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Responding when time is of the essence: An analysis of signal timing in the macaque superior colliculus during reflexive visually guided reaching

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Abstract

The superior colliculus (SC) is a subcortical structure well known for contributing to saccades and reflexive orienting. SC neurons in primates are also active during arm movements, including those involving voluntary reaching. What is not known is whether SC neurons could contribute to reflexive visually guided reaches. A marker for such reaches is the express visuomotor response (EVR), which is generated on upper limb muscles in monkeys within 65 milliseconds. Here, we recorded the activity of SC neurons while two monkeys performed a task known to produce EVRs. When accounting for efferent delays, our results show that the SC neurons respond early enough to initiate EVRs. Our results show a potential role for the SC in initiating reflexive visually guided reaches and lay the groundwork for performing a comparative analysis of signal timing across cortical and subcortical areas when time is of the essence.

Keywords

Superior Colliculus; Visually Guided Reaching; Express Visuomotor Response; Rapid Sensorimotor Transformation; Visuomotor Control; Primates

Summary for Lay Audience

Visually guided reaching is a critical aspect of primate behaviour, crucial for interacting with their surroundings. Many studies have explored the role of cortical areas in voluntary, visually directed reaching. Equally important, our brain possesses a remarkable capacity to rapidly transform visual inputs into actions. For instance, recent research has shown that humans can initiate muscle movements toward a target in less than 100 milliseconds after seeing it. We refer to this rapid reaction as "express visuomotor response." A recent study from our lab shows that these responses can occur even earlier (~65 ms after stimulus onset) in monkeys. This raises questions about whether the cortical areas involved in deliberative reaches can process information quickly enough to produce express visuomotor responses. An alternative hypothesis is that these responses are generated by a subcortical pathway, involving the midbrain superior colliculus. Here, we test this hypothesis directly by recording from the superior colliculus.

We recorded data from the superior colliculus of two macaque monkeys reaching in a task where they had to reach for a moving target. Our findings show that visually related information in this task arrives within ~50 ms into different layers of the superior colliculus, which is early enough to generate express visuomotor responses. Our results set the stage for comparative analysis of signal timing in this task across cortical and subcortical areas, aiming to better understand visual-to-motor transformations when time is of the essence.

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Table of Contents

List of Tables

List of Figures

List of Appendices

List of Abbreviations

CSD	Current source density
EMG	Electromyography or Electromyographic
EVR	Express visuomotor response
FEF	Frontal eye fields
LGN	Lateral geniculate nucleus
M1	Primary motor cortex
ms	Milliseconds
NHP	non-human primate
PMd	Dorsal premotor cortex
PMv	Ventral premotor cortex
PPC	Posterior parietal cortex
ROC	Receiver-operating characteristic
RF	Receptive field
RT	Reaction time
SC	Superior Colliculus
SCi	Intermediate Superior Colliculus
SCd	Deep Superior Colliculus
SCs	Superficial Superior Colliculus
V1	Primary visual cortex

Chapter 1

1 Introduction

In the life of primates, visually guided reaching is not just a routine action but a critical adaptive behaviour that enhances survival through efficient foraging and complex social interactions. This behaviour requires sophisticated orchestration of activity in visual and motor systems, where both cortical and subcortical structures are deeply intertwined. Broadly speaking, the motor cortex plays a vital role in initiating and directing voluntary movements such as reaching and grasping, through direct pathways like the corticospinal tract that project to motor neurons in the spinal cord. Movement commands are also intricately modulated and refined by subcortical structures, including the brainstem and circuits within the spinal cord. These structures integrate sensory feedback and adapt movements to environmental contingencies, forming a nested loop of control that facilitates a spectrum of actions, from quick reflexes to deliberate, visually guided movements.

During voluntary visually guided reaching movements, the time to initiate a movement in response to a visual stimulus is generally accepted to be ~200-300 milliseconds. However, we live in a dynamic and uncertain world, and sudden changes in visual input may demand very rapid responses. When time is of the essence, visual-to-motor transformations can occur remarkably quickly at latencies which approach minimum afferent and efferent conduction delays. The key hypothesis that will be tested in this thesis is that such short latency responses, unlike voluntary visually guided reaching movements, arise from a subcortical tecto-reticulo-spinal circuit that runs in parallel with corticospinal circuits. Understanding the visuomotor response timing in the brain in these behaviours can provide valuable insights into the hierarchies of the underlying neural circuits.

This introduction will first discuss visuomotor response (signal) timing and content across cortical brain areas involved in the generation of voluntary visually guided reaches. Subsequently, it will address rapid responses in reflexive visually guided tasks, particularly focusing on bursts of muscle activity termed express visuomotor responses. The second part of this introduction will delve into the potential neural substrates of express visuomotor responses across cortical areas and the potential involvement of brainstem circuits, especially the superior colliculus, in facilitating these swift reactions. To investigate the hypothesis that the superior colliculus initiates these rapid responses, this study analyzes the signal timing in the superior colliculus of two monkeys performing an emerging target task—a task that has been shown to elicit express visuomotor responses in both humans and monkeys. The study aims to determine if the timing of signal arrival in the superior colliculus is sufficiently prompt to initiate express visuomotor responses.

1.1 Visually guided reaching

1.1.1 Neural mechanisms of voluntary visually guided reaching

Imagine a monkey perched on a tree, contemplating which fruit to reach for and eat. This seemingly simple action of initiating a reach to the visual cue involves a complex integration of visual information and motor commands, orchestrated by a network of specialized brain regions. Our brains continuously interact with the environment, perceiving stimuli, selecting actions (e.g., which fruit to pick), and specifying how to execute these actions (e.g., which muscles to contract and when).

In the realm of visually guided movement, Cisek (2007) proposed the affordance competition hypothesis, which suggests that multiple potential actions are simultaneously represented in the brain, competing for selection. This competition is influenced by the affordances of the environment—opportunities for action provided by objects—and is resolved through the interplay of sensory information (bottom-up) and motor plans (top-down). Factors such as the value of potential goals and the cost to attain them also influence the selection process (Cisek & Kalaska, 2010). These processes are generated by highly distributed cortical and subcortical circuits, allowing the brain to dynamically select the most appropriate action based on the current context. This sophisticated process is facilitated by the brain's visual information processing through two distinct pathways in the cerebral cortex.

The dorsal stream, often referred to as the "where" pathway, is crucial for processing spatial relationships and guiding actions based on spatial awareness (Mishkin & Ungerleider, 1982). Goodale & Milner (1992) proposed that the dorsal stream mediates certain aspects of visually guided behaviour. Further studies suggested that it specifies action parameters by transforming sensory information about objects into actionable commands (Andersen & Buneo, 2003; Cisek, 2007; Kalaska et al., 1998; Passingham & Toni, 2001; Sakagami & Pan, 2007). This pathway involves interconnected areas in the posterior parietal and caudal frontal cortex, such as the medial intraparietal area (MIP), which is connected to frontal regions involved in reaching, like the dorsal premotor cortex (PMd) (Johnson et al., 1996; Wise et al., 1997). Collectively, the dorsal stream enables the brain to navigate spatial environments effectively and execute visually guided actions.

Conversely, the ventral stream, known as the "what" pathway, is responsible for identifying and recognizing stimulus features such as shape, colour, and texture, thereby aiding in discerning object identity and assessing the subjective value of potential actions (Pasupathy & Connor, 2002; Sugase et al., 1999; Tanaka et al., 1991; Wallis, 2007). It has been suggested that the dorsal and ventral streams may be integrated to form a unified representation of the world in the ventrolateral prefrontal cortex, which then projects to the dorsolateral prefrontal cortex and premotor regions, ultimately influencing action selection (Sakagami & Pan, 2007). Meanwhile, attention significantly influences the processing of visual information within both the dorsal and ventral streams by enhancing neural activity in regions corresponding to the focus of attention and suppressing activity in unattended regions, thus prioritizing relevant stimuli for processing and optimizing action selection (Boynton, 2005; Colby & Goldberg, 1999; Treue, 2001).

Ultimately, the execution of selected actions must involve the motor periphery, hence signals have to flow through the spinal cord, peripheral nerves, and muscles. In the case of voluntary reaching, after a motor plan is selected and specified, motor commands are transmitted from the brain through the motor cortex to the brainstem and spinal cord (Figure 1). Motor neurons there transmit these commands to the muscles, orchestrating coordinated contractions that enable movement. Typically, human reaction time (RT) for reaching toward a visually presented target ranges from 200-300 ms, as measured by hand kinematics such as velocity (Welford et al., 1980). To achieve a more precise measurement of these reaction times, researchers have recorded electromyographic (EMG) recordings from limb muscles. These recordings effectively bypass electromechanical delays between the neural command for movement initiation and the actual movement, such as delays caused by limb inertia (Norman & Komi, 1979). Notably, the transmission delay from the primary motor cortex to shoulder muscles is remarkably brief, taking about 10-15 ms in humans (Bawa et al., 2004).

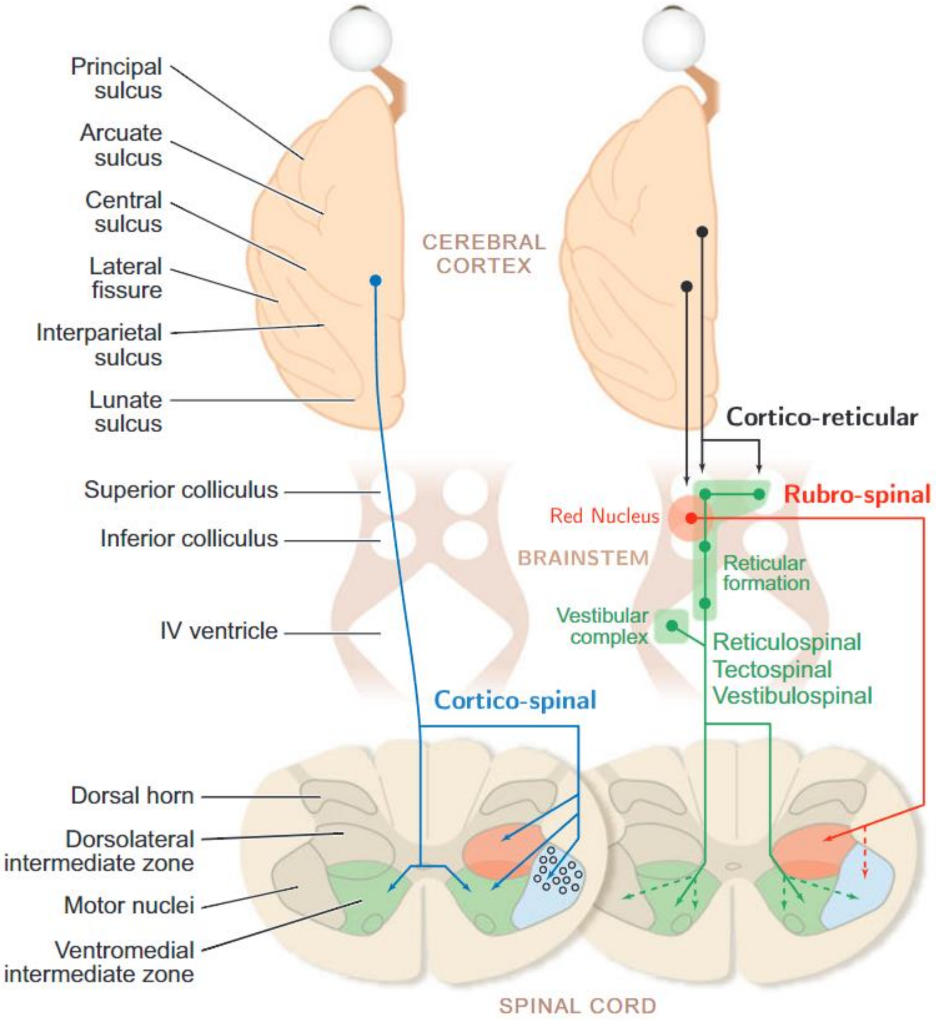

Figure 1. Schematic illustration of the descending motor pathways involved in visually guided reaching.

The corticospinal pathway (left, depicted in blue) begins in the cerebral cortex and primarily terminates in the contralateral side of spinal cord. It includes cortico-motoneurons that project directly to motor nuclei. The reticulospinal (green) and rubrospinal (red) pathways originate in the brainstem, with the reticulospinal pathway projecting bilaterally to the spinal cord and the rubrospinal pathway projecting contralaterally. Modified from Lemon (2008).

1.1.2 Temporal dynamics of information processing in cortex

Upon the presentation of a visual stimulus, the majority of retinal ganglion cells transmit sensory information to the lateral geniculate nucleus (LGN). From the LGN, this information is then relayed to the primary visual cortex (V1), and then successive hierarchical levels of the cortex are rapidly activated through feedforward connections. This process, known as the fast feedforward sweep (Lamme & Roelfsema, 2000) or the fast dorsal specification system (Milner & Goodale, 1995), is the first wave of the cortical cascade of neural activations triggered by visual sensory input.

The timing of signals in the monkey brain during visually guided reaching was largely understood about 20 years ago. Lamme and Roelfsema (2000) performed a meta-analysis of 48 studies on visual response latencies in macaque monkeys. These studies investigated various cortical regions, including visual, parietal, frontal, and motor areas, to characterize the feedforward sweep. Notably, it takes about 60 ms for visual afferents to be relayed to the PMd. Neurons in the middle temporal (MT) area and the frontal eye fields (FEF) are activated almost as quickly as cells in area V1, within ~40-50 ms. These areas receive visual information not only from the LGN but also from other subcortical structures. For example, area MT receives significant input from the superior colliculus, which can sustain MT cell responsiveness even in the absence of V1 (Rodman et al., 1990). This alternative pathway might provide visual input to the parietal cortex before the geniculostriate pathway (Nowak & Bullier, 1997). Importantly, large differences exist between the latencies of the dorsal and ventral streams, with the dorsal stream being faster due to the higher speed of the magno-pathway compared to the parvo-pathway. Lamme and Roelfsema (2000) also noted considerable variances between studies. These discrepancies likely arise from variations in how researchers calculated latency, the type of visual stimuli employed, and the behavioural state of the animals.

The primary motor cortex (M1/area 4) receives visual information from the posterior parietal cortex (PPC) and the dorsal premotor cortex (PMd/area 6) using cortico-cortical connections (Bakola et al., 2010; Innocenti et al., 2014; Johnson et al., 1996; Marconi et al., 2001; Matelli et al., 1998). The PPC sends connections to M1 and PMd from areas PE and PEc, respectively. In area PEc, neurons are responsive to various reach-related signals, including hand and/or eye position, movement direction, retinal position, and the motion direction of visual stimuli (Battaglia-Mayer et al., 2001, 2000). They also respond to reach distance (Ferraina et al., 2009) and integrate all this information within their global tuning field (Battaglia-Mayer et al., 2001).

Simultaneously with the initial sweep, slower selection processes occur, introducing task-relevant biases. This integrates the pure visual response with top-down modulation and distinguishes targets from distractors leading to the selection of a distinct motor response (Corbetta & Shulman, 2002). For example, neurons in the dorsal premotor cortex respond to cue locations for two potential movements within 50-70 ms. However, they begin to predict the monkey’s choice, sensory-motor mapping rules, and motor commands sometime later, at ~110-130 ms (Cisek & Kalaska, 2005; Crammond & Kalaska, 1994; Gail et al., 2009). Similar two-wave information processing is observed in other parts of the dorsal and ventral streams (Ledberg et al., 2007) and the oculomotor system (Bichot & Schall, 1999; Sato & Schall, 2003).

In summary, following the presentation of a visual stimulus in visually guided reaching movements, continuous and parallel processes emerge as two waves of activation. The first wave crudely specifies a range of options in less than 100 ms, while the second wave selects among them approximately 120–150 ms after stimulus onset. This indicates that the brain can rapidly specify multiple potential actions within its fast frontoparietal sensorimotor control system but requires about 150 ms to integrate sufficient information to make a decision.

However, in our ever-changing and unpredictable world, sudden environmental changes may require rapid responses. In the next section, I will explore how our rapid responses enable us to adapt swiftly to visual changes, ensuring our actions remain effective even in unpredictable situations.

