the surface of CST-treated cells may have been more extensively folded and therefore competent for transport (Fig. 3A). Alternatively, they may have been incompletely folded molecules not retained in the ER by a CST-compromised quality control system. Calnexin has been shown to be part of the retention apparatus present in the ER (*19*, *20*). The observation that incorporation of G protein from the cell surface into virus particles drops by 90% in the presence of CST suggests that much of it is, in fact, defective (*21*). The apparent transport of defective G protein to the cell surface suggests that calnexin serves not only as a folding factor for G protein but also as a retention factor.

Our results reveal that calnexin is a true chaperone in the sense that it associates transiently with G protein and promotes its folding. Because our data were obtained in living cells, they are likely to reflect a physiologically relevant activity. Our observations, moreover, provide evidence for sequential BiP and calnexin action during G protein folding in the ER. Indications of ordered chaperone binding have been found in mitochondria in vivo and for protein refolding in the presence of bacterial chaperones in vitro (*22*, *23*). In all these cases, including that of G protein, the initial interaction involves a member of the Hsp70 family of chaperones. In the mitochondrial and bacterial systems, subsequent interaction occurs with a member of the Hsp60 family. In the ER, which seems to be devoid of Hsp60 homologs, calnexin may have the role of secondary chaperone.

Although a large number of proteins have been shown to associate transiently with calnexin, including about 20 different proteins in CHO cells (Fig. 2) (*8*), only some are likely to be strictly dependent on it for folding. In fact, G protein belongs to a subfraction of glycoproteins whose folding is inhibited by CST and by other glucosidase inhibitors (*13*, *24*). Among the proteins that can fold independently is HA. Although it normally forms a complex with calnexin, HA folding is not inhibited by CST (*6*). Apparently calnexin constitutes a link in the folding, assembly, and retention machinery of the ER that is used by many glycoproteins but is essential for only some.

