THE SUPERIOR COLLICULUS

NEW APPROACHES FOR STUDYING SENSORIMOTOR INTEGRATION

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3 Concurrent, Distributed Control of Saccade Initiation in the Frontal Eye Field and Superior Colliculus

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3.1 INTRODUCTION

A central problem in neuroscience is the localization of function. Significant progress on this has been made in the oculomotor system. With progress has come the realization that function is usually not localized within a single structure but rather it is distributed across a network of brain areas. In this review, we contrast two brain areas that play a critical role in the planning and initiation of saccadic eye movements: the superior colliculus (SC) and the frontal eye fields (FEF). We describe the

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role of these structures in the control of visual fixation and initiation of saccadic eye movements by contrasting neural discharges recorded from neurons in each area in a variety of oculomotor tasks.

3.2 THE TIME TO INITIATE A SACCADE

In flight, saccades are incredibly predictable. The velocity and duration of a saccade is mechanistically related to the amplitude of the saccade.[1] However, the time of initiation of the movement is exceedingly unpredictable. Numerous experiments have measured the time that elapses from presentation of a visual stimulus until initiation of a saccade. Each experiment finds that this saccadic reaction time (SRT) ranges from rarely less than 100 ms to as much as 500 ms or more. Moreover, SRT can vary over a wide range across a block of trials even within a single task with constant stimuli and unchanging instructions. The origin of the delay and variability of SRT is a central problem that has received increasing attention with, it is fair to say, notable progress toward its elucidation.

Many models have been developed to explain the stochastic variability of reaction time.[2] Accumulator models have been evaluated in terms of brain function. Accumulator models suppose that in response to a stimulus, some signal grows until it reaches a threshold thereby triggering a movement in response to the stimulus. Models of this sort include three sources for the stochastic variability evident in reaction times (Figure 3.1). One type of accumulator model (Figure 3.1A), assumes that the threshold is constant, but that the average rate of growth of the accumulator is random across trials.[3,4] This architecture can account for a broad range of reaction times measured in a variety of tasks.[5,6] Another type of accumulator model (Figure 3.1B) supposes that the variability in reaction time arises from randomness in the level of the trigger threshold.[7,8] A third scenario (Figure 3.1C) could employ a fixed threshold but a *variable baseline* at target onset.[9] Although this latter model is the mathematical equivalent of variable threshold, it would be implemented very differently in the brain. The alternative models cannot be distinguished on the basis of performance data alone. As a matter of fact, it has been shown that random accumulator and random threshold models generate equivalent predictions.[10]

How are aspects of these models instantiated at the level of the single cell, a single brain area, and the entire saccadic generating circuitry? We first review the saccade generating circuitry including the connectivity between the FEF and the SC. We then review neurophysiological experiments that provide information that seems to differentiate the possibilities illustrated in Figure 3.1.

3.3 OVERVIEW OF THE SACCADE GENERATION NETWORK

A network of cortical and subcortical structures is required for the accurate and timely control of saccadic eye movements (Figure 3.2), including regions within the cerebral cortex, thalamus, basal ganglia, cerebellum, SC, and brainstem reticular formation. Details of this network are reviewed elsewhere.[11–18]

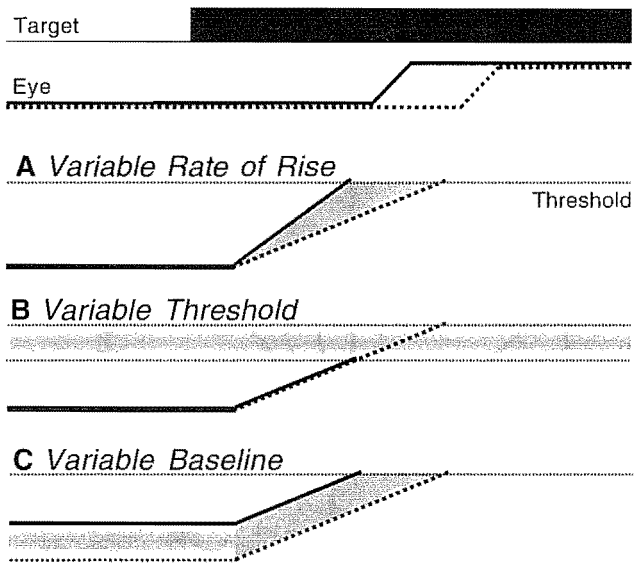

FIGURE 3.1 Accumulator models of saccade initiation. (A) Variability in saccadic reaction time (SRT) could be the result of a variable rate of rise toward the saccadic threshold. (B) Variability in SRT could be the result of a variable threshold. (C) Variability in SRT could be the result of variability in baseline activity before accumulation begins.

3.3.1 Brainstem Saccade Generator

The saccadic burst generator circuit is housed in the brainstem reticular formation.[13,17] Burst neurons (BNs) in the reticular formation innervate the extraocular muscle motoneurons (MNs) to provide the high-frequency burst of spikes necessary to move the eyes. BNs are silent during fixation and discharge action potentials for saccades in a specific direction. Excitatory burst neurons (EBNs) monosynaptically excite the one-direction motoneurons, while inhibitory burst neurons (IBNs), which receive their input from the EBNs, inhibit the antagonist MNs. The EBNs and IBNs for horizontal saccades are located in the pontine and medullary reticular formation, while the BNs for vertical saccades are located in the mesencephalic reticular formation.

Other neurons in the brainstem reticular formation are believed to control the discharge of EBNs and IBNs. The EBNs and IBNs for horizontal and vertical systems are subject to potent monosynaptic inhibition from omnipause neurons (OPNs), also located in the paramedian pontine reticular formation (PPRF), which discharge tonically during all fixations and pause for saccades in all directions. Thus, to generate a saccade, OPNs must first be silenced and then the appropriate pools of EBNs and IBNs are activated to produce the burst in the corresponding MN pools. Following completion of the saccade, OPNs are reactivated to inhibit the EBNs and IBNs.

Neurons with tonic activity proportional to the angle of the eyes in the orbit are also present in the brainstem and they innervate the MNs as well. The activation from these neurons results in the amount of innervation of the MNs to resist the centripetal viscoelastic forces and keep the eyes at an eccentric location in the orbit.