1.1.3 Rapid responses in reflexive tasks

Our dynamic environment necessitates continuous monitoring and updating of our actions and motor commands to align with task goals. Such updating relies on information from sensory systems like vision (Franklin & Wolpert, 2008; Hansen et al., 2008; Pélisson et al., 1986; Saunders & Knill, 2004), proprioception (Sainburg et al., 1995; Scott, 2012), audition (Boyer et al., 2013), the vestibular system (Bresciani et al., 2002), and fast internal loops which predict the sensory consequences of movement commands (Desmurget & Grafton, 2000). This adaptability is especially vital when time is of the essence. Consider a scenario where a monkey contemplates reaching for a fruit hanging from a tree branch. Suddenly, a gust of wind dislodges the fruit. Almost instantly, the monkey initiates its reach, now aiming to catch the fruit before it hits the ground. In fact, reaching to moving objects can decrease reaction time. Perfiliev and colleagues (2010) investigated this phenomenon using a naturalistic task in which both humans and monkeys were required to intercept a moving object travelling from right to left or vice versa. Humans exhibited an average reaction time of 165 ms, with an average EMG onset of 145 ms and the earliest EMG responses occurring between 90 and 110 ms (Figure 2). In contrast, monkeys demonstrated reaction times ranging from 120 to 200 ms (EMG was not recorded). In more cognitively demanding conditions, where human participants were asked to use the opposite arm to reach for moving targets, their reaction times increased by 70 ms. Interestingly, similar innate mechanisms were observed in cats and kittens, where kittens as young as 7 to 11 weeks displayed alternating goal-directed limb movements in response to moving targets, suggesting a hard-wired reflexive mechanism for rapid responses.

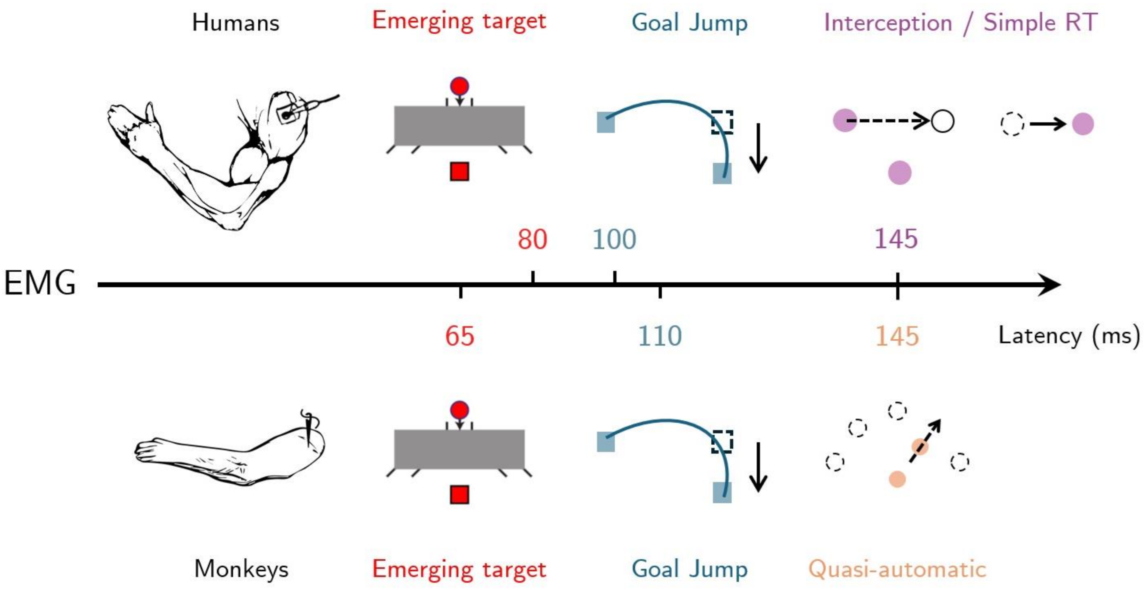

Figure 2. Average EMG onset latencies in reflexive tasks in humans and monkeys.

Average EMG onset latencies of upper limb muscles from different studies are summarized for both humans (top row) and monkeys (bottom row), indicating the time from visual stimulus onset to EMG signal onset. Values for humans, obtained using surface EMG electrodes, and for monkeys, obtained using intramuscular EMG electrodes, are presented. While variations in stimulus properties, onset detection methods, and subjects' behavioural states may affect these latencies, only the average values from the corresponding studies are included (For details and specific references see the main text).

In the two described tasks, the subject was initially unaware of the goal location. However, consider scenarios where the stimulus and the required behavioural response are pre-cued, akin to a runner anticipating the starter gun. In such situations, known as Simple Reaction Time (SRT) tasks, visual, auditory, and somatosensory stimuli can trigger a motor response of the arm, as the sensory input functions as a "go" signal. Consequently, muscle activity typically occurs within 110–170 ms, with SRTs increasing for more complex motor actions that involve multiple phases or segments (Henry & Rogers, 1960; Maslovat et al., 2014).

Similarly, we are capable of swiftly adjusting an ongoing reaching movement in response to changes in the visual target. To uncover the key features and control mechanisms of this adjustment process, various studies have employed tasks that alter or remove target information to study rapid movements. One notable task used for this purpose is the "double-step" paradigm (also known as the target/goal jump). In this task, participants are instructed to reach a visually displayed target as quickly and accurately as possible (single step). During some trials, while planning or executing the movement, a second target appears and the first target disappears, creating the perception that the target has moved (double step). Unlike eye saccades, which are rapid and generally not corrected mid-flight, hand movement trajectories are rapidly adjusted online in response to the second target (for review, see Battaglia-Mayer et al., 2014, 2013; Gaveau et al., 2014; Prablanc et al., 2003).

Early studies by Soechting and Lacquaniti (1983), along with subsequent research have demonstrated that humans can adjust their movements within 100 to 200 milliseconds after a target displacement. This rapid adjustment is evident regardless of when the target displacement occurs, supporting the idea that motor commands are updated continuously (Oostwoud Wijdenes et al., 2011). This adjustment happens even without conscious awareness of an error (Christensen et al., 2008; Goodale et al., 1986). Additionally, the latency of this rapid correction depends on the visual features of the displaced target; increases in visual features such as luminance, contrast, and size evoke the most rapid corrections, while manipulations of attributes such as colour, form, and texture elicit corrections of approximately 50 milliseconds later (Veerman et al., 2008). This dichotomy parallels the timing differences in the dorsal and ventral streams mentioned in the previous section.

Studies of EMG activity reveal that EMG signals diverge in double-step trials compared to single-step conditions, with a latency of ~100 ms after the target location changes, preceding alterations in hand trajectories (Fautrelle et al., 2010; Reichenbach et al., 2009; Soechting & Lacquaniti, 1983). This response likely represents a low-level reflexive action (Cressman et al., 2006; Diedrichsen et al., 2004; McIntosh et al., 2010; Pisella et al., 2000; Striemer et al., 2010) that is engaged even during very slow movements

(Cressman et al., 2010). In more cognitively challenging double-step tasks, such as instructing participants to ignore the target jump (Striemer et al., 2010) or to respond in the opposite direction of the target displacement (Day & Lyon, 2000), the behaviour shows two distinct phases. Notably, similar classes of early and late responses were observed during reaches initiated from a stationary start position, although the early, more automatic response was much weaker in these cases (Day & Lyon, 2000).

1.1.4 Express visuomotor responses (EVRs)

The fast feedforward sweep, once thought to be confined to brain activity, may also influence motor responses under certain conditions. During rapid corrective responses with shorter reaction times, a distinct burst of directionally-tuned EMG activity emerges, time-locked to the stimulus onset (Kozak et al., 2019). This burst is directionally tuned, with EMG activity increasing or decreasing for stimulus locations to which the muscle would serve as an agonist or antagonist, respectively. A related phenomenon was first observed many years ago in the oculomotor system, where it was documented as express saccades (Fischer & Boch, 1983). Later, Corneil et al. (2004) observed a similar burst in neck muscles used for head turning in non-human primates. In their study, the animals, either head-restrained or unrestrained, were tasked with making leftward and rightward visually guided saccades after a “gap” interval between the disappearance of the fixation point and the appearance of the stimulus. This technique induces more express saccades (Munoz et al., 2000) and can also hasten arm movements (Gribble et al., 2002).

Building on this concept, Pruszynski et al. (2010) noted analogous EMG patterns in human upper limb muscles during visually guided reaching tasks. They identified two distinct bursts of EMG activity in subjects performing a gap task. The first burst, occurring at 80-120 ms, was time-locked to the target's appearance rather than the movement onset and was termed the stimulus-locked response (SLR). A second distinct burst aligned with the movement onset resembled the muscle activity preceding voluntary movement. This type of rapid muscle activity has been known by several names, including Rapid Visuomotor Response (Glover & Baker, 2019) and Rapid Adaptive Behavior (Novembre & Iannetti, 2021). However, the term Express Visuomotor Response (EVR), as proposed by Contemori et al. (2021a), is chosen here for its more mechanistic connotation. EVRs have now also been reported in human neck (Goonetilleke et al., 2015) and lower leg muscles (Billen et al., 2023).

There are notable similarities between the visuomotor properties of EVRs, which are triggered from a static posture, and the early phases of rapid, online corrective movements in response to changes in visual targets. Both responses are distinguished by their swift initiation and reflexive nature. For instance, the approximately 100-ms latency of the EVR aligns with previously reported EMG response latencies to displaced visual stimuli (Fautrelle et al., 2010; Soechting & Lacquaniti, 1983), and is timely enough to influence reach kinematics within approximately 150 ms (Carlton, 1981). Additionally, higher contrast or lower spatial frequency stimuli provoke earlier and more pronounced EVRs, similar to the response properties observed in online corrections (Kozak & Corneil, 2021; Wood et al., 2015). These rapid responses are also processed within a hand-centric frame of reference, considering the stimulus location relative to the hand, rather than the eye position (Diedrichsen et al., 2004; Gu et al., 2018). Interestingly, similar to express saccades, the latency of EVRs and online corrective movements remains consistent across varying task demands (Gu et al., 2018; McIntosh et al., 2010; Oostwoud Wijdenes et al., 2011); however, increasing task complexity tends to diminish the amplitude of these express visuomotor responses (Gu et al., 2018, 2016). In conditions where participants must reach away from a target, their hand initially moves towards the new target location before correcting to align with the intended direction. This reflexive behaviour is characteristic of both online corrections and EVRs, wherein movements are directed toward the stimulus, independent of the final intended direction (Atsma et al., 2018; Chapman & Corneil, 2011; Corneil et al., 2008; Day & Lyon, 2000; Gu et al., 2016).

The magnitude of EVRs has been found to negatively correlate with the latency at which voluntary movements begin (Contemori et al., 2021a; Corneil et al., 2004; Pruszynski et al., 2010). Although rapid responses can still occur in the absence of EVRs, they typically take longer to initiate (Kozak et al., 2019). In earlier research using the gap task, the prevalence of EVRs never exceeded 75%, indicating that not all subjects generated an EVR in response to the stimuli (Gu et al., 2016; Pruszynski et al., 2010; Wood et al., 2015). In their study, Pruszynski and colleagues (2010) could not detect EVRs using surface EMG recordings and observed EVRs in only seven of 16 participants when using intramuscular electrodes. However, Kozak and colleagues (Kozak et al., 2020) developed the emerging target task, which significantly improved the generation of EVRs. In this task, participants are required to intercept a moving target that emerges from either the left or right side of a barrier after being hidden behind it. Using this paradigm, Kozak et al. (2020) reported EVRs using surface EMG electrodes in all five participants. Extensive work since, including studies by Kozak & Corneil (2021), Contemori et al. (2021a, 2022, 2023) and others, has shown that almost every human subject exhibits an EVR with this paradigm. The EVRs evoked with this paradigm were larger in magnitude and present in all participants, suggesting that previously reported low prevalence might be due to less effective stimulus paradigms rather than an inability to generate an EVR within a given participant. The enhanced detection of EVRs with this paradigm is attributed to the predictable timing and implied motion of the target behind the occluder (Contemori et al., 2021a; Kozak et al., 2020).

Using this task, Cecala and colleagues (2023) recorded intramuscular EMG from the posterior, medial, and anterior heads of the deltoid muscle of two monkeys and observed similar responses occurring as quickly as ~65 ms (Figure 3). Such latencies approach minimum afferent and efferent conduction delays between the retina and muscles, establishing a new benchmark for how rapidly the brain transforms vision into action. What neural mechanisms could facilitate such very rapid muscle responses? The subsequent section will delve into the potential neural substrates of EVRs, examining both cortical and subcortical regions that could plausibly be involved in the generation of these rapid responses.

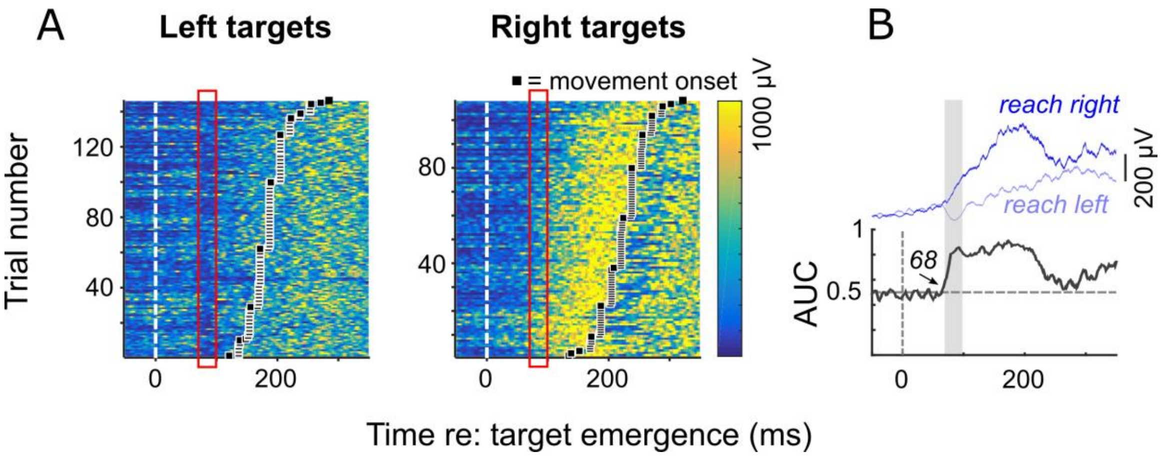

Figure 3. EVRs in monkey upper limb muscle during the emerging target task.

A. Trial-by-trial EMG activity was recorded intramuscularly from the anterior deltoid muscle during leftward and rightward reaches, aligned with target emergence. The color represents the magnitude of EMG activity, with trials sorted by movement onset, indicated by black squares. The EMG activity increases for rightward reaches and decreases for leftward reaches. B. Time-series receiver operating characteristics (ROC) analysis (AUC: area under the curve) and mean EMG activity for leftward (light blue) and rightward (dark blue) reaches shows a divergence of EMG activity at 68 ms. The 25-ms interval following the detection of the express visuomotor response is highlighted by red rectangles in A and gray rectangles in B. Adapted from Cecala et al. (2023).

1.2 Neural substrate of rapid responses

The key point here is that a detailed study of EVRs permits objective tests of hypotheses about the underlying neural substrates. This section will examine the neural circuitry that could potentially be involved in EVRs. It will begin by exploring whether regions commonly associated with visually guided reaching—namely, PPC, PMd, and M1—could also contribute to the earliest phase of limb muscle recruitment during rapid visually guided reaches. We will review evidence for their involvement and analyse the timing of neural signals in these regions during reflexive tasks described in the previous section. The key question is whether the signal timing in these areas is sufficiently prompt to effectively initiate EVRs. Subsequently, this section will pivot to an alternative hypothesis: that EVRs might be mediated through a subcortical pathway, offering a different perspective on the underlying neural substrate supporting EVRs.

1.2.1 Potential cortical substrate of rapid responses

As discussed in the previous section, both EVRs and early phases of rapid corrective responses exhibit similar characteristics. Rapid corrective responses also share notable similarities with voluntary visually guided reaching movements. At the kinematic level, the adjustment of a reaching trajectory in response to a shift in target location can be decomposed as the overlay of two trajectories: one extending from the starting point to the initial target, and a subsequent, delayed trajectory leading from the initial to the final target (Flash & Henis, 1991). At the muscular level, these corrective actions can be understood through the modulation in amplitude and timing of the muscle synergies employed in straightforward point-to-point movements (d’Avella et al., 2011). At the neural level, changes in neural activity patterns in the premotor, motor, and parietal cortices of monkeys during targeted reaching and trajectory corrections transition from those associated with the original movement direction to those linked with the new direction. Moreover, the neural activity changes related to hand path adjustments are predictably similar to those observed in direct reaches (Archambault et al., 2009, 2011). These consistent patterns across kinematic, muscular, and neural levels have led some researchers to suggest that a common cortical control mechanism supports both rapid corrective movements and voluntary visually guided reaching. According to this theory, rapid adjustments in arm movement are initially steered by quick visual feedback processed through the dorsal stream, while slower feedback refines the hand’s positioning at the target (for review see: Paillard, 1996).

