mimicry by HSV-1 (KOS) is essential for disease induction in genetically susceptible hosts under all circumstances. Mimicry mechanisms may be particularly important in translating relatively low level viral infections into an autoimmune response. Infections by higher concentrations of HSV-1 (KOS) or by more virulent strains of HSV-1 may induce inflammatory responses that are sufficient to provoke autoimmune disease without the need for molecular mimicry. A comparison of HSK in transgenic mice with T cells that carry a receptor specific for an HSV-1 (KOS) viral peptide mimic or an unrelated peptide should further clarify the relative roles of mimicry and inflammation in the pathogenesis of virally induced autoimmune disease.

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15. Culture flasks (75 cm^2) were seeded at a density of 1×10^6 Vero cells per flask. Cells were infected with wild-type KOS or KOS/UL6^m mutant viruses at a multiplicity of infection of 10 PFU per cell. Uninfected and infected cells were harvested 18 to 20 hours after infection by scraping into the medium and were centrifuged at 1500 revolutions per minute and 4°C for 10 min. The cell pellet was resuspended in 5 ml of phosphate-buffered saline (PBS), repelleted, and resuspended again in 1 ml of PBS. The cell suspension was stored at −70°C overnight, thawed at 37°C, and sonicated for 1 min. Samples were pelleted at 4°C for 10 min, and the supernatant fluid was divided into aliquots and stored at −70°C. Protein concentrations were determined by measuring absorbance at 280 nm and using bovine serum albumin as a standard.
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An Area Specialized for Spatial Working Memory in Human Frontal Cortex

Susan M. Courtney,* Laurent Petit, José Ma. Maisog, Leslie G. Ungerleider, James V. Haxby

Working memory is the process of maintaining an active representation of information so that it is available for use. In monkeys, a prefrontal cortical region important for spatial working memory lies in and around the principal sulcus, but in humans the location, and even the existence, of a region for spatial working memory is in dispute. By using functional magnetic resonance imaging in humans, an area in the superior frontal sulcus was identified that is specialized for spatial working memory. This area is located more superiorly and posteriorly in the human than in the monkey brain, which may explain why it was not recognized previously.

Studies of working memory in monkeys (*1*) and humans (*2*–*7*) have emphasized the important role of the prefrontal cortex. Physiological evidence for this role comes from studies demonstrating sustained activity in prefrontal cortex during working memory delays (*1*, *6*–*8*). In monkeys, the dorsolateral prefrontal cortex within and surrounding the principal sulcus appears to be involved primarily in working memory for spatial locations, whereas the region ventral to it on the inferior convexity appears to be more involved in working memory for patterns, colors, objects, and faces (*1*, *9*). The prefrontal region for spatial working memory in monkeys is located just anterior to a region for the control of eye movements, the frontal eye field (FEF), which is on the anterior bank of the arcuate sulcus (*10*).

Most functional brain imaging studies of spatial working memory in humans have focused on the dorsolateral frontal region defined by Brodmann as area 46 (*5*, *11*, *12*), because the spatial working memory region in monkeys lies within that area (*13*). While performance of spatial working memory tasks activates Brodmann area (BA) 46 (*5*, *11*, *12*), performance of working memory tasks involving other types of information, such as verbal and visual object information, does so as well [for example, see (*3*, *6*, *7*, *12*, *14*, *15*)]. Therefore, the existence of a prefrontal cortical area in humans that is specialized for spatial working memory has been questioned [for example, see (*16*)].

Here we provide evidence that a human frontal area specialized for spatial working

Laboratory of Brain and Cognition, National Institute of Mental Health, Building 10, Room 4C104, 10 Center Drive, Bethesda, MD 20892–1366, USA.

*To whom correspondence should be addressed. E-mail: Susan_Courtney@nih.gov

memory does indeed exist, but it is not in BA 46. Rather than focusing on cytoarchitectonically defined BA 46, we focused our investigation on cortical areas in the vicinity of a functionally defined landmark that lies near the spatial working memory area in the monkey, the FEF. Imaging studies of eye movements have localized the human FEF to the precentral sulcus (*17, 18*). Because the monkey spatial working memory area lies just anterior to the FEF, we predicted that the human spatial working memory area might also lie just anterior to the FEF, perhaps within the superior frontal sulcus. Thus, we hypothesized that the location of this region for spatial working memory, like the human FEF, is relatively more superior and posterior than a similar functional region in monkey frontal cortex and has a different BA designation. Imaging studies of spatial working memory that have included dorsal and posterior frontal areas have consistently found activation in the vicinity of the superior frontal sulcus (*5, 12, 15, 18–21*), but a mnemonic role for this region has largely been dismissed because of its presumed location in premotor cortex or the FEF [but see (*15, 18, 21*)].