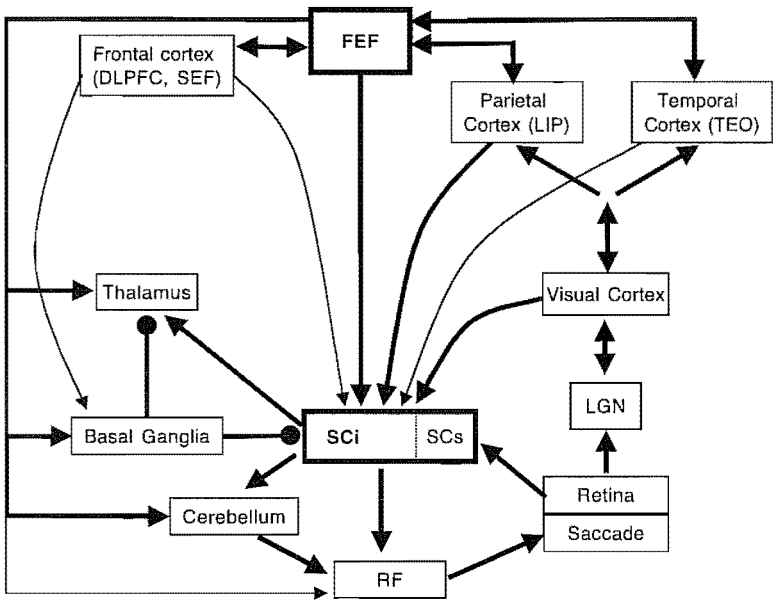

FIGURE 3.2 Schematic of brain areas and pathways involved in saccade generation. See text for additional details. Abbreviations: CN: caudate nucleus; DLPFC: dorsolateral prefrontal cortex; FEF: frontal eye fields; GPe: external segment of globus pallidus; LGN: lateral geniculate nucleus; LIP: lateral intraparietal area; RF: reticular formation; SCi: intermediate layers of superior colliculus; SCs: superficial layers of superior colliculus; SEF: supplementary eye fields; SNr: substantia nigra pars reticulata; STN: subthalamic nucleus.

These tonic neurons, which comprise the neural integrator, are located primarily in the medial vestibular nucleus and the nucleus prepositus hypoglossi for horizontal position control and in the interstitial nucleus of Cajal for vertical control.

Long-lead burst neurons (LLBNs), also located in the brainstem reticular formation, discharge a high frequency burst of action potentials for saccades into the contralateral hemifield. In addition to the burst, these cells also have a low frequency buildup of activity before the burst. It is believed that at least some LLBNs are innervated by descending projections from higher centers such as the SC and FEF and project directly to the EBNs and IBNs to provide the burst input.

3.3.2 Superior Colliculus

The superior colliculus (SC) is a laminated structure in the dorsal mesencephalon. The dorsal-most superficial layers of the SC contain neurons that receive direct retinal inputs as well as inputs from other visual areas.[19] The retinotectal projection arises from no more than 10% of all the ganglion cells.[20] The superficial layers of the SC also receive major afferent inputs from primary visual cortex and many extrastriate visual areas in occipital, parietal, and temporal lobes, as well as areas in the frontal lobe. The superficial layers of the SC project to the dorsal lateral geniculate nucleus, the pregeniculate nucleus, the inferior and lateral pulvinar, and

the pretectum. As a result of these retinal and other visual afferents, neurons in the superficial SC have well defined visual receptive fields, and there is an orderly retinotopic map in the superior colliculus with the fovea represented rostrally, and the upper visual field represented medially.[21,22]

The input to and output of the intermediate layers of the SC are diverse. The intermediate layers receive input from a variety of cortical areas including primary visual cortex, extrastriate visual areas, posterior parietal cortex, temporal cortex, the supplementary and frontal eye fields, and prefrontal cortex[23–28]. Subcortical afferents to the intermediate layers include the reticular nucleus and the pregeniculate nucleus; the pretectum; various midbrain structures including in particular the substantia nigra pars reticularis; various pontine and medullary nuclei, including the nucleus reticularis tegmenti pontis; deep cerebellar nuclei and finally the cervical spinal cord (see References 29 and 30 for reviews). The efferents of the intermediate layers of the SC are just as widespread. Ascending projections travel to numerous thalamic nuclei including the ventral anterior, ventral lateral, mediodorsal, central lateral, anterior, medial, and inferior pulvinar, lateral dorsal, reticular thalamic nuclei.[31] Descending projections terminate in the ipsilateral substantia nigra pars reticulata, mesencephalic reticular formation, pons, medulla and spinal cord, and in the contralateral pons, including PPRF, medulla, and spinal cord.[32]

The intermediate layers of the SC contain neurons with discharges that are correlated with saccadic eye movements and visual fixation.[33–49] These neurons are organized into a two-dimensional motor map coding for saccades directed to the contralateral visual field.[50] Neurons increasing their discharges before and during saccades — referred to hereafter as *saccade neurons* — are distributed throughout the extent of these intermediate layers. Each saccade neuron discharges for a range of amplitude and direction saccades that define a movement field.[42,45,46] These saccade neurons can be divided into subclasses based upon prelude[33,51,52] or buildup[42,53,54] activity preceding the saccadic burst. Buildup neurons have low frequency preamble activity before the saccade burst and many of these neurons also have open-ended movement fields.[42] Burst neurons lack the prelude or low frequency buildup activity. There is probably a continuum between these two classes of saccade neurons.[42,55]

Neurons exhibiting tonic discharge during visual fixation and a pause during most saccades — *fixation neurons* — are restricted mainly to the rostro-lateral pole of the motor map beneath the superficial layer's representation of the fovea, forming a continuum with the saccade neurons.[55,56] Fixation neurons have been prescribed a role in the maintenance of active visual fixation;[41,57] however, they may also participate in the execution of microsaccades,[57] smooth pursuit,[58,59] and vergence eye movements.[60]

Local inhibitory connections may help shape the reciprocal activity patterns of saccade and fixation neurons.[18,37,38,55,57] The findings that most saccade and fixation neurons are inhibited at very short latency after microstimulation of remote collicular regions[61] and that injection of GABAergic agonists and antagonists in the rostral[57] versus caudal SC[62] produces reciprocal effects on behavior provides credence to this hypothesis.

The SC can directly influence saccade generation through its direct projection onto LLBNs in the brainstem reticular formation.[63,64] Besides providing a signal that

specifies where to make the saccade, the SC also provides a trigger signal through its projection to the OPNs in the brainstem, which are excited monosynaptically but inhibited polysynaptically by stimulation of the intermediate layers of the SC.[64]

Early studies revealed that ablation of the SC impairs the ability to generate saccades, but many of these effects recover with time.[65] However, there remain lasting deficits in saccade initiation that are revealed as increases in saccadic reaction time.[66] More recently, reversible inactivation of focal regions within the SC has revealed that the SC is critical for saccade initiation.[62,67–69]

3.3.3 Cerebral Cortex — Frontal Eye Field

Visual inputs guiding saccades are delivered through the retino-geniculo-cortical pathway as well as through a direct retino-tectal projection. Visual information for the guidance of saccades is processed through multiple extrastriate visual areas. Areas in the temporal lobe represent the visual features of objects and are modulated by the covert allocation of attention.[70,71] Areas in the parietal lobe, such as the lateral intraparietal area (LIP) represent the location and relevance of objects in retinocentric and craniocentric coordinates at the interface of the sensory-motor transformation.[72,73] LIP delivers visual and extraretinal signals to the intermediate layers of the SC[74] as well as to the frontal eye fields (FEF),[75] located in the rostral bank of the arcuate sulcus in macaque monkeys. Broadly considered, the FEF participates in the transformation of visual signals into saccade motor commands.[14]

FEF is innervated in a topographic fashion by areas in both the dorsal and ventral streams of extrastriate visual cortex.[76] As a result of this extensive connectivity with extrastriate visual cortical areas, many neurons in FEF respond to visual stimuli. Physiological recordings in the FEF of monkeys trained to shift gaze to visual targets have found that roughly half of the neurons have visual responses.[77,78] Recent research has demonstrated how these visually responsive neurons in FEF participate in the selection of visual targets for saccades.[79–81]

FEF is also known to play a direct role in producing saccadic eye movements. Low intensity microstimulation of FEF elicits saccades.[82] This direct influence is presumably mediated by a subpopulation of neurons in FEF that discharge specifically before and during saccades.[79,83] These saccade neurons in the FEF appear to be the functional equivalent of the saccade neurons with buildup activity observed in the SC. FEF is also populated by fixation neurons that seem to parallel their counterparts in the SC.[84]

Hanes and Wurtz[69] showed that it was not possible to elicit saccades with microstimulation of the FEF, following reversible deactivation of the SC. Thus, although the FEF and SC have parallel projections to the saccadic premotor circuitry in the brainstem, they may not be weighted equally. Evidence suggests that the serial pathway from FEF to SC to brainstem is dominant.

