [where $r(x, x')$ is zero in cases using global inhibition]; $\rho$ is the density of the neurons (assumed to be uniform in SC space); $H(x, t)$ is the external input to the neuron at locus $x$ at time $t$; $G(t)$ is the strength of the global inhibition (which is zero when using lateral inhibition); $\sigma(z)$ is the piecewise-linear activation function consisting of a threshold and a saturation such that $\sigma(z) = 0$ if $z \leq 0$, $z$ (if $0 < z \leq \eta$), and $\eta$ (if $z > \eta$). This integral–partial differential equation (IPDE) was solved (MATLAB, The MathWorks) using discretization methods. Specifically, the two-dimensional plane of the SC was subdivided into small compartments. To facilitate computer simulations, we chose compartments distributed uniformly with respect to visual space (each is $1 \times 1'$) by translating the uniform neural density on the SC to the density in visual space. Thus the IPDE was approximated by a set of ordinary differential equations describing the activities of the representative neuron in each compartment. The parameters were set to: $\tau = 1; \rho = 200$; and $\eta = 1$. Because we are interested in the qualitative rather than quantitative properties of the dynamics, we simply set the time constant $\tau$ to be unity; thus the variable $t$ represents only relative time under this parameter set. Specifically, it would be inappropriate to compare the value of $t$ between the lateral inhibition case (Figs. 3, 5, and 6A) and the global inhibition case (Fig. 6B).

**Simulating inputs and inactivation**

Inputs representing visual target signals were simulated either by adding positive constants to the equations of $\partial r(x, t)/\partial t$ (persistent input) or by setting the initial conditions $r(x, 0)$ to some positive values (transient input) for all the discretized compartments included in circles around the input locations. Specifically, we assumed $H(x, t) = 0.1$ for all $t$ (all the figures except for Fig. 5) or set $r(x, 0) = 1$ (Fig. 3). The radius of the circle around the input locations was set to 0.1 mm (all the figures except for Fig. 5) or 0.2 mm (Fig. 5). To simulate partial inactivation of SC in Fig. 7, we set $H(x, t) = -1.00$ for all $t$ for all the compartments included in a 0.3-mm-radius circle centered at $(R, \theta) = (7.5', 30')$. In the simulation with double stimuli in Fig. 8, we applied two persistent inputs at $(R, \theta) = (20', 45')$ and $(R, \theta) = (20', -45')$, whose strengths differ moderately: $H(t, x)$ values of 0.1 and 0.12, respectively.

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