REFERENCES AND NOTES

1. A. Helenius, T. Marquardt, I. Braakman, *Trends Cell Biol.* **2**, 227 (1992).
2. M.-J. Gething and J. Sambrook, *Nature* **355**, 33 (1992).
3. J. K. Rose and C. J. Gallione, *J. Virol.* **39**, 519 (1981).
4. R. W. Doms, D. S. Keller, A. Helenius, W. E. Balch, *J. Cell Biol.* **105**, 1957 (1987).
5. C. E. Machamer, R. W. Doms, D. G. Bole, A. Helenius, J. K. Rose, *J. Biol. Chem.* **265**, 6879 (1990).
6. C. Hammond, I. Braakman, A. Helenius, *Proc. Natl. Acad. Sci. U.S.A.* **91**, 913 (1994).
7. S. Munro and H. R. B. Pelham, *Cell* **46**, 291 (1986).
8. J. J. M. Bergeron, M. B. Brenner, D. Y. Thomas, D. B. Williams, *Trends Biochem. Sci.* **19**, 124 (1994); E. Degen and D. B. Williams, *J. Cell Biol.* **112**, 1099 (1991).
9. W.-J. Ou, P. H. Cameron, D. Y. Thomas, J. J. M. Bergeron, *Nature* **364**, 771 (1993).
10. C. Hammond and A. Helenius, *Curr. Biol.* **3**, 884 (1993).
11. Because of the limited amounts of BiP antibody available to us, immunoprecipitations could not be performed quantitatively. A longer film exposure than that shown in Fig. 1A was used to show the binding kinetics for the BiP (GRP78) coprecipitations.
12. Because VSV shuts off host protein synthesis [D. D. Dunigan and J. M. Lucas-Lenard, *J. Virol.* **45**, 618 (1983)], G protein is the most abundant itinerant protein in the ER. Thus, any BiP seen coprecipitating with calnexin antibodies (and vice versa) is likely to be bound to G protein.
13. A. Helenius, *Mol. Biol. Cell* **5**, 253 (1994).
14. Internal labeling in both control and CST-treated cells showed G protein in a perinuclear pattern typical of that of the Golgi apparatus, a pattern expected for a highly expressed protein en route to the cell surface.
15. J. Saraste and K. Svensson, *J. Cell Sci.* **100**, 415 (1991).
16. H.-P. Hauri and A. Schweizer, *Curr. Opin. Cell Biol.* **4**, 600 (1992).
17. C. Hammond and A. Helenius, *J. Cell Biol.* **126**, 41 (1994).
18. Control cells showed BiP in the ER and p58 in a typical punctate, predominantly perinuclear pattern.
19. S. Rajagopalan, Y. Xu, M. B. Brenner, *Science* **263**, 387 (1994).
20. M. R. Jackson, M. F. Cohen-Doyle, P. A. Peterson, D. B. Williams, *ibid.*, p. 384.
21. S. Schlesinger, C. Malfer, M. J. Schlesinger, *J. Biol. Chem.* **259**, 7597 (1984).
22. F.-U. Hartl, R. Hlodan, T. Langer, *Trends Biochem. Sci.* **19**, 20 (1994).
23. R. A. Stuart, D. M. Cyr, E. A. Craig, W. Neupert, *ibid.*, p. 87.
24. A. D. Elbein, *FASEB J.* **5**, 3055 (1991).
25. A. De Silva, I. Braakman, A. Helenius, *J. Cell Biol.* **120**, 647 (1993).
26. Before pulse labeling, cells were washed twice with phosphate-buffered saline (PBS) and incubated for 15 min in methionine-deficient media. Pulse media contained 0.4 mCi/ml of [^{35}S]methionine (L-[^{35}S] in vitro cell labeling mix; >1000 Ci/mM; Amersham). After labeling, we initiated incubations by adding media containing 4.5 mM methionine and 500 μM cycloheximide [I. Braakman, H. Hoover-Litty, K. Wagner, A. Helenius, *J. Cell Biol.* **114**, 401 (1991)].
27. Antibodies to calnexin and VSV G were as previously described (*17*). Cells were lysed in a buffer containing 2% CHAPS, 200 mM NaCl, 50 mM Hepes (pH 7.6), and chymostatin, leupeptin, antipain, and pepstatin (10 μg/ml each). Nuclei were pelleted by centrifugation for 5 min at 15,000*g*, and lysates were rotated at 4°C with antibody and Protein A sepharose beads (Sigma) for 3 hours.
28. Triton X-100–SDS wash buffer contained 0.1% SDS, 0.05% Triton X-100, 10 mM tris (pH 8.0), and 300 mM NaCl. CHAPS wash buffer contained 0.5% CHAPS, 50 mM Hepes (pH 7.6), and 200 mM NaCl.
29. Loss of G protein signal in Fig. 1A was seen when cells were solubilized in CHAPS, which was necessary for coprecipitation. Signal loss was not seen when cells were solubilized in 1% SDS.

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Anatomical Evidence for Cerebellar and Basal Ganglia Involvement in Higher Cognitive Function

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The possibility that neurons in the basal ganglia and cerebellum innervate areas of the cerebral cortex that are involved in cognitive function has been a controversial subject. Here, retrograde transneuronal transport of herpes simplex virus type 1 (HSV1) was used to identify subcortical neurons that project via the thalamus to area 46 of the primate prefrontal cortex. This cortical area is known to be involved in spatial working memory. Many neurons in restricted regions of the dentate nucleus of the cerebellum and in the internal segment of the globus pallidus were labeled by transneuronal transport of virus from area 46. The location of these neurons was different from those labeled after HSV1 transport from motor areas of the cerebral cortex. These observations define an anatomical substrate for the involvement of basal ganglia and cerebellar output in higher cognitive function.

The basal ganglia and cerebellum have long been regarded as contributing to the planning and execution of movement; however, there have been suggestions that these two structures are also involved in nonmotor or cognitive function. For example, Alexander, DeLong, and Strick (*1*) proposed that the basal ganglia participate in five separate loops with motor and nonmotor areas of the cerebral cortex. According to their scheme, the nonmotor output of the basal ganglia targets three cortical areas via the thalamus: dorsolateral prefrontal cortex, lateral orbitofrontal cortex, and anterior cingulate cortex. As a result of these connections, the output of the basal ganglia is

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thought to influence the higher order functions subserved by each of these cortical areas.

