

#### **REVIEW ARTICLE**

# **CORTICAL-SUBCORTICAL INTERACTIONS IN GOAL-DIRECTED BEHAVIOR**



**PHYSIOLOGICAL** 

REVIEWS

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## **KEY WORDS**

attention; cortical-subcortical interactions; sensorimotor transformation; striatum; superior colliculus

# **CLINICAL HIGHLIGHTS**

Clinical researchers have long noted the importance of subcortical networks, and their interactions with cortical networks, in neuropsychiatric disorders. Although methodological limitations have posed challenges to studying these interactions in humans, as technological and computational approaches advance, so too does our ability to investigate these interactions in humans and animals alike. Indeed, these advances help us observe remarkable similarities in basic principles of not just brain organization but network activity as well. For example, aberrant activity in the default mode cortical network is correlated to depressive phenotypes in both humans and rodents. Although the role of subcortical networks in neuropsychiatric conditions in humans is an emerging topic of research, early studies find an important role for prefrontal-subcortical interactions in major depressive disorder, schizophrenia, and bipolar disorder. Although network imaging and perturbation in humans is still very limited, state-of-the-art techniques in animals serve as an important complement to our emerging understanding of these brainwide network interactions. In this review, we describe basic principles of cortical and subcortical circuits and their interactions as they relate to driving goal-oriented behavior in mammals. By reframing our understanding of these networks from a regionally defined and hierarchical perspective to one of dynamic, circuit-specific, brainwide cooperation, we may be able to identify multiple targets for more effective functional therapeutics.

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# **CORTICAL-SUBCORTICAL INTERACTIONS IN GOAL-DIRECTED BEHAVIOR**

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### Abstract

Flexibly selecting appropriate actions in response to complex, ever-changing environments requires both cortical and subcortical regions, which are typically described as participating in a strict hierarchy. In this traditional view, highly specialized subcortical circuits allow for efficient responses to salient stimuli, at the cost of adaptability and context specificity, which are attributed to the neocortex. Their interactions are often described as the cortex providing top-down command signals for subcortical structures to implement; however, as available technologies develop, studies increasingly demonstrate that behavior is represented by brainwide activity and that even subcortical structures contain early signals of choice, suggesting that behavioral functions emerge as a result of different regions interacting as truly collaborative networks. In this review, we discuss the field's evolving understanding of how cortical and subcortical regions in placental mammals interact cooperatively, not only via top-down cortical-subcortical inputs but through bottom-up interactions, especially via the thalamus. We describe our current understanding of the circuitry of both the cortex and two exemplar subcortical structures, the superior colliculus and striatum, to identify which information is prioritized by which regions. We then describe the functional circuits these regions form with one another, and the thalamus, to create parallel loops and complex networks for brainwide information flow. Finally, we challenge the classic view that functional modules are contained within specific brain regions; instead, we propose that certain regions prioritize specific types of information over others, but the subnetworks they form, defined by their anatomical connections and functional dynamics, are the basis of true specialization.

attention; cortical-subcortical interactions; sensorimotor transformation; striatum; superior colliculus

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## 1. INTRODUCTION

The primary function of the nervous system is to provide an organism with a means to react to, and subsequently act upon, its environment, thereby promoting its survival. Over time, these nervous systems have evolved, allowing some animals to not only respond to stimuli but learn, form strategies, and even coordinate actions over time to achieve goals. A great deal of neuroscience research has focused on the neural mechanisms for these higher-order functions, with the core of this work aimed at understanding the role of the neocortex. A

#### CLINICAL HIGHLIGHTS

Clinical researchers have long noted the importance of subcortical networks, and their interactions with cortical networks, in neuropsychiatric disorders. Although methodological limitations have posed challenges to studying these interactions in humans, as technological and computational approaches advance, so too does our ability to investigate these interactions in humans and animals alike. Indeed, these advances help us observe remarkable similarities in basic principles of not just brain organization but network activity as well. For example, aberrant activity in the default mode cortical network is correlated to depressive phenotypes in both humans and rodents. Although the role of subcortical networks in neuropsychiatric conditions in humans is an emerging topic of research, early studies find an important role for prefrontal-subcortical interactions in major depressive disorder, schizophrenia, and bipolar disorder. Although network imaging and perturbation in humans is still very limited, state-of-the-art techniques in animals serve as an important complement to our emerging understanding of these brainwide network interactions. In this review, we describe basic principles of cortical and subcortical circuits and their interactions as they relate to driving goal-oriented behavior in mammals. By reframing our understanding of these networks from a regionally defined and hierarchical perspective to one of dynamic, circuit-specific, brainwide cooperation, we may be able to identify multiple targets for more effective functional therapeutics.

relatively recent development, the introduction and proliferation of the neocortex in the mammalian brain, correlates with the emergence of more complex behaviors and cognition (e.g., decision-making, cognitive flexibility, perception, control of attention). This is in contrast to the much older subcortical domain of the mammalian brain, which contains structures generally considered to house more primitive functions (e.g., reflexes, basic sensory processing, identification of aversive and appetitive stimuli, motivation), which are highly conserved. Although both the cortical and subcortical domains must interact to some extent during both reactive and goal-directed behavior, the relationship between the two is usually framed as one of "top-down control," in which the new intelligent cortex commands the old primitive subcortex; indeed, an abundance of evidence supports the notion that the prefrontal cortices exert a wide range of influence over subcortical and lower cortical regions (1–3). Yet this cortex-forward explanation for cognition and behavior often ignores a critical fact-that the cortex did not evolve in isolation. Indeed, although popular notions of brain organization in placental mammals assume that the relatively recent development of neocortex is the origin of many cognitive abilities, these and other "primitive" structures, like the brain stem, the cerebellum, and the limbic system, have also undergone profound changes across evolution (4–6), suggesting parallel, not sequential, development of the nervous system. As the neocortex emerged, it necessarily integrated into existing subcortical structures, which, by accepting cortical inputs, also incorporated their possible function into that of modulating local circuitry (7). Thus, instead of replacing subcortical functions, the cortical role is necessarily molded by them.

In fact, the simultaneous early (sensory input) and later (motor output) position of subcortical structures in brainwide circuits means they have a great deal of influence on goal-driven behavior. By the time sensory information reaches the cortex, it has already been processed by earlier structures, passed along subcortical networks, and filtered by the thalamus (FIGURE 1). The thalamus acts as an obligate relay for other subcortical signals relaying sensory (except olfaction) and other information before their arrival in the cortex, which universally receives thalamic inputs. On the way out of the brain and to the spinal cord, additional funneling occurs for a majority of corticosubcortical projections that do not target motor output nuclei directly but are either filtered again through the thalamus or interact with the local circuitry of other subcortical structures. Here, cortical modulation faces additional constraints. The superior colliculus (SC), along with the rest of the midbrain selection network, for example, performs quick sensorimotor transformations that enable its control of orienting and gaze, defined by its



**FIGURE 1.** Cortical and subcortical networks interact via the thalamus to form multiple loops and parallel pathways. Cortical areas (blue) are heavily interconnected via direct cortico-cortical projections (blue arrows) and indirectly through the thalamus (green) to form cortico-thalamo-cortical loops. Subcortical structures are heavily interconnected (red arrows) via both excitatory and inhibitory pathways, both directly, as exemplified by the basal ganglia-collicular pathway, and indirectly through the thalamus. The thalamus serves as a bridge between these two systems, receiving information from both cortical and subcortical networks and potentially influencing both via its reciprocal outputs, such that the cortex and subcortical structures can communicate with one another indirectly.

sophisticated spatiomotor map (8, 9). These functions are facilitated by its direct connectivity to both sensory organs and motor outputs, which are not available to the cortex, imposing a temporal and physical constraint on cortical modulation of its intrinsic functions. Another example, the striatum, contains complex parallel loops that process limbic, sensorimotor, and cognitive signals from the cortex and other areas to generate habitual or goal-oriented voluntary behavior (10, 11). Far from unique, these examples represent a mandatory cortical-subcortical relationship, as the cortex neither receives nor sends information directly to/from the periphery or spinal cord in most cases (FIGURE 1). Whatever the computational power of the cortex, goal-directed behavior is dependent on both domains, as is our understanding of its underlying mechanisms.

Although cortical and subcortical contributions to simpler behaviors have historically been studied separately, modern technological and analytical advances now allow for their simultaneous investigation. Accordingly, studies combining techniques such as anatomical tracing, multisite recordings, projection-specific optogenetics, and sophisticated behavioral paradigms have begun to shed light on specific interactions between cortical and subcortical computations and their roles in behavior (12–17). In this review, we aim to provide readers with a comprehensive, integrated view on the complementary roles of cortical and subcortical regions in brainwide circuits underlying goal-directed behaviors in mammals. Although "goal-directed behaviors" can span various modalities, here we focus largely on those in the visual and visuomotor domain, for which there exists a broad range of literature. Specifically, we 1) describe subcortical contributions to both simple and complex behavior, with emphasis on the roles of the superior colliculus and striatum, two example regions with critical roles in visual and visuomotor processing; 2) discuss the computational power of the cortex and its importance for cognition and executive function; 3) illustrate the importance of cortical-subcortical interactions; and 4) highlight the role of the thalamus as a critical bridge between these two domains of the brain. Overall, we argue the importance of considering cortical and subcortical contributions as occurring concurrently, rather than independently or top down, in understanding brain functions underlying behavior and cognition.

# 2. SUBCORTICAL CONTRIBUTIONS TO COGNITION AND BEHAVIOR

The subcortical brain consists of ancient solutions to critical survival functions and includes everything beneath the cortex, notably the hindbrain (brain stem and cerebellum), midbrain (colliculi, tegmentum, and cerebral peduncles), and parts of the forebrain (the thalamus and hypothalamus), in order of evolutionary emergence (18). These distinct, specialized structures are responsible for critical life-sustaining functions (e.g., regulation of breathing and food seeking) as well as primitive behaviors (e.g., navigating environments and avoiding/approaching stimuli). Despite their high degree of differentiation, subcortical structures share many common themes. They are highly interactive with the outside world and have privileged access to the inputs and outputs of the body; indeed, their connectivity often clearly delineates their function. These structures form elaborate subcortical networks, specialized for processing and transforming specific types of information. Unlike the canonical circuits of the cortical layers, the efferents and afferents of subcortical structures are often organized via clearly defined motifs, like layers, matrixes, and nuclei, which segregate information flow into distinct streams. This subcortical architecture enables the quick and robust mapping of salient stimuli onto stereotyped actions, learning schema, and even cognitive representations. Indeed, although they lack many of the key features that provide the computational power and breadth evident in the cortex (see sect. 3), complex roles for many subcortical structures have been readily observed, ranging from the long-established role of the hippocampus in learning, memory, and context representation (19) to the relatively recent emergence of research into cerebellar contributions to social cognition (20), reward processing (21), and other functions. Here we focus on the superior colliculus (SC) and striatum, two subcortical regions with highly developed bodies of literature in several species that are known to be involved in different aspects of goal-directed behavior. In this section, we review the anatomy, connectivity, and functions of the SC and striatum; by discussing the transformation and generation of information within these regions, we highlight the independent contributions of these regions to behavior, how these functions are implemented, and the potential upon which cortical modulations may act.

## 2.1. Superior Colliculus

An organism's ability to quickly and robustly distinguish between undesirable stimuli to avoid (e.g., predators) and desirable stimuli to approach (e.g., prey) can make the difference between death and survival. The superior colliculus (SC), or optic tectum in nonvertebrates, is a highly conserved midbrain structure that serves as an ancient solution to this universal evolutionary problem. By integrating multisensory inputs with direct outputs to motor nuclei, the SC/tectum can quickly coordinate appropriate orienting movements in response to salient sensory stimuli (22–24). These responses can be quite precise: in addition to controlling coarse movements of the entire body, the SC can exert fine-grained control over the position of individual limbs, head, neck, whiskers, pinnae, and, perhaps most prominently, the eyes (25). Indeed, much of the classic work on the SC focuses on its role in the control of saccades (the rapid movements of the eyes from one fixation point to another) and describes its detailed coordination of these and other oculomotor functions (26-28). However, the role of the SC extends far beyond simpler sensorimotor transformations. In primates, the SC's role in controlling eye movement includes not only triggering saccades and pursuing moving objects but also visually guided decision-making (29) and even the control of spatial attention (30). Studies increasingly find a similarly sophisticated role for the SC in rodents, and in both there is a long-standing interest in understanding its interactions with cortical regions involved in perception, action selection, and visual attention (12, 31–35). Long the subject of neurophysiological and anatomical studies across many species, the anatomy, physiology, and intrinsic functions of the SC are remarkably well understood, thus serving as an exciting example of a subcortical structure that is both directly responsible for mediating some goal-driven behaviors and a key part of known cortico-subcortical circuits for cognitive functions. Below we review key elements of the organization and function

of the SC and examine how these elements contribute to goal-driven behavior, independent of the cortex.

## 2.1.1. Organization and sensorimotor functions.

In accordance with its ancient origins, the basic organization of the superior colliculus is highly consistent

across species (23). One of its most distinctive features is its laminar structure, which consists of two anatomically and functionally distinct layers that are themselves composed of several sublaminae (FIGURE 2A). These two regions of the SC, the superficial layer (sSC) and intermediate/deep layers (idSC), differ greatly in both inter- and intra-areal connectivity and maintain functional differences



**FIGURE 2.** Superior colliculus (SC) connectivity and functional topography in mice. *A* and *B*: differential inputs target superficial (sSC; green) and intermediate (blue)/deep (red) gray layers (idSC) of the SC. *A, top*: sagittal view of the brain, highlighting major cortical and subcortical inputs to the sSC (green) and idSC (purple), with SC in gray. *Bottom*: schematic of coronal view of the SC, showing how inputs to the idSC vary across the mediolateral axis. Superficial SC (green) receives inputs from retina and visual cortices across its width. Intermediate and deep layers broadly receive similar inputs but are targeted by some unique projections (bolded). *B, top*: as in *A* but depicting output targets of the SC. *Bottom*: as in *A* but depicting SC outputs. The sSC targets the lateral geniculate nucleus (LGN), parabigeminal nucleus (PbG), and lateral posterior thalamus (LP), as well as the idSC. Although the idSC broadly targets the brain stem, its outputs differ across the mediolateral axis, with lateral SC outputs forming a crossed pathway to the contralateral predorsal bundle and medial outputs to the ipsilateral cuneiform area remaining uncrossed. *C, left*: schematic of the azimuth/nasotemporal (color) and elevation/dorsoventral (black-white) axes of visual space. *Right*: mapping of visual space as depicted on *left* onto contralateral SC (horizontal plane); nasotemporal visual space is represented across the anteroposterior axis of SC, whereas dorsoventral visual space is represented across the mediolateral axis of the SC. Dashed lines indicate example section in *D. D*: schematic of coronal view of the SC, depicting sensorimotor topographies of the SC layers. The sSC contains a visual map and triggers defensive (freeze/escape) responses. The idSC contains integrated sensorimotor maps that trigger behavioral responses across layers (turning for the intermediate SC, avoid/approach responses for the deep SC), which also differ in direction across the mediolateral axis.

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that reflect its role as both a sensory and a motor structure.