We investigated the role of the superior frontal sulcus in spatial working memory by using functional magnetic resonance imaging (fMRI). We used four criteria to determine whether this area is specialized for spatial working memory: (i) the area must show sustained activity during spatial working memory delays; (ii) such sustained activity must be greater during spatial working memory delays than during delays in other types of working memory tasks, in this case working memory for faces; (iii) the sustained activity during spatial working memory delays cannot be attributable to preparation for a motor response, which would indicate a premotor rather than a mnemonic function; and (iv) the area must be distinct from the FEF.

Functional MRI scans were obtained while 11 healthy human volunteers (8 males and 3 females) alternately performed individual trials of spatial working memory and sensorimotor control tasks (Fig. 1). Activations associated with face working memory were also investigated in seven of these subjects, and those associated with visually guided saccades were investigated in the other four. Multiple regression analysis of the time course of the activation was used to identify voxels that were significantly activated by each task and to distinguish between activations that were due to different cognitive components of the tasks (*7, 22*). Activated voxels in frontal cortex were assigned to two dorsal regions of interest (the superior frontal sulcus and the precentral sulcus) and two ventral regions of interest (middle frontal cortex and inferior frontal cortex) based on anatomic criteria (*23*).

All subjects showed sustained activity during spatial working memory delays (regressor 6) (Fig. 1) in dorsal frontal cortex. Within dorsal frontal cortex, all subjects had a more extensive region of sustained activity in the superior frontal sulcus than in the precentral sulcus. Across subjects, 66% (median) of dorsal frontal cortex demonstrating sustained activity was in the superior frontal sulcus. By contrast, 69% of dorsal frontal cortex demonstrating only transient activity during the presentation of visual stimuli (regressor 1) was in the precentral sulcus, just posterior and lateral to the sustained activation in the superior frontal sulcus. This difference between the localizations of sustained and transient activity demonstrates two functionally distinct areas in the dorsal frontal cortex ($P < 0.002$ for response-type by sulcus interaction). Thus, the superior frontal sulcus meets our first criterion for a spatial working memory area by demonstrating sustained activity during delays.

To determine whether the region showing sustained activity in the superior frontal sulcus is specifically involved in spatial working memory rather than more generally in any working memory task, fMRI data were obtained ($n = 7$) during performance of a face working memory task that used identical stimuli, timing, and motor response, as did the spatial working memory task (Fig. 1). The superior frontal sulcus bilaterally showed significantly more sustained activity during spatial than during face working memory delays (5.4 cm^3 versus 2.3 cm^3 of cortex, 0.48% versus 0.37% mean signal change, respectively, summed across both hemispheres; $P < 0.01$ for both spatial extent and signal intensity change) (Fig. 2). By contrast, left inferior frontal cortex showed significantly more sustained activity during face than during spatial working memory delays (4.9 cm^3 versus 2.7 cm^3, 0.44% versus 0.21%, for left inferior frontal cortex; $P < 0.05$ for both comparisons). The left middle frontal cortex showed significantly more cortical area activated by face working memory than by spatial working memory (8.9 cm^3 versus 5.7 cm^3; $P < 0.05$), but the difference in activation based on the change in mean signal intensity failed to reach significance (0.36% versus 0.22%; $P > 0.1$). The difference between face and spatial working memory in the right ventral frontal cortex failed to reach significance for the middle or the inferior regions (*24*). There were no hemisphere effects for spatial working memory ($P > 0.1$ for superior, middle, and inferior frontal regions) (*25*). This comparison of spatial and face working memory demonstrates a double dissociation (region by task interaction; $P < 0.01$ for both spatial extent and signal intensity change) with the superior frontal sulcus showing more sustained activity during spatial working memory delays and with the left inferior frontal region showing more sustained activity during face working memory delays. This comparison also demonstrates that the sustained activity in the superior frontal sulcus cannot be attributed to preparation for a motor response because the spatial and face working memory tasks required the same types of responses after delays. In short, the results of this comparison show that the superior frontal sulcus meets our second and third criteria for a spatial working memory area.

