

Overt Responses during Covert Orienting

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A distributed network of cortical and subcortical brain areas controls our oculomotor behavior. This network includes the superior colliculus (SC), which coordinates an ancient visual grasp reflex via outputs that ramify widely within the brainstem and spinal cord, accessing saccadic and other premotor and autonomic circuits. In this Review, we discuss recent results correlating subliminal SC activity in the absence of saccades with diverse components of the visual grasp reflex, including neck and limb muscle recruitment, pupil dilation, and microsaccade propensity. Such subtle manifestations of covert orienting are accessible in the motor periphery and may provide the next generation of oculomotor biomarkers in health and disease.

Introduction

Humans and other primates are largely visual animals. Because of the nonuniformity of how we acquire and analyze information from the visual world, we have evolved an elegant *oculomotor system* that optimizes image acquisition by the retina. The oculomotor system includes both the low-level machinery to rapidly reposition our line of sight onto a target of interest, and the high-level circuitry to implement the flexible strategies necessary to operate efficiently in a complex and dynamic environment.

The oculomotor system consists of a brain network distributed across cortical and subcortical sites (Figure 1). This network includes the frontal eye fields (FEFs) and supplementary eye fields (SEFs) within the frontal cortex, and the lateral intraparietal area (area LIP) in the parietal cortex, and a number of recent reviews have summarized how these and other areas implement strategic control of orienting and the allocation of visuospatial attention (Bisley and Goldberg, 2010; Krauzlis et al., 2013; Schall, 2013; Squire et al., 2013). Here, we focus on the diversity of body responses that are controlled by the oculomotor system, with a particular focus on how such responses are coordinated by the *superior colliculus* (SC). The SC is extensively interconnected with the frontal and parietal components of the oculomotor system via ascending connections through the thalamus (White and Munoz, 2011; Wurtz et al., 2011) (Figure 1A); consequently, inactivation of the SC can produce behavioral deficits similar to what is seen after frontal or parietal lesions (Lovejoy and Krauzlis, 2010; Song et al., 2011). However, the SC is also a phylogenetically ancient structure that coordinates a diverse repertoire of movements and processes that together define the *orienting response* (Sokolov, 1963) via widely ramifying and potent projections to numerous downstream targets (Figure 1B). Some components of the orienting response are easily apparent, such as the movements of the eyes, head, and/or body that *overtly* shift the line of sight. Other components of orienting are more subtle and can include the *covert* allocation of visuospatial attention in the absence of saccades, modulation of the autonomic system to cause pupil dilation, or changes in the patterns of small fixational eye movements called microsaccades.

There is substantial overlap between the components of the oculomotor system that enable strategic control and those mediating the diverse components of the orienting response. This overlap is perhaps best exemplified in the SC (Figure 1). In the first half of this Review, we will summarize a series of key anatomical and physiological findings that detail the functional content and targets of signals sent downstream from the SC. As will become clear, signals issued from the SC are widely distributed to different targets in the brainstem (the branching of one SC efferent is shown in the box in Figure 1B), but the processing of SC signals at each target is not necessarily the same. In the second half of this Review, we will consider the implications of such differential processing, as it provides a unifying explanation for a series of observations from a diverse literature primarily (although not exclusively) in monkeys and humans that show that “covert” orienting may not be so covert after all but can instead lead to quantifiable changes in the motor periphery. Recognition of such subtle signatures of the orienting response is important both because they can themselves influence subsequent visual processing, and because they may offer novel ways of assessing the oculomotor system in both health and disease.

The Superior Colliculus: The Hub of the Orienting Response

The SC (optic tectum in nonmammals) has long been recognized as a key locus for multisensory integration and for how sensory signals are converted into motor actions to guide orienting (for review see Gandhi and Katnani, 2011; Stein and Meredith, 1993). The basic circuitry and function of the SC or its homolog is highly conserved across phylogeny; it first appeared in fish and amphibians and is present in reptiles, birds, and mammals (Dean et al., 1989; Ingle, 1983; Knudsen, 2011). In foveate animals, the SC coordinates the “visual grasp reflex” (Hess et al., 1946) that aligns the line of sight with a novel sensory stimulus. The SC also coordinates a more global orienting response that includes momentary changes in pupil dilation, a galvanic skin response, and changes in heart rate, blood pressure, and brain

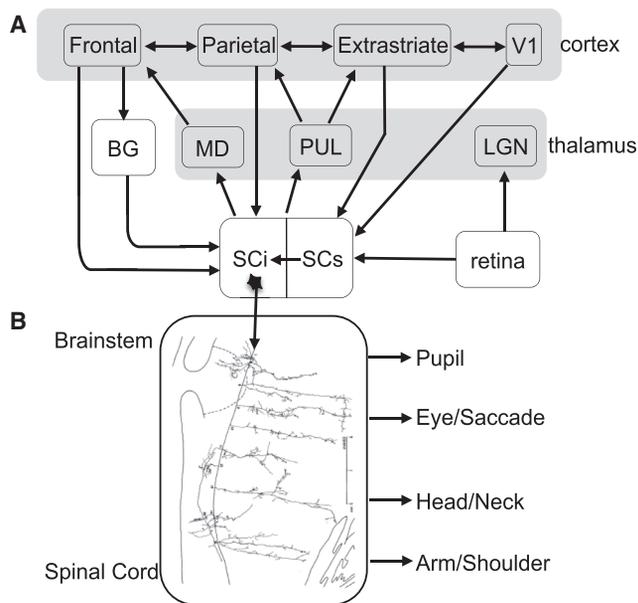


Figure 1. Schematic of the Primate Visual Orienting Circuit
The intermediate layer of the superior colliculus (SCi) is a critical node interfacing with other cortical and subcortical structures (shown in A; arrows show major projections between areas). The SCi also issues efferent signals to the brainstem premotor circuitry for pupil control, saccade generation, and head and body movements (shown in B). The axonal trajectory highlighted in the Brainstem box in (B) is derived from an intra-axonal injection of HRP into a cat tecto-reticulo-spinal neuron (adapted from Figure 8 in Grantyn and Grantyn, 1982). Abbreviations are the following: BG, basal ganglia; LGN, lateral geniculate nucleus; MD, medial dorsal nucleus of thalamus; PUL, pulvinar; SCs, superficial layer of superior colliculus; V1, primary visual cortex.

wave activity. These coordinated responses serve to prepare the body for possible action (Sokolov, 1963).

Anatomically, the SC is a multilayered structure (Figure 2A) that can be subdivided functionally into superficial layers (SCs), intermediate layers (SCi), and deep layers (for simplicity, we will term the intermediate and deep layers of the SC together as the SCi). The SCs receive visual information via direct projections from the retina and via indirect projections from the retino-geniculate-cortical pathway (see White and Munoz, 2011 for review), with the projections terminating deeper as one moves from striate through to extrastriate areas (Tigges and Tigges, 1981) (Figure 2A). SCs neurons are organized into a retinotopically coded map of contralateral visual space, with most SCs neurons discharging a phasic burst of action potentials ~40–70 ms after presentation of a visual stimulus in a restricted region of the visual field that defines the neuron’s response field (Figure 2B). The SCs also project directly to the SCi (Behan and Appell, 1992; Helms et al., 2004; Saito and Isa, 2005), facilitating visuomotor transformations by aligning the visual representations in the SCs with the motor responses mediated by the SCi (Isa, 2002). The SCi also receives convergent sensory, cognitive, and motor-related inputs from multiple cortical and subcortical sources.

