

Stimulus–Response Incompatibility Activates Cortex Proximate to Three Eye Fields

Elisha P. Merriam,^{*1} Carol L. Colby,^{*} Keith R. Thulborn,[†] Beatriz Luna,[‡]
Carl R. Olson,^{*} and John A. Sweeney[‡]

^{*}Department of Neuroscience, [‡]Department of Psychiatry, and [†]Department of Radiology, The Center for the Neural Basis of Cognition, University of Pittsburgh, Pittsburgh, Pennsylvania 15213

Received July 6, 2000; published online March 19, 2001

We used functional magnetic resonance imaging (fMRI) to investigate cortical activation during the performance of three oculomotor tasks that impose increasing levels of cognitive demand. (1) In a visually guided saccade (VGS) task, subjects made saccades to flashed targets. (2) In a compatible task, subjects made leftward and rightward saccades in response to foveal presentation of the uppercase words “LEFT” or “RIGHT.” (3) In a mixed task, subjects made rightward saccades in response to the lowercase word “left” and leftward saccades in response to the lowercase word “right” on incompatible trials (60%). The remaining 40% of trials required compatible responses to uppercase words. The VGS and compatible tasks, when compared to fixation, activated the three cortical eye fields: the supplementary eye field (SEF), the frontal eye field (FEF), and the parietal eye field (PEF). The mixed task, when compared to the compatible task, activated three additional cortical regions proximate to the three eye fields: (1) rostral to the SEF in medial frontal cortex; (2) rostral to the FEF in dorsolateral prefrontal cortex (DLPFC); (3) rostral and lateral to the PEF in posterior parietal cortex. These areas may contribute to the suppression of prepotent responses and in holding novel visuomotor associations in working memory. © 2001 Academic Press

INTRODUCTION

A fundamental question regarding the nature of voluntary motor control is whether different cortical systems are involved in generating a given response depending on the conditions under which the response is initiated. For example, studies have shown that a specific set of brain regions are activated

during the early stages of learning sequences of movements and that the regions recruited by a motor task change during learning (Sakai *et al.*, 1998). Stimulus–response (S-R) incompatibility tasks are useful for probing cognitive processes subserving voluntary response generation because stimulus–response relationships of varying complexity can be used to elicit the same motor response. Extensive behavioral and electropsychophysical research has been dedicated to examining motor responses generated during S-R incompatibility conditions (Christensen *et al.*, 1996), though little is known about the cortical basis of such cognitive functions.

Previous functional imaging studies of S-R incompatibility, or response conflict, have consistently implicated the anterior cingulate cortex (Paus *et al.*, 1993) and the inferior frontal gyrus (Taylor *et al.*, 1997) as sites of executive function during task performance. However, the effects of S-R incompatibility on cortical motor areas are not yet well characterized. In the present study, we used fMRI to investigate activation during the performance of an oculomotor S-R incompatibility task. In our S-R incompatibility task, automatic response tendencies were inappropriate and conflicted with the correct responses. We contrasted activation in this task to activation in two control tasks that were matched for number of saccades and orbital position, but that required responses compatible with the stimuli.

Anatomical studies in monkeys (Cavada and Goldman-Rakic, 1989; Bates and Goldman-Rakic, 1993) have shown that subregions in lateral frontal cortex are densely interconnected with specific regions of medial frontal and parietal cortex. These regions together may comprise a circuit for the higher order control of response generation. We therefore predicted that the spatial resolution of fMRI would permit us to selectively activate this circuit. Specifically, we hypothesized that distinct regions proximate to the well defined cortical eye fields (Luna *et*

¹ To whom correspondence should be addressed. 115 Mellon Institute, 4400 Fifth Avenue, Pittsburgh, PA 15213. E-mail: eli@cnbc.cmu.edu.

al., 1998) would be preferentially activated by the S-R incompatibility task because of its greater demands on both attentional and motor control systems.

MATERIALS AND METHODS

Subjects and Behavioral Tasks

Subjects were eleven right-handed volunteers (seven female; mean age 25.4 years (SD = 6.1)). Written consent and experimental procedures for this study complied with the Code of Ethics of the World Medical Association (1964 Declaration of Helsinki). In a pre-scan session, subjects were acclimated to the confinement of the scanner environment and familiarized with the tasks. All subjects were experienced in performing eye movement and cognitive tasks in a laboratory setting, and had practiced performing the three tasks for 30 min during the prescan session.

