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Caudate nucleus as a component of networks controlling behavior

Jonathan Graff-Radford, MD
Lindsy Williams, MD
David T. Jones, MD
Eduardo E. Benarroch, MD

Correspondence to J. Graff-Radford: GraffRadford.Jonathan@mayo.edu

The striatum participates in parallel corticobasal ganglia–thalamocortical loops interconnecting its different territories with areas of the frontal lobe, forming partially segregated motor, oculomotor, associative, and limbic circuits.[1] Human studies using resting-state fMRI[2–4] and diffusion tensor imaging[5–10] confirm the presence of a functional parcellation of the human striatum, particularly the caudate nucleus,[11] based on segregated corticostriatal connections. However, the corticostriatal connections are complex, and there are extensive interactions among functional territories.[12] Furthermore, the distinct territories of the striatum are functionally linked to cortical networks rather than specific cortical regions.[13] There are specific patterns of coactivation of different portions of the striatum and cerebral cortex across distinct psychological tasks, which only partially overlap the parcellation of the striatum based on steady-state connectivity.[14] The caudate nucleus contains several neuronal clusters that are functionally connected to cortical areas that are part of distributed networks involved in cognitive and emotional processing. This extensive connectivity explains the profound impairment in multiple cognitive and behavioral domains resulting from lesions of the caudate nucleus in humans.[15,16] The following 2 representative cases illustrate the profound consequences of caudate lesions in cognition and behavior and the associated widespread changes in frontal lobe metabolism.

Patient 1. A 60-year-old right-handed man was evaluated for cognitive and behavioral changes. Two years prior to presentation, he awoke with left-sided facial weakness that resolved the following day. A head CT scan showed a right basal ganglia infarction involving the caudate nucleus. When he returned to work, he was unable to supervise other employees, keep track of his schedule and meetings, and remember the details of the meetings. His wife noticed that after the stroke he has also experienced substantial personality changes, particularly lack of empathy. For example, he did not seem to care when his young grandchild was undergoing an evaluation for leukemia. He commented, "That's just the way it is sometimes. I didn't sleep well last night." She also noted that he had developed a craving for sweets and ate ice cream daily. Neuropsychological testing was normal with the exception of impaired performance on the Wisconsin Card Sorting Test. Brain MRI showed an old right caudate infarct extending to the putamen. 18C-Fluorodeoxyglucose (FDG) PET scan showed hypometabolism in the right frontal lobe involving dorsolateral and medial prefrontal cortex as well as the right anterior cingulate (figure 1).

Patient 2. A 56-year-old man was evaluated for striking behavioral changes following an episode of abrupt onset of left facial droop. At that time, a head MRI showed an infarct involving the right striatum. Following the stroke, his wife noticed he was less attentive to his hygiene and appearance than before the event. For example, he did not always comb his hair before going to work, and may wear dirty clothes or shirts with holes in them. He lost interest in fishing or hunting, which were prior hobbies. His wife also reports that he developed hypersexuality, including increased interest in having sexual intercourse with her, visiting a variety of pornography sites, and looking at websites to solicit for sexual relations. Brain MRI showed an old right striatal infarct. FDG-PET revealed asymmetric right frontal hypometabolism in addition to contralateral left cerebellar hypometabolism (figure 2).

DISCUSSION In patient 1, the lesion spans the head of the caudate, anterior part of internal capsule, and anterior putamen. The FDG-PET demonstrates the striking ipsilateral frontal hypometabolism affecting the dorsolateral prefrontal cortex, anterior cingulate, and medial prefrontal cortex. Dorsolateral prefrontal dysfunction has been associated with impaired

GLOSSARY
FDG = fluorodeoxyglucose.

From the Department of Neurology, Mayo Clinic, Rochester, MN.