Similarly, Leiner, Leiner, and Dow (*2*) have suggested that cerebellar output is directed to prefrontal as well as motor areas of the cerebral cortex. They noted that, in the course of hominid evolution, the lateral output nucleus of the cerebellum (the dentate) undergoes a marked expansion that parallels the expansion of cerebral cortex in the frontal lobe. They argued that the increase in the size of the dentate is accompanied by an increase in the extent of the cortical areas in the frontal lobe that are influenced by dentate output. As a consequence, they proposed that cerebellar function in humans has expanded to include involvement in certain language and cognitive tasks. The absence of experimental anatomical support for a cerebellar projection to the prefrontal cortex via the thalamus has led to considerable controversy concerning the participation of the cerebellum in cognitive processing (*2*, *3*).

In this study we examined whether the dorsolateral prefrontal cortex (dlPFC) is the target of output from the basal ganglia and the cerebellum. We chose to study the dlPFC, Walker's area 46 (*4*), because it is one of the best-characterized nonmotor regions of the frontal lobe (*5*). There is considerable evidence that the dlPFC is involved in "spatial working memory" and guides behavior on the basis of transiently stored information rather than immediate external cues (*6*). The dlPFC also appears to be involved in planning the order and timing of future behavior (*5*).

Many output neurons in the basal ganglia and cerebellum project to thalamic neurons which, in turn, innervate regions of the cerebral cortex. To examine whether some of these basal ganglia and cerebellar neurons connect with thalamic neurons that innervate the dlPFC, we injected the McIntyre-B strain of herpes simplex virus type 1 (HSV1) into area 46 of cebus monkeys (*Cebus apella*, $n = 3$) (Fig. 1) (*7*). The McIntyre-B strain of HSV1 is transported transneuronally in the retrograde direction by neurons in cerebello-thalamocortical and pallido-thalamocortical pathways of primates (*8*, *9*). All injection sites were confined to the region of area 46 in the principal sulcus (PS) and did not spread to adjacent cortical regions, such as the frontal eye field (FEF) in area 8 (Fig. 1) (*10*).

The cortical injections of HSV1 labeled many neurons in portions of three thalamic nuclei known to innervate the dlPFC: ventralis anterior pars parvocellularis (VApc), medialis dorsalis (MD), and ventralis lateralis pars caudalis (VLc) (*11*). In addition, retrograde transneuronal transport of HSV1 from the dlPFC labeled many neurons in

