

The temporal lobe is a target of output from the basal ganglia

(inferotemporal cortex/substantia nigra/virus transport/*Cebus apella*)

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ABSTRACT The basal ganglia are known to receive inputs from widespread regions of the cerebral cortex, such as the frontal, parietal, and temporal lobes. Of these cortical areas, only the frontal lobe is thought to be the target of basal ganglia output. One of the cortical regions that is a source of input to the basal ganglia is area TE, in inferotemporal cortex. This cortical area is thought to be critically involved in the recognition and discrimination of visual objects. Using retrograde transneuronal transport of herpes simplex virus type 1, we have found that one of the output nuclei of the basal ganglia, the substantia nigra pars reticulata, projects via the thalamus to TE. Thus, TE is not only a source of input to the basal ganglia, but also is a target of basal ganglia output. This result implies that the output of the basal ganglia influences higher order aspects of visual processing. In addition, we propose that dysfunction of the basal ganglia loop with TE leads to alterations in visual perception, including visual hallucinations.

The basal ganglia are subcortical structures that have long been regarded as involved in the control of movement. The input structures of the basal ganglia (the caudate, putamen, and ventral striatum) are known to receive projections from widespread regions of the cerebral cortex, such as the frontal, parietal, and temporal lobes. To date, however, only motor areas in the frontal lobe and regions of the prefrontal cortex have been shown to be the target of output from the primate basal ganglia via the thalamus (1–5). Consequently, basal ganglia loops with the cerebral cortex have been thought to “funnel” or collect information from diverse cortical areas in order to direct motor output and the executive functions of the frontal lobe (6). In this report, we provide evidence that the output of the basal ganglia targets at least one visual area in inferotemporal cortex.

Inferotemporal cortex of primates contains two major visual areas, TE and TEO (7). Ungerleider and colleagues have proposed that “these two areas form the last stations of an occipitotemporal processing pathway which begins in V1 and projects forward through areas V2 and V4 . . .” (8, 9). There is considerable behavioral evidence that TE and TEO play a critical role in the visual recognition and discrimination of objects. TE appears to be especially involved in tasks that require visual memory (9–12). Some TE neurons display activity that is specifically related to the visual presentation of complex objects and patterns including faces (9–13). One of the outputs of TE is to the “visual striatum” (i.e., the tail of the caudate, and caudal/ventral portions of the putamen) (8, 14–16). Mishkin and colleagues (17, 18) have proposed that this input to the basal ganglia ultimately influences cortical motor areas and is involved in the formation of visuomotor associations or “habit memories.” On the other hand, TE receives input from the nucleus ventralis anterior pars mag-

nocellularis (VAmc) of Olszewski (8, 16, 19). Since portions of VAmc are known to receive input from substantia nigra pars reticulata (SNpr), we thought it possible that TE could be the target of output from the basal ganglia via the thalamus.

MATERIALS AND METHODS

To examine this hypothesis, we first used conventional methods of neuroanatomical tracing to confirm that neurons in the VAmc of *Cebus apella* ($n = 1$) project to TE. Next, we used retrograde transneuronal transport of the McIntyre-B strain of herpes simplex virus type 1 (HSV-1) (1–5, 20) from TE of *Cebus apella* ($n = 3$) to determine whether the thalamic neurons in VAmc which project to TE are, in fact, the target of output from SNpr. Briefly, monkeys were anesthetized with isoflurane/nitrous oxide (1.5–2.5%), and a craniotomy was made over the temporal lobe. The dura was incised and injections of tracer were placed into TE by using a 5 μ l Hamilton syringe with a 32-gauge needle. The placement of injections was based on current maps of TE and surface landmarks (7–16). Injections were made 1.0–2.0 mm below the cortical surface at 24–42 sites, which were separated by 1 mm except to avoid blood vessels. Each site was injected with 0.05–0.10 μ l of tracer (either 2.5% of Diamidino Yellow or 9.9×10^9 plaque forming units/ml of the McIntyre-B strain of HSV-1). The procedures and care provided experimental animals conformed to the regulations detailed in the *Guide for the Care and Use of Laboratory Animals* (21) and were approved by the appropriate Institutional Animal Care and Use Committees.