Considering the PPC's pivotal role in the online guidance of hand movements, researchers have proposed that corrective movements are mediated through a cortical pathway involving the PPC. This hypothesis is supported by Desmurget et al., (1999), who demonstrated that applying transcranial magnetic stimulation (TMS) to the human PPC during double-step tasks inhibited trajectory corrections, causing movements to persist toward the initial target. Complementary findings by Pisella et al., (2000) showed that a stroke patient with bilateral parietal cortex lesions could accurately point to stationary targets but had significant difficulties in adjusting movements to shifted targets at the motion's onset. This patient exhibited fewer rapid movement corrections and a higher proportion of slow corrective movements than controls, resulting in prolonged total movement duration. Additional studies on patients with unilateral lesions further corroborate these findings while using the contralesional arm (Blangero et al., 2008; Mutha et al., 2014). Additionally, a reversible inactivation study on monkeys by Battaglia-Mayer et al., (2013) found that bilateral deactivation of the superior parietal lobule (specifically areas PE/PE) significantly increased trajectory variability and delayed both the preparation and execution of corrective reach and eye movements. These findings reinforced the idea that the PPC plays a crucial role in the online adjustment of goal-directed movements, a conclusion supported by imaging studies (Desmurget et al., 2001; Diedrichsen et al., 2005).

Lesion studies have also illuminated the crucial role of the premotor and motor cortices in initiating rapid corrective responses. Buiatti et al., (2013) found that individuals with premotor lesions exhibited slower corrections in their movement trajectories, although their accuracy was not compromised. Similarly, Mutha et al., (2014) reported that patients with focal damage to the frontal cortex, specifically the inferior frontal gyrus and parts of the PMd and M1 in the right hemisphere, faced difficulties in suppressing ongoing movements and initiating new ones with their ipsilesional arm. The timing of these new responses was significantly delayed following damage to the right frontal region, whereas patients with left parietal damage experienced no timing delays but demonstrated accuracy deficits when using their right arm.

Importantly, both studies examining the roles of PPC and PMd indicate deficits in the initiation of rapid movement adjustments, yet none of these studies recorded EMGs to further validate these findings. Thus, it is unclear whether such signalling in premotor, motor, and parietal cortices is quick enough to effectively trigger rapid responses, or whether they could be involved in subsequent phases of movement guidance. The next section will delve into the timing of these signals, assessing whether they meet the demands of EVRs and other rapid responses.

1.2.1.1 Signal timing in cortical areas in rapid responses

Comparatively few non-human primates (NHPs) studies have examined neural timing in reflexive visually guided reaching tasks. Georgopoulos and colleagues (1983) were pioneers in studying single neuron activity in monkeys performing single- and double-step tasks. Their data show a reaction time of approximately 250 ms after target displacement, obtained from hand velocity. They recorded from the motor cortex of three monkeys during these tasks and observed similar activity patterns in both conditions, with higher activity during corrected movements. They attributed this increased activity to the higher hand velocity during corrections. Notably, they reported an increase in cell discharge in the anterior bank of the central sulcus approximately 100 ms after the appearance of the second target and before the hand movement, comparable to that observed in single-step trials.

Further expanding on this, Archambault et al., (2011) recorded activity from single neurons in PMd, M1, and PPC. They reported hand reaction times obtained from hand trajectory changes of 320 ms and 275 ms for the first and the second targets, respectively. They found that PMd exhibited pre-movement activity peaks after the presentation of both the first and second targets, while M1 was responsible for initiating hand movement and continuously controlling hand kinematics. Additionally, PPC displayed a sustained activity pattern throughout the movement, independent of the timing of the second target presentation, which they attributed to the detailed control and specification of the new trajectory's kinematics. They identified the exact moments when the activity patterns for single-step and double-step reaches began to diverge in the same neurons, noting that PMd showed changes 70 ms after a target jump, followed by M1 at 107 ms, and PPC at 127 ms (Figure 4). Observing this sequence, they suggested that the higher-order command to initiate the change of hand path is first encoded in the premotor cortex, then in the motor and parietal cortices. In this process, PMd provides an early command signal to update motor output when environmental conditions and the overall motor plan change. M1 plays a direct and early role in providing precise control of hand kinematics, while PPC continuously estimates limb kinematics dependent on sensory feedback (Archambault et al., 2015).

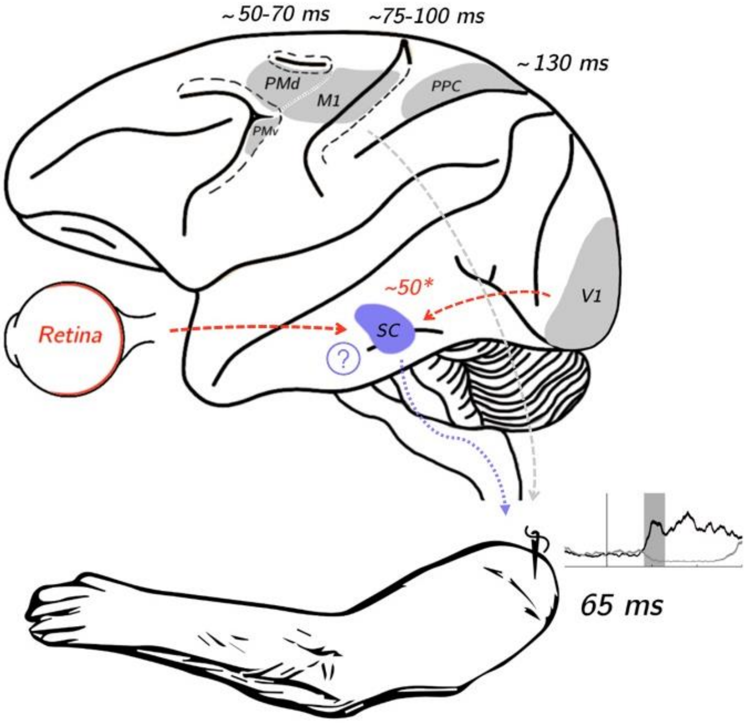

Figure 4. Signal timing in potential cortical and subcortical substrates of EVRs.

Cecala et al. (2023) demonstrated that upper limb muscle activity in monkeys during a reflexive reaching task exhibits goal-directed responses at ~65 ms after target onset. In tasks requiring rapid responses, studies show a sequence of neural activations across cortical areas: the PMd responds first at around 50-70 ms, followed by the M1 at 75-100 ms, and the PPC at approximately 130 ms (see the text

for more details). Another hypothesis suggests that EVRs may originate from the superior colliculus, a midbrain structure receiving visual input from the retina and V1 (as indicated by red arrows). The asterisk shows the visual latencies reported in SC during oculomotor tasks (Rezvani & Corneil, 2008). This thesis aims to establish the timing of visual signals in the superior colliculus in reflexive tasks.

Moreover, similar patterns of activity were noted following the presentation of the first target. The earliest activity in both the frontal and parietal cortices was detected 60 ms after target onset. On average, PMd cells were engaged within 120 ms post target-appearance, M1 cells at 180 ms, and PPC cells at 200 ms. This leading role of the premotor cortex, crucial in initiating motor commands, has been corroborated by other studies with similar latencies, although in different task conditions (Johnson et al., 1996; Kalaska & Crammond, 1992; Pesaran et al., 2008; Westendorff et al., 2010). However, some studies have observed very early onset activity in the primary motor cortex, as early as 50 ms (Reimer & Hatsopoulos, 2010). To reconcile this finding with the others recording from M1, it is important to note that the timing of neural activity onset is significantly influenced by factors such as the recording location and the different layers within a brain region. Not all neurons within a given area receive their inputs via the shortest possible routes. For instance, decision-related activity in PMd emerges earlier in superficial layers compared to deeper layers (Chandrasekaran et al., 2017). Moreover, previous research suggests that faster timing may reside in neurons sampled from the caudal part of M1 (Cisek et al., 2003; Crammond & Kalaska, 1996, 2000; Rathelot & Strick, 2009; Witham et al., 2016) consistent with the delay in onset times of proximal versus distal cortical sites (Murphy et al., 1985).

In another study by Dickey et al. (2013), neural activity in PMd, M1, and ventral premotor cortex (PMv) was recorded from three monkeys during 1-dimensional single-joint (elbow) movements with and without a change in target location. They reported an average reaction time obtained from hand velocity of 215 ms after a target jump which was similar to the reaction time after a single-target presentation. Consistent with previous studies, they showed that the premotor cortex responded to the double-step target jump earlier than M1, with no significant difference in mean neural onsets between neurons in PMd and PMv.

In the mentioned NHP studies, the reaction times (200-300 ms) are notably slower than those reported by Perfiliev et al. (2010) for an intercepting task (120-200 ms). It is also higher than corrective responses in humans (~100 ms), which is surprising given that hand reaction times to visual targets are generally faster in monkeys than in humans. This discrepancy might be due to the extensive training that monkeys undergo, leading them to adopt different strategies. For instance, monkeys might wait longer after the initial target presentation or move more slowly to minimize errors and maximize reward probability. This strategy could be particularly relevant given that the likelihood of encountering a double-step condition is lower than that of a single-step condition in these experiments. Additionally, variations in reaction times and the onset of neural activity between these NHP studies could be linked to differences in experimental design, such as the use of different stimuli or the need for different spatial transformations, and methodological approaches, such as applying non-causal filters to neural data.

Interestingly, a recent study by Cross and colleagues (2024) found hand reaction times in monkeys to be closer to those typically observed in humans. They observed hand velocity changes at ~139 ms after a visual target jump for two monkeys. Chronic EMGs recorded from the shoulder, arm, and chest muscles indicated an onset time of ~110 ms post-target displacement, although they did not analyse EMG responses on a trial-by-trial basis to determine if EVRs were present. Additionally, neurons in the arm region of M1 showed divergent activity patterns approximately 80 ms after the target displacement, corresponding to different locations.

Neural activity has also been recorded in other reflexive tasks. Using the Quasi-automatic task, described in the previous section, Lara et al. (2018) analysed the population activity of neurons within PMd and M1. Monkeys had reaction times of ~200 milliseconds obtained from hand velocity, with the earliest EMG activity appearing around 90 milliseconds. Despite the quick reaction times, no EVRs were observed in the muscle recordings for this task. They distinguished between neuronal activity in preparatory and movement-specific subspaces and reported signal timing more aligned to movement onset rather than the target onset, a key difference from the EVR. Activity in the preparatory subspace was found to precede that in the movement subspace by roughly 40 milliseconds. As activity in the movement subspace increased, the preparatory subspace activity decreased, overlapping for about 100 milliseconds. The activation of the movement subspace occurred just prior to detectable changes in EMG, with a latency of approximately 21 milliseconds. They concluded that if movement-subspace activity is what cortico-motoneurons rely on, its onset occurs early enough to contribute to the initiation of muscle activity.

These studies collectively outline a consistent sequence of neural activations across cortical areas during reflexive tasks, with the PMd responding first at approximately 50-70 ms after target presentation, followed by the M1 at 75-100 ms, and the PPC at around 130 ms (Figure 2). Notably, the activity of most neurons in PMd and M1 occurs before any observable changes in hand movement or EMG activity, where recorded. In contrast, in PPC the activity in most cells lagged hand kinematics, although both leading and lagging types were seen in all areas. Importantly, studies that recorded EMGs either did not analyze single-trial muscle activity for detecting EVRs or failed to detect them. Considering Cecala's findings that EVRs can occur on average as early as 65 ms in monkeys and the afferent delay between cortical neurons and muscles (~10 ms) it remains uncertain, based on latency alone, whether the premotor and motor cortex can generate EVRs.

1.2.2 Potential subcortical substrate

An alternative hypothesis suggests that rapid responses are mediated through a subcortical pathway rather than the corticospinal pathway typically associated with voluntary reach movements. Supporting evidence comes from a study of a patient with complete agenesis of the corpus callosum, the structure connecting the left and right cortical hemispheres (Day & Brown, 2001). The researchers hypothesized that movements requiring interhemispheric communication would exhibit delayed reaction times compared to those that did not. Their findings confirmed significant reaction time differences (~35 ms) in this patient, unlike healthy controls, for visually guided reach movements from a static starting posture when the visual stimulus was in the opposite visual hemifield compared to the same hemifield. However, online corrections to target displacements were rapid (~120 ms) and unaffected by the visual hemifield of the stimulus or the hand used, suggesting the involvement of subcortical pathways. Day has since suggested that the superior colliculus (SC) and underlying mesencephalic reticular formation may play a critical role in mediating these rapid visuomotor reach responses (Day, 2014). This section will explore this circuitry and investigate its involvement in EVRs generated by eye and neck muscles, providing evidence of its role in these behaviours.

1.2.2.1 Superior colliculus: connections, and functions

The superior colliculus (SC) is a laminar structure seated on the roof of the midbrain underneath the thalamus, also known as the optic tectum in non-mammals. It is highly conserved across species and plays a vital role in integrating sensory inputs and coordinating a diverse repertoire of movements and processes that together define the orienting response. The SC is composed of seven anatomical layers organized into three primary layers: superficial (SCs), intermediate (SCi), and deep (SCd) layers, each contributing to different aspects of sensory and motor integration. This general organization is present in all vertebrates, although the different layers can vary in prominence and subdivision (for review see: May, 2006).

The superficial layers of the SC are primarily visual, receiving direct inputs from the contralateral and ipsilateral retina along with indirect inputs from the visual cortex, forming a detailed retinotopic map of the visual field (May, 2006; Pollack & Hickey, 1979). Visual neurons in the SCs respond rapidly (on average within 50 ms) to visual stimuli in a restricted region of the visual field that defines the neuron’s response field. The SCs responses are modulated by stimulus properties such as contrast and spatial frequency (Chen et al., 2018; Marino et al., 2012, 2015). Some of the SCs efferent axons project directly to the SCi (Saito & Isa, 2005).

The SCi and SCd layers of the SC are more involved in the visuomotor transformation and are typically known for their role in saccade generation. These layers integrate a confluence of inputs from over 40 different cortical and subcortical projections, enabling flexible response properties (Edwards et al., 1979; Huerta & Harting, 1984). Functionally, the SCi/d are sometimes lumped together, as they are more similar to each other than the SCs.

More specifically, the SCi contain both visual and motor related neurons, facilitating the transformation of sensory input into motor commands for saccadic eye movements (Kojima & Soetedjo, 2017; Phongphanphanee et al., 2011). These layers include inhibitory GABAergic interneurons and excitatory interneurons, which can suppress and enhance SCs activity, respectively (Basso et al., 2021). There is some evidence that suggests that SCi visual-related activity depends on the indirect corticotectal pathway, with inactivation of either the LGN or primary visual cortex selectively abolishing SCi responses (Schiller et al., 1974, 1979; Takaura et al., 2011; Yu et al., 2024). Nonetheless, in non-reflexive saccade tasks, visual signal timing increases modestly with depth. Visual signals are processed first in the superficial layers before being relayed to the intermediate layers (Massot et al., 2019). In addition to SC’s retinotopic map, the SC also hosts a representation of saccadic eye movement space. According to the dual coding hypothesis, the spatial location of maximal discharge of movement neurons within the collicular map determines the direction of saccades, while the frequency of discharge regulates their speed (Edelman & Goldberg, 2001).

The SCd receive diverse inputs from various sensory modalities, including visual, auditory, and somatosensory information, as well as projections from the prefrontal and parietal cortex and subcortical structures (Meredith & Stein, 1986; Sparks & Hartwich-Young, 1989). These layers integrate multimodal signals to guide behavioural responses and initiate orienting reflexes like saccades (May, 2006). The SCd also plays a crucial role in controlling movements of the eyes, head, neck, and limbs through connections with the reticular formation and spinal cord (for review see: Corneil & Munoz, 2014).

Often, eye movements are studied in head-restrained conditions; however, in the natural world, gaze shifts involve coordinated movements of both the eyes and the head, and the Sci/d is involved in more than just simple head-fixed saccadic eye movements (for review see Gandhi & Katnani, 2011). Under head-unrestrained conditions, the SC coordinates eye and head movements for gaze shifts. Electrical stimulation of the SCi/d evokes coordinated eye-head gaze shifts, consistent in size and direction regardless of initial positions, suggesting the SCi/d encodes desired gaze shifts rather than specific eye or head movements (Corneil et al., 2002b; Freedman et al., 1996).

The SCi/d broadcasts its output signals widely through both ascending and descending projections to various targets. In the oculomotor system, ascending projections from the SCi/d through the medial dorsal (MD) nucleus of the thalamus relay an efference copy signal of an impending saccade to the frontal cortex (Sommer & Wurtz, 2004). Output neurons from the SCi/d 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 centres and a descending branch that crosses the midline and courses via the predorsal bundle through the brainstem to the upper cervical spinal cord (Grantyn & Grantyn, 1982; Moschovakis et al., 1996; Rodgers et al., 2006). Moreover, the SC integrates auditory and somatosensory maps that are aligned with its visual and movement representations. These multisensory mappings align sensory modalities for coherent spatial processing, facilitating coordinated responses to multimodal stimuli (Frens & Van Opstal, 1998; Wallace et al., 1996). Such integration underscores the SC's role not only in visual processing but also in multisensory integration and spatial awareness, contributing to adaptive behaviours in dynamic environments.