Visually guided saccade task. Subjects fixated a central circular stimulus (0.5° of visual angle) for 750 ms. When the central stimulus was extinguished, a white circular target subtending 1.0° of visual angle appeared unpredictably at locations 8° to the right or left. Subjects were instructed to look toward these targets. The targets remained present until the central stimulus reappeared 750 ms later, cueing subjects to resume central fixation.

Compatible task. The compatible task required subjects to generate eye movements in response to semantic cues. Subjects fixated a central circular target (0.5° of visual angle) for 750 ms after which the words "LEFT" or "RIGHT" (uppercase white letters) appeared centrally for 100 ms. Subjects were instructed to execute a saccade in the direction indicated toward one of two static targets 8° to the left or right of fixation. After 750 ms, the central target reappeared and subjects fixated it.

Mixed task. In this task, subjects were instructed to execute a saccade in the direction opposite to that indicated by lowercase words ("right" and "left"). These incompatible trials occurred 60% of the time and were randomly intermixed with compatible trials. Pilot behavioral testing indicated that a 60/40 ratio of incompatible/compatible trials maximized reaction time on incompatible trials.

The experimental design consisted of 10.5 cycles of alternating 30 s blocks of two tasks. Three experiments were performed on each subject, contrasting the VGS task with fixation, the compatible task with fixation, and the mixed task with the compatible task.

Image Acquisition and Data Analysis

Functional images were acquired with gradient-echo, resonant echoplanar imaging using a 1.5 Tesla whole

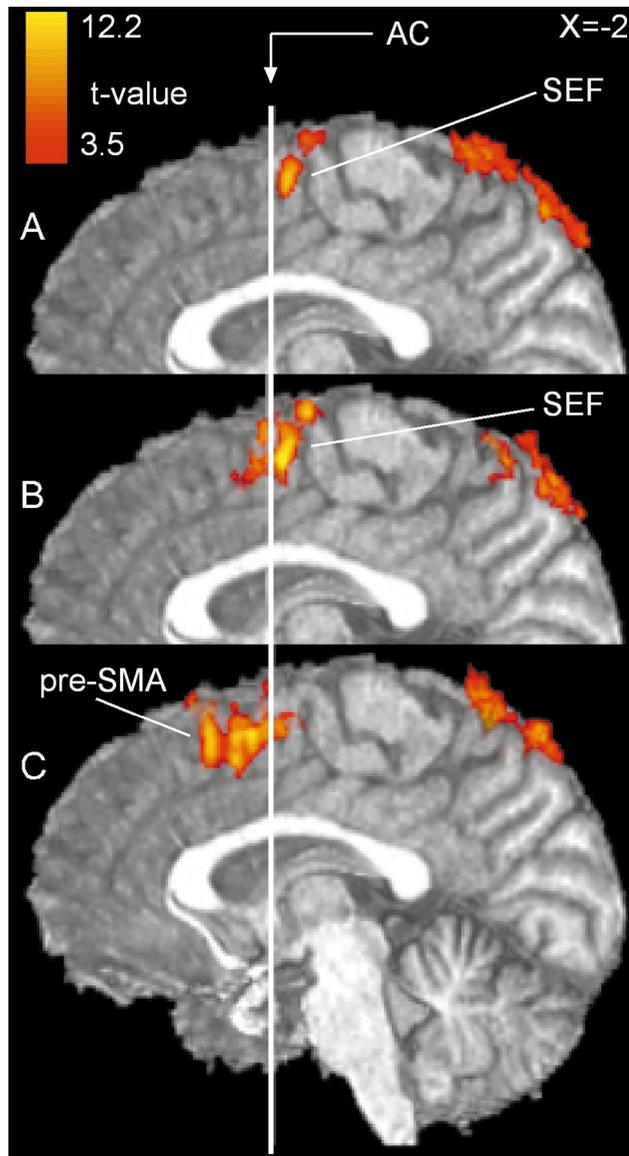


FIG. 1. Group average map of activation in dorsal midline neocortex during three task comparisons: (A) visually guided saccade task vs fixation; (B) compatible response task vs fixation; (C) mixed vs compatible tasks. Functional data from 11 subjects are superimposed on a single subject's anatomy. Threshold for activation was $t \geq 3.5$. AC, anterior commissure; SEF, supplementary eye field; pre-SMA, presupplementary motor area.