Five days after HSV-1 injections or 14 days after Diamidino Yellow injections, animals were deeply anesthetized with Ketamine (25 mg/kg, i.m.) and Nembutal (36 mg/kg, i.p.). They were then perfused transcardially with 0.1M phosphate-buffered saline (PBS, pH 7.4), followed by 4% paraformaldehyde in 0.1 M PBS, and 4% paraformaldehyde in 0.1 M PBS with 10% glycerin. Serial coronal sections through the brain were cut at 50 μ m with a freezing microtome. Sections from the animal injected with Diamidino Yellow were immediately mounted and coverslipped. Free-floating sections from the animals injected with HSV-1 were reacted immunohistochemically to demonstrate the presence of virus-specific antigen (20) using the avidin/biotin/peroxidase method (ABC, Vectastain). Immunoreactivity was developed by incubation in a solution prepared by mixing equal volumes of 0.1% 3,3'-diaminobenzidine tetrahydrochloride and 0.02% hydrogen peroxide. At least every other section was reacted in this manner. Injection sites, section outlines, and labeled neurons were plotted by using a computer-based charting system (MD2, Minnesota Datametrics, Minneapolis). This system uses optical encoders to measure X–Y movements of the microscope stage and stores the coordinates of charted structures. We

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Abbreviations: TE, area of inferotemporal cortex; HSV-1, herpes simplex virus type 1; VAmc, ventralis anterior pars magnocellularis; SNpr, substantia nigra pars reticulata; STN, subthalamic nucleus.

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plotted every fourth section through the injection site and every other section through the basal ganglia. Cell counts are based on these plots.

RESULTS

Injections of Diamidino Yellow into TE labeled many neurons in VAmc. As indicated by Ungerleider and colleagues (8, 16), the labeled neurons we observed in VAmc were found largely in the medial and caudal portions of this nucleus. We also found many labeled neurons in other thalamic nuclei that are known to innervate TE, such as the pulvinar nucleus, the nucleus lateralis posterior, and various intralaminar nuclei (8, 16).

Injections of HSV-1 into TE (Fig. 1) also labeled many neurons in VAmc (Fig. 2 *A* and *B*) and in the other thalamic nuclei noted above. In addition, retrograde transneuronal transport of HSV-1 labeled "second-order" neurons in SNpr (mean = 81) (Fig. 2 *C* and *D* and Fig. 3). The labeling in SNpr is most likely due to retrograde transneuronal transport of

