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The Neostriatal Mosaic: Striatal Patch-Matrix Organization Is Related to Cortical Lamination

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The basal ganglia, of which the striatum is the major component, process inputs from virtually all cerebral cortical areas to affect motor, emotional, and cognitive behaviors. Insights into how these seemingly disparate functions may be integrated have emerged from studies that have demonstrated that the mammalian striatum is composed of two compartments arranged as a mosaic, the patches and the matrix, which differ in their neurochemical and neuroanatomical properties. In this study, projections from prefrontal, cingulate, and motor cortical areas to the striatal compartments were examined with the *Phaseolus vulgaris*–leucoagglutinin (PHA-L) anterograde axonal tracer in rats. Each cortical area projects to both the patches and the matrix of the striatum; however, deep layer V and layer VI corticostriatal neurons project principally to the patches, whereas superficial layer V and layer III and II corticostriatal neurons project principally to the matrix. The relative contribution of patch and matrix corticostriatal projections varies among the cortical areas examined such that allocortical areas provide a greater number of inputs to the patches than to the matrix, whereas the reverse obtains for neocortical areas. These results demonstrate that the compartmental organization of corticostriatal inputs is related to their laminar origin and secondarily to the cytoarchitectonic area of origin.

THE STRIATUM, WHICH COMPRISES the caudate, putamen, and accumbens nuclei, is composed of two distinct compartments, termed the patches and matrix, that are arranged as a mosaic (*1–4*). Neurochemical markers are differentially distributed in these compartments. For example, patches are rich in μ-opiate receptor binding sites (*3*), whereas the matrix contains calbindin D_{28kD} immunoreactive neurons and a rich plexus of somatostatin fibers (*5*). Neuroanatomical studies have established that the compartmental patterns of cortical (*2, 4, 6, 7*), thalamic (*3, 8*), and dopaminergic (*9*) inputs and the patterns of the outputs of the patches and matrix (*4, 5, 10*) reflect segregated input-output systems. Previous studies have related the compartmental organization of corticostriatal inputs to the cortical area of origin (*4, 6*), that is, the prelimbic cortex has been shown to project to the patch compartment, whereas most neocortical areas examined, including motor and visual cortices, have been shown to project to the matrix. The prelimbic cortex receives major inputs from limbic brain areas, including the amygdala (*11*), and the amygdala has been shown to project directly to the patches (*12*). These findings might suggest that limbic-related systems provide the major input to the patches, whereas neocortical areas provide inputs to the matrix. Before accepting as a general rule this allocortical versus neocortical segregation of patch and matrix inputs, a more thorough examination of the compartmental organization of corticostriatal projections was initiated.

Iontophoretic injections of the anterogradely transported axonal tracer *Phaseolus vulgaris*–leucoagglutinin (PHA-L) (*13*) were stereotaxically placed into the frontal cortex of 150 adult Sprague-Dawley rats. After 2 weeks the brains were processed by standard immunohistochemical procedures (*14*) to localize the PHA-L, which had been incorporated into neurons at the injection site in the cortex and anterogradely transported in the axons. Adjacent sections through the striatum were processed for immunohistochemical staining of calbindin D_{28kD}, a striatal matrix-specific marker (*5*), to identify the distribution of PHA-L–labeled corticostriatal inputs to either the matrix or patch striatal compartments. The cortical areas injected were the infralimbic,