2.1.1.1. SUPERFICIAL LAYER AND VISUAL PROPERTIES. Although the sSC receives few long-range projections, those it does receive prescribe it a clear sensory role (FIGURE 2A). Technically multimodal, the sSC is most known as a visual region, in part because of the substantial retinal input it receives in most mammals; in the mouse, the sSC is targeted by as many as 90% of retinal ganglion cells [but in primates, this may be as low as 10% (36)]. These bilateral retinal afferents carry visual information and target the dorsal sSC in a retinotopic manner (37), providing the basis for the visual map of the contralateral field contained in each hemisphere of the SC (38-42) (FIGURE 2C). Although these visual maps are not as refined as those found in the visual cortex, visually responsive neurons in the SC encode more than light intensity. Motion and direction sensitivity have been observed in the sSC of all mammalian species studied so far, including cats (43) and primates (44, 45), with additional visual response diversity found in rodents (46-48), a possible compensation for their less functionally specialized visual cortex. Indeed, two-photon imaging has revealed an additional retinotopic, columnar organization of orientation sensitivity (49, 50) and motion direction (51), a property possibly unique to the rodent SC that may contribute to its motor functions (see sect. 2.1.1.2). However, the validity of these claims is disputed (52).

In addition to representing visual space for internal sensorimotor transformations, the sSC uses visual information to target other critical nodes in subcortical visuomotor networks, including the lateral geniculate nucleus (LGN), parabigeminal nucleus (PbG), and pulvinar nuclei of the thalamus (LP; FIGURES 2B and 3B) (53). The anatomical and physiological characteristics of the sSC's four cell types, horizontal, stellate, widefield (WF), and narrow field (NF) (54, 55), provide insight into how the sSC may leverage its outputs to promote appropriate responses to visual stimuli. Horizontal cells (inhibitory) and stellate cells (excitatory) both represent different moving stimuli, horizontal cells showing preferences for large, sudden movements whereas stellate cells preferably fire for small, steady movements (56); these functionally complementary cell types also both target the LGN and PbG, providing the sSC with a means to flexibly influence both visual processing via LGN (FIGURE 3B, Ref. 57) and the generation of orienting movements (via PbG; Ref. 58). Widefield and narrow field cells, both excitatory cell types, fire preferentially for stimuli moving across wider or narrower receptive fields, respectively, and have different preferred output targets. Whereas WF cells project mostly to LP, NF cells project mostly to



FIGURE 3. Organization of cortical inputs to superior colliculus (SC) and SC outputs to thalamus vary along the mediolateral axis. A: horizontal plane view of the mouse cortex; different cortical regions target the SC across the mediolateral axis; red corresponds roughly to primary visual cortex, gold to higher visual cortex, green to associative cortex, and blue to frontal cortex. B: the SC labeled roughly by cortical inputs (relative to A); there are 4 distinct regions of the intermediate/deep layers of SC (idSC), which have differential outputs to thalamus. The superficial layer of SC (sSC) is targeted by visual cortex; this layer of the SC also projects to the lateral geniculate nucleus (LGN) and lateral posterior (LP) nuclei of the thalamus via distinct cell types. Horizontal (HZ) and stellar (ST) project to the LGN, whereas widefield (WF) cells project to LP. The more lateral sections of the idSC project to medial dorsal (MD) nuclei in the thalamus. These collicular-thalamic outputs provide the basis for cortico-tectalthalamo-cortical loops. NF, narrow field.

the PbG and, more locally, to the intermediate and deep layers of the SC (54, 56). Finally, whereas horizontal and stellate cells primarily receive retinal input, WF and NF cells receive more cortical input (37), a potential mechanism for the differential control of the sSC's functions by both bottom-up (retinal) and topdown (cortical) processes.

In combination, the organization of its inputs and outputs overlaid atop cell type differences suggests multiple mechanisms through which the sSC may participate in several aspects of visuomotor processing. Retinal inputs to the horizontal and stellate cells of the sSC convey information about movement and space, providing the sensory basis needed for orienting and gaze control. These sSC cells also target the LGN, a first-order thalamic nucleus with direct projections to the primary visual cortex (see sect. 5.5.2), an opportunity for indirect influence of early visual processing in the cortex by the sSC, perhaps by conveying motion direction information. NF cells, meanwhile, project both directly to the intermediate and deep layers of the SC, providing a sensory basis for the SC's visuomotor map, and, along with horizontal and stellate cells, to the PbG, creating communication channels between the SC and the amygdala, a critical interaction for mediating gaze shift and avoidance responses (59–61). Furthermore, the organization of the SC's inputs and outputs suggests a dialogue between the SC and the visual cortex; whereas cortical input to NF and WF cells in the SC provides a means for classic topdown control, the output of WF cells to LP, a higher-order thalamic nucleus (see sect. 5.5.2), also provides a potential route for indirect tecto-cortical communication. These tecto-thalamo-cortico-tectal interactions and their role in both visual processing and visual attention are the subject of emerging studies in mice (62).

#### 2.1.1.2. INTERMEDIATE/DEEP LAYERS AND SENSORIMOTOR

**PROPERTIES.** In sharp contrast to the clearly visual circuits of the sSC, the idSC receives extensive inputs from across the brain, including cortical, subcortical, and even spinal regions (63) (**FIGURE 2A**), which align with its combined multisensory and motor functions. Projections from the sSC to the idSC (64, 65), may provide the idSC with access to its retinotopic map, which is integrated with additional inputs from higher-order visual cortex, sensory cortices (including primary sensory cortex and auditory cortex), and the inferior colliculus (66–70) to form a rich multimodal, retinotopic map of space (**FIGURE 2C**). This topography forms the basis for the SC's well-established role in coordinating movements toward or away from particular points in space.

The visuomotor functions of the SC of highly visual animals have been the subject of extensive study, perhaps because of its role in coordinating saccades, the precise, rapid movement of the eyes used to bring a visual area in or out of the fovea, which are easy to measure in controlled environments. For decades, neuronal activity correlated with eye movements has been recorded in the idSC of both cats (71, 72) and primates (73, 74). Stimulation of the idSC also triggers saccade movements to specific, invariant locations of the contralateral visual field (75, 76), whereas their inactivation impairs performance on visual tasks for the same locations (30, 77). Indeed, these orderly, linked representations of space and movement are a defining characteristic of the SC and are not exclusive to saccades. In addition to coordinating saccades (75, 78-80), the SC also coordinates eye and head movements (27, 28, 81-83) and other full body and reaching movements (84) in cats and primates. Similar findings have been made in rodents, in which the idSC mediates eye-head movements (85), a rodent equivalent to eye gaze shifts (but see Refs. 86–88), approach/avoidance responses, and prey capture, described at length below. Although the circuit mechanisms that result in these spatiomotor maps are not well understood, anatomical and molecular tools have allowed for the identification of additional organizational motifs in the rodent SC. A 2019 study by Masullo et al. observed molecularly defined motor clusters in the idSC of mice (417). These mediolaterally organized modules correspond to specific angles of three-dimensional head movements and form a motor map mirroring the retinotopic columnar organization of visual responses observed by some in the sSC. Similar findings of complex structural organization within the idSC of rodents, such as honeycombs (89) and patches (90), have been reported previously. Although the significance of these structures is not yet well understood, they may have important functional implications for the combined sensorimotor role of the idSC.

Finally, although the idSC itself plays a significant role in the coordination of eye gaze and orienting movements alike, it enacts these movements by interacting with other motor structures. Although the role of the idSC's ascending projections via the medial dorsal nucleus of the thalamus (FIGURE 3B) are not yet clear, the functions of its descending projections to the brain stem are well defined. Its control of saccades in the vertical and horizontal direction is attributed to its projections to the paramedian pontine reticular formation and rostral interstitial nucleus of the medial longitudinal fasciculus, respectively (91). This coordination of seemingly contradictory orienting responses, like approach and avoidance, can also be explained by the mediolateral organization of the SC. Broadly, stimulation of the medial idSC in rodents triggers avoidance responses, whereas the lateral idSC is associated with approach (92–95) (FIGURE 2D). This division corresponds to similarly organized outputs along descending pathways of the SC. The crossing outputs of the lateral idSC to the predorsal bundle promote contraversive/approach responses (92, 96), whereas its ipsilateral outputs, originating from the medial idSC, project to the cuneiform area and are associated with defensive responses (93, 97, 98) (FIGURE **2B**); these findings have been confirmed recently with optogenetics (99). Finally, although cortical projections to the idSC can modulate its motor functions [for example, the frontal eye fields in primates can trigger and modulate

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saccades (100)], cortical control over these actions is ultimately limited by its interactions with the internal circuitry of the idSC.

### 2.1.2. Contributions to goal-driven behavior.

2.1.2.1. ORIENTING RESPONSES AND RELATED FUNCTIONS. As discussed above, although research on the functions of the SC has predominantly focused on its role in guiding gaze in visual space, it is prominently involved in coordinating appropriate orienting responses (approach or defense) in a stimulus-dependent manner. Classic studies in several species demonstrate the importance of the idSC for basic orienting responses; lesions of the SC result in severe impairments in turning toward or away from salient stimuli (101–106). This role in orienting responses extends far beyond coordination of movement; the SC is also involved in coordinating prey capture (107), approach to reward (102, 108), and defensive responses (61, 97, 109-111). However, the ability of the SC to differentiate between appropriate responses extends beyond a binary decision to turn toward a particular point in space; indeed, some degree of context specificity is required even for seemingly simple reactions, as in defensive behaviors. In mice, visual stimuli associated with predator approach, such as looming stimuli, can elicit two types of defensive responses: escape and freezing. Although seemingly simple, this decision must be quick and correct, or else an animal risks death. Fleeing, and thus alerting a looming predator to one's presence, may be fatal in situations where no shelter is to be found; similarly, not moving when an escape can be made may facilitate capture instead (112). Not only do sSC neurons in mice respond preferentially to looming stimuli over nonlooming stimuli (47), but their distinct outputs to LP and the PbG (and thus indirectly to the amygdala) appear to be critical for triggering escape and freezing responses (FIGURE 2, B and D), respectively (59, 60), supporting a role in the SC in mediating context-dependent action selection. Although this is less studied in primates, some evidence suggests that the SC also coordinates defensive behaviors, such as cowering and attack, in nonhuman primates (110), a function that may also be mediated by its interactions with the amygdala (113).

The context dependence of action selection in the SC has been demonstrated even in nonvisual contexts. SC activity appears to reflect a sensitivity to aversive stimuli more generally, including footshocks (114), heat (115), and pinches (116). The SC may perform a similar function for approach responses to appetitive stimuli as well. In primates, the neurons in the SC of monkeys with primary visual cortex (V1) ablations convey reward expectation signals to midbrain dopamine neurons in response to

salient visual stimuli, which may contribute to associative learning (117). Furthermore, in addition to coordinating movements to initiate prey capture in mice (107, 118), SC neurons seem to contain information about potential rewards, which it uses to promote appetitive locomotion toward prey via projections to the substantia nigra pars compacta (SNc) (119). Overall, these findings support a role for the SC not only in transforming a salient stimulus into a motor response but indeed in identifying the type of salient stimulus in order to respond appropriately.

Finally, in both rodents and primates, the SC has been identified as a crucial structure for task-switching behaviors. The neural mechanisms underlying the ability to flexibly identify an appropriate action has been tested in primates extensively with the pro/antisaccade task, in which a monkey is cued to look toward a peripheral target (prosaccade) or away from it (antisaccade) to receive a reward (35, 120, 121). The rodent equivalent for this task requires cued rats to orient toward a nose-poke port indicated by a visual stimulus (prochoice) or away from it (antichoice) to obtain rewards (31). In both, the "anti" response requires longer reaction times and more time to master and is prone to higher error rates and movement variability, suggesting a higher cognitive demand compared with the reflexive "pro" response (120). These tasks require the inhibition of one behavior while simultaneously promoting another and thus are used as a tool to study behavioral flexibility. Although the influence of the prefrontal cortex (PFC) on the SC during this task is a matter of ongoing investigation (see sect. 4.2.3), several studies highlight the role of the SC beyond motor signals. For example, in primates, the instruction to go "pro" or "anti" results in differential preparatory activity in the SC (122), a feature thought to reflect the inhibition of a reflexive saccade (35), although the origin of this inhibitory signal is unclear. In rats, different subpopulations of SC encode pro/antichoice information and reach a decision before prefrontal cortex (13); indeed, pharmacological inactivation of the SC in rats impairs antichoices but not prochoices, suggesting a leading role for the SC in task switching during visually guided decision-making (31). Altogether, this suggests that the SC has access to information beyond its retinotopic, multimodal maps, which it uses to direct appropriate decisions via its guick, robust sensorimotor transformation circuits. It is likely that at least some component of this generalizability and flexibility of SC function is provided by cortical modulation (see sect. 4.2) or other inputs.

**2.1.2.2. SPATIAL ATTENTION.** Elaborating on the SC's ability to selectively and flexibly respond to both visual and nonvisual salient stimuli, recent perspectives describe a role for the SC in more cognitive functions. Of

course, there is an obvious overlap between orienting (turning the body to align to/away from a particular stimulus) and visual attention (here defined as the prioritization of neural resources and responses for a particular stimulus). However, the contribution of the SC to attentionrelated functions is complex and has been increasingly suggested to extend beyond implementation (e.g., saccades, gaze control, head turning). Although stimulation of the idSC in primates can trigger saccades to particular locations in visual space (75), subthreshold microstimulation instead enhances performance for the same location without triggering a saccade for both motion direction discrimination (123) and detection of a stimulus (124), without increasing the likelihood of a response overall, supporting an important role for the SC in mediating spatial attention. Although this may be assumed to reflect an interruption of cortical mechanisms for control of visual attention, some studies suggest that the SC may be able to direct or mediate attention in its own right (125). Indeed, although reversible SC inactivation results in deficits in directing spatial attention, it does not also disrupt cortical signatures of spatial attention. This supports the existence of independent mechanisms for visual attention in the cortex and superior colliculus (77), although the extent of this is subject to much debate (see sect. 4.2). Although much is known about the descending projections of the SC, its prominent ascending projections to the thalamus, including medial dorsal (MD) and lateral posterior (LP) (FIGURE 3B), are less understood but offer a route for contribution to cortical functions, including influencing visual attention in cortex indirectly via the thalamus (see sect. 5.5.2). Furthermore, although the study of visual attention in rodents is still in its infancy, signatures of visual attention and visual decision-making have been identified in the SC. Inhibition of the SC in mice results in deficits specific to visual attention in visual change detection tasks, especially in the presence of distractors (126). In both primates and rodents, the SC has been shown to encode both the target of a response (127–129) and initiation of a movement toward it (80, 96, 130, 131), with emerging studies finding additional encoding of target acquisition as well (132).

Although the interactions of these signals are not well understood, several models describe a priority map of space and action, in which different motor plans compete in a winner-take-all manner. In this push-pull model, potential responses change the distribution of activity across the priority map, such that responses toward one location are facilitated and responses away are inhibited until a threshold is reached and the response is initiated (131, 133). Although this is usually described in the context of saccades and their neuronal signatures, the existence of such a priority map, and the ways in which extrinsic outputs may interact with it, would lay the groundwork for the premotor theory of attention, in which attention is directed to a particular location via motor preparation directed toward it (134). The veracity of this theory is contentious, with studies finding inconsistent evidence in support (see for review Ref. 135). Several other theories attempt to explain the undeniable overlap between attention and oculomotor control. One alternative theory, the biased competition model, is an abridged version of the premotor model that proposes that attention is the result of competition between inputs for representation within sensory and motor systems, such that representations are biased toward salient stimuli (136-138). Critically, despite key differences, these and other models for attention all highlight the intricate balance between sensory, motor, and spatial representations, as well as the interplay between bottom-up and top-down contributions to attention, making the SC a prominent candidate region for its study.