A Diversity of Functionally Related Signals Is Present in the SCi

Such a confluence of projections is one of the reasons the SCi is thought to serve an integrative function, merging sensory infor-

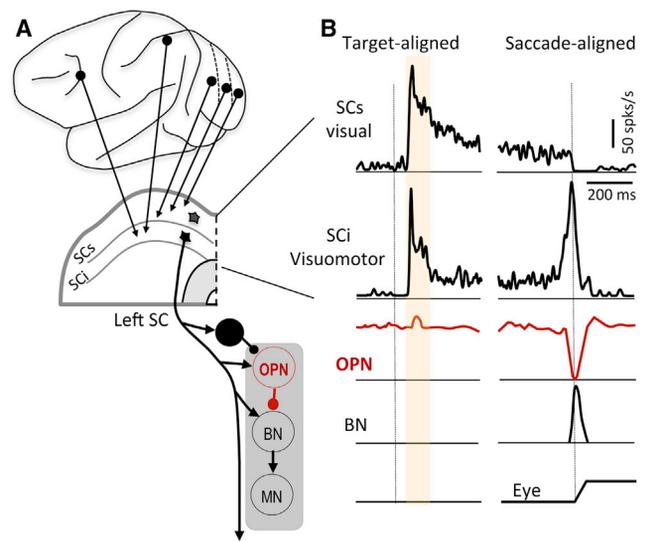


Figure 2. Saccades
(A) Illustration of SC layers, with schematic inputs from striate, extrastriate, parietal, and frontal cortex graded by depth (Tigges and Tigges, 1981). Some of the neuronal projections of an SCi visuomotor neuron are illustrated. (B) Response properties of two types of SC neurons, aligned on target appearance (left column) and saccade onset (right column) in a delayed saccade task. SCs visual neurons are located in the superficial layers of the SC. SCi visuomotor neurons are a subtype of saccade-related burst neuron located in the intermediate layers of the SC. Also shown are the response properties of an omnipause neurons (OPN, in maroon), a burst neuron (BN), and the movement of the eye. The 200 ms scale bar applies to all data. MN, extraocular muscle motoneuron.

mation from bottom-up sources with top-down, goal-related signals into a strategically appropriate motor response. In monkeys trained to look at visual stimuli presented in an otherwise dark room, a subset of visuomotor neurons within the SCi discharge a transient burst of action potentials after the appearance of a visual stimulus in their response field and another burst of action potentials before and during saccades to the same spatial location (Figure 2B) (Mohler and Wurtz, 1976; Sparks et al., 1976). Saccade-related neurons in the SCi, including visuomotor neurons, are organized into an oculocentrically coded map that specifies saccade vectors into the contralateral visual field and lies in register with the retinotopic map in the overlying SCs.

The timing and magnitude of visual responses in the SCi are critical for determining oculomotor behavior in a host of visuomotor tasks (Fecteau et al., 2004; Marino et al., 2012; White et al., 2009), and manipulations of the characteristics of the visual stimulus have predictable effects on sensorimotor activity within the SCi and on subsequent behavior. For example, reducing the visual luminance of a stimulus relative to background not only decreases the magnitude of the visual response, but also increases the onset latency of the visual response and the subsequent saccadic reaction time (Marino et al., 2012). Presenting isoluminant color stimuli can also delay the onset of the visual responses in the SCi and prolong saccadic reaction times (White et al., 2009). These lags can be quite substantial: visual responses in the SCi to high-luminance stimuli can precede those elicited by isoluminant stimuli by ~30–35 ms, accounting for much of the increase in saccadic reaction time.

Finally, visuomotor neurons in the SCi can also be activated outside of explicit visual or saccade-related events within a behavioral paradigm. For example, many saccade-related neurons in the SCi exhibit lower-frequency, persistent activity that correlates with numerous aspects of top-down control, such as the allocation of visuospatial attention, motor preparation, reward, target selection, and decision making (Basso and Wurtz, 1997; Dorris and Munoz, 1998; Glimcher and Sparks, 1992; Horwitz and Newsome, 1999; Ignashchenkova et al., 2004; Ikeda and Hikosaka, 2003; Kim and Basso, 2008; McPeck and Keller, 2002; Rezvani and Corneil, 2008). Neurons in the SCi may also exhibit responses to auditory or tactile stimuli (Groh and Sparks, 1996; Jay and Sparks, 1987; Populin and Yin, 2002), although such responses do not display the same robustness as visual responses in the SCi of monkeys. Recordings of SCi activity have also revealed other types of motor responses linked to movements of the head (Walton et al., 2007) or limb and hand (Werner et al., 1997) that need not be linked to saccades and may not display the oculocentric topography characteristic of canonical SCi visuomotor neurons (Stuphorn et al., 2000; Walton et al., 2007).

In summary, activity within the SCi spans the sensorimotor continuum, with profiles of activity that not only align with explicit sensory and motor events, but also correlate with numerous aspects of top-down control, including the covert allocation of visuospatial attention. We now consider the output of the SCi. Are all the functionally diverse signals that are present in the SCi conveyed to downstream targets?

Functional Content and Targets of Signals Emanating from the SCi

The SCi broadcasts its output signals widely via both ascending and descending projections to numerous targets. Ascending projections of the SCi through the medial dorsal (MD) nucleus of the thalamus relay an efference copy signal of an upcoming saccade to the frontal cortex (Sommer and Wurtz, 2004), which is a potentially important signal for maintaining visual stability across saccades (Sommer and Wurtz, 2008). Output neurons from the SCi also provide axons for the *tecto-reticulo-spinal* tract. These axons descend in the predorsal bundle and give off an ascending branch that projects to midbrain saccade centers (whether the same or different neurons project to MD and the midbrain saccade centers has not been determined), and a descending branch that crosses the midline and courses via the predorsal bundle through the brainstem to the upper cervical spinal cord (Grantyn and Grantyn, 1982; Moschovakis et al., 1996). Some three decades ago, elegant and painstaking work in the cat and monkey stained individual SCi efferents with intra-axonally injected horseradish peroxidase and revealed the substantial and regular branching of these axons as they descended through the brainstem (Grantyn and Grantyn, 1982; Scudder et al., 1996); such an extensive profile is also seen in other species (Serenó, 1985). We show one such efferent from the work of Grantyn and Grantyn (1982) in the cat in Figure 1B; note the extensive ramifications as the axon projects down through the brainstem, accessing not only multiple saccade centers, but also many other areas involved in coordinating other components of the orienting response.

A subsequent study using antidromic identification provided further characterization of the signals issued by the SCi (Rodgers et al., 2006). Antidromic identification is a method that exploits an axon's ability to propagate an action potential in either direction from a point of electrical stimulation, allowing an experimenter to test whether the axon of a recorded neuron does indeed project to the stimulated area. While recording SCi neurons in trained monkeys, Rodgers and colleagues (2006) stimulated the predorsal bundle in the pons. They showed that over half of the saccade-related SCi neurons that projected through the predorsal bundle were visuomotor neurons that conveyed both visual- and saccade-related information. Although this study did not employ many different sensory-motor tasks, it nonetheless demonstrated that phasic visual responses in the SCi project downstream to efferent targets.