body scanner (Signa, General Electric Medical Systems). Seven axial slices were acquired from the dorsal surface of the brain to the superior aspect of the corpus callosum, which included all cortical eye fields and other regions of interest. Scanning parameters were: TE = 50 ms; flip angle = 90° ; single shot; FOV = 40×20 cm; acquisition matrix = 128×64 , voxel size = $3.125 \times 3.125 \times 5$ mm with 1 mm gap; TR = 1.5 s; 420 images/slice. Locally developed FIASCO software (Eddy *et al.*, 1996) was used

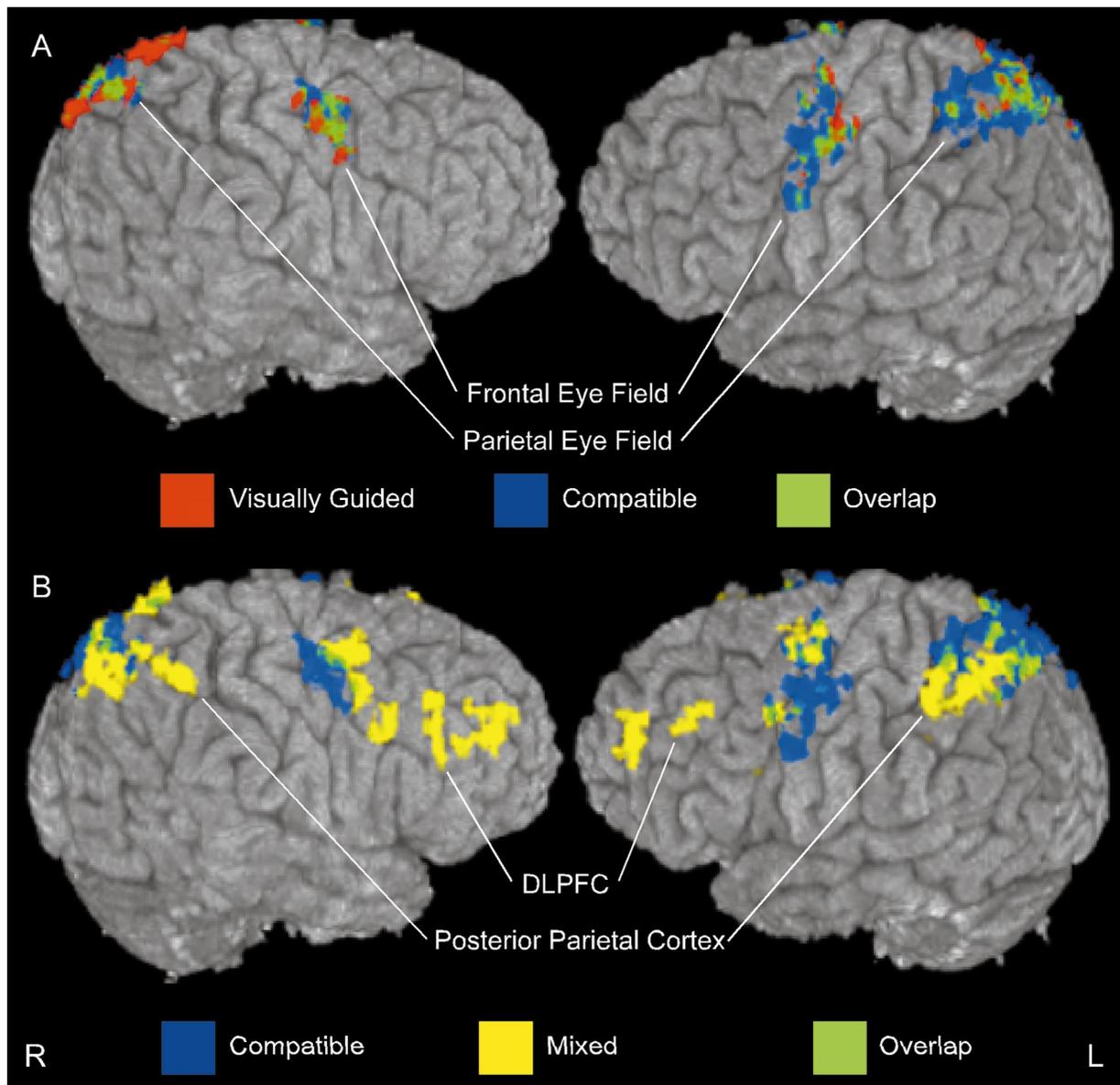


FIG. 2. 3-D surface renderings of group average activation maps for three task comparisons. (A) Visually guided saccade and compatible tasks vs fixation; (B) compatible task vs fixation and mixed vs compatible tasks. Functional data from 11 subjects are superimposed over a single subject's anatomy. Threshold for activation was $t \geq 3.5$. DLPFC, dorsolateral prefrontal cortex.