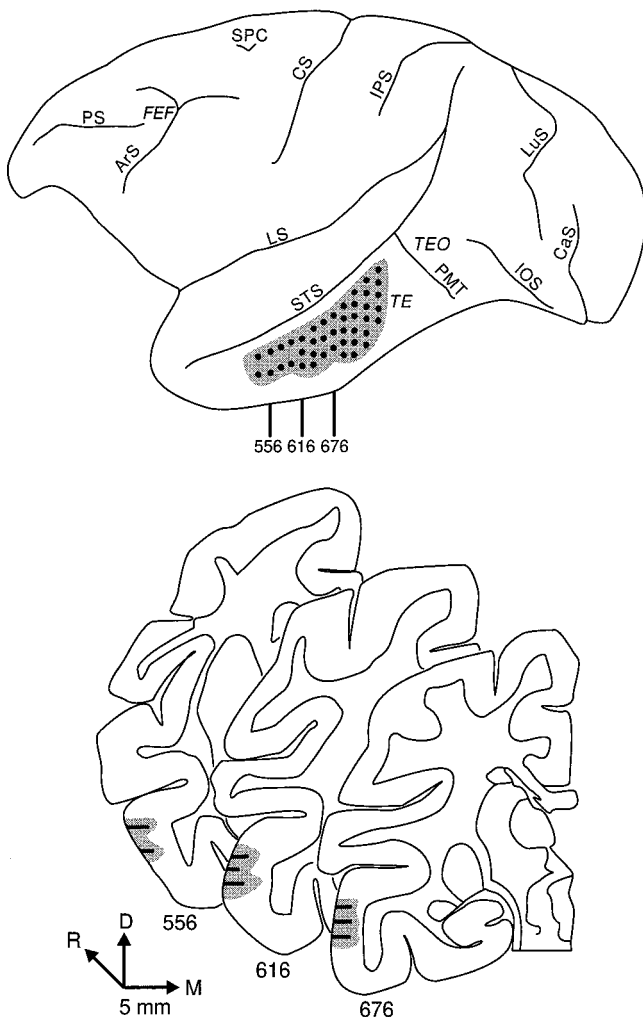


FIG. 1. HSV-1 injection sites in TE. (*Upper*), Lateral view of a monkey brain showing the location of HSV-1 injection sites into TE. Large solid circles represent needle entry points, and the shaded area indicates the spread of HSV-1 during injections. (*Lower*) Coronal sections through the injection site at the locations indicated above. Heavy lines indicate the needle tracks. ArS, arcuate sulcus; CC, crus cerebri; CS, central sulcus; CaS, calcarine sulcus; D, dorsal; FEF, frontal eye field; IOS, inferior occipital sulcus; IPS, intraparietal sulcus; LS, lateral sulcus; LuS, lunate sulcus; M, medial; PMT, posterior middle temporal sulcus; PS, principal sulcus; R, rostral; RN, red nucleus; SPC, superior precentral dimple; STS, superior temporal sulcus.

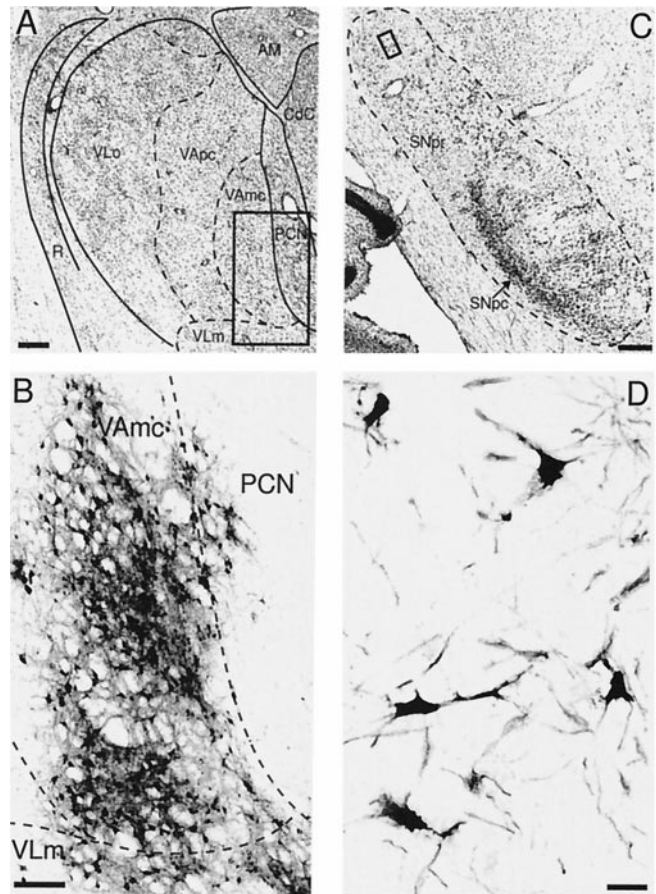


FIG. 2. Neurons labeled by retrograde transport of HSV-1 from TE. (*A*) Nissl-stained section of the thalamus at the level of VAmc. (Bar = 500 μ m.) (*B*) First-order neurons in VAmc labeled by transport of virus from TE. The section adjacent to that shown in *A* was processed to demonstrate HSV-1 labeling. The region displayed is an enlargement of the boxed area in *A*. (Bar = 200 μ m.) Thalamic abbreviations in *A* and *B* are according to Olszewski (19). (*C*) Nissl-stained section at the level of SNpr. (Bar = 500 μ m.) (*D*) Second-order neurons in SNpr labeled by retrograde transneuronal transport of HSV-1 from TE. The section adjacent to that shown in *C* was processed to demonstrate HSV-1 labeling. The region displayed is an enlargement of the boxed area in *C*. SNpc, substantia nigra pars compacta. (Bar = 50 μ m.)

virus via VAmc since this is the only thalamic nucleus that both projects to TE and receives nigral input.