FEF can influence saccade production through three pathways. One pathway is a major projection to the ipsilateral SC concentrated in the intermediate layers but extending to superficial and deep layers.[23,26,28,85,86] This projection is topographically organized with lateral FEF projecting to rostral SC and medial FEF, to caudal SC.[24] Another major pathway is through the basal ganglia via the ipsilateral striatum and

subthalamic nucleus.[86–89] FEF efferents terminate in the region of caudate where neural activity related to saccade production is recorded.[90–92] The terminations in the striatum are topographically organized; the medial aspect of FEF projects to the central part of the head and body of the caudate and dorsomedial putamen while the lateral portion of FEF terminates ventrolaterally in the caudate and ventromedially in the putamen.[89]

The third pathway is a projection to mesencephalic and pontine nuclei.[26,28,93–96] The FEF projects weakly and inconsistently to the ipsilateral nucleus of Darkschewitsch, interstitial nucleus of Cajal, and rostral interstitial nucleus of the medial longitudinal fasciculus. FEF also projects weakly to the paramedian pontine reticular formation and nucleus prepositus hypoglossi and slightly more strongly to the nucleus raphe interpositus. These projections tend to be mainly ipsilateral, but some studies report some contralateral fibers as well. The FEF projection is stronger and clearly bilateral to the nucleus reticularis tegmenti pontis.

Many studies have shown that FEF is reciprocally connected in a topographic manner with a longitudinal zone of thalamic nuclei bordering the internal medullary lamina extending from the ventroanterior nucleus to the medial pulvinar.[26,87,89] The densest connections of FEF are with the lateral part of the mediodorsal nucleus and the medial part of the ventroanterior nucleus. FEF is more weakly connected with the more medial and caudal parts of the mediodorsal nucleus, with area X of the ventrolateral nucleus and with the caudal ventrolateral nucleus and medial pulvinar. Some but not all studies have reported weak FEF connections with the paracentral, centrolateral, and central superior lateral intralaminar nuclei. The FEF connections with the paralaminar nuclei is topographically organized with the dorsomedial part of FEF projecting dorsally and the ventrolateral part of FEF projecting ventrally. The thalamic zones most heavily connected with FEF are themselves innervated by oculomotor afferents from the intermediate and deep layers of the superior colliculus, the substantia nigra pars reticulata, and the dentate nucleus of the cerebellum.[97,98]

Reversible inactivation of FEF impairs monkeys' ability to make saccades.[99–101] This observation complements earlier observations that ablation of FEF causes an initial severe impairment in saccade production that recovers over time.[65,66,102]

Saccade and fixation neurons in the FEF innervate neurons in the intermediate layers of the superior colliculus directly[103–105] and the premotor circuitry in the brainstem reticular formation.[106]

To summarize, the SC and the FEF can influence one another through at least five paths. (1) FEF projects topographically to the intermediate layers of the SC. (2) The intermediate layers of the SC project to the lateral segment of the mediodorsal nucleus that in turn projects to FEF.[107,108] (3) FEF projects to the caudate nucleus, which inhibits the substantia nigra pars reticulata, which inhibits the SC. The substantia nigra pars reticulate also projects to thalamic nuclei that innervate the FEF. (4) The sector of the caudate nucleus receiving FEF afferents also projects to the external segment of the globus pallidus, which in turn projects to the subthalamic nucleus, which influences the substantia nigra pars reticulata. (5) The FEF and SC both project to nucleus reticularis tegmenti pontis, which innervate sectors of the cerebellum that ultimately influence the SC.

3.4 ROLE OF SC AND FEF IN SACCADE INITIATION

The pattern of movement-related activity recorded in the FEF and SC of monkeys performing various saccade tasks has been analyzed to evaluate the alternative models of reaction time (Figure 3.1). Several paradigms have been developed to investigate the neural processes involved in saccade initiation. These tasks range from those requiring reflexive or automatic responses to visual stimuli to those that require less reflexive and more voluntary processing. Another task requires subjects to inhibit the initiation of a partially prepared saccade. We will review several of these tasks here and show how the SC and FEF are involved in the generation of both reflexive (automatic) and voluntary saccadic eye movements.

3.4.1 Reflexive Saccades – The Gap Saccade Task

The gap saccade task[109] requires a subject simply to generate an automatic saccade to a suddenly appearing visual stimulus. Each trial is initiated by the appearance of a central fixation point. After a period of visual fixation, the fixation point disappears leaving the subject momentarily in complete darkness (the gap period) until an eccentric visual target appears. The subject is required to maintain central fixation during the gap period and then initiate a targeting saccade after the detection of the visual target. The disappearance of the fixation point can both release the fixation system and act as a temporal warning signal allowing the subject to prepare for the impending target appearance.[110–116] The introduction of a gap period (e.g., 200 ms) leads to a general reduction in SRT, known as the *gap effect*. It is therefore likely that the excitability levels of various elements of the saccade generating circuitry are altered during the gap period prior to target appearance. Munoz and colleagues[16,42,53,54,114,117,118] have recorded from several different classes of oculomotor neurons in the FEF, the substantia nigra pars reticulata, the SC intermediate layers, and the brainstem paramedian pontine reticular formation while monkeys performed the gap saccade task. Figure 3.3 shows representative examples of the single-cell activity patterns that were correlated to aspects of the task. In these experiments, the gap duration was fixed at 200 ms and the target appeared randomly at a single location in either the right or left hemifield, one location being centered in the response field of the neuron under study. The activation functions for individual neurons shown in Figure 3.3 are aligned on target appearance (left column) and saccade initiation (right column).