to deghost, correct for in-plane head motion, reconstruct images, and to perform voxelwise t tests comparing the conditions of interest. Using public-domain AFNI software (Cox *et al.*, 1996), activation maps of individual subjects were resampled to 1 mm^3 using nearest neighbor interpolation, overlaid onto high-resolution structural images, transformed into Talairach space, and smoothed with a small 3-D Gaussian filter with a sigma of 0.7 mm. Individual activation maps were then averaged across subjects to generate group activation maps. Group t maps were thresholded for significance using a cluster-size method to reduce the risk of Type 1 errors associated with

multiple comparisons (Forman *et al.*, 1995). A cluster size of 8 contiguous voxels over a volume of 200 mm^3 with a t value threshold of 3.5 was used as a statistical significance criterion. Thresholded activation maps were projected onto 3-D renderings of the cortical surface for anatomical localization and visualization.

RESULTS AND DISCUSSION

Comparison of visually guided saccades with fixation revealed activation in all three cortical eye fields: SEF (Fig. 1A), FEF, and PEF (Fig. 2A, red and green). The

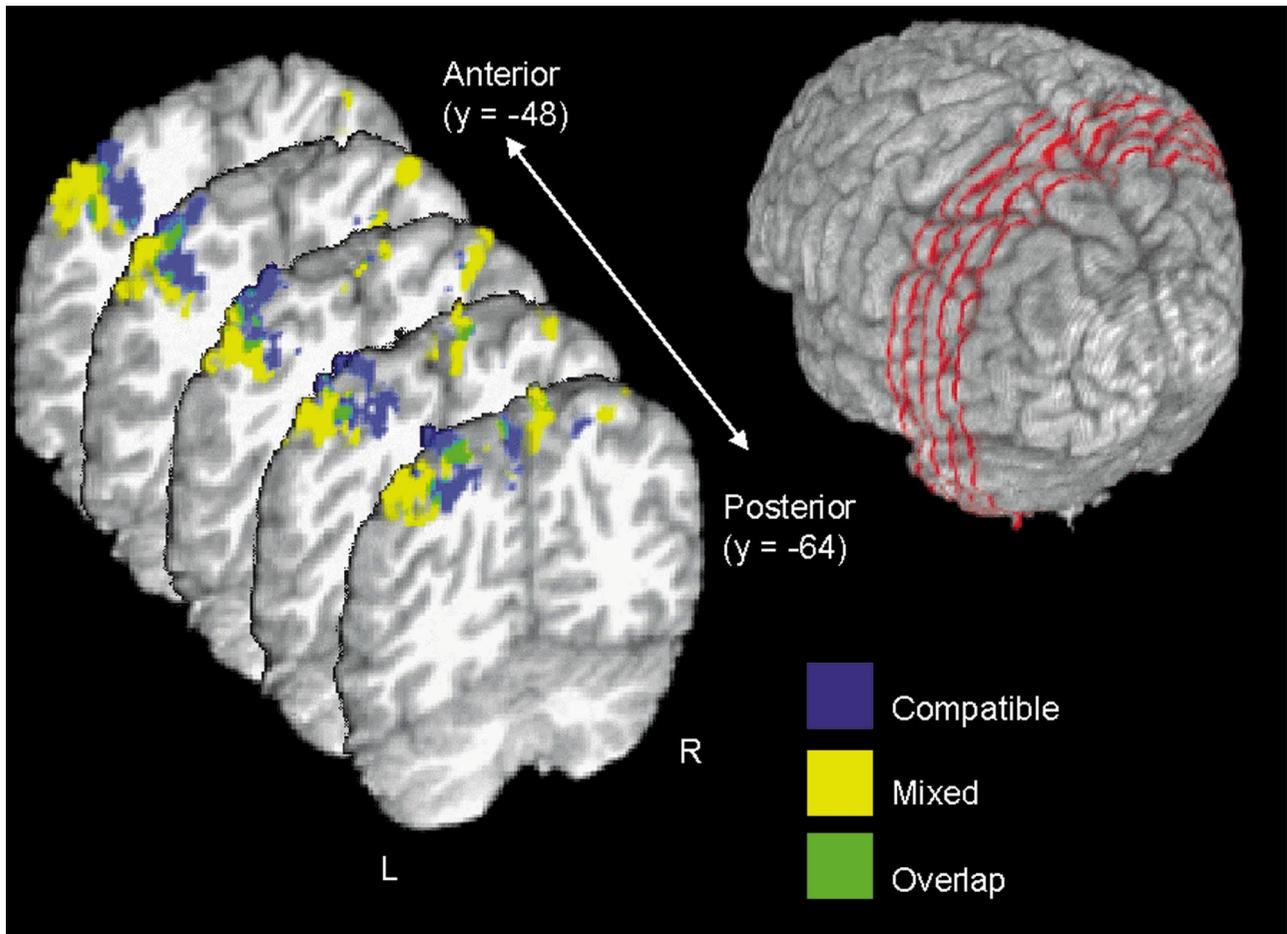


FIG. 3. Coronal views ($-48 > y > -64$) of group average activation maps showing parietal activation from the compatible vs fixation comparison (blue) and the mixed vs compatible comparison (yellow). Regions of overlap are shown in green. Threshold for activation was $t \geq 3.5$.

same zones were activated by the compatible task when compared to fixation (Fig. 1B; Fig. 2A, blue and green; Table 1).²

The mixed task, as compared to the compatible task, elicited additional activation in cortex proximate to each of the three eye fields (Table 1). In medial frontal cortex, the locus of activation was immediately rostral to the SEF, rostral to the anterior commissure, and superior to the cingulate sulcus (Fig. 1C). On the lateral surface of frontal cortex, the locus of activation was in the rostral aspect of the middle frontal gyrus, well anterior to the FEF activation observed in the