We stress two key observations from these findings. First, tecto-reticulo-spinal neurons distribute widely to numerous downstream targets. These targets include the premotor centers that generate saccadic eye movements, the premotor centers for head and limb control, and autonomic centers that can influence pupil dilation. Second, the functional diversity of signals present in the SCi is also conveyed to downstream targets. In the following sections, we outline what is known about some of the major downstream targets of tecto-reticulo-spinal neurons. We begin with the brainstem saccade circuit, which is endowed with a unique processing capability that helps differentiate covert from overt orienting.

The Saccadic Burst Generator Is Potentially Gated by Omnipause Neurons

The SCi provides critical input to the brainstem saccade circuit. Anatomically, projections from the SCi travel through the predorsal bundle and terminate extensively in regions of the reticular formation housing the premotor burst neurons that subsequently innervate the extraocular muscle motoneurons to provide the high-frequency pulse to drive a saccade (for review, see Moschovakis et al., 1996; Munoz et al., 2000; Scudder et al., 2002; Sparks, 2002). The burst generator houses two types of burst neurons that act respectively to either excite (*excitatory* burst neurons [EBNs]) or inhibit (*inhibitory* burst neurons [IBNs]) extraocular muscle motoneurons to enable rapid saccades.

Burst neurons are themselves subjected to potent inhibition from omnipause neurons (OPNs), located in the nucleus raphe interpositus. OPNs discharge tonically during stable fixation but pause just before saccades in all directions (Figure 2B). In order to generate a saccade, OPNs must be silenced and the appropriate pools of burst neurons must be activated to produce the saccade command that is sent to the extraocular muscle motoneurons (Figure 2B). Just before saccade completion, OPNs are reactivated, reestablishing the potent inhibition on the brainstem burst generator.

A cascade of events therefore precedes the initiation of saccadic eye movements (Figure 2B), including development of a saccadic burst in the SCi ~20 ms before a saccade, a rapid silencing in the activity of OPNs, which disinhibits the burst generator, permitting the rapid activation of the subpopulation of burst neurons excited by the SCi to deliver a short, high-frequency pulse of activity to the appropriate population of

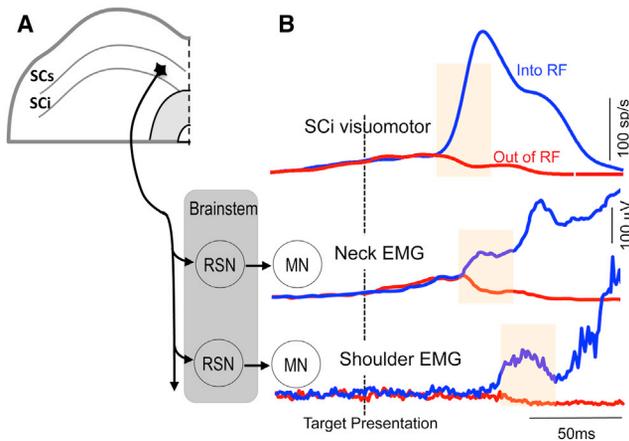


Figure 3. Neck and Limb Muscles

(A) Projections of an SCi visuomotor neuron via the predorsal bundle to reticulospinal neurons (RSNs), which then project onto neck or limb motoneurons (MN).

(B) Spike density function of SCi visuomotor neuron (top row), neck muscle recruitment (middle row; from Figure 1 of [Cornell et al., 2004](#)), and limb muscle recruitment (bottom row; from Figure 2 of [Pruszynski et al., 2010](#)), aligned to presentation of a visual target either into (blue traces) or out of (red traces) the response field (RF). Shaded boxes highlight the interval exhibiting the visual responses.

extraocular muscle motoneurons. The precise details of how the brainstem burst generator and OPNs rapidly switch between these modes remain to be determined, but it is clear that signals from the SCi play an important, although not exclusive, role (for review, see [Scudder et al., 2002](#); [Sparks, 2002](#)). Microstimulation of the SCi leads to monosynaptic activation of both OPNs and brainstem burst neurons ([Paré and Guitton, 1994](#); [Raybourn and Keller, 1977](#)), with the strongest excitation of the OPNs emanating from the rostral SC ([Büttner-Ennever et al., 1999](#); [Gandhi and Keller, 1997](#)). SCi microstimulation also leads to potent disinaptic inhibition of OPNs ([Paré and Guitton, 1994](#); [Raybourn and Keller, 1977](#)), which presumably helps silence the OPNs to permit burst neuron firing. Recent work shows that the central mesencephalic reticular formation that resides below the SCi may provide the substrate for this disinaptic inhibition on the OPNs ([Wang et al., 2013](#)).

Experiments that have manipulated OPN activity demonstrate its potent inhibition of the brainstem burst generator. Electrical stimulation of the OPN region prevents spontaneous saccades for the duration of stimulation ([Keller, 1974](#)) and can also rapidly interrupt saccades in midflight ([Keller and Edelman, 1994](#)). Conversely, because OPN activity ceases during blinks, small airpuffs to the eyes that provoke blinks provide a means to experimentally silence OPN activity, disinhibiting the brainstem burst generator. This technique can be combined with behavioral tasks, with precisely timed air puffs permitting tests of saccade feedback ([Goossens and Van Opstal, 2000](#)) or unmasking saccadic programs in preparation ([Katnani and Gandhi, 2013](#)).

The potent inhibition of OPNs onto burst neurons provides a neurobiological substrate for how the brainstem burst generator can differentiate saccade versus nonsaccadic signals among the diversity of signals conveyed from the SCi via the predorsal

bundle. For most visually guided saccades, the visual signal emanating from the SCi is prevented from driving the burst generator by potent OPN inhibition; in fact, OPNs themselves can display small visual responses ([Everling et al., 1998](#)), presumably mediated by the SCi, that serves to additionally suppress the burst generator ([Figure 2B](#)). Depending on the degree of expectation ([Dorris et al., 1997](#)), the visual response in the SCi can become the motor response to drive an *express saccade* ([Dorris et al., 1997](#); [Edelman and Keller, 1996](#)), which occurs at latencies that approach the minimal synaptic delay between the retina and the extraocular muscle motoneurons.

Express saccades are the exception that proves the rule: most of the time, visual responses do not drive the brainstem burst generator. The framework outlined above provides a straightforward explanation for this by emphasizing the potent OPN inhibition onto the brainstem burst generator. While other brain areas are undoubtedly also involved in the ensuring that reflexive saccades are not made to every salient visual stimulus (and in doing so provide additional time for saccade target selection), it is clear that the OPNs can potentially inhibit the visual signal that goes to the brainstem burst generator. A similar line of reasoning can explain why other nonsaccadic profiles of SCi activity, such as that related to covert orienting of visuospatial attention, also fails to engage the brainstem burst generator.