Within the FEF, saccade neurons are silent during visual fixation but some of them begin to discharge at a low frequency during the gap period (Figure 3.3A; blue trace; see color insert), starting about 100 ms after the FP disappears,[104,119] while others remain silent until after the target appears (Figure 3.3A, green trace). Saccade neurons then discharge a high frequency visuomotor response after the target appears in their response field and a saccade is initiated (Figure 3.3A; right panel, blue and green traces). FEF fixation neurons (Figure 3.3A; red traces) have a very different pattern of discharge: they are tonically active during visual fixation and there is often

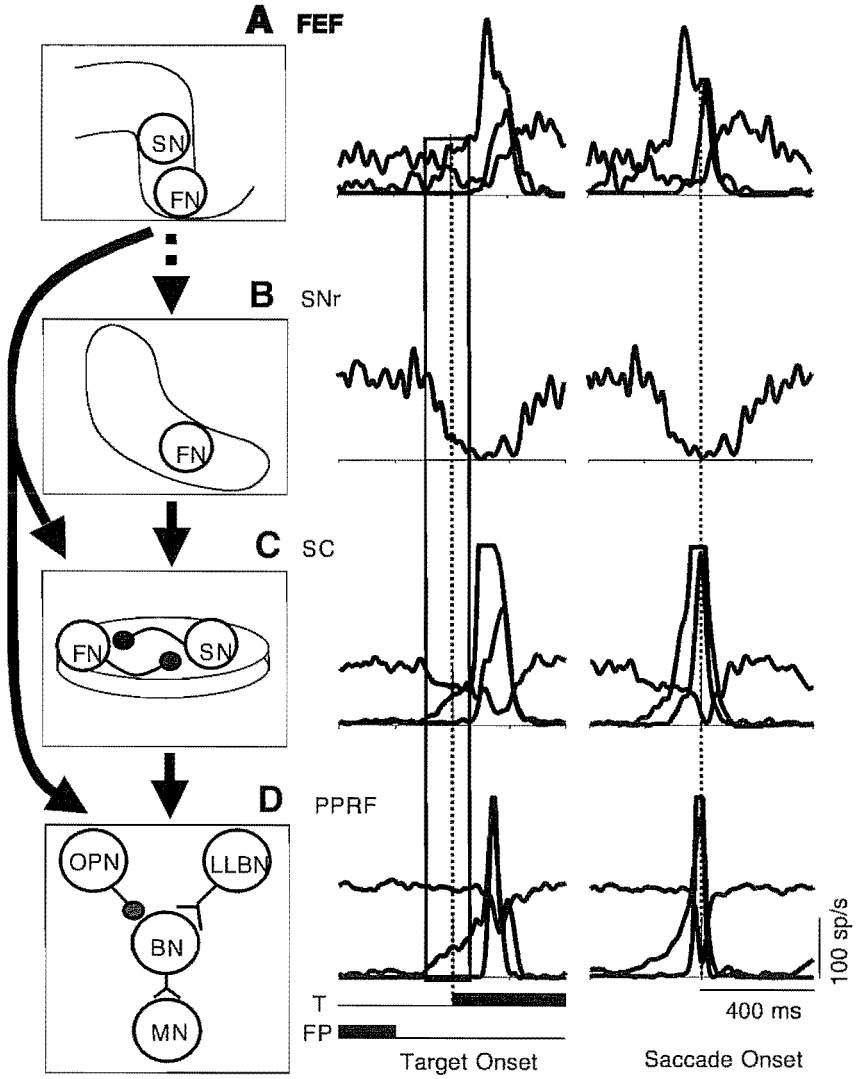

FIGURE 3.3 (See color insert following page 176.) Discharge of neurons in the frontal eye fields (A), substantia nigra pars reticulata (B), intermediate layers of the superior colliculus (C), and paramedian pontine reticular formation (D) during the gap-saccade paradigm. The spike density waveforms are aligned on target appearance (left column) and saccade onset (right column). Cells at all three levels are modulated by the gap period. Saccade neurons are silent during visual fixation of the fixation point and then increase their discharge for saccades. Of these saccade neurons, some become active before target appearance (blue traces), while others remain silent until after target appearance (green traces). Neurons with tonic activity during fixation have a drop in discharge rate during the gap and saccade initiation (red traces). Vertical gray bar denotes the end of gap epoch, highlighting neurons that change their activity during the gap period. Abbreviations: BN: burst neuron; FN: fixation neuron; LLBN: long-lead burst neuron; MN: motoneuron; OPN: omnipause neuron; SN: saccade neuron.

a drop in this activity approximately 100 ms into the gap period. Many FEF fixation neurons also have a pause in their discharge during the initiation of the saccade to the target and a subsequent postsaccadic enhancement in their discharge.[84,103]

Within the substantia nigra pars reticulata, there are also neurons whose discharge is modulated during the gap period of the gap saccade paradigm.[118] Neurons in the SNr that decrease or pause their discharge during saccades, pause neurons,[120,121] can also have a drop in their tonic discharge during the gap period (Figure 3.3B; red traces).

Within the SC, the fixation neurons (Figure 3.3C; red traces) have discharges that are similar to the FEF fixation neurons: they are tonically active during visual fixation, but reduce their activity about 100 ms into the gap period before pausing completely for the ensuing saccades.[114] Reciprocally, the SC saccade-related neurons are silent during visual fixation and discharge a high frequency burst of action potentials for saccades into their response field.[42,44] During the gap period, some of the SC saccade neurons — buildup neurons — additionally display low-frequency pretarget discharges (Figure 3.3C; blue trace), while others — burst neurons — remain silent (Figure 3.3C; green trace).[42,53] Both burst and buildup neurons will then discharge a high frequency burst for the saccade and many of these neurons will also discharge a burst time-locked to target appearance.

In the reticular formation, OPNs continue to discharge at the same tonic rate before and after FP disappearance in the gap task (Figure 3.3 red traces). They do not exhibit the gap-related reduction in activity that was observed among many fixation neurons in the FEF, substantia nigra pars reticulata, or SC.[16,117] In comparison, LLBNs also display low-frequency pretarget activity during the gap period (Figure 3.3D; blue traces) that is similar to that recorded in the SC and FEF. The BNs lack any gap-related activity; they only discharge a high frequency burst for the contraversive saccade (Figure 3.3D; green traces).

Thus fixation and saccade signals interact at several stages of the neuraxis (e.g., FEF, SC, and PPRF) during the gap saccade paradigm. Although we see neurons at several different levels of the circuit being modulated during the gap period, we also see an evolution of processing from FEF, to SC, to the PPRF. One important distinction is that OPNs maintain their tonic discharge during the gap period while fixation neurons in the SC and FEF show a drop in discharge rate. OPN discharge must be maintained to inhibit BNs and avoid premature initiation of saccades. It was hypothesized that a major component of the input to the brainstem OPNs arose from fixation neurons in the superior colliculus.[38,41] If this is true, how do the OPNs maintain the same tonic rate during the gap period? It has been hypothesized that OPNs receive excitatory inputs from both fixation and saccade neurons in the SC.[64,117] Increased input from saccade neurons with buildup activity occurs when input from fixation neurons is reduced. A constant input onto the OPNs ensures that their high tonic discharge continues during the gap period and that, via their potent inhibition of BNs, low-frequency pretarget signals do not trigger a saccade prematurely. Then, when a saccade is triggered, the high frequency burst in the SC is relayed via an inhibitory interneuron to inhibit the OPNs for the duration of the saccade.

