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A simple ordering of neocortical areas established by the compartmental organization of their striatal projections

(frontal cortex/striosomes/acetylcholinesterase/basal ganglia)

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ABSTRACT **The compartmental organization of corticostriatal projections from the fronto-orbito-insular cortex was studied in the cat. Cortical areas in this field were found to have a highly organized projection to the striatum, selectively innervating striosomes dorsally and predominantly avoiding them ventrally within their striatal fields of termination. These observations have two important implications for striatal processing. First, some cortical areas preferentially terminate in different compartments in different parts of the striatum. Therefore, the sources of input to striosomes and matrix are not categorical but switch according to the striatal region considered. Second, three properties of the bicompartmental termination pattern—one-dimensionality, common polarization, and multiple positions at which the pattern switched from "fills" to "avoids"—allowed us to order the corticostriatal projections with respect to one another. This ordering of the striatal projections of cortical areas implies an ordering of the cortical areas themselves, one that is independent of transcortical connections. For the corticostriatal projections described in this report, the ordering is ⟨parietal, dorsomedial prefrontal, ventrolateral prefrontal, insular, rostral temporal⟩ cortex. Our analysis suggests that a major function of striatal compartmentalization is to segregate and then bring together inputs from cortical areas at different positions in this ordering. The ordering may also serve as a simple format for specifying corticostriatal connections in development.**

The cerebral cortex is made up of layers and columns (1, 2). These structures organize the subcortical and local connections of a cortical area to allow for selective convergence and divergence of information during cortical processing (3). Anatomical studies employing tract-tracing techniques have suggested that a major additional task for cortical layering is to place interconnected cortical areas in a hierarchical order. This hierarchy has been interpreted functionally as establishing a specific progressivity in cortical processing (4–6). The cortical visual system of the primate offers the most explicit examples of this proposed hierarchical processing. Motion information, for example, is thought to undergo successive analyses by (*i*) layer IVb of area 17, (*ii*) then by the so-called thick stripes of area 18, (*iii*) area MT of prestriate cortex, and (*iv*) certain of the visual areas of posterior parietal cortex (5–8).

The mammalian striatum also has a modular organization. It is made up of intermingled histochemically distinct tissue compartments, striosomes and matrix (9–11), that differ in their input–output anatomy (10, 12–14). Anatomical studies have identified specific populations of striatal neurons that interconnect these two compartments (14–17), suggesting that a central function of striatal tissue is to bring together the inputs to striosomes and to the surrounding matrix in restricted and highly specific ways. Insight into this function has been hindered by a lack of understanding of the differences between the information delivered to striosomes and matrix. However, because the striatum lacks medium- and long-distance association connections comparable to those of the cortex, the functional roles of the striatal compartments cannot be to establish a simple hierarchy of stages of information processing. We have tested whether there could be other sorts of organizing principles at work. We report here an analysis of corticostriatal connections indicating that corticostriatal circuits can be ordered simply and consistently with respect to one another according to their predominant compartmental terminations. This ordering of corticostriatal projections implies an equivalent ordering of the cortical areas themselves. Furthermore, it suggests that a global principle, different from but possibly as fundamental as the hierarchical ordering of cortical areas, might underlie the functional roles of striatal compartmentalization.

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MATERIALS AND METHODS

Healthy adult cats were deeply anesthetized with two to four doses of ketamine hydrochloride (13 mg/kg) and xylazine (0.6 mg/kg). Deposits of radiolabeled amino acids ([^{3}H]leucine and [^{3}H]proline, or [^{35}S]methionine) were delivered intracerebrally with a 1-μl Hamilton syringe. Approximately 80–150 nl of tracer at a concentration of 75–200 μCi/nl (1 Ci = 37 GBq) were injected at each site. Two days to 4 weeks postoperatively, the cats were deeply anesthetized with barbiturate and perfused transcardially with a heparinized 0.9% NaCl solution followed by 4% paraformaldehyde in a 0.1 M dibasic phosphate-buffered saline (PBS) solution (pH 7.4). The perfusion was completed with a fixative-free PBS rinse with up to 10% sucrose added. Following cryoprotection in a 30% sucrose/PBS wash, the brains were cut at 30 μm on a sledge microtome. One out of every six tissue sections through the striatum was processed for autoradiography to demonstrate the anterogradely transported label. Sections were defatted, dipped in Kodak NTB-2 emulsion, and stored at −20°C for up to 34 weeks. The autoradiograms were developed in Kodak D-19 at 12–16°C for 3 min, and Nissl substance was stained with cresylecht violet. Striosomes were identified in serially adjoining sections prepared for acetylcholinesterase (AChE) histochemistry with the thiocholine staining method (9, 18).