### 2.2. Striatum

Although some behaviors only require the transformation of sensory stimuli into one of a few responses, most voluntary behavior requires the selection of a single action within a vast space of possible motor programs. This complex action selection process involves the integration of various signals, including sensory and contexinformation from the environment, tual past experiences, and internally generated goals. These signals often compete, necessitating a mechanism to select the maximally adaptive, most appropriate action in different situations. Such a mechanism would require the brain to 1) maintain and represent both goals and signals separately (so that they can be updated and manipulated independently) and 2) select one action among alternatives to be implemented by downstream motor structures.

In the mammalian brain, many of these action selection mechanisms are thought to be localized within a cluster of subcortical nuclei known as the basal ganglia (BG), the structure, cell types, and major pathways of which have been remarkably conserved throughout evolution. From the simple nuclei of lampreys to the expanded brain structures in primates, the basal ganglia have increased in size and specialized into subdivisions to control more complex and diverse behavioral and motor patterns (139). Nevertheless, several key circuit features remain unchanged: the reliance on inhibition and disinhibition of motor pattern generators to directly control voluntary behavior, the balance between opposing influences of the direct and indirect pathways, and the modulation by dopaminergic inputs to enhance or suppress action repertoires during learning (139, 140). As one of the main input sites to the basal ganglia (140), the

striatum is uniquely situated as the interface between cortex and the rest of the basal ganglia; this role in basal ganglia circuitry provides it with a critical role in mediating cortico-subcortical interactions. First, the striatum is the entry point of cortical inputs into the basal ganglia and therefore serves to transform diverse types of signals from the cortex, from sensory, cognitive to motor, into action selection signals that inhibit or disinhibit motor programs in the relevant motor modules (10, 141, 142). Second, the striatum is a major recipient of dopaminergic inputs from the midbrain and substantia nigra, which are an important source of signals for enhancing or suppressing actions during learning (10, 143). Finally, the internal organization of the striatum provides a potential mechanism for its role in action selection via several means: its direct and indirect pathways (144), division into striosomes and matrixes (142), and its remarkable segregation of cortical sensorimotor, limbic, and cognitive inputs into parallel loops (145, 146), which originate from and return to the same site of input (11, 147, 148) (see sect. 4.3.1).

#### 2.2.1. Organization and motor functions.

As the input nucleus of the basal ganglia (140), the striatum sends its projections to the intrinsic nuclei [globus pallidus external (GPe) and substantia nigra pars compacta (SNc)], which then project to the output nuclei: the entopeduncular nucleus [EP, in mice; globus pallidus internal (GPi) in primates] and substantia nigra pars reticulata (SNr) (FIGURE 4) (140). Outputs from these basal ganglia structures either inhibit midbrain structures, such as the SC, or project to the thalamus, which sends these feedback signals back to cortex (149). The details of these structures and their anatomical organization have been the topic of many detailed studies (144). However, several features regarding the organization of the striatum and its relation to the basal ganglia are important to highlight as they might provide important clues and principles for the transformation of cortical inputs through the striatum and into the rest of the basal ganglia pathways.

**2.2.1.1. DIRECT AND INDIRECT PATHWAYS.** The basal ganglia play a key role in the control of voluntary movements, a function thought to be mediated by their parallel loops, which exist at several levels. Early studies of basal ganglia circuits proposed a simple model that divided these loops into two major pathways originating in the striatum: direct (to promote actions) and indirect (to suppress actions) (144). Through these two pathways, the striatum directly modulates downstream motor structures via inhibitory output nuclei of the basal ganglia, the EP/GPi, and the substantia nigra pars reticulata (SNr) (FIGURE 4) (150). These pathways are distinct both



**FIGURE 4.** The direct, indirect, and hyperdirect pathways through cortex, basal ganglia, and thalamus. Three pathways originate from distributed regions of the cortex. In both the direct and indirect pathways, projections from cortical layer 5 target either the D1 cells (direct) or D2 cells (indirect) in the striatum. The direct pathway involves two inhibitory synapses: D1 cells in the striatum inhibit the entopeduncular nucleus [EP; globus pallidus internal (GPi) in primates] or the substantia nigra pars reticulata (SNr), which then send inhibitory projections to the thalamus or midbrain nuclei, including the superior colliculus (SC) and midbrain locomotor region (MLR). In the indirect pathway, D2 cells inhibit the globus pallidus external (GPe), which inhibits the subthalamic nucleus (STN), an excitatory nucleus that projects to the EP/GPi and SNr. The hyperdirect pathway involves direct glutamatergic projections from the cortex to the STN, foregoing the direct/indirect pathways altogether.

molecularly, via their involvement of neurons expressing D1 and D2 dopamine (DA) receptors (151), and via their target sites (FIGURE 4). The direct pathway originates in the D1-expressing neurons of the striatum, which project directly to the EP/GPi and substantia nigra reticulata (SNr) to inhibit its activity. The indirect pathway, meanwhile, consists of striatal D2 neurons instead inhibiting the globus pallidus external (GPe), which normally inhibits the EP/GPi, SNr, and subthalamic nucleus (STN) (142). Among its diffuse projections, the SNr sends massive inhibitory projections to the SC, which controls orienting behavior (152), as well as the mesencephalic locomotor region (MLR), an evolutionarily conserved midbrain region acting as a hub for locomotion control (153–155). Indeed, optogenetics activation of SPN-D1 in STR induces locomotion, whereas optogenetics activation of SPN-D2 in STR halts locomotion (155). These faciliatory or suppressive effects are correlated with MLR neuronal activity(155) and inversely correlate with neuronal activity in the SNr (156), further suggesting the inhibitory influence of SNr over MLR.

Among the basal ganglia nuclei, the subthalamic nucleus (STN) is especially strategically positioned to deliver a timely control of locomotion. This nucleus is often the locus for deep brain stimulation to alleviate motor symptoms for Parkinson's disease (157) and has often been implicated in inhibitory control and stopping (158–

162). In rodents, a conditional knockout of vGlut2 in the STN, which reduces but does not completely eliminate glutamatergic transmission, induces hyperlocomotion (163). Lesions of STN also induce impulsive responding (160, 164, 165). More recently, in mice, optogenetics areal activation of STN excitatory cells disrupts self-initiated bouts of licking (161). The STN projects directly to the SNr, and optogenetics activation of both a subpopulation of STN excitatory neurons and their axons in SNr promoted sleep and reduced locomotion (166). In turn, STN directly projects to MLR, although the functional role of this projection is unclear (157). Thus, the interplay of the direct, indirect, and hyperdirect pathways through the striatum and basal ganglia enables fast control of movements and locomotion, which are well suited to direct animal behavior in changing environments.

The anatomical division of striatal circuits into direct and indirect pathways is directly related to the function of these in terms of facilitating or stopping movements, in particular locomotion. Optogenetic activation of SPN-D1 in STR induces locomotion, whereas optogenetics activation of SPN-D2 in STR halts locomotion (155). This effect on locomotion is correlated with MLR neuronal activity (155) and is inversely correlated with neuronal activity in the SNr (156), further suggesting the inhibitory control of SNr onto MLR. In terms of stopping locomotion, the STN is another important nucleus in the basal ganglia that is involved in "short-circuiting" the halting circuitry. Through these distinct pathways (direct, indirect, and hyperdirect; FIGURE 4), the striatum coordinates locomotion and actions of animals. Furthermore, by providing cortex to access the information in these pathways, striatal function is open to be modulated by cortical inputs. These motor functions of the striatum do not exist in a vacuum but are tightly linked to the inputs it receives from sensory cortical structures via connections to the basal ganglia (167).

Besides the functional division into the direct and indirect pathways, which are mediated respectively by D1 and D2 cells in the striatum, an influential anatomical division of the striatum involves the separation between striosomes and matrix compartments. Histologically, the two compartments display clear and distinctive markers. The matrix compartments are rich in calbindin, acetylcholinesterase, and somatostatin, whereas striosomes are rich in mu-opioid receptors (168). Together, striosomes and matrix preferentially receive distinct inputs from different regions of the cortex that are involved in sensorimotor, associative, or limbic functions (169–174), and the outputs originating from these compartments, most notably the striatum-SNc projection, show important specialization and differentiation that might be a basis for a segregation into parallel functional loops (175-180). However, although the direct and indirect divisions

of the striatum seem to map on to opposing influences of the two pathways in movement facilitation or suppression, the functional distinctions between striosomes and matrix are the subject of ongoing studies (142, 168, 181).

#### 2.2.2. Contributions to goal-directed behavior.

2.2.2.1. VALUE ENCODING AND REPRESENTATION. The role of the striatum in action selection is closely related to its role in reward processing and value assignment. As organisms select between competing motor programs, they need to make use of external feedback to evaluate which actions to enhance and which ones to suppress. External rewards and value signals from the environment are thus important selective signals that contribute significantly to action selection: rewarded actions are more likely to be sustained, whereas unrewarded or negatively reinforced actions are more likely to be eliminated. To serve these functions, modulatory dopaminergic inputs from the midbrain, STN, and ventral tegmental area (VTA) are highly significant (10, 144, 182). These inputs represent reward prediction errors, the difference between the current and expected reward (183). Through influencing synaptic plasticity of corticostriatal inputs, they offer a mechanism for the brain to update action values in an efficient manner, where the values will be updated if and only if there is a mismatch between what is expected and what is actually observed after the action execution. In other words, unexpected rewards should promote the enhancement of, while unexpected errors should reduce the efficacy of, cortical inputs that control the corresponding actions. Importantly, reward prediction errors might be further divided into different types of learning that are appropriate for different scenarios (FIGURE 5). For example, DA projections to the ventral striatum promote stimulus-outcome associations in Pavlovian learning, which is useful in cases where associations need to be learned between a stimulus (for example, a rustling sound) and an outcome (such as the presence of a predator). On the other hand, DA projections to the dorsal striatum induce stimulus-response or action-outcome association (10), for instance, when associating a lever push to the delivery of a water reward. Both these forms of learning are important for action selection: stimulus-outcome associations help animals to form fast and automatic responses to relevant stimuli from the environments, and stimulus-response and action-outcome associations help animals to select appropriate actions through evaluating their potential outcomes.

If dopaminergic inputs represent reward prediction errors, how might the striatum integrate these signals to update and maintain the values of actions in a given

#### ♠ CORTICAL-SUBCORTICAL INTERACTIONS IN GOAL-DIRECTED BEHAVIOR



**FIGURE 5.** Cortical-striatal inputs influence reward encoding and value-guided decision-making. *Top*: flowchart representing the hierarchical flow of information between cortical regions, from sensory processing [in sensory cortices: visual (VIS), primary somatosensory (SSp), auditory (AUD)] to the inference of task rules and environmental states [in prefrontal cortex (PFC) and orbitofrontal cortex (OFC)]. These inform possible action and strategy switches mediated by the anterior cingulate cortex (ACC) and finally sent to motor areas for execution. *Bottom*: role of cortical inputs on striatum-mediated learning. Colored arrows represent the projections from cortical areas to the striatum, as in **FIGURE 7**. Importantly, projections to the dorsomedial striatum (red) facilitate model-based learning, whereas projections to the dorsolateral striatum (green) facilitate model-free learning. Also shown are the dopaminergic (DA) inputs to the striatum from the ventral tegmental area (VTA) and substania nigra pars compacta (SNc), which provide signals conveying reward prediction error (dashed arrows). These inputs might be subdivided into two projections, one to the dorsal striatum, which mediates stimulus-outcome associations. MC, motor cortex; V1, primary visual cortex.

task? How might these value representations then help the brain select between competing motor programs? To probe the representation of action values in the dorsal striatum, Samejima et al. (184) asked monkeys to select one of two actions (left or right) on each trial and varied the reward probabilities of these two actions in a blockwise manner. This blockwise manipulation of reward allowed the authors to adjust the relative values of the two actions while controlling for the direction of movement. For example, consider the difference between "90-10" blocks (where left actions were rewarded 90% of the time and right actions were rewarded 10% of the time) and "50-10" blocks. In both types of blocks, animals should select the left actions more frequently, but their estimates of the value of the left actions differ: in the first block left actions should have a value of 0.9, whereas in the second block this value should be 0.5. The authors were able to fit a reinforcement learning model to the monkeys' choices to estimate this fluctuation in the animal's valuation of the two actions on each trial. By correlating these value estimates with the neural activity recorded from striatal neurons, they found that the activity of a large fraction of striatal projection neurons was highly correlated with the action values in the delay epoch, before any movement was made by the animal. Following up on this result, Lau and Glimcher (185) showed that, in addition to action values, phasically active neurons in the striatum also represent the value of the chosen action in each block. Thus, these studies showed that action values are represented in striatum neurons, but are these representations causally relevant for the animal's choices on each trial? An optogenetic experiment by Tai et al (186) confirmed the causal relevance of these value representations in the striatum. By manipulating the activity of striatal dopamine D1 and D2 neurons, the authors were able to induce shifts in action values that are revealed through changes in the choices made by the animals (186). Together, these physiological results suggest a mechanism where action values and chosen values are directly represented and continuously updated in striatal circuits and directly influence downstream pathways with these value and reward representations from moment to moment.

**2.2.2.2. LEARNING.** The convergence of reward signals in the striatum begs the question of how these reward signals can be optimally used by the brain to drive behavior. An important hypothesis is that reward signals are used for learning. In this context, previous studies tried to characterize striatal learning function in terms of two broad categories: model-free and model-based learning.

In model-free learning, agents learn to associate a cue with a habitual sequence of actions to obtain rewards. For instance, after being trained to press a

lever to obtain food rewards, mice learn to associate the stimulus (the lever) with an action (a lever press). When overtrained, mice will continue to press the lever even when the reward is devalued [for example, by feeding to satiety or by pairing with a poison (187)]. Thus, these habitual actions are highly inflexible, and they require time to unlearn. This type of learning is crucial for the formation of habits or "chunked" sequences in response to a stimulus (188–191).

In contrast to the inflexibility of model-free learning, agents using model-based learning maintain a cognitive map of transitions and contingencies. These maps allow agents to select actions based on their knowledge of these transition probabilities and by using "tree searches" through the state diagrams they have created of the environment (192). In the example above with a devalued outcome, a mouse that uses model-based learning will quickly abandon the food lever after knowing that the lever presses fail to produce positive rewards. Thus, model-based actions are more flexible and can adapt quickly to changes in the world state. On the other hand, they are more difficult to compute and maintain in working memory and especially costly when the state transitions are complex (192, 193).

A rich body of experimental results provides empirical support for the idea that the striatum is crucially involved in both model-free and model-based learning (10). Remarkably, evidence suggests that these functions are localized to different areas of the striatum: the dorsolateral striatum mediates model-free actions, whereas the dorsomedial striatum mediates model-based actions (10). Finally, the ventral striatum (NAc) seems to be involved in stimulus-outcome association (in Pavlovian conditioning tasks). Physiological recordings in the striatum indicate that activity is high in dorsomedial striatum during the acquisition of the skill and in dorsolateral striatum as animals are expert (194) (although other studies have revealed more complex dynamics between these two subregions (195, 196).