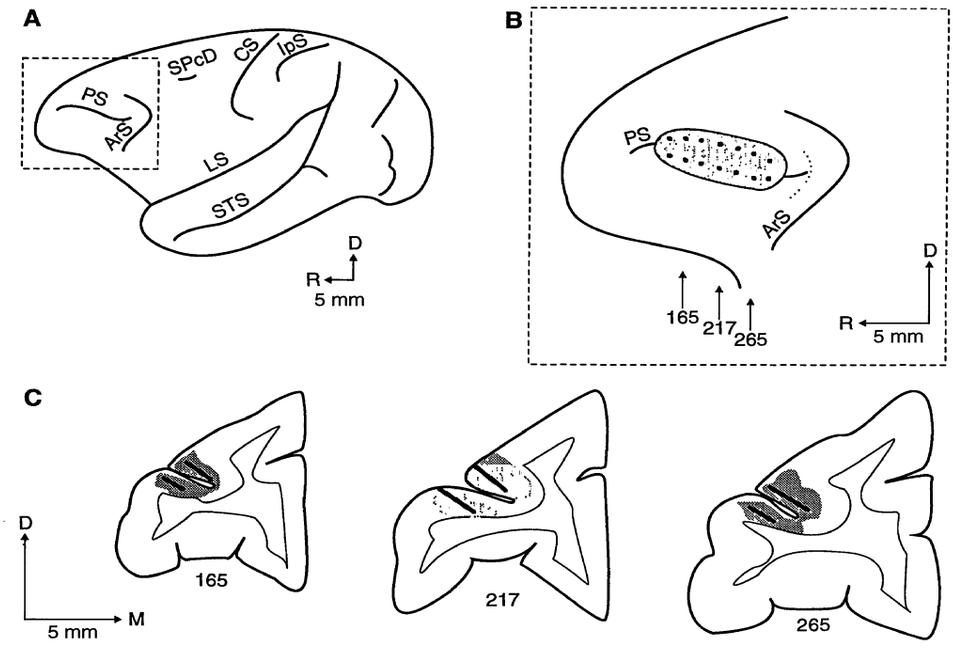

Fig. 1. HSV1 injection sites along the principal sulcus in a cebus monkey (F1). (**A**) Lateral view of the cebus brain. (**B**) Enlargement of the area enclosed by the dashed line in (A). Solid circles represent needle entry points, and the shaded area indicates the spread of HSV1 from the injection sites. The dotted line defines the boundary between Walker's areas 46 and 8 in F1. The numbered arrows indicate the location of sections in (C). (**C**) Coronal sections through the injection site. Heavy lines indicate needle tracks, and the shaded areas indicate the spread of HSV1. ArS, superior limb of the arcuate sulcus; CS, central sulcus; D, dorsal; lpS, intraparietal sulcus; LS, lateral sulcus; M, medial; PS, principal sulcus; R, rostral; SPcD, superior precentral dimple; STS, superior temporal sulcus.

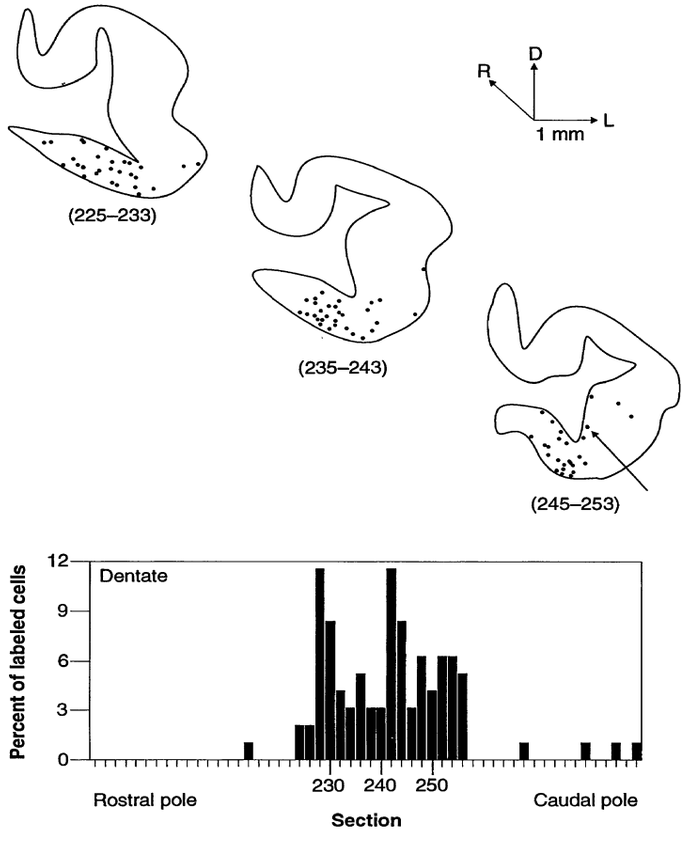

Fig. 2. Labeled neurons in the dentate nucleus. (**Top**) Coronal sections at three representative levels through the dentate. The solid dots indicate the positions of neurons labeled by retrograde transneuronal transport observed in five sections spaced 100 to 150 μm apart (section numbers are at the bottom in parentheses). The arrow indicates the location of the labeled neuron shown in Fig. 3A. (**Bottom**) Plot of the rostro-caudal distribution of labeled cells in the dentate. The location of some sections is shown along the abscissa. L, lateral.

the dentate nucleus of the cerebellum (mean = 122, range = 91–181) and in the internal segment of the globus pallidus (GPi) (mean = 332, range = 318–346) (*12*). Most of the labeled neurons in the dentate were found contralateral to the cortical injection site. These neurons were confined to the most ventral portion of the nucleus and were concentrated rostro-caudally in the middle third of the dentate (Fig. 2). This region of the dentate clearly differs from the more dorsal regions of this nucleus, which were labeled by retrograde transneuronal transport from the primary motor cortex (M1) or ventral premotor area (PMv) (*13*), and the more caudal region of the dentate, which was labeled by retrograde transneuronal transport from the FEF (*14*). The dorsal part of the dentate is where neurons with marked changes in activity during single joint or reaching movements have been found (*15*).

