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An integrative role for the superior colliculus in selecting targets for movements

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Wolf AB, Lintz MJ, Costabile JD, Thompson JA, Stubblefield EA, Felsen G. An integrative role for the superior colliculus in selecting targets for movements. J Neurophysiol 114: 2118–2131, 2015. First published July 22, 2015; doi:10.1152/jn.00262.2015.—A fundamental goal of systems neuroscience is to understand the neural mechanisms underlying decision making. The midbrain superior colliculus (SC) is known to be central to the selection of one among many potential spatial targets for movements, which represents an important form of decision making that is tractable to rigorous experimental investigation. In this review, we first discuss data from mammalian models—including primates, cats, and rodents—that inform our understanding of how neural activity in the SC underlies the selection of targets for movements. We then examine the anatomy and physiology of inputs to the SC from three key regions that are themselves implicated in motor decisions—the basal ganglia, parabrachial region, and neocortex—and discuss how they may influence SC activity related to target selection. Finally, we discuss the potential for methodological advances to further our understanding of the neural bases of target selection. Our overarching goal is to synthesize what is known about how the SC and its inputs act together to mediate the selection of targets for movements, to highlight open questions about this process, and to spur future studies addressing these questions.

decision making; motor planning; substantia nigra; pedunculopontine tegmental nucleus; laterodorsal tegmental nucleus

ELUCIDATING THE NEURAL MECHANISMS of decision making is a fundamental goal of neurobiology (Glimcher 2003; Gold and Shadlen 2007; Hikosaka et al. 2014; Sugrue et al. 2005). Among the many forms of common decisions, one that is both critical for survival and amenable to study across a range of model systems is the process of selecting a spatial target for movement from among several alternatives (Wolpert and Landy 2012). Targets—considered here as the spatial locations themselves—for movements are selected based on several sensory and nonsensory factors, including stimulus input, the learned value associated with each target (e.g., based on previous experience), and internally generated goals (Gold and Shadlen 2007). Understanding how and where these factors are integrated in the nervous system in order to select a target for movement is an active area of research.

Accumulating evidence points to the mammalian superior colliculus (SC) playing an important role in the selection of spatial targets for movement, particularly when cued by sensory stimuli (Krauzlis et al. 2004). While we focus here on the mammalian SC, the analogous structure in other vertebrates, the optic tectum, serves a similar function (Dutta and Gutfreund 2014; Mysore and Knudsen 2011; Nevin et al. 2010). The SC is a midbrain structure composed of seven distinct cytoarchitectonically defined layers and can be divided into superficial and deep functional subdivisions. While the superficial subdivision receives visual input, the deep subdivision of the SC—comprising the gray and white sublayers of the intermediate and deep layers of the SC—receives somatosensory, auditory, and visual input and is a source of commands to downstream reticular premotor nuclei that contribute to the production of coordinated orienting movements to spatial tar-
getis (King 2004; Sparks and Hartwich-Young 1989). Critically, the deep subdivision of the SC also receives input from a wide range of cortical and subcortical structures (Edwards et al. 1979; Fries 1984; Sparks and Hartwich-Young 1989). Therefore, the SC is well positioned to serve as a functional hub in the interconnected network of brain regions underlying the integration of multisensory and contextual information in order to select a target for orienting movements (Platt et al. 2004; Stein and Rowland 2011). Examining how this integration occurs is important in its own right for understanding goal-directed behavior, and can also serve as a model for studying how multiple brain regions can work together to process information and transform neural representations.

An exhaustive examination of every functional input to the SC would be beyond the scope of this review. Instead, after first describing intrinsic SC processing underlying target selection for movement, we focus on three inputs that have been examined in the context of their influence on intrinsic SC processing: GABAergic input from the substantia nigra pars reticulata (SNr), cholinergic input from the parabrachial region [primarily composed of the pedunculopontine tegmental nucleus (PPTg) and laterodorsal tegmental nucleus (LDTg)], and glutamatergic input from neocortical regions (Fig. 1A). These three projections converge anatomically in discrete zones in the deep subdivision of the SC (Fig. 1B; Illing and Graybiel 1985), suggesting that they may play complementary functional roles. We discuss below the data and theories bearing upon these roles. It is our hope that this review, by synthesizing data from a range of studies to provide a comprehensive description of what is currently known about how the SC and its inputs select targets for movements, will stimulate future study in this field.