3.4.2 Express Saccades: A Special Class of Visually Guided Saccade

Using the gap paradigm often results in a bimodal distribution of SRTs (Figure 3.4A), with a first mode (~100 ms) of *express* saccades and a second mode (~150 ms) of *regular* saccades.[122–124] Express saccades have SRTs that approach the minimal time required for the visual response to travel from the retina, through the brain, to the MN to trigger a motor action.[125] When the spatial location of the saccade target and the probability of its presentation are varied, it can be demonstrated that the disengagement of fixation afforded by the disappearance of the central fixation point leads to a general reduction in SRT, the gap effect.[16,114] However, the introduction of the gap period does not guarantee that express saccades will be generated. Rather, express saccade occurrence is determined by factors such as predictability in the location and timing of appearance of the saccadic target.[116]

Given the special nature of express saccades, an obvious question is do they conform to any of the threshold models of saccadic initiation illustrated in Figure 3.1? Textbooks commonly state that the SC produces reflexive saccades and the FEF produces voluntary saccades. One basis for this seems to be the observation that lesions of the SC but not the FEF prevent express saccade production.[66] It has been supposed, therefore, that FEF is not essential for, nor perhaps even involved in, producing express saccades. However, evidence from recent neurophysiological studies has shown that saccade neurons in the FEF have elevated pretarget activity preceding express saccades,[104] in a manner that parallels what is observed in the SC.[56,126] Thus it remains to be determined whether the FEF activation during express saccades is required to help initiate them, or the result of feedback from the SC.[107,108]

Figure 3.4B and C shows the discharge of individual saccade neurons recorded in the FEF and the SC during the execution of express and regular saccades. There are two important observations to make. First, prior to the execution of express saccades, saccade neurons in the both the FEF and SC have a higher level of pretarget discharge during the gap period, which is consistent with the hypothesis that higher pretarget activity results in shorter SRT.[53,54,104] Second, many saccade neurons have two bursts of action potentials after target appearance for regular saccades, an early, small stimulus-related burst and a later, larger saccade-related burst, but only one burst before express saccades that is equally well aligned on both stimulus presentation and saccade onset.[53,104,126] For express saccades, it is as if the two bursts of activity merged into one *visuo-motor* burst of sufficient magnitude to trigger the saccade with an express latency.

The pretarget activity that appears on saccade neurons during the gap period in the gap paradigm is hypothesized to move the system closer to the threshold for saccade initiation.[53,54,104] When the transient, stimulus-related burst of activity arrives in the SC, it is added to the early pretarget activity. If this early pretarget activity is of sufficient strength, then the visual burst drives the system over the threshold producing an express saccade. If the pretarget activity is low, then the visual burst does not reach the threshold for saccade initiation, and the system must wait for a

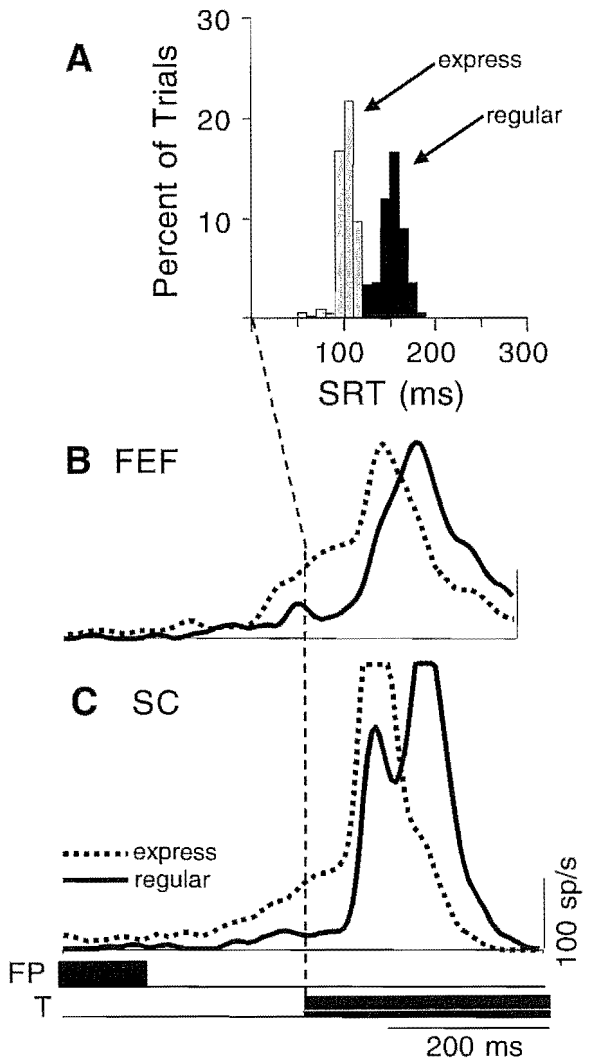

FIGURE 3.4 (A) Distribution of saccadic reaction times in the gap paradigm, highlighting the bimodal distribution of express and regular latency saccades. (B, C) Discharge of an individual FEF and SC neuron, respectively, during generation of express and regular latency saccades.

later signal, which delays saccade initiation and produces a regular-latency saccade. According to this hypothesis, two events are required for express saccades: a high level of pretarget activity and a transient response caused by either the appearance of a new target or motion of an existing target.

3.4.3 Control of Saccade Production — The Countermanding Task

The countermanding task can be used to investigate the control over automatic responses by infrequently presenting an imperative stop signal in a reaction time task.[127,128] The subjects' task is to cancel the planned movement if the stop signal is presented. In the saccade version,[129] monkeys were trained to make a saccade to a peripheral target that appeared when the fixation spot disappeared (Figure 3.5A). On a fraction of trials a *stop signal* was presented (Figure 3.5B); in these experiments the stop signal was the reappearance of the fixation spot. In response to the stop signal, the monkeys were to withhold the planned movement, which they did with variable success. In other words, monkeys could either cancel the planned movement (in which case they earned reinforcement) or fail to cancel the movement (in which case the trial was aborted).

Logan and Cowan[127] showed that performance on this task can be accounted for by a race between a process that generates the movement and a process that cancels the movement. This race model provides an estimate of the *stop signal reaction time*, which is the time needed to cancel the planned movement. The stop signal reaction time corresponds to estimates of the time needed to reprogram a saccade in double-step saccade tasks.[130,131] Oculomotor stop signal reaction times with a foveal spot signal average around 80 to 100 ms in monkeys[129] and are slightly longer in humans.[132–135] This may not be surprising in view of the common observation that saccade latencies in the monkey are somewhat shorter than in humans. Human studies have also examined the influence of nonfoveal and nonvisual stop signals on saccadic countermanding.[133–135]

To collect data in the countermanding task, it is necessary to have no stop signal in most trials. These data afford a kind of analysis that can indicate how the activity of single neurons is related to the initiation of saccades (Figure 3.6A). By grouping trials according to saccade latency, it becomes clear that saccades are initiated when the activity of saccade neurons in the FEF reach a particular level.[83] This relationship has been observed for SC neurons[53,54] and also holds true for movements of the limbs.[136] The variability in reaction time can be accounted for mainly by the time taken by the activity of movement-related neurons to reach the threshold. The origin of such variability in the growth of movement-related activity is not known but may include the state of neuromodulatory systems.[137] The relation of movement-related neural activity to reaction time corresponds to an accumulator architecture with variable growth to a fixed threshold (Figure 3.1A) and directly contradicts an architecture with a fixed growth process and random threshold (Figure 3.1B).

