THE SUPERIOR COLLICULUS

NEW APPROACHES FOR STUDYING SENSORIMOTOR INTEGRATION

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William C. Hall
Adonis Moschovakis

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1 Situating the Superior Colliculus within the Gaze Control Network

Michael L. Platt, Brian Lau, and Paul W. Glimcher

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1.1 INTRODUCTION

A wealth of evidence, much of it reviewed in this book, suggests that the superior colliculus (SC) plays a crucial role in the control of orienting eye and head movements. Activity in the superior colliculus, for example, predicts both the metrics and the timing of orienting movements. Electrical microstimulation of the SC, to take another example, can be used to elicit saccadic eye movements that are virtually indistinguishable from naturally occurring saccades. Based upon data like these, many neurobiologists have come to regard the SC as a command center from which nearly all saccades are generated. Thus, the SC has come to be viewed as a *final common path* for the generation of rapid eye movements in the same sense that Sherrington used the term final common path to describe alpha-motor neurons in the spinal cord. For most oculomotor scientists, activity in the SC is assumed to reflect the cumulative output of the neural systems that select and execute orienting movements.

Although some data raise questions about the validity of this framework (e.g., References 1 and 2), the SC is in fact almost ideally situated to perform this proposed role (Figure 1.1). We now know that the SC receives dense inputs from the frontal

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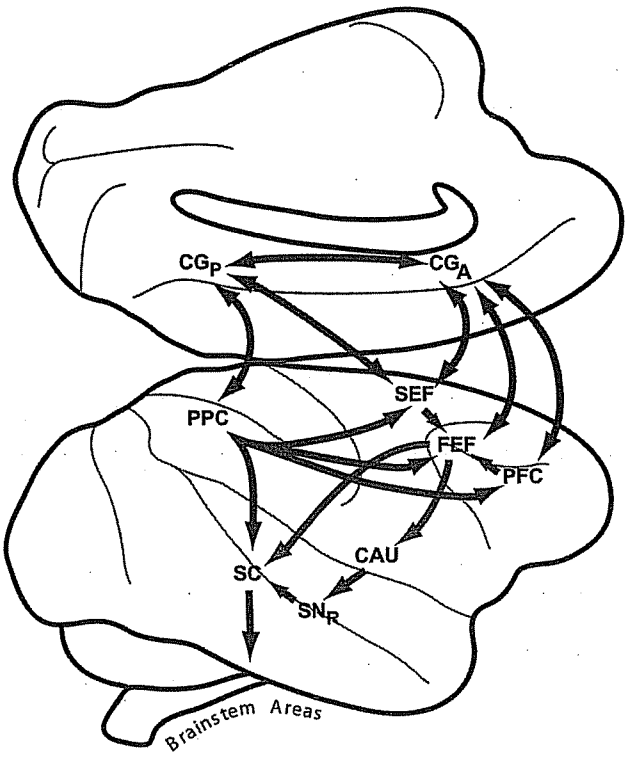

FIGURE 1.1 Some, but not all, of the major connections between elements in the orienting movement control network in the macaque brain, in which the superior colliculus (SC) serves as the final common path. Top: medial surface; bottom: lateral surface. Sensory input pathways are not diagrammed.

eye fields (FEF), which serve as cortical centers for the regulation of orienting eye movements. It also receives a strong and physiologically important input from the substantia nigra pars reticulata (SNr), which serves as the principal oculomotor output structure for the entire basal ganglia. Finally, the SC receives projections from a number of other cortical areas that link it with neural groups which process sensory data, participate in sensorimotor transformations, and compute decisions selecting movements for execution. Together, these observations provide a compelling rationale for suspecting that the SC, at least under some conditions, may indeed serve as a final common pathway for the generation of orienting movements.

In this chapter, we provide an overview of several of the important areas that appear to generate or modulate neural signals, such as those carried by the SC, associated with orienting movements. It begins by examining the frontal cortical areas, which appear to regulate the SC more directly than any other areas. The FEF is the structure probably most closely allied to the SC and it has been known to play a critical role in the generation of orienting eye movements since the time of Ferrier.[3] More than any other structure, the circuitry of the FEF seems to closely parallel the functional properties of the SC circuits to which it projects. Indeed, Schiller and

colleagues[1] demonstrated that after collicular ablation a monkey's ability to make saccadic eye movements recovers if the FEF is left intact. The FEF thus appears to represent a pathway by which frontal cortical areas can program saccades for execution by influencing either the SC or its brainstem targets. The FEF, in turn, seems to be strongly influenced by the supplementary eye fields (SEF), a higher order cortical structure that may participate in decisions about which movement to produce. A review of these two areas forms the first part of this chapter.

These frontal areas, however, are not the only cortical regions that influence the colliculus. Parietal cortex also includes what appear to be saccadic control areas, as do regions of the cingulate and prefrontal cortices. While it is not yet entirely clear what role these areas play in eye movement production, there is compelling evidence that they participate in sensorimotor transformations, control the allocation of attention, aid in the identification of erroneously executed movements, and participate in the assessment of whether a recently completed movement was of value. Together, these areas probably provide some of the highest-level cognitive input that the SC receives and they form the subject of the second part of this review.

Finally, it has been known for some time that the SC receives strong and direct inhibitory projections from the basal ganglia via the SNr. Hikosaka and Wurtz were the first to study these areas and to demonstrate how crucial these inhibitory projections are to the normal functioning of the systems regulating orienting movements. Subsequent work by Hikosaka and others has both reinforced this early conclusion and expanded the field within which the basal ganglia appear to make computations. We now believe that the basal ganglia play a critical evaluative role in assessing the value of each orienting movement to the animal, predicting the value of upcoming orienting movements based on those assessments, and updating representations of value after movement completion, using both inhibitory and excitatory signals.

These three sets of areas represent most, but not all, of the primary and secondary orienting inputs that reach the SC. Other areas, some of which are mentioned briefly within this review, also make important connections with the SC but are not yet well enough understood to be reviewed here. These three groups of areas should thus be viewed as a current, and certainly incomplete, description of the important inputs to the SC. Many of the areas described here are also strongly interconnected with each other, another important observation that is only briefly discussed here. However incomplete, current knowledge does suggest that these three groups of areas carry critical signals that eventually coalesce in neuronal activation within the map of orienting movements in the SC. These inputs thus provide a flexible and adaptive network for controlling the phylogenetically ancient tectal orienting system, and, as demonstrated in this review, this network is increasingly, although not yet completely, understood.

1.2 FRONTAL EYE FIELDS

The FEF have been recognized as a critical cortical structure for controlling eye movements since Ferrier's[3] observation that electrical stimulation of the surface of the brain overlying this structure elicited saccades. Subsequent work using intracortical microstimulation demonstrated that fixed-vector saccades can be evoked

using currents in the microampere range, and that the direction and amplitude of these saccades is topographically mapped in the FEF.[4,5] These saccades are evoked with short latencies, and are likely mediated by projections from the FEF to the SC,[6–9] although direct connections with brainstem oculomotor areas may also be important.[7,10,11] Hanes and Wurtz[12] recently showed that when the SC is temporarily inactivated, using muscimol or lidocaine, saccades could no longer be elicited through microstimulation in the FEF. This suggests that in the intact animal the FEF most likely exerts its influence via projections to the SC, although studies by Schiller and colleagues[1] demonstrated that monkeys eventually produce saccadic eye movements following recovery from permanent lesions of either the SC or the FEF.

A wealth of anatomical and physiological evidence indicates that the FEF is not simply a motor structure. Rather, it is well situated to link visual information to eye movements (reviewed by Schall and Thompson[13]). Single-unit recordings in the FEF have revealed distinct cell classes that fire in relation to the presentation of visual stimuli, saccades, fixation, and pursuit eye movements.[14–19] Anatomically, the FEF receives dense inputs from the dorsal and ventral visual streams,[20,21] and is interconnected with the oculomotor lateral intraparietal area (LIP),[20,22] the SEF [23,24] and the dorsolateral prefrontal cortex.[25,26] In this section, we review recent work on how different cell classes in the FEF participate in the transformation of visual target information into a saccadic motor command.