The SCi Drive to the Head and Body Is Not Gated by OPNs

In addition to projecting to the saccadic burst generator, descending SCi axons in the predorsal bundle issue multiple collaterals to the ventrolateral and dorsomedial reticular formation housing reticulospinal neurons that project down the spinal cord ([Figure 3A](#)) ([Isa and Sasaki, 2002](#); [Scudder et al., 1996](#); [Takahashi et al., 2014](#)). This component of the descending tecto-reticulo-spinal system is involved in the control of orienting head and body movements. Although the visual axis in humans and monkeys can be shifted solely by a saccadic eye movement within a range of $\sim 50^\circ$ – 60° , humans and monkeys typically also move their heads during horizontal gaze shifts larger than $\sim 15^\circ$ ([Stahl, 1999](#); [Tomlinson and Bahra, 1986](#)) and also tend to move their body for movements greater than $\sim 40^\circ$ ([Land, 2004](#); [McCluskey and Cullen, 2007](#)). Stimulation of the SCi evokes coordinated eye-head gaze shifts ([Freedman et al., 1996](#)), and the activity of saccade-related neurons in the SCi encodes the movement of the visual axis in space, rather than the underlying component of the eyes or head ([Choi and Guitton, 2009](#); [Freedman and Sparks, 1997](#)). From the perspective of a sensorimotor transformation, the gaze-related signal encoded at the level of the SCi is subsequently fractionated into the appropriate muscle-based command to move the eyes, head, and body. Exactly how this is done downstream from the SCi remains unclear.

The eyes, head, and body have very different biomechanical properties. For example, the head is a much heavier structure than the eye, and as a consequence of a greater inertial lag, head movements usually start after eye movements during gaze shifts. However, precise electromyographic (EMG) recording of neck muscle activity, which circumvents this inertial lag, shows that the head is not merely slavishly following the eye. Instead, neck muscle recruitment in monkeys and humans can

start with or even well in advance of the command for a saccadic gaze shift (Corneil et al., 2004; Zangemeister and Stark, 1982), suggesting a degree of independence between the issuance of the initiation of eye and head components. Behavioral studies in humans have provided compelling evidence that orienting head movements are initiated while a decision to shift gaze can still be withheld (Corneil and Elsley, 2005; Goonetilleke et al., 2010). Pairing neck EMG recordings with either extracellular stimulation or recording has reinforced this perspective: stimulation of the SC, FEF, or SEF evokes neck EMG responses or head movements that begin well in advance, or even independent, of any evoked saccade (Chapman et al., 2012; Corneil et al., 2002, 2010; Pélisson et al., 2001). The low-frequency activity characteristic of visuomotor SCi neurons can also recruit neck muscles and head movements well in advance of a saccadic gaze shift (Rezvani and Corneil, 2008).

One explanation of these findings is that the OPNs, which as noted above potentially inhibit the saccadic burst generator, do not exert similar inhibition on head premotor structures. Because of this, the premotor elements for head control are paradoxically more, not less, responsive to inputs from the SCi, despite the head's larger inertia. This concept of *selective inhibition*, by which we mean that the OPN inhibition on the brainstem burst generator is not applied to the head, received experimental support in monkeys by findings showing that electrical stimulation of the OPN region can brake or delay saccadic gaze shifts without systematically slowing or delaying an accompanying head movement (Gandhi and Sparks, 2007). Although OPNs in cats do project onto reticulospinal neurons (Grantyn et al., 2010), a portion of the drive to the head in cats does appear to escape OPN inhibition (Paré and Guitton, 1998).

To illustrate one implication of selective inhibition, consider the functional consequence of the visual response issued by visuomotor neurons in the SCi, carried along the predorsal bundle. With the notable exception of express saccades (see above), potent OPN inhibition prevents such visual signals from driving the saccadic burst generator (Munoz et al., 2000). However, the same visual signals can elicit time-locked, short-latency (<100 ms) recruitment of a neck muscle synergy that serves to turn the head toward the visual target (Corneil et al., 2004). We show such recruitment from the neck muscle of a monkey (middle row of Figure 3B); note how neck muscle activity increases or decreases <100 ms after the presentation of ipsilateral (blue trace) or contralateral (red trace) visual targets, respectively. This visual response on the neck begins ~10 ms after the visual response in SCi visuomotor neurons (top row of Figure 3B), presumably because of the time needed for signals to propagate through the circuit shown in Figure 3A (Rezvani and Corneil, 2008). The visual response on the neck is essentially the motor program for a reflexive “express” head movement that is present on every trial, regardless of the timing of the accompanying saccade. Importantly, while the timing of the visual response on the neck is constant from trial to trial, the magnitude of recruitment during the visual burst varies inversely with the saccadic reaction time (Corneil et al., 2004). Such an inverse relationship is also seen in the magnitude of the visual response on visuomotor neurons in the SCi and the ensuing saccadic reaction time (Fecteau et al., 2004; Marino et al., 2012; White et al., 2009).

OPN inhibition also appears to be absent on the body and limb component of the orienting reflex, although this has not been as well studied as the head. The targets of descending projections from the SCi include centers housing reticulospinal or propriospinal neurons that project further down the spinal cord (Alstermark and Isa, 2012; Illert et al., 1978; Werner et al., 1997), primarily targeting axial muscles of the torso or proximal limb muscles. Consistent with this anatomy (Figure 3A), electrical stimulation of the SCi also evokes body and limb motion in cats or monkeys (Courjon et al., 2004; Hess et al., 1946; Philipp and Hoffmann, 2014), and a subset of SCi neurons in monkeys are related to limb motion and limb muscle activity either with or without saccadic eye movements (Stuphorn et al., 2000; Werner et al., 1997). Overall, these results are consistent with a role of the SC in body orientation, which has ecological relevance for quadrupedal animals, as well as in reaching and eye-hand coordination.

A subset of the arm-related neurons in the SCi in the monkey also displays visual responses (Werner et al., 1997). A recent study of limb-muscle recruitment in humans demonstrated that proximal limb muscles can also display visual responses (bottom row of Figure 3B) (Pruszynski et al., 2010). As with the visual responses reported on neck muscles in monkeys, visual responses on human limb muscles arise at extremely short latencies (<100 ms), regardless of the ensuing limb reaction time, and the magnitude of recruitment during this visual response covaried inversely with the reaction time of a reach movement to the visual target (Pruszynski et al., 2010). Recruitment along the polysynaptic tecto-reticulo-spinal pathway may also underlie the extremely rapid online corrections of limb motion that can occur at near-reflexive latencies in cats, monkeys, and humans (Fautrelle et al., 2010; Perfiliev et al., 2010).

One of the surprising conclusions reached by recent detailed studies on neck or limb recruitment is that the first wave of recruitment can be stimulus locked at reflexive latencies, even when measurable movement of the eyes, head, or limb begins much later. Such findings speak to the importance of the OPNs, which may have coevolved with the fovea, in usually preventing express saccades. The absence of OPN inhibition on the premotor elements for the head and limb may be beneficial in permitting some “warm up” of these segments prior to the commitment to shift gaze, and an accompanying decrease in the activity of antagonist neck muscles may prevent resistive lengthening contractions (Corneil et al., 2004). Vestibular and spinal reflexes may also negate any retinal slip arising from small motion of the head or limb before a gaze shift. Regardless of its functional purpose, the absence of OPN inhibition on head and limb elements differs dramatically from the potent OPN inhibition on the brainstem burst generator; accordingly, neck or limb recruitment may reflect developing SCi activity well before any gaze shift. We will return to further implications arising from this insight below but first consider how the pupillary component of the orienting response is governed.