Usually, brain structures are attributed a function in motor control if it can be shown that they play a role in producing movements. The countermanding paradigm permits the investigation of another facet of control, the cancellation of a planned

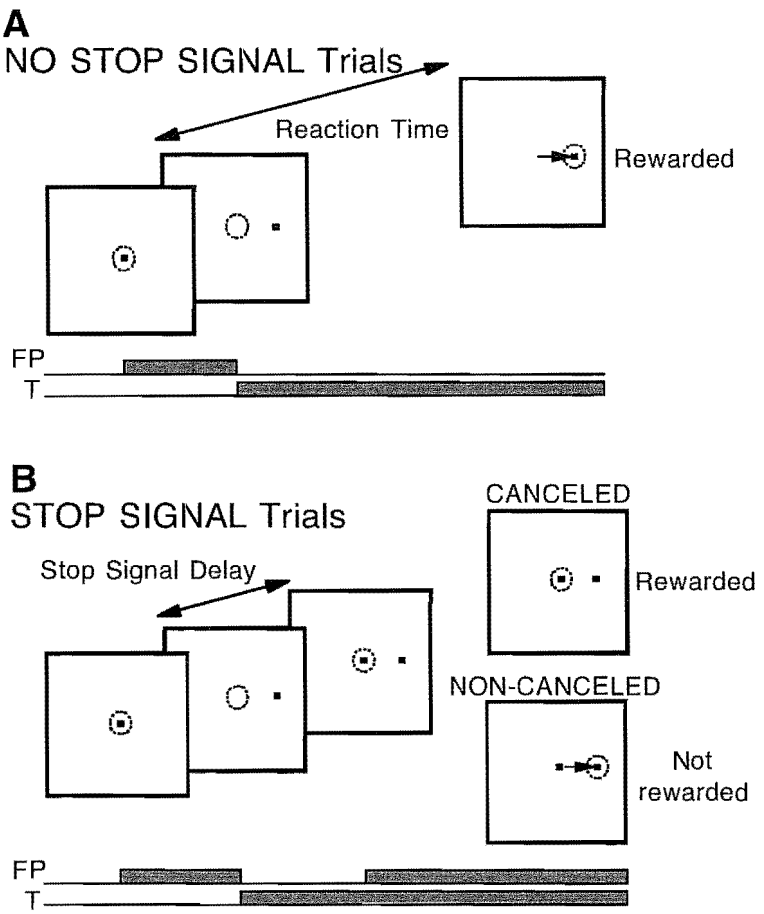

FIGURE 3.5 The countermanding paradigm, consisting of NO STOP SIGNAL trials (75%) and STOP SIGNAL trials (25%). On NO STOP trials, the monkey is reward for initially fixating the central fixation point (FP) and then making a saccadic eye movement to the eccentric target (T). On STOP SIGNAL trials, the monkey is rewarded for canceling the saccade to T after the stop signal (reappearance of FP) is presented.

movement. The chief virtue of the countermanding paradigm is that one can determine whether single neurons generate signals that are logically sufficient not only to initiate movements but also to prevent the production of movements. The logic of the countermanding paradigm establishes two criteria a neuron must meet to play a direct role in the control of movement. First, the neuron must discharge differently when a saccade is initiated versus when a saccade is withheld. Second, this difference in activity must occur by the time that the movement is canceled, i.e., within the stop-signal reaction time.

Neural activity in FEF and SC has been described when monkeys performing the countermanding task cancel partially prepared saccades.[84,138] The activity of

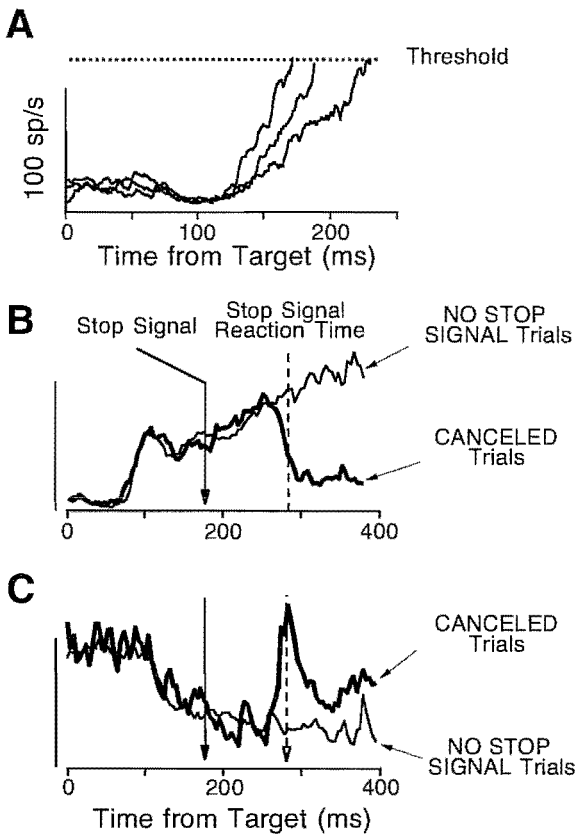

FIGURE 3.6 Discharge of FEF saccade (blues traces) and fixation (red traces) neurons in the oculomotor countermanding task. (A) Discharge of an individual saccade neuron for saccades of different saccadic reaction times (SRT). The slope of the buildup or accumulation of activity was correlated to SRT: the fastest rate of rise preceded the fastest SRTs, the slowest rate of rise preceded the slowest SRTs. (B, C) Discharge of FEF saccade (B) and fixation (C) neurons for NO STOP trials (thin lines) and correctly canceled STOP SIGNAL trials (thick lines). The STOP SIGNAL was presented 180 ms after the target appeared. Note that both saccade and fixation neurons altered their discharge accordingly to halt the initiation of a saccade on STOP SIGNAL trials, before the calculated stop signal reaction time.

saccade-related neurons, which began to grow toward the trigger threshold, failed to reach the threshold activation level when movements were canceled (Figure 3.6B). Instead, when planned saccades were canceled, the activity of saccade neurons decreased rapidly after the stop signal was presented (thick trace in Figure 3.6B). When the saccades were produced in trials with no stop signal, the activity of saccade-related neurons continued to accumulate toward the threshold (thin trace in Figure 3.6B). The same growth of activity to the threshold was observed when the saccade was produced in spite of the stop signal. Moreover, the activity associated with

canceling as compared to executing the saccade became different before the stop signal reaction time had elapsed. Similar patterns of activation have been reported for saccade-related neurons in the SC. Therefore, the activity of saccade neurons in the FEF and SC is sufficient to specify whether or not a saccade will be produced.

A reciprocal pattern of neural activity was observed in fixation neurons in FEF[84] (Figure 3.6C) and the SC.[138] If partially prepared eye movements were canceled, fixation neurons that had decreased firing generated a rapid burst of activity before the stop signal reaction time (thick trace in Figure 3.6C). This rapid increase in fixation neuron activity was not observed in trials with no stop signal (thin trace in Figure 3.6C) or before noncanceled saccades.