The labeled neurons in the dentate had round cell bodies, with multiple dendrites originating from the soma (Fig. 3A), features typical of dentate neurons that project to the thalamus (*13*, *14*). Prior studies have shown that some of these dentate neurons terminate in the MD and VLc (*16*, *17*). Thus, our results provide evidence that the dlPFC is a cortical target of a cerebello-thalamocortical pathway from the dentate, and that this pathway is distinct from those innervating motor areas of the cerebral cortex.

In the GPi, labeled neurons were found largely ipsilateral to the cortical injection site in the dlPFC. These neurons were located in the most dorsomedial region of the inner and outer portions of the internal segment and were concentrated rostro-caudally in the middle third of the nucleus (Fig. 4). This region of the GPi clearly differs from the more ventral and lateral regions of the GPi which were labeled by retrograde transneuronal transport from M1, PMv, or the supplementary motor area (SMA) (*13*). These more ventral and lateral regions of the GPi contain neurons that display marked changes in activity during single joint or reaching movements (*18*).

Labeled GPi neurons had elliptical cell bodies, with one or more dendrites radiating from each pole of the soma (Fig. 3B), features typical of GPi neurons that project to the thalamus (*19*). It is generally agreed that some of these GPi neurons terminate in the VApc (*20*). Thus, our results provide evidence that the dlPFC is a cortical target of a distinct pallido-thalamocortical pathway from the GPi.

These observations have important implications for theories about the functional organization of basal ganglia and cerebellar loops with the cerebral cortex. According to one view, these loops provide a means for linking widespread regions of the cerebral cortex, such as prefrontal and posterior parietal cortex, with motor output at the level of the primary motor cortex. Such loops would serve to "funnel" information into the motor system to generate commands for movement (*21*). Our results support an alternative view (*1*, *2*), one in which part of the output of the basal ganglia and cerebellum is directed back to regions of the prefrontal cortex that are known to project to these subcortical structures (*22*). This creates the potential for closed loops between the prefrontal cortex and both the basal ganglia and cerebellum. These loops would operate in parallel with those serving motor areas of the cerebral cortex but would have a "cognitive" rather than a "motor" function.

Considerable evidence indicates that the basal ganglia participate in aspects of cognitive function. Individuals affected by Parkinson's disease and Huntington's disease, two well-known basal ganglia disorders, show cognitive deficits as well as motor symptoms (*23*). Patients with focal lesions of the GPi have deficits on tests of working memory and rule-based learning (for example, Wisconsin Card Sorting Test) (*24*). These deficits are considered indices of frontal lobe dysfunction.

The concept that the cerebellum is involved in cognitive function is a relatively recent one which has lacked extensive experimental support (*2*, *3*). There are a number of reports that patients with cerebellar pathology have some cognitive deficits (*25*). In addition, a positron emission tomography (PET) study found that an inferior and lateral part of the right cerebellar hemisphere was activated during a task that required rule-based generation of words (*26*, *27*). This activation was spatially separate from that found during motor tasks, including speech (*26*). Finally, support for the

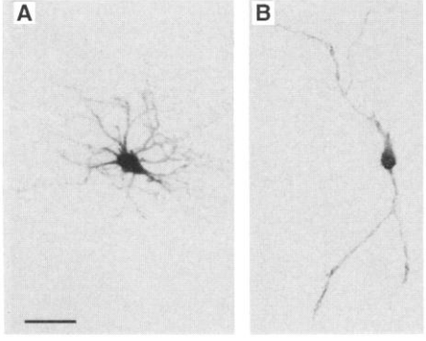

Fig. 3. Neurons labeled by retrograde transneuronal transport of HSV1 from area 46. (**A**) Dentate neuron. The location of the cell is indicated by the arrow in Fig. 2. (**B**) GPi neuron. The location of the cell is indicated by the arrow in Fig. 4. Scale bar, 50 μm.

