Priority Communication

Biological Psychiatry

Circuit-Based Corticostriatal Homologies Between Rat and Primate

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ABSTRACT

BACKGROUND: Understanding the neural mechanisms of psychiatric disorders requires the use of rodent models; however, frontal-striatal homologies between rodents and primates are unclear. In contrast, within the striatum, the shell of the nucleus accumbens, the hippocampal projection zone, and the amygdala projection zone (referred to as the striatal emotion processing network [EPN]) are conserved across species. We used the relationship between the EPN and projections from the anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) to assess network similarities across rats and monkeys.

METHODS: We first compared the location and extent of each major component of the EPN in rats and macaques. Next, we used anatomic cases with anterograde injections in ACC/OFC to determine the extent to which corticostriatal terminal fields overlapped with these components and with each other.

RESULTS: The location and size of each component of the EPN were similar across species, containing projections primarily from infralimbic cortex in rats and area 25 in monkeys. Other ACC/OFC terminals overlapped extensively with infralimbic cortex/area 25 projections, supporting cross-species similarities in OFC topography. However, dorsal ACC had different connectivity profiles across species. These results were used to segment the monkey and rat striata according to ACC/OFC inputs.

CONCLUSIONS: Based on connectivity with the EPN, and consistent with prior literature, the infralimbic cortex and area 25 are likely homologues. We also see evidence of OFC homologies. Along with segmenting the striatum and identifying striatal hubs of overlapping inputs, these results help to translate findings between rodent models and human pathology.

Keywords: Cingulate, Homology, Infralimbic, Orbitofrontal, Prefrontal, Prelimbic

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Abnormalities of anterior cingulate cortex (ACC)- and orbitofrontal cortex (OFC)-striatal circuits are at the root of several psychiatric disorders, including posttraumatic stress disorder, obsessive-compulsive disorder, addiction, and major depressive disorder (1–4). Although studies in humans highlight the association between these circuits and disease, research on rodents is essential for understanding the mechanisms underlying normal and abnormal brain function. However, translating results from rodents to humans is challenging, as ACC/OFC homologies between rodents and humans remain controversial. In contrast, human-nonhuman primate (NHP) ACC/OFC homologies are fairly well established (5–7). Importantly, studies in NHPs and rats have demonstrated the topography of corticostriatal anatomic projections (Table 1). Thus, NHPs provide a key intermediate step to delineate homologies central for linking rodent mechanistic studies to human pathologies.

The ACC regions include areas 25 (a25), 32 (a32), and 24 (a24) in NHPs and infralimbic (IL), prelimbic (PL), and cingulate (Cg) in rats. Although IL and a25 are largely seen as homologues and share emotion processing functions, PL and Cg homologies have generated significant controversy. These areas share certain functional features with the dorsolateral prefrontal cortex (PFC) of NHPs (8,9), but cytoarchitecture and connectivity point toward PL and Cg as homologous with a32 and a24 in primates, respectively (7,10–12). Based on cytoarchitectonic similarity, the rat may possess regions homologous only to agranular NHP OFC (10). In contrast, based on thalamic projections, the entire primate OFC may be encapsulated within the rat lateral OFC (13).

In this article, we used a striatal-centric approach to examine network homologies. We started with three well-conserved and well-defined structures: the shell of the nucleus accumbens (NAccS), the hippocampus, and the amygdala. The location, histochemistry, connections, and functions of the NAccS, hippocampus, and amygdala are similar across rodents and NHPs (14–22). Importantly, these structures are central to emotion processing (23–25). Within the ventral striatum, the NAccS is uniquely histochemically identifiable (26) and has distinct hypothalamic and extended amygdala projections (27). Likewise, the projections from the amygdala and the hippocampus to the striatum are consistent and

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Table 1. Injection Sites and Sources