The contributions of ventral and dorsal striatum might be loosely associated with the actor-critic framework in the reinforcement learning literature: the dorsal striatum learns about stimulus-action association and implements action policies, whereas the ventral striatum learns about the values of states, for example in Pavlovian conditioning (197).

#### 2.3. Summary

Although subcortical structures may have originated as an efficient means to promote survival, they have since undertaken increasingly complex functions and play critical roles in goal-directed behaviors. Although we only discuss the SC and striatum in detail in this review, some basic principles of these structures can apply to many other subcortical structures, though, of course, their functions are as diverse as their local circuitry. In addition to the simultaneous early and late position of subcortical structures in the brain, which affords them a great deal of influence over the information available to the cortex and the ultimate selection of actions, these structures perform a variety of complex computations that contribute to sensorimotor, limbic, associative, and cognitive functions. Overall, these structures are highly specialized for the transformation of specific types of information, a characteristic delineated by their connectivity and organization. Although this necessarily restricts their computational and functional potential, the internal functional and anatomical schema of many of these regions reflect stable, orderly representations and clear routes for mapping external stimuli into behavior.

As described above, the prominent role of the SC in spatial attention and visual decision-making is constrained by both its representation of space, provided by early inputs, and the motor actions it can coordinate via limited descending projections to the brain stem. The striatum, on the other hand, receives a variety of complex, multimodal information with which it can enable complex learning schemes but is also limited by its inflexibility. Indeed, in these and other subcortical areas, we see an emphasis on the quick integration of salient signals to prioritize some actions while suppressing others via the balance of activity, something the cortex can influence via top-down projections. And alt hough the cortex is obligated to interact with these subcortical structures, because of its limited direct projections to motor nuclei in the brain stem/spinal cord, these very limitations facilitate cortical intervention. The internal topography of these regions, and the flow of information through them, provide clear points for specific intervention by the cortex. Of course, this interaction is not unidirectional; these structures are not only heavily interconnected with one another, but many send ascending projections to key thalamic nuclei, which provide an indirect route to the cortex (see sect. 5.5); thus, these structures may influence not just the implementation of actions for which they are best suited but also the very information that the cortex has access to, a topic discussed at length below.

## 3. CORTICAL CONTRIBUTIONS TO COGNITION AND BEHAVIOR

The development of the neocortex marks an important evolutionary milestone and coincides with a significant increase in complexity and flexibility in animal behavior. Cortex has greatly expanded in mammals, and, most notably, there has been a rapid increase in size of the prefrontal cortex (PFC) in primates and humans on a short evolutionary timescale that is thought to increase the capacity for executive functions, working memory, and cognition in these species (198). Accordingly, studies of the neural bases of cognition have long focused on the role of the cortex in mediating higher-order, complex, and context-dependent behavior. Signatures of decision-making and other executive functions have been observed in the cortex, especially higher cortices (199–201), and neural activity patterns in the cortex are markedly more complex than those found in the subcortical domains, often requiring a population perspective to understand these patterns and how they relate to behavior (202, 203).

Given the nontrivial role of subcortical regions in mediating complex behavior and action selection that goes far beyond sensorimotor responses (see sect. 2), it is often a challenge to ascertain to what extent and the mechanisms by which cortical areas might be able to augment the intrinsic function of subcortical structures. From this perspective, previous studies of the cortical functions might be grouped into two distinct yet overlapping domains regarding the role of the cortex in overall brain function. On one hand, a considerable body of work adopts a "top-down" view of cortical function. This account suggests that the main role of the cortex, and especially higher-order cortices, is akin to a CEO of a corporation: the cortex is the center of complex decisionmaking and sends out its outputs to direct and control the function of "lower-level" brain areas to serve the decisions that the cortex has made. Two examples of this view are 1 the suggestions that the PFC exerts topdown control of subcortical structures (such as its interactions with the SC for saccade suppression) and 2) models of the role of orbitofrontal cortex (OFC) as a "response inhibitor" in reward-guided decisions, exerting its influence on default responses that are partially mediated by the striatum (204). This proposal stems from our intuition, together with empirical support from decision-making studies, that complex decisions originate from localized, single brain areas and are then broadcast to the rest of the brain. On the other hand, a complementary view of cortical function is that of "concurrence" and cooperation with subcortical areas. In this view, the role of the cortex is more like that of a domain expert in a dynamic organization, where it contains valuable knowledge of the world, holds vast experience from prior exposures to events and their outcomes, and harbors flexible mechanisms to alter and inform the decision-making process in response to environmental contexts. Yet it has to work with the rest of the brain, like a team member in a diverse group with intricate patterns of feedback loops and parallel streams of processing, to influence the operation and actions of the whole team (7, 205).

To better understand experimental support for these two views and their implications for our understanding of cortical-subcortical interactions, in this section we outline the anatomical and functional features of cortex that are critical for its role in behavior and explore how those features might contribute to the interaction between cortex and subcortical regions. We start with a discussion of the unique features of cortical organization that set it apart from subcortical structures: its laminar organization, intracortical recurrence and inhibition, and division into distinct hierarchies. We then discuss how these features might support various functions that have traditionally been viewed as cortical-centric: feature extraction and complex sensory processing, predictive processing, motor learning, working memory, and executive function. Understanding of these features of cortical organization and function is important for several reasons. First, the anatomical information constrains models of brain function by specifying the possible interactions, connections, and pathways through which cortex can influence subcortical structures and vice versa. Second, a broad understanding of the higher-order functions of the cortex will provide valuable context for how these functions might replace, supplement, or add on to intrinsic functions of subcortical structures. The nature of these cortical-subcortical interactions is further explored in sect. 4, where we specifically focus on interactions between cortex and two regions, the superior colliculus and striatum, via feedback from the thalamus. These are instructive examples given the apparently complex intrinsic functions of the superior colliculus and striatum in the domain of attention and action selection. How cortex modifies these functions of these regions through feedback loop can help qualify and evaluate our views of the "top-down" and "concurrent" models of cortical function.

## 3.1. Laminar Organization and Intracortical Activity

A significant principle of organization of cortex is its laminar structure: cortex is divided into distinct layers whose inputs and outputs seem to obey remarkably common arrangements throughout all cortical regions. This uniformity has led to various proposals that repeated elements of circuits ("canonical microcircuits") play an important role in performing shared computations in different cortical pathways (206–208). Furthermore, the laminar architecture of cortex is uniquely suited to the simultaneous segregation and aggregation of disparate inputs and outputs (208, 209). In particular, the communication between cortical areas (interareal connections) and with subcortical areas including the thalamus occur in distinct layers of cortex (**FIGURE 6**). Projections to and



**FIGURE 6.** Hierarchical organization of cortical areas. Schematic of canonical intracortical connections, illustrating laminar organization of feedforward and feedback connections. Feedforward projections from sensory cortex target layer 4 of higher-order cortex, where these cells project to layers 2/3 and layer 5. In contrast, feedback projections are sent from deep layers of the cortex (layers 5 and 6) to layers 1, 5, and 6, avoiding layer 4 of sensory cortex. This pattern of feedforward and feedback connectivity defines the hierarchy of cortical regions. CT, corticothalamic; IT, intratelencephalic; PT, pyramidal tract.

from thalamus dominate cortical layers 1, 4, and 6. More specifically, inputs from the thalamus, which might relay information passed down by subcortical structures, enter layers 1, 4, and 6, while the cortex can communicate back to the thalamus and other subcortical structures via its outputs in layers 5 and 6. In contrast, intracortical interactions take place in layer 2/3 (**FIGURE 7**) (207, 208). In combination, this specificity might help to segregate the different types of inputs and outputs in the cortex to different and independent channels depending on the type of interaction (cortical or subcortical). These signals can then get integrated in the cortex or further sorted out by relevance to the currently active computation.

#### 3.1.1. Hierarchical organization.

The laminar organization of the cortex gives rise to a natural notion of "hierarchy" within cortical areas. This hierarchy might be defined based on the pattern of laminar origin and destination, dividing cortical areas into layers in a well-defined order with "feedforward" and "feedback" connections between different levels of the hierarchy (207, 210, 211). In particular, feedforward connections originate from superficial layers (2/3) of cortex and terminate in layer 4 (granular layer; **FIGURE 7**). Feedback connections, on the other hand, might originate from deep layers (5/6) and avoid layer 4 of the cortex (211), and in fact they often outnumber the feedforward inputs to neurons in lower levels of the hierarchy (212). Furthermore, as important sources of inputs and targets of cortical neurons, different nuclei of the thalamus can

be incorporated into the above hierarchy based on the laminar pattern of corticothalamic (CT) or thalamocortical (TC) projections (see also sect. 5.1): thalamic projections to layer 4 are described as driving and feedforward, whereas input to layer 1 is categorized as modulatory and feedback (213) (**FIGURE 6**). Similarly, based on physiological properties, layer 6 projections to thalamus are classified as feedback, and projections from layer 5 are feedforward (214). Together, these types of connection are capable of forming diverse circuit motifs such as feedforward cascades, feedforward and feedback inhibition, as well as mutual inhibition (215), which can implement repeated types of circuit motifs such as divisive normalization, thresholding, and filtering that can be reused across many different types of cortical processing (216–218).

# 3.1.2. Intercortical connectivity, recurrent networks, and inhibition.

The abundant interactions between cortical regions via projections in layers 2/3 are unique in their breadth and complexity. Cortical regions are heavily interconnected and communicate with one another extensively (219), both within and across cerebral hemispheres; these global cortical circuits provide a uniquely comprehensive means for sharing and integrating complex,



**FIGURE 7.** Cortical outputs to subcortical areas originate from distinct cell types. The thalamus is the exclusive noncortical target of corticothalamic (CT) neurons found in layer 6. Pyramidal tract (PT) neurons in layer 5 are specialized for subcortical projections and send target many different subcortical areas including the thalamus, superior colliculus, striatum, and spinal cord. Although PT neurons may have a single main subcortical target, many PT neurons also send projections simultaneously to different subcortical regions. Intratelencephalic (IT) neurons are found throughout cortical layers and are specialized for cortico-cortical communication. Although their key targets are other cortical areas, some IT neurons also collateralize to the striatum and other subcortical areas, to a limited extent.

multiplexed information. Zooming out to the macroscopic view, recurrent organization is observed between cortical areas. Recurrent feedforward and feedback pathways form a hierarchical organization of different cortical areas and especially between levels in the cortical hierarchy (207, 220, 221).

The recurrent local excitation and inhibition that arises from these intracortical circuits underlies key local cortical computations such as selectivity, normalization, and gain control (222-227). Within a cortical area, sparse excitatory recurrent connectivity is observed in all layers and between all cortical excitatory cell types (219, 228). When recurrently connected excitatory and inhibitory neurons are driven by external input, neural activity in the population dynamically evolves to settle into a state of balanced excitatory and inhibitory activity (229). Such excitatory/inhibitory (E/I) balance and recurrent dynamics have been proposed to underlie many key local cortical computations such as selectivity, normalization, and gain control (222-227). Disruption of E/I balance has thus been implicated in cortical dysfunctions in many neurodevelopmental conditions (see for recent reviews Refs. 230, 231). The expression of these cortical dynamics is elaborated by the diversity of inhibitory cell types within the cortex, which provide not only feedforward inhibition to excitatory neurons but also disinhibition by targeting other interneurons (208, 232, 233). In sum, the interconnectivity of diverse cortical excitatory and inhibitory cell types greatly expands the capacity for information processing and storage in the cortex, providing flexibility to spatiotemporal cortical recurrent dynamics that contribute to cortical computation power. As we see below, many subcortical regions do not share this cellular and physiological diversity or extent of recurrent connectivity for local computations.

## 3.2. Functional Roles and Specialization of Cortical Areas

The hierarchical organization, inhibitory circuits, and recurrent connections are important anatomical features that help the cortex implement complex functions and sustain spatiotemporal dynamics in its interconnected circuits. In recent years, powerful computational models of cognition have been developed, taking inspiration from these organizational principles, to increase the complexity and capability of machine learning systems: for example, hierarchical visual cortical organization inspires convolutional networks for image processing that are able to extract complex, higher-order features from raw inputs (234, 235); hierarchical organization inspires models of predictive coding (236, 237), whereas recurrence and intercortical connections are the basis of recurrent neural network models that maintain working

memory and house rich dynamics that support computations that are extended in time (238-240). In this section, we give a brief overview of these higher-order cortical functions and discuss how they might emerge from the anatomical features of the cortex. The discussion here serves to launch our investigation of corticalsubcortical interactions in sect. 4. The understanding of cortical function will allow us to build an initial model of what the cortex might be able to achieve by its own intrinsic circuitry without the need for feedback or inputs from subcortical structures. This model will then be layered on with contributions from subcortical regions through the various feedback loops and interactions with cortical regions. Additionally, the types of information processed in cortical circuits dictate the contents of cortical projections out to subcortical regions. In particular, we expect the richness in information and dynamics of cortical activity to be preserved in the subcortical projections, which might play significant roles in enhancing, suppressing, or providing contextual cues that modulate the intrinsic functions of these regions, such as information about environmental states, rules, and internal needs of the organism.

### **3.2.1.** Sensory feature extraction.

The hierarchical organization of the cortex motivates models of sensory processing where information is received and transformed through successive stages in the pathway (211, 241). In this manner, different stages (or regions of cortex) implement a feature extraction that abstracts from the raw input features to increasingly higher-order representations. The most well-studied example of this type of architecture is the primate ventral stream, where early visual areas such as V1 compute simple features such as edges, whereas areas further down start to build increasingly complex features and object representations (241, 242). In rodents, although visual areas perform more primitive visual transformations, physiological recordings revealed reliable clustering of visual areas as well as distinct functional hierarchies within these areas that coincide with the anatomical hierarchy (243, 244). This architecture of the visual processing pathway is the motivation behind convolutional neural networks and layered architecture that have revolutionized machine learning and image recognition in artificial systems (234, 235).

The organization of the cortex provides another benefit in sensory processing, with top-down feedback helping to modulate and modify the processing in lower layers according to internal expectations or environmental contexts (245). Feedback from higher- to lower-order cortical regions might be crucial to implement various forms of predictive processing, where top-down inputs try to predict the incoming sensory information or the activity of lower-level nodes and bottom-up inputs convey prediction errors that cannot be explained by these predictions (236, 237). Coupled with this theoretical framework and the empirical arrangements of cortical circuits, other powerful computational models have been developed to achieve the capabilities of cortex in sequence recognition and prediction (244). Thus, the hierarchical architecture of the cortex might be an important anatomical feature that helps it extract meaningful and complex features from sensory information that might be useful for performing subsequent computations and generating an understanding of the environment.