To determine whether this region in the superior frontal sulcus is distinct from the FEF, we compared the locations of activations during the spatial working memory task with activations evoked during a saccadic eye movement task in the same scanning session ($n = 4$) (Fig. 3). As expected from previous results (*17, 18*), most of the dorsal frontal cortex activated during the eye movement task (85% median across subjects) was in the precentral sulcus, thereby identifying the location of the FEF in each subject and distinguishing it from the region of sustained activity in the superior frontal sulcus (Fig. 3). In three of four subjects, the centroid of sustained activity was significantly anterior to the centroid of eye movement–related activity in both right and left hemispheres (mean difference = 8.5 mm; $P < 0.005$ in all cases). The fourth subject showed the same trend, but the difference (3.5 mm) did not reach statistical significance because the areas of sustained activity were less extensive than in the other subjects. In addition, the face task was designed to require the same types of eye movements as the spatial task and yet showed significantly less sustained activity in the superior frontal sulcus, further supporting our assertion that the sustained activity there is related to spatial working memory and not to oculomotor control. Thus, the region of sustained activity in the superior frontal sulcus is distinct from the FEF, thereby meeting our fourth criterion for a spatial working memory area (*26*).

The results of the current fMRI study indicate that there is a functional area in the superior frontal sulcus that shows sustained activity during spatial working memory delays. Sustained activity in this region was greater during spatial than during face working memory delays, demonstrating that the superior frontal sulcus plays a predominant role in spatial working mem-

ory compared with object working memory. Because these two tasks were matched for motor preparation and motor response, sustained activity in the superior frontal sulcus cannot be attributed to manual motor function. Moreover, this area is distinct from, and just anterior to, the human FEF, demonstrating a correspondence to the topological relationship that has been