Attention and task demands can selectively influence the magnitude, but not latency, of the initial visual-related activity (Everling et al., 1999; Goldberg & Wurtz, 1972; Krauzlis et al., 2013). Reciprocally, the SC influences attention and decision-making through its connections with the basal ganglia and cortical areas. Inactivation of the SC affects visual selection and attention. Furthermore, electrical stimulation of the SC confirms its role in modulating decision thresholds (Crapse et al., 2018), and collicular manipulations can bias choice behaviours (Carello & Krauzlis, 2004; Lovejoy & Krauzlis, 2010) and target selection, even for non-saccadic responses (Song et al., 2011). In line with other sensorimotor areas discussed in previous sections, in SC, the same neurons appear to first reflect decision-related variables such as the quality of evidence in favour of a given choice and then later encode the metrics of the action used to report the decision (Kim & Basso, 2008).

1.2.2.2 Express saccades are mediated through the SC

SC, due to its strategic location and extensive subcortical pathways, plays a pivotal role in mediating reflexive orienting behaviours by rapidly integrating multisensory inputs and directing appropriate motor responses towards salient stimuli in the surrounding environment (Isa et al., 2021). In primates, this integrative function is particularly evident in the domain of visually guided saccades, where saccadic reaction times sometimes exhibit a bimodal distribution. Human and NHPs saccades, when voluntarily initiated, typically have latencies exceeding 120 milliseconds, which form the second peak of this distribution. Conversely, the first peak comprises express saccades, notable for their rapid onset—occurring within 100 milliseconds after stimulus onset in humans (Fischer & Ramsperger, 1984) and within 75 milliseconds in NHPs (Fischer & Boch, 1983). Electrophysiology studies in NHPs show that, during normal saccades, there is a delay between the visual burst offset and the motor burst onset in the SC. Under specific conditions, this visual burst, along with pre-sensory activity, can directly initiate a motor burst in SCi/d, thus triggering express saccades (Dorris & Munoz, 1998; Edelman & Keller, 1996; Sparks et al., 2000). The timing of the visual stimulus relative to the fixation point, the removal of the fixation point just before the appearance of a new visual target in order to reduce the inhibition imposed by the fixation-related neurons, predictability of target location, and the overall readiness of the saccadic system all contribute to the facilitation of express saccades. Additionally, the activity within a subcortical pathway involving the SCi/d and the influence of cortical regions, particularly FEF, modulate the initiation of these rapid eye movements (Dash et al., 2020). Disruptions to SCi/d permanently eliminate express saccades to the contralateral visual field without affecting regular saccades (Schiller et al., 1987).

Express saccades and EVRs share several notable similarities, potentially consistent with a common neural underpinning. Both express saccades and EVRs exhibit latencies that approach the minimal time required for the conduction of visual information from the retina to the generation of a motor command, reflecting their rapid response characteristics (Cecala et al., 2023; Munoz et al., 2000). They show a preference for low spatial frequency images, which enhance superior colliculus (SC) activity—a preference further amplified by higher reward expectations, leading to an increase in express saccade generation and elevated SC activity (Chen & Hafed, 2018; Kozak et al., 2019; Rezvani & Corneil, 2008). Both express saccades and EVRs are optimally evoked by high-contrast stimuli, with lowered contrast negatively impacting their occurrence (Bell et al., 2006; Marino et al., 2015; Wood et al., 2015). Additionally, both are tuned to direct the eye, head, or limb toward the visual stimulus regardless of task instructions (Chapman & Corneil, 2011; Everling et al., 1999b; Gu et al., 2016). These parallels highlight the integrated nature of visual and motor processing within the SC, emphasizing its role in facilitating rapid and efficient visuomotor responses toward a stimulus.

1.2.2.3 Visual responses in SCi/d trigger EVR in the neck muscles

Descending axons from the SCi/d travel through the predorsal bundle and send multiple collaterals to the ventrolateral and dorsomedial reticular formation, which houses reticulospinal neurons projecting signals down the spinal cord (Isa & Sasaki, 2002; Scudder et al., 1996; Takahashi et al., 2014). This neural circuitry supports a hierarchical organization of motor responses, often sequencing head movements to precede eye movements, as described by Zangemeister and Stark (1982). Notably, low-frequency stimulation of the SC induces low-level EMG activity in the deep neck muscles on the contralateral side, even when the head is restrained (Corneil et al., 2002b). When the head is unrestrained, similar stimulation below the threshold to evoke a saccade can trigger head-only movements, with the eyes counter-rotating in their orbits due to the vestibulo-ocular reflex (Corneil et al., 2002a). These observations suggest that SC output is processed differentially by the downstream premotor centres for saccadic versus head control, exhibiting selective gating. The premotor circuits for saccades, which generate the saccadic eye component of the gaze shift, are strongly inhibited by pontine omnipause neurons (OPNs), preventing premature eye movements until the SC output reaches a threshold, typically associated with a high-frequency burst. In contrast, OPN inhibition does not appear to influence the premotor circuits for orienting head movement, allowing SC circuits below the saccade threshold to initiate neck muscle signals and head-only movements before saccadic gaze shifts (Corneil & Munoz, 2014).

Corneil et al. (2004) observed EVRs on monkey neck muscles at extremely short latencies of 60–90 ms while the animals were doing visually guided saccades with fixed heads. Similar responses have been observed in humans, typically occurring around 95 ms post-stimulus (Goonetilleke et al., 2015). Importantly, the magnitude of these EVRs inversely correlates with the saccadic reaction time, resembling the relationship between the magnitude of the visual response in the SC and saccadic reaction times. This is consistent with the selective gating hypothesis and supports the supposition that the visual responses in SCi produce the EVR in the neck muscles (Corneil et al., 2008). Moreover, Rezvani and Corneil (2008) showed, by simultaneously recording SCi/d neuron activity and EMG activity of head-turning neck muscles, that the magnitude of neck muscle recruitment positively correlated on a trial-by-trial basis with the level of low-frequency SCi/d activity. Additionally, SCi/d activity discriminated the side of target presentation approximately 11 ms earlier than neck EMG activity, consistent with the efferent delay from the SCi/d to the neck muscles (Corneil et al., 2002b).

1.2.2.4 The role of SCi/d in reach control

The SC is traditionally associated with gaze control, but evidence also indicates its involvement in reach control. A subset of SC neurons, known as reach-related neurons, contribute to limb motion and muscle activity, both with and without accompanying saccadic eye movements (Stuphorn et al., 2000; Werner, et al., 1997a). These neurons are active before and during reach movements, primarily of the contralateral arm, and correlate well with upper limb muscle activity (Stuphorn et al., 1999). Interestingly, some reach-related neurons also exhibit visual responses, indicating an integration of visual and motor functions (Werner et al., 1997a).

Unlike the orderly retinotopic organization of other SC layers, reach-related neurons are predominantly found in the SCi and SCd, mainly in the lateral SC and the underlying mesencephalic reticular formation (Stuphorn et al., 2000, 1999; Werner, 1993; Werner et al. 1997a; 1997b). This anatomical setup is consistent with findings that electrical stimulation of these SC layers elicits body and limb movements in cats and monkeys (Courjon et al., 2004; Philipp & Hoffmann, 2014). Human imaging studies also show increased BOLD activity in the SC during contralateral reach movements (Linzenbold & Himmelbach, 2012). Moreover, a distinct subpopulation of intermediate and deep SC neurons possesses a somatosensory component. These neurons are active when the hand touches and pushes a target but remain inactive during the reach phase (Nagy et al., 2006).

The role of the SC in reaching is further supported by the extensive projections it receives from areas of the dorsal stream, such as the PPC and early extrastriate cortex (Asanuma et al., 1985; Fries, 1984). Additionally, strong projections from the ipsilateral M1 (Fries, 1985), PMd (Distler & Hoffmann, 2015), and PMv (Borra et al., 2014) target the lateral part of the deep SC and the underlying reticular formation, where reach-related neurons are located and from which descending tecto-fugal projections arise. Furthermore, the SCi/d project to centres containing reticulospinal and propriospinal neurons, which extend further down the spinal cord to target axial and proximal limb muscles (Alstermark & Isa, 2012; Illert & Tanaka, 1978; Werner et al., 1997b). Overall, this evidence suggests that the SC could be significantly involved in arm and hand movements, integrating visual information to influence both eye and arm movements. The SC is ideally situated to support complex motor behaviours like reaching and grasping.

Despite the extensive research on visually guided reaching and the role of the SC in rapid motor responses, a significant gap in knowledge persists: the timing of neural signals in the monkey SC during reflexive reaching tasks has never been directly studied. This gap is critical because understanding the exact temporal dynamics in the SC could provide crucial insights into the mechanisms underlying EVRs.

1.3 The current study

The goal of this thesis is to test the hypothesis that the SC initiates the EVRs. To test this hypothesis, neural activity was recorded from the SC of two macaque monkeys performing the emerging target task, which is known to provoke EVRs on upper limb muscles in ~65 ms. It was found that visually related information in this task reaches the movement-related layers of the superior colliculus within approximately 51 ms. Although simultaneous EMG and superior colliculus recordings were not conducted, the timing of this information's arrival is sufficiently early to trigger EVRs, accounting for an estimated ~15 ms efferent delay along the tecto-reticulo-spinal pathway.

Chapter 2

2 Methods

2.1 Subjects and physiological procedures

One male and one female monkey (Macaca mulatta, monkeys Gr and Be, weighing 8.5 and 11.5 kg, ages 13 and 11 years, respectively) were used in these experiments. All training, surgical, and experimental procedures were in accordance with the Canadian Council on Animal Care policy on the use of laboratory animals (Olfert, 1993) and approved by the Animal Use Subcommittee of the University of Western Ontario Council on Animal Care (Appendix 1). The monkeys' weights were monitored daily, and their health was under the close supervision of the university veterinarians.

Each monkey underwent a sterile surgical procedure enabling head-immobilized measurements of eye movements, and extracellular recording within the SC. In both surgeries, anesthesia was induced with ketamine and a loading dose of propofol and maintained with a drip infusion of propofol and midazolam. Heart rate, blood pressure, respiratory rate, and body temperature were monitored closely during the surgery. Antibiotics (cefazolin) were administered pre- and postoperatively, and anti-inflammatories (metacam) and analgesics (buprenorphine) were administered postoperatively. A head holder and a recording chamber were embedded in an acrylic implant, with the recording chamber positioned over a 19-mm craniotomy tilted ~35-38° posterior in the sagittal plane, allowing a surface-normal approach to the SC. This surgery was conducted before training for Monkey Gr, whereas Monkey Be had undergone four months of head-free training prior to headpost placement. Following the recovery of more than one week, the animals were trained again on the tasks described below. For the training and experimental sessions, the monkeys were seated in a custom-designed primate chair, which restrained their left arm, torso, and hips, while allowing free movement of the right arm in a three-dimensional workspace. The headpost facilitated the restraint of the head during these sessions. During head-free training, head movement was minimally restricted by a custom-made 3D-printed nose cone. The experimental setup was in a dimly lit room. The monkeys were monitored via a video camera. Visual stimuli and behavioural control were administered through the MATLAB toolbox MonkeyLogic (Hwang et al., 2019). All visual stimuli were presented on a 42-inch, colour touch-sensitive monitor (4202L Elo Touch Solutions, Inc., Milpitas, CA) positioned 30 cm in front of the monkeys. The monitor had a spatial resolution of 1920 × 1080 pixels and a refresh rate of 60 Hz. We collected eye position signals from either an ISCAN camera (ETL200, sampling rate 240 Hz) or a chair-mounted eye tracker (EyeLink II, sampling rate 500 Hz) in monkeys Gr and Be, respectively.

2.2 Behavioural paradigms

2.2.1 The emerging target task

Monkeys performed visually guided reaches to stimuli presented within the context of an emerging target task (Cecala et al., 2023; Kozak et al., 2020). The task involves a moving stimulus that temporarily disappears behind an occluder and then emerges in motion at either the left or right outlet (Figure 5). This task was chosen as it engenders express visuomotor responses in most human subjects (Contemori et al., 2021a, 2021b; Kearsley et al., 2022; Kozak & Corneil, 2021) and in nonhuman primates (Cecala et al., 2023). Monkey Gr in this study was one of the subjects in the study of Cecala et al. (2023) and hence is known to generate EVRs. All trials started with a red ‘start position’ stimulus that appeared at a central location below a gray rectangular occluder. The monkeys were required to touch and hold the location of this start position stimulus within a computer-defined window of 7 cm for 500 ms. Following this, a red target stimulus appeared above the occluder. It then dropped vertically at a constant velocity of 20 cm/s and then disappeared behind the occluder. To make the task more natural for the animal and to avoid neural suppression in the SC due to fixation (Munoz & Wurtz, 1993), there were no constraints on where the animal could look after the initial fixation period, although the gaze was monitored during the task. After a fixed latency of 300 ms, a red target then emerged in motion below the occluder at either the right or left outlet (referred to as target onset). At the same time, the start position stimulus disappeared and a secondary visual stimulus that lay under a photodiode (and hence was unseen by the monkey) was presented for data alignment purposes. To obtain a reward, the monkeys had to maintain contact on the start position until target emergence below the barrier, and then reach to touch the colored target (within an 11 cm radius). The moving-coloured target that appeared below the barrier started 15 cm to the right or left of the start position stimulus and then moved in a lateral-downward direction (45 deg below horizontal) at 20 cm/s.

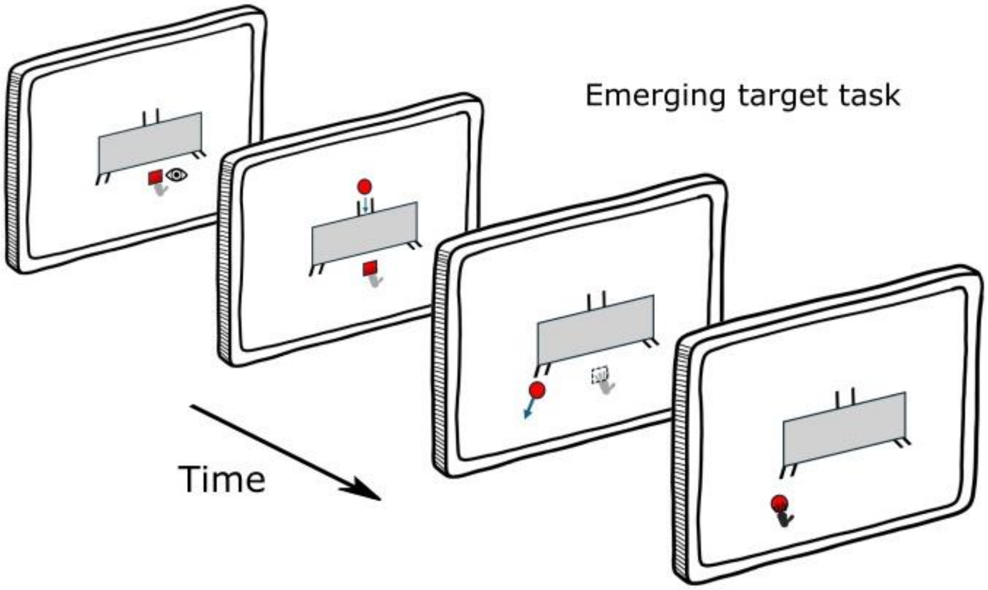

Figure 5. Emerging target task.

Each trial begins with the monkey fixating on a start position located below an occluder with its eyes and touching the same position with its hand, holding both for 500 ms. A target then appears above the occluder, moves vertically, and disappears behind it for 300 ms. Upon reappearing from either the left or right outlet, the target moves downward and laterally, and the monkey must reach toward it to receive a reward. The background was originally black, but it is shown as white here for visualization purposes.

2.2.2 Functional classification tasks

In addition to recording neural activity in the Emerging Target Task, we also recorded neural activity in two additional tasks, the Eye-Only (Figure 6A) and Eye-Hand tasks (Figure 6B). The primary purpose of this was to functionally classify whether SC neurons were influenced by the requirement to make an arm movement or not. Additionally, we categorized the neurons based on their association with visual target presentation, saccade generation, or the generation of a reach movement. In the Eye-Only task, monkey Gr fixated on the centre of the screen with both its eyes and hand for 300-500 ms. A target then appeared 15 cm to either the left or right of the screen, and the monkey made a saccade to the target while keeping its hand in contact with the touchscreen at the centre point. Monkey Be was not trained to keep the hand in contact in this task, so for monkey Be the Eye-Only task was performed with the right hand constrained within the primate chair. The Eye-Hand task was the same for both monkeys and required them to position both their eye and hand at the centre point with both its eyes and hand. After the target appeared, the monkeys made a coordinated saccade-and-reach movement to the target.

Within a typical experimental day, we collected data in separate blocks, first from the Eye-Only task, then the Eye-Hand task, and finally from the emerging target task. Within a block of trials, left and right trials were presented with equal frequency but randomly interleaved. A 1000-ms inter-trial interval was presented between trials.