compatible and VGS paradigms (Fig. 2B). In parietal cortex, the locus of activation was just lateral to the PEF (Fig. 3, yellow and green) as defined by the compatible task (Fig. 3, blue and green). Parietal activation also extended farther rostrally in the mixed task relative to the compatible task (Fig. 2B).

These results demonstrate that performance of eye movements during the mixed task activates regions of cortex proximate to each of the cortical eye fields (FEF, SEF, and PEF). In lateral frontal cortex, activation in the mixed task was rostral to the FEF, as mapped by the compatible and VGS tasks. This activation in dorsolateral prefrontal cortex (DLPFC) may be related to the need to suppress prepotent responses on incompatible trials, a possibility supported by clinical evidence (Guitton *et al.*, 1985; Perret, 1974). Furthermore, imaging studies have reported similar activations in frontal cortex during other voluntary response suppression

² It is noteworthy that FEF activation in the compatible task extended ventrally into the inferior branch of the left precentral sulcus (Fig. 2a). This region is dorsal and posterior to Broca's area, and its activation may reflect engagement of left hemisphere language systems in the interpretation of semantic cues for oculomotor responses.

TABLE 1

Localization of Active Regions in Dorsal Cortex in Talairach Space during Performance of the Visually Guided Saccade Task, the Compatible Task, and the Mixed Task

	Visually guided vs fixation		Compatible vs fixation		Mixed vs compatible	
	Left	Right	Left	Right	Left	Right
FEF	-47, -9, 52	42, -8, 57	-32, -7, 51	41, -8, 56	-31, -3, 63	33, 2, 62
DLPFC	—	—	—	—	-36, 52, 30	33, 49, 31
PEF	-21, -71, 53	17, -75, 54	-20, -74, 54	17, -75, 54	-26, -75, 49	19, -81, 47
PPC _{RL}	—	—	—	—	-39, -57, 50	40, -52, 55
SEF	-2, -5, 58	—	-2, -4, 55	—	—	—
Pre-SMA	—	—	—	—	0, 6, 53	—

Note. FEF, frontal eye field; DLPFC, dorsolateral prefrontal cortex; PEF, parietal eye field; PPC_{RL}, rostromedial posterior parietal cortex; SEF, supplementary eye field; pre-SMA, presupplementary motor area.

paradigms (Konishi *et al.*, 1999; Jonides *et al.*, 1998; Sweeney *et al.*, 1996).