The labeled neurons in SNpr had elliptical somas, with one or more dendrites radiating from each pole (Fig. 2 *C* and *D*). These features are typical of nigral neurons that project to the thalamus (22). Most labeled neurons in SNpr were found ipsilateral to the TE injection site and were located dorsally in the caudal third of the nucleus (Fig. 3). This appears to be the same portion of SNpr that, in studies with conventional tracers, receives a projection from the visual striatum (14, 23, 24) and sends a projection to caudal VAmc (25). Furthermore, physiological studies have found that this region of SNpr contains some neurons that display changes in activity related to the presentation of visual stimuli (26).

As part of other studies, we have injected HSV-1 into several different motor and prefrontal areas of cortex (1–5). No labeled neurons were found in SNpr after virus injections into the arm representations of the primary motor cortex, supplementary motor area, or ventral premotor area (1, 2). In contrast, labeled neurons were found in SNpr after virus injections into the face representation of the primary motor cortex (unpublished observation), the frontal eye field (3), and

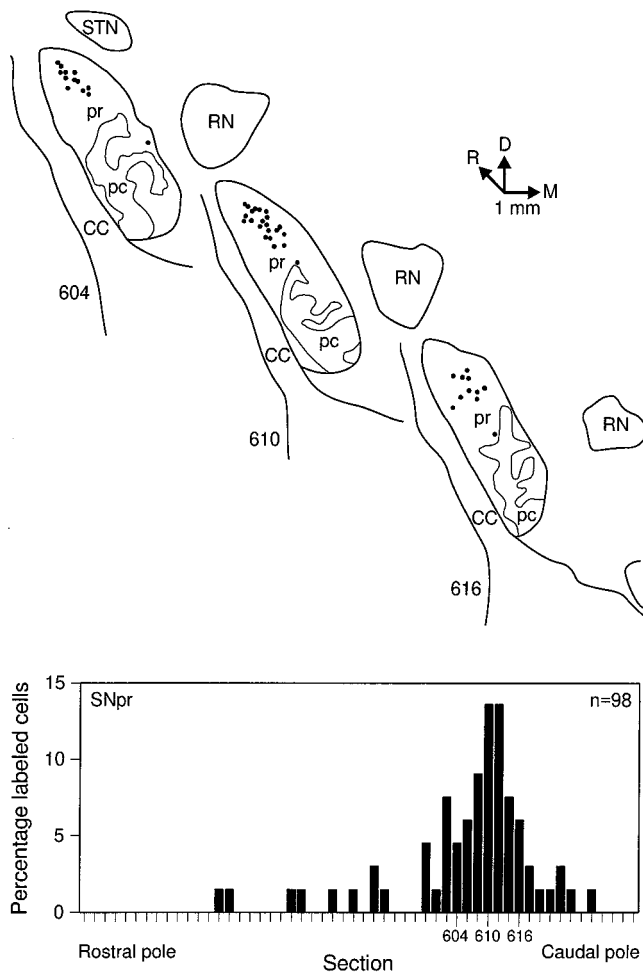


FIG. 3. Distribution of HSV-1-infected neurons in SNpr ipsilateral to the TE injection site. (Upper) Coronal sections at three representative levels through SNpr in a single animal. Solid dots indicate the positions of neurons labeled by retrograde transneuronal transport. Labeled neurons found in three sections, spaced 100 μ m apart, are overlapped on the outline of the middle section (section number at the lower left of each drawing). (Lower) Plot of the rostro-caudal distribution of labeled cells in the SNpr. The locations of the sections shown above are indicated along the abscissa. pc, Pars compacta; pr, pars reticulata; STN, subthalamic nucleus.

areas 9, 12, and 46 of prefrontal cortex (5). However, the distribution of labeled neurons in SNpr after these injections was clearly different than the distribution of labeled neurons in the present study. Thus, the SNpr projection via the thalamus to TE appears to be separate from SNpr projections to other cortical areas.