Activity in Superior Colliculus Underlying Selection of Targets for Movements

While early recordings in head-fixed primates established a clear relationship between activity in specific regions of the deep subdivision of the SC and the initiation of saccadic eye movements to specific locations in the contralateral visual field (Goldberg and Wurtz 1972a, 1972b; Lee et al. 1988; Wurtz and Goldberg 1972), subsequent work demonstrated that SC activity was not particularly related to saccades but to orienting movements in general (Sparks 1999). Specifically, the SC seems to similarly encode spatial targets for multistep saccades (Bergeron et al. 2003) and smooth eye movements (Carello and Krauzlis 2004; Krauzlis 2004; Missal et al. 1996). In addition, SC activity represents orienting movements of the head and body (Corneil et al. 2002; Felsen and Mainen 2008; Freedman et al. 1996; Gandhi and Katnani 2011; Guillaume and Pélisson 2001; Walton et al. 2007) as well as of the limbs (i.e., reaching movements; Courjon et al. 2004; Philipp and Hoffmann 2014; Werner et al. 1997), although the topographic organization within the SC of targets for these forms of movements may be less precise than it is for eye movements (Gandhi and Katnani 2011; Philipp and Hoffmann 2014; Walton et al. 2007). While the SC has been most intensively studied in the context of visuomotor transformations, it has been shown to mediate responses to nonvisual inputs as well (Aronoff et al. 2010; Bajo et al. 2010; Felsen and Mainen 2008; Groh and Sparks 1996; Jay and Sparks 1987). Together, this body of work demonstrates that the SC is critical for initiating coordinated orienting movements to targets, independent of the specific motor groups involved and independent of sensory modality.

This role is consistent with traditional cognitive theories positing that separate brain regions mediate the selection and initiation of actions in a serial fashion (Miller et al. 1960). Under this view, input to the SC would specify the target for movement and the SC would contribute to the coordination of the desired movement via its well-described downstream motor projections (Dean et al. 1989; Gandhi and Katnani 2011). However, much experimental and theoretical work has suggested that, in organisms engaged in continually sensing and acting on their environment, these processes may be mediated in parallel by overlapping sets of brain regions (Cisek 2007; Cisek and Kalaska 2010; Gold and Shadlen 2000; Hernandez et al. 2002). Consistent with this view, and extending it to subcortical structures, many studies have suggested that the SC is involved in selecting spatial targets for movements as well as...
Early work addressing target selection in the SC extended the classic head-fixed primate paradigm to focus on activity during an enforced delay period preceding saccade initiation, during which the direction of upcoming movement is known and can be prepared (Glimcher and Sparks 1992). Such “prelude” activity, displayed by “buildup” neurons, typically exhibits as a modest increase during the delay period, leading to a burst of activity at the time of contraversive saccade initiation (Fig. 2; Dorris et al. 1997; Mays and Sparks 1980; Munoz and Wurtz 1995). The fact that the prelude activity occurs well before the saccade is initiated and predicts its direction provided a first indication that it may be playing a role beyond movement initiation. Indeed, manipulation of SC activity has been shown to predictably bias target selection even in the absence of an effect on overt movements (Carello and Krauzlis 2004; Glimcher and Sparks 1993; Song et al. 2011), consistent with this idea.

Subsequent studies examined prelude activity in the SC using behavioral tasks in which the difficulty of selecting the correct target for movement varied across trials. For example, one set of studies systematically varied the number of potential targets, and therefore the probability that a particular target would be selected. These studies found that the level of prelude activity reflected the probability of selecting the target in the response field of that neuron (Basso and Wurtz 1997, 1998; Dorris and Munoz 1998; Krauzlis et al. 2004; McPeek and Keller 2002a). Other studies varied the strength of the stimulus that cued target selection and found that prelude activity more reliably predicted which target would be selected for stronger stimuli (i.e., easier trials) than weaker stimuli (i.e., more difficult trials). Interestingly, this increased reliability was largely due to a dependence of activity on difficulty for movements away from, but not toward, the preferred target of the neuron. Specifically, for movements away from the preferred target, weaker stimuli elicited relatively high firing rates (Felsen and Mainen 2012; Horwitz and Newsome 2001a; Ratcliff et al. 2007; Thevarajah et al. 2009). Together, these data suggest that prelude activity represents targets for movements that are considered but are not ultimately selected, providing further support for such selection occurring in the SC itself or via its influence on premotor nuclei, as opposed to upstream of the SC.

Given that multiple potential targets for movement are represented in SC activity, what is the mechanism by which only one is ultimately selected? Early studies proposed that the selected target corresponded to a population average weighted by the activity of all active SC neurons, as proposed in other motor systems (Georgopoulos et al. 1982; Sparks et al. 1976). This hypothesis was corroborated by the results of experiments in which inhibiting one population of SC neurons biased the resulting saccade away from the region of space it represented (Lee et al. 1988). However, when spatially segregated targets are considered, distinct populations of SC neurons representing these targets are active, and a population code would predict that an average location between the targets would be selected. Instead, one of the represented targets can be selected, which implies a competition between circuits representing distinct spatial targets (how this competition might be realized neurobiologically is described below). This framework would predict that subtly manipulating the activity of SC neurons representing one target may have a greater influence on target selection as trial difficulty increases, in which activity is increasingly balanced between the competing circuits. Indeed, studies that have manipulated the activity of one group of SC neurons—presumably corresponding to one of the targets—have indeed observed a larger effect on difficult than on easy trials (Fig. 3; McPeek and Keller 2004; Song et al. 2011; Stubblefield et al. 2013; Thevarajah et al. 2009). Other studies have taken advantage of the known topographic representation of target locations in the SC to demonstrate that inactivating neurons representing one location biases target selection away from the inactivated locus (McPeek and Keller 2004; Nummela and Krauzlis 2010, 2011). This idea also applies to the decision to either move to a target or maintain at the current location (Krauzlis et al. 2004): Inactivating neurons in the rostral SC, which represent low-amplitude movements or no movement (i.e., maintaining fixation) (Dorris et al. 1997; Dorris and Munoz 1998; Hafed et al. 2009; Munoz and Wurtz 1992, 1993a), disrupt fixation and result in irrepressible saccades to distal targets (Goffart et al. 2012; Munoz and Wurtz 1993b). In addition, this framework would predict that on more difficult trials activity in competing circuits would be more balanced, leading to a higher likelihood of selecting the incorrect target. This idea was tested by a study that simultaneously recorded activity in four SC neurons in primates performing an oddball detection task in which one neuron represented the location of
the correct target while the other three represented the location of the distractors. Behavioral performance was found to correlate with the difference in prelude activity between the “target” neuron and the “distractor” neurons rather than with the magnitude of activity in either population (Kim and Basso 2008). Together, these inactivation and recording studies establish a clear relationship between representations of spatial targets in the SC and the selection of a spatial target for an orienting movement.