RESULTS

Fiber projections to the striatum (caudate nucleus and putamen) were demonstrated by autoradiography in 53 cats and were related to the distribution of striosomes identified as enzyme-poor zones in serially adjoining sections stained for AChE activity (9). As is well-known (19, 20), different

Abbreviation: AChE, acetylcholinesterase.

cortical areas have different fields of termination in the striatum, some quite limited and others quite extensive. Within these fields of termination, some cortical areas have been found to project predominately (but not exclusively) to striosomes, and others have been shown to innervate principally (but not exclusively) the matrix tissue (12, 21–23).

The principal finding in the present set of experiments is that a sweep of cortex extending from medial prefrontal cortex to the insula sends fibers to both striatal compartments in a highly selective manner: these fibers innervate striosomes dorsally and avoid them ventrally within their striatal fields of termination. Fig. 1 illustrates this pattern by an example in which the transition between the dorsal "fills" and the ventral "avoids" was particularly abrupt. The autoradiogram shown was selected from a case in which a small deposit of radiolabeled amino acids was placed in the dorsomedial prefrontal cortex of the contralateral hemisphere (see Fig. 1 *Inset A'*). A dorsal fill/ventral avoid pattern of innervation was documented in 26 cats. In no case was the opposite pattern of dorsal avoids with ventral fills observed.

Within cases, the relative position in the dorsoventral axis of the transitions between fills and avoids was maintained throughout the rostrocaudal extent of the projection except near the rostral pole of the caudate nucleus, where the position of the transition shifted ventrally. Across cases, however, the dorsoventral elevation at which the pattern of compartmental innervation switched from fills to avoids was not preserved, but shifted with the corticostriatal projection studied. We therefore systematically compared the patterns in all cases, choosing mid-rostrocaudal levels of the caudate nucleus as the region for the analysis. It was possible to order the corticostriatal projection patterns along a single axis according to the dorsoventral position at which the transition from fills to avoids occurred. Fig. 2 illustrates this ordering for five cases with deposits in posterior parietal (charting 1), dorsomedial prefrontal (charting 2), ventrolateral prefrontal (charting 3), insular (charting 4), and rostral temporal (charting 5) cortices. The sequence runs from an all-avoid (i.e., preferentially matrix-directed) projection from the parietal cortex to the dorsal caudate nucleus (Fig. 2, charting 1), through a series of three cases with dorsal fill/ventral avoid patterns having progressively more ventral elevations of the switch, to a termination pattern in which striosomes are preferentially filled to the base of the caudate nucleus (Fig. 2, charting 5).

That a property of these cortical areas, that is, the compartmental pattern of their innervation of striatum, can be ordered implies that the cortical areas themselves can be ordered with respect to one another. This ordering is not limited to the cortical areas illustrated. The posterior cingulate cortex, for example, principally innervates the striatal matrix in the dorsal and medial caudate nucleus (22) and so can be placed with parietal cortex at the left end of the ordering; the ventromedial prefrontal cortex shares the right end of the ordering with the rostral temporal cortex as it also preferentially innervates striosomes throughout the ventral caudate nucleus (ref. 25; unpublished results).

These findings may not be restricted to the compartmental organization of corticostriatal projections from the association areas of cortex. Sensory and motor cortices also project to the striatum but predominantly terminate in the putamen and the lateral caudate nucleus (19, 26). Analysis of our more limited case material for this striatal territory suggests that cortical areas projecting to the lateral striatum can also be ordered according to their corticostriatal projection patterns (unpublished results). For example, primary somatosensory cortex can be placed with the anterior parietal cortex at the left end of this ordering as both project predominantly to extrastriosomal matrix in the dorsolateral caudate nucleus and putamen (21, 25, 27).