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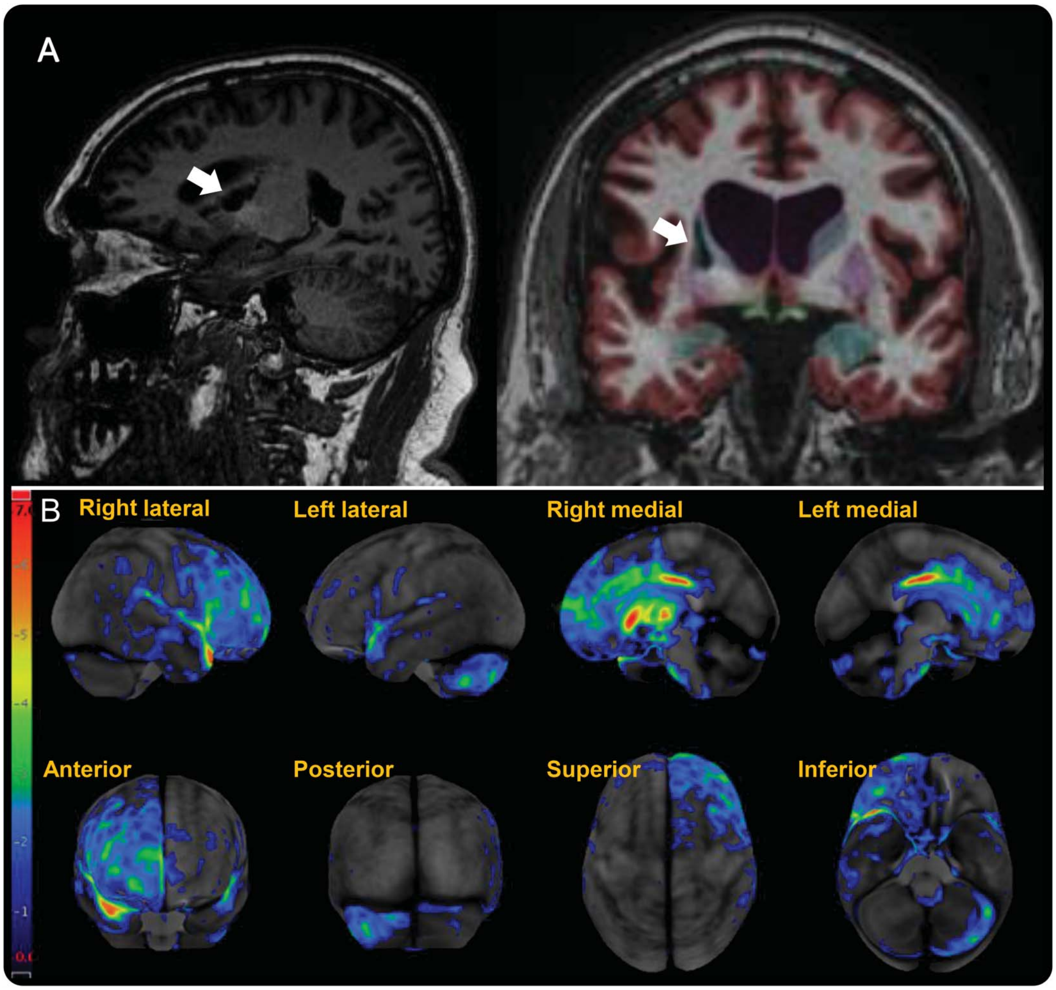
Figure 1 Neuroimaging findings in a 60-year-old right-handed man with acute onset executive dysfunction and loss of empathy following a right basal ganglia infarct affecting the caudate