#### 3.2.2. Working memory and motor preparation.

Whereas hierarchical organization enables the cortex to implement complex functions for feature extraction, cortical recurrent connectivity gives rise to persistent and dynamic modes of activity that sustain these computations over a much longer timescale than that of singleneuron activities (240, 246). These persistent modes can hold information over extended periods and are the basis of short-term and working memory in multiple task domains, from evidence accumulation (247), sequential sensory comparison (248), motor execution (249) or timing tasks (250). To illustrate just one example, we focus on the domain of sensorimotor transformation and how cortex can hold its upcoming decision and motor commands in memory before action execution. Previous studies from our laboratory and others highlight the contribution of diverse regions and especially the motor cortex in maintaining choice information during the delay epochs (between stimulus presentation and action execution) (251). Although stimulus-evoked activities first emerge in the sensory cortex, neural activity in the frontal motor cortex (fMC) encodes the upcoming decision early in the trial and shows persistent activity that scales with the duration of the delay period of the task, until the choice is eventually executed. Most notably, optogenetic inhibition of the fMC during the delay period results in suboptimal choices of animals in many tasks: performance in a visual go/no-go task decreases to chance levels (251), whereas behavior in a bidirectional (left/right) licking task becomes biased toward the ipsilateral side of the inhibition (252). Moreover, perturbation studies also demonstrated the remarkable robustness of neural dynamics to optogenetic interventions: after a transient perturbation of neural activity on one hemisphere of the motor cortex, the activity of this side was able to guickly recover to the level seen on unperturbed trials (253). Interestingly, this recovery is dependent on long-range inputs from the contralateral motor cortex: severing the connection between the two hemispheres abolished

the recovery in the perturbed side of the brain (254). Thus, these sets of studies highlight two important contributions of recurrent and long-range connections of the cortex. First, they demonstrate the sequential flow of information across the cortex during decision-making and the remarkable role of the motor cortex in maintaining choice information in short-term memory during delay epochs. Second, recurrent connections give rise to robustness in neural activity, as any deviation from normal activity can be rescued by the ongoing and reverberating dynamics throughout the rest of the network.

#### 3.2.3. Higher-order functions and representations.

Unlike primary sensory or motor areas where single neurons are thought to encode single features of the sensory stimuli or movement parameters, the neural representation in higher-order cortices such as the PFC and motor cortex is markedly more complex (249, 255-257). An important feature of neural activity in these areas is mixed selectivity, where single neurons can show mixed responses to multiple features of the task, often nonlinearly combined to form a highly nontrivial representation of sensory, motor, and internal variables (240, 257). Theoretical studies highlight the importance of these nonlinear representations, arguing that they expand the computational complexity of the neural circuits as neural activities can be brought to a higherdimensional representation, helping to implement a more diverse array of input-output transformations (202, 203). Indeed, the study of these abstract neural spaces and their representation has been vastly influential both in building an expanded conceptual understanding of neural computation (through mappings between representational spaces) (258) and in developing technical methods of characterizing the population activity in these areas (259).

An immediate result of top-down feedback and recurrence in the cortex is that brainwide activity in the cortex might represent multiple task variables at the same time and sensory and motor information might be observed not only in localized brain areas but through many different stages of cortical processing. Recent studies highlighted this distributed nature of cortical activity. For instance, in rodents trained in a visually guided or auditory-guided decision-making task, signatures of movement, both instructed and uninstructed, dominate the activity of multiple cortical areas (260). Even in the visual cortex, a region thought to focus extensively on representing visual information, about one-third of the variance in the population activity can be predicted by behavioral variables (261). These results once again highlight the distributed nature of cortical computations

not just when animals are engaged in complex decisionmaking task but also during spontaneous behavior. Multiplexing of sensory, behavior, and internal variables is therefore a hallmark of cortical processing through many different task domains, and these complex representations are likely to be preserved as they are sent to subcortical structures to modulate their functions.

## 4. CORTICAL-SUBCORTICAL INTERACTIONS

So far, we have discussed how the cortical and subcortical domains of the brain both play critical roles in goaldriven behavior. Subcortical structures retain privileged access to rudimentary sensory inputs and motor outputs, which allows them to quickly and efficiently enact sensorimotor transformations. Their structural differentiation into functional nuclei allows for the careful organization of multimodal information and the ability to command distinct, competing pathways to selectively promote and suppress actions, or even anticipate stimuli. The neocortex, meanwhile, exhibits impressive computational power, enabled by its laminar structure, robust inhibitory network, hierarchal organization, and recurrent connectivity. These features provide the cortex with the capability to support context determination, higher-order learning, short-term memory, and generalizability of information. These two systems work in tandem to drive voluntary behavior and cognition -but how and what do they communicate?

Typically, this communication is framed from a cortex-dominant perspective, with cortex using environmental cues and internal representations to extract important information, select a choice, and modulate the responses of subcortical structures. However, this framework neglects that only a subset of these interactions are direct; the majority of cortical-subcortical communication is necessarily routed through the thalamus. Indeed, even the information used by the cortex to modulate downstream structures is obtained primarily through the thalamus.

As a relay for the communication of most sensory (except olfaction) and subcortical signals to the cortex, the thalamus has long been described as a bridge between these two systems of the brain. Although it is typically described as serving as a sort of quality filter for this bottom-up information, recent perspectives highlight its role as an integrative hub and potential to influence the cortex and its functions. Throughout evolution, the thalamus has undergone expansion that paralleled that of the neocortex (262). Because of their intimate reciprocal relationship with the cortex, thalamic activity is not only critical for ongoing cortical activity (213) but also during development for the formation of functional thalamocortical circuits and cortical specializations (263). Furthermore, the thalamus employs reciprocal connectivity with the cortex, all of which receives thalamic input. Receiving as much information as it shares, the thalamus also communicates back down to subcortical structures, providing another important mechanism for top-down control. For that reason, the thalamus is necessarily involved in a broad range of functions, particularly where cortical-subcortical interaction is key, including sensorimotor control, regulation of attention, arousal, and motivational states. Thus, to understand the cooperation of these two systems we must necessarily examine the role of the thalamus in facilitating their communication.

Here, we describe mechanisms for the interaction of the cortical and subcortical domains of the brain, giving examples of direct cortical-subcortical communication via top-down projections from cortex to our exemplar regions, the striatum and superior colliculus, and then discuss potential common principles of cortical modulation.

#### 4.1. Cortical Outputs to Subcortical Areas

The cortex contains multiple long-range projection types that not only have laminar specificity but also can be molecularly defined (264). The cortex sends outputs to subcortical areas through pyramidal tract (PT) and corticothalamic (CT) neurons in layers 5 and 6 (FIGURE 7). The thalamus is the only subcortical target of L6 output neurons, which send their axons exclusively to the thalamus and collateralize in the local cortical column. Thus, L6 CT neurons are uniquely specialized for corticothalamic communication and form small but numerous synapses onto thalamic neurons (214). In contrast, L5 PT neurons can project to many subcortical areas, including the superior colliculus, striatum, and other brain stem and spinal motor centers (265). Intratelencephalic (IT) neurons are found throughout cortical layers and primarily project to other cortical areas and the striatum but can also collateralize in subcortical areas (264). The distinction of cortical cell classes specialized for cortical (IT) and subcortical (PT and CT) communication reveals parallel but functionally segregated streams of information flow. Even within these cell classes, functional properties of these cells have been shown to be specialized to their specific cortical or subcortical targets (266, 267).

Importantly, the molecularly distinct properties of cortical IT and PT neurons have provided the means to address a key question: How do cortical outputs to subcortical areas differ from cortico-cortical outputs? Indeed, a recent widefield imaging study showed cortexwide differential functional activity of IT and PT cortical classes in an active sensory discrimination task that also depends on the cortical area examined (268). IT and PT neurons exhibited different sensory, spatial-selective and choiceselective activity in different cortical areas. When these cortical classes were separately inactivated, parietal PT inactivation during stimulus presentation caused greater disruption in performance than IT inactivation (268), suggesting that the PT subcortical projections may have stronger contributions to perceptual decision-making than parietal outputs to other cortical areas like the frontal cortex. Furthermore, cell type-specific inactivation also showed that subcortically projecting PT neurons in the frontal cortex are critically necessary for motor execution of responses (268). A different study showed that mice trained on a closed-loop calcium imaging brainmachine interface were more efficient in learning to control motor cortical PT neurons than IT neurons (269), perhaps because of contributions of the subcortical targets of PT neurons to learning. In sum, although IT and PT neurons interact in local cortical circuits and can gate mutual outputs (270), PT neurons have distinct functional specializations relative to IT cortico-cortical projections. These cortical projections to subcortical areas are important in learning and decision-making behavior during motor execution and sensory processing.

#### 4.2. Cortical-Tectal Pathway

Above we described the organization and function of the SC, highlighting its sensory and motor topographies, which enable the quick and efficient mapping of sensory stimuli to various behavioral responses in a retinotopic manner. These highly integrated, multimodal representations of space are orderly and highly consistent, and the links between these maps and resulting motor outputs are clearly delineated by the various subcortical connectivity of the SC. However, the SC, and especially the idSC, its sensorimotor layer, receives various direct inputs from the cortex, including sensory, motor, and prefrontal cortex, suggesting that its functions are subject to extensive modulation. Although the roles of sensory and motor cortex onto the SC seem relatively straightforward, the importance of the SC in circuits for visual decision-making and spatial attention also makes it a valuable target site for the prefrontal cortex. How do these cortical regions interact with the existing topographies of the SC to promote, suppress, or otherwise modulate its function? In this section, we describe the organization and function of cortical drive to the layers of the SC.

#### 4.2.1. Organization of inputs.

Although cortico-tectal interactions have long been of functional interest, the organization of cortical inputs to the SC has only recently been examined in great detail. In sect. 2.1.1, we described a coarse division of the SC into (roughly) medial and lateral (**FIGURE 2**); however, this

division comes mostly from functional studies in which refining this organization was not a priority, much less how cortical inputs map onto it. A few recent studies have attempted to expand our knowledge of additional organizational elements in the mouse SC. In an impressively detailed anatomical study, Benavidez et al. (67) used injections of anterograde tracers across the entire cortex of adult mice to label cortical targets in the SC, resulting in the identification of additional organizational motifs, mostly within the idSC. Not only do these divisions roughly follow the classic medial/lateral functional distinctions of the SC but they refine them further, into four zones defined by corticotectal input: medial (SC.m), centromedial (SC.cm), centrolateral (SC.cl), and lateral (SC.l). Although the medial and lateral zone are most distinct, reflecting primary visual and somatic/prefrontal inputs (with no visual input), respectively, the centromedial and centrolateral zones receive more multimodal and higher-order associative inputs, differing in specifics (FIGURE 3). For example, the SC.cm receives more direct inputs from audiovisual areas, the ventral anterior cingulate (ACC), and the retrosplenial cortex, whereas the SC.cl receives inputs from visual, dorsal ACC, and somatic cortices. This organization suggests a gradient of cortical input, from visual to prefrontal, that may map onto distinct cortico-tectal networks. Benavidez et al. posit several possible cortico-tectal networks. The more medial networks, SC.m and SC.cm, mediate spatial, visual, and defensive behaviors, functions that may be subserved by the largely spatial and somatic inputs. The lateral network, on the other hand, may coordinate appetitive and approach behaviors, meaning that the preferential prefrontal inputs to this region function to provide emotional and goal-related information. Finally, and importantly, the projections of the ACC to the two central regions, SC.cm and SC.cl, which integrate a variety of multimodal sensory information, may have important implications for visual attention behavior, as discussed below.

Another recent study identifies further refinement of the corticotectal organization of the mouse SC by way of inhibitory and excitatory cells. Using monosynaptic rabies tracing in molecularly defined cell types, Gad2 for neurons expressing GABAergic and Vglut2 for glutamatergic cells, Doykos et al. (271) identified differential patterns of cortical inputs to the idSC. First, although the majority of idSC cells are excitatory (roughly 70% are glutamatergic, compared to 30% GABAergic) (272, 273), on average excitatory neurons were found to receive far more inputs from other brain areas, especially cortex, than would be expected if these inputs were proportional. These excitatory neurons tend to be targeted by sensory and motor cortical regions, whereas inhibitory neurons largely receive inputs from visual cortex and the anterior cingulate. A further distinction also exists along the rostrocaudal axis. Although cortical inputs

preferentially target both rostral excitatory and inhibitory neurons, the vast majority of inputs to inhibitory neurons are rostral. Given the rostrocaudal organization of movement space in the idSC, this may have interesting implications for the top-down modulation of SC modulation.

## 4.2.2. Visuo-collicular functions.

As described above, the superficial and intermediate/ deep layers of the SC have differential connectivity with the cortex, which relates closely to their functions. The sSC, in line with its visual role, receives input from the visual cortex across its mediolateral axis; however, it also receives profuse input from the retina. What additional information could the visual cortex be providing to the superficial layer? Although great care has been taken to investigate the nature of visual cortex input to the SC in mice, its nature in awake, behaving animals is still unclear, likely because of the number of studies conducted in anesthetized mice and insufficient means of reducing brain activity, such as cooling. However, more recent studies using optogenetics in awake mice have begun to identify the main role of the V1-SC projection. One study combining looming stimuli with optogenetics and electrophysiology determined that inactivation of V1 reduces the amplitude of sSC visual responses but does not affect other properties of these neuronal responses, including selectivity for a particular stimulus (274). Another recent study using a bright light to provoke SCmediated arrest behavior found not only that the V1-SC modulates the frequency of these responses but also that activation of this projection alone is enough to trigger the behavior (275). This same study also found a reduction in the amplitude of SC responses to the same stimulus with silencing of V1. Finally, it has been shown that the V1-SC projection can suppress neuronal signals of perceptual pop-out in the SC, a phenomenon in which some unique characteristic of a stimulus evokes a greater response to it than dissimilar distractors (276).

Together, these findings suggest that the role of the V1-SC projection is that of gain control of the SC's visual responses; this modulation of visual processing in the SC may have an indirect effect on its subsequent selection of a corresponding response. This may also provide for a cortical mechanism whereby reflexive responses (like visual pop-out) can be selectively suppressed, providing a cortical means for the flexible modulation of attention.

# 4.2.3. Prefrontal cortex-superior colliculus functions.

As the purported nexus of executive function, the prefrontal cortex (PFC) has long been thought to exert topdown control over cortical and subcortical structures via its long-range projections (277–279). Although the exact regions of the PFC that project to the SC vary across species, one prominent projection appears to be analogous. The region known as the frontal eye fields (FEFs) in primates (33), the frontal orienting fields (FOFs) in rodents (31), and the anterior cingulate (ACC) in mice (12) is associated with visuomotor processing and self-initiated actions and is known to project to the idSC.

In the primate, the FEF and SC are both involved in the generation and modulation of saccades (280–282). Neural activity in the FEF correlates to visual stimuli and saccade generation (283), and its activation and inactivation result in deficits similar in those in the SC (284). Furthermore, although stimulation of either region can potentially trigger a saccade to a particular location, stimulation of the FEF can also selectively facilitate, redirect, or outright suppress task-related saccades (Refs. 285, 286, but see Refs. 287, 288). Thus, these abilities of the FEF provide it with a mechanism to potentially impose a goal by directly exciting or facilitating the SC's innate abilities.

Similar findings have been made in the rodent visuomotor system. Although rodents have largely not been shown to use saccades for visually driven behaviors (but see Refs. 289, 290), as described above they readily exhibit other signatures of orienting, such as turns of the body or head, to which the FOF and ACC contribute. In addition to projecting directly to the SC (291), the FOF appears to parallel the SC in orienting tasks, with both displaying preparatory signals that predict orientation direction that, when disrupted, result in severe behavioral deficits (34). Comparable findings have been made in the mouse ACC, which has been shown to play an important role in visual attention (292, 293) and project directly to the SC (294). Furthermore, the ACC seems to have a role similarly parallel to the SC, where it and the SC influence orienting choices in a visual task, and the ACC-SC projection selectively modulates these choices (12).