Because incompatible trials were intermixed with compatible trials, activation in DLPFC may also reflect the requirement to attend to and hold in working memory two aspects of the cue (word case and semantic content) and their associated response requirements. This possibility is consistent with previous reports in the single unit literature of rule-dependent activity in monkey DLPFC (White and Wise, 1999; Asaad *et al.*, 2000). The zone of activation coincided with locations in DLPFC thought to play a role in the executive control of spatial cognitive and motor processes, particularly in maintaining sensory information and response plans over time (Fuster, 1992; Sweeney *et al.*, 1996; Courtney *et al.*, 1997). Further studies are needed to determine the degree to which activation in this region reflects the suppression of task-inappropriate responses rather than a more general role in the guidance of motor output according to complex rules.

In medial frontal cortex, activation in the mixed task was rostral to the SEF in a region that coincides with the presupplementary motor area (pre-SMA; Picard and Strick, 1996). This area has been activated in previous imaging studies during both manual and oculomotor sequence learning tasks (Kawashima *et al.*, 1998; Boeker *et al.*, 1998; Petit *et al.*, 1996; Hikosaka *et al.*, 1996; Sakai *et al.*, 1998) and during the performance of tasks requiring a delayed response (Petit *et al.*, 1999; Sweeney *et al.*, 1998). The pre-SMA is thought to play a central role in the acquisition of novel visuomotor associations (Hikosaka *et al.*, 1999). The activation observed here may therefore reflect the learning and use of novel associations between the lower case stimuli and the task appropriate but incompatible oculomotor responses.

In parietal cortex, activation during the VGS and compatible tasks coincides with areas in parietal cortex in and around the intraparietal sulcus that have been

reported in earlier fMRI studies of eye movements and attention (Corbetta *et al.*, 1999; Luna *et al.*, 1998). This region may be functionally comparable to the lateral intraparietal area (LIP) in the monkey (Colby and Goldberg, 1999), which exhibits both visual and saccade-related activity. However, recent work has placed human LIP near the medial surface of superior parietal cortex (Sereno *et al.*, 2000) and the exact relationship between subregions within human and monkey parietal cortex is still unclear. Previous imaging studies have emphasized the degree to which activation in parietal cortex generalizes over a variety of attention tasks (Wojciulik and Kanwisher, 1999). Activation in the mixed task was clearly rostral and lateral to that seen in the two control paradigms. This is the first demonstration of clear segregations within parietal cortex of regions differentially activated when tasks vary in voluntary attentional demands.

Anatomic and neurophysiologic studies in monkeys indicate that multiple cortical pathways are involved in controlling motor output. One pathway, comprising LIP, SEF, and FEF, is specialized for controlling eye movements (Bruce, 1990). Adjacent to each of these fields is a cortical district that participates in more complex cognitive functions: area 7a (Andersen *et al.*, 1998), pre-SMA (Tanji, 1996), and DLPFC (Funahashi *et al.*, 1991). These areas are densely interconnected (Cavada and Goldman-Rakic, 1989; Bates and Goldman-Rakic, 1993; Luppino *et al.*, 1993), and may comprise a higher-order circuit for guiding eye movements based on internal plans and decisions (Goldman-Rakic, 1988). Our results suggest that a parallel system exists in humans.

ACKNOWLEDGMENTS

We thank Drs. William Eddy, Christopher Genovese, and Joel Welling and other members of the Pittsburgh fMRI Data Analysis Group for developing brain image analysis methodologies used in

this study. We also thank the staff of the University of Pittsburgh MR Research Center for their assistance. This work was supported by NASA, MH42969, MH45156, MH01433, NS35949, and the McDonnell-Pew Program in Cognitive Neuroscience. Preliminary presentations of this study were made at the Annual Meetings of the Society for Neuroscience and the Cognitive Neuroscience Society.