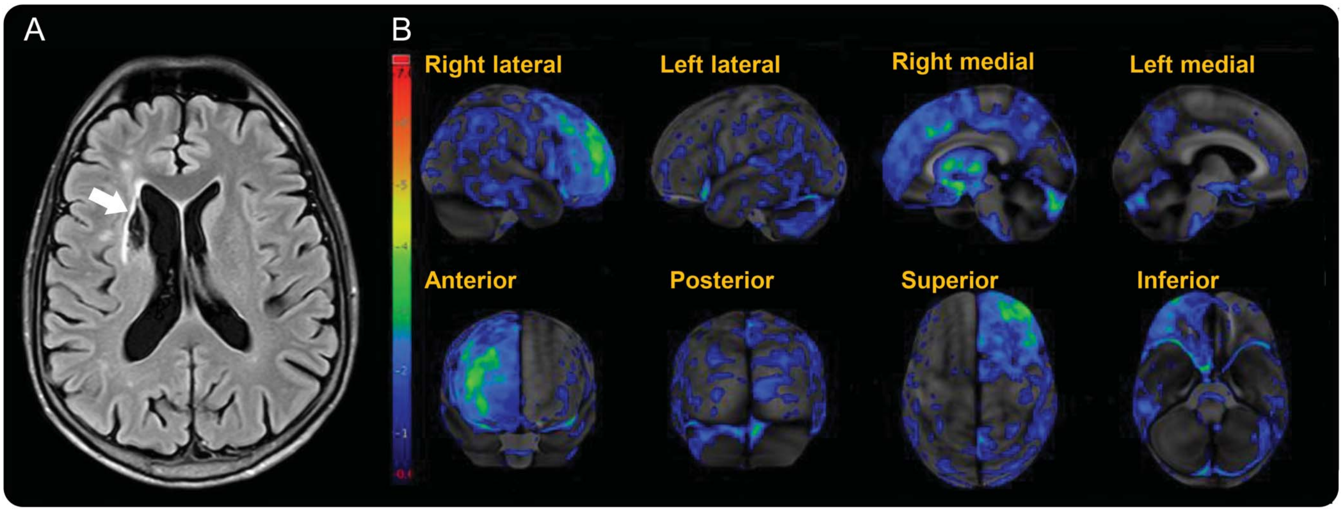
(A) Sagittal T1 MRI scan demonstrates caudate infarct (white arrow). Coronal MRI scan (NeuroQuant [CorTechs Labs, San Diego, CA]) with caudate highlighted in blue demonstrates the infarct. (B) Statistical map shows regions of significant hypometabolism relative to age-matched controls (GE Cortex ID). Fluorodeoxyglucose PET scan shows hypometabolism in the right striatum, in addition to the right medial prefrontal cortex, dorsolateral prefrontal cortex, and right anterior cingulate cortex.

performance on the Wisconsin Card Sorting Task, as seen in this patient. Loss of empathy, characterized by deficits in affective perspective-taking, has been associated with right prefrontal lesions. In patient 2, the lesion involved the head of the caudate extending into the putamen. As in patient 1, there was dorsolateral prefrontal and anterior cingulate cortex hypometabolism. In this case, there was also hypometabolism of the contralateral cerebellar hemisphere. This patient developed profound apathy, which is common after dorsolateral caudate strokes, as well as hypersexuality, which occurs with caudate lesions. In behavioral variant FTD, hypersexuality has been associated with right frontal dysfunction associated with right putamen atrophy; therefore, extension into the putamen may have contributed to hypersexuality in this case. The finding of cerebellar hypometabolism in this case is consistent with resting-state fMRI studies that have demonstrated the connectivity of the caudate with both the ipsilateral dorsolateral prefrontal cortex and contralateral cerebellum, as part of networks involved in executive and cognitive processes. Emerging concepts regarding the anatomical and functional organization of the caudate provides further insight into the mechanism underlying the neurologic manifestations in these 2 cases.

ORGANIZATION OF THE CORTICOSTRIATAL CIRCUITS

Connectivity of the striatum with the cerebral cortex. Based on its pattern of connectivity in primates, the striatum has been subdivided into a ventral and a dorsal striatum.[12] The ventral striatum includes the nucleus accumbens and the medial and ventral portions of the caudate and putamen. The dorsal striatum includes the central and dorsolateral portions of the caudate nucleus and the putamen. Cortical

Figure 2 **Neuroimaging findings in a 56-year-old man with acute changes in personality and behavior following a right basal ganglia infarct**