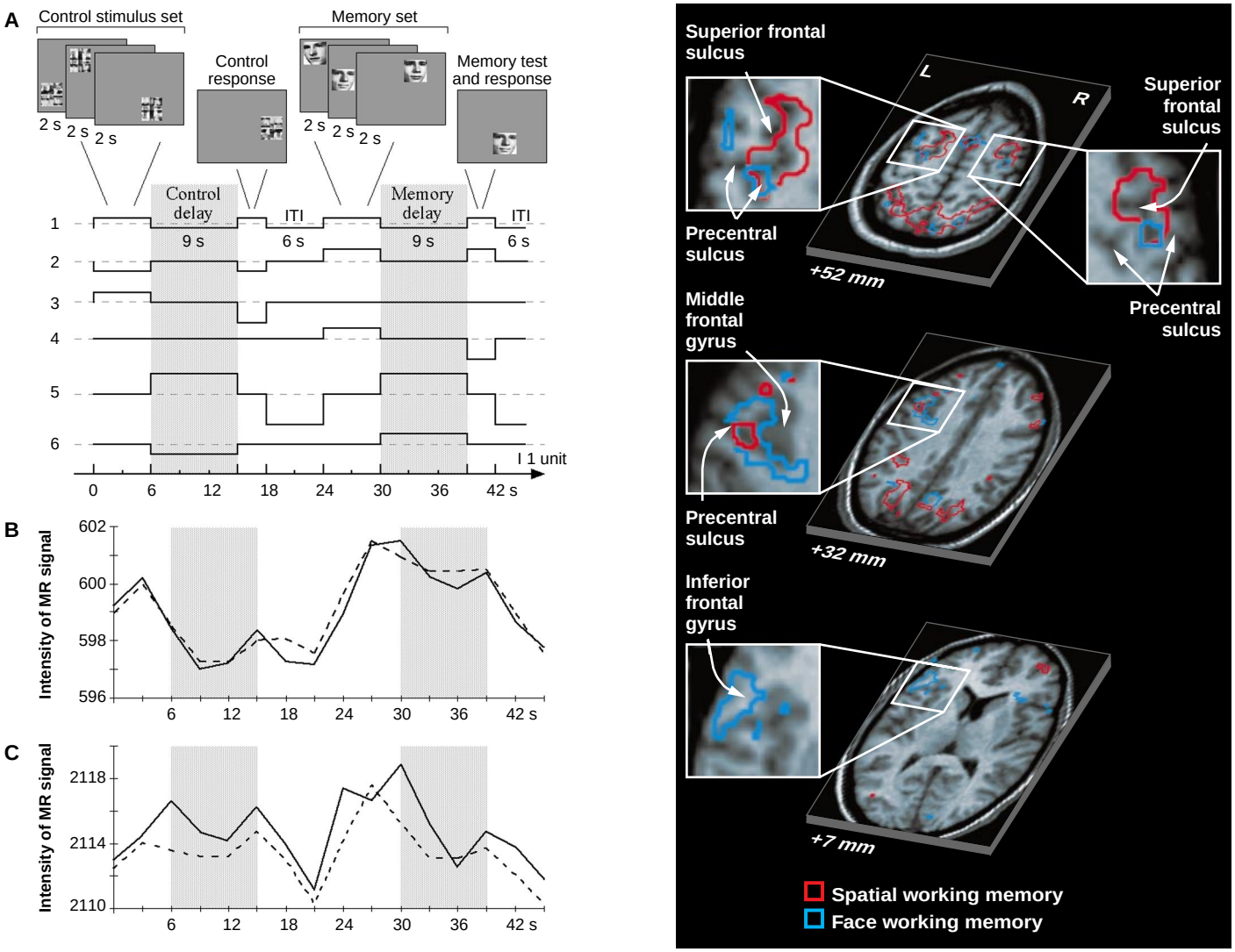

Fig. 1 (**left**). (**A**) A face and a spatial location working memory task, which used the same stimuli and were equated for difficulty. Subjects saw a series of three faces, each presented for 2 s in a different location on the screen, followed by a 9-s memory delay. Then a single test face appeared in some location on the screen for 3 s, followed by a 6-s intertrial interval. Before each series, subjects were instructed to remember the locations or the identities of the three faces in the memory set. For the spatial task, the subject indicated with a left or right button press whether the test location was the same as one of the three locations presented in the memory set, regardless of which face marked that location. For the face memory task, the subject indicated whether the test face was the same as one of the three faces observed in the memory set, regardless of the location where the face appeared. For the sensorimotor control task, scrambled faces appeared (control stimulus set), and when the fourth scrambled picture appeared after the delay, subjects pressed both buttons (control response). For the control and working memory tasks, subjects were instructed to look directly at each picture as it appeared and to avoid moving their eyes during delay. All subjects gave written informed consent. fMRI time series data were analyzed by multiple regression (*7, 22*). Contrasts between task components are shown below the task diagram: (1) visual stimulation versus no visual stimulation; (2) memory stimuli versus control stimuli; (3) control stimulus set versus control response; (4) memory stimulus set versus test stimulus and response; (5) delays during anticipation of response versus intertrial intervals; (6) memory delays versus control delays. Contrasts were constructed a priori so the sum of values over the time series equals zero and the crossproducts of all pairs of contrasts equal zero, demonstrating orthogonality. These contrasts make it possible to obtain independent estimates of activity levels during every phase of the task. The specific contrasts were chosen to test the hypotheses that motivated this study. Each time series was convolved with a Gaussian model of the hemodynamic response to produce the six regressors used in the analysis. Multiple regression simultaneously calculates a weighting coefficient for each regressor so the sum of the regressors multiplied by their weighting coefficients provides the best fit to the data. (**B** and **C**) fMRI time series data (solid line) and the corresponding fitted response functions (dashed line) from regression analysis. (B) One voxel in the superior frontal sulcus showing sustained activity during the working memory delay (regression coefficients: 2.06*, 0.75*, 0.43, 0.32, 0.23*, 1.43*). (C) One voxel from the precentral sulcus showing only transient activity during stimulus presentation (regression coefficients: 3.56*, 0.79, −0.73, 1.14, 0.57*, −0.03). Asterisks mark regressors that account for a significant portion of the variance in that voxel independent of the variance attributable to the other regressors. **Fig. 2** (**right**). Areas with significant sustained activity in a single subject during the working memory delay for faces (blue outline) and for spatial locations (red outline) overlaid onto the subject's Talairach normalized anatomical MR image. Level above the bicommissural plane is indicated for each axial section. Twenty-one contiguous axial slices were obtained in series of 88 scans each (repeat time, 3 s; echo time, 40 ms; flip angle 90°). Slices were either 5 or 6 mm thick as needed to cover the entire brain. L, left; R, right.

described in the monkey between a frontal cortical area for spatial working memory and the FEF [for example, see (*27*)]. However, in the monkey the frontal cortical area for spatial working memory is within the principal sulcus and surrounding cortex just anterior to the FEF, which is on the anterior bank of the arcuate sulcus. Our data indicate that the homologous functional areas in the human brain are in the superior frontal and precentral sulci, respectively, and thus occupy a relatively more superior and posterior location. The location of this spatial working memory area in humans, superior and posterior to BA 46, may explain why it was not recognized in previous studies.