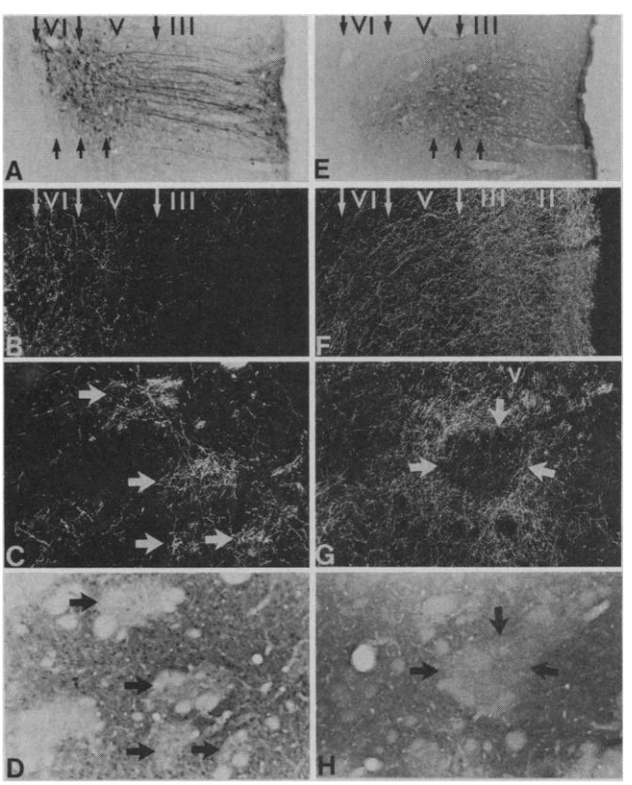

Fig. 1. Photomicrographs of PHA-L labeling after injections into the prelimbic cortex in two animals. In the first animal (A to D), PHA-L–injected neurons are located in layer VI and deep layer V (**A**). Axonal labeling is observed in the deep layers of the homotypic contralateral cortex (**B**) and in the striatal patches (arrows in **C**), which are marked by low levels of calbindin immunoreactivity in the adjacent section (arrows in **D**). In the second animal (E to H), PHA-L–injected neurons are located in upper layer V and in layers II and III (**E**). Axonal labeling is observed in the superficial layers of the contralateral homotypic cortex (**F**) and in the striatal matrix (**G**), which is marked by calbindin immunoreactivity in the adjacent section (**H**).

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prelimbic, and anterior cingulate cortices on the medial bank of the frontal pole, the medial agranular motor cortex on the medial shoulder of the frontal pole, and the lateral agranular motor cortex on the dorsal surface of the frontal pole. Three criteria were used to determine that PHA-L–labeled neurons at the injection site in a single case were confined to a single cytoarchitecturally defined cortical area: (i) the location of the PHA-L–labeled neurons at the injection site, (ii) the distribution of the crossed corticocortical projection, which is densest in the contralateral homotypic cortex, and (iii) the distribution of labeled afferents in the thalamus.

Neurons with PHA-L labeling were confined to the prelimbic cortex in 20 cases. In the thalamus, labeled afferents were distributed most densely in the mediodorsal nucleus. A dense input was labeled in the homotypic cortical area contralateral to the injection. Although the patterns of thalamic and cortical labeling in each of the prelimbic injection cases were similar, there were variations in the laminar distributions of the crossed corticocortical projection among animals, which was related to the laminar location of the labeled neurons at the injection site (Figs. 1 and 2). In the first animal, the majority of PHA-L–injected neurons was located in layers VI and deep layer V of the prelimbic cortex, and the input to the contralateral homotypic cortical area was restricted to these same layers. In the second animal, the majority of PHA-L–injected neurons were located in superficial layer V and layers II and III of the prelimbic cortex, and the input to the contralateral cortex was distributed also to these more superficial laminae. Labeled corticostriatal inputs for these two animals were similarly distributed in the medial striatum, but differed in terms of their relative distributions to the patch and matrix compartments. In the case of the deep cortical injection, striatal inputs were distributed primarily to the patches, whereas in the case of the more superficial laminar injection, the labeled inputs were distributed primarily to the striatal matrix (*15*).