DISCUSSION

The present results suggest that the region of SNpr that receives input from TE by way of the visual striatum (14, 23, 24) projects back upon TE via the thalamus. Thus, we propose that at least a portion of the anatomical connections between TE and the basal ganglia form a topographically closed loop circuit (Fig. 4). This proposal has broad implications for concepts about basal ganglia function and suggests that the basal ganglia loop with TE is involved in higher order aspects of visual processing. Thus, our observations may help to explain the origin of some deficits in visual perception seen following damage to basal ganglia circuits. For example, monkeys with lesions of the visual striatum are impaired in the learning and retention of visual discriminations of complex

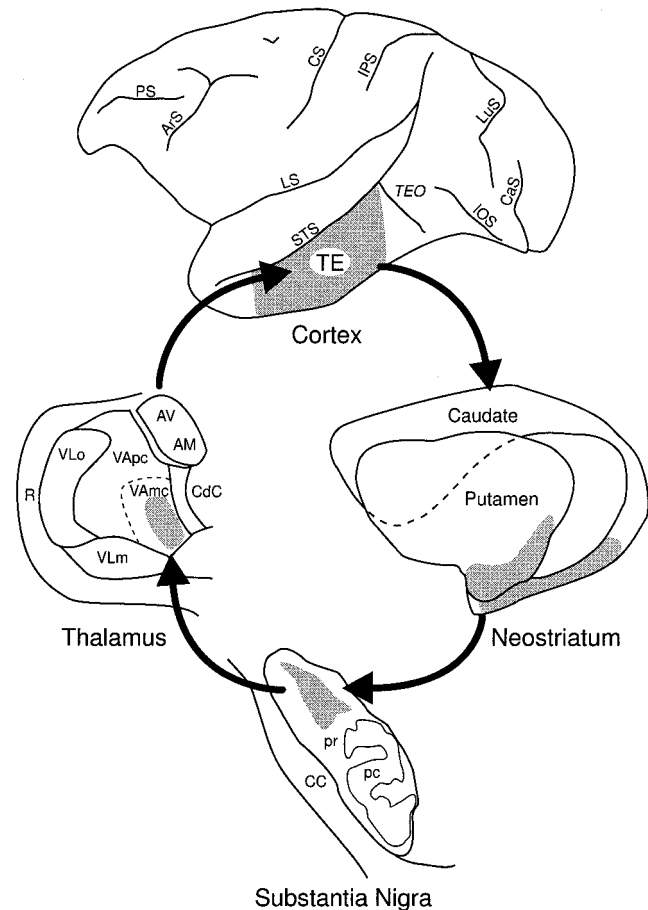


FIG. 4. Proposed basal ganglia loop with TE. Shading indicates the portion of each structure that contributes to this circuit. Abbreviations as in Figs. 1–3.

objects (27, 28). Similarly, patients in the early stages of Huntington disease, in which neurons in the tail of the caudate are among the first to degenerate (29), display deficits in the recognition and discrimination of faces and facial expressions (30). These deficits in visual function may be the consequence of alterations in nigral output to TE caused by the striatal pathology.

Our findings also suggest that the models of basal ganglia circuitry that have been used to explain the pathophysiological basis of movement disorders (31, 32), can be used to explain disorders of visual perception that are generated by basal ganglia dysfunction (Fig. 5). For example, visual hallucinations have been reported in humans following medial lesions in SNpr or brainstem compression (33, 34). This syndrome, termed "peduncular hallucinosis," most often involves seeing fully-formed images of people or animals and occurs on a background of intact attention and arousal (33). It is likely that medial lesions in SNpr, and conditions resulting in brainstem compression, interrupt the powerful excitatory input from the subthalamic nucleus (STN) to neurons in dorsolateral SNpr that are part of the basal ganglia loop with TE. This is because the projection from STN to SNpr passes through the cerebral peduncle and enters the ventromedial portion of SNpr before distributing its fibers throughout the rest of the nucleus (35). SNpr neurons normally exert a tonic inhibitory effect on neurons in the thalamus. Thus, one of the net results of interrupting STN input to SNpr would be to remove an inhibitory input to thalamic neurons in VAmc and consequently produce an abnormal increase in thalamic input to TE (Fig. 5 Left). This increase in thalamic drive could result in abnormal excitation of TE, which has been experimentally