This difference in functional neuroanatomy between monkeys and humans suggests that the spatial working memory area and the FEF in humans have been displaced by the expansion of the more inferior and anterior portions of the lateral prefrontal cortex over the course of primate brain evolution. Comparison of monkey and human functional neuroanatomy indicates that displacement of regions in the human brain may be due to the emergence of phylogenetically newer regions. For example, extrastriate visual areas specialized for spatial vision have a more superior location in parietal cortex in the human than in the monkey, whereas those specialized for object vision have a more inferior location in temporal cortex [for review, see (*28*)]. Displacement of both sets of visual areas away from the posterior perisylvian cortex may be related to the emergence of language mediated by phylogenetically newer cortical areas such as BA 39 and BA 40. The specific displacement of functional areas in dorsal frontal cortex that we have identified may likewise be related to the emergence of other cognitive abilities, either distinctively human or greatly elaborated in humans, mediated by new functional areas in prefrontal cortex. Examples of these abilities may include abstract reasoning, complex problem solving, and planning for the future, consistent with behavioral symptoms in patients with frontal lobe damage (*29*).

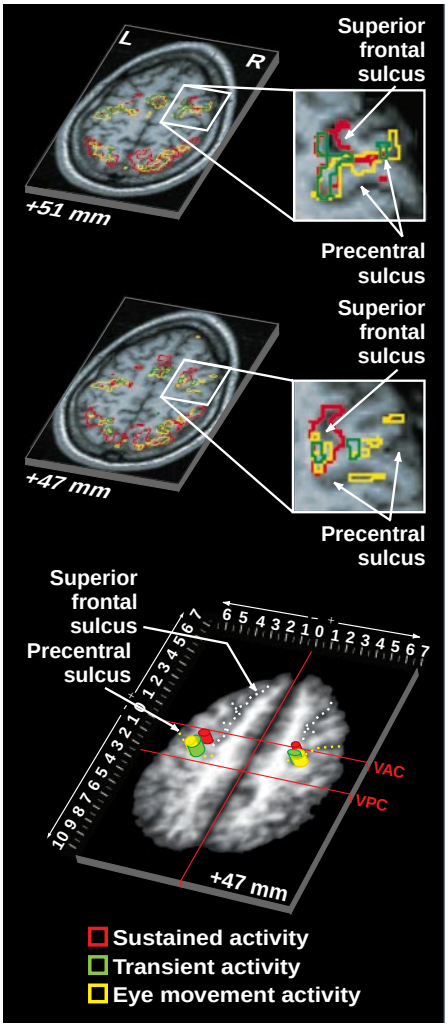

Fig. 3. (Top) Results from a single subject for the spatial working memory task and the saccadic eye movement task. For the eye movement task, subjects made a random series of horizontal visually guided saccades with an average amplitude of 12° (range, 5° to 20°). Subjects performed saccades during 15-s blocks interleaved with 15-s blocks in which subjects saw a blank screen and were instructed to look at the center of the screen and avoid moving their eyes. Yellow outline indicates the region activated by the saccadic eye movement task. Green outline indicates the region activated transiently during the presentation of the stimuli in the working memory task. Red outline indicates the region that showed sustained activation during the working memory delay. (Bottom) White dotted line marks superior frontal sulcus. Yellow dotted line marks precentral sulcus. Mean locations of the local maximum *Z*-scores for saccadic eye movements (yellow) and for transient (green) and sustained (red) activity during the spatial working memory task are shown on the average of the Talairach normalized anatomical MRI scans from the four subjects who performed both the spatial working memory and the saccadic eye movement tasks. Center and radii of the cylinders indicate mean and standard deviations of the locations of local maxima, respectively. Saccades: left, −33 ± 8 , −16 ± 9, +46 ± 5; right, +29 ± 8, −9 ± 4, +45 ± 5. Transient: −35 ± 6 , −17 ± 7, +45 ± 6; +30 ± 8, −8 ± 7, +46 ± 4. Sustained: −31 ± 7, −7 ± 5, +46 ± 4; +27 ± 5, −5 ± 4, +49 ± 5. Note that the sustained spatial working memory activation is just anterior to the transient and saccade activations. L, left; R, right. VAC and VPC, vertical planes passing through the anterior and posterior commissures, respectively.