Injections in the infralimbic, anterior cingulate (Figs. 2 and 3), and lateral and medial agranular cortices (Fig. 4) showed similar patterns of the laminar origin of striatal patch and matrix inputs as observed with the prelimbic injections. These cases revealed additional organizational features. First, there was a rough topographic organization of the inputs from cortical areas to the striatum, with ventral and dorsal cortical areas projecting to ventral and dorsal striatal regions, respectively. This topographic organization applied to inputs of both compartments such that patches innervated by a particular cortical area were surrounded by matrix innervated by the same cortex. Second, there was a difference in the relative contribution of the different cortical areas in the density of inputs to the patch compartment, with the densest inputs from the infralimbic and prelimbic cortex, moderate inputs from the anterior cingulate cortex, and rather sparse, albeit distinct, inputs from the medial and lateral agranular cortices. These findings are consistent with studies in which retrogradely transported tracers have demonstrated a transition of the laminar distribution of corticostriatal neurons from the prelimbic cortex, where most cells are located throughout layer V and some in layer VI, to the agranular motor cortex, where the majority are located in superficial layer V and in layer III (*16,* 17). A similar, although more complex, laminar organization of corticostriatal neurons in primates and dogs has shown a greater concentration of corticostriatal neurons in infragranular layers in allocortical areas as compared with a greater number of supragranular corticostriatal neurons in neocortical areas (*18*). Third, some injections into superficial layer V resulted in discontinuous patterns of inputs to the striatal matrix (Fig. 4G). Such patterns are not to be confused with inputs to the striatal patch compartment and are related to other aspects of corticostriatal organization.

Reports that the prelimbic cortex projected to the striatal patches and neocortical areas to the matrix most likely reflected the labeling of the predominant type of corticostriatal projection from each area (*4, 6*). Although the present data reaffirm that the cortical area of origin is an important determinant of the relative contribution of inputs to the striatal compartments, they suggest additionally that the underlying organization is related to the laminar origin of those inputs. Previous studies have stressed the relation between striatal patches and connections with the limbic system, for example, from the amygdala (*12*) and prelimbic cortex (*4, 6*). However, such connections are regionally specific to the ventral and medial striatum. Moreover, a reassessment of the suggestion that the striatal patch-

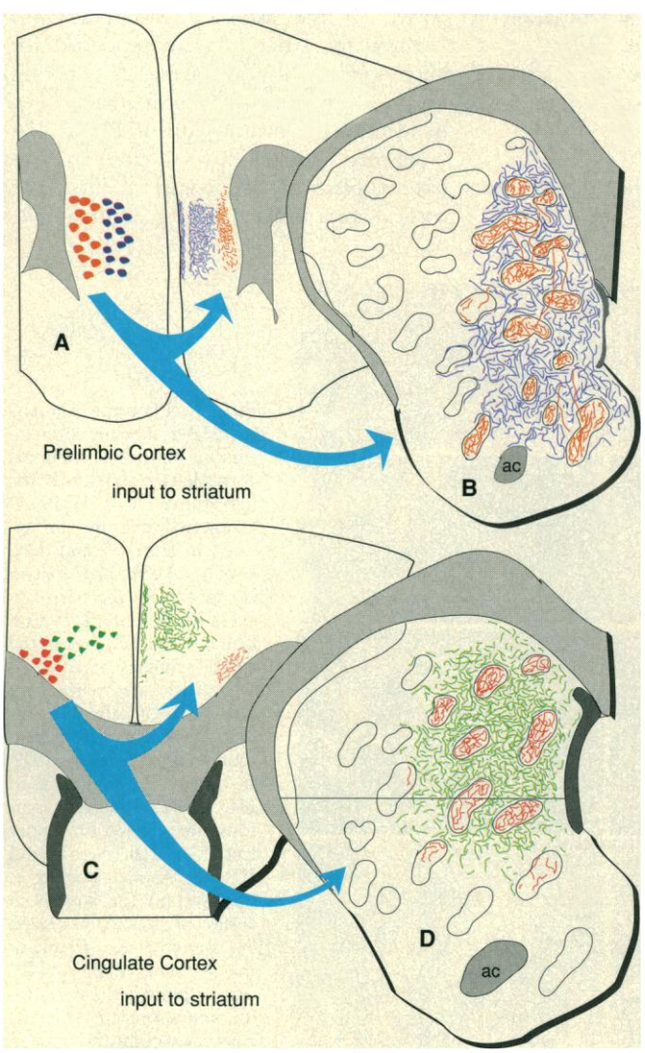

Fig. 2. The patterns of PHA-L labeling in the cortex and striatum from injections in the prelimbic cortex (**A** and **B**) and anterior cingulate cortex (**C** and **D**). In this diagrammatic representation, camera lucida tracings from individual animals were merged to depict labeling from layer VI and deep layer V neurons (cells and axons labeled orange or red) and superficial layer V and layer II and III neurons (cells and axons labeled blue or green) in a single cortical area. Injections into both cortical areas show a correlation between the laminar location of the PHA-L–labeled neurons at the injection site, the laminar distribution of projections to the contralateral homotypic cortical area, and the specific targeting of labeled inputs to striatal patches (from deep layer injections) and striatal matrix (from superficial layer injections).