The SCi Drive to the Pupil Is Also Not Subjected to OPN Inhibition

Another target of the SCi is the premotor circuitry mediating the pupillary light and darkness reflex (Figure 4A), which together

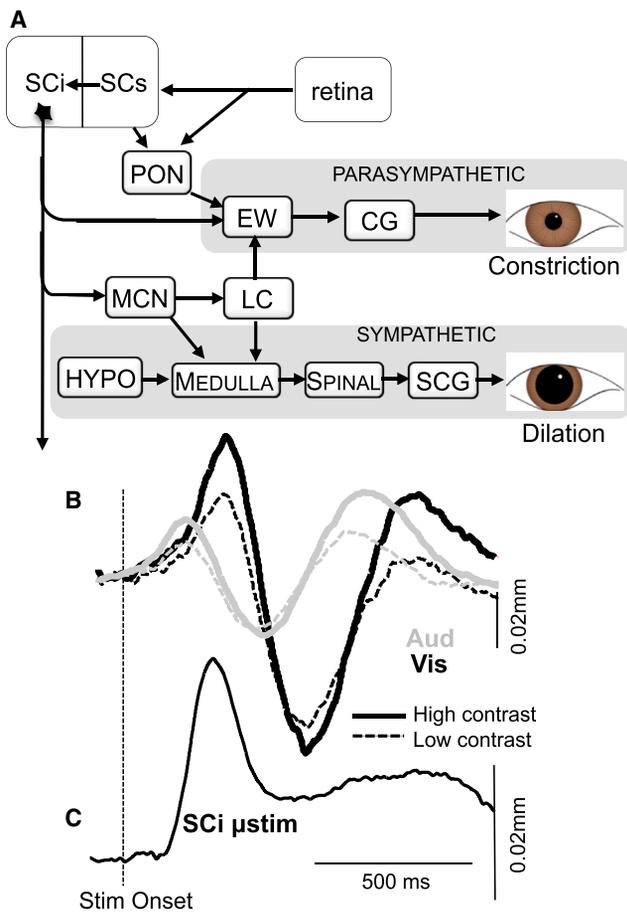


Figure 4. Pupil Response

(A) Circuitry mediating pupil constriction or dilation; note input to this circuit from the SCi.

(B) Effects of contrast on pupil dynamics, for either visual or auditory stimuli (adapted from Wang et al., 2014). Each trace shows the average pupil response to a stimulus presented for 100 ms. Pupil responses to visual stimuli scaled with contrast (high contrast: 13 cd/m²; low contrast: 9 cd/m²). Pupil responses to auditory stimuli scaled with sound intensity (90 or 80 dB, 100 Hz pure tone).

(C) Pupil dilation after subthreshold electrical microstimulation of the SCi resembled the early component of the pupil response to salient stimuli (adapted from Wang et al., 2012). Abbreviations are the following: EW, Edinger-Westphal nucleus; Hypoth, hypothalamus; LC, locus coeruleus; MCN, mesencephalic cuneiform nucleus; PON, pretectal olivary nucleus; SCG, superior cervical ganglion.

serves to regulate pupil size for global luminance levels (Loewenfeld, 1999). The modulation of pupil size is thought to regulate the tradeoff between sensitivity and sharpness for the optimization of image quality on the retina (Campbell and Gregory, 1960; Laughlin, 1992; Leibowitz, 1952). Pupil dilation and constriction are controlled by sympathetic and parasympathetic pathways, respectively (Figure 4A). The parasympathetic pathway underlies illumination-dependent pupil constriction. Information about illumination is carried via retinal ganglion cells that project directly to the pretectal olivary nucleus (PON). PON neurons project bilaterally to the Edinger-Westphal (EW) nucleus (May et al., 2008) that contains the parasympathetic, preganglionic neurons that project to the ciliary ganglion to control pupillary constriction mus-

cles of the iris (Gamlin, 2006). In addition, pupil size is also controlled by the dilator muscle that is innervated by sympathetic nerves from the superior cervical ganglion (SCG), which is driven by a sympathetic circuit originating in the hypothalamus (Loewenfeld, 1999).

The SCi has direct connections to the pupil pathways (Figure 4A). Specifically, the SCi projects directly and indirectly to EW (Harting et al., 1980) and the mesencephalic cuneiform nucleus (MCN) (Huerta and Harting, 1984; May, 2006), a brainstem area regulating stress-related and defensive responses (Dean et al., 1989).

The pupil has long been characterized as an essential component of the orienting response because it is also modulated by salient events in the environment (Lynn, 1966; Sokolov, 1963). The pupil dilates transiently after presentation of salient stimuli (Bala and Takahashi, 2000; Netser et al., 2010; Wang et al., 2014). Figure 4B shows greater pupil dilation with increasingly intense visual stimuli (here, contrast is used as a proxy for salience). These changes are not due to any changes in global luminance because qualitatively similar responses are evoked by loud auditory stimuli (Figure 4B). Although it is assumed that salience-evoked pupil dilation serves to increase visual sensitivity, supporting empirical evidence is lacking (Nieuwenhuis et al., 2010). OPNs do not appear to project to the EW in cats or monkeys (Langer and Kaneko, 1983; Strassman et al., 1987). Consistent with a presumed lack of OPN inhibition on the pupil circuitry, microstimulation of the SCi at current levels below that required to evoke saccades (and therefore silence OPNs) elicited transient pupil dilation in monkeys without any saccades (Wang et al., 2012) (Figure 4C); subsaccadic stimulation of the optic tectum in owls also elicits pupil dilation (Netser et al., 2010). Projections from SCi to EW and MCN may underlie this response either by activating the sympathetic (pupil dilation) pathway, inhibiting the parasympathetic (pupil constriction) pathway, or both. Further, manipulating visual contrast in the monkey modulates both visual responses in the SCi (Marino et al., 2012) and transient pupil dilation (Figure 4B), and as mentioned above pupil dilation can also be induced by presenting auditory stimuli (Wang et al., 2014). Thus, multisensory processing in the SCi (Stein and Meredith, 1993) may also mediate the pupil responses evoked by salient stimuli. Finally, while the robustness of the link between the SCi and salience-evoked pupil dilation remains to be established with recording studies in the monkey, very recent evidence in the owl links aspects of activity in the optic tectum with pupil dilation responses (Netser et al., 2014). Thus, like the neck and shoulder, the SCi has the necessary projections and response properties to modulate salient pupil responses, independent of the OPNs.

Microsaccades: Readouts of the Balance of SCi Activity

Even when the eyes appear to be fixating stably on a target, they are quite often in motion via very small fixational eye movements. One type of fixational eye movement is a microsaccade, which is a small (typically less than 1°) but fast conjugate movement of the eyes. Seminal reviews on the history, function, and neurobiology of microsaccades have been published in recent years (Hafed, 2011; Martinez-Conde et al., 2013; Rolfs, 2009). Microsaccades reduce perceptual fading by refreshing the visual image,

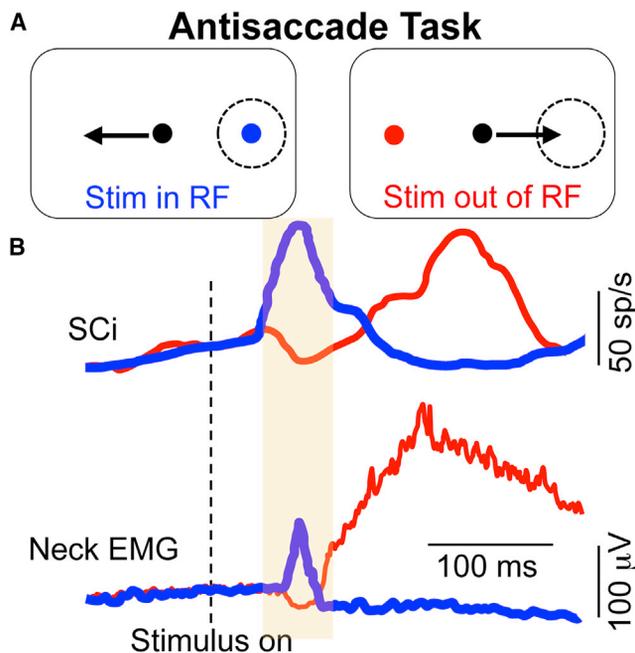


Figure 5. The Antisaccade Task

(A) The antisaccade task requires subjects to look away from a presented stimulus.