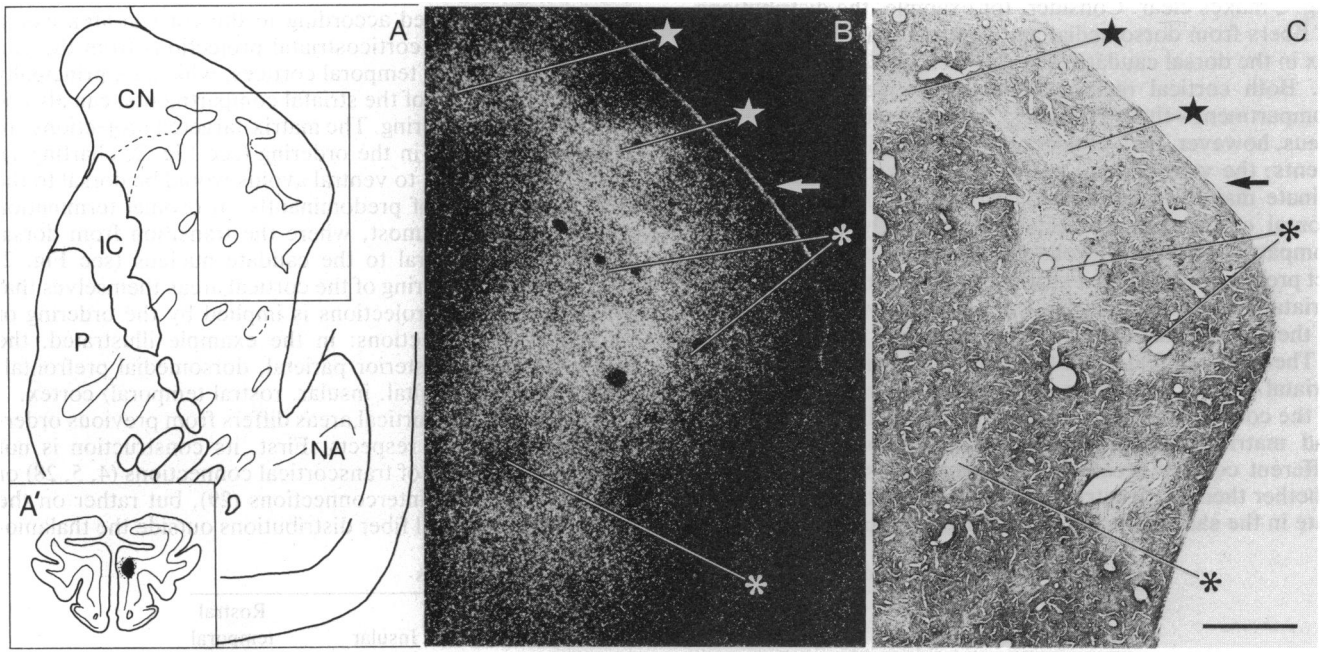

FIG. 1. Corticostriatal fibers from frontal cortex preferentially innervate (fill) striosomes dorsally and avoid them (preferentially innervate matrix) ventrally within their striatal terminal fields. (*A*) Line drawing of an AChE-stained cross section through the striatum. AChE-poor striosomes are outlined. Photomicrographs of the area enclosed in the box are shown in *B* and *C*. The section in *B* was processed for autoradiography to demonstrate corticostriatal terminals. The section in *C* serially adjoins that in *B* and was processed for AChE activity. Fibers were labeled by a deposit of [^{3}H]proline and [^{3}H]leucine placed in the medial prefrontal cortex contralaterally (case CRCx-35). A similar pattern of labeling was observed in the ipsilateral caudate nucleus. (*Inset A'*) Charting of the injection site. The stars in *B* and *C* indicate dorsal AChE-poor striosomes that are preferentially innervated by the cortical fibers; the asterisks mark more ventral striosomes that are selectively avoided. The arrow indicates the dorsoventral level at which the switch from the dorsal fill to the ventral avoid pattern occurs. CN, caudate nucleus; IC, internal capsule; NA, nucleus accumbens; P, putamen. (Exposure time, 31 weeks; bar = 0.5 mm.)