matrix organization is related to a simple dichotomy between "limbic" and "nonlimbic" function is required, given the present findings of prelimbic cortex inputs to the striatal matrix and neocortical (medial and lateral agranular cortices) inputs to the patches in the dorsal striatum. The differences in the projections from different cortical areas to the two compartments are relative, as each area examined provides inputs to both striatal patch and matrix compartments. Thus, these findings indicate a more fundamental principle of patch-matrix function is related to an organization in all cortical areas that segregates the outputs of separate types of cortical neurons to differentially affect the striatal patch and matrix neurons.

The laminar organization of the cerebral cortex is related to the aggregation of pyramidal neurons that have common axonal projection targets (*19*). A number of different subtypes of corticostriatal neurons have been described that differ on the basis of axon collaterals to other brain sites, such as to the pyramidal tract, thalamus, contralateral cortex, and contralateral striatum (*17, 20*). Corticostriatal neurons also show differences in local axon collaterals with different patterns of laminar and regional spread (*17, 20*). Although the laminar and sublaminar distributions of subtypes of corticostriatal neurons have not been established, these types of connectional distinctions presumably underlie the functional significance of the laminar origins of corticostriatal projections to the striatal patch and matrix compartments. As previously demonstrated, patch and matrix neurons provide different inputs to the location of the dopaminergic neurons and neurons expressing γ-aminobutyric acid (GABA) in the substantia nigra, respectively (*4, 5, 10*). Thus the laminar segregation of the outputs of corticostriatal neurons provides pathways for each cortical area to differentially affect these compartmentally organized output pathways of the striatum.

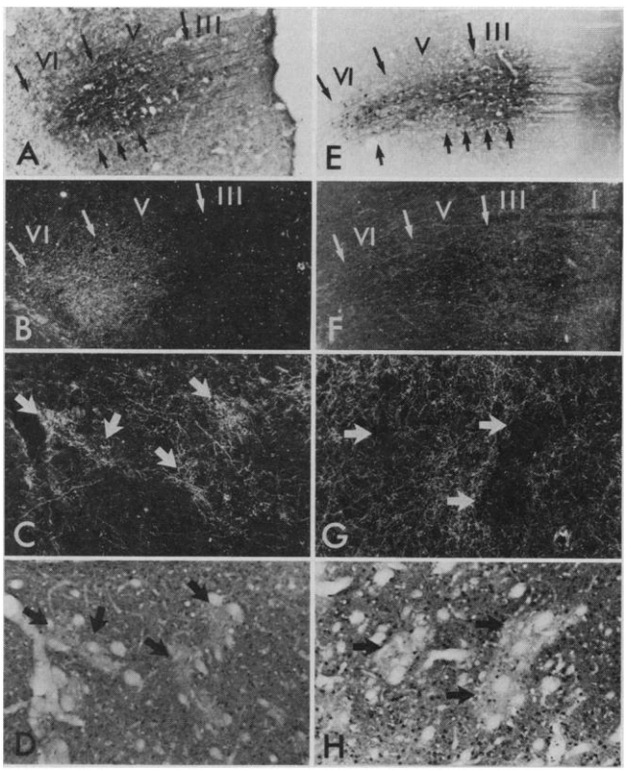

Fig. 3. Photomicrographs of PHA-L labeling after injections into the anterior cingulate cortex. In the first animal (A to D), PHA-L–injected neurons are located in layer VI and deep layer V (**A**). Axonal labeling is observed in the deep layers of the homotypic contralateral cortex (**B**) and in the striatal patches (arrows in **C**), which are marked by low levels of calbindin immunoreactivity in the adjacent section (arrows in **D**). In the second animal (E to H), a few labeled neurons are in deep layer V and layer VI, but the majority are located in upper layer V and in layers II and III (**E**). Axonal labeling is observed in the superficial layers of the contralateral homotypic cortex (**F**) and in the striatal matrix (**G**), which is marked by calbindin immunoreactivity in the adjacent section (**H**).