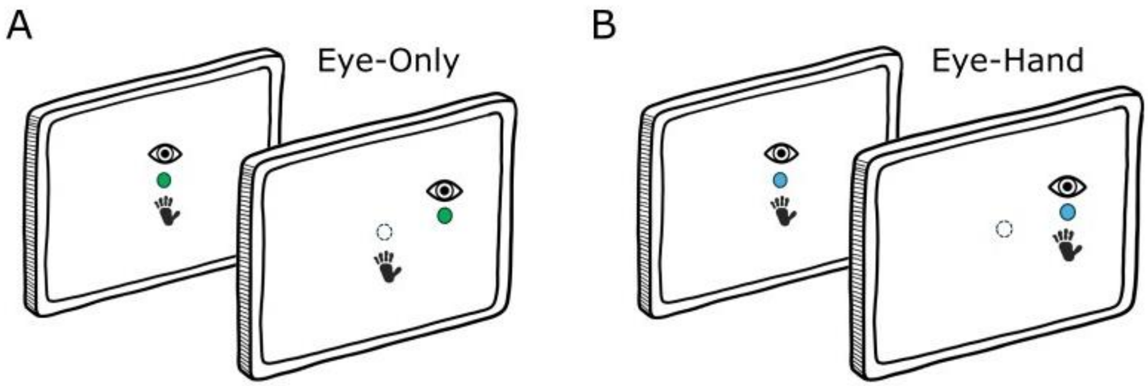

Figure 6. Functional classification tasks.

In the Eye-Only task (A), monkey Gr fixated on a central point with both their eyes and hand for 300-500 ms. Afterward, a target appeared 15 cm to the left or right, prompting the monkey to make a saccade to the target while keeping their hand in place. Monkey Be performed the Eye-Only task with the right hand constrained within the primate chair. In the Eye-Hand task (B), both monkeys positioned their eyes and hand at the central point. Upon target presentation, they performed a coordinated saccade-and-reach movement to the target. These tasks were also used to differentiate SC neuron responses related to visual target presentation, saccade generation, and reach movements. The background in both tasks was originally black, but it is shown as white here for visualization purposes.

2.3 Behavioural analysis

Behavioural analog data, including eye-tracker and touchscreen inputs, were recorded using both the MonkeyLogic toolbox and a Grapevine system (Ripple Neuro). Saccade onsets were initially identified using a velocity criterion of 30°/s from -500 ms relative to target onset to the end of each trial. These onsets were then verified and corrected, if necessary, using a customized graphical user interface (GUI) developed in MATLAB. Arm movement onsets were determined by the first deviations in the horizontal or vertical axis before the animal lifted its hands from the screen. All arm movement onsets were verified and corrected, if needed, within the same MATLAB GUI.

Monkey Gr reached toward the incorrect location in 12.2% of trials, compared to 14.0% for Monkey Be. To detect anticipatory saccades, a saccade reaction time threshold of 70 ms for Monkey Gr and 60 ms for Monkey Be was established by comparing the cumulative distribution function of reaction times for incorrect and correct trials. Although eye position was not constrained during the gap period in the emerging target task, we observed that Monkey Gr made anticipatory saccades in the wrong direction, first looking incorrectly after target onset in 8.9% of trials. For Monkey Be, this occurred in 13.3% of trials. To ensure that the recorded SC activity reflected consistent target-directed behaviors, we discarded trials from further analysis if the monkey initiated a saccade within 100 ms before target onset, made anticipatory saccades after target onset, or initially reached in the wrong direction and then corrected it. These criteria helped ensure that the eyes were stable at the time of target presentation and that the neural activity was associated with the intended task performance.

2.4 Neural recording and electrophysiology analysis

Before the series of experiments began, a grid was placed inside the recording chamber to standardize the exploration of the SC. During each recording session, a Plexon S-probe (Plexon, Inc.) was inserted through a metal guide tube into one location of the grid in the SC chamber using a customized microdrive (NAN Instruments, Ltd.). Once in the SC, the probe was left to settle for 40 mins before starting the experimental session to stabilise the tissue and improve recording quality. The arrays had either 16 or 32 contacts, with inter-contact spacing of 300 µm or 150 µm, respectively. Neural activity was amplified, digitized, and recorded using the Grapevine Neural Interface Processor (Ripple Neuro, Inc.) at a sampling rate of 30k, and visualized with the associated Trellis interface. Additionally, eye movements, behavioural markers, and trial information were recorded using the same system. Neural activity was band-pass filtered between 500 Hz and 5 kHz to record spiking activity and between 0.1-250 Hz to record local field potentials (LFPs). Overall, the neural dataset includes recordings from the left superior colliculus of monkeys Gr and Be across 16 and 12 sessions, respectively (one penetration per session).

Continuous spike-channel data collected during the experimental session were sorted offline with Kilosort2 (Pachitariu et al., 2016), and manually curated using Phy (https://github.com/cortex-lab/phy). This manual curation ensured that all sorted units had plausible inter-spike interval distributions and waveform shapes consistent with action potentials. Units that did not maintain their activity in all three blocks were subsequently removed. Ultimately, a total of 503 units remained, recorded across 30 sessions (Monkey Gr: 18 sessions/143 neurons, Monkey Be: 12 sessions/360 neurons).

To localize the response fields of neurons in the SC, heatmaps based on neuronal activity during saccades were generated. Since the electrode track was directed orthogonal to the SC surface, most neuronal receptive fields (RFs) of a given recording location overlapped. The heatmap was generated based on the neuron's normalized activity from 50 ms before to 50 ms after all saccades performed by the monkey in that session, including those made in the inter-trial interval. Neural spiking activity from the SC was plotted as a function of saccade direction and amplitude. The centre of the receptive field was then determined by identifying the maximum activity on the heatmap. Using this method, 283 out of 503 units had circumscribed RFs and were the only ones used in analyses requiring the location on the SC map. To simplify terminology throughout this thesis, "receptive field" will hereafter specifically refer to the centre of the receptive field.

Figure 7A illustrates the receptive field for the most superficial neuron recorded in each session, mapped on the SC retinotopic map to show the penetration location on the SC surface. Depending on the electrode trajectory, the RFs of deeper recorded neurons could vary, as shown in Figure 7B. The receptive field of the recorded neurons ranged from 3.7° to 39° in eccentricity and lay within 78° of the horizontal meridian, with the majority being almost horizontal, having eccentricities between 15° and 30° (178 out of 283 neurons, 63%), and being near the target emergence location.

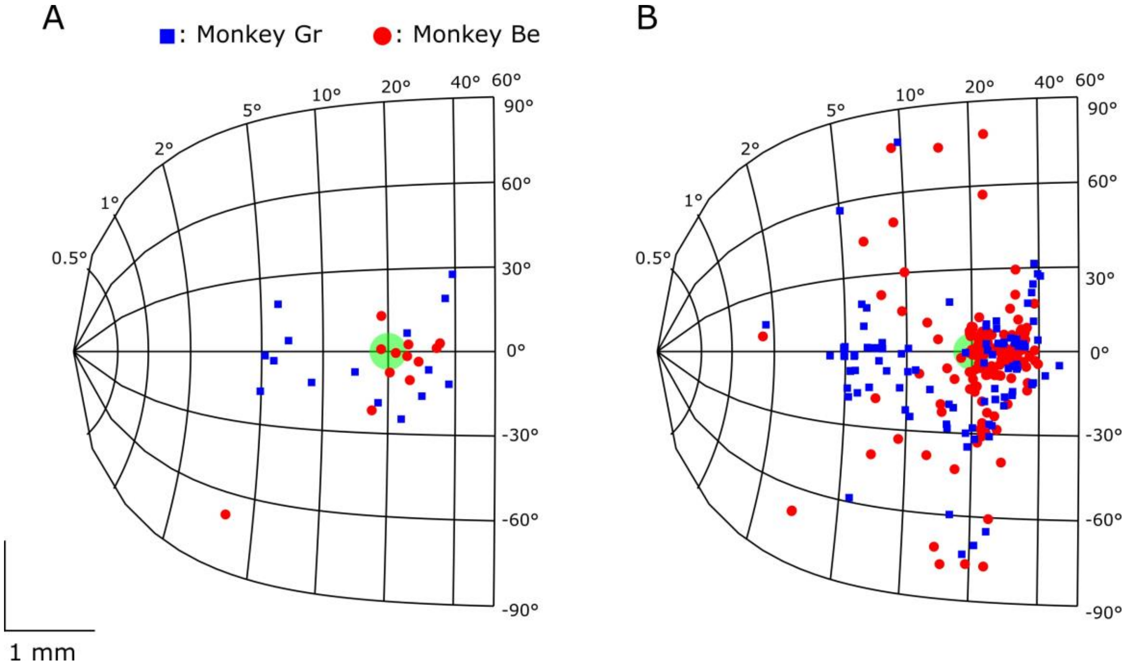

Figure 7. Penetration locations and receptive fields of recorded neurons.

(A) Receptive fields of the most superficial neuron from each experimental session, indicating penetration locations on the SC retinotopic map. (B) Receptive fields of all recorded units on the SC map. Data from Monkey Be are represented by red circles, while data from Monkey Grover are shown with blue squares. The green circle indicates the location relative to the fixation point in the visual field. The SC map is plotted based on the map from Ottes et al., (1986).

To isolate consistent neural responses and minimize noise from unsuccessful trials, we used only data from successfully completed trials where spikes occurred between 40 and 100 ms from target onset in at least 10% of trials. To assess the relationship between neural activity under various conditions, continuous spike density functions were constructed at a 1 ms resolution. Each spike was convolved with an asymmetric function resembling a postsynaptic potential (with growth and decay time constants of 1 and 20 ms, respectively) (Hanes et al., 1995) to generate the activation waveform. This method more accurately reflects that spikes exert an effect forward in time but not backward, compared to a standard Gaussian function.

2.5 Determination of neuronal depth in the SC

In each recording session, while lowering the electrode, the surface of the SC was determined as the depth where luminance-based visual modulation first appeared in the lowermost channels. After identifying the SC surface, the electrode was lowered an additional 3-4 mm until known characteristics of SC activity related to visual target presentation and/or contralateral saccade generation were observed in most channels. Due to potential electrode movement while settling, the SC surface was identified offline for each recording session. Current source density (CSD) analysis was employed for this purpose for trials where targets were presented on the contralateral side, following an approach used previously by Massot et al., (2019). In brief, CSD is the second spatial derivative of the LFP and estimates the distribution of current sinks and sources within a tissue volume, as a function of space and time (Nicholson & Freeman, 1975). In the SC, CSD analysis highlighted a strong sink following target onset (Figure 8). After computing the CSD from 0 to 100 milliseconds relative to target onset, we specifically looked for a "zero-crossing" point. This point is where the CSD transitions from positive to negative, indicating a shift from source to sink in the current flow. The channel that is closest to this zero-crossing is then noted as the “surface contact” for that session. The depth of each recorded unit was then calculated relative to the depth of the surface contact. The iCSD method from the csdplotter toolbox (https://github.com/espenhgn/CSDplotter) was used to generate the CSD. Most sessions were recorded with at least the most superficial contact kept out of the SC, meaning that the surface contact in the SC could be identified. In three sessions from Monkey Be, the shallowest contact lay deeper than the SC surface and for these sessions we used the relative depth measured by how far the electrode was moved down from the SC surface using the microdrive.

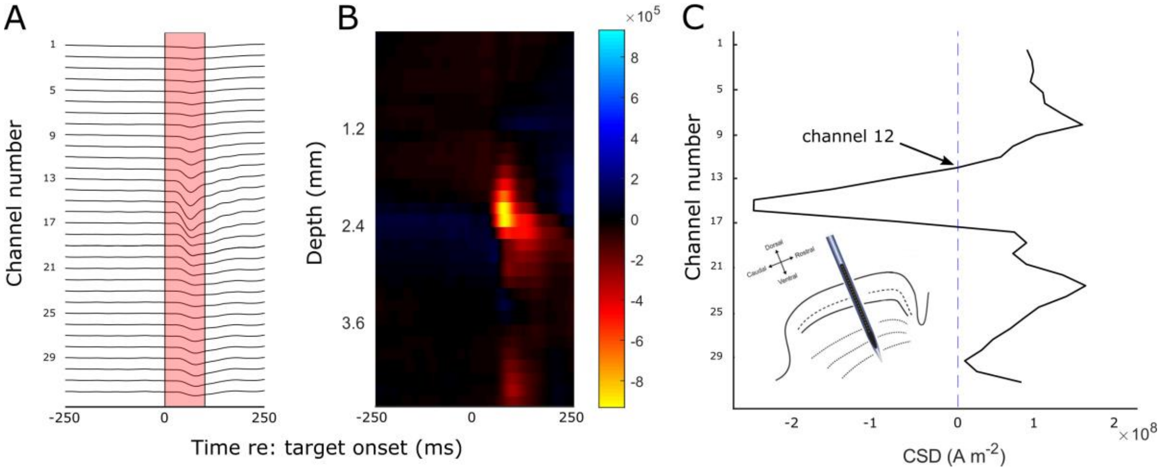

Figure 8. Determination of SC surface using CSD.

(A) Average local field potentials (LFPs) from correct trials with contralateral target presentation were plotted for all channels of a 32-contact electrode array in an example experimental session. (B) The resulting CSD plot, derived from these LFP signals, indicates current sources (positive values) and current sinks (negative values) (Depth from the first contact). (C) The CSD profile, averaged over the 0 to 100 ms interval (highlighted by the red box in (A)), was utilized to identify the SC surface. The surface contact is determined where the CSD profile crosses zero, as shown by the black arrow, marking channel 12 as the SC surface in this example. The depths of other channels were determined relative to this identified surface. The inset in (C) illustrates a multichannel laminar electrode recording from the SC, positioned nearly orthogonal to the SC surface (Adapted from Heusser et al., (2022)).

2.6 Signal timing analysis

To quantitatively determine when spiking activity in the SC neurons began to discriminate between ipsilaterally and contralaterally presented targets after target presentation, receiver operating characteristics (ROC) analysis, as described by Rezvani & Corneil, (2008), was employed for every time sample (1 ms) for rightward versus leftward reaching conditions in each block. This metric indicates the probability that an ideal observer could correctly identify the side of stimulus presentation based on neural activity. For each sample, the area under the ROC curve (ROC value) was calculated from 100 ms before to 500 ms after stimulus presentation using the convolved spike trains. An ROC value of 0.5 signifies chance performance, while a value of 0.0 or 1.0 indicates perfect performance. Time-series ROC plots were used to define the “discrimination time,” which is the point at which the ROC metric exceeded 0.6 for eight out of ten consecutive points. The threshold of 0.6 was selected because it surpasses the 95% confidence interval of data randomly shuffled with a bootstrap procedure in the 100 ms preceding target onset. To remove any potential bias contributed by the low-frequency discharge from the gap period before the target onset, a detrending procedure was applied. A linear trend was estimated between -100 to 30 ms relative to target onset. This linear trend was then extrapolated to the remaining time points and subtracted from the ROC values. ROC analyses were conducted with a minimum of 23 trials per direction (Mean ± standard deviation: 70 ± 23 trials).

2.7 Neuronal classification

In our study, we functionally classified neurons within the SC by visually inspecting their activation patterns across specific time windows during Eye-Only and Eye-Hand tasks: from 40 to 80 milliseconds after visual target onset, 50 milliseconds before to 50 milliseconds after saccade onset, and 100 milliseconds before to 100 milliseconds after the initiation of an arm movement for contralateral targets. Neurons that exhibited enhanced activity in the Eye-Hand task, compared to the Eye-Only task, were classified as "reach-modulated." We further categorized the neurons into several functional types based on their response patterns: purely visual (only active in response to target onset, categorized as “V”), purely saccadic (only active during the execution of saccades, S), visual-saccadic (active in response to target onset and during the execution of saccades, VS), purely reach-modulated (different activity in classification tasks, R), visual-reach (active in response to target onset and different activity in classification tasks, VR), saccadic-reach (active during the execution of saccades and different activity in classification tasks, SR), and visual-saccadic-reach (active in response to target onset, active during the execution of saccades, and different activity in classification tasks, VSR). The nomenclature for these neuron types corresponds to the labels used by Werner et al. (1997b). Neurons displaying complex behaviours or responses to untested parameters were excluded.

2.8 Statistical Analysis

Statistical analyses were conducted using MATLAB (version R2021b, The MathWorks Inc., Natick, Massachusetts, USA). Paired t-tests or one-way repeated measures ANOVAs were applied to analyze the results, unless stated otherwise, with post-hoc tests adjusted using Bonferroni correction when appropriate.

Chapter 3

3 Results

3.1 Emerging target task elicit very rapid responses

Both Monkey Gr and Monkey Be performed the emerging target task with remarkably fast eye and hand reaction times (Figure 9, first row in A and B). In the emerging target task, Monkey Gr exhibited eye reaction times averaging 95 ± 14 ms, with nearly all falling within the express saccade window (72.8% Express; Express saccade window: <100 ms). Similarly, Monkey Be displayed rapid eye reaction times, averaging 124 ± 46 ms, which included both express and regular saccades (41.1% Express). Both monkeys also demonstrated very fast hand reaction times, with Monkey Gr reaching the target at 118 ± 29 ms and Monkey Be at 242 ± 58 ms. Notably, saccade onsets in both animals, always occurred earlier than reach onsets.