How is this competition mediated? In particular, do competing populations of neurons actively inhibit one another (Dorris et al. 2007; Lo and Wang 2006; Munoz and Fecteau 2011; Munoz and Istvan 1998; Munoz and Wurtz 1993a; Trappenberg et al. 2001) or does their activity “race,” independently, to a fixed threshold (Paré and Hanes 2003; Ratcliff et al. 2007, 2011)? Addressing this question requires closer examination of the role of intrinsic inhibition in the SC in target selection. Presumably, GABAergic SC neurons, which comprise up to 30% of neurons in the SC (Mize 1988, 1992), play a critical role. Anatomical and slice studies have found that these neurons project within and between SC layers and from one SC to the other, and the majority are spontaneously active and fast spiking (Behan and Appell 1990; Sooksawate et al. 2011). Thus these neurons have been thought to potentially provide mutually inhibitory input between regions of the deep subdivision of the SC representing distinct targets. Consistent with this possibility, functional inhibition has been demonstrated in slices (Bayguinov et al. 2015; Lee and Hall 2006; Meredith and Ramoa 1998; Phongphanphonee et al. 2014; Sooksawate et al. 2011), and an in vivo study in primates found that SC neurons representing saccade targets were inhibited shortly after electrical stimulation of either SC (Munoz and Istvan 1998). However, other studies have found no evidence for functional inhibition between competing populations of SC neurons (Ratcliff et al. 2011), and inhibitory influence is less spatially extensive than excitatory influences (Phongphanphonee et al. 2014). This restricted spatial extent of inhibition is not consistent with the requirement for long-range inhibition in winner-take-all models (Trappenberg et al. 2001; White and Munoz 2011); instead the pattern of excitation and inhibition suggests a role in integrating information across the SC. Critically, the function of these GABAergic neurons has not been directly examined in behaving animals, because of methodological obstacles in targeting these neurons for study (although the effect of pharmacologically manipulating GABAergic signaling in the SC has been studied, as described above). Future studies that directly record or manipulate these neurons in vivo—for example, with cell type-specific tools such as optogenetics (Cardin 2012) or chemogenetics (Urban and Roth 2015)—have the potential to determine the functional role of intrinsic inhibition in the SC and advance our understanding of how targets are selected for movement.

Thus questions remain about how intrinsic SC activity underlies the selection of targets for movements. It is even possible that SC activity reflects an abstract “priority map” for target selection rather than the competition, discussed above, between circuits representing distinct targets (McPeek and Keller 2002b; Song et al. 2011). In addition, the SC receives input from numerous brain regions, and little is known about how this input influences processing within the SC. In the following sections, we examine how three of these regions—the SNr, the parabrachial region, and the neocortex (Fig. 1)—contribute to target selection via their input to the SC.

GABAergic Input to Superior Colliculus from Substantia Nigra Pars Reticulata

In general, the basal ganglia are thought to control movement initiation via phasic release from tonic inhibition of downstream motor structures (Gulley et al. 2002; Mink 1996; Mink and Thach 1993); we refer to this idea as the “disinhibition model.” The GABAergic projection from the SNr to the SC mediates basal ganglia control of orienting movements to spatial targets (Hikosaka et al. 2006; Utter and Basso 2008). Accordingly, some of the first studies of SNr activity, SC activity, and orienting movements were consistent with the disinhibition model: In tonically active nigroreticular neurons in primates and cats, a decrease in activity corresponded to a burst of activity in the ipsilateral SC and the initiation of a contraversive orienting movement (Hikosaka and Wurtz 1983; Joseph and Bousaoud 1985). A similar relationship between the activity of SNr and tectospinal SC motor output neurons was observed in rats (Chevalier et al. 1985). Projections of the nigroretical pathway are segregated in a manner similar to the organization of the output channels from the striatum to the SNr (Deniau and Chevalier 1992; Redgrave et al. 1992; Williams and Faull 1985). These studies suggest a simple serial process by which specific striatontigeral neurons inhibit specific nigroreticular neurons, which control the initiation of orienting movements to spatial targets (Hikosaka et al. 2000). However, several pieces of evidence complicate this view and suggest that SNr input to the SC may play a broader role in motor control, perhaps including the selection of targets for orienting movements (Basso and Sommer 2011; Deniau et al. 2007; Shires et al. 2010).