This modulation before the stop signal reaction time was never observed in neurons with only visual responses and no saccade-related modulation of discharges. The visually responsive cells that had no saccade-related activation were either not modulated when planned saccades were canceled or the modulation occurred well after the stop signal reaction time. Thus, not every neuron in FEF or SC plays a direct role in the control of saccade production. Rather this function may be limited to only saccade-related and fixation neurons.

The findings from SC and FEF using the countermanding paradigm indicate that the preparation of a movement can be a controlled process; it can be canceled if the growth of the activation toward the trigger threshold is sufficiently slow. These data strongly support the rise to threshold model illustrated in Figure 3.1 and reinforce the parallel nature of the signals observed in the SC and FEF.

3.4.4 Voluntary Saccade Production — The Antisaccade Task

Many tasks have also been devised to investigate the role of various brain regions in the generation of voluntary, nonautomatic responses. Intention can be investigated by manipulating the type of eye movement response required when a stimulus is presented. In the prosaccade task, an automatic visuomotor response is required, whereas in an antisaccade task,[139] this automatic response must be inhibited and instead a voluntary response is required to the stimulus mirror position. Contrasting pro- and antisaccade responses recorded in the same experiment can reveal and dissociate aspects of sensory, intention, and premotor processing. Everling and coworkers[104,140–142] recorded the activity of saccade-related neurons in the SC and FEF while monkeys performed a task with randomly interleaved prosaccade (saccade toward the stimulus) and antisaccade (saccade away from the stimulus to the opposite side) trials. Within a block of trials, the color of the initial fixation point conveys the instruction to generate either a prosaccade or antisaccade. On prosaccade trials, the same saccade neurons activated by the stimulus are required to drive the saccade. However, on antisaccade trials, the cells activated by the appearance of the target stimulus must be suppressed so that saccade neurons on the opposite side of the brain can drive the correct antisaccade away from the stimulus.

Figure 3.7 shows the discharge of saccade neurons recorded in the FEF and SC for correct prosaccade (thin traces) and antisaccade (thick traces) tasks when the target stimulus appeared in the response field of the neuron (Figure 3.7A and D),

or the saccade was required into the response field of the neuron (Figure 3.7B and E). There are several important observations to note. First, saccade neurons in both the SC and FEF discharged at a lower frequency during fixation of the central fixation point on antisaccade trials (thick traces below thin traces in gray bar in Figure 3.7A, B, D, and E). Second, following appearance of the target stimulus in the saccade neuron's response field (Figure 3.7A and D), a visual response was elicited on both pro- and antisaccade trials. Third, when the saccade was initiated into the response field of the saccade neurons being recorded (Figure 3.7B and E), there was often a drop in activity associated with the appearance of the target stimulus that is the result of inhibitory input resulting from target appearance elsewhere in the visual field. Fourth, following the stimulus related decrease in activity (Figure 3.7B and E), there was an increase in activity of saccade neurons that is aligned with initiation of the correct antisaccade away from the target stimulus. Thus, consistent with SRT distributions,[142] the saccade burst in the FEF and SC is delayed on antisaccade trials compared to prosaccade trials. Finally, on antisaccade trials, the peak of the saccade burst is less for antisaccades than prosaccades.[104,141] In fact, the magnitude of the antisaccade response of many saccade neurons in the SC and FEF is less than the visual response created by the appearance of the visual stimulus. Therefore, presumably other structures or cells must contribute activity toward the threshold for the initiation of a correct antisaccade. One such structure could be the SEF, which has neurons that are more active for antisaccades compared to prosaccades.[143]

What is the nature of the signal used to reduce saccade neuron excitability prior to target appearance in the antisaccade task? Fixation neurons in the FEF and the SC have a discharge pattern on pro- and antisaccade trials that is opposite to saccade neurons. Consistent with their role in saccade suppression, the fixation neurons are more active during the instructed fixation period preceding target appearance on antisaccade trials (thick traces above thin traces in gray bar in Figure 3.7C and F). Thus, to perform the antisaccade task correctly, fixation activity is enhanced prior to target appearance and this acts as a suppression signal in both the FEF and SC to reduce excitability of saccade neurons prior to target appearance. Thus, it is not the case that the SC is silent for antisaccade generation as earlier hypothesized.[144] Rather, fixation neurons in the FEF and SC appear to work in concert to inhibit saccade neurons at the time of target appearance to suppress the initiation of the reflexive prosaccade; saccade neurons in the FEF and SC are then activated to initiate the correct antisaccade.[104,140,141]

The antisaccade task also provides a means to test the threshold models of saccade initiation (Figure 3.1). If there is indeed a fixed threshold for saccade initiation, there should be predictable changes in the discharge of saccade neurons in the FEF and SC for correct and incorrect antisaccades. Figure 3.8A shows the distribution of latencies among correct and error trials. Note that direction errors (reflexive saccades triggered toward the target) were initiated with shorter SRT than correct antisaccades and most of these errors have SRTs in the range of express saccades. Does a high level of pretarget activity in the SC, which shortens the SRT of visually triggered saccades in the gap task (Figure 3.4), increase the occurrence of direction errors in the antisaccade task, by allowing the stimulus-related burst to trigger a reflexive saccade? Neurophysiological recordings from the FEF and SC

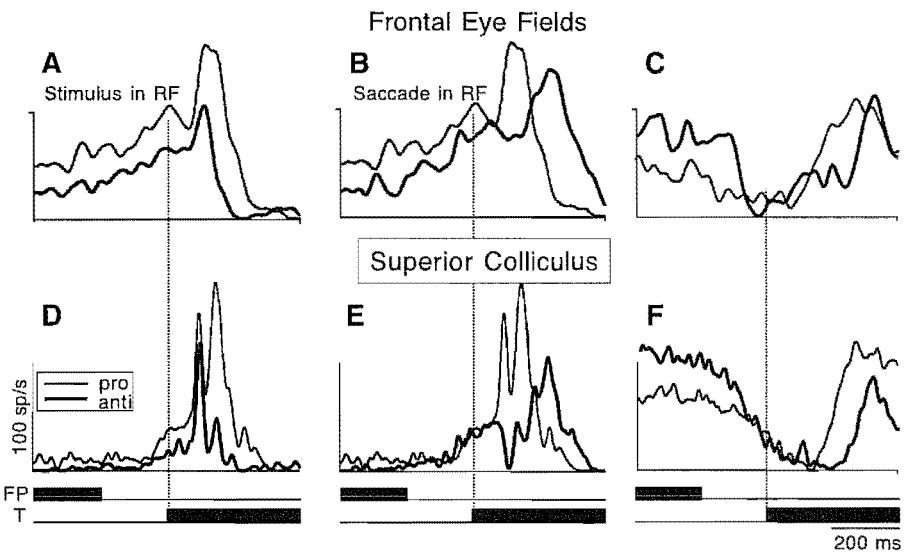

FIGURE 3.7 Discharge of saccade (A, B, D, E) and fixation (C, F) neurons in the FEF (top row) and SC (bottom row) the combined antisaccade (thick traces) and prosaccade (thin traces) task. (A, D) Stimulus appears in the saccade neuron's response field and the saccade is either in (prosaccade) or away from (antisaccade) the response field. (B, E) Saccade is into the saccade neuron's response field and stimulus is either in (prosaccade) or out of (antisaccade) response field. (C, F) Discharge of fixation neuron for pro- and antisaccade trials. Note that during the instructed fixation period (gray bar), the saccade neurons are more active on prosaccade trials, while the fixation neurons are more active on antisaccade trials.