(B) Spike density function of an SCi visuomotor neuron and recruitment of a neck muscle, aligned to stimulus presentation. Note in both that the visual response to stimulus presentation (shaded box) in the RF persists, even though the ensuing saccade goes in the opposite direction. In contrast, a brief decrease of activity occurs when the stimulus is presented opposite to the RF, followed by increased activity associated with the saccade into the RF (neck EMG adapted from Figure 4 of [Chapman and Cornel, 2011](#)).

influencing the subsequent processing of visual information throughout the visual pathways ([Martinez-Conde et al., 2013](#)). The rate and directionality of microsaccades can also be altered by task demands ([Ko et al., 2010](#)); hence, microsaccades form an essential part of an oculomotor feedback strategy that aids high-resolution visual processing.

From a mechanistic standpoint, microsaccades are generated by the SCi and brainstem burst generator in the same way as larger saccades. Microsaccades require brief pauses in OPN activity and a mirroring short burst of activity in the appropriate burst neurons ([Brien et al., 2009](#); [Van Gisbergen et al., 1981](#)), which are themselves driven by saccade-related bursts of activity in the rostral SCi encoding foveal locations ([Hafed et al., 2009](#)). One hypothesis regarding the role of the rostral SCi is that the balance of activity across both SCi determines eye position during stable fixation. Prior to microsaccades, this balance becomes transiently perturbed ([Goffart et al., 2012](#)), perhaps because of an endogenous oscillation ([Hafed and Ignashchenkova, 2013](#)). This equilibrium hypothesis is consistent with the random distribution of microsaccade directions during fixation and with the alterations in the distribution of microsaccades following inactivation of the rostral SCi ([Hafed et al., 2009](#)).

The presentation of a sudden visual stimulus alters the production and metrics of microsaccades: the overall probability of microsaccade occurrence drops ~100–150 ms after presen-

tation of a salient visual or auditory stimulus, but any rare microsaccades that are generated in this interval tend to be biased in the direction of the stimulus ([Engbert and Kliegl, 2003](#); [Hafed and Clark, 2002](#); [Pastukhov and Braun, 2010](#)). A recent model of the role of the SCi in microsaccade generation has provided a novel explanation of these results ([Hafed and Ignashchenkova, 2013](#)), suggesting that those few microsaccades that are biased toward a cue were advanced enough to escape the reset of an oscillatory mechanism. Consistent with the equilibrium hypothesis discussed above, the metrics of such cue-directed microsaccades reflect a balance of activity between the rostral SCi and the representation of the peripheral visual stimulus in the more caudal SCi ([Hafed and Ignashchenkova, 2013](#)). Although microsaccades are governed by the OPNs in the same way as larger saccades, the spatiotemporal evolution of microsaccades, for example after peripheral stimulus presentation, can reflect aspects of SCi activity even if a larger saccade is not executed. The insights into SCi activity that can be gained through an examination of microsaccades can parallel the insights that can be gained via measurements of neck or limb muscle activity or pupil dilation, but note that neck or limb muscle activity or pupil dilation are continuous measures, whereas microsaccades are discrete events.

Up to now, we have focused on why different components of the orienting response can be separated from saccadic output due to selective inhibition on OPNs, particularly following presentation of a single visual stimulus. These results provide tantalizing hints about a potential relationship between SCi activity and nonsaccadic components of the orienting response that may be accessible well before saccade generation. Because of the linkages between the SCi and cortical regions that provide cognitive control, it is possible that cognitive processes that engage the SCi may percolate through to those effector systems that avoid the OPN gate. We now explore whether the concept of selective inhibition on OPNs extends to progressively more complicated tasks, focusing on results where the profile of SCi activity has been well-established in behaving monkeys. While not every nonsaccadic measure has been made in every experiment, it is becoming increasingly clear that nonsaccadic components of the orienting response may provide unique opportunities for direct quantification of cognitive processing within the oculomotor system.

Sensorimotor Transformations and Representation of Task Set during the Antisaccade Task

The antisaccade task requires that subjects look away from a visual stimulus to the diametrically opposite location ([Figure 5A](#); [Munoz and Everling, 2004](#)). This task requires suppression of the automatic orienting response to the stimulus and the transformation of stimulus encoding in one hemisphere into an oculomotor command in the other hemisphere. The neural correlates of this sensorimotor transformation have been recorded in the SCi ([Everling et al., 1999](#)) and FEF ([Everling and Munoz, 2000](#)); in both structures, the visual response to stimulus presentation develops on one side, but saccade-related activity is generated on the other side ([Figure 5B](#), top row).

The antisaccade task provides a simple platform to test the concept of selective inhibition of OPNs on portions of the

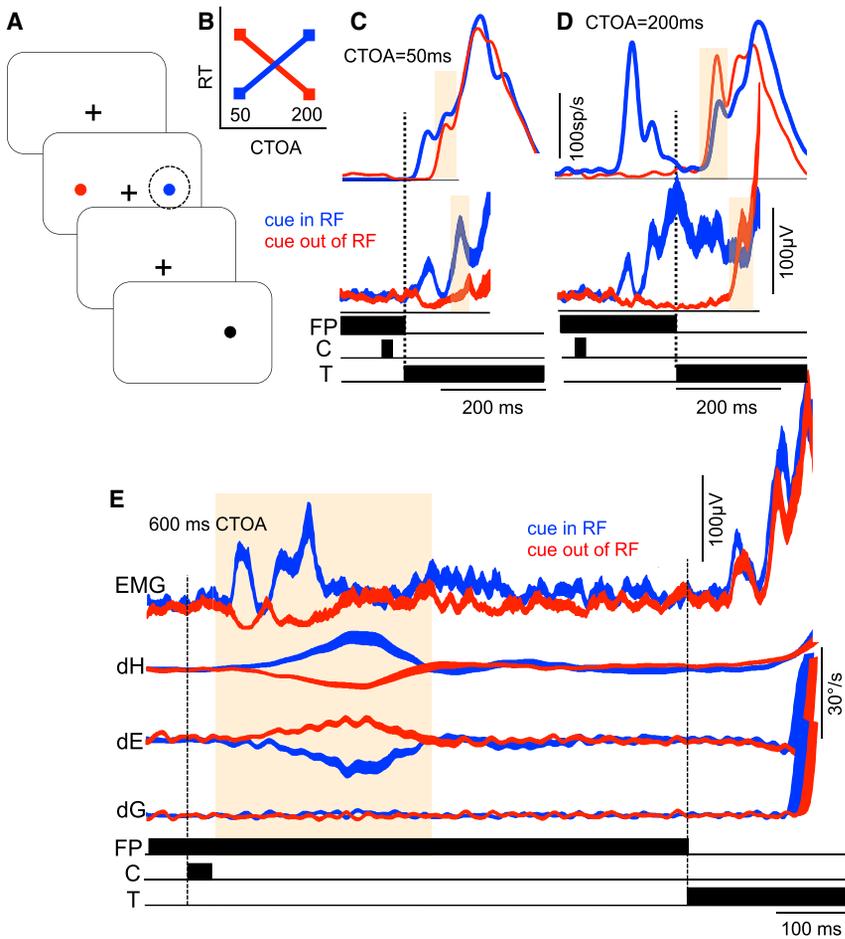


Figure 6. The Cueing Task

(A) The cueing task, in which a peripheral cue is presented at the same (a valid cue) or opposite (an invalid cue) location as a future target (cue-target onset asynchrony [CTOA]). The cue is usually the same color as the target but is shown here as different colors to represent cue validity.