Visually guided eye movements require the conversion of visual information into a motor response. This conversion can be viewed as a sequence of two decisions: first deciding where to look and then deciding when to look. Deciding where to look is the result of sensory processing and specifies the goal of an eye movement. Deciding when to look is the result of motor preparation and is revealed by commitment to a particular eye movement. Schall and colleagues developed a visual search task to explore the role of the FEF in decisions about where to look. They trained monkeys to shift gaze to an oddball target that differed in color or shape from an array of distractors. A subset of FEF neurons responded with an increase in activity following the appearance of the visual array. Although the initial neural activity did not distinguish between whether the oddball or a distractor fell within the cell's receptive field, later activity clearly discriminated between the two. If the oddball was in the cell's receptive field, its firing rate remained elevated; otherwise it became sharply attenuated. Schall and colleagues hypothesized that the time at which FEF neurons reliably discriminate the oddball from the distractors marks the completion of sensory processing, or the decision computing where to look.[27] The idea that visually responsive neurons are involved with sensory processing predicts that manipulating the difficulty of sensory discrimination should affect reaction times by changing the time it takes to discriminate the oddball from the distractors. Schall and colleagues tested this prediction by making search more difficult by either increasing the number of distractors[28] or increasing the similarity between the target and the distractors.[29] These studies showed that the amount of time it took for visually responsive FEF neurons to reliably discriminate between the oddball and the distractors was prolonged as the difficulty of the task increased. This delay was accompanied by a proportional increase in saccadic reaction time, indicating that prolonged sensory processing leads to delayed motor responses.

Although the decisions that compute where and when to look are conceptually separable, it is possible that the two processes blend seamlessly together, and the activity of visually responsive neurons may also reflect motor preparation or the commitment to a response. Schall and colleagues argued against this by showing that (1) the time to reliable discrimination by visually responsive neurons is uncorrelated with saccadic reaction time for a fixed level of task difficulty,[27] and (2) these neurons continue to signal the oddball even if the monkey is required to maintain fixation,[30] or makes a movement to another location.[31] These experiments demonstrate that the activity of visually responsive neurons can be dissociated from the overt motor response. However, the commitment to a particular eye movement can itself be distinguished from motor preparation; many potential actions can be prepared despite the fact that only one can be produced. Therefore it remains possible that the activity of these neurons reflects covert motor preparation.

The distinction between commitment and motor preparation is supported by two recent studies of how the output of sensory processing is transferred to the neural elements controlling motor preparation. In considering these studies, it is worth keeping two possibilities in mind. One possibility is that transfer occurs after target selection; the system generating the motor response simply receives the final outcome of sensory processing. Alternatively, transfer could be continuous; the motor response is prepared as sensory processing proceeds. Bichot and colleagues[32] tested these alternatives by recording from movement-related cells in the FEF. In contrast to visually responsive neurons, these cells exhibit a burst of activity during saccades of a particular amplitude and direction, and respond little if at all to visual stimuli.[17,19] Bichot and colleagues recorded from these movement-related neurons while monkeys performed a visual search task where the oddball was defined by a conjunction of shape and color. They reasoned that if transfer followed target selection, then the activity of movement-related neurons should reflect the metrics of the upcoming saccade. If, on the other hand, there is partial transfer of sensory information, they predicted that a neuron's activity should depend on the properties of the distractor falling within its movement field. They found that movement-related cells were differentially active before saccades that shifted gaze to locations outside of a cell's movement field; these neurons tended to be more active for distractors that shared a feature with the oddball compared to distractors that did not share any features. This result clearly demonstrates that movement-related neurons receive sensory information. Bichot and colleagues [32] also noted that the metrics of the eye movements to a particular oddball target were unaffected by the activity of neurons responding to the surrounding distractors; saccade trajectories were not curved towards similar distractors, as might be expected if saccades to distractors were concurrently programmed (e.g., McPeek and Keller[33]). Thus, the differential activity of the movement-related neurons to distractors can be dissociated from the overt motor response.

Both the presence of sensory activity in movement-related cells and the dissociation of this activity from the final motor outcome can be explained if the commitment to a particular eye movement is achieved by a winner-take-all rule, a process where selection is based on which neuron (or population of related neurons) achieves the highest level of activity. One possible mechanism for achieving a winner-take-

all rule is a simple threshold; the final motor outcome is specified by whichever neuron attains a particular level of activity first (see References 34 and 35). According to this model, the differential activity observed by Bichot and colleagues represents covert motor planning (also see work by McPeek and Keller[36] for related results in the SC). However, in their task, the monkeys made eye movements after committing to that action, and it is impossible to know whether the increased activation for similar distractors represents covert motor preparation.

Gold and Shadlen[37] determined the ongoing degree of motor preparation by using electrical microstimulation to probe the state of the FEF *prior* to commitment. They trained monkeys to shift gaze to one of two targets depending on the direction of a random-dot motion stimulus. By varying the fraction of coherently moving dots as well as the duration of motion viewing, Gold and Shadlen manipulated the monkey's ability to determine the correct direction of motion. On some trials, they microstimulated a site in the FEF immediately after the offset of the motion stimulus, before the monkey voluntarily initiated a saccade to a choice target. Microstimulation evoked a saccade orthogonal to the axis of motion, which was followed by a voluntary corrective saccade to the desired target. Gold and Shadlen reasoned that if the motor elements of the FEF continuously converted sensory information into motor preparation, then the direction of the evoked saccades should depend on motion coherence and viewing duration. They confirmed this prediction by showing that the endpoints of the evoked saccades deviated in the direction of the monkey's eventual choice, and that higher motion coherences or longer viewing durations led to larger deviations compared to weaker motion coherences or shorter viewing durations (Figure 1.2). They explained their results using a model that integrates the difference in activity between populations of motion detectors representing the

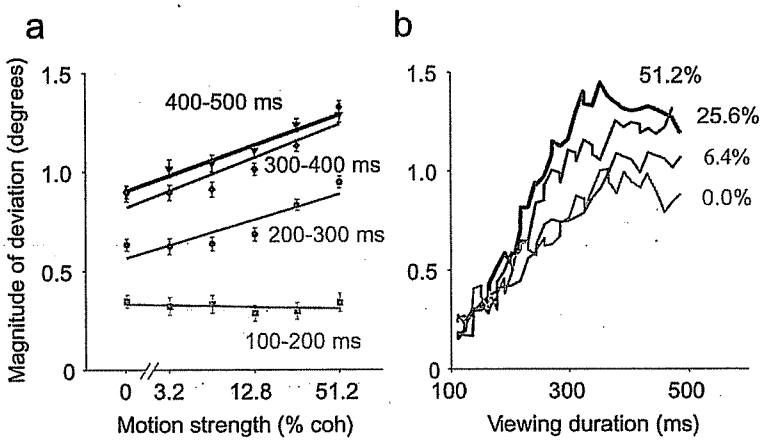

FIGURE 1.2 Gradual conversion of visual motion signals into oculomotor commands revealed by microstimulation of the FEF. Magnitude of evoked-saccade deviation toward the chosen target, plotted against (a) motion strength and (b) viewing duration. (From Gold, J.I. and Shadlen, M.N., Representation of a perceptual decision in developing oculomotor commands, *Nature*, 404, 390, 2000. Reprinted by permission from *Nature* ©2000.)

correct and incorrect directions of motion. Thus, probing the state of the FEF prior to commitment revealed a vector-averaging that depended on the quality and duration of motion information. This finding is strong evidence against the idea the motor elements of the FEF simply receive the final outcome of sensory processing.