In summary, the V1-SC projection seems to selectively modulate the salience of a visual stimulus, whereas the PFC-SC projection selectively biases responses to visual stimuli. In combination, these two cortico-subcortical projections provide at least two distinct mechanisms for top-down control of visual behavior and even attention.

## 4.3. Cortical-Striatal Pathway

We discussed above how the "intrinsic" circuits in the striatum and basal ganglia can carry out diverse functions through their interactions with the motor circuits (to exert sensorimotor control) and with the subcortical dopaminergic system (to mediate stimulus-outcome or action-outcome associations). These circuits form the

basis of action selection (habitual or model free) as well as value representation in subcortical areas used for limbic or value-guided learning. However, the functions of the striatum and basal ganglia are limited in several ways. These circuits are not flexible enough to capture the context-dependent changes in contingencies required to effectively navigate complex situations. For example, an action that yields rewards in the short term might become costly over longer time horizons; the typical route for the transformation of sensory information to action selection that serves well for one goal may be insufficient or even harmful for another, requiring modulation or interruption of these default responses (295, 296). This context-dependent combination of adaptation to new information and subsequent change in response may be mediated by the cortex. Cortical inputs to the striatum continuously interact with the local circuitry and innate functions of the striatum through projections from the sensorimotor, limbic, and cognitive cortical areas (144, 297). How does such top-down control operate to coordinate between these distinct sets of functions?

Although many cortical regions send excitatory and glutamatergic inputs to the striatum (168), in this review we dissect the contribution of three major projections: the motor cortex, which provides sensorimotor modulations critical for learning motor skills (298), and the anterior cingulate cortex (ACC) and the orbitofrontal cortex (OFC), which jointly supplement associative and limbic functions (204, 296, 299). First, we discuss commonalities in top-down circuit motifs, highlighting the incredible topography and segregation of inputs maintained by the striatum. Then, we describe how these cortical regions mediate different sensorimotor control, error monitoring, state- or rule-based representation. Finally, we discuss how these cortical inputs expand upon the existing capabilities of striatal circuits to enable flexibility in action selection and reward learning.

#### 4.3.1. Topographic organization.

One major feature of cortical-striatal projections is in their topographic organization, which itself may determine the potential for their integration via the basal ganglia. Early experiments initially revealed a topographic map in the striatum in which inputs from different areas of cortex target distinct zones in the striatum (147) (FIGURE 8); this topography has been further refined in recent years with the aid of computational neuroanatomical tools and circuit tracing techniques (145, 146). The striatum can be divided into three major sections (dorsomedial, dorsolateral, and ventral), which broadly correspond to inputs from distinct cortical regions (associative, sensorimotor, and limbic, respectively) (145). Indeed, as we describe in sect. 2.2, these divisions of the striatum



FIGURE 8. Topographic organization of cortical-basal ganglia-thalamocortical circuits. Projections from the cortex to the striatum may be divided into distinct projection zones, where cognitive regions [such as anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC), red] preferentially project to the dorsomedial striatum, sensorimotor regions [such as motor cortex (MC, green] project to the dorsolateral striatum, and limbic regions [such as prelimbic cortex (PL) and infralimbic (IL), blue] preferentially project to the ventral striatum. This topography is preserved in downstream projections from the striatum to the globus pallidus external (GPe), substantia nigra pars reticulata (SNr), and different nuclei of the thalamus [shown here is the ventromedial nucleus (VM) as one example]. Thalamic projections back to the cortex complete the feedback loop and also preserve the topography of the originating cortical inputs. These segregated and independent loops through the cortex, basal ganglia, and thalamus are equipped to serve distinct functions (see FIGURE 5).

correspond to distinct modes of learning. Although the dorsolateral striatum plays an important role in habitual actions and inflexible sensorimotor transformations, which are model free, the dorsomedial striatum is prominently involved in driving goal-directed behavior (10, 187). The convergence of cortical inputs occurs in a similar fashion; projections from primary sensory and motor cortices target the dorsolateral striatum (145, 146), whereas the dorsomedial striatum receives inputs from higher-order cortices, including the ACC and OFC (145), which assume more limbic and cognitive functions (147) (FIGURE 8). These divisions are also observed in the physiology of the striatum and its input sites; a recent study using simultaneous Neuropixels recordings in these cortical areas and their respective target zones of the striatum identified correlated activity in both sites (14).

This evidence suggests that cortical inputs to the striatum segregate into distinct streams that deliver cognitive, sensorimotor, and limbic signals to the appropriate zone of the striatum that processes these signals. Remarkably, these parallel striatal streams remain largely segregated throughout the basal ganglia (300) and subsequently through basal ganglia outputs to the thalamus (FIGURE 8). Indeed, as we see below, the topography of cortical projections to the striatum is preserved through its projections to the thalamus and back to cortex. What is the significance of this segregation and specificity in topography in striatal and basal ganglia organization? Various theoretical proposals suggest that these loops are important in action selection and might support the maintenance of concurrent goals of organisms that might be selected from moment to moment depending on the current needs and context (11, 142, 148). Separating the multiple sources of signals might serve to ensure minimal interference and allow simultaneous updating of these signals in downstream selection mechanisms. The inhibitory basal ganglia circuits might be a substrate of such a selection computation. An alternative perspective of these parallel loops is evolutionary (139): as animal behavior became more complex, striatal modules of simple organisms became duplicated and reused to control a more diverse range of behavioral modules (such as feeding, orienting, saccades, and locomotion). The duplication of these modules in the basal ganglia and striatum might have resulted in the multiple parallel pathways through the cortex and thalamus in the mammalian brain, each evolving to cope with a different type of behavioral demand.

## 4.3.2. Orbitofrontal-striatal interactions.

The OFC-to-striatum projection interaction demonstrates how both areas are key players in rewardquided decision-making (FIGURE 5). We have seen that different zones in the striatum assume roles in model-free or model-based learning. Despite its role in action selection, the OFC does not have direct access to the motor areas of the cortex, necessitating its cooperation with subcortical structures directly (301). Thus, it comes as no surprise that OFC projections to subcortical structures, including the ventral striatum (VS; Ref. 302), play an important role in influencing sensory-guided action selection. In addition to direct, dense projections from the OFC to the ventral striatum (10, 145), several studies find a functional coupling between these two areas. OFC and striatal activity are closely coupled, with both OFC and striatal neurons displaying a similar reversal of reward-related responses in reversal learning paradigms (295). This relationship seems to be nonredundant: whereas lesions of the OFC in rats lead to altered representations of reward magnitude in the VS (303), altering the activity of neurons in the intact OFC also leads to modulations of striatal neuronal activity, as well as increases in repetitive behavior (304, 305). In

addition to the ventral striatum, the OFC also interacts with both the dorsolateral and dorsomedial striatum. This dual interaction might help to coordinate the switch from model-free to model-based modes of action that are encoded in these two subcompartments of the striatum (301, 306) (**FIGURE 5**). Other perspectives, based on computational models of OFC-striatum and OFCamygdala interactions, suggest a role of OFC in maintaining a working memory of action outcomes and using this information to supplement the less flexible intrinsic functions of the basal ganglia (295). This account is consistent with the notion that OFC represents and maintains information about the task states and maintaining that state to provide the context for accurate decision-making (296).

## 4.3.3. Cingulate-striatal interactions.

Previous studies have highlighted an important role of the primate ACC in error monitoring, integrating information over long timescales, and triggering context-specific behavioral changes (both during simple behaviors like foraging and in more complex behavior like hierarchical, rule-based decision-making) (299, 307, 308). Given its projections to the striatum, the ACC is thus a prominent candidate region for providing change signals to the striatum and thereby triggering behavioral or even strategic changes.

Like the OFC, the striatal targets of the ACC's projections suggest specific functional roles (FIGURE 5). The ACC's outputs target the dorsomedial and ventral striatum, involved in model-based learning and stimulus-outcome pairing (a type of model-free learning), respectively (309). One possible function for this cortico-striatal projection is in facilitating the switch between these learning modes (192, 310). At the computational level, model-free and model-based components can be thought of as a competition between a fast "caching" system and a slower but more flexible system that represents the reward contingencies of world state transitions (192). Although the striatum is well suited to implementing learning habitual actions on its own, it lacks the flexibility to adapt to the introduction of uncertainty, something the ACC may provide. Experimental evidence points to a crucial role of ACC in conflict monitoring (299).

One potential mechanism relies on the potential for external striatal inputs to bias the value encoding toward one of two competing actions (186). The modulation from ACC or prelimbic cortex (PL) is shown most clearly in cost-benefit conflicts where actions of the agent might be determined based on the need to minimize the cost or maximize the reward. In this case, a top-down modulation of ACC might set the threshold or balance between these two competing goals of the agent (171, 309, 311). This mechanism would be consistent with ACC's roles in selecting actions based on cost-benefit conflicts, especially when they involve an expense of effort to obtain rewards (309). In recent years, various circuit-level interrogations in the mouse model have confirmed the predictions of this top-down biasing model. In particular, specifically activating the ACC-striatum projection indeed causes shifts in reward-guided behavior, as demonstrated by an increase in reward-seeking (312), and a shift toward the higher-reward option in cost-benefit comparison (171).

The other mechanism by which top-down projections from ACC might influence intrinsic cortical and subcortical functions is through error detection and the monitoring of task performance. In this account, ACC detects errors in the performance and broadcasts the need to switch behavioral strategies to either sensory areas (to enhance sensory processing) or possibly subcortical areas to signal a switch in behavioral strategies. Consistent with this hypothesis, in a hierarchical decisionmaking task, switch-related information is strongly represented in the ACC population, and inactivating ACC also decreases the probability of switching (307). In a visually guided task that requires mice to pay attention to a large number of alternatives, activating ACC top-down projections to the visual cortex enhances behavioral performance after error trials (313). This top-down perspective of the ACC is attractive, especially considering the compositionality of behavior: ACC might be acting to demarcate behavioral units (or "options") on longer timescales, whereas the basal ganglia might be more concerned with the implementation details of each unit (314), acting to execute the motor actions that comprise a sequence of chunked actions (315, 316).

#### 4.3.4. Motor cortex inputs and STN.

Although neural activity in the motor cortex reflects movement parameters (317), optogenetic inactivation experiments revealed that the motor cortex is not necessary for movement execution (298). Emerging evidence suggests that the area might instead play a causal role in motor learning (298, 318), as well as coping with variability and movement perturbations (319, 320). Physiological recordings from output neurons in the motor cortex suggest two types of activity: preparatory activity that supports motor planning and command activity that supports motor execution (256, 321–323). Preparatory activity is shown to reverberate in cortico-thalamic loops (324) and appears long before movement onset. On the other hand, executive command activity may appear at different epochs of movement to signal initiation, stopping, or sustaining movement. Such command signals may often arise to signal prediction errors or perturbations (319, 325), a feature prevalent in both intracortical projections (326) and subcortical projections mediated by pyramidal tract (PT) neurons (319). This information might be crucial to modulate activity in the direct and indirect pathways of the basal ganglia and is used in combination with reward signals in striatal networks to orchestrate learning.

Alongside the striatum, the STN can be considered an additional input nucleus to the basal ganglia, which funnels cortical inputs to the output nuclei through the hyperdirect pathway (327, 328). During stop-signal reaction tasks and go/no-go tasks, STN stopping activity in humans is generally preceded by cortical activity in the hyperdirect pathway, emanating notably from the right inferior frontal cortex and the pre-supplementary motor area (pre-SMA) (159, 160, 329, 330). In mice, this structure coincides with the medial secondary motor cortex (M2) (331). This region is also part of a visual subnetwork (331, 332), given medial M2's dense projections to visual areas (326, 332, 333) and reciprocal connections with retrosplenial cortex (334), strongly suggesting an integrated source of sensory and motor information that projects to the striatum and STN.

As outlined in sect. 2.2, the striatum can be subdivided into the motor, associative, and limbic projection zones, and this topographic organization is also seen in the STN and the hyperdirect pathway (145, 150, 157, 335, 336). The STN receives projections from most of the frontal cortex and the medial M2 area, a rich source of visual and motor inputs that is ideal for visuomotor transformation and integration. This positions the cortico-subthalamic projection from M2 as a key player in controlling visually guided movements. Indeed, a recent study shows that the M2-STN pathway sends stop signals to control visually guided locomotion (337), demonstrating how an integrated cortical input might modulate the intrinsic function of basal ganglia outputs. Such cortical inputs might disrupt basal ganglia operation through the STN, via its "hold your horses" function (295, 328, 338), allowing animals to delay action selection if needed. STN projects to the external globus pallidus, which in turn projects back to the striatum, which could alter striatal dynamics to pause, and serve as a source of stop signals to striatum (339).

## 5. THALAMUS AS A GATEWAY OF CORTICAL-SUBCORTICAL COMMUNICATION

The thalamus sits at the intersection of external sensory inputs, subcortical structures, and the cortex. The cortex is the main recipient of thalamic outputs, and indeed all cortical areas receive thalamic input. With the exception of the olfactory system, all sensory input also has to first be routed through the thalamus before arriving in the cortex. Although most subcortical structures receive direct cortical input, with the exception of neuromodulatory afferents, most subcortical structures lack direct excitatory projections back to the cortex and thus depend critically on the thalamus to convey its feedback to the cortex. The extensive connectivity of the thalamus positions it as a brainwide nexus that facilitates cortical and subcortical interactions. For that reason, the thalamus has been involved in a myriad of functions, including memory, selective attention, contextual processing, sensory filtering, movement control, action selection, and arousal regulation (340–347).

Here, we aim to illustrate the role of the thalamus as an integrative hub and active gate that allows for flexible cortical and subcortical interactions. First, we describe the thalamic circuitry and its long-range connectivity that define its integrative functions. To demonstrate the dynamic interplay between the cortex and the thalamus, we then present examples seen in the bidirectional modulation of sensory processing through spatiotemporal thalamic circuit mechanisms, where the reciprocal thalamocortical interaction has been most studied. We present evidence from motor and prefrontal systems to show that neither the cortex nor thalamus can function optimally in isolation and how their recurrent interaction has been particularly implicated in complex behaviors. Finally, we show how the thalamus not only serves as a critical bridge to close the loop between the cortex and subcortical structures like the SC and striatum but can also incorporate subcortical inputs into open loops by funneling them through other cortical streams or broadcasting subcortical information to multiple cortical areas (FIGURE 9C).