REFERENCES

- Andersen, R. A., Snyder, L. H., Bradley, D. C., and Xing, J. 1997. Multimodal representation of space in the posterior parietal cortex and its use in planning movements. *Annu. Rev. Neurosci.* **20**: 303–330.
- Anderson, T. J., Jenkins, I. H., Brooks, D. J., Hawken, M. B., Frackowiak, R. S. J., and Kennard, C. 1994. Cortical control of saccades and fixation in man. A PET study. *Brain* **117**: 1073–1084.
- Bates, J. F., and Goldman-Rakic, P. S. 1993. Prefrontal connections of medial motor areas in the rhesus monkey. *J. Comp. Neurol.* **336**: 211–228.
- Bruce, C. J. 1990. In *From Signal and Sense: Local and Global Order in Perceptual Maps* (Edelman, G. M., Gall, W. E., and Cowan, W. M., Ed.), pp. 261–314. New York.
- Braun D., Weber, H., Mergner, T., and Schulte-Monting, J. 1992. Saccadic reaction times in patients with frontal and parietal lesions. *Brain* **115**: 1359–1386.
- Cavada, C., and Goldman-Rakic, P. S. 1989. Posterior parietal cortex in rhesus monkey: II. Evidence for segregated corticocortical networks linking sensory and limbic areas with the frontal lobe. *J. Comp. Neurol.* **287**: 422–445.
- Christensen, C. A., Ford, J. M., and Pfefferbaum, A. 1996. The effect of stimulus-response incompatibility on P3 latency depends on the task but not on age. *Biol. Psychol.* **44**: 121–141.
- Colby, C. L., and Goldberg, M. E. 1999. Space and attention in parietal cortex. *Annu. Rev. Neurosci.* **22**: 319–349.
- Connolly, J. D., Goodale, M. A., Desouza, J. F. X., Menon, R. S., and Vilis, T. 2000. A comparison of frontoparietal fMRI activation during anti-saccades and anti-pointing. *J. Neurophysiol.* **84**: 1645–1655.
- Corbetta, M., Akbudak, E., Conturo, T. E., Snyder, A. Z., Ollinger, J. M., Drury, H. A., Linenweber, M. R., Petersen, S. E., Raichle, M. E., Van Essen, D. C., and Shulman, G. L. 1998. A common network of functional areas for attention and eye movements. *Neuron* **21**: 761–773.
- Courtney, S. M., Ungerleider, L. G., Keil, K., and Haxby, J. V. 1997. Transient and sustained activity in a distributed neural system for human working memory. *Nature* **386**: 608–611.
- Cox, R. W. 1996. AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Comput. Biomed. Res.* **29**: 162–173.
- Eddy, W. F., Fitzgerald, M., Genovese, C. R., Mockus, A., and Noll, D. C. 1996. Functional image analysis software—Computational olo. In *Proceedings in Computational Statistics* (Prat, A., Ed.), Physica-Verlag, Heidelberg.
- Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A., and Noll, D. C. 1995. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): Use of a cluster-size threshold. *Magn. Reson. Med.* **33**: 636–647.
- Fox, P. T., Fox, J. M., Raichle, M. E., and Burde, R. M. 1985. The role of cerebral cortex in the generation of voluntary saccades: A positron emission tomographic study. *J. Neurophysiol.* **54**: 348–369.
- Funahashi, S., Bruce, C. J., and Goldman-Rakic, P. S. 1991. Neuronal activity related to saccadic eye movements in the monkey's dorsolateral prefrontal cortex. *J. Neurophysiol.* **65**: 1464–1483.
- Fuster, J. M. 1992. Prefrontal neurons and the cognitive foundation of motor action. *Adv. Neurol.* **57**: 351–360.
- Goldman-Rakic, P. S. 1988. Topography of cognition: Parallel distributed networks in primate association cortex. *Annu. Rev. Neurosci.* **11**: 137–156.
- Guitton, D., Buchtel, H. A., and Douglas, R. M. 1985. Frontal lobe lesions in man cause difficulties in suppressing reflexive glances and in generating goal-directed saccades. *Exp. Brain Res.* **58**: 455–472.
- Hikosaka, O., Sakai, K., Miyauchi, S., Takino, R., Sasaki, Y., and Putz, B. 1996. Activation of human presupplementary motor area in learning of sequential procedures: A functional MRI study. *J. Neurophysiol.* **76**: 617–621.
- Hikosaka, O., Nakahara, H., Rand, M. K., Sakai, K., Lu, X., Nakamura, K., Miyachi, S., and Doya, K. 1999. Parallel neural networks for learning sequential procedures. *Trends Neurosci.* **22**: 464–471.
- Jonides, J., Smith, E. E., Marshuetz, C., Koeppe, R. A., and Reuter-Lorenz, P. S. 1998. Inhibition in verbal working memory revealed by brain activation. *Proc. Natl. Acad. Sci. USA* **95**: 8410–8413.
- Kawashima, R., Tanji, J., Okada, K., Sugiura, M., Sato, K., Kinomura, S., Inoue, K., Ogawa, A., and Fukuda, H. 1998. Oculomotor sequence learning: A positron emission tomography study. *Exp. Brain Res.* **122**: 1–8.
- Konishi, S., Nakajima, K., Uchida, I., Kikyo, H., Kameyama, M., and Miyashita, Y. 1999. Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. *Brain* **122**: 981–991.
- Luna, B., Thulborn, K. R., Strojwas, M. H., McCurtain, B. J., Berman, R. A., Genovese, C. R., and Sweeney, J. A. 1998. Dorsal cortical regions subserving visually guided saccades in humans: An fMRI study. *Cereb. Cortex* **8**: 40–47.
- Luppino, G., Matelli, M., Camarda, R., and Rizzolatti, G. 1993. Corticocortical connections of area F3 (SMA-proper) and area F6 (pre-SMA) in the macaque monkey. *J. Comp. Neurol.* **338**: 114–140.
- Milner, B. 1982. Some cognitive effects of frontal-lobe lesions in man. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* **298**: 211–226.
- O'Driscoll, G. A., Alpert, N. M., Matthysse, S. W., Levy, D. L., Rauch, S. L., and Holzman, P. S. 1995. Functional neuroanatomy of anti-saccade eye movements investigated with positron emission tomography. *Neurobiology* **92**: 925–929.
- O'Sullivan, E. P., Jenkins, I. H., Henderson, L., Kennard, C., and Brooks, D. J. 1995. The functional anatomy of remembered saccades: A PET study. *Neuroreport* **6**: 2141–2144.
- Paus, T., Petrides, M., Evans, A. C., and Meyer, E. 1993. Role of the human anterior cingulate cortex in the control of oculomotor, manual, and speech responses: A positron emission tomography study. *J. Neurophysiol.* **70**: 453–469.
- Perret, E. 1974. The left frontal lobe of man and the suppression of habitual responses in verbal categorical behaviour. *Neuropsychologia* **12**: 323–330.
- Petit, L., Courtney, S. M., Ungerleider, L. G., and Haxby, J. 1998. Sustained activity in the medial wall during working memory delays. *J. Neurosci.* **18**: 9429–9437.
- Petit, L., Orssaud, C., Tzourio, N., Crivello, F., Berthoz, A., and Mazoyer, B. 1996. Functional anatomy of a prelearned sequence of horizontal saccades in humans. *J. Neurosci.* **16**: 3714–3726.
- Picard, N., and Strick, P. L. 1996. Motor areas of the medial wall: A review of their location and functional activation. *Cereb. Cortex* **6**: 342–353.