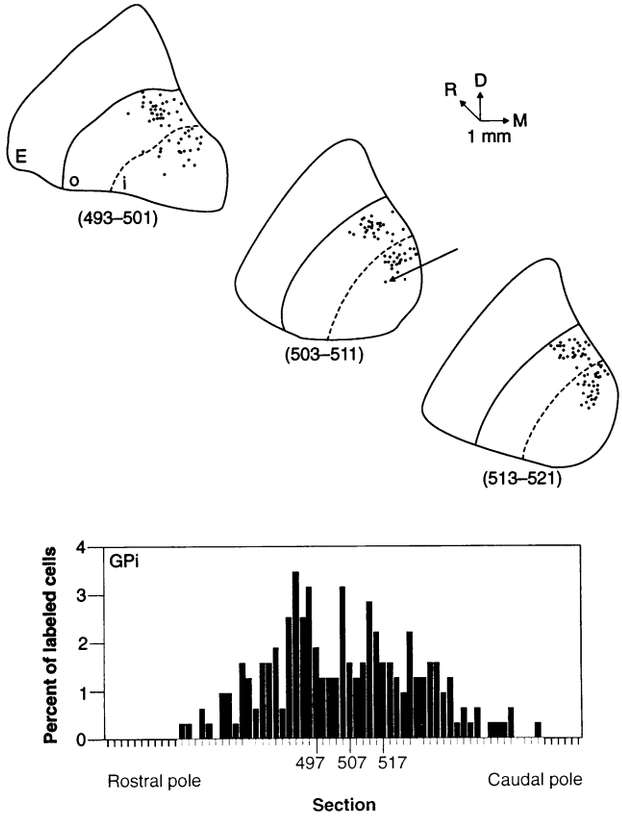

Fig. 4. Labeled neurons in the GPi. (**Top**) Coronal sections at three representative levels through the GPi (see the legend in Fig. 2 for conventions). The arrow indicates the location of the labeled neuron shown in Fig. 3B. (**Bottom**) Plot of the rostro-caudal distribution of labeled cells in the GPi. E, external segment of the globus pallidus; o, outer portion of the GPi; i, inner portion of the GPi.

involvement of cerebellar output in cognitive function has come from a study of functional activation in the human dentate nucleus with magnetic resonance imaging (*28*). In this study the dentate displayed a large bilateral activation when subjects attempted to solve a pegboard puzzle. The extent of this activation was three to four times greater than that seen during visually guided movements of the pegs.

In conclusion, our results demonstrate that cerebellar and basal ganglia outputs gain access to the prefrontal cortex. These connections provide part of the anatomical substrate for the involvement of these subcortical nuclei in cognitive processing. Thus, we believe that the cerebellum and basal ganglia should no longer be considered as purely motor structures. Instead, concepts about their function should be broadened to include involvement in cognitive processes such as working memory, rule-based learning, and planning future behavior.