One set of studies focused on the relationship between SNr activity and orienting movements. These studies showed that the activity of many SNr neurons is modulated well before movement initiation (Handel and Glimcher 1999), depends on the magnitude of reward associated with the movement...
(Bryden et al. 2011; Handel and Glimcher 2000; Sato and Hikosaka 2002), and depends on the number of potential targets for movements (Basso and Wurtz 2002). Notably, SNr activity was often found to increase preceding (and even during) contralateral movement initiation (Fig. 4A; Gulely et al. 2002; Handel and Glimcher 1999; Lintz and Felsen 2014; Sato and Hikosaka 2002). In addition, microstimulating SNr neurons had a greater effect on saccades to remembered targets than on visually guided saccades (Basso and Liu 2007), particularly when the stimulation occurred during the delay period preceding saccade initiation (Mahamed et al. 2014). Thus the relationship between SNr activity and contraversive orienting movements is more complicated than the disinhibition model would predict.

A second set of studies suggesting a broader role for SNr input to the SC examined the anatomy and physiology of this input. First, while the disinhibition model is based on ipsilaterally projecting (i.e., “uncrossed”) nigrostriatal neurons, some (“crossed”) nigrostriatal neurons project contralaterally (Beckstead et al. 1981; Chevalier et al. 1981; Deniau et al. 1977; Gerfen et al. 1982; Jayaraman et al. 1977; Liu and Basso 2008) and a small number project to both SCs (Cebrián et al. 2005). Given that crossed nigrostriatal projections are also inhibitory, they would appear to promote movements ipsiversive to the phasically inactivated SNr, inconsistent with the disinhibition model. Second, in addition to the influence of SNr activity on bursting SC neurons that initiate movements (Hikosaka and Wurtz 1983), SNr input modulates the activity of buildup SC neurons (Liu and Basso 2008) thought to subserve the selection of targets for movement (but see Corniel et al. 2007). Finally, uncrossed nigrostriatal neurons project to GABAergic SC neurons—which, as discussed above, may mediate the interaction between SC circuits representing competing movements—as often as they project to glutamatergic SC neurons (Kaneda et al. 2010), further suggesting a broader role for the SNr than simple disinhibition.

Given these findings, how might input from the SNr modulate SC activity underlying the selection of orienting movements? Can these findings be reconciled with the idea that the SNr controls motor output via phasic release from tonic inhibition? One possibility is that the diversity of SNr activity preceding movement can be explained by the diversity of downstream targets of SNr neurons. SNr neurons project to several motor-related regions besides the SC, including the thalamus and the PPTg (Saitoh et al. 2003; Utter and Basso 2008), as well as nonmotor regions such as the substantia nigra pars compacta (Pan et al. 2013; Saitoh et al. 2004; Tepper et al. 1995). The range of activity profiles observed in SNr may reflect the distinct roles of these downstream pathways. Even within the nigrostriatal projection, the targeted SC (ipsilateral or contralateral to the source of the projection) may explain why the activity of some SNr neurons increases, while the activity of others decreases, preceding identical movements. Specifically, a crossed nigrostriatal neuron exhibiting an increase in activity, and an uncrossed nigrostriatal neuron exhibiting a decrease in activity, would promote the common goal of contraversive movement (relative to the side of the SNr). This idea is supported by a study in cats that found that the activity of crossed nigrostriatal neurons increases, while the activity of uncrossed neurons decreases, in response to visual stimuli (Jiang et al. 2003). Similarly, it is possible that the activity profile relates to the type of neurons (e.g., glutamatergic or GABAergic) to which the SNr neuron projects. Given that some neurons have complex activity profiles that change during the course of the trial (Handel and Glimcher 1999), it may be the case that individual neurons contribute to multiple aspects of motor control, including selecting the target, planning the movement, and initiating the movement (Basso and Sommer 2011). Future experiments can begin to test these ideas by targeting recordings to specific types of SNr neurons—for example, based on whether they project to the ipsilateral or contralateral SC—with techniques such as optogenetics (Gadina et al. 2010; Lima et al. 2009).

Although many details remain to be determined, it is clear that the SNr plays a broader role in modulating SC activity than via simple disinhibition. As discussed below, one idea is that the SNr provides value-related information to the target selection process by biasing activity in SC circuits such that spatial targets associated with the highest value are most likely to be selected (Hikosaka et al. 2006).