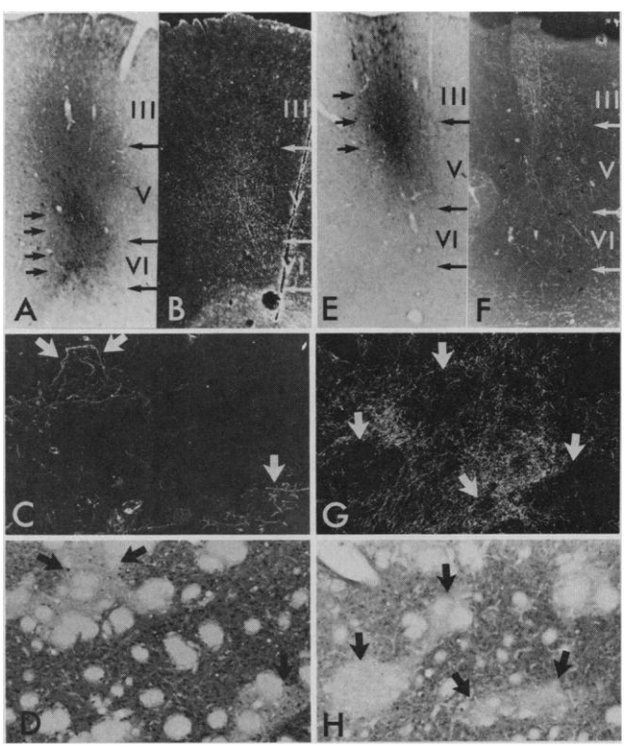

Fig. 4. Photomicrographs of PHA-L labeling after injections into the medial agranular motor cortex. In the first animal (A to D), labeled neurons are located in layer VI and deep layer V (arrows in **A**). Axonal labeling is observed in the deep layers of the homotypic contralateral cortex (**B**) and in the striatal patches (arrows in **C**), which are marked by low levels of calbindin immunoreactivity in the adjacent sections (arrows in **D**). In the second animal (E to H), labeled neurons are located in upper layer V and in layers II and III (arrows in **E**). Axonal labeling is observed in the superficial layers of the contralateral homotypic cortex (**F**) and in the striatal matrix (**G**), which is marked by calbindin immunoreactivity in the adjacent section (**H**).

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14. When the rats were anesthetized with sodium pentobarbital, a 2.5% solution of PHA-L diluted in 0.05*M* sodium phosphate buffer (*p*H 7.8) was introduced by iontophoresis into the cortex through glass micropipettes (tip diameter 10 to 15 μm) with a positive current of 5 μA applied every other 7 s for 15 min. After 14 days, the animals were deeply anesthetized and perfused transcardially with 0.9% saline followed by 4% formaldehyde in 0.1*M* sodi-

um phosphate–buffered saline (PBS, *p*H 7.4). After saturation with 20% sucrose, the frozen brains were cut on a microtome into 30-μm-thick sections, which were processed by immunohistochemical procedures to obtain labeling of axonally transported PHA-L. Sections reacted for immunohistochemical labeling were first incubated for 48 hours at 4°C in potassium PBS plus 2% normal goat serum and 0.5% Triton X-100 to which had been added rabbit antiserum directed against PHA-L (diluted 1:2000, Vector Labs). After incubation in the primary antiserum, sections were processed with the avidin-biotin immunoperoxidase method (*5, 7, 12, 15*).

15. The particular crossed corticortical axons that were labeled were not assumed to be collaterals of axons also projecting to the striatum. Rather, it was the consistent correlation between the laminar location of the labeled neurons, the laminar distribution of the crossed corticocortical projection, and the distribution of labeled inputs to the patch or matrix compartment that indicated that the laminar distribution of labeled corticostriatal neurons determined the compartmental distribution of their striatal projections. From the set of cases with prelimbic injections (n = 20), seven showed inputs directed principally to patches, five showed inputs directed principally to matrix, and seven showed inputs to both compartments. In the last case these inputs had both deep and superficial layer neurons injected.
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"Apparently big science isn't big enough for both of them."