REFERENCES AND NOTES

1. G. E. Alexander, M. R. DeLong, P. L. Strick, *Annu. Rev. Neurosci.* **9**, 357 (1986).
2. H. C. Leiner, A. L. Leiner, R. S. Dow, *Behav. Brain Res.* **44**, 113 (1991); *Trends Neurosci.* **16**, 444 (1993).
3. J. R. Bloedel, *Trends Neurosci.* **16**, 451 (1993); M. Glickstein, *ibid.*, p. 450; M. Ito, *ibid.*, p. 448. In addition, Sasaki *et al.* [K. Sasaki, K. Jinnai, H. Gemba, S. Hashimoto, N. Mizuno, *Exp. Brain Res.* **37**, 193 (1979)] have presented electrophysiological evidence for a projection from the dentate to a cortical region at the border of areas 6 and 9. Subsequent results suggest that this projection is to the supplementary eye field (SEF), a cortical area involved in oculomotor function (*17*).
4. A. E. Walker, *J. Comp. Neurol.* **73**, 59 (1940).
5. For review, see J. M. Fuster, *Cerebral Cortex*, A. Peters and E. Jones, Eds. (Plenum, New York, 1985), pp. 151–177; *The Prefrontal Cortex* (Raven, New York, ed. 2, 1989).
6. P. S. Goldman-Rakic, in *Progress in Brain Research*, H. B. M. Uylings, C. G. Van Eden, J. P. C. DeBruin, M. A. Corner, M. G. P. Feenstra, Eds. (Elsevier Science, New York, 1990), pp. 325–336.
7. For complete surgical details, see J. W. Holsapple, J. B. Preston, P. L. Strick, *J. Neurosci.* **11**, 2644 (1991). Briefly, animals were anesthetized with Telazol (initial dose 20 mg per kilogram of body weight, supplemental dose 5 to 7 mg/kg) or Isoflurane–nitrous oxide. After a craniotomy over the left prefrontal cortex, injections of HSV1 were made with a 5-μl Hamilton syringe with a 32-gauge needle, and their placement was determined by surface landmarks and prior magnetic resonance images. Injections were made into both banks of the principal sulcus by inserting the syringe needle at 14 to 15 sites. Small amounts of HSV1 (0.05 to 0.10 μl; 3.2 to 8.2 × 10^8 plaque forming units/ml) were injected at sites 1.5 to 7.2 mm below the cortical surface. Between 42 to 71 sites were injected in each animal. Animals were euthanized 5 days after virus inoculation, and the brain of each animal was processed to demonstrate the location of virus-specific antigen [for complete details, see P. L. Strick and J. P. Card, in *Experimental Neuroanatomy: A Practical Approach*, J. P. Bolam, Ed. (Oxford Univ. Press, Oxford, 1993), pp. 81–101]. All procedures were in accordance with institutional guidelines for the care and use of animals.
8. M. C. Zemanick, P. L. Strick, R. D. Dix, *Proc. Natl. Acad. Sci. U.S.A.* **88**, 8048 (1991).
9. We set the survival time at 5 days to limit retrograde transneuronal transport to movement from first to second order neurons [(*8*), see also J. E. Hoover and P. L. Strick, *Soc. Neurosci. Abstr.* **19**, 1590 (1993)]. None of the animals with virus injections into area 46 demonstrated any labeling of third order neurons in cerebellar cortex. Thus, we can rule out the possibility that the subcortical labeling we observed after virus injections into area 46 was due to transport to another cortical area, because such labeling would require movement through three orders of synaptic connections: (i) transport from area 46 to another area connected with it, (ii) transport from cortex to thalamus, and (iii) transport from thalamus to a subcortical site.
10. We have used the cytoarchitectonic criteria of Walker (*4*) and Barbas and Pandya [H. Barbas and D. N. Pandya, *J. Comp. Neurol.* **286**, 353 (1989)] to identify the border of area 46 with adjacent cortical areas. On the basis of these data, the injections into area 46 were placed at least 3 mm rostral to the caudal end of the PS, to avoid involvement of the FEF in area 8, and no more than 2 mm away from the center of the PS, to avoid the SEF. Further evidence that virus did not spread from our injection sites to involve the FEF comes from our finding that virus injections directly into the FEF (defined electrophysiologically) resulted in labeled neurons in the very caudal pole of the dentate (*14*). The neurons labeled by our area 46 injections were located much more rostrally. In this regard it is also important to note that FEF injections of virus led to large numbers of labeled neurons in the substantia nigra pars reticulata (*14*), whereas area 46 injections did not.