Despite the differences in reaction times between the monkeys, both exhibited qualitatively similar eye and hand trajectories during the emerging target task as illustrated by the heatmap (Figure 9, second row in A and B). After the moving target appeared on top of the occluder, they tracked it until it disappeared behind the occluder. During the 300 ms gap period, they occasionally made saccades to the right and left target locations, and if not, they looked at the bottom of the occluder. Once the target emerged, they consistently performed both a saccade and a reach to intercept the moving target, even though only hand interception was required.

In classification tasks, most eye reaction times fell within the normal saccade window, with only 2.4% of express saccades for Monkey Gr and 17.99% for Monkey Be (Figure 9, third row in A and B). Both monkeys performed significantly faster in the emerging target task compared to the classification tasks. In classification tasks, hand reaction times are slower on average by 199 ms for Monkey Gr (Independent samples t-test; t-statistic: 93.18, 95% Confidence interval of the mean difference: [194.67, 203.04] ms, $p < 0.001$) and 118 ms for Monkey Be (Independent samples t-test; t-statistic: 32.07, 95% Confidence interval of the mean difference: [111.46, 125.98] ms, $p < 0.001$).

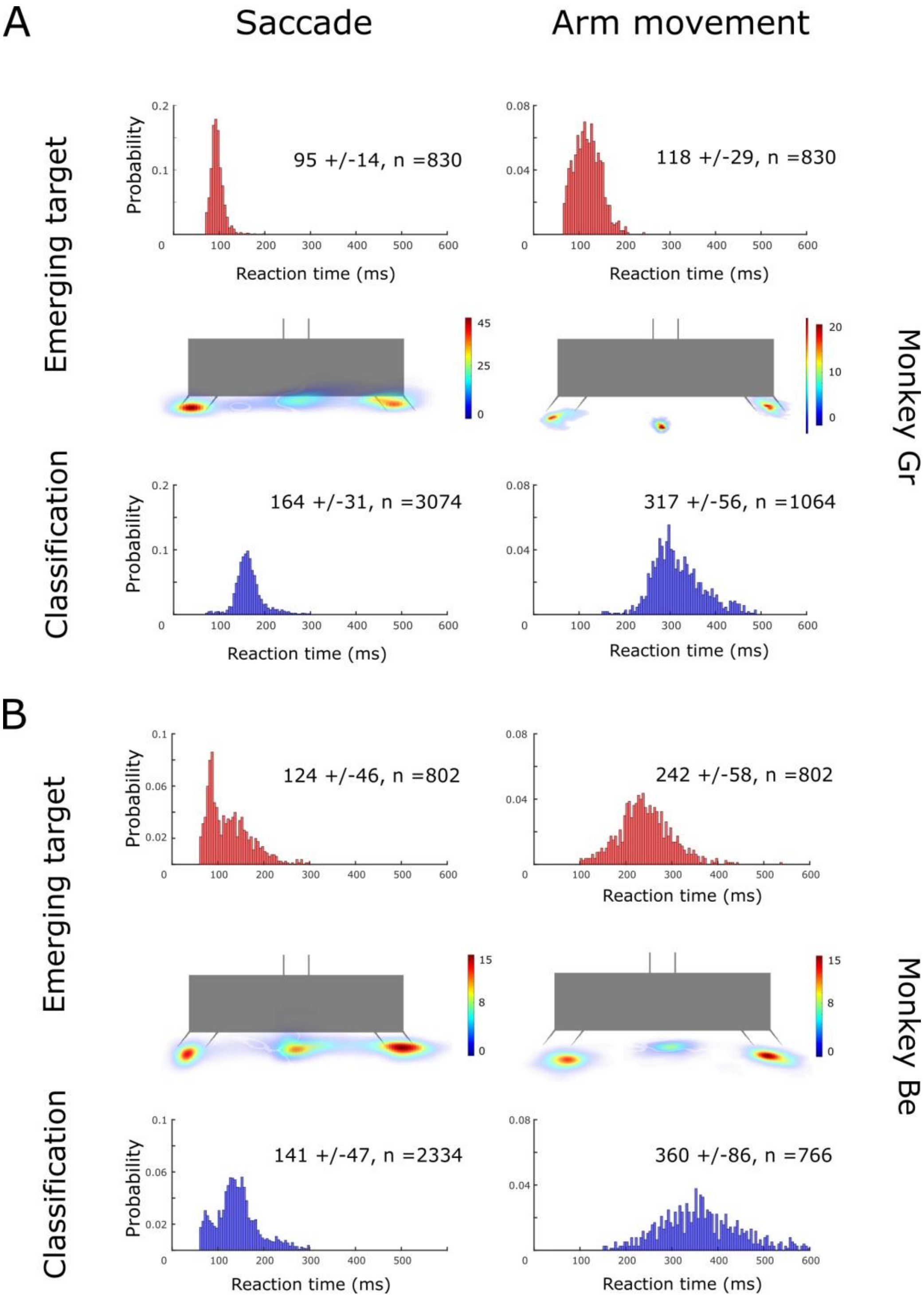

Figure 9. Behavioural summary of two monkeys in the current study.

(A) Monkey Gr and (B) Monkey Be performed the emerging target task (first row, depicted in red) with faster eye and hand movements compared to the classification tasks (third row, depicted in blue). For Monkey Gr, most eye movements fell within the express saccade range (<100 ms). In contrast, Monkey Be's eye movement reaction times included both regular and express saccades, with a higher proportion of express saccades compared to regular saccades than in the classification tasks. Although Monkey Be had longer eye and arm movement reaction times than Monkey Gr, their times were still faster than those in normal tasks. In the classification tasks, most eye movement reaction times for both monkeys fell within the regular range. The second row in each panel (A and B) displays heatmap plots of eye and arm movements in the emerging target task, with colors indicating the z-score values. The heatmaps are generated using 2D histogram counts of the binned data and are smoothed with a Gaussian filter. Only correct trials, as defined in the methods section, are included in the figures. Each figure also presents mean and standard deviation values. The left column in both panels shows data for eye movements, while the right column shows data for arm movements. Eye movement reaction times in classification tasks are combined from both the Eye-Only and Eye-Hand task.

3.2 Timing of visual responses in SC in emerging target task

Of the 503 recorded neurons, 256 exhibited a visual response (Monkey Gr: 62, Monkey Be: 189 neurons) to target emergence in the emerging target task. Figure 10 shows the activity of an example neuron from monkey Gr during this task. The neuron’s responses are depicted for rightward (contralateral to the recorded SC, shown in dark colour) and leftward (ipsilateral to the recorded SC, shown in light colour) target conditions relative to target onset and saccade onset. This neuron exhibits a clear visual burst following target emergence. To determine when discrimination between target locations occurs, a time-series receiver-operating characteristic (ROC) analysis was performed. As shown in Figure 10C, the discrimination time (ROC latency) for this neuron is 46 ms.

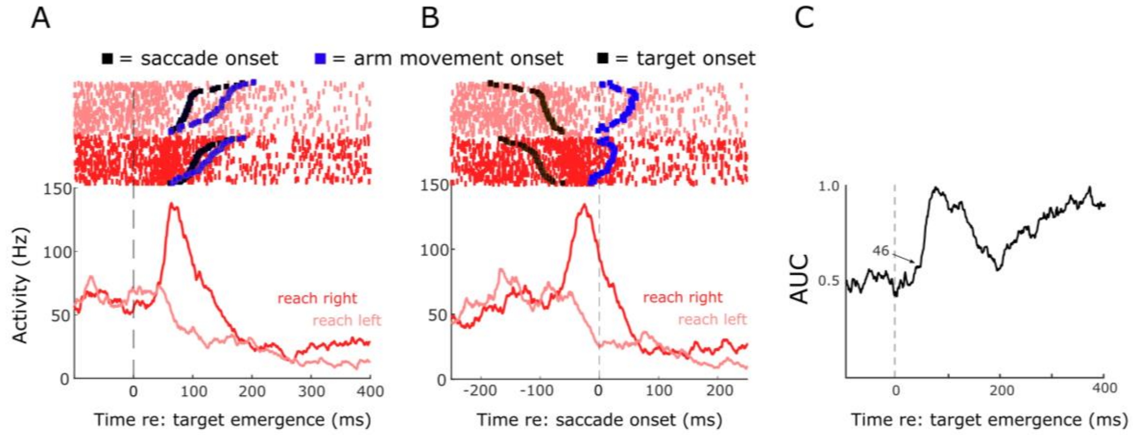

Figure 10. Activity of an example neuron in the emerging target task.

(A) and (B) showcase the average activity of an example neuron during the emerging target task, aligned with target onset and saccade onset, respectively. Rasters above each panel in (A) and (B) illustrate the timing of spikes in different trials. Trials are sorted by saccade onsets, with dark red representing activity during rightward reaches (contralateral to recording SC) and light red representing activity during leftward reaches (ipsilateral to recording SC). This neuron exhibits a prominent visual burst following the target's appearance on the right side. A clear distinction in activity between rightward and leftward reaches emerges at 46 ms, as highlighted by the time-series ROC in (C) (AUC: area under curve). In (A), black squares indicate saccade onsets, while in (B), black squares indicate target onsets relative to saccade onsets. In both (A) and (B) blue squares mark arm movement onsets.

The analysis was repeated across the sample of SC neurons that exhibited visual bursts for both monkeys (Figure 11). A ROC latency of 50.8 ± 4.7 ms (range: 42-65) was observed for neurons recorded from Monkey Gr. For neurons from Monkey Be, the ROC latency was 51.8 ± 6.0 ms (range: 38-68), with no significant difference between the monkeys ($p = 0.207$; Mann-Whitney U test). Although EMG was not recorded in this study, Cecala et al. (2023) recorded EMG data in emerging target task from two monkeys (64.2 ± 9.9 ms; range: 48-91), one of which was Monkey Gr from this study. A comparison of the ROC latencies calculated from EMG signals for rightward and leftward reaches with the ROC latencies of the SC population recorded in this study reveals a discernible ~13 ms difference, supporting the estimated efferent delay within the tecto-reticulo-spinal pathway. Since no significant difference in ROC latencies was found between animals, recorded neurons were combined for following analysis to increase statistical power.

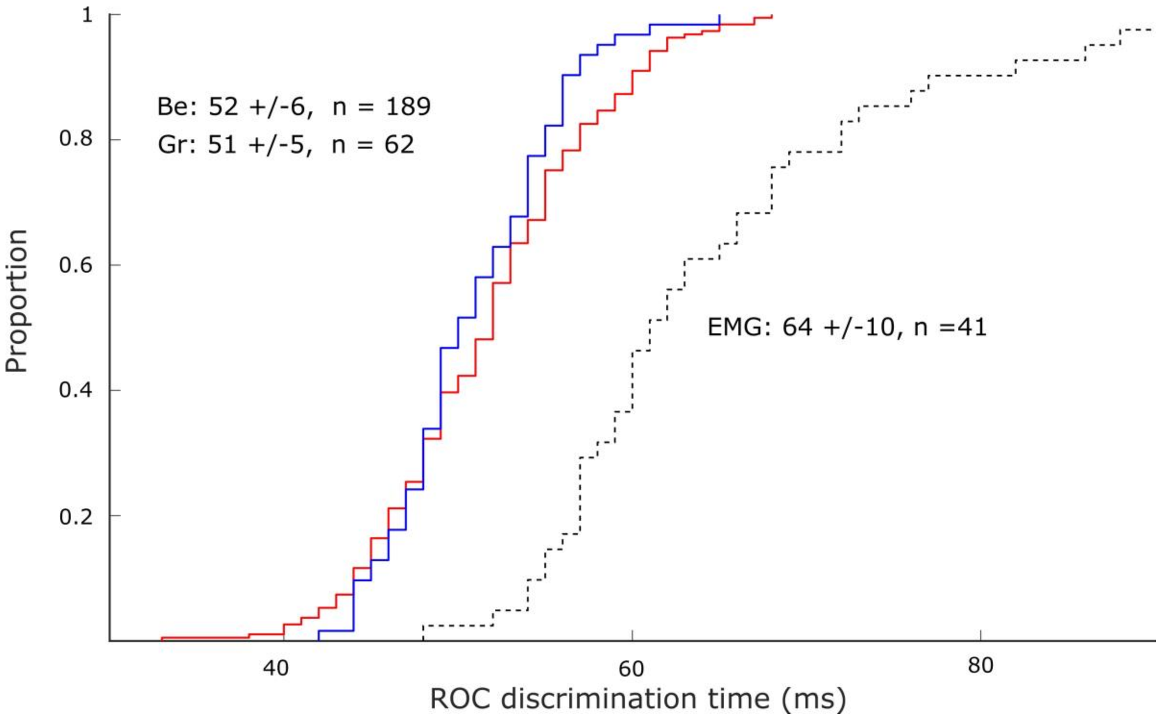

Figure 11. Cumulative distribution function (CDF) of discrimination latencies recorded from SC neurons.

The CDFs of discrimination latencies of SC neurons in Monkey Gr (blue) and Monkey Be (red) in the current study, are compared to discrimination latencies obtained from EMG recordings in two monkeys, including Monkey Gr, from Cecala's 2023 study (dotted line). SC neurons demonstrated a faster discrimination of target location, ~13 ms quicker than the EMG responses (z-value (Mann-Whitney): 8.0394; p-value < 0.001).

3.3 Timing of visual responses across the depth of SC

Werner et al. (1997b) demonstrated that the highest concentration of reach-related neurons is located in SCd. Therefore, we examined whether the timing of visual-related information changes as a function of depth. In Figure 12A, the ROC latencies for neurons exhibiting visual bursts are plotted as a function of recording depth. No significant change in ROC latencies with depth was found, as indicated by the p-value of the depth coefficient (p = 0.7581) in the linear regression analysis.

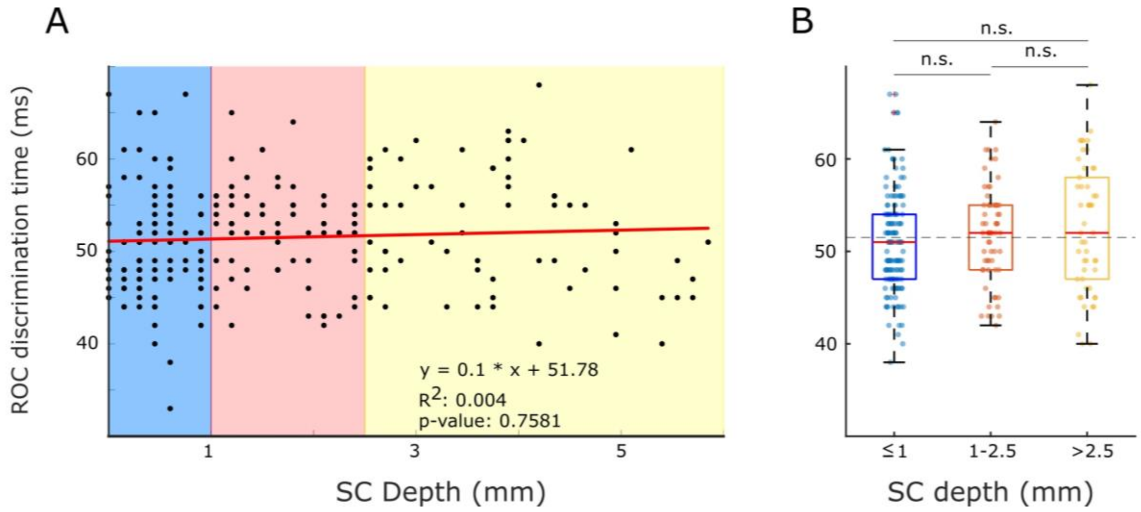

Figure 12. Discrimination latencies across the depth of the SC.

(A) Scatterplot of discrimination latencies for all units from both monkeys, shown in black. Linear regression analysis revealed no significant changes in discrimination latencies across different depths of the SC. (B) Discrimination latencies are binned by depth in SC: Blue: ≤ 1 mm), Red: 1-2.5 mm, and yellow: >2.5 mm. The coloured windows in (A) indicate these respective depth ranges.

Notably, cells with short latency responses were found throughout the depth of the SC (Figure 12B). In more shallow regions (depth <= 1 mm), 77 out of 144 cells (53%) had ROC latencies shorter than the overall average. Slightly deeper to this (1 mm < depth <= 2.5 mm), 26 out of 62 neurons (42%) had shorter ROC latencies. In the deepest depths (depth > 2.5 mm), 24 out of 50 neurons (48%) exhibited ROC latencies shorter than the overall average. A one-way ANOVA test of mean ROC discrimination times revealed no statistically significant differences among these groups ($F_{(2, 253)} = 0.23$, p-value: 0.79).