Fig. 4. Examples of neural recordings from rodents performing behavioral tasks requiring the selection of a target for movement. A: smoothed peristimulus time histograms (mean ± SE) for 2 SNr neurons recorded in a mouse performing the task shown in Fig. 2A. Black, activity associated with selecting contralateral target; gray, activity associated with selecting ipsilateral target. Stimulus presentation is shown as the gradient along the x-axis, and go signal is shown as a vertical dotted line. Some neurons exhibit higher activity preceding movement to contraversive target (as at top), and some exhibit higher activity preceding movement to ipsiversive target (as at bottom). Data from Lintz and Felsen (2014). B: as in A, for 2 mouse PPTg neurons. Data from Thompson and Felsen (2013). C: as in A, for 2 rat frontal orienting field (FOF) neurons. Rat FOF is thought to be homologous to primate frontal eye field (FEF). In this task, target selection was cued by an auditory rather than olfactory stimulus. Data from Erlich et al. (2011). For comparable data recorded in primates in a similar experimental paradigm, see Handel and Glimcher (1999) (SNr), Okada and Kobayashi (2008) (PPTg), and Sommer and Wurtz (2000) (FEF).
Cholinergic Input to Superior Colliculus from Parabrachial Region

The SC receives cholinergic innervation via two distinct pathways that independently innervate either the superficial or deep subdivision (Hall et al. 1989). Experiments in rodents, cats, and primates have mapped the immunohistochemical profile and the afferent topography of the SC and have demonstrated that the cholinergic innervation of the superficial subdivision originates from the brain stem’s parabigeminal nucleus (Feig et al. 1992; Graybiel 1978; Hall et al. 1989; Mufson et al. 1986; Roldán et al. 1983) whereas the deep subdivision innervation arises from the parabrachial region, primarily composed of the PPTg and the LDTg (Beninato and Spencer 1986; Graybiel 1978; Hall et al. 1989; Harting and Van LIESHOUT 1991; Illing and Graybiel 1985; Jones and Webster 1988; Ma et al. 1991; Stubblefield et al. 2015; Wallace and Fredens 1988; Wooll and Butcher 1986). We focus on this latter innervation because the deep subdivision of the SC is directly involved in selecting targets for movements, although the superficial cholinergic input could in turn modulate intralaminar processing within the SC (Ghitani et al. 2014; Isa et al. 1998; Lee et al. 1997). Notably, the cholinergic input to the deep subdivision appears to overlap with that of the SNr input described above (Harting and Van LIESHOUT 1991; Illing and Graybiel 1985).

Electrophysiological studies in slices, anesthetized animals, and awake animals have found that the overall effect of acetylcholine (ACh) in the SC is excitatory (Bezdudnaya and Castro-Alamancos 2014; Isa and Hall 2009; Li et al. 2004; Sooksawate et al. 2008, 2011; Sooksawate and Isa 2006; Stubblefield et al. 2015). Stimulation of endogenous release of ACh in the SC in an in vivo preparation demonstrated variability in the magnitude and timescale of this excitatory influence, consistent with both monosynaptic and polysynaptic cholinergic input (Stubblefield et al. 2015). These studies suggest that endogenous cholinergic input serves to promote SC-dependent motor output. Consistent with this idea, infusing nicotine into the intermediate layers of one SC induces rotational behavior in rats (Weldon et al. 1983) and decreases reaction time in a saccade task in primates (Aizawa et al. 1999; Watanabe et al. 2005).

Although the PPTg and LDTg have not been as extensively examined in behavioral contexts as have the SC and the SNr, electrophysiological studies in multiple animal models and various behavioral paradigms demonstrate a role for these regions in goal-directed motor control (Martinez-Gonzalez et al. 2011; Mena-Segovia et al. 2004; Winn 2006, 2008). Specifically, the activity of PPTg neurons correlates with orienting movements of the eyes, body, and limbs (Dormont et al. 1998; Kobayashi et al. 2002; Matsumura et al. 1997; Norton et al. 2011; Okada and Kobayashi 2009; Thompson and Felsen 2013; see example neurons recorded in freely moving mice shown in Fig. 4B), and LDTg activity shows task-dependent modulation preceding and during movements in rats navigating a radial arm maze (Redila et al. 2015). Given the similar timing of activity exhibited by neurons in these areas and SC neurons (Felsen and Mainen 2012; Thompson and Felsen 2013; see examples in Fig. 2B and Fig. 4B) as well as the anatomical and physiological data discussed above, the PPTg and LDTg are likely to modulate movement-related activity in the SC (Kobayashi and Isa 2002). Separate studies using similar behavioral paradigms have shown that the firing rates of most (but not all; see Fig. 2B and Fig. 4B) PPTg and SC neurons prior to movement initiation are higher for contraversive than ipsiversive movements (Felsen and Mainen 2012; Horwitz and Newsome 2001a; Okada and Kobayashi 2009; Thompson and Felsen 2013). These studies, along with anatomical studies showing stronger input from the ipsilateral than the contralateral PPTg (Beninato and Spencer 1986; Hall et al. 1989; Krauthamer et al. 1995; Li et al. 2004), suggest that the uncrossed PPTg-SC projection plays a primary role in motor output. However, the PPTg and LDTg both project widely to several other motor regions (Jenkinson et al. 2009; Oh et al. 1991), and to our knowledge no studies have specifically targeted SC-projecting PPTg or LDTg neurons for recording. Thus the specific functional role of the cholinergic input to the SC, and whether it relates to the selection of targets for movement, remains unknown.