It also seems unlikely that motor elements downstream of the FEF, like the SC, receive only the final outcome of the sensory processing guiding target selection. Sommer and Wurtz[38] used antidromic stimulation to show that the FEF sends visual-, memory-, and motor-related signals to the SC. This suggests that the observations made by Gold and Shadlen[37] and Bichot and colleagues[32] are probably not unique to the FEF. In fact, signals related to all stages of the visuomotor transformation have been observed in the SC,[2,39–41] area LIP,[35,42,43] and the dorsolateral prefrontal cortex.[44]

Making decisions requires assessing the relative value of potential actions in addition to analyzing the sensory evidence favoring one action over others (see References 45 and 46). Leon and Shadlen recently showed that FEF neurons are not modulated by reward magnitude, suggesting that signals in the FEF must at least be combined with signals representing the value of potential actions. These value judgments must also be learned, requiring the integration of the outcomes of previous actions over extended periods of time. In the following sections, we review evidence indicating that a number of other cortical areas compute these critical decision variables.

1.3 SUPPLEMENTARY EYE FIELDS

The SEF is located on the dorsomedial aspect of the frontal lobe. Early work indicated that the SEF was involved in eye movements,[48] but Schlag and Schlag-Rey[49] were the first to thoroughly characterize the oculomotor properties of the SEF. They identified the SEF as an area rostral to the supplementary motor area where saccades could be elicited by electrical microstimulation using low currents. Interestingly, a large region of cortex where saccades cannot be elicited by microstimulation separates the SEF from the FEF, and numerous studies have been directed at determining the anatomical and physiological differences between the frontal cortical eye fields.

A role for the supplementary eye fields in the guidance of eye movements is indicated by its anatomical connectivity with a number of cortical and subcortical oculomotor structures. In general, the pattern of connectivity for the SEF overlaps broadly with that of the FEF, with which it is densely interconnected.[23,24,50] The differences in connectivity have been reviewed in detail elsewhere (see Reference 51), but several are worth noting here. Compared to the FEF, the SEF: (1) receives less input from higher-level visual areas, (2) is more extensively interconnected with the prefrontal cortices, and (3) is much more densely interconnected with the anterior and posterior cingulate motor areas.

Both cortical eye fields project directly to the SC. Fibers from the SEF terminate densely in layers I, IV, and VI but not II or III of the SC.[23,52] In contrast, the FEF sends additional projections to the visual layers II and III.[7] One further consistent difference is that tracer injections of similar size yield more tangentially widespread distributions of label from the SEF in comparison to the FEF.[23,52] In addition to influencing eye movements through its direct projections to the SC and to the FEF,

the SEF innervates a number of oculomotor areas in the brainstem including the nucleus raphe interpositus, interstitial nucleus of Cajal, nucleus prepositus hypogossi, and the nucleus reticularis tegmenti pontis.[52] While SEF microstimulation can elicit saccades following lesions of the FEF or SC,[53] the direct brainstem projections do not seem to independently move the eyes since paired lesions of the FEF and the SC virtually eliminate all saccadic eye movements.[1]

Physiological studies using single-unit recording (e.g., see References 49, 54, and 55) and intracortical microstimulation (e.g., see References 49, 57, and 58) have largely focused on the oculomotor function of the SEF. More recently, investigators have begun to explore the response properties of SEF neurons using complex behavioral tasks. These tasks have revealed differences between the FEF and the SEF, and for the remainder of this section, we review work that suggests that the SEF participates in (1) signaling the context and consequences of directed eye movements, (2) the learning and storage of visuomotor associations, and (3) the execution of temporally extended motor programs.

One prerequisite for adaptive, goal-directed behavior is the ability to monitor performance, which requires recognizing the outcomes of prior actions. In a recent set of experiments, Stuphorn, Taylor, and Schall[60] implicated the SEF in performance monitoring. They trained monkeys to perform an oculomotor countermanding task that required a gaze shift to an eccentric target within 500 milliseconds after extinction of a central fixation point. On a fraction of these trials reappearance of the fixation point instructed the monkeys to cancel the planned eye movement and maintain fixation to receive a juice reward. Stuphorn and colleagues identified several types of neuronal activity in the SEF related to performance monitoring. Some neurons showed increased firing rates following a failure to cancel a saccade, regardless of its direction or endpoint. Complementing these error-detecting neurons were cells that showed an increase in firing rate that peaked immediately after the receipt of primary or secondary reinforcement (see also Amador et al.[61]; Mann et al.[62]). Together with the error-detecting neurons, these reward neurons appear to signal the outcomes of an eye movement in the context of an operant task.

A third class of neurons became active whenever the monkeys successfully cancelled a planned eye-movement. Similar responses have been noted in the SEF following correct movement cancellation during go/no-go tasks,[54,62] but Stuphorn and colleagues extended these findings by showing that the magnitude of this activity was correlated with the likelihood that the monkeys failed to cancel a movement. Since the monkeys were making more errors, and presumably receiving fewer rewards, it is possible that these neurons signal overall task difficulty or reward rate. They may also signal the degree of conflict between the desire to initiate a movement and the desire to cancel a movement plan.[60,63] This hypothesis is consistent with increased activation of SEF neurons during anti-saccades,[64] which require the suppression of reflexive or memory-guided pro-saccades. Importantly, the SEF response types identified by Stuphorn and colleagues were not observed in the FEF of monkeys performing the countermanding task,[19] indicating that the SEF and FEF send distinct, but complementary, information to the SC. Together, the findings described above indicate that the SEF is well situated to signal the context and consequences of directed eye movements for the guidance of goal-directed behavior.

The ability to monitor the context and consequences of actions is not only useful for guiding learned behavior, but is necessary for acquiring novel behaviors. The premotor cortex is critical for learning arbitrary associations between visual stimuli and actions.[65] Prompted by physiological work showing changes during visuomotor learning in the premotor cortex,[66] Chen and Wise[67] trained monkeys to associate directions of gaze with arbitrary visual images in order to explore the role of the SEF in learning visuomotor mappings. They found that many neurons in the SEF increased their activity in parallel with behavioral learning. Moreover, the magnitude and time-course of this learning-dependent activity came to resemble responses to familiar stimuli associated with the same direction of gaze. Chen and Wise[68] also observed that over the course of learning the preferred direction of directionally selective neurons could actually reorient to match that of well-learned associations. This lability of tuning is reminiscent of work by Mann, Thau, and Schiller showing that the saccade evoked by microstimulating at a particular cortical location could actually change depending on the current task requirements.[62] The learning-dependent neurons identified by Chen and Wise were much more common in the SEF than the FEF,[69] and they hypothesized that the SEF computes the appropriate goal for a particular context, which it then transmits to the FEF for eye movement programming. This is supported by the recent finding that SEF neurons signal the goal of an impending saccade in a free-choice task over a second before the movement is actually made, nearly 500 milliseconds before similar differential activity is observed in the FEF or area LIP.[70]

The concept of visuomotor association extends naturally to include the dimension of time. That is, the appropriate action may differ depending on the temporal context of the task, and keeping track of time or numerical order is important for performing the task correctly. For instance, stopping at a red light or driving at a green light are clearly arbitrary mappings, but the appropriate action to take at a yellow light depends on when the traffic light transitioned from green to yellow. Many behaviors, such as visually guided motor sequences, can be described as visuomotor mappings that unfold in time.