11. J. Kievit and H. G. J. M. Kuypers, *Exp. Brain Res.* **29**, 299 (1977); P. S. Goldman-Rakic and L. J. Porrino, *J. Comp. Neurol.* **242**, 535 (1985); L. D. Selemon and P. S. Goldman-Rakic, *J. Neurosci.* **8**, 4049 (1988); H. Barbas, T. H. Haswell Henion, C. R. Dermon, *J. Comp. Neurol.* **313**, 65 (1991); J. Olszewski, *The Thalamus of the* Macaca mulatta*: An Atlas for Use with the Stereotaxic Instrument* (Karger, Basel, 1952).
12. Injection sites, section outlines, and labeled neurons were plotted with a computer-based charting system (MD2, Minnesota Datametrics). This system uses optical encoders to measure *x-y* movements of the microscope stage and stores the coordinates of charted structures. We plotted every fourth section through the injection site and every other section through the dentate and GPi. Cell counts are based on these plots.
13. R. Wiesendanger and M. Wiesendanger, *Exp. Brain Res.* **59**, 105 (1985); P. J. Orioli and P. L. Strick, *J. Comp. Neurol.* **288**, 612 (1989); J. E. Hoover and P. L. Strick, *Science* **259**, 819 (1993); P. L. Strick, J. E. Hoover, H. Mushiake, in *Role of the Cerebellum and Basal Ganglia in Voluntary Movement*, N. Mano, I. Hamada, M. R. DeLong, Eds. (Elsevier Science, New York, 1993), pp. 171–180.
14. J. C. Lynch, J. E. Hoover, P. L. Strick, *Exp. Brain Res.*, in press.
15. R. Wetts, J. F. Kalaska, A. M. Smith, *J. Neurophysiol.* **54**, 231 (1985); P. L. E. van Kan, J. C. Houk, A. R. Gibson, *ibid.* **69**, 57 (1993).
16. T. Kusama, M. Mabuchi, T. Sumino, *Proc. Jpn. Acad.* **47**, 505 (1971); J. Kievit and H. G. J. M. Kuypers, in *Corticothalamic Projections and Sensorimotor Activities*, T. Frigyesi, E. Rinvik, M. D. Yahr, Eds. (Raven, New York, 1972), pp. 91–114; G. Percheron, *J. Hirnforschung* **18**, 375 (1977); G. B. Stanton, *J. Comp. Neurol.* **190**, 699 (1980).
17. T. Yamamoto, K. Yoshida, H. Yoshikawa, Y. Kishimoto, H. Oka, *Brain Res.* **579**, 315 (1992).
18. M. R. DeLong, *J. Neurophysiol.* **34**, 414 (1971); M. E. Anderson and F. B. Horak, *ibid.* **54**, 433 (1985); J. W. Mink and W. T. Thach, *ibid.* **65**, 273 (1991).
19. A. Parent and L. D. Bellefeuille, *Brain Res.* **245**, 201 (1982).
20. W. J. H. Nauta and W. R. Mehler, *Brain Res.* **1**, 3 (1966); J. S. Kuo and M. B. Carpenter, *J. Comp. Neurol.* **151**, 201 (1973); R. Kim, K. Nakano, A. Jayaraman, M. B. Carpenter, *ibid.* **169**, 263 (1976); J. L. DeVito and M. E. Anderson, *Exp. Brain Res.* **46**, 107 (1982).
21. E. V. Evarts and W. T. Thach, *Annu. Rev. Physiology* **31**, 451 (1969); J. M. Kemp and T. P. S. Powell, *Phil. Trans. R. Soc. London B* **262**, 441 (1971).
22. P. S. Goldman-Rakic and W. J. H. Nauta, *J. Comp. Neurol.* **171**, 369 (1977); E. H. Yeterian and G. W. Van Hoesen, *Brain Res.* **139**, 43 (1978); P. Brodal, *Neuroscience* **4**, 193 (1979); G. R. Leichnetz, D. J. Smith, R. F. Spencer, *J. Comp. Neurol.* **228**, 388 (1984); M. Glickstein, J. G. May, B. E. Mercier, *ibid.* **235**, 343 (1985); L. D. Selemon and P. S. Goldman-Rakic, *J. Neurosci.* **5**, 776 (1985).
23. N. Butters, D. Sax, K. Montgomery, S. Tarlow, *Arch. Neurol.* **35**, 585 (1978); A. E. Taylor, J. A. Saint-Cyr, A. E. Lang, *Brain* **109**, 845 (1986).
24. R. L. Sturb, *Arch. Neurol.* **46**, 1024 (1989); J. L. Cummings, *ibid.* **50**, 873 (1993).
25. J. D. Schmahmann, *ibid.* **48**, 1178 (1991); N. A. Akshoomoff and E. Courchesne, *Behav. Neurosci.* **106**, 731 (1992); J. Grafman *et al.*, *Neurology* **42**, 1493 (1992); A. G. M. Canavan, R. Sprengelmeyer, H. C. Deiner, V. Homberg, *Behav. Neurosci.* **108**, 475 (1994).
26. J. A. Fiez, S. E. Petersen, M. K. Cheney, M. E. Raichle, *Brain* **115**, 155 (1992); S. E. Petersen and J. A. Fiez, *Annu. Rev. Neurosci.* **16**, 509 (1993).
27. These investigators also described a patient with a right cerebellar lesion whose performance was impaired on a semantic processing task similar to the one used in their PET study.
28. S.-G. Kim, K. Uğurbil, P. L. Strick, *Science* **265**, 949 (1994).

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