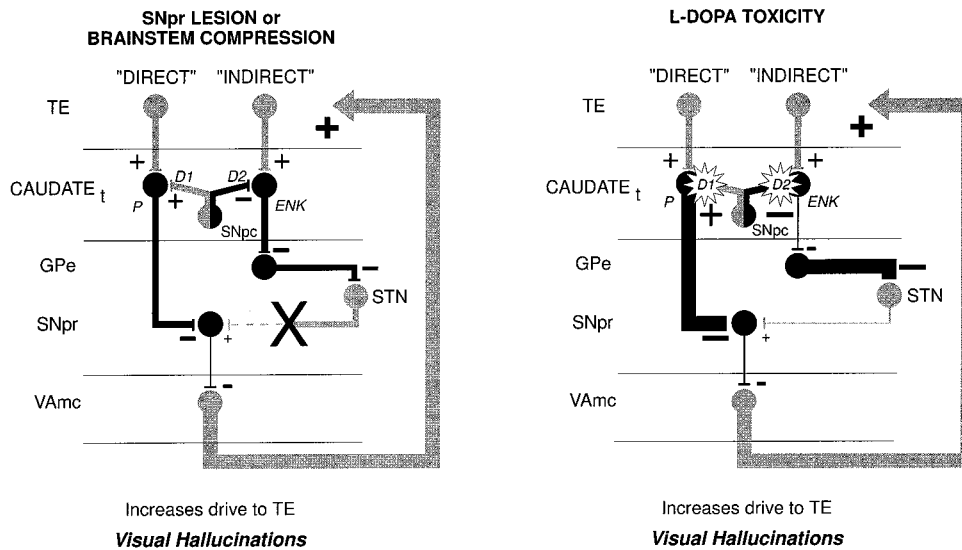


FIG. 5. Consequences of dysfunction in basal ganglia loops with TE. (Left) Visual hallucinations due to SNpr lesions or brainstem compression. (Right) Visual hallucinations due to L-dopa toxicity. Brain sites and the connections between these regions are indicated by circles and lines. Light shading and a positive sign (+) indicate that a connection is excitatory. Dark shading and a negative sign (-) indicate a connection is inhibitory. Increases or decreases in line thickness and +/- symbol size are used to indicate abnormal increases or decreases in activity. The dashed line indicates an interruption of a pathway, and the large X indicates the site of this interruption. The starburst (*) indicates the site of action of L-dopa and other dopaminergic drugs in the striatum. CAUDATE_t, tail of the caudate; D1, type-1 dopamine receptor; D2, type-2 dopamine receptor; DIRECT, the direct pathway through the basal ganglia; E, enkephalin-positive projection; GPe, external segment of the globus pallidus; INDIRECT, the indirect pathway through the basal ganglia, that involves the STN; P, substance P-positive projection.

shown to cause visual hallucinations in humans (36). The hemiballistic movements that follow STN lesions have been thought to be produced by a similar mechanism (decreased pallidal output leading to an abnormal increase in thalamic input to motor areas of cortex) (31, 32).

Similarly, visual hallucinations which are strikingly similar to those produced by SNpr lesions are a major side effect of the use of L-dopa, or other dopaminergic agents, for the treatment of Parkinson disease. Approximately 30 percent of Parkinson disease patients treated in this manner experience this puzzling side effect (37, 38). We speculate that the hallucinations in these patients are due to excessive stimulation of dopamine receptors in the visual striatum, which ultimately leads to a net decrease in SNpr activity and an abnormal increase in thalamic input to TE (Fig. 5 Right). The dyskinesias that can accompany the use of dopaminergic drugs have been thought to be produced by a similar mechanism (decreased basal ganglia output causing an abnormal increase in thalamic input to motor areas of cortex) (31, 32).

Given these models, we wonder whether the visual hallucinations associated with schizophrenia could also be mediated by abnormal activity in the basal ganglia loop with TE. This speculation is supported by a recent functional imaging study that reported that schizophrenics experiencing hallucinations display significant changes in blood flow at several brain sites that are part of the TE loop (e.g., temporal cortex, putamen and thalamus) (39). In fact, neuroleptic drugs used to treat the visual hallucinations of schizophrenia are dopamine antagonists (40). The therapeutic effects of these drugs may be due, in part, to their action on dopamine receptors in the visual striatum, which would alter activity in the basal ganglia loop with TE.

Finally, it is likely that TE is not the only cortical region outside the frontal lobe to be the target of basal ganglia output. Anatomical studies in a variety of primates have indicated that selected regions of VAmc that receive input from SNpr could project not only to TE, but also to several other cortical areas related to the visual system (8, 41-47). Thus, as has been suggested for some non-primate species (48, 49), the basal

ganglia influence on the cerebral cortex of primates may be considerably more widespread than generally thought.

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