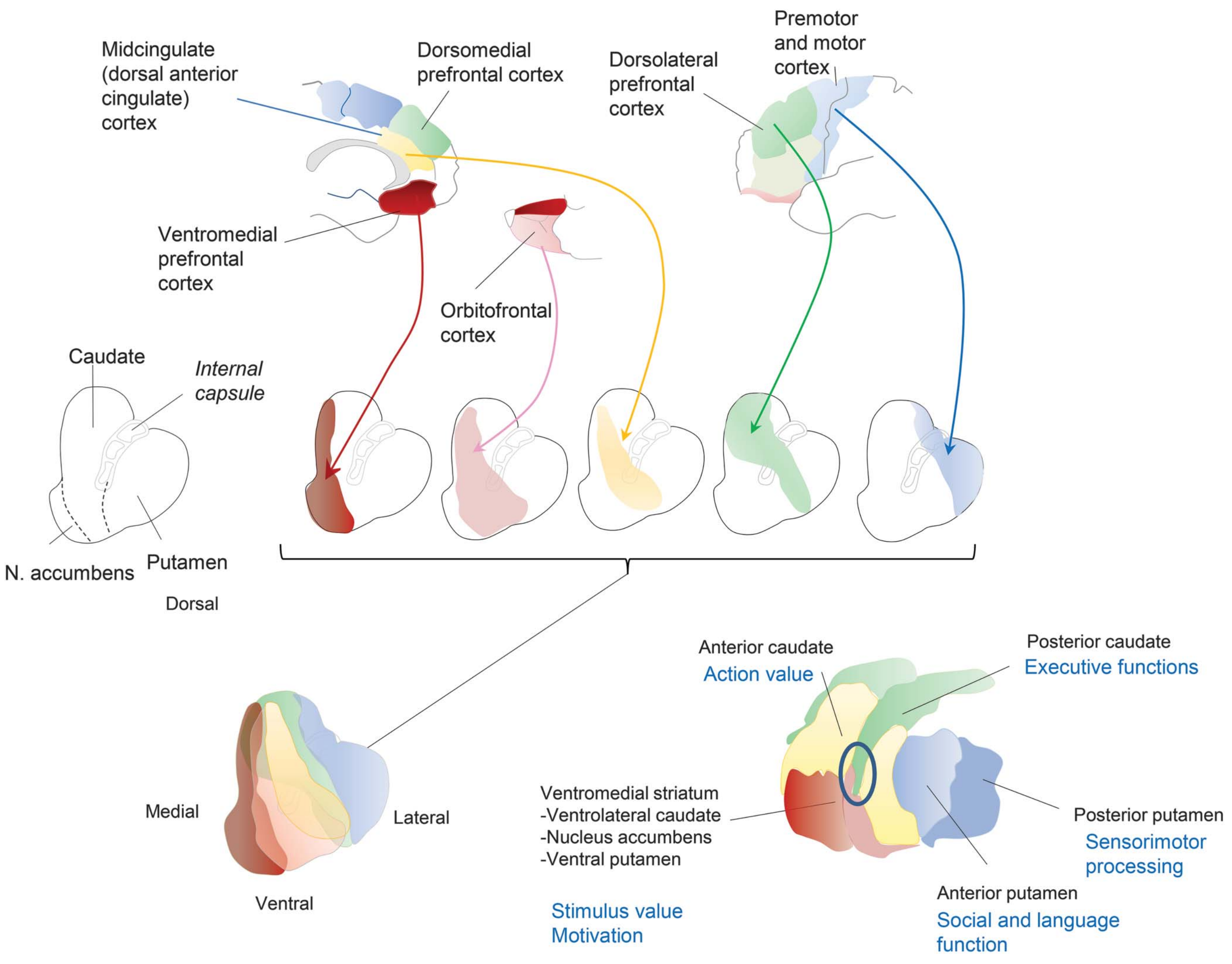
(A) T2 fluid-attenuated inversion recovery MRI demonstrates right caudate infarct extending into the anterior internal capsule and the anterior putamen (white arrow). (B) Statistical map shows regions of significant hypometabolism relative to age-matched controls (GE Cortex ID). Fluorodeoxyglucose PET scan shows hypometabolism in the right striatum, in addition to the right medial prefrontal cortex, dorsolateral prefrontal cortex, and right anterior cingulate cortex. There is also contralateral cerebellar hypometabolism.