3.4 Timing of visual responses in different neuron types

Different types of SC neurons were recorded at various depths, ranging from 0 to 6300 µm relative to SC surface. By comparing the activity of neurons across all tasks relative to target onset, saccade onset, and arm-movement onset, different types of SC neurons were identified. The vast majority of recorded neurons showed task related activity and were visually responsive (V cells), eye-movement-related (saccadic cells, S), arm-movement-modulated (reach cells, R), or exhibited combinations of these three modulation patterns. Figure 13 shows the same neuron as in Figure 10, depicting the spiking activity for the classification tasks for contralaterally presented targets. It shows an extended period of activity after the burst following target onset, leading up to either the eye or hand movement in the eye-hand task. This indicates that the neuron is more responsive during the eye-hand task compared to the eye-only task. The neuron also exhibits a similar visual/saccadic burst during all tasks (ROC latency in the emerging target task: 46 ms), leading to its classification as a visual-saccadic-reach (VSR) neuron.

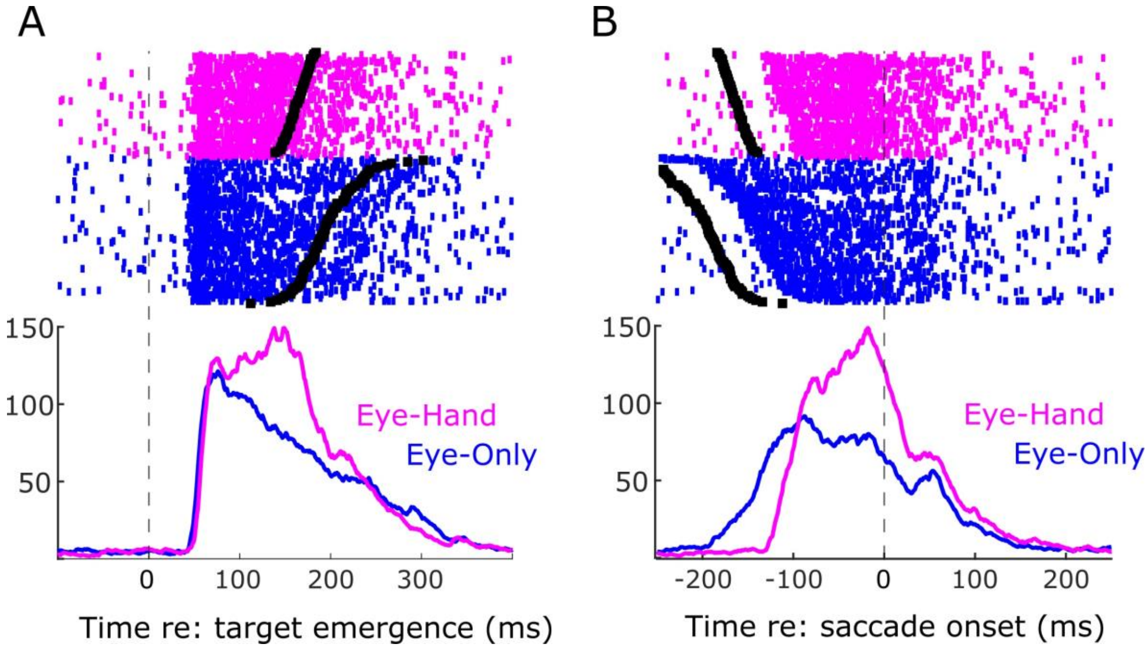

Figure 13. The average activity of the same neuron shown in Figure 10 during the functional classification tasks.

The average activity this neuron is depicted during the functional classification tasks, aligned to target onset (A) and saccade onset (B). This neuron is clearly more active during the Eye-Hand task (magenta) compared to the Eye-Only task (blue). It also exhibits a visual/saccadic burst in both tasks, thus classified as a visual-saccadic-reach (VSR) neuron. Rasters above each panel in (A) and (B) illustrate the timing of spikes across different trials. Black squares in (A) indicate saccade onset, while in (B) they indicate target onset. Trials are sorted by saccade reaction time. Magenta: Eye-Hand, blue: Eye-Only.

Previous studies have documented a heterogeneity of neural responses within the SC (Munoz & Wurtz, 1993; Werner et al., 1997b). Consistent with these findings, we recorded diverse neural responses from the SC. Figure 14 illustrates examples of differently classified neurons in the emerging target task and the functional classification tasks.

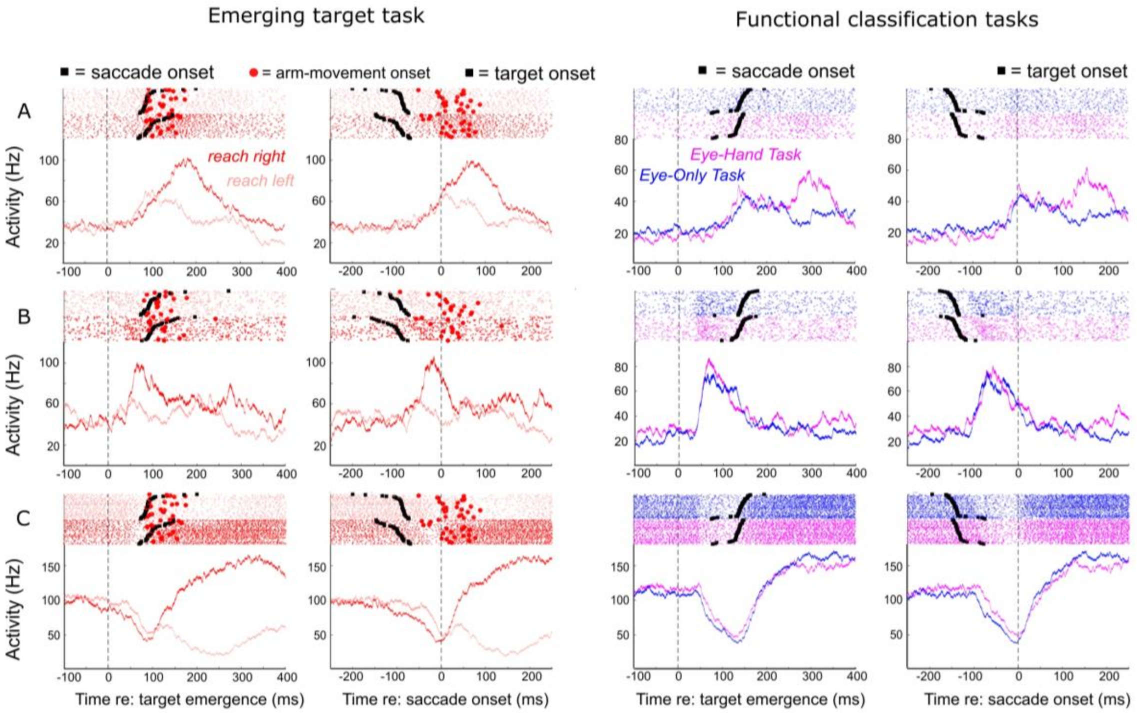

Figure 14. Different types of neurons were recorded in the SC and classified using functional classification tasks.

Each row displays the average activity and rasters of spiking activity for a single neuron during the emerging target task (first and second columns, aligned to target onset and saccade onset, respectively) and the functional classification tasks (third and fourth columns, also aligned to target onset and saccade onset, respectively). In the emerging target task, dark red represents activity for rightward reaches, while light red represents leftward reaches. In the functional classification tasks, magenta denotes the Eye-Hand task, and blue denotes the Eye-Only task. A: This neuron exhibits increased activity during the Eye-Hand task compared to the Eye-Only task, with saccadic activity present in both tasks but no visual burst, classifying it as a saccade-reach (SR) neuron. B: This neuron shows a visual/saccadic burst in all tasks but was not differentially active in the Eye-Hand task, classifying it as a visual-saccadic (VS) neuron (ROC latency in the emerging target task: 54 ms). C: This neuron, recorded from the rostral SC, displays fixation-related activity that decreases around saccade onset in all tasks, and is classified as an "other" (O) neuron. All three neurons were recorded from Monkey Be.

The numbers and recording depths of different cell types are summarized in Table 1. Among the recorded neurons, 256 were visually responsive to the onset of the emerging target. As shown in Table 1, 15 (5.9%) cells were purely visual (V), 156 (61%) exhibited additional saccadic modulation (VS), 18 units (7.0%) were also active with arm movements (VR), and 67 neurons (26%) modulated their activity with both saccades and arm movements (VSR). Around half of the visual neurons were found above a depth of 2.2 mm (8 out of 15, 53%; mean 1.7 ± 1.2 mm, median 1.8 mm). As indicated by Werner et al. (1997b), visual responses were primarily found above 2.2 mm but were present at all depths and across all cell types.

Neurons that produced bursts of activity around eye movement onset were termed saccadic (412 neurons). Among all saccadic cells, 144 (35%) were purely saccadic (S), 156 (38%) were visual-saccadic (VS), 29 (7%) were modulated by arm movements but did not have visual bursts (SR), and 67 (16%) modulated their activity with both target onset and arm movements (VSR). Consistent with previous studies (Werner et al., 1997b), purely saccadic neurons were generally located deeper than visual cells (mean 2.1 ± 1.5 mm, median 1.8 mm).

A total of 128 neurons showed modulation with arm-movement activity. Cells with pure reach-modulated activity, on average, were located deeper than the other two groups (mean 3.7 ± 0.5 mm, median 3.6 mm). Twelve cells were identified as reach cells (R) with no visual or saccadic modulation. Additionally, 18 (14%) cells showed visual activity, 29 cells (23%) displayed saccadic activity in addition to arm movement modulation, and 67 (52%) modulated their activity with both target onset and eye movements (VSR).

Table 1. Classification and depth distribution of functionally categorized neurons in SC.

Recorded neurons were categorized as follows: V (visual), S (saccadic), VS (visual-saccadic), R (reach), VR (visual-reach), SR (saccadic-reach), VSR (visual-saccadic-reach), and O (others). Neurons exhibiting multiple response types were included in more than one category.

Type	**n**	**Recording depth (mm)**			
		mean	median	Min.	Max.
V	15	1.7	1.8	0	4.5
S	144	2.1	1.8	0	6.15
VS	156	1.9	1.35	0	5.85
R	12	3.7	3.6	2.1	4.05
VR	18	0.9	0.9	0	2.4
SR	29	1.8	1.95	0	4.5
VSR	67	1.3	0.9	0	5.7
O	46	2.2	3.3	0	6.3
All visual	256	1.7	1.2	0	5.85
All saccadic	412	1.8	1.5	0	6.15
All reach	128	1.5	1.2	0	5.7

We then investigated the ROC latencies in different neuron populations in SC during a reflexive reaching task. Figure 15 shows the ROC discrimination latencies for visually responsive neurons. Among these neurons, those additionally modulated by reaching movements (VR) exhibited significantly higher latencies compared to the visual-saccadic (VS) and visual-saccadic-reach (VSR) types (one-way ANOVA: $F_{(3,\ 253)} = 6.19$, $p < 0.001$). Notably, neurons responsive to visual information and modulated by both saccades and arm movements (VSR) had similar discrimination times to those of purely visual (V) and visual-saccadic (VS) neurons.

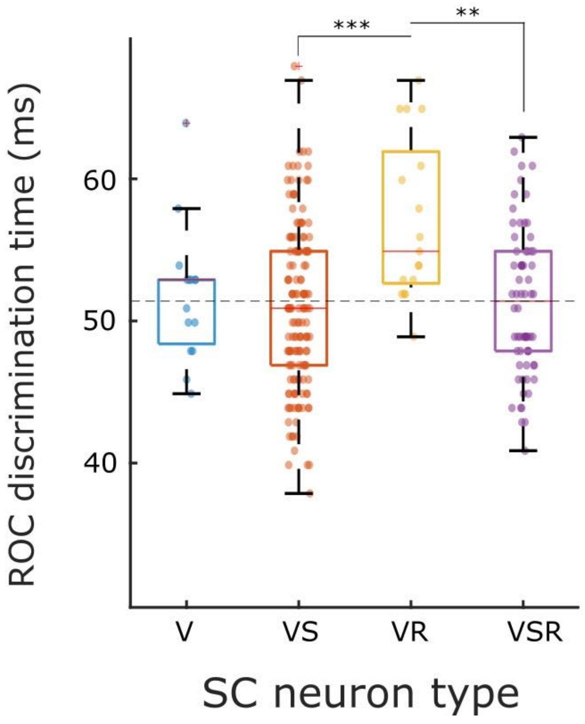

Figure 15. ROC discrimination latencies for various neuron types that exhibit a visual burst.

The types include V (Visual), VS (Visual-saccadic), VR (Visual-reach), and VSR (Visual-saccadic-reach). ROC latencies in visual-reach (VR) neurons are significantly higher compared to those in visual-saccadic (VS) and visual-saccadic-reach (VSR) neurons (: p-value < 0.01, ***: p-value < 0.001).**

3.5 Timing of visual responses in lower vs. upper visual field in SC

Hafed and Chen (2016) found that neurons in the upper visual field locations of the SC respond faster to visual targets than those in the lower visual field. Motivated by these findings, we analyzed signal timing across different SC locations following target emergence in the emerging target task. We examined the ROC discrimination time as a function of direction from the horizontal meridian (Figure 16). Our results revealed no significant change in ROC latencies in the emerging target task along the medio-lateral axis of the SC, as evidenced by a p-value of 0.7730 for the depth coefficient in the linear regression analysis. Furthermore, the average ROC latencies for neurons in the upper visual field did not significantly differ from those in the lower visual field (p-value: 0.5210).

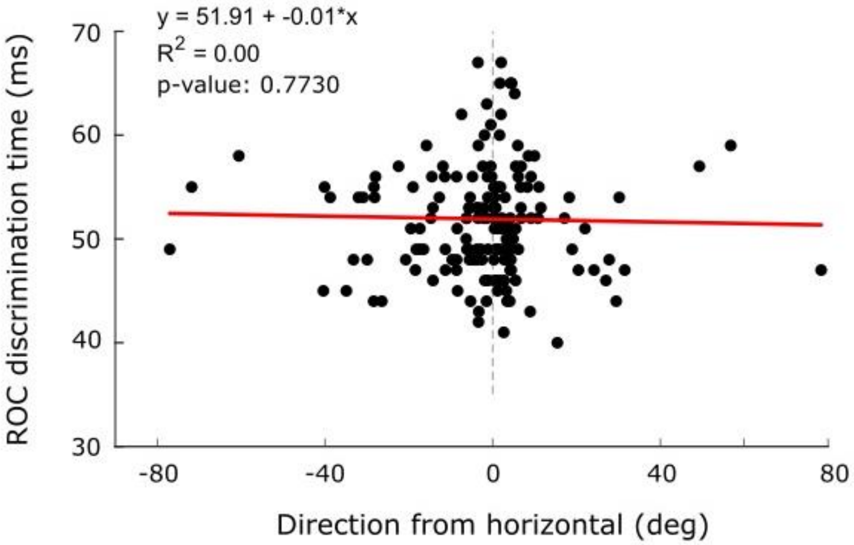

Figure 16. ROC discrimination time as a function of direction from horizontal meridian.

Scatterplot of discrimination latencies for all units are show from both monkeys, shown in black. Linear regression analysis indicates no significant change in latencies along the SC medio-lateral axis.

Chapter 4

4 Discussion

4.1 General discussion

We investigated the timing of visual signals in the SC during a reflexive visually guided reaching task. Our aim was to determine whether the activity of SC neurons occurs early enough to potentially initiate EVRs in the upper limb muscles, in order to test the hypothesis that the SC initiates the most rapid visually guided reaching responses. We trained two macaque monkeys to perform the Emerging Target task, which is known to elicit express visuomotor responses in both humans and monkeys (Cecala et al., 2023; Kozak et al., 2020). Behavioural data revealed that both monkeys exhibited exceptionally rapid reactions to target emergence, with majority of eye movements classified as express saccades (<100 ms). The reaching movements also demonstrated remarkably short reaction times consistent with previous studies on reflexive reaching behaviours. For instance, Perfiliev et al. (2010) reported reaction times in the 120-200 ms range when monkeys performed reflexive reaching towards moving objects, although they did not measure limb muscle EMG. Another study by Lara et al. (2018) monitored upper limb muscle activity in monkeys performing a 'quasi-automatic' task, which required intercepting a target moving radially on a touch screen. This task resulted in average reaction times of approximately 200 ms, closely aligning with our observations. However, the Lara study did not report any EMG activity resembling EVRs. In contrast, previous work by Cecala et al. (2023) demonstrated EVRs as quickly as ~65 ms in upper limb muscles of monkeys using the emerging target task, establishing a benchmark for premotor events. In our study, we recorded neural data from the SC of Monkey Gr, the same subject as in Cecala's study, and Monkey Be, to further investigate these early neural signals.