confirm this prediction. Saccade neurons in both the FEF and SC have greater pretarget discharge prior to error trials.[104,140] When this low frequency pretarget activity combines with the visual transient response produced by the appearance of the visual stimulus, a direction error is triggered at express latency. On correct trials, the pretarget discharge is reduced and the transient visual response cannot surpass the saccade threshold. The stimulus was presented in the neuron's response field so that the opposite FEF and SC are required to drive the correct antisaccade. The appearance of the visual stimulus triggers a phasic response in the neurons. On error trials, excessive pretarget activity during the gap allows the stimulus-related response to exceed a threshold and trigger an erroneous prosaccade. Most importantly, note that almost all of the erroneous prosaccades are triggered at express saccade latencies.[142] On correct trials, the pretarget activity is reduced prior to stimulus appearance so that the transient stimulus-related burst does not exceed the threshold activation. Thus, once again the level of pretarget activity among saccade neurons predicts, not only saccade latency, but also the selection of the saccade: too much pretarget activity leads to the initiation of a visually triggered reflexive saccade. This is consistent with the variable baseline model illustrated in Figure 3.1C. To initiate a voluntary antisaccade, pretarget activity within the FEF and SC must be reduced. The reduction of excitability of saccade neurons in the FEF and SC during antisaccade trials may

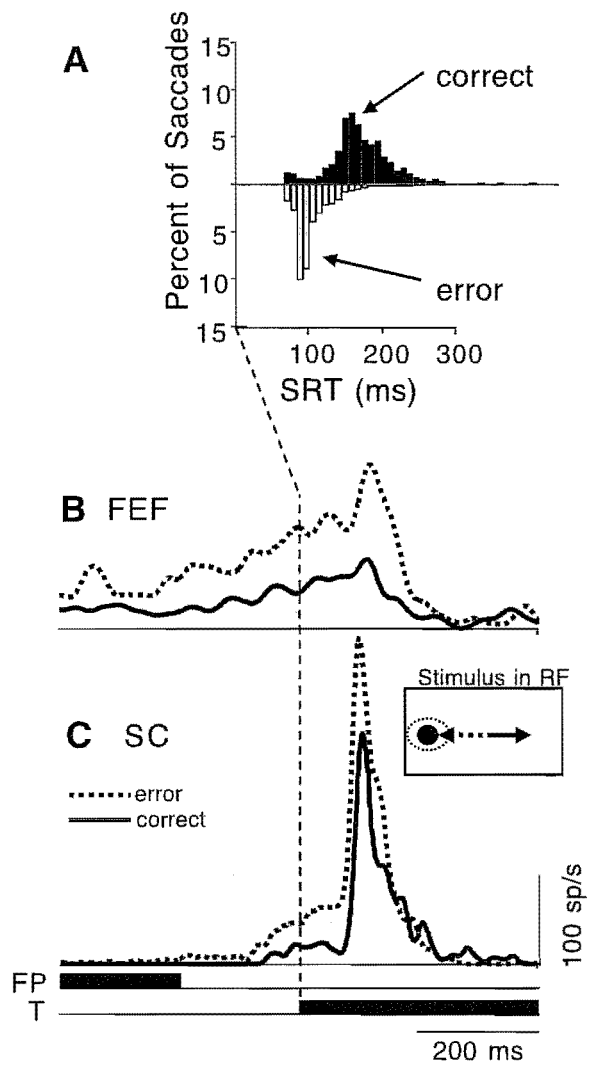

FIGURE 3.8 (A) Distribution of saccadic reaction times in the gap antisaccade paradigm, highlighting the bimodal distribution of correct (black bars) and direction errors (gray bars). (B, C) Discharge of saccade neurons in the FEF and SC associated with correct (solid traces) and erroneous (dotted traces) antisaccades when the stimulus appeared in the neuron's response field. Note the high level of pretarget activity associated with error trials.

be imposed by the supplementary eye field in which neurons are *more* active before and during antisaccades.[143] Another possible source of this control signal is the dorsolateral prefrontal cortex.[145,146]

3.5 CONCLUSIONS

Numerous lines of evidence lead to the conclusion that the FEF and SC function as two critical nodes in a network of saccade generation. Function is distributed across this network, and neurons with common discharge properties can be identified at multiple levels in the circuit, from the cortex, to the basal ganglia, to the SC, to the brainstem reticular formation. The connectivity between areas contributes somewhat to specificity, but there is substantial overlap in function. Although the FEF and SC together are essential for saccade generation, specific function is distributed across the network.

The rise to threshold architecture (Figure 3.1) can account for many of the observations of individual neurons recorded while animals perform very different saccade tasks and can therefore account for much of the behavior. We have described some of the important pre- and posttarget factors that contribute to either altering the baseline or the rate of rise of accumulation toward the threshold. In addition, the threshold level may vary between tasks. All of these mechanisms afford different levels of control over the saccade generating circuitry.

The results we have reviewed present an increasingly clear account of the neural basis of saccade generation. However, a number of outstanding questions remain. For example, how is the initiation of a saccade controlled? The ultimate switch is the balance of activation in the push-pull network of BNs and OPNs in the brainstem.[17] Therefore, it will be necessary to record single unit activity in these structures during tasks like countermanding. Furthermore, a paradox confronts us. Thousands of neurons are necessary to produce a saccade, but the averaged signal from single neurons in SC and FEF are sufficient to specify whether and when gaze will shift. This paradox can be addressed through simultaneous recording of presaccadic activity in multiple neurons throughout the saccade-generating circuit to clarify the mechanisms by which activity is coordinated.

How is activation coordinated across structures? As described above, FEF and SC can influence each other through several anatomical pathways. Most directly, FEF projects to SC, which projects to the thalamus, which then projects back to the FEF. The transmission time of these pathways is 2 to 3 msec.[103,104,107] Even allowing for 10 to 20 ms synaptic integration times, these delays allow enough time for SC and FEF to mutually influence the state of the other in the 100 ms interval during which saccade preparation usually occurs.

Another key issue involves how saccade latency is adjusted to perform tasks. A given visual stimulus can elicit a saccade with a latency less than 100 ms in the context of the gap paradigm or a latency exceeding 400 ms in the context of the countermanding task. How is the context of the task sensed and then how does it influence performance? One avenue of research indicates that areas in the medial frontal lobe such as SEF and parts of the anterior cingulate cortex are sensitive to the consequences of saccades, which is prerequisite for adaptive behavior.[147]

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