(B) Reaction times (RTs) to the target vary depending on the CTOA and the side of the cue relative to the target.

(C and D) Spike density function of an SCi visuo-motor neuron (top) and neck muscle recruitment (bottom) during the 50 and 200 ms CTOA conditions for target presentation into the response field, segregated for cue and target in RF (blue traces) or cue out of RF and target in RF (red traces). Note increased SCi activity and neck muscle recruitment following cue presentation. Shaded boxes in (C) and (D) highlight the visual response to the target, which depends on cue side and CTOA and correlates to the RT.

(E) Neck muscle recruitment and velocities of head (dH), eye-in-head (dE), and gaze (dG) for the 600 ms CTOA condition (SCi activity not shown for brevity). Note how cue presentation elicits a small orienting head movement that is compensated for by eye-in-head motion in the opposite direction to keep gaze stable on the fixation point. SCi activity adapted from Figure 3 of Fecteau et al. (2004); neck EMG and movement traces adapted from Figures 1 and 2 of Corneil et al. (2008).

descending SCi signal. On correct antisaccade trials, the initial visual response conveyed by the SCi on one side does not recruit the brainstem burst generator. Recordings of neck muscle activity in monkeys performing this task revealed that the visual response on the neck persists, even though such a visual response encodes a head movement in the wrong direction (Figure 5B, bottom row) (Chapman and Corneil, 2011). Following the visual response on the neck, movement-related activity develops that moves the head in the correct direction. If the head is free to move, the visual response on the neck produces very subtle head motion in the wrong direction (Chapman and Corneil, 2011), with gaze remaining stable because of the actions of the vestibulo-ocular reflex.

Correct performance in the antisaccade task also requires the correct task set, as subjects need to prepare to generate an antisaccade before stimulus presentation. Correlates of the task set to prepare for a prosaccade (where the subject looks to the stimulus) or antisaccade are seen throughout the oculomotor system. In the SCi, preparation for an antisaccade is associated with increased activity in the rostral SCi and an accompanying decrease in activity in the caudal SCi (Everling et al., 1999). Such rebalancing of SCi activity makes the subject less prone to the generation of antisaccade errors, wherein the subject incorrectly looks to the peripheral stimulus (i.e., generates a

prosaccade on an antisaccade trial). Correlates of task set are also seen in the activity of neck muscles, with smaller levels of neck EMG activity preceding antisaccades (Chapman and Corneil, 2011, 2014). Correlates of task set are also seen in the temporal profile of microsaccades preceding stimulus presentation, with a decreasing rate of microsaccades accompanying the consolidation of the antisaccade instruction (Watanabe et al., 2013), consistent with the equilibrium hypothesis (Goffart et al., 2012) for microsaccade generation noted above. Impressively, both neck muscle activity and microsaccade rate can predict subject performance before stimulus onset; for both measures, the levels attained before antisaccade errors resemble that observed before prosaccades, reinforcing how these measures reflect task set.

Visuospatial Attention and Cueing Tasks

Another behavioral paradigm that has been used extensively to investigate both neurophysiology and a variety of motor actions is the cueing task (Posner and Cohen, 1984). In this task (Figure 6A), subjects maintain fixation during the brief presentation of a cue and then look to a target presented coincident with the disappearance of a central fixation point (see Klein, 2000 for review). In both monkeys and humans, the reaction time of a response to the target is a function of both cue position relative to the target (a valid or invalid cue is presented at the same or opposite location of the target, respectively), the probability of the cue predicting the target (cue validity), and the timing of the cue relative to the target (the cue-target onset asynchrony

[CTOA]) (Figure 6B). If the cue does not predict subsequent target location, reaction times are shorter for valid versus invalid cues at short CTOAs (i.e., 50 ms CTOA; this has been termed attention capture [Jonides et al., 1981]) but longer for valid versus invalid cues at longer CTOAs (i.e., 200 ms CTOA; this has been termed inhibition of return [Posner et al., 1985]).

This cueing paradigm provides a controlled means for investigating the influence of the cue on the processing of the subsequent target and also for investigating how this influence changes with manipulations of cue validity. Recordings of SCi visuomotor neurons show that cue presentation induces a robust visual response for stimuli presented in the neuron's response field, followed by a period of more sustained activity that persists to the time of target presentation (Figures 6C and 6D) (Fecteau et al., 2004). The subsequent phasic visual response to the target is accentuated for CTOAs associated with attention capture (i.e., 50 ms) but muted for CTOAs associated with inhibition of return (i.e., 200 ms; shaded rectangles in Figures 6C and 6D; Fecteau et al., 2004). Neck muscle recruitment in this task follows the same profile (Figures 6C and 6D) (Corneil et al., 2008), emphasizing once again how closely neck muscle recruitment parallels the activity of SCi visuomotor neurons, even well before saccade onset.

Perhaps the most intriguing observation was made when the monkey's head was unrestrained on trials with longer CTOAs (i.e., 600 ms CTOA): in this configuration, cue presentation elicited a subtle head turn toward the cue, but gaze remained stable upon the central fixation point due to the vestibulo-ocular reflex (Figure 6E) (Corneil et al., 2008). Clearly in this situation, overt orienting of the head occurred during the presumed covert capture of visuospatial attention.

The spatiotemporal profile of microsaccades also changes substantially in a cueing task. Microsaccade rate drops soon after cue onset in cueing tasks, but the few microsaccades that do occur after cue onset are biased systematically toward the cue (Engbert and Kliegl, 2003; Hafed and Clark, 2002). The link between SCi activity and microsaccade propensity has also been demonstrated in a different behavioral task that dissociated the locus of attention from saccade preparation (Lovejoy and Krauzlis, 2010). In this task, monkeys deployed visuospatial attention to a cued location in space and then used a motion stimulus presented at that location to direct a subsequent saccade to a different location (e.g., a motion stimulus presented at a right-up location could instruct the monkey to look left-down). As in humans, monkeys generated fewer microsaccades after cue presentation, but any microsaccades that were generated were biased toward to the cue (Hafed et al., 2011). Moreover, microsaccade tendencies correlated with overall performance: trials with microsaccades directed toward the cued location were performed correctly more often than trials with microsaccades directed away from the cue. Microsaccade propensity also decreased near the end of the trial, perhaps to ensure retinal stability just prior to the instructive motion stimulus. Decreases in microsaccades at critical time intervals have also been reported in humans in other tasks (Pastukhov and Braun, 2010; Poletti and Rucci, 2010). Finally, inactivation of that portion of the caudal SCi encoding the peripheral visual cue disrupted the tendency for microsaccades to be directed toward the cue; instead, they

tended to beat in the opposite direction (Hafed et al., 2013). Overall, these results reinforce the role played by the SCi in linking microsaccades and the covert allocation of visuospatial attention.