inputs to the striatum are topographically organized (figure 3). The ventromedial portion primarily receives inputs from limbic areas, the central portion from associative cortical areas, and the dorsolateral portion from sensorimotor areas.[12] Whereas classical concepts of corticobasal ganglia–thalamocortical interactions emphasized the presence of parallel motor, cognitive, and emotional processing channels,[1] there are extensive interactions among functional territories of the striatum.[17–19] These interactions occur in specific regions due to convergence of terminal fields from different functional cortical regions, particularly at the level of the caudate nucleus. For example, the orbitofrontal and anterior cingulate cortices project to the ventromedial portion of the caudate (as well as nucleus accumbens and rostral putamen); the ventromedial prefrontal cortex projects to the medial portion of the caudate (as well as the shell of the nucleus accumbens); the midcingulate (also known as dorsal anterior cingulate) cortex extensively projects to the central caudate (and to a lesser extent the putamen); and the dorsolateral prefrontal cortex projects primarily to the rostral central region of the caudate.[12] There is an extensive rostrocaudal distribution of prefrontal projections to the caudate nucleus that interface with those of other cortical areas. For example, dorsolateral prefrontal projections to the central portion of the caudate overlap with those from the superior temporal gyrus; projections from the orbitofrontal and medial prefrontal cortex to medial portions of the caudate overlap with those of the inferior temporal cortex.[12]

Subcortical connectivity of the caudate nucleus. The different portions of the caudate nucleus, via their projections to the globus pallidus and substantia nigra pars reticulata, control the activity of neurons in the ventral anterior and mediodorsal nuclei of the thalamus that project to the prefrontal cortex. These connections are to a large extent topographically organized.[1,12] The caudate nucleus, like other portions of the striatum, participates in bidirectional communication with the cerebellum, forming parallel functional loops involving the thalamus and cerebral cortex.[20,21] These interactions occur via different pathways. They include projections of the striatum to the pallidum and then via the subthalamic nucleus to the pontine nuclei targeting the cerebellum; projections from the cerebellar nuclei to intralaminar thalamic nuclei targeting the striatum; and inputs from nigral, pallidal, and cerebellar thalamic territories to partially overlapping areas of the frontal lobe.[20,21] Consistent with these findings, probability maps show a highly reproducible connectivity of different portions of the striatum, not only with different areas of the cerebral cortex but also with the cerebellum.[22] Resting-state functional connectivity MRI shows that the cerebellum participates in intrinsic connectivity networks involved in executive control, episodic memory, self-reflection, salience detection, and sensorimotor function.[23] For example, there is connectivity of the caudate with the ipsilateral dorsolateral prefrontal cortex and contralateral cerebellum as part of networks involved in executive cognitive processes.

The caudate nucleus as an interface for emotional and cognitive processing. On the basis of criteria that include both cortical connectivity and putative functions, the caudate nucleus has been subdivided into

Figure 3 **Corticostriatal connections and functional correlations of the distinct territories of the striatum**



Cortical inputs to the striatum are topographically organized but there is convergence of terminal fields from different functional cortical regions. The orbitofrontal and anterior cingulate cortices project to the ventromedial portion of the caudate, nucleus accumbens, and rostral putamen; the ventromedial prefrontal cortex to the medial portion of the caudate and shell of the nucleus accumbens; the midcingulate (dorsal anterior cingulate) cortex to the central caudate (and to a lesser extent the putamen); the dorsolateral prefrontal cortex to the rostral central region of the caudate; and the sensorimotor cortex primarily to the dorsal and posterior putamen. Results from a meta-analysis of the patterns of coactivation of different portions of the striatum. The anterior caudate (head) has a role in cognitive and emotional functions; the posterior caudate (body) in executive functions; the ventral caudate together with the ventral putamen and nucleus accumbens in representation of stimulus value and stimulus-driven motivation; the anterior putamen in social and language functions; and the posterior putamen in sensory processing. (Modified from *Dialogues in Clinical Neuroscience* with the permission of the publisher [Association La Conférence Hippocrate, Suresnes, France][12] and W.M. Pauli.[14])