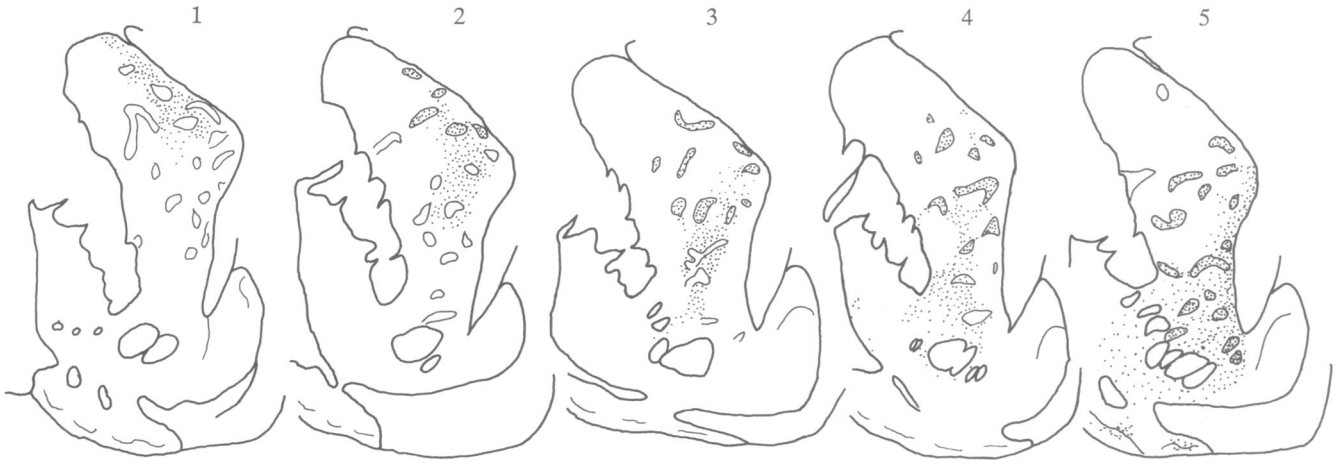

FIG. 2. Patterns of corticostriatal projection to mid-levels of the caudate nucleus observed in five cases with tracer deposits in posterior parietal, dorsomedial prefrontal, ventrolateral prefrontal, insular, and rostral temporal cortices (chartings 1–5, respectively). The AChE-poor striosomes are shown by outlines, and the patterns of termination of corticostriatal fibers observed in serially-adjacent autoradiograms are indicated by stippling. The projection patterns are arranged and numbered 1–5 according to the dorsoventral elevation at which the striatal compartment preferentially innervated switches from striosomes to matrix. This ordering of corticostriatal termination patterns implies an ordering across the cortical areas injected in these cases.

DISCUSSION

The central finding of this report is that corticostriatal projections from fronto-insular cortex terminate preferentially in striosomes dorsally and in matrix tissue ventrally within their striatal terminal fields. Thus, for a large district of frontal and lateral cortex, the compartmental target of corticostriatal projections cannot be simply typed as being predominantly the striosomes or principally the extrastriosomal matrix. This bicompartmental pattern of termination creates a remarkable complexity in the relationship between corticostriatal projections from different cortical areas, as an examination of Fig. 2 makes clear. Consider, for example, the distributions of fibers from dorsomedial and ventrolateral prefrontal cortex in the dorsal caudate nucleus (see Fig. 2, chartings 2 and 3). Both cortical regions project selectively to the same compartment—the striosomes. In the central caudate nucleus, however, they project principally to different compartments; the ventrolateral prefrontal cortex continues to terminate mainly in the striosomes, but the dorsomedial prefrontal cortex here projects predominantly to the matrix compartment. The ventrolateral prefrontal cortex does project preferentially to the extrastriosomal matrix in a part of its striatal terminal field but only at a yet more ventral location, in the ventral part of the caudate nucleus.

The essential feature of this organization is that, from one striatal district to another, there is a systematic realignment of the cortical areas that project, respectively, to striosomes and matrix. This organization raises two questions. Do different cortical areas have characteristics that determine whether their corticostriatal fibers will predominantly terminate in the same or in different striatal compartments? And, do these characteristics suggest any general description of the difference between the inputs of striosomes and those of matrix? The key to answering these questions may be the finding that corticostriatal projection patterns can be ordered with respect to each other in a straightforward way.