Work in humans suggests that the SEF is necessary for the correct execution of oculomotor sequences. Both patients with lesions including the SEF[71] as well as normal subjects undergoing transcranial magnetic stimulation of the SEF[72,73] show increases in errors while performing sequences of memory-guided saccades. This agrees with the findings in monkeys that lesions[74] and reversible inactivation[75] of the SEF induce mild deficits in performing sequences of two saccades. Lu, Matsuzawa, and Hikosaka[76] explored the role that single-neurons in the SEF have in oculomotor sequencing. They trained monkeys to perform sequences of five saccades, where each saccade was made from a central fixation point to one of four targets. Only two of the four potential targets were presented prior to each saccade, and the monkeys were free to make a movement to one of the two upon extinction of the fixation target. A critical feature of the task was that a pair of targets could appear more than once in a sequence, so that a leftward saccade might be required for the first movement, but a rightward saccade might be required for the second movement, even though the targets were identical. Lu and colleagues found that nearly three-quarters of the task-related neurons in the SEF responded in a sequence-

selective manner while the monkeys performed well-learned sequences. These neurons fired differentially depending on which sequence the monkey was performing. Lu and colleagues hypothesized that different oculomotor sequences might be encoded by separate populations of SEF neurons.

Taken together, these studies reveal that the SEF is functionally and anatomically distinct from the FEF. The SEF appears to be involved with the learning and monitoring of eye movements, or sequences of eye movements, that are directed to accomplish a goal. However, there exist numerous cell classes in the SEF, and further experiments are required to show what types of information the SEF sends to the FEF and the SC.

1.4 PARIETAL CORTEX

The parietal lobe, in particular the inferior parietal lobule, has long been recognized as crucial to normal visuospatial orienting. Patients with damage to parietal cortex often present with a syndrome, known as hemineglect, characterized by an inability or reluctance to orient, and sometimes even acknowledge, visual stimuli contralateral to the lesion.[77–79] Both reversible inactivation and acute lesions of the inferior parietal lobule in monkeys induce saccades that are slowed and hypometric when guided by visible and, in particular, remembered targets contralateral to the lesion.[80,81] Disturbances of visuospatial orienting associated with parietal dysfunction in both humans and monkeys thus suggest that this region plays an important role in the sensory-motor transformations that orient gaze.

This hypothesis is supported by the anatomical connections of parietal cortex. Extrastriate visual areas associated with the dorsal stream,[82] such as area V3, area MT, and area MST, project directly to the inferior parietal lobule, in particular the LIP and area 7a.[26,83,84] Parietal cortex, in particular area LIP, in turn projects directly to both the FEF[22] and the SC.[25] Portions of parietal cortex, especially area LIP, are thus ideally situated to intervene between visual signals and movements of the eyes. Projections back to parietal cortex from FEF[20,22] and SC[85] suggest that signals in these areas can significantly influence ongoing sensory-motor processing in the parietal lobe.

Electrophysiological recordings from single neurons in parietal cortex strongly support the proposal that this brain region participates in the transformation of sensory signals into oculomotor commands. In the 1970s, Mountcastle and colleagues demonstrated that neurons in parietal cortex were activated when monkeys made visually guided saccades to a restricted region of space.[86,87] Following these important early studies, Robinson, Goldberg and colleagues[88] showed that, in addition to firing action potentials prior to saccade onset, many parietal neurons responded following the illumination of a visual stimulus that subjects were instructed to ignore. Moreover, these responses were enhanced when subjects were instructed to attend to the stimulus, either overtly with a gaze shift or covertly in order to detect the dimming of that stimulus.[89,90] Around the same time, Gnadt and Andersen[91] demonstrated that many LIP neurons were also activated during the delay period intervening between the offset of a visual target and the onset of a gaze shift

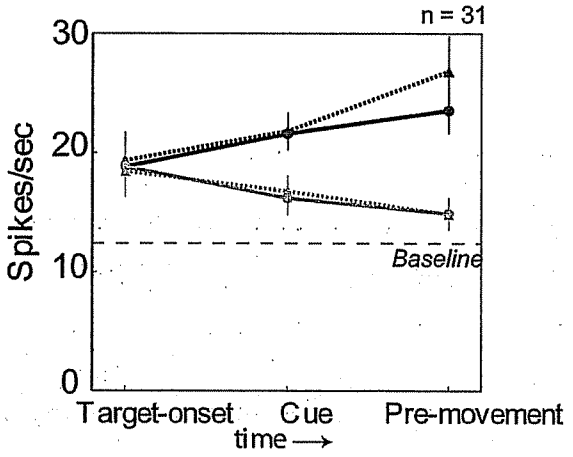

FIGURE 1.3 Neuronal activity in area LIP discriminates saccade targets (black lines) from distractors (grey lines), but not distractor relevance (solid vs. dotted grey lines). (Adapted from Platt, M.L. and Glimcher, P.W., Responses of intraparietal neurons to saccadic targets and visual distractors, *J Neurophysiol*, 78, 1574, 1997. With permission.)

to the remembered location of that target. Subsequent studies extended these observations to saccades guided by acoustic stimuli.[92–94]

These neurophysiological studies revealed that signals in parietal cortex could be linked to sensory encoding, motor preparation, spatial memory, or covert attention. Many attempts were made to unequivocally assign signals in parietal cortex to the representation of a single category of information. In our own work,[95] we attempted to dissociate visual, attentional, and saccade preparatory signals in LIP using a task in which a centrally located color cue instructed a monkey that a gaze shift to one of two diametrically opposed yellow lights (the *target*) would be rewarded (Figure 1.3). Subjects were required to maintain gaze at the central colored light until cued to initiate the required movement. In one block of trials, offset of the central colored light cued the subject to shift gaze rapidly to the target (Figure 1.3: *solid lines*), while in a second block of trials offset of the light to which the subject was not instructed to shift gaze (the *distractor*) served as the saccade initiation cue (Figure 1.3: *dotted lines*).

We probed the activation of LIP neurons under three conditions: (1) when the response field stimulus was a saccade target (Figure 1.3: *black lines*)); (2) when the response field stimulus was a behaviorally irrelevant distractor (Figure 1.3: *grey solid line*); and (3) when the response field stimulus was a behaviorally meaningful distractor (Figure 1.3: *grey dotted line*). We made two primary observations. First, the neuronal activity associated with saccade targets was always greater than the activity associated with either relevant or irrelevant distractors. Second, the neuronal activity associated with distractors was independent of their behavioral relevance. These observations led us to conclude initially that the activation of LIP neurons signals the amplitude and direction of an impending saccade, rather than the location of a visual stimulus or the amount of attention allocated to a particular visual

stimulus. However, the observation that neuronal activity associated with distractors did not fall to baseline levels of activity (Figure 1.3: *dashed line*) was difficult to reconcile with this hypothesis. If the activation of LIP neurons signaled an impending saccade, then why should there be any activity in LIP associated with distractors?

In the final analysis, our study failed to unequivocally separate visual, attentional, and motor preparatory signals in LIP. Many other attempts to segregate LIP signals into exclusive categories have also yielded inconclusive results (e.g., see References 90, 92, 96–98), although some researchers have succeeded at classifying subpopulations of parietal neurons as predominately sensory or motor.[99,100] Intriguingly, some of these studies indicated that some parietal neurons were activated by both visual and motor events, even when these events were spatially and temporally segregated.[100] These observations argue against any simplistic categorization of signals carried by parietal neurons as exclusively sensory, motor, or attentional in nature. Instead, parietal cortex may participate in a network that transforms incoming sensory signals into motor plans according to current behavioral goals.

Shadlen and Newsome[42,43] explicitly tested this hypothesis in an experiment requiring monkeys to report, with a gaze shift to one of two response targets, the net direction of motion in a random dot display. The difficulty of the discrimination was varied by systematically changing the proportion of dots moving coherently in any one direction. Intriguingly, neuronal activity in area LIP was higher whenever the motion stimulus was consistent with a movement into the response field compared to motion consistent with a movement out of the response field. Moreover, the rate at which neuronal activity increased from stimulus onset to saccade onset was a direct function of motion strength. The temporal profile of LIP activation in this task is consistent with the temporal integration of motion signals, such as those carried by neurons in the middle temporal area MT,[101] associated with a particular gaze shift. These data indicate that the information carried by LIP neurons reflects the gradual transformation of visual signals into oculomotor commands. Based on the results of this experiment, Shadlen and Newsome concluded that area LIP plays a role in the decision processes linking visual perception with orienting saccades.