Rat	IL	PL	Cg	OFC	Hipp	Amyg	Totals
Deniau Collection		4	2	2			8
Groenewegen Collection	2	1	2	7	2	5	19
Haber Collection						1	1
Kelley and Domesick (30)					1		
Krettek and Price (28)						4	4
Reep *et al.* (72)				1			1
Hurley *et al.* (73)	1						1
Sesack *et al.* (74)		3	1				4
Zeng and Stuesse (75)		1					1
Vertes Collection (76,77)	1	1		2			4
Totals	4	10	5	12	3	10	54
Nonhuman Primate	vmPFC	OFC	dACC	dmPFC	Hipp	Amyg	Totals
Friedman *et al.* (20)					2	5	7
Cho *et al.* (78)						4	4
Haber Collection	3	9	7	7	1	2	29
Chiba *et al.* (79)	2		1				3
Ferry *et al.* (80)	2	11	1				14
Totals	7	20	9	7	3	11	57

Amyg, amygdala; Cg, cingulate; dACC, dorsal anterior cingulate cortex; dmPFC, dorsomedial prefrontal cortex; Hipp, hippocampus; IL, infralimbic cortex; OFC, orbitofrontal cortex; PL, prelimbic cortex; vmPFC, ventromedial prefrontal cortex.

reliable across species (20,28–31). Thus, we focused first on frontal connectivity with the NAccS, the hippocampal-striatal projection zone, and the amygdala-striatal projection zone, which together we refer to as the striatal emotion processing network (EPN). In contrast to these well-defined areas, the NAccS "core" describes the area outside of the shell (26,27). However, the lateral and dorsal boundary of the core is ambiguous, from both histochemical and connectivity perspectives (27,32), and it merges imperceptibly into the dorsal striatum. Thus, the lack of a precise dorsolateral boundary made a cross-species analysis of the core difficult.

In both NHPs and rodents, parts of the ACC/OFC project to the striatal EPN to varying degrees (33–37). We find that IL in rats and a25 in NHPs are the primary source of cortical input to the striatal EPN. Projections from other ACC/OFC areas overlap less with the EPN, but do overlap with IL/a25 terminal fields that are outside the EPN. We propose that the degree of overlap between these areas with the striatal EPN and IL/a25 indicates the extent to which they functionally interact with the EPN system. This provides critical data to the question of homologies, allowing us to improve on cross-species inferences about ACC/OFC-striatal networks.

METHODS AND MATERIALS

Overview

Starting with a sizable database of corticostriatal, hippocampal-striatal, and amygdala-striatal connectivities from our collections in the NHP (*Macaca fascicularis/mulatta/nemestrina*) and rat (*Rattus norvegicus;* Sprague Dawley, Wistar, hooded strains), we selected cases based on good tracer transport and lack of contamination (Figure 1) (29,31,33–36,38,39). To ensure that there were no gaps in areas of interest, we supplemented with new cases from our own collections and the literature. The connectivity overlap between each region of the ACC/OFC and the striatal EPN was compared between NHPs and rats to identify the locations of and relationships among ACC/OFC corticostriatal terminal fields. Based on these analyses, we established similarities between specific ACC/OFC regions across species and segmented the striatum accordingly.

Data Collection

Using material from the Haber, Groenewegen, and Deniau labs' histologically processed collections, we outlined injection sites

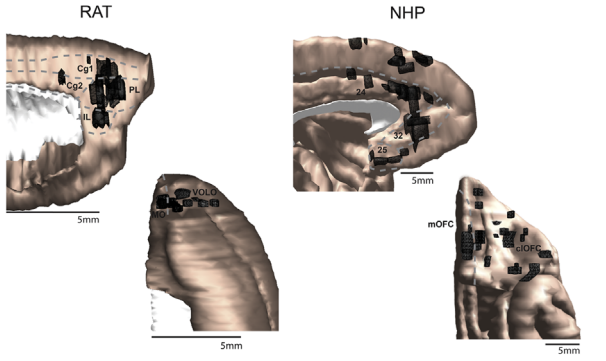

Figure 1. Injection sites. Injection sites for the rat (left) and nonhuman primate (NHP) (right) are shown in black on the medial (top) and orbital (bottom) frontal cortices. Approximate regional boundaries are demarcated with gray dotted lines. As in all figures, the rat brain has been enlarged relative to its actual size in comparison to the NHP brain for comparison purposes. Scale bars = 5 mm. Cg1/2, cingulate areas 1/2; clOFC, central/lateral orbitofrontal cortex; IL, infralimbic cortex; MO, medial orbital cortex; mOFC, medial orbitofrontal cortex; PL, prelimbic cortex; VOLO, ventrolateral orbital cortex.