Cueing tasks have also been used to examine the changes in pupil size during covert attention. For example, two recent studies have shown differential pupil responses during the covert allocation of visuospatial attention to bright or dim stimuli (Binda et al., 2013; Mathôt et al., 2013). In the latter study, the size of the effect of attention on the pupil predicted the behavioral benefit of the cue; subjects with larger pupil response differences to bright versus dim stimuli tended to react sooner on validly versus invalidly cue trials. Such findings fit in with a growing literature relating measures of pupil size to a variety of cognitive processes (Eldar et al., 2013; Nassar et al., 2012). The neural substrate that mediates the relationship between cognitive states and pupil dilation is unknown, but the locus coeruleus (LC)-norepinephrine system is regularly implicated (Aston-Jones and Cohen, 2005). The functional implications of cognitively mediated changes in pupil size on subsequent visual processing remains to be determined. Nonetheless, there is the intriguing possibility that, like microsaccades, changes in pupil size driven by task demands or bottom-up saliency may help optimize detailed processing of incoming visual signals.

Cortical Inputs

Returning to Figure 1, we now consider the role played by cortical inputs to the SCi, focusing primarily on the FEF. Like the SCi, the FEF is also recognized for having important roles in both saccade production via inputs to the brainstem and numerous cognitive processes, including the covert allocation of visuospatial attention, via feedback projections to extrastriate cortex (for review, see Squire et al., 2013). The spatial locus of visuospatial attention can be manipulated experimentally by electrically microstimulating the oculomotor system at subthreshold levels insufficient to evoke saccades. This has been done in monkeys using electrical microstimulation in the SCi (Cavanaugh and Wurtz, 2004; Müller et al., 2005) or the frontal eye fields (FEFs) (Moore and Fallah, 2001), in owls via electrical microstimulation of the FEF homolog (Winkowski and Knudsen, 2006), and in humans via transcranial magnetic stimulation (TMS) of the FEF (Grosbras and Paus, 2002). The behavioral and neurophysiological consequences of such stimulation are very similar to those elicited by voluntary shifts of visuospatial attention.

Both electrical microstimulation and TMS are coarse methods of activation that cannot selectively activate feedforward or feedback pathways. In light of the concept of selective inhibition of OPNs only on the saccadic system, what are the effects of subsaccadic levels of stimulation on the other, nonsaccadic, components of the orienting response? As mentioned above, subsaccadic microstimulation of the SCi in monkeys can induce neck muscle recruitment and head movements (Corneil et al., 2002; Pélisson et al., 2001) and can also induce pupil dilation (Wang et al., 2012). Consistent with the strong projections from the FEF to the SCi, subsaccadic levels of stimulation current to the FEF in monkeys can also evoke neck muscle recruitment and head movements in a very similar manner (Corneil et al., 2010). In humans, TMS of the FEF can also evoke a neck muscle

response (Goonetilleke et al., 2011). Furthermore, in both humans and monkeys larger neck muscle responses are evoked if the stimulated area is more actively engaged at the time of stimulation, meaning that evoked neck muscle responses can probe the engagement of the oculomotor system (Chapman and Corneil, 2014; Corneil et al., 2007; Goonetilleke et al., 2011). Because of this, and because subsaccadic microstimulation does not evoke a saccade, neck muscle responses evoked by precisely timed microstimulation can be used to construct a time course of how the engagement of the oculomotor system evolves during a behavioral task. While it remains to be determined whether cortical stimulation can also induce pupil dilation, a particularly exciting possibility is how well this line of thinking could generalize to humans, perhaps offering direct measures of oculomotor engagement at a temporal resolution usually reserved for neurophysiological studies in animals.

Conclusions and Future Directions

A central consideration throughout this Review has been the differential downstream processing of the signals carried by tectoreticulo-spinal neurons. We have placed particular emphasis on the concept of selective inhibition on OPNs on downstream saccadic circuits, but not on the other components of the orienting response. In this regard, OPNs enforce a binary nature to saccade control, perhaps because of the demands of foveal vision, which is unique throughout the body. Other effectors, including those involved in the orienting response, are not so tightly controlled. The apparent lack of OPN inhibition of everything but the saccadic premotor circuits is all the more important given the widespread collateralization of tectoreticulo-spinal neurons.

We foresee a number of important different directions for future research. Most immediately, it is apparent that a wealth of information is available in continuous recordings of other components of the orienting response at the neck, limb, and pupil. Such measures may provide online reflections of oculomotor activity well in advance of saccades but more work needs to be done to determine the neurobiological links between these measures and with cortical and subcortical oculomotor activity, and with an eventual saccade that may be executed. Such research is calling into question the very concept of a strict distinction between covert and overt forms of orienting, as what would be classified as covert orienting due to the lack of a saccade may nevertheless produce overt recruitment at other effectors. Examinations of microsaccade propensity and metrics also offer additional insights into developing oculomotor programs in a more probabilistic manner.

Much of the work cited in this Review has employed relatively simple behavioral paradigms that fail to capture the complexity and richness of the natural environment. As the oculomotor system evolved to operate in the real world, a full appreciation of its properties and capabilities requires more realistic stimuli and the opportunity to engage in more naturalistic behaviors. This is no small challenge, particularly given the experimental expediency afforded by restraining the head and body. Recent work examining microsaccades during more complex visual stimuli (Rucci et al., 2007) or during more challenging tasks (Ko et al., 2010) has led to a growing appreciation these movements play in not

only refreshing the retinal image, but also as part of a motor-to-sensory that optimizes visual foraging. Recognition of the potential ways in which microsaccades, pupil dilation, and head movements alter the retinal image, and how these movements change during a task or with the allocation of visuospatial attention, will also be critical for recording experiments in striate and extrastriate cortices. Embracing more naturalistic paradigms and behaviors also promises to reveal more about the ways in which the various components of the orienting response can be controlled in different contexts. For example, gaze direction is a powerful social cue in primates, and eye contact is of utmost importance in social interactions as a sign of dominance. Submissive primates probably employ a strategy to accrue the benefits of covert orienting without necessarily shifting the line of sight, but how this is done remains unknown.

Finally, eye movements have long served as a key diagnostic indicator in neurological health and disease (Leigh and Kennard, 2004; Leigh and Zee, 2006). In parallel with continuing methodological advances in eye tracking that sensitively track microsaccades and pupil dilation, opportunities are becoming available to quantitatively assess diseases and therapies in novel ways. Measures of microsaccades, pupil dilation, and neck and limb muscle recruitment could provide the next generation of biomarkers in health and disease by virtue of the absence of OPN inhibition. For example, in basal ganglia disorders like Parkinson's disease (Cameron et al., 2010) or Huntington's disease (Peltsch et al., 2008), there are changes in voluntary saccade performance that are presumably attributable to changes in the inhibitory drive to the SCi from the substantia nigra pars reticulata. Subtle changes of processing in the SCi as a result of changes in basal ganglia function may manifest on other nonsaccadic components of the orienting response like pupil dilation, microsaccades, and neck and limb recruitment. Careful, noninvasive measurements of such nonsaccadic components may provide a rich source of insights into normal or abnormal covert processes.

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