While the decision to shift gaze is often guided by immediate perception, target choice, like other types of decisions, can also be influenced by prior experience.[46,102,103] Indeed, a wealth of psychological and economic studies of decision-making has demonstrated that most actions are chosen as a systematic function of their outcomes in the past.[104,105] This perspective suggests that, if parietal cortex does participate in the oculomotor decision process, then parietal neurons will also carry information reflecting the outcome of prior saccades. We tested this proposal in a series of studies in which we systematically varied the amount of reward and the probability of reward associated with a gaze shift of a particular direction and amplitude.

In the first study, we cued monkeys on each trial to shift gaze to one of two peripheral yellow lights, one of which was positioned within the response field of a LIP neuron under study. Across blocks of trials, the volume of fruit juice associated with correct gaze shifts to each peripheral light was systematically varied, while the total amount of fruit juice associated with both lights was held constant. For most LIP neurons, firing rate was systematically modulated by the relative value associated with gaze shifts into the response field (Figure 1.4a). Moreover, the modulation of

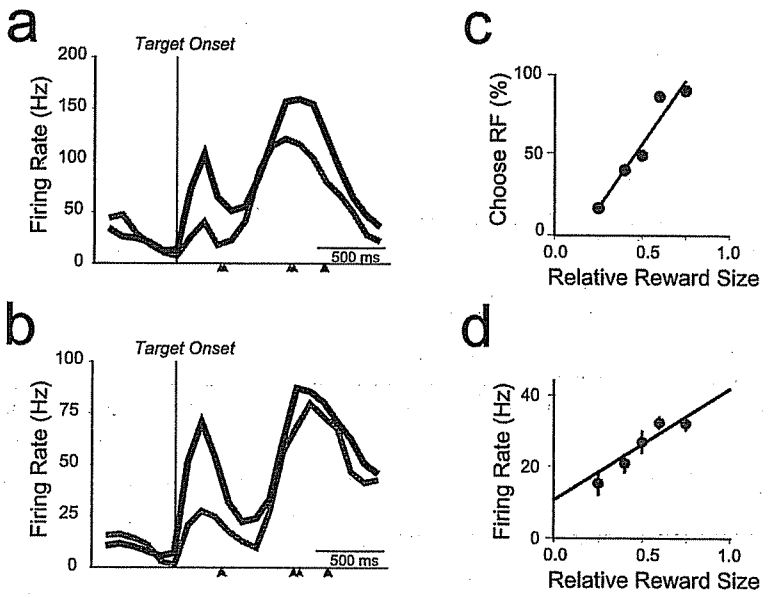

FIGURE 1.4 Representation of saccade value in area LIP. Increases in reward size (a) or probability (b) increase the activity of single LIP neurons on a cued saccade task. Thick black lines, high value; thick grey lines, low value. Arrows indicate average times of saccade direction cue, saccade initiation cue, and movement onset, on high (black) and low (grey) value trials. When monkeys are permitted to freely choose between two differentially reinforced targets, both movement choice (c) and neuronal activity associated with gaze shifts to the response field target (d) are a systematic function of relative movement value. (Adapted from Platt, M.L., Neural correlates of decisions, *Curr Opin Neurobiol*, 12, 141, 2002. With permission.)

firing rate by reward size peaked early in each trial and diminished around the time of the saccade.[102] Similar results were found when we held the amount of reward constant and varied the probability that the subject would be required to shift gaze to a target in the response field of each neuron under study (Figure 1.4b).

These data demonstrate that LIP neurons carry information reflecting the amount and probability of reward associated with a particular saccade, two variables known from behavioral studies to influence decision-making. The results of this study, however, do not address whether parietal neurons carry information correlated with the decisions subjects actually make when choosing between saccades associated with different value. To address this question, we conducted another experiment in which we permitted monkeys to choose freely between two targets, one of which was positioned within the response field of a neuron under study. Across blocks of trials, the volume of fruit juice delivered for shifting gaze to each target was systematically varied, as in the previous experiment. Under these conditions, both the choices subjects made and neuronal activity in parietal cortex were a systematic function of saccade value (Figure 1.4c,d). In fact, reward-related modulations in neuronal activity occurred before the onset of the peripheral targets (see also Coe

et al.[70]; Shadlen and Newsome[43]), further reinforcing the conclusion that representations in LIP are not purely sensory.

Taken together, the available evidence suggests that neurons in parietal cortex represent the information, be it sensory data or reward expectations derived from prior experience, favoring the generation of one saccade over another. Adopting a Bayesian approach, Gold and Shadlen[46] proposed that neurons in parietal, as well as prefrontal, cortex compute the logarithm of the likelihood ratio associated with potential saccades by integrating current sensory evidence favoring each particular gaze shift with estimates of its behavioral value. According to these authors, the oculomotor system is then biased to generate the saccade associated with the highest log likelihood ratio. This proposal specifically suggests that parietal neurons integrate information from multiple sources and over time to derive the optimal oculomotor response. While this powerful model succeeds in accounting for many of the observed physiological response properties of LIP neurons, thus suggesting that parietal cortex may indeed serve as a log likelihood estimator for orienting saccades, the role of attention in this process remains to be fully explicated.

1.5 PREFRONTAL CORTEX

The prefrontal cortex (PFC) has been implicated in a wide array of behavioral and cognitive functions, including working memory,[106–108] attention,[65,109] planning,[65] decision-making,[44,110] motivation and emotion,[111,112] and executive control.[109,113,114] The prefrontal cortex itself may be divided into a more ventral and medial aspect principally comprised of Brodmann's areas 11, 12, 13, and 14,[115] and including for the purposes of this chapter the frontopolar cortex area 10,[116] as well as a more dorsal and lateral aspect, principally comprised of areas 9 and 46.[115,117,118] Medial PFC has been postulated by some researchers to be more strongly involved in emotional control and decision-making,[111,112,119–121] whereas lateral PFC has been argued to be more strongly involved in working memory, attention, and planning.[122–124]

The earliest suggestions that prefrontal cortex contributes to higher cognitive functions derived from neurological studies of patients with prefrontal lesions (e.g., see Reference 125), as well as studies of behavioral performance in lesioned monkeys (e.g., see Reference 119). Specifically, these early studies suggested that damage to primarily dorsal and lateral aspects of prefrontal cortex was associated with deficits in working memory, as measured by performance on delayed response tasks, whereas damage to primarily ventral and medial portions of prefrontal cortex was associated with deficits in behavioral inhibition, as measured by performance on discrimination reversal and go/no-go tasks. The foregoing distinctions, however, remain controversial, in part due to a lack of correspondence between humans and monkeys both in terms of the effects of lesions of these subregions on behavior and in terms of the underlying anatomy.[125,126] In fact, subsequent ablation studies in monkeys [122,123,127,128] have demonstrated that deficits in working memory and behavioral inhibition can be induced by damage to either dorsolateral or ventromedial prefrontal cortex, thereby blurring the distinctions drawn between the putative functions of these regions based on lesion studies.

Neurophysiological studies have also been employed in an effort to probe the function of prefrontal cortex. Early studies demonstrated that lateral PFC neurons maintain activation during delay periods on delayed response tasks,[124] consistent with findings from studies of monkeys and humans with prefrontal lesions demonstrating impaired performance on these same tasks. In addition, it has been argued that lateral PFC neurons are segregated anatomically according to the type of information held in working memory. Specifically, neurons in dorsolateral areas 9 and 46 were initially thought to be active during delay periods only when responses were directed to a specific location,[124,129,130] whereas neurons located in the inferior prefrontal convexity were thought to respond during delay periods only when particular objects needed to be remembered independent of their spatial location.[131] Recent work, however, suggests the possibility that subpopulations of prefrontal neurons within each of these areas may process either spatial information, object attributes, or both,[132,133] thus mitigating any strong conclusions regarding segregation of function within the lateral PFC.