## 5.1. Thalamic Organization

The thalamus is organized into multiple functionally specialized nuclei, each with a unique complement of reciprocal cortical connectivity (207) and subcortical inputs. Firstorder nuclei [such as the dorsal lateral geniculate nucleus (dLGN) and medial geniculate nucleus (MGN)] receive their driving input from a subcortical source; for example, dLGN receives direct driving input from sensory organs (e.g., retina) and provides feedforward sensory input to the primary visual cortex (V1). Higher-order (HO) relay nuclei, such as the pulvinar/lateral posterior (LP) nucleus and the medial dorsal (MD) nucleus, instead receive their driving input from cortical neurons (FIGURE 9A). Whether first order or higher order, sensory nuclei all have modality-specific topographical organization (348, 349). Some higher-order nuclei, such as LP, have more than a single map of sensory space: two retinotopic maps across LP subregions reflect its driving input from different sources, V1 and SC (348, 349). Although higher-order sensory nuclei have modalityspecific driving inputs, they integrate information from and project to multiple sensory systems and are often responsive to multimodal stimuli. Beyond the sensory domain, many higher-order thalamic nuclei have specialized functional domains also reflected in their subcortical inputs and cortical reciprocal connections. For example, MD has exclusive reciprocal connections with multiple prefrontal and frontal cortical areas (**FIGURE 9C**), whereas the motor ventral lateral (VL) thalamus integrates cerebellar and striatal inputs and has reciprocal connectivity of these thalamic functional domains positions these nuclei as hubs bridging distinct but dynamically interacting cortical areas.

## 5.1.1. Local circuitry.

A key feature of local thalamic organization is the lack of local excitatory inputs to other thalamic neurons: all excitatory drive to thalamic neurons originates from external input. Thus, most thalamic nuclei are best defined by their subcortical and cortical external input. Thalamic nuclei contain very sparse, if any, interneuron populations (262). Instead of interneuron-mediated inhibition, the major source of intrathalamic inhibition comes from the thalamic reticular nucleus (TRN), which exclusively sends outputs to other thalamic nuclei (FIGURE 9A). The TRN forms a GABAergic sheath around the thalamus and contains molecularly defined subpopulations that project to both first- and higher-order thalamic regions (350). Thalamocortical neurons input to the TRN, and the mutual inhibition from TRN sits at the core of intrathalamic dynamics (351). External inputs to thalamic nuclei often collateralize in or specifically target the TRN, to powerfully control thalamic gain and thalamic firing modes and entrain the thalamus in distinct oscillatory bands to control brainwide states of arousal (352–354). As the TRN itself is organized into many parallel subcircuits based on its thalamic partners (265, 350, 355–357), brain areas that do not have direct inputs to specific thalamic nuclei are still able to exert indirect influence via these TRN subcircuits.

## 5.1.2. Thalamocortical outputs.

The cortex is the major output of thalamic relay neurons, with the thalamus targeting cortical areas with a few distinct motifs (358). Thalamocortical inputs carrying feedforward sensory information send their axons to the input layer 4 of its corresponding primary sensory cortex, with some collaterals in layer 1 (FIGURE 9C). As with the sensory inputs to the thalamus, the feedforward thalamocortical projections preserve modality-specific sensory topography, such as the retinotopic organization



**FIGURE 9.** Motifs of thalamocortical interactions. *A*: first-order and higher-order sensory thalamic nuclei receive different cortical inputs. First-order nuclei, like dorsal lateral geniculate nucleus (dLGN), predominantly receive inputs from L6 corticothalamic (CT) neurons, whereas higher-order nuclei, like LP, can receive both from L6 CT neurons and driving input from L5 neurons. Both pyramidal tract (PT) and CT inputs to the thalamus can collateralize to the GABAergic thalamic reticular nucleus (TRN), which in turn provides feedforward inhibition to different thalamic nuclei. *B*: higher-order nuclei like lateral posterior (LP) are also able to provide indirect transthalamic pathways between cortical areas. For example, although profuse direct mutual connections exist between primary visual cortex (V1) and anterior cingulate cortex (ACC), these cortical areas also project to LP, allowing indirect communication. C: additional examples of thalamocortical projection motifs. *Left*: first-order sensory nuclei like dLGN project to the sensory cortex (V1) mainly to L4 but also send axons to L1 and L6. They typically do not project to other cortical areas beyond their main target. *Center*: in contrast, higher-order sensory nuclei such as LP target a diverse set of cortical areas that are not limited to the sensory cortices and also simultaneously project to other sensory (e.g. auditory cortex), parietal (not shown), and prefrontal areas like prelimbic cortex (PL) and ACC. Single LP neurons tend to have multiple targets. *Right*: other higher-order thalamic nuclei do not have sole cortical targets like dLGN to V1 but instead project to multiple cortical areas that are functionally linked, as exemplified by medial dorsal (MD), which bridges many prefrontal cortical areas like PL and ACC into functional modules.

of dLGN inputs to V1. In the cortex, thalamocortical axons send direct input to both excitatory and inhibitory neurons.

Another distinct thalamocortical motif involves single thalamic neurons with widespread projections to multiple cortical areas (FIGURE 9C). This property is most prominently exhibited by "matrixlike" thalamic neurons that have broadly distributed projections to superficial layers of the cortex. Matrixlike neurons are found in greatest abundance in HO thalamic nuclei but are also present in first-order nuclei. These thalamic inputs to multiple different cortical areas serve as indirect transthalamic routes of communication between cortical areas. Mapping of transthalamic pathways revealed that these pathways parallel the direct cortico-cortical pathways (349, 359, 360), which convey different information from intracortical pathways to the same target area (361) (**FIGURE 9**, **B** and **C**). The widespread thalamic axons also provide a route for cross-modal sensory integration: many HO sensory thalamic nuclei receive inputs from and project to other sensory cortices beyond the driving sensory domain. For instance, despite receiving visual driving input, LP also projects to the primary auditory cortex (A1), and its input can improve auditory signal-to-noise ratio in A1 (362).

A hublike property of the thalamus is evident in its output to the cortex. Each cortical area can receive input from a diverse range of thalamic nuclei. For example, even the primary visual cortex receives input from at least 6–8 other thalamic areas apart from the dLGN, whereas integrative cortical areas such as the prefrontal cortex can receive inputs from as many as 25 different thalamic areas (363).

## 5.1.3. Corticothalamic inputs.

As described in sect. 4.1, the thalamus can receive inputs from the cortex from both layers 5 and 6. Although L6 is more specialized for corticothalamic communication, the thalamus also receives collaterals from L5 neurons that target other subcortical areas including the SC and striatum. At the single-cell level, CT input from the different layers also differs in the organization of their inputs onto thalamic neurons. L6 CT have a many-to-many architecture in that many CT neurons converge on the same thalamic cells (high convergence) and a single CT neuron sends input to multiple thalamic neurons (high divergence). This contrasts with the few-to-few organization of L5 projections that has low convergence and divergence (364).

High-throughout functional connectivity mapping has revealed principles of cortexwide influences on the thalamus. Specifically, just as cortical areas receive convergent input from multiple thalamic nuclei, single thalamic nuclei also tend to receive inputs from many different cortical regions (365). Although the corticothalamic impact at each of these nuclei can be driving or modulatory, depending on the cortical and laminar source of input, this logic of connectivity brings to the fore the integrative hublike properties of the thalamus.

## 5.2. Corticothalamic Interactions in Modulation of Sensory Processing

## 5.2.1. Modulation of sensory processing.

Ongoing reciprocal interaction between the thalamus and cortex is a critical element of thalamic function. Whereas the thalamus serves as an important source of feedforward input to the cortex, reciprocal feedback from cortical structures is integral to thalamic function. In this section, we illustrate how the cortex is not a passive recipient of feedforward sensory information from the thalamus. Rather, cortical feedback to the thalamus can actively tune the granularity or select for the modality of incoming sensory information.

## 5.2.2. Spatial modulation.

In the sensory domain, the topographic organization and spatial specificity of corticothalamic fibers are critical for the cortex to exert spatial modulation over incoming inputs (366, 367). This organization allows for surround suppression, a canonical neural computation that underlies selective attention and tuning sharpness. For instance, LGN neurons have classical center-surround retinotopic receptive fields and, additionally, a larger region around the classical receptive field where visual stimuli presented in this peripheral surround suppress the responses in the classical receptive field (368, 369). Cortical feedback amplifies sensory responses in both the excitatory classical receptive field and the magnitude of peripheral surround suppression, effectively sharpening LGN receptive fields. Loss of cortical feedback results in reduced sensory responses in the classical receptive field and relief of the suppressive impact of stimuli in the peripheral surround, resulting in degraded spatial tuning of LGN responses (368, 370–373). Comparable mechanisms depending on cortical feedback have also been described in the auditory (374, 375) and somatosensory (376) systems. Importantly, modulating sensory tuning through surround suppressive mechanisms also occurs in the reciprocal direction, from the thalamus to the cortex, such as observed with LP input to V1, which engages cortical inhibitory neurons to increase surround suppression and sharpen tuning (377). Here, it is evident that sensory tuning is achieved by the dynamic bidirectional interaction between feedforward thalamocortical inputs from firstorder sensory nuclei and feedback corticothalamic inputs. This can be further modulated in a context-dependent manner through higher-order thalamic nuclei like LP.

## 5.2.3. Temporal modulation.

In considering how the cortex and thalamus interact, precise temporal control of activity has emerged as a strategy that is made possible by the wiring of corticothalamic pathways. CT inputs from L6 to thalamic neurons often collateralize in the TRN, simultaneously exerting a monosynaptic excitation and a disynaptic inhibition via TRN to the same thalamocortical neurons (324, 376, 378). This circuit motif results in an interesting frequency-dependent impact of CT activity on thalamic gain due to short-term synaptic plasticity of the synapses in this triad. When CT neurons fire at low frequencies, thalamic neuronal activity is briefly enhanced and then becomes suppressed as soon as the disynaptic TRN-thalamocortical relay inhibition dominates. At high CT firing frequencies, however, excitatory CT projections exhibit short-term facilitation, whereas responses evoked by GABAergic TRN-TC synapses undergo short-term depression. As such, high-frequency CT activity is able to overcome the depressing disynaptic inhibition from TRN (376) and result in sustained enhancement of thalamic activity. Beyond control of thalamic firing rates, the dynamics of this frequency-dependent control of thalamic gain is an effective strategy for constraining thalamic gain to specific time windows. Theoretical models have also proposed that dynamics of this corticothalamic triad can form the basis of difference computations of two competing percepts (379), which may allow encoding of confidence comparisons between two percepts.

The timing of thalamic input arriving in the cortex plays an important role in cortical sensory representations: desynchronized thalamic input is less effective in driving the activation of cortical ensembles, whereas synchronous inputs even from different thalamic nuclei can result in supralinear integration in the cortex (380–383). Thalamic neurons have distinct tonic and burst firing modes, a consequence of their T-type Ca<sup>2+</sup> channels. After a period of quiescence (>100 ms) due to membrane hyperpolarization, excitatory inputs coinciding with the inactivated state of the T-type  $Ca^{2+}$  channels trigger  $Ca^{2+}$  influx, leading to high-frequency (~100 Hz) burst firing in thalamic neurons. The precise timing of L6 CT feedback to the sensory thalamus controls these firing modes (324, 384). In first-order sensory thalamic nuclei, tonic and burst spiking in awake animals have been associated with facilitating modes of stimulus discrimination and detection, respectively (324, 376, 385). Stimulus-evoked burst firing is particularly effective in triggering nonlinear dendritic integration to reach the threshold for firing at the soma to facilitate sensory detection (386). On the other hand, sparser tonic firing allows a greater linearity and bandwidth for information coding through varying interspike intervals, thereby promoting discriminability between stimuli (385-387). With higher-order nuclei, precise temporal patterning of thalamocortical input has been shown to be important for engaging cortical disinhibition that facilitates long-term potentiation (388).

Taken together, the cortex and thalamus mutually engage respective local circuitries to bidirectionally sculpt and control the flow of feedforward sensory information. This demonstrates that the thalamus contains the circuitry for spatiotemporal information filtering, yet it is critically in tandem with cortical feedback that these filters are actively and flexibly modulated.

#### 5.3. Cortico-Thalamo-Cortical Loops

In sect. 5.2, we showed how bidirectional interactions can shape feedforward sensory information. Although

the recurrent nature of the cortico-thalamo-cortical loops is present in sensory systems, the activity within these loops is dominated by sensory information external to the organism. In other systems not largely driven by external sensory inputs, such as the motor and prefrontal systems, closed cortico-thalamo-cortical loops can sustain recurrent patterns of activity that are essential for behavior (**FIGURE 10**).

#### 5.3.1. Motor system.

The thalamus, particularly the motor nuclei [ventral anterior (VA), ventral medial (VM), and ventral lateral (VL)], plays a critical role in the control of movement, particularly in bridging motor cortical and subcortical structures like the basal ganglia and cerebellum. This role in movement control spans movement preparation, initiation, and execution. Indeed, inactivation of motor thalamic (VM) axons to the premotor anterior lateral motor (ALM) was sufficient to disrupt initiation and vigor of cue-triggered licking (390). Furthermore, in a task where mice had to delay motor responses, the motor thalamus exhibited persistent preparatory activity during the delay before movements. This persistent activity also drove preparatory activity and action selectivity in ALM (391). Importantly, inactivation of either the motor thalamus or ALM alone caused disrupted activity in both areas and led to contralesional neglect. In addition, Sauerbrei et al. (392) recently showed that even after movement initiation cortical dynamics triggered by an initial state alone was insufficient for completing movement execution. Upon action initiation, time-varying thalamic input throughout the movement remains critical for driving the cortical dynamical patterns for the successful execution of skilled forelimb movements (392). Taken together, the above studies highlight that reciprocal excitation in the motor cortico-thalamo-cortical loops is crucial in effective preparation, initiation, and execution of movements.

#### 5.3.2. Working memory.

Our discussion above highlighting recurrent loops in motor preparatory activity illustrates its potential role as a substrate for maintaining working memory. Although local recurrence in prefrontal cortical circuits has been associated with maintaining working memory, mounting evidence points to its associated MD thalamus as critical for sustaining the cortical dynamics during working memory delays (15, 393).

## 5.4. Thalamus Gates Subcortical Activity

The thalamus is the obligate relay for most subcortical pathways to the cortex. Just as the thalamus can actively gate



**FIGURE 10.** Role of the thalamus in limbic, motor, and sensory processing. *A*: segregated streams of limbic (orange) and motor (green) striatal pathways can be integrated at the thalamus by different nuclei. Adapted from Aoki et al. (389), with permission from *eLife*. Thalamic medial dorsal (MD) and ventral medial (VM) nuclei close the limbic and motor loops back to medial prefrontal cortex (mPFC) and primary/secondary motor cortex (M1/M2), respectively. Because of VM integrating inputs from both medial and lateral substantia nigra (SNr), limbic striatal paths are able to influence the motor loop (yellow), whereas the motor loop does not integrate into the limbic system through this loop. *B*: cortico-tectal-thalamo-cortical loops in a candidate visual processing pathway. Anterior cingulate cortex (ACC), visual cortex [primary (V1), secondary (V2)], lateral posterior (LP), and the superior colliculus (SC) form a circuit through which visual processing can be modulated using top-down (blue) and bottom-up (purple) circuit motifs. In addition to direct cortico-cortical modulation by ACC-V1 projections and cortico-tectal modulation by ACC-SC projections, the reciprocal ACC-LP-ACC circuit can indirectly regulate visual processing, potentially broadcasting modulatory signals via the multiple outputs of thalamic LP neurons. The SC can also influence visual processing in cortex via its outputs to the LP.

sensory input, subcortical pathways through the thalamus can undergo similar routing that facilitates action selection across a flexible range of contexts. Adaptive responding to new contexts appears particularly dependent on thalamic activity. For example, Alcaraz et al. (394) showed that in the dmPFC and MD loop corticothalamic and thalamocortical pathways differentially contribute to value-driven decisions. During extinction learning, both pathways are important for updating ongoing decisions with new action-outcome values. However, when action-outcome contingencies were altered, inactivating the thalamocortical (MD-dmPFC) but not the corticothalamic (dmPFC-MD) pathway prevented adaptive responding. Similarly, the paraventricular thalamus (PVT), which receives input from many subcortical limbic systems, has been shown to mediate context-dependent salience encoding to gate associative learning (395, 396) and adaptively tune conflicting behaviors during motivational conflict (397). Thus, with cognitive and limbic functions of the thalamus, flexible context-dependent gating of subcortical drive is a central thalamic contribution. In this section, we examine some circuit mechanisms by which the thalamus might serve as an active filter for subcortical inputs from the striatum and SC.