- Sakai, K., Hikosaka, O., Miyauchi, S., Takino, R., Sasaki, Y., and Putz, B. 1998. Transition of brain activation from frontal to parietal areas in visuomotor sequence learning. *J. Neurosci.* **18**: 1827–1840.
- Sereno, M. I., Pitzalis, S., and Martinez, A. 2000. Possible homologue of area LIP in humans. *Soc. Neurosci. Abstr.* **26**.
- Sweeney, J. A., Luna, B., Krisky, C. M., Genovese, C. R., and Thulborn, K. R. 1998. Distinct subregions of SEF involved in memory and sensory-guided saccades in humans identified by fMRI. *Soc. Neurosci. Abstr.* **24**.
- Sweeney, J. A., Mintun, M. A., Kwee, S., Wiseman, M. B., Brown, D. L., Rosenberg, D. R., and Carl, J. R. 1996. A positron emission tomography study of voluntary saccadic eye movements and spatial working memory. *J. Neurophysiol.* **75**: 454–468.
- Taylor, S. F., Kornblum, S., Lauber, E. J., Minoshima, S., and Koeppe, R. A. 1997. Isolation of specific interference processing in the Stroop task: PET activation studies. *Neuroimage* **6**: 81–92.
- Wojciulik, E., and Kanwisher, N. 1999. The generality of parietal involvement in visual attention. *Neuron* **23**: 747–764.