One possibility, however, is that cholinergic input to the SC serves to modulate the competition between circuits representing targets for movement, similar to how other brain stem sources of cholinergic input modulate sensory representations in target structures (Castro-Alamancos 2004; Froemke et al. 2007; Goard and Dan 2009; Kilgard and Merzenich 1998; Ma and Luo 2012; Rothermel et al. 2014). Indeed, cholinergic input to brain stem nuclei has been proposed to modulate motor-related functions, including locomotor activity (Steckler et al. 1994) and muscle control (Kelland and Asdourian 1989). Given that the activity of many PPTg neurons increases preceding movement (Thompson and Felsen 2013), this excitatory cholinergic input could serve to bias the selection of particular targets for movement, providing a counterbalance to the spatially overlapping inhibitory input from the SNr (Harting and Van LIESHOUT 1991; Illing and Graybiel 1985) that has also been proposed to bias target selection (Hikosaka et al. 2006; Kobayashi and Isa 2002). Thus the SC may integrate antagonistic influences from two major neural systems—inhbition from the basal ganglia and excitation from the mesencephalic cholinergic system—that may serve to modulate its intrinsic processing underlying the selection of targets for movement, as well as the influence of the converging cortical inputs discussed below.

Glutamatergic Input to Superior Colliculus from Neocortex

In an early landmark study demonstrating the importance of cortical influence on the SC, hemianopsia due to removal of the contralateral occipitotemporal cortex was shown to be mediated by inter-SC interaction: subsequent removal of the SC contralateral to the lesioned cortex reversed the deficit (Sprague 1966). A series of subsequent studies found that excitatory cortical input to the deep subdivision of the SC arrives from a wide range of neocortical regions (Fries 1984), including the frontal eye field (FEF), supplementary eye field (SEF), lateral intraparietal area (LIP), and dorsolateral prefrontal cortex (DLPFC), as well as from parietal networks important for reaching behavior (Borra et al. 2014; Distler and Hoffmann 2015; Lock et al. 2003; Munoz and Everling 2004; Paré and Wurtz 2001; Sommer and Wurtz 2001; Sparkes 1986). The majority of these inputs originate in ipsilateral cortical regions, but SEF, FEF, premotor cortex, and the supplementary
motor area have been shown to project contralaterally as well (Distel and Fries 1982; Shook et al. 1990). While the roles of many of these regions in decision making have been extensively studied in their own right, we focus here on how they may directly influence target selection processes in the SC. Although many of these cortical regions project directly to brain stem premotor circuits (Schnyder et al. 1985; Segrays and Goldberg 1987; Sommer and Wurtz 2000, 2001; Wurtz et al. 2001). However, more cortical neurons tend to represent the stimulus than the motor response, and more SC neurons tend to represent the motor response than the stimulus, providing further evidence that the SC functions along with its cortical inputs to transform stimulus representations to motor representations (Wurtz et al. 2001). Particularly for nonvisual stimuli, such cortical stimulus representations may be an important source of sensory input to the SC. Another study found that the distribution of activity profiles of FEF-recipient SC neurons during visuomotor tasks was similar to that of the SC population as a whole (e.g., some FEF-recipient SC neurons exhibit buildup and/or burst activity), although the activity of SC neurons with purely visual responses (Horwitz and New- some 2001b) does not appear to be modulated by FEF stimula- tion (Helminski and Segrays 2003).

During an antisaccade task requiring that some saccades be made to the direction opposite the visual cue, in which the cortex is thought to be involved in suppressing the reflexive behavior to orient to the stimulus (Munoz and Everling 2004), interesting differences emerged between SC-projecting neurons in the FEF and DLPFC. Specifically, activity in FEF neurons increased more preceding prosaccades (i.e., to the visual cue) than antisaccades (i.e., away from the visual cue) (Everling and Munoz 2000), while activity in DLPFC neurons showed the opposite effect (Johnston and Everling 2006). These results suggest that FEF and DLPFC may be playing distinct roles in influencing the selection of targets for movement in the SC—one possibility is that FEF functions to categorize continuous evidence into a binary choice (Erlich et al. 2015; Hanks et al. 2015)—although the mechanism underlying these opposing downstream effects is not clear (Everling and Johnston 2015).

Some corticocortical input spatially overlaps with inputs from the SNr and PPTg (Fig. 1B; Illing and Graybiel 1985). What is the functional relevance of this overlap? As discussed above, the GABAergic and cholinergic input may modulate intrinsic SC activity related to target selection. The cortical input, in contrast, could serve as the primary source of information to the SC. This “driver-modulator” framework (Lee and Sherman 2010) would predict that a range of morphologically distinct axon terminals would be observed in the SC, suggesting a diversity of forms of synaptic transmission, which is indeed the case (Norita 1980). In addition, the modulator pathways would be expected to give rise to thin axons and project to distal dendrites, which is again consistent with ultrastructural data (Fig. 1B; Behan et al. 1987; Jeon et al. 1993). This framework may therefore prove useful in thinking about information integration in the SC, as it has in sensory systems (Lee and Sherman 2010). Below, we discuss what complementary information each of these inputs may provide to the SC in order to influence the selection of targets for movements.