either ventral and dorsal regions[24–29] or anterior (head) and posterior (body) portions.[11,30,31] The ventral caudate, via its interconnections with the orbitofrontal, medial prefrontal, and anterior and midcingulate cortical areas, participates in emotional and affective aspects of behavior such as reward processing.[24,25] The dorsal caudate, which is primarily connected with to the dorsolateral prefrontal cortex, is involved in cognitive and executive functions, such as spatial working memory.[26–28] Other functional connectivity studies showed that the head of the caudate participates in cognition and emotion networks, whereas the body of the caudate participates in perceptual and action controlling functions.[11] Results from a meta-analysis of the patterns of coactivation of different portions of the striatum with the cerebral cortex during specific cognitive tasks indicated that the anterior caudate (head) has a role in cognitive and emotional functions, such as evaluation of value of different actions; the posterior caudate (body) in executive functions such as working memory, set shifting, and inhibitory control; and the ventral caudate, together with the ventral putamen and nucleus accumbens, in representation of stimulus value and stimulus-driven motivation.[14]

CLINICAL CORRELATIONS **Stroke.** The caudate nucleus is perfused by deep perforators of the carotid system. These include branches of the anterior cerebral artery, such as the recurrent artery of Heubner, irrigating the inferior head of the caudate, and the anterior lenticulostriate arteries, irrigating the anterior head of the caudate. The major portion of the caudate head is irrigated by the lateral lenticulostriate arteries that are branches of the middle cerebral artery.[32] Strategic vascular lesions affecting the caudate may thus produce cognitive and behavioral syndromes that mimic those occurring following frontal lesions.[15,16] Similar to the cases presented here, focal vascular lesions of the caudate head resulted in impaired social cognition, including loss of empathy; this was associated with hypoperfusion of the caudate and in ventromedial prefrontal cortex.[16] Patients with caudate lesions may also develop apathy, disinhibition, or a major affective disturbance.[15] The cognitive and behavioral manifestations of caudate lesions also mimic those observed following selective thalamic lesions producing functional thalamocortical disconnection.[33]

Neurodegenerative and psychiatric disorders. There is a major involvement of the caudate in neurodegenerative disorders that are associated with prominent cognitive and behavioral manifestations; typical examples are Huntington disease[34] and frontotemporal dementia, particularly that associated with fused in sarcoma neuropathology.[35] Involvement of the caudate has been has also been identified in psychiatric disorders such as schizophrenia,[36]depression,[37] and obsessive-compulsive disorders.[38]

PERSPECTIVE The cognitive and emotional consequences of caudate lesions associated with widespread hypometabolism in the prefrontal cortex and, as illustrated in patient 2, the contralateral cerebellum emphasizes the concept of network disorder as a cause of cognitive and behavioral manifestations of vascular, neurodegenerative, and psychiatric disorders. Thus, lesions of the striatum, as well as those involving the thalamus[23] or the cerebellum,[39] may produce the same spectrum of cognitive and affective syndromes as those associated with disorders affecting different portions of the prefrontal cortex. Whereas these syndromes show strong similarities, subtle differences exist, which probably reflect the specific contribution of neuronal processing in the striatum, cerebellum, thalamus, and cortex within each cognitive and emotional network.

AUTHOR CONTRIBUTIONS

J. Graff-Radford: design and conceptualization, analysis of data, drafting the manuscript. L. Williams: interpretation of data, revising the manuscript for intellectual content. D. Jones: interpretation of data, revising the manuscript for intellectual content. E. Benarroch: design and conceptualization, analysis of data, drafting the manuscript, and revising the manuscript for intellectual content.

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