The ordering we propose is founded on three properties of the termination of striatal projections from fronto-insular cortex. First, the bicompartmental patterns of termination are organized along a single dimension (the dorsoventral axis). Second, they are polarized in a common direction (fills were always dorsal). Third, they can assume multiple values (the striatal elevation of the transition from dorsal fills to ventral avoids shifted according to the cortical area examined). Importantly, corticostriatal projections from the cingulate, parietal, and temporal cortices, which are principally targeted to just one of the striatal compartments, can also be included in this ordering. The matrix-targeted projections are positioned leftmost in the ordering (see Fig. 2, charting 1), where the transition to ventral avoids would be dorsal to the striatum. Patterns of predominantly striosomal termination are positioned rightmost, where the transition from dorsal fills would be ventral to the caudate nucleus (see Fig. 2, charting 5). An ordering of the cortical areas themselves that give rise to these projections is implied by the ordering of corticostriatal projections: in the example illustrated, the order would be ⟨posterior parietal, dorsomedial prefrontal, ventrolateral prefrontal, insular, rostral temporal⟩ cortex.

This ordering of cortical areas differs from previous orderings in two crucial respects. First, its construction is not based on the details of transcortical connections (4, 5, 28) or on thalamocortical interconnections (29), but rather on the properties of cortical fiber distributions outside the thalamo-

Table 1. Ordering of cortical areas according to their striosomal affiliations

Striatal region	Parietal	Dorsomedial prefrontal	Ventrolateral prefrontal	Insular	Rostral temporal
Dorsal CN	Avoids	Fills	Fills		
Central CN		Avoids	Fills	Fills	Fills
Ventral CN			Avoids	Fills	Fills
Basal CN				Avoids	Fills

Compartmental affiliations of corticostriatal projections illustrated in Fig. 2 are entered here in tabular form. This rendering of the data suggests that, for each striatal district in the dorsoventral axis, cortical areas that principally fill striosomes are ordered to the right of those that predominantly innervate matrix. Positions left blank in the table indicate that fibers traced from the cortical area in question do not innervate this striatal district. CN, caudate nucleus.

cortical system. Second, previous orderings have concerned the progression of connections leading from sensory and motor cortices to association cortex and into the limbic system (4, 5, 28, 30). Our ordering is largely orthogonal to these schemes, as it places rostral temporal cortex and parietal cortex not at the ends of pathways leading away from sensory cortex, but at opposite ends of an ordering of the so-called higher order association areas of the cerebral cortex.

For striatal compartmentalization, this ordering of cortical areas suggests that a simple difference characterizes cortical areas that preferentially innervate striosomes and those that favor matrix tissue within any region of the caudate nucleus. Table 1, where the information on corticostriatal projections charted in Fig. 2 is recorded in tabular form, illustrates this point. Cortical areas are entered from left to right according to their positions in the ordering, and the compartmental segregations of their fibers in each striatal district are noted. Inspection of each row demonstrates that, *for a given striatal region*, cortical areas that fill striosomes *always fall to the right* of those that preferentially innervate matrix tissue. This analysis indicates that a major role for compartmentalization of corticostriatal connections is to bring into juxtaposition in a systematic fashion inputs from cortical areas at different positions in the ordering, rather than to carry out a simple form of sequential processing.

We know of no functional properties that vary systematically across this ordering of cortical areas. However, cortex placed at the left (parietal) end of the ordering, such as cingulate cortex, is linked to Papez (hippocampal) circuitry, whereas cortex placed at the opposite end of the ordering, such as rostral temporal cortex, is affiliated with the amygdala-centered division of the limbic system (31). Recent behavioral work has focused on the functional distinctions between the hippocampal and amygdalar divisions of the limbic system (32). It suggests that, at least for memory function, Papez (hippocampal) circuitry may be important for remembering the spatial position of objects, whereas the amygdaloid complex may contribute more to associations based on object identity, including the emotional importance of objects (33–36). A major task for future work is to identify how these behavioral distinctions might apply to extrapyramidal functions, including those related to motor planning, and to identify what other functional properties also vary across this ordering of cortical areas.

Finally, our observations that one-dimensional orderings might underlie a quite complex pattern of neuronal innervation may also be important in understanding the development of the forebrain. The pattern of corticostriatal fiber terminations described here is significantly simplified if analyzed, first, by the position of the cortical area in a one-dimensional ordering and, second, according to the dorsoventral axis in its striatal terminal field. Both a simple ordering of cortical areas and position in the dorsoventral axis of the striatum could be established by chemical gradients acting early in development, a mechanism now known to be involved in specifying body pattern (24, 37).

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