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10. In the monkey, physiological maps of the FEF based on single-unit activity (*30*) and low-threshold microstimulation (*31*) demonstrated that the FEF occupies the anterior bank of the arcuate sulcus, from the lip of the prearcuate gyrus to the floor of the sulcus, a region generally considered to be BA 8. Stanton *et al*. (*32*) showed that the FEF can also be identified histologically as the region in the anterior bank of the arcuate sulcus containing the highest concentration of large layer V pyramidal cells. They considered it to be a separate cytoarchitectonic area that straddles the border between BA 6 and BA 8.
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23. Both precentral and superior frontal sulci in each hemisphere were anatomically defined in each subject by using their Talairach normalized axial structural MR images from 39 to 55 mm above the bicommissural plane, based on the extent of FEF activation in previous studies (*17*). The region of interest delineating the precentral sulcus included 6 mm of the cortex on each bank of the sulcus from, and including, the junction with the superior frontal sulcus to the lateral convexity. The region of interest delineating the superior frontal sulcus included 6 mm of the cortex along each of the banks of the sulcus from the limit of the precentral region of interest forward to the anterior convexity. The inferior and middle frontal cortical regions of interest were broadly defined as all cortex anterior to the 6 mm of cortex on the anterior bank of the precentral sulcus from 38 to 16 mm above the bicommissural plane for the middle frontal cortex and from 15 mm above to 12 mm below the bicommissural plane for the inferior frontal cortex. The division between middle and inferior frontal regions was chosen to be midway between the mean locations of all areas reported as BA 45 or 47 and all areas reported as BA 9 or 46 in recent working memory imaging reviews (*3*, *16*). These ventral regions were defined once for all subjects by using the average of all 11 subjects' structural MR images. Thus,

this analysis did not include medial and orbital frontal regions; neither of these regions showed content-specific sustained activity.
24. In the right hemisphere, the differences between the spatial extents of sustained activation for face and spatial working memory were 6.1 and 3.3 cm^3 and 0.31 and 0.23% signal change in the middle frontal cortex, and 1.8 and 1.8 cm^3 and 0.39 and 0.25% in the inferior frontal cortex (medians across subjects; $P > 0.1$ for all comparisons).
25. Others (*2*, *4*, *20*) have also directly contrasted object and spatial working memory and, as we did, they found evidence for domain specificity in prefrontal cortex. However, their evidence indicated that domain specificity is primarily a hemispheric laterality effect, with left frontal regions specialized for object working memory and right frontal regions specialized for spatial working memory. In our previous studies of face (*7*, *14*) and in this study of spatial working memory, we found activations with similar coordinates, but the activations tended to be bilateral. Smith *et al.* (*2*) attributed the left lateralization of object working memory to rehearsal of a symbolically or linguistically encoded representation of the object. In this study and previously (*14*) we have seen left lateralization for face working memory under conditions that encouraged more symbolic or verbal encoding of faces, but we have also seen right lateralization under conditions that allowed for more image-based encoding (*14*, *15*). We argue that laterality effects in visual memory may be influenced by a variety of factors, such as memory set size, retention interval length, and item familiarity, all of which may affect the extent to which subjects engage in symbolic or verbal encoding and rehearsal.
26. Whereas activation in the superior frontal sulcus was overwhelmingly associated with sustained activity during spatial working memory (89% of activated cortex), activation in the precentral sulcus was a mixture of voxels demonstrating sustained (53%) and transient (43%) activity during working memory as well as saccade-related activity (74%; median percentages for four subjects include overlap). The presence of both sustained and transient activity in the precentral sulcus at the level of the FEF is consistent with results of physiological studies in monkeys that have demonstrated that some FEF neurons show sustained activity during fixation or during the delays in memory-guided saccade tasks, and others show transient activity during saccadic and pursuit eye movements (*27, 33*). Transient activity observed in the precentral sulcus is likely to be related to eye movements to the locations where pictures appeared, because subjects were instructed to look directly at each picture as it was shown and to avoid moving their eyes during delay periods. Regions of the precentral sulcus activated by the spatial working memory task but not by the saccadic eye movement task may be related to mechanisms of oculomotor control other than those controlling horizontal saccades. However, it is highly unlikely that sustained activity in the superior frontal sulcus is related to oculomotor control because current and previous eye movement studies in humans have localized activity related to visually guided saccades, self-paced saccades, smooth pursuit, and fixation within or posterior to the precentral sulcus and not within the superior frontal sulcus (*17*, *18*).
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Propagating Activity Patterns in Large-Scale Inhibitory Neuronal Networks