Discussion

We have reviewed a wealth of data on how the SC selects targets for movements. The emerging framework posits target selection as the outcome of a competition between SC circuits representing specific targets, although the precise nature of this competition—i.e., whether SC circuits directly inhibit each other—is unclear. Notably, SC activity appears to represent the target abstractly, independent of whether the movement will be achieved by the eyes, head, body, or limbs. Indeed, this activity may even reflect the selection of a target to attend to, without any overt motor component at all (Carello and Krauzlis 2004; Corneil and Munoz 2014; Krauzlis et al. 2013; Lovejoy and Krauzlis 2010). Instead, the specific combination of motor output required to achieve the goal of orienting to the target appears to be represented in the activity of brain stem premotor nuclei coordinated, in part, by the SC (Gandhi and Katnani 2011). Thus the SC provides a convenient hub at which several neural systems can influence the selection of a target for movement, before specifying the particular manner in which that movement is achieved (Song et al. 2011; Song and McPeek 2015).

We then discussed how several of these systems may influence the competition in the SC underlying target selection for movement. Briefly, the basal ganglia exert GABA-mediated inhibitory influence via the SNr, the parabrachial region exerts ACh-mediated excitatory influence via the PPTg and LDtg, and cortex exerts glutamate-mediated excitatory influence via several interconnected regions (Fig. 1). What might be the functional relevance of the input received from all of these regions? One possibility is that each of these systems conveys complementary information critical to target selection beyond the relevant sensory input, perhaps related to internally generated behavioral goals, as suggested by microstimulation experiments and modeling work (Dorris et al. 2007; Trappenberg et al. 2001).

For example, animals generally act to maximize reward, and it is therefore important to select a target based in part on the likelihood that moving to that target will lead to a reward. Notably, the SC, PPTg, and SNr all provide direct input to dopaminergic neurons in the ventral tegmental area and substantia nigra pars compacta that are responsible for signaling a reward prediction error (Kobayashi and Okada 2007; Norton et al. 2011; Okada et al. 2009; Redgrave et al. 2010; Redgrave and Gurney 2006; Schultz et al. 1997; Watabe-Uchida et al. 2012). The basal ganglia, in particular, have been proposed to provide information about the value associated with targets for movements (Hikosaka et al. 2006); for example, the activity of movement-related caudate and SNr neurons is modulated by whether an upcoming movement will be rewarded (Laureys et al. 2002; Sato and Hikosaka 2002). These data led to
the idea that the SNr biases the pattern of activity in SC circuits during target selection such that, upon cortical input, rewarded movements are facilitated and unrewarded movements are suppressed (Hikosaka et al. 2006). The cholinergic input from the parabrachial region may provide complementary contextual information relevant to selecting a target for movement, perhaps in the form of “motor attention” (Goldberg and Segraves 1987). In addition to its dependence on the direction of upcoming orienting movements as described above, the activity of PPTg neurons has been shown to depend on reward (Kobayashi and Okada 2007; Norton et al. 2011; Okada et al. 2009; Thompson and Felsen 2013), and the direction dependence often long outlasts the choice (Thompson and Felsen 2013). These findings raise the possibility that PPTg activity could reflect movement choices and the resulting rewards in the recent past, which could be informative for selecting upcoming targets for movement (Lau and Glimcher 2008). Together, the complementary GABAergic and cholinergic input may function to tune the map of spatial targets represented in the SC according to their relative values, in advance of upcoming movement. This modulation would serve to bias the likelihood that, upon receiving parallel cortical input driving competing targets for movements, the highest-valued target will be selected. Indeed, the results of an analysis comparing several leading models for reading out SC activity to select a target found that a probabilistic model, which is well suited to integrating precisely these types of prior probabilities, most accurately predicted which targets were selected by the behaving animal (Kim and Basso 2010; Wolpert and Landy 2012).

These ideas are akin to those in models proposed by Hikosaka and colleagues (2006) and Lo and Wang (2006) to explain how cortical and basal ganglia input are integrated in the SC during visuomotor tasks, as well as to a model proposed by Kobayashi and Isa (2002), which also incorporated PPTg input. While these models can explain some neural and behavioral data (Aizawa et al. 1999; Lauwereyns et al. 2002), they do not capture the full range of connectivity and neural activity observed. For example, they incorporate ipsilateral, but not contralateral, input to the SC and burst, but not buildup, neurons. An open question is therefore how to extend and refine these models in order to synthesize the heterogeneous anatomical and physiological data observed (note that the example neurons shown in Fig. 2 and Fig. 4 exhibit diversity within each region).

Along these lines, the interactions in the network model that we have described here (Fig. 1A) are necessarily simplified. Most importantly, we have only discussed descending input to the SC, while the SC also provides ascending output that may mediate several functions, including attention (Krauzlis et al. 2014) and corollary discharge (Sommer and Wurtz 2008). In fact, activity in the SC and basal ganglia may be a primary driver of orienting attention, and while the mechanisms underlying attention in the SC are not fully understood, they may be similar to those we have described here (Krauzlis et al. 2013). In addition, we have not discussed how orienting movements to targets relate to other motor output in which the SC has been implicated, such as escape, avoidance, and freezing behaviors (Dean et al. 1986, 1989; Sahibzada et al. 1986). Finally, many of the input regions discussed are themselves interconnected. Thus there is the opportunity for multiple parallel and serial pathways for motor control through the SC, as well as recurrent loops. The fact that the timing of premovement activity across populations of neurons within these regions is heterogeneous (Felsen and Mainen 2012; Thompson and Felsen 2013) supports the idea that the flow of information may not be unidirectional. As discussed below, methods to examine cell type-specific functions could help illuminate these more complex processing features.