Anatomically, dorsolateral PFC is well-situated to participate in oculomotor control. Dorsolateral PFC principally receives inputs from posterior parietal cortex (area 7a), medial parietal cortex (area 7m), posterior cingulate cortex (areas 23 and 31), retrosplenial cortex,[25] and the parvicellular mediodorsal nucleus of the thalamus,[134] areas thought to be important for visuospatial and mnemonic functions based on neurophysiological and neurological data. In turn, the dorsolateral prefrontal cortex projects directly to the intermediate and deep layers of the SC,[6,25,135] the FEF, and posterior parietal cortex,[25,26] as well as to the midline reticular formation of the pons.[6,25] The prefrontal cortex also projects directly to other brain areas known from physiological and neurological data to have functions related to vision and eye movements, including the anterior and posterior cingulate cortex, the caudate nucleus, and the pulvinar.[25,136]

These anatomical data suggest that dorsolateral PFC may participate directly in oculomotor processing. In support of this contention, Goldman-Rakic and colleagues first demonstrated that dorsolateral PFC neurons maintain activation during the delay period when subjects perform memory-guided saccade trials,[108,129,137] in a fashion similar to delay period responses of neurons in area LIP of posterior parietal cortex on the same type of task.[91] Moreover, muscimol inactivation of small sites in dorsolateral PFC results in deficits for contraversive memory-guided saccades with error proportional to delay period length.[138]

More recent neurophysiological studies have demonstrated that, in addition to contributing to memory-guided saccades, dorsolateral PFC neurons carry information correlated with the sensory evidence favoring the generation of a particular eye movement. Specifically, Kim and Shadlen[44] reported that the activation of lateral PFC neurons is correlated with both the level of coherent motion and psychophysical performance in a random-dot motion discrimination task, in which decisions were reported with an eye movement. Similarly, Constantinidis, Goldman-Rakic, and colleagues[139] showed that the activation of lateral PFC neurons, even during a delay period, is correlated with both brightness and psychophysical performance on a luminance discrimination task, in which decisions were also reported with a saccade.

These data are consistent with the proposal that populations of dorsolateral PFC neurons encode information used to compute an oculomotor decision, particularly when that information must be stored in memory during a delay. This supposition is supported by the observation that dorsolateral PFC neurons are also sensitive to learned rules specifying the location of a saccade target.[133] The observation that some dorsolateral PFC neurons preferentially encode visual stimulus attributes such as location and brightness, independent of saccade metrics,[140] while other dorsolateral PFC neurons encode saccade metrics, independent of visual stimulus attributes,[141] suggests that, like posterior parietal cortex, dorsolateral PFC may also be involved in the sensory-motor transformations that link sensory representations with oculomotor outputs.

These data support the inclusion of the dorsolateral PFC within the oculomotor system. The observation of strong interconnections between dorsolateral PFC and ventromedial PFC, which is itself robustly interconnected with the amygdala and temporal visual cortical areas (reviewed in Rolls[111,121]) suggests that dorsolateral PFC may participate in the oculomotor decision process by integrating information across multiple sensory modalities with motivational and emotional information derived from past experience.[46] Indeed, the sensitivity of lateral PFC neurons to reward[47,140] suggests that afferents from ventromedial and orbitofrontal PFC may be specifically dedicated to processing the motivational content of saccades under consideration by the oculomotor decision network, although more global motivational inputs from midbrain dopamine neurons may also contribute to these computations in lateral PFC.[142] The complexity of processing intimated by the wide array of anatomical interconnections shared by PFC suggests that, by virtue of its simplicity, oculomotor control will continue to serve as a useful model for PFC function in general.

1.6 CINGULATE CORTEX

Although the cingulate cortex, within the depths of the cingulate sulcus as well as along the medial wall of the cingulate gyrus, has long been recognized as an important site of visceral, motivational, and emotional information-processing,[143,144] it has also been linked to both visual[145–147] and motor[148–150] processing based on anatomical and physiological evidence. Recently, two areas within cingulate cortex have been implicated specifically in oculomotor processing. A region in anterior cingulate cortex (CGa), located in Brodmann's area 24 in medial frontal cortex, has been shown by both clinical and functional imaging studies to contribute to the control of voluntary saccades.[151–154] A portion of posterior cingulate cortex (CGp), lying along the ventral bank of the cingulate sulcus as well as along the cingulate gyrus and comprised principally of Brodmann's areas 23, 29, 30, and 31, has also been implicated in the control of eye movements and visual attention based on anatomical,[145,147,155–157] electrophysiological,[146,149] and neuroimaging studies.[151,152,158,159]

Anatomically, cingulate cortex does not communicate directly with the SC. Cingulate cortex does, however, make extensive connections with other areas involved in oculomotor control. As noted previously, both the CGa and the CGp are strongly interconnected with the SEF,[23] with limited reciprocal connections with the

FEF.[160–162] In addition, lateral PFC areas 9 and 46 project heavily to both anterior and posterior cingulate cortex.[25,161,163–165]

Moreover, the lateral and medial surfaces of the parietal lobe are strongly interconnected with cingulate cortex. Area 7m, on the medial surface of the parietal lobe, is reciprocally interconnected with CGp, and to a lesser extent, CGa.[22,161,166,167] Area 7m is reciprocally connected with area LIP,[22] and stimulation in area 7m has recently been shown to evoke saccadic eye movements with currents as low as 50 microamperes.[168] In addition, the lateral surface of the inferior parietal lobule (area 7 or PG) is also reciprocally interconnected with CGp,[22,161] and retrosplenial cortex within the cingulate gyrus projects to areas 7a and LIP as well.[22] Finally, autoradiographic experiments suggest that the prefrontal and parietal projections to cingulate cortex may interdigitate in a columnar fashion, suggesting a topographical convergence of information in these areas.[25]

In addition to these oculomotor and visuospatial connections, cingulate cortex makes direct anatomical contact with brain areas involved in motivational processing. Nearly all parts of orbitofrontal cortex, for example, project to both CGa and CGp.[161] Moreover, anterior cingulate cortex receives substantial projections from the amygdala.[155,169,170] In turn, anterior cingulate cortex projects to the laterobasal and central nuclei of the amygdala.[171,172] Finally, anterior and posterior cingulate cortices are also strongly interconnected, thereby permitting extensive communication of motivational, as well as visuospatial and oculomotor, information.[162] These anatomical data suggest the hypothesis that cingulate cortex contributes motivational information to the oculomotor decision process.[103,156,173,174]

Anterior cingulate cortex has been implicated in oculomotor control principally through recent neuroimaging and neurological studies. Specifically, several recent studies have revealed hemodynamic changes in anterior cingulate cortex using PET[151–153] and fMRI[159] imaging in humans asked to shift gaze to visible or remembered targets. The potential importance of anterior cingulate cortex for oculomotor control suggested by neuroimaging studies is buttressed by recent neurological studies demonstrating deficits in oculomotor performance, including visually guided saccades, memory-guided saccades, antisaccades, and memorized sequences of visually guided saccades, in patients with damage to this area.[154,175] While these studies demonstrate that anterior cingulate cortex participates in the cortical control of saccades, they do not address the possibility that this region contributes motivational information to the oculomotor decision process.