J. Rinzel,* D. Terman, X.-J. Wang, B. Ermentrout

The propagation of activity is studied in a spatially structured network model of γ-aminobutyric acid–containing (GABAergic) neurons exhibiting postinhibitory rebound. In contrast to excitatory-coupled networks, recruitment spreads very slowly because cells fire only after the postsynaptic conductance decays, and with two possible propagation modes. If the connection strength decreases monotonically with distance (on-center), then propagation occurs in a discontinuous manner. If the self- and nearby connections are absent (off-center), propagation can proceed smoothly. Modest changes in the synaptic reversal potential can result in depolarization-mediated waves that are 25 times faster. Functional and developmental roles for these behaviors and implications for thalamic circuitry are suggested.

Reciprocally inhibitory neural circuits are known to be a fundamental substrate for rhythmogenesis in animals' central pattern generator systems (*1*). Subnetworks of mutually connected neurons were also found in various systems of the mammalian brain, such as the hippocampus, neocortex, and thalamus (*2*). The operation and significance of such interneuronal networks are not well understood. Recent studies showed that synaptic inhibition can synchronize cells, thereby contributing to the generation of large-scale rhythmic activities observed in the thalamus and hippocampus (*3*–*5*). Another possible function is disinhibition, where the interneurons projecting to a principal neuron are selectively inhibited by another group of interneurons. This mechanism would require specialized connectivity patterns between mutually inhibitory cells and with principal neurons (on-center or off-center), which are generally difficult to identify by anatomical and electrophysiological experiments. In the present work, we demonstrate by model simulations that the spatiotemporal activity patterns of an interneuronal population display a number of unique dynamic features. The qualitative characteristics dramatically depend on, and therefore can subserve as predictive indicators of, the underlying synaptic circuit architecture.

As a specific example, the thalamocortical (TC) relay neurons receive powerful recurrent inhibition from GABAergic cells in the thalamic reticular nucleus (RE). How this feedback inhibition is organized spatially will determine in part its role in the sensory information processing within the thalamus (*6*). The RE-mediated synaptic inhibition is also critically involved in the generation of the synchronous thalamic spindle oscillations during light sleep (*3*). Moreover, in the thalamic slice models one finds spatiotemporally organized activity in the form of propagating waves, which are waves that move very slowly (~1 mm/s), on each cycle recruiting additional inactive cells in a distinctive, non-smooth, "lurching" manner (*7, 8*). In this paper, we consider a spatially structured network of GABAergic neurons, which may be interpreted as a reduction from a two-population thalamic network. The idea is that because the TC-to-RE projection is topographic and acts via rapid glutamate receptors of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) type, the excitation in a TC cell would result in a barrage of inhibitory postsynaptic potentials (IPSPs) in the neighboring TC cells (through the disynaptic TC-RE-TC loop). In this idealized view (of the isolated thalamic circuit), the TC cell layer acts ef-

J. Rinzel, Mathematical Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892, USA.
D. Terman, Department of Mathematics, Ohio State University, Columbus, OH 43210, USA.
X.-J. Wang, Center for Complex Systems and Department of Physics, Brandeis University, Waltham, MA 02254, USA.
B. Ermentrout, Department of Mathematics, University of Pittsburgh, Pittsburgh, PA 15260, USA.

*Present address: Center for Neural Science and Courant Institute of Mathematical Sciences, New York University, New York, NY 10003, USA. To whom correspondence should be addressed at the Center for Neural Science, 4 Washington Place, Room 809, New York University, New York, NY 10003, USA. E-mail: rinzel@cns.nyu.edu