Although we have limited the scope of our discussion to cortical, SNr, and parabrachial input to the SC, the SC receives a host of other inputs (Edwards et al. 1979; Sparks and Hartwich-Young 1989). For example, cerebellar nuclei provide excitatory input to the same SC neurons that receive inhibition from the SNr (Westby et al. 1994), and inhibition of the cerebellar caudal fastigial nucleus alters gaze direction during fixation (Guerrasio et al. 2010) and disrupts gaze fixation in the presence of a competing target (Fukushima et al. 2011). These findings demonstrate a cerebellar contribution to SC-mediated fixation and its release (Goffart et al. 2012; Quinet and Goffart 2015). As the functional roles of this input, and others, are more thoroughly examined, they can be incorporated into the integrative framework presented here. Despite the wealth of data collected in the studies we describe, an obstacle to further progress is that our methods for examining the neural bases of selecting targets for movement are insufficient for obtaining a detailed circuit-level description of the process. While we predict that different types of neurons in the SC (e.g., excitatory vs. inhibitory, projection vs. local) play different functional roles in selecting targets for movements, these predictions have not been tested because it is difficult to identify specific neuron types in vivo. For example, to our knowledge no in vivo studies in the SC have recorded from identified GABAergic neurons, despite their critical role in SC processing and despite some understanding of their anatomy and physiology from slice studies (Isa and Hall 2009; Sooksawate et al. 2011, 2012). New methods are beginning to allow for such targeted recordings. For example, restricting expression of ChR2 to GABAergic neurons would allow them to be identified during awake behaving recordings (Cardin 2012; Cardin et al. 2010; Lima et al. 2009; Roux et al. 2014). These experiments are currently feasible in mouse models because of the availability of transgenic mouse lines allowing for cell type-specific expression of optogenetic proteins (Taniguchi et al. 2011; Zhao et al. 2011) and technology to photostimulate and record neural activity in behaving animals (Anikeeva et al. 2011). While this particular approach requires transgenic animals and is thus less well suited for use in primates, it is worth noting that other optogenetic tools can be applied to primates (Dieter et al. 2011; Jazayeri et al. 2012), including in the SC (Cavanaugh et al. 2012). For example, targeting neurons on the basis of their projection pattern (Gradinaru et al. 2010) would be feasible in the primate model.

While primates share the most homology with humans and remain an essential model for studying SC function, the potential afforded by new molecular tools suggests that we consider the complementary utility of rodent model systems. The control of head and body movements in rodents is not identical to the control of eye movements in primates, but the homology between these systems appears to be sufficient to make findings applicable across species (Takakusaki et al.
and recordings in the regions discussed here appear fairly similar in rodents and primates (compare data shown in Fig. 2 and Fig. 4 with those in the papers referred to in their legends). In addition, rodents have been more commonly utilized in slice studies (Isa and Hall 2009). In vivo work in rodents therefore allows us to bridge the gap between in vivo and ex vivo paradigms: For example, complementary in vivo and slice experiments can be performed in the same transgenic mouse line to look at systems and cellular components of SC function. In addition, rodent models provide other useful features, beyond the ease of optogenetic applications noted above, for examining the neural bases of decision making (Carandini and Churchland 2013). First, rodents are more convenient than primates for studying SC control of freely moving behavior (Felsen and Mainen 2008; Hirokawa et al. 2011). Second, the applicability to mouse models of genetically encoded voltage and calcium indicators allows the activity of populations of genetically specified neurons to be imaged (Broussard et al. 2014; Tian et al. 2012); this technology was recently applied to the SC (Feinberg and Meister 2015). Such imaging combined with novel head-mounted microscopes will allow for imaging of population activity during freely moving behavioral tasks (Barretto et al. 2011; Chen et al. 2013; Flusberg et al. 2008; Ghosh et al. 2011; Wilt et al. 2009). Thus rodents are likely to provide a complementary model to primates in future studies addressing open questions about how the SC and its inputs mediate the selection of targets for movements.

Concluding remarks. The results from a range of studies, across several species and motor effector systems, suggest a framework in which activity in the deep subdivision of the SC contributes to the selection of targets for orienting movements. Other studies have provided insight into how inputs to the SC, from the basal ganglia, parabrachial region, and neocortex, may influence SC activity in order to tune the probability of selecting a particular target consistent with internally generated goals. However, despite much work, several open questions remain about how the SC and these—as well as other—input regions mediate the selection of targets for movements. These questions can be addressed by future experiments identifying the functional roles of specific cell types in these circuits, and by theoretical models incorporating the richness of anatomical and physiological data observed.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS


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