The activation patterns of anterior cingulate neurons have just begun to be studied in monkeys performing oculomotor tasks. In a recent review, Schall and colleagues[63] reported that some CGa neurons respond to primary reinforcers, as well as to visual targets, on saccade countermanding tasks. Intriguingly, electrophysiological studies have also demonstrated that neurons in anterior cingulate cortex carry signals related to both expected and experienced reward outcomes associated with manual responses,[176,177] and that these signals can faithfully predict movement choices.[176] Although the preliminary nature of the data reported by Schall and colleagues precludes drawing any strong conclusions regarding the specific role of anterior cingulate cortex in oculomotor control, the results of these studies do suggest the possibility that one role of CGa may be to monitor the motivational outcomes of

visually guided saccades. Such signals could serve to update representations of expected saccade value computed during ongoing oculomotor decision processing in parietal and prefrontal cortex.[63,156,178]

Recent neurophysiological and neuroimaging studies have also implicated posterior cingulate cortex in eye movement processing. Olson and Musil[146] first demonstrated that single neurons in posterior cingulate cortex of the cat fire action potentials in response to visual stimulation, and also respond following saccadic eye movements. Olson, Goldberg, and colleagues later demonstrated that CGp neurons are activated just after saccade onset when monkeys shift gaze to contralateral visual targets.[149] Moreover, they reported that the activity of many CGp neurons is modulated by both eye position and saccade direction and amplitude.

Subsequent studies have confirmed the temporal pattern of neuronal activation in CGp reported by Olson and colleagues, but have also suggested that many CGp neurons are activated following the delivery of juice reinforcement on delayed saccade trials as well.[174,179,180] The post-saccadic and post-reward responses of most CGp neurons are also modulated by reward magnitude.[174,180] These neurophysiological reports suggest that CGp may participate in the assignment of motivational value to oculomotor signals, thereby contributing to the neural decision processes that eventually generate movements of the eyes.

In addition to these neurophysiological studies in animals, one recent neuroimaging study has reported hemodynamic changes in posterior cingulate cortex in humans instructed to shift gaze to a visual target.[159] In that study, fMRI scans were made in human subjects while they either fixated a central stimulus, shifted gaze to one of seven visual targets, or smoothly pursued a small target moving at an average speed of 10 degrees/sec along the horizontal meridian. The authors found that many cortical areas, including CGp and CGa, were activated in both the pursuit and saccade conditions. Intriguingly, activation in CGp was greater for smooth pursuit than for saccades, and peak activation was localized within the depths of the cingulate sulcus, just anterior to the marginal ramus. The locus of this activation is consistent with the region in which neurons with oculomotor responses have been recorded in the monkey.[149,179] In agreement with CGp activation revealed in humans using fMRI, Porro and colleagues[181] recently used the 2-deoxyglucose technique to demonstrate increased metabolic activity in the cingulate gyrus and retrosplenial cortex during ketamine-induced oculomotor nystagmus in the rat.

In summary, anatomical data implicate both anterior and posterior cingulate cortex in the cortical control of eye movements. Recent observations of cingulate activation during and after eye movements accord well with this implication. Moreover, anatomical and electrophysiological data intimate that cingulate cortex may play an important role in assigning motivational value to oculomotor signals, and may contribute to the reward-related modulation of saccade-related activity observed in area LIP, the dorsolateral PFC, and the SEF. These data suggest that frontal, parietal, and cingulate cortices may form a network for oculomotor decision-making that contributes to the selection, preparation, and initiation of a gaze shift by downstream oculomotor control structures in the FEF and SC.[178] This hypothesis awaits further testing with neurophysiological techniques in animals and neuroimaging techniques in humans.

1.7 BASAL GANGLIA

In primates, a wide array of brain areas involved in oculomotor processing project to the caudate nucleus of the basal ganglia. Dense inputs to the caudate nucleus originate in a number of oculomotor areas including the FEF, SEF, area LIP, dorsolateral PFC, and the cingulate cortices.[25,182–184] The caudate nucleus, in turn, sends its principal outputs to the substantia nigra pars reticulata (SNr), which together with the globus pallidus serve as the principal output nuclei of the basal ganglia. The SNr is composed largely of GABA-ergic neurons[185], and receives inhibitory inputs from the caudate[186,187] and excitatory inputs from the subthalamic nucleus.[188] The SNr projects back to many of the cortical areas that innervate the caudate, principally via the ventral anterior and mediodorsal nuclei of the thalamus.[189–191] In addition, anatomical studies have clearly established that the SNr sends projections to the intermediate layers of the superior colliculus.[185,192] This nigrotectal pathway forms both a major output of the SNr and a major afferent source for the SC,[193–195] placing the basal ganglia in a position to influence oculomotor signals impinging on the SC.

Hikosaka and colleagues have developed a model of saccadic initiation that synthesizes a large body of anatomical, physiological and clinical work. They propose that cortical signals from areas like the FEF access the caudate and are then conducted as inhibitory signals to the SNr. This inhibition produces a decrease in SNr activity, which releases the SC from tonic inhibition, permitting the initiation of a saccade. This hypothesis is supported by five physiological observations (reviewed in detail by Hikosaka and Wurtz,[196]; Hikosaka et al.[197]). (1) Neurons in the SNr have high baseline firing rates, and show decreases in firing rate during oculomotor tasks.[198–201] (2) Many saccade-related neurons in the SNr can be antidromically activated by microstimulating the intermediate layers of the SC,[202] and SNr microstimulation evokes monosynaptic hyperpolarization in the SC.[203–204] (3) GABA powerfully modulates SC function; injection of the GABA agonist muscimol or the GABA antagonist bicuculline into the SC results in severe deficits in generating saccades and inhibiting saccades, respectively.[205] (4) Injecting muscimol into the SNr increases saccade frequency and substantially reduces the average duration of intersaccadic fixation, similar to the effects seen when bicuculline is injected into the SC.[206,207] (5) Electrical microstimulation of the caudate nucleus can inhibit some SNr neurons,[208] and these cells show saccade-related decreases in activation that coincide temporally with saccade-related increases in caudate activity. Taken together, this body of evidence provides strong support for the role of the SNr in disinhibiting SC neurons.

While decreases in SNr activity are consistent with disinhibition of the SC, recent work has revealed a population of SNr neurons that show saccade-related *increases* in activity.[209–211] Handel and Glimcher[209] identified four classes of SNr activity using a delayed saccade task. Two classes showed decreases in activity similar to that originally observed by Hikosaka and Wurtz. Handel and Glimcher also described two novel cell classes, comprising 41% of the neurons they recorded from, which showed increases in activity during their saccade task. One class, termed bursters, showed increases in activity following the presentation of contralateral

saccadic targets and/or before the generation of saccades. The second class, termed pause-bursters, showed increased activation following target presentation in the contralateral hemisphere but decreased activation following target presentation in the ipsilateral hemisphere. All four classes of SNr neurons showed a strong tendency for maximal modulation from a high baseline during contralateral saccades, regardless of whether the modulation was an increase or a decrease from baseline. Quantitative analyses revealed that the movement fields of all SNr neurons were well described as tilted planes. This is distinct from movement fields in the SC, area LIP, and the FEF, which are better characterized as Gaussian,[17,212,213] suggesting that SNr neurons specify the metrics of upcoming saccades in a quantitatively different manner from neurons in the SC.

It is noteworthy that while Hikosaka and colleagues[208] observed decreases in SNr activity following microstimulation of the caudate nucleus, nearly half of their visual- or saccade-related SNr cells showed either excitation or complex combinations of excitation and inhibition after caudate stimulation. Hikosaka and colleagues suggest that increases may be caused by excitatory inputs from the subthalamic nucleus, which is disinhibited by caudate excitation.[197,208] This indirect pathway may also mediate the increases in firing rate seen in bursters and pause-bursters, but it remains unclear what role these neurons have in generating saccades. One possibility is that these neurons act to inhibit competing saccades at the level of the SC, thereby aiding in the selection of a single movement.[210,214] A related idea is that bursters and pause-bursters inhibit fixation neurons in the rostral SC,[215] facilitating gaze shifts from the current locus of fixation. Thus, neurons with increases in activity could complement the direct nigrotectal disinhibition mediated by neurons showing decreases in activity.