## 5.5. Cortical-Subcortical Loops through the Thalamus

## 5.5.1. Cortico-striatal-thalamo-cortical loops.

Corticostriatal inputs are routed through the basal ganglia output nuclei [substantia nigra pars reticulata (SNr) and globus pallidus (GP)]. Apart from recently reported hyperdirect projections from GP to the frontal cortex (143), most basal ganglia outputs must first go through the thalamus to be relayed back to the cortex. This is significant because the thalamic bridge closes the cortical-subcortical loop to allow for resonance across this macroscale circuit. Reverberating activity through cortico-striatal-thalamo-cortical loops can serve comparable functions as cortico-thalamo-cortical loops described in sect. 5.3, but basal ganglia inputs to the thalamus are largely inhibitory.

Second, the thalamus provides a site of integration for parallel and functionally distinct versions of corticostriatal-thalamo-cortical loops, which correspond to the sensorimotor, limbic, and cognitive cortical-subcortical domains (147) (**FIGURE 10**). An advantage of segregated parallel loops is the rapid availability of multiple actions that can then be selected or dynamically prioritized in a context-dependent manner (148). More recent work confirms that these parallel striatal streams remain largely segregated throughout the basal ganglia (300) and that integration of parallel pathways or competitive action selection likely occurs outside the basal ganglia.

The thalamus is one such site of integration where segregated loops may interact. For example, striatal limbic loops [medial (m)PFC-dorsomedial striatum (DMS)medial SNr] are able to influence both mPFC and M1 because the motor thalamus integrates inputs from both medial and lateral SNr. In contrast, the motor loop (M1-DLS-lateral SNr) closes back to M1 without influence onto the mPFC, since lateral SNr input is not integrated by the mPFC-projecting MD thalamus (389) (**FIGURE 10**). Thus, different thalamic nuclei can integrate subcortical outputs to selectively route through different cortical targets, thereby allowing a striatal limbic loop to influence with motor system. In doing so, the thalamus not only closes corticostriatal loops it also creates additional open loops to integrate striatal outputs with other cortical areas. Furthermore, although not all thalamic nuclei receive basal ganglia outputs, other open loops can be created when basal ganglia (BG) outputs target the TRN, through which GP outputs have been also shown to modulate activity in sensory nuclei LGN and MGN (398).

#### 5.5.2. Cortico-tectal-thalamo-cortical loops.

As described in sect. 2.1, the superior colliculus (SC) has been proposed to represent an early visual saliency map that precedes visual cortical processing to facilitate rapid innate responses to behaviorally relevant stimuli. Indeed, such salience encoding is observed in the SC even earlier than in the visual cortex (399). The SC is able to feed this information forward to the cortex through the thalamus (**FIGURE 3**). For example, V1 gain has been shown to be modulated by the SC input through both dLGN (400) and LP (62, 377). Beyond the visual system, SC activation has also been shown to modulate S1 gain via the posterior medial (POm) thalamus (401) (**FIGURE 10**).

Prefrontal cortical areas can also engage subcortical circuits to modulate activity in sensory cortices. A recent example is seen in the ACC-SC-LP-V1 circuit, where activating an ACC-SC pathway enhances visual discrimination performance and visual tuning in V1 (62) (FIGURE 10). ACC has direct projections to V1, and activating the ACC-V1 pathway has a similar effect of improving visual performance (62, 332, 333). What then might be the purpose of the parallel subcortical route of modulation? Interestingly, activating the ACC-SC-LP pathway appears to have a greater enhancement of behavioral visual discriminability than directly activating the ACC-V1 pathway (62). An intriguing possibility is that the transthalamic LP pathway, by virtue of LP's distributed projections, could allow top-down modulation from ACC to have a broader effect over multiple visual cortical areas beyond V1. Thus, just as with striatal inputs, the thalamus provides a site for closing cortical-subcortical loops while also distributing subcortical activity along multiple cortical streams (342).

#### 5.6. Thalamostriatal Loops

The thalamus itself does not send outputs to many subcortical structures; nevertheless, it is able to serve as a parallel pathway from the cortex to striatum but also make up additional thalamostriatal loops. Thalamostriatal projections originate from various thalamic nuclei including HO sensory nuclei LP (349) and motor and limbic nuclei (402). They project to the striatum with a topographic organization that also overlaps with topographically matched corticostriatal projections (403, 404). Thus, parallel thalamostriatal and corticostriatal projections show convergence throughout the striatum. The redundancy of these loops has made precise dissection of thalamostriatal contributions especially challenging. Indeed, anatomical mapping has revealed that thalamostriatal projections from majority of thalamic nuclei are in fact collaterals of thalamocortical projections (404).

A key exception is seen in thalamostriatal projections from the centromedial (CM) and parafascicular (Pf) nucleus, which appear to have dedicated thalamostriatal projections distinct from thalamocortical neurons (405). Pf and the motor cortex have been shown to exert comparable gain modulation over striatal neurons (406). Behaviorally, these projections have been implicated in the initiation, pacing, and execution of sequential movements (407, 408). Furthermore, thalamostriatal projections appear to target striatal cholinergic interneurons, providing contextual input, to minimize interference between new and existing learning (409). Taken together, the thalamostriatal projections appear to provide critical context upon which to condition available actions and learned contingencies. Thus, besides their direct corticostriatal inputs, the cortex can also interact with striatal circuits by influencing thalamostriatal gating.

#### 5.7. Other Subcortical-Subcortical Interactions

In addition to cortical loops, the striatum and basal ganglia are also involved in subcortical loops involving multiple areas (SC, periaqueductal gray, pedunculopontine nucleus, cuneiform area and parabrachial complex, pontine and medullary reticular nuclei). The SC, for instance, is involved in several closed feedback loops that originate from its sensory and motor layers and project to different nuclei of the thalamus, before being routed through the striatum and back to the SC via the substantia nigra pars reticulata (11). These different streams of feedback loops might help to separate the different types of information in the SC to separate processing pathways (410).

Thus, the striatum is an integral part of a large number of reentrant circuits that involve cortex, thalamus, and other subcortical regions. The functions served by these loops span the cognitive, sensorimotor, and limbic domains, vastly different types of signals that are often in conflict in terms of task demands, which requires mechanisms to appropriately prioritize and coordinate between these signals. This diversity of top-down inputs suggests complex modulation by the cortex with signals that might be competing or cooperating within the basal ganglia pathways, eventually getting filtered and selected to gain access to downstream motor circuits (7).

## 6. CONCLUSIONS AND FUTURE DIRECTIONS

Our review has emphasized that adaptive behavior is the outcome of the collaborative interaction between cortical and subcortical structures. Throughout, we have highlighted the circuit organization and functional roles of select cortical and subcortical structures, as well as how interactions between these areas support specific behavioral functions. Importantly, each of the subcortical regions highlighted has intrinsic architectures that developed over evolution to subserve different behavioral priorities and coevolved with the emerging interconnectivity with the cortex. Finally, a corollary of the distributed network rather than rigidly hierarchical view of cortical-subcortical interactions is that function, and functional specialization, arises from specific subnetworks defined by their anatomical connections and functional dynamics.

As technological developments enable much greater scales for recording neural activity in cortical and subcortical areas simultaneously, it is becoming increasingly appreciated that some behaviors are associated with global brainwide activity. Behavioral task variables are distributed across multiple cortical and subcortical areas, rarely just localized in single nuclei (239, 411). Furthermore, non-task-related spontaneous movements appear to influence brainwide activity (260, 261). This emerging appreciation for global, distributed activity challenges the notion that function can be localized in a specific and restricted area. Rather, function appears to emerge from the collaborative interaction between cortical and subcortical areas, with their connectivity defining functional modules. Each node in a functional module may contribute to its associated function with regionspecific computations. The computational strategies used by cortical and subcortical areas are necessarily constrained by architectural features of their circuits and can achieve similar behavioral computations through different circuit implementations. For example, Steinmetz et al. (411) found robust left/right choice information in a visual perceptual decision-making task among select cortical and midbrain structures, including frontal cortex and the SC, whereas such choice encoding was relatively scant in other brain areas recorded simultaneously. The cooperative nature of cortical and midbrain structures in choice encoding was evident in the simultaneous emergence of choice encoding across these structures with no temporal lag (411). How might these structures differentially contribute to choice?

Interestingly, the interhemispheric organization of choice information differed between the frontal cortex and the SC. Whereas individual cortical neurons have been found to encode action selection more generally, such as choices for left and right actions (12, 34, 411), neurons in the SC predominantly encode contralateral movements (34, 411). This functional difference between the cortex and the SC likely reflects differences in the intrinsic organization of cortical and collicular circuits: interhemispheric interactions in the cortex appear to be synergistic (254), whereas competition and mutual inhibition dominates intercollicular interactions (29, 412-414). When choices have to be held in short-term memory because of task demands, the memory is concurrently maintained by FOF and SC in a dynamical attractor that together evolves toward two basins of attraction representing the two lateralized categorical decisions (34). An important question then is: how does the cortex interface with the SC to influence choice behavior? We propose that such cortical-subcortical interactions respect the intrinsic architectures and leverage the functions of their targets. An intriguing possibility suggested by our recent work is that the cortex may modulate the interhemispheric competition in the SC to influence choice behavior. During a two-choice visually guided task, we found that cortical inputs from the ACC to the SC promote ipsilateral choices, which is opposite to the choice preference of the SC (12). In this task, the ACC seems to modulate interhemispheric interactions, possibly by inhibiting activity of choice-selective SC neurons in the hemisphere directly targeted by the ACC or by recruiting callosal excitatory neurons that increase activity in the opposite SC. Taken together, behaviorally relevant computations are often distributed in multiple discrete yet interconnected regions. To resolve the computations contributed by each node, and clarify the specific information conveyed by each connection, we need to leverage experimental tools that not only enable examination of these circuits with target projection specificity but also critically consider the intrinsic circuits that receive these projections and decode this information.

The unique intrinsic circuits in different subcortical structures also mean that even if the cortex sends the same information simultaneously to each of them, the information may be decoded differently. Furthermore, the cortex simultaneously sends outputs to many different subcortical regions that themselves are interconnected (see sects. 5.5, 5.6). In fact, such connectivity would have evolutionarily preceded cortical expansion. Many of these subcortical-subcortical interactions are still areas of active inquiry. It remains an open question how cortical inputs may influence subcortical-subcortical interactions. One way to address this is by simultaneously recording from

different subcortical structures, such as from the output nucleus of the basal ganglia (SNr) and the SC, while manipulating cortical input to these structures in a projection-specific manner. As the SNr projects directly to the SC and SC sends indirect input to the basal ganglia via the thalamus and other subcortical structures, such an experiment will provide perspective on how cortical inputs to each structure may affect information processing in the other and how cortical inputs regulate this. This could also shed light on the significance of having cortical projections to multiple different subcortical regions that may share contributions to a behavior but be differentially filtered through their intrinsic circuits. Given that the longrange outputs of SNr are inhibitory and those of SC are excitatory, it will be interesting to resolve whether cortical inputs to the basal ganglia and SC serve to promote competitive or synergistic cross-regional interactions for action selection.

The reciprocal connectivity of the cortex and subcortex forms global recurrent loops that are of larger scale than local recurrent loops. These interactions form macroscale dynamical attractors that demonstrate that ongoing cortical-subcortical communication is critical for behavioral control. Perturbing activity at any node in such attractors can break down ongoing attractor dynamics. Importantly, as had emerged in domains of working memory and motor execution, this dynamical interaction between the cortex and subcortical structures underlies working memory maintenance and successful execution of movements. In motor execution, subcortical drive does not simply set an initial cortical state that dynamically unfolds locally in the motor cortex: cortical dynamics alone is unable to sustain motor planning and execution without ongoing activity from the motor thalamus and the basal ganglia (391, 392).

Conceptualizing functions as emergent properties of cross-regional interactions has important implications for how we interpret perturbation studies. Although increasingly precise perturbations (such as by optogenetic or other genetically defined strategies) may begin to narrow candidate regions with causal contributions to behavior, the extensive brainwide recurrent connectivity we have reviewed greatly complicates our inferences. A recent study showed that in cognitively demanding tasks, such as those involving working memory, behavioral performance was vulnerable to inactivation of many more different cortical regions than simple visually guided decisions (239). This may speak to the widespread involvement of many cortical regions in higher cognitive functions, or it can also reflect the critical role of sustained activity through reverberating cortical and subcortical loops to support working memory. Global excitation/inhibition balance that supports such computations can easily be disrupted by strong activity perturbation from just one cortical area. Regional attributions to functions would thus be confounded.

In addition, recurrent loops also bring to the fore the role of temporally patterned activity as a mechanism for cognitive computations. Such temporal codes have been particularly investigated in the form of oscillatory activity such as those generated by corticothalamic loops. Yet beyond sustaining oscillations, there is increasing evidence that timing of cortical input to subcortical areas like the thalamus (and vice versa) carries meaningful information (e.g., see sect. 5.2.3). Optogenetic silencing, such as through activating GABAergic neurons in the cortex, often spreads beyond the site of stimulation (239, 415) and disrupts both rate and temporal codes, making it challenging to resolve contributions between them. Likewise, the vast majority of optogenetic activation studies have leveraged the preponderance of rate coding to drive neurons at high frequencies. Studies that tested optogenetic activation at varying frequencies have found behavioral effects evoked by specific optimal frequencies or stimulation patterns that do not necessarily scale with rate (416). Finally, the importance of temporal codes is evident where optogenetic activation patterns that disrupt intrinsic temporal spike patterns can also result in behavioral disruption despite providing comparable drive (324, 392). It is likely that such temporally patterned activity interacts with downstream cortical and subcortical microcircuits in meaningful ways to drive behavior. Large-scale electrophysiological recordings during a variety of behaviors have provided us access to physiologically realistic firing patterns. Furthermore, with strategies such as optotagging allowing us to precisely examine firing patterns of molecularly and projection-defined populations, we propose that attaining insights from optogenetic manipulations will benefit greatly from utilizing realistic firing patterns to effectively engage downstream circuits in a more physiological manner.

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## DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

## AUTHOR CONTRIBUTIONS

K.G.C. and Y.N.L. conceived and designed research; K.G.C., Y.N.L., and N.M.L. prepared figures; K.G.C., Y.N.L., N.M.L., E.A., R.H., and M.S. drafted manuscript; K.G.C., Y.N.L., N.M.L., E.A., R.H., and M.S. edited and revised manuscript; K.G.C., Y.N.L., N.M.L., E.A., R.H., and M.S. approved final version of manuscript.

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#### ♠ CORTICAL-SUBCORTICAL INTERACTIONS IN GOAL-DIRECTED BEHAVIOR

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