Neurons in the SNr are not obligately linked to the production of all saccades, and exhibit differential activity depending on behavioral context (e.g., Hikosaka and Wurtz,[198–200]). Early observations suggested that SNr neurons were never modulated during spontaneous eye movements.[198] One important difference between a spontaneous saccade and a saccade made in an operant task is the reinforcement contingency, which raises the possibility that SNr neurons participate in coding the value of rewards associated with particular movements. This is supported by the fact that most SNr neurons are only modulated during saccades that occur in close temporal proximity to rewards. Handel and Glimcher[216] compared firing rates during fixational saccades that aligned the eyes with a central stimulus to begin a trial with firing rates during terminal saccades that aligned the eyes with an eccentric target at the end of a trial. Although both types of saccade predicted reward, only terminal saccades were immediately followed by reward (Figure 1.5). A quantitative movement field analysis showed that all SNr neurons were modulated during terminal saccades, but were unmodulated or only weakly modulated during fixational movements. These results suggest that SNr neurons carry signals related to the reinforcement that can be expected for a particular eye movement.

Sato and Hikosaka[211] explicitly tested the hypothesis that SNr neurons are modulated by reward contingencies. They trained monkeys to make memory-guided saccades to one of two eccentric targets. One of the targets was randomly cued on each trial, and for blocks of 40 trials, only movements to one target were rewarded.

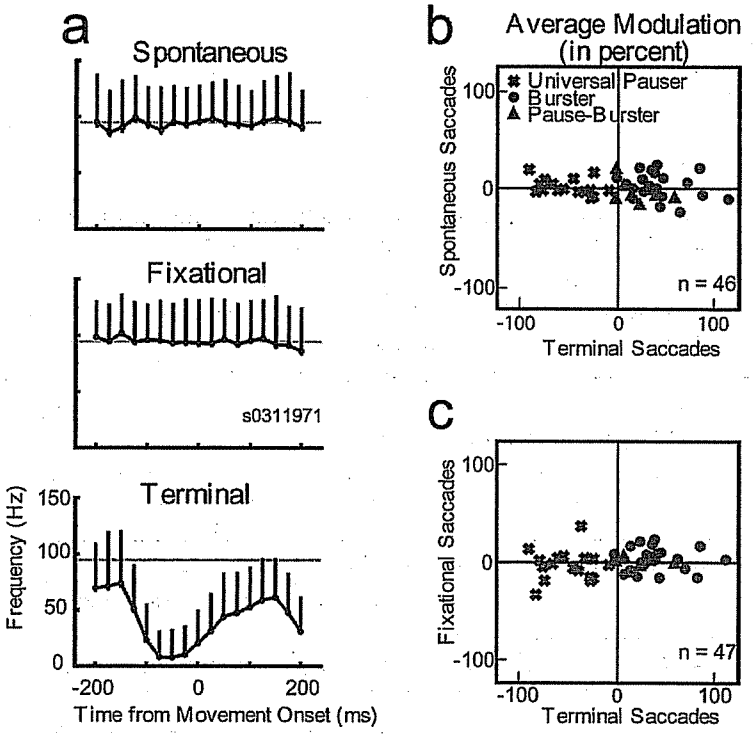

FIGURE 1.5 (a) Comparison of activity for a typical universal pauser during spontaneous, fixational and terminal saccades. Perievent histograms show the mean rate, standard deviations (upward bars), and standard errors (downward bars) in 25 millisecond bins. Gray line indicates baseline activity. Correlations between spontaneous and terminal saccades (b) and fixational and terminal saccades (c). Average modulation is derived from planar fits across all possible movements for each neuron, and is expressed as a percentage relative to baseline activity. (Adapted from Handel, A. and Glimcher, P.W., Contextual modulation of substantia nigra pars reticulata neurons, *J Neurophysiol*, 83, 3042, 2000. With permission.)

Movements to the other target, while unrewarded, were still required. Sato and Hikosaka observed that half their neurons showed decreases in response to a visual cue, and tended to decrease more when the cue indicated an upcoming reward. The remaining neurons showed increases in response to visual cues, and were more heterogeneous in their response properties. Of the cells differentially modulated by reward contingency, roughly half increased their activity more when the cue indicated an upcoming reward, while the other half increased their activity more when the cue indicated no reward. Sato and Hikosaka hypothesize that the larger decreases in activity act to increase the likelihood of a saccade to the rewarded target by selectively disinhibiting the SC. This idea is supported by behavioral work showing that monkeys performing this differential reward task reliably produce faster saccades to the rewarded target.[217]

Projections from the caudate nucleus are a likely source of the reward-related effects observed by Sato and Hikosaka. Caudate neurons show responses related to

receipt of reward, expectation of reward, and reward contingency during a variety of oculomotor tasks.[218–221] Kawagoe and colleagues[219] identified one class of caudate neurons that increased their activity when a particular target was rewarded, and a second class that decreased their activity when a particular target was rewarded. Caudate neurons receive reward-related information from a variety of sources including the dopaminergic neurons in the SNc,[222] as well as the orbitofrontal cortex.[182] These caudate neurons, which are thought to project to the SNr, could produce reward-dependent decreases or increases of activity in the SNr.

The dopamine neurons in the SNc are another potential source of the reward-related activity in the SNr. SNc neurons discharge following receipt of rewards or sensory stimuli that predict rewards (reviewed by Schultz[223]), and there is abundant evidence that the two nuclei of the substantia nigra are functionally integrated. Anatomical studies of the nucleus show large apical dendrites extending from the SNc into the SNr, forming an anatomical substrate for this interaction.[224] Dopamine can be released from these dendritic processes,[225] and D1 and D2 dopamine receptors have been localized in the SNr.[226] Finally, dopamine application has been shown to affect both spontaneous activity and striatonigral GABA-ergic inhibition in the SNr.[227,228] While all of these anatomical and physiological data indicate that it is possible for SNc activity to modulate SNr activity, it nonetheless remains the case that very little is known about how these two cell groups jointly process information or participate in the generation of eye movements.

The behavioral contingency of neural activity in the caudate nucleus and the SNr suggest that the oculomotor functions of these areas may be more closely related to the selection, planning and initiation of reinforced movements than simply to the generation of movements per se. The results described above represent part of a growing body of evidence (reviewed in References 229 and 230) that a major function of the basal ganglia is the acquisition of goal-directed behavior.

1.8 SUMMARY

The foregoing review suggests that the SC receives orienting signals originating in areas that appear to be computationally similar, like the FEF, and from areas that appear to be computationally distinct, like the posterior cingulate cortex. All of these areas form a coherent and heavily interconnected network that can select orienting movements from the animal's repertoire for execution based upon sensory and nonsensory signals.

The basal ganglia, for example, appear to carry information important for the execution of saccades that yield rewards. These signals also make their way to the frontal cortices via the thalamus where they can alter activity in those areas and thereby influence saccade generation. In a similar way, parietal areas that participate in saccade generation send strong projections to areas like the FEF, as well as to the SC, thereby apparently influencing saccade generation via more than one route. It is for this reason that it is critical that we begin to think of the SC as a participant, albeit a critical one, in an orienting movement control *network*.

The importance of this observation becomes especially clear when we consider the activity that has already been documented in each of these areas. Current evidence

indicates that when a saccade is produced all of these areas work together, generating a common set of signals that leads to the regulation and generation of a single orienting movement. We know very little about how this complex network-level coordination is achieved. We know almost nothing, for example, about whether the SC receives conflicting signals under some conditions or about how such conflicting signals might be resolved either by the SC itself or by the larger network in which it is embedded. Obviously, if we are to truly understand the functional role of the SC we will have to understand the larger network in which it is embedded.

The work reviewed briefly in this chapter represents the first stages of a process aimed at understanding the role of the SC within a larger framework. We are now just beginning to understand what each of these other areas does and how it might influence the SC. The next step will be to begin to ask how these areas interact as a network in order to define more fully the functional role of the SC itself.

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