Our findings reveal that SC neurons can differentiate visual information related to various target locations within 51 ms in the emerging target task. This raises an important question: is this rapid enough to initiate EVRs? Anatomically, a significant number of tecto-spinal neurons are situated within the intermediate and deep layers of the SC, specifically in its posterior and lateral sections, although they are less prevalent in NHPs than neurons that contribute to the tecto-reticulo-spinal pathways (Castiglioni et al., 1978; Nudo et al., 1993; Robinson et al., 1994). These SC neurons have bilateral and reciprocal connections with the central mesencephalic reticular formation, which sends descending fibers to the ipsilateral spinal cord and receives ascending projections from the same site (Horn, 2006; May, 2006). Functionally, the pontomedullary reticular formation (PMRF) shows rapid response capabilities. For instance, stimulus-triggered excitation occurs in the ipsilateral upper arm flexors and contralateral upper arm extensors within approximately 8 milliseconds (Davidson & Buford, 2004). Moreover, Corneil et al. (2002b) observed facilitation latencies of about 13 ms for neck muscles following SCd stimulation. Relevant to this, Rezvani and Corneil (2008) identified an ~11 ms difference between the ROC discrimination times of SCd neurons and the EMG responses in neck muscles through trial-by-trial analysis. Considering these interactions and timings, an efferent lag of approximately 15 ms can be inferred. Therefore, factoring in this 15 ms efferent lag, the 51 ms discrimination ability of SC neurons is indeed swift enough to initiate EVRs, which manifest at around 65 ms in upper limb muscles.

Short latency discrimination times were observed throughout the depth of the SC, including in the vicinity of reach-related neurons. Werner et al. (1997b) were the first to show that a population of neurons in the primate SC and the underlying reticular formation are active both before and during arm movements involved in reaching. These neurons were recorded across the SC's depth, predominantly in the deeper layers, and below the SC in the mesencephalic reticular formation. Some of these neurons also exhibited visual responses and saccadic bursts, with characteristics indistinguishable from typical visual or saccade neurons in the SC. Although we categorized “reach-neurons” differently, our findings also indicate that pure reach neurons are, on average, located deeper than other neuron classes. Notably, results from Werner et al. (1997b) showed that neurons exhibiting visual responses were present from the SC surface to a recording depth of 6 mm, which aligns with our observations. In oculomotor tasks, the timing of visual responses in the intermediate layers of the SC appears to be delayed compared to the superficial layers. Using linear array electrodes, Massot et al. (2019) recorded from

SC neurons in visually guided and memory-guided saccade tasks. When the target was presented in the neurons' receptive field, they observed longer visual latencies from the dorsal to ventral layers, with visual latencies in the intermediate layers being approximately 10 ms later than in the superficial layers. However, our results do not confirm this trend in reflexive reaching tasks, when target is presented at a fixed spatial location. Although there are differences in methodologies of calculating response latencies, in this task, ROC latencies in the intermediate and deep layers of the SC were only 2 ms later than those in the superficial layers (~50 ms). Additionally, in the deep layers, about half of the neurons with visual responses had ROC latencies below the average latencies of all the neurons. This finding is intriguing, as visual-related activity in the intermediate and deep layers may originate from the superficial layers through interlaminar connections (May, 2006) or via an indirect corticotectal pathway. Inactivation of either the lateral geniculate nucleus (LGN) or primary visual cortex selectively diminishes SCi responses, while the sensory responses of visual neurons in the superficial layers remain largely unaffected (Schiller et al., 1979; Schiller et al., 1974; Takaura et al., 2011; Yu et al., 2024). During reflexive tasks, one possibility could be that the intermediate and deep layers rely more on the indirect corticotectal pathway. Another possibility is that, under normal conditions, other inhibitory inputs might suppress the interlaminar flow from the superficial to deep layers, and in cases of removal of this inhibition, the sensory burst could be unmasked. A similar phenomenon has been shown in the oculomotor functions of the SC, where the removal of fixation-related inhibition results in premature gaze shifts (Jagadisan & Gandhi, 2016). Such modulation of inhibition could be a result of top-down signals that prime this circuitry for rapid response execution. We observed preparatory activity in certain neurons before the target appeared during the gap period in the emerging target task (see Figures 10 and 13). Such preparatory activity, presumably from cortical areas, may relate to the encoding of temporal certainty and/or implied motion that has been proposed to be critical for EVR generation in the emerging target task (Contemori et al., 2021a, 2023; Kozak et al., 2020).

Neurons across different regions of the SC exhibit similar visual signal latencies. Reach neurons, as recorded by Werner et al. (1997b), were predominantly concentrated in the lateral and slightly anterior parts of the SC. However, these neurons are also distributed throughout much of the SC, with a notable concentration in the regions corresponding to the lower visual field (Stuphorn et al., 2000; Werner et al., 1997b). Stimulation studies corroborate these findings, demonstrating that electrical microstimulation in the lateral half of the SC, particularly in areas representing the lower visual field, effectively elicited arm movements. Additionally, it was observed that the more lateral and posterior the penetration sites, the more superficial the elicited arm movements were (Philipp & Hoffmann, 2014). Importantly, Hafed and Chen (2016) demonstrated that neurons located in the upper visual field locations of the SC respond faster to visual targets compared to those in the lower visual field. Despite these findings, our study did not observe significant differences in visual signal latencies along the medio-lateral axes of the SC, nor between locations on the SC map associated with the lower and upper visual fields. However, this result is limited by the small number of neurons recorded in the lateral part of the SC and by the fact that the target was not presented at the centre of a given neuron's receptive field.

Our collective findings, for the first time in a reflexive reaching task, demonstrate that neurons within the SC, regardless of their depth or specific location, are capable of discriminating visual information early enough to facilitate the generation of EVRs.

4.2 Future directions and Limitations

Although Monkey Gr demonstrated EVRs in the emerging target task in Cecala's study (2023), it is crucial to verify that Monkey Be can also generate EVRs. To accomplish this, simultaneous recordings of neural and muscle activity during the same task are recommended. This approach will not only provide additional insights but also enable trial-by-trial correlation analysis between SC neural activity and EVRs in upper limb muscle, similar to findings reported by Rezvani and Corneil (2008) in monkey neck muscles.

Moreover, inactivation studies are crucial for establishing causal links. Should the SC be responsible for generating EVRs, we can predict that inactivating the deep layers can increase latency and reduce the amplitude of EVRs by diminishing the vigor of descending neural drive. Conversely, inactivating the PMd is expected to decrease the magnitude of these responses without affecting latency, similar to the effects observed with FEF inactivation on SCd visual activity in oculomotor tasks (Dash et al., 2018). Notably, Song et al. (2011) reported deficits in target selection but not in reaching movements to the target in the inactivated field when they inactivated the monkeys' SC during a reach target selection task, although they inactivated the intermediate layers of SC in a task not requiring as rapid responses as ours. By conducting these further studies, we can better delineate the roles of SC and other brain regions in the generation of EVRs and enhance our overall understanding of motor control mechanisms in reflexive visually guided reaching.

Our findings leave open the possibility that the motor cortices could be responsible for generating EVRs. Considering Cecala's finding that EVRs can occur as quickly as 65 ms in monkeys, paired with the roughly 10 ms afferent delay between cortical neurons and muscles, it remains plausible that the motor cortex elicits EVRs. Notably, alongside the corticospinal tract, the PMd projects to the SC, specifically targeting the deep layers of its lateral part and the underlying reticular formation—regions where reach-related neurons have been observed (Distler & Hoffmann, 2015). Moreover, as discussed in the introduction, previous studies utilizing reflexive tasks have not effectively required animals to reach as fast as possible to generate EVRs reliably. Therefore, establishing signal timing in cortical areas during reflexive tasks, especially the emerging target task known to elicit EVRs in monkeys, will likely deepen our understanding of the potential neural mechanisms responsible for generating EVRs.

To render the task more naturalistic, we did not enforce any constraints on the animal's gaze following the initial fixation. Consequently, the activity of SC neurons during periods when the target was occluded may be associated with any saccades the animal executed. While we rigorously excluded trials where saccades occurred close to the emergence of the target, implementing these constraints could reveal whether the buildup of activity in SCd neurons correlates with upper limb muscle activity, similar to the correlation between SCd neuron activity and neck muscle activity demonstrated by Rezvani & Corneil (2008).

Furthermore, the only data available for the monkeys' hand movements came from the touch screen, limiting our ability to monitor actions after the monkeys lifted their hands from the screen. This restriction likely excluded important behavioural data from analysis. Implementing more comprehensive behavioural tracking would enhance the analysis of the monkeys' behaviour and prevent the inclusion of error trials. Notably, Monkey Gr's arm movements were swift, aligning with previous data from Cecala's study. In contrast, Monkey Be demonstrated slower reaction times, yet crucially, no significant differences were found in the signal timing within the SC for both monkeys, suggesting that the SC receives visual responses early enough to potentially generate EVRs.

Finally, It is important to clarify how reach cells were previously characterized. Werner et al. (1997a) and subsequent researchers identified these cells using delayed tasks in which there is a temporal delay between the appearance of a visual target, eye movement, and arm movement. In contrast, our study distinguishes reach cells by comparing neural activity across eye-only and eye-hand tasks, specifically focusing on their activity in relation to visual stimuli, and eye and arm movement. To emphasize this methodological distinction, we use the term 'arm-movement-modulated' rather than 'arm-movement-related' in our methods section. Notably, Reyes-Puerta et al. (2011) studied eye hand coordination in SC using similar tasks—referred to as saccade-only and coupled-saccade-reach tasks—and observed that neurons in the caudal regions of the SC exhibit reduced saccade-related activity in the eye-hand tasks. While we also detected such neurons, we did not label them as reach neurons. Instead, we defined reach neurons as those showing heightened activity when aligning neuron activity to target onset and saccade onset between these tasks. Additionally, the recording depth in previous studies reporting reach-related neurons (Werner et al., 1997b) were often measured from the microdrive once the electrode entered the SC. In contrast, our study employed a more objective method for recording depth, which should provide deeper insights into the spatio-temporal pattern of activity in the SC.

4.3 Conclusions

In this study, we investigated the temporal dynamics of visually evoked responses in the superior colliculus during a reflexive visually guided reaching task known as emerging target task. Our experiments with two macaque monkeys revealed that visual information in this task, reaches the movement-related layers of the SC within approximately 50 milliseconds. This rapid processing speed is sufficiently early to trigger express visuomotor responses, accounting for an estimated ~15 ms efferent delay along the tecto-reticulo-spinal pathway. Our results highlight the SC's capacity to process and relay visual information with remarkable speed, potentially facilitating the early onset of rapid motor responses. Importantly, these findings enrich our understanding of the SC as a key node in the sensorimotor network, capable of integrating visual inputs and triggering swift motor actions, a crucial adaptation for survival in dynamic environments. Furthermore, the observed latency of visual signal processing in the SC supports the hypothesis that this structure can contribute to the generation of EVRs. Although our study did not include simultaneous EMG recordings, the consistency of the neural response timings with known muscular response latencies from previous study on the same task provides a strong inferential basis for this relationship. More broadly, our results lay the groundwork for a comparative analysis of signal timing in this task across cortical and subcortical regions, aiming to enhance our comprehension of visual-to-motor transformations in situations when time is of the essence.

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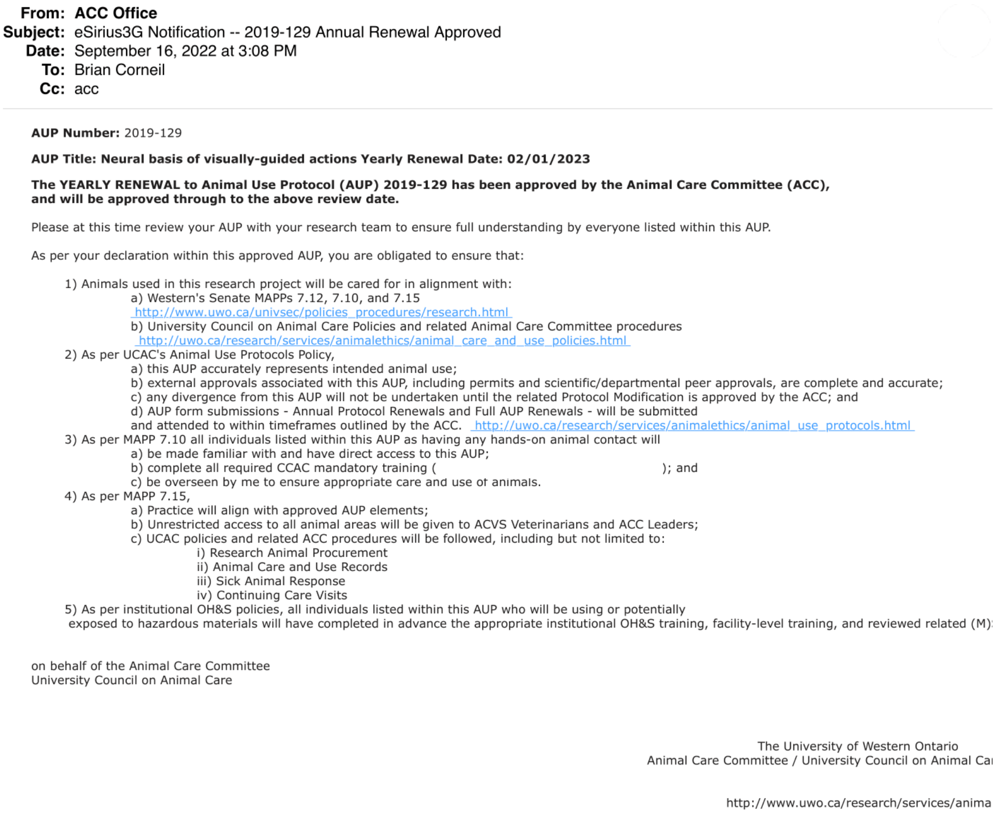
Appendices

Appendix A. Ethics Approval



From: **ACC Office**
Subject: eSirius3G Notification -- 2019-129 Annual Renewal Approved
Date: September 16, 2022 at 3:08 PM
To: Brian Corneil
Cc: acc

AUP Number: 2019-129

AUP Title: Neural basis of visually-guided actions Yearly Renewal Date: 02/01/2023

The YEARLY RENEWAL to Animal Use Protocol (AUP) 2019-129 has been approved by the Animal Care Committee (ACC), and will be approved through to the above review date.

Please at this time review your AUP with your research team to ensure full understanding by everyone listed within this AUP.

As per your declaration within this approved AUP, you are obligated to ensure that:

1) Animals used in this research project will be cared for in alignment with:
    a) Western's Senate MAPPs 7.12, 7.10, and 7.15
    http://www.uwo.ca/univsec/policies_procedures/research.html
    b) University Council on Animal Care Policies and related Animal Care Committee procedures
    http://uwo.ca/research/services/animalethics/animal_care_and_use_policies.html
2) As per UCAC's Animal Use Protocols Policy,
    a) this AUP accurately represents intended animal use;
    b) external approvals associated with this AUP, including permits and scientific/departmental peer approvals, are complete and accurate;
    c) any divergence from this AUP will not be undertaken until the related Protocol Modification is approved by the ACC; and
    d) AUP form submissions - Annual Protocol Renewals and Full AUP Renewals - will be submitted
    and attended to within timeframes outlined by the ACC. http://uwo.ca/research/services/animalethics/animal_use_protocols.html
3) As per MAPP 7.10 all individuals listed within this AUP as having any hands-on animal contact will
    a) be made familiar with and have direct access to this AUP;
    b) complete all required CCAC mandatory training ( ); and
    c) be overseen by me to ensure appropriate care and use of animals.
4) As per MAPP 7.15,
    a) Practice will align with approved AUP elements;
    b) Unrestricted access to all animal areas will be given to ACVS Veterinarians and ACC Leaders;
    c) UCAC policies and related ACC procedures will be followed, including but not limited to:
        i) Research Animal Procurement
        ii) Animal Care and Use Records
        iii) Sick Animal Response
        iv) Continuing Care Visits
5) As per institutional OH&S policies, all individuals listed within this AUP who will be using or potentially exposed to hazardous materials will have completed in advance the appropriate institutional OH&S training, facility-level training, and reviewed related (M)

on behalf of the Animal Care Committee
University Council on Animal Care

The University of Western Ontario
Animal Care Committee / University Council on Animal Ca

http://www.uwo.ca/research/services/anima

Curriculum Vitae

Name:	Amirhossein Asadian
Post-secondary Education and Degrees:	Sharif University of Technology Tehran, Iran 2017-2022 B.Sc. The University of Western Ontario London, Ontario, Canada 2022-2024 M.Sc.
Related Work Experience:	Teaching Assistant The University of Western Ontario 2022-2024
Poster Presentation:	Asadian A., Cecala A., Nuijten P., Lehmann S., Pruszynski A., Corneil B. “Responding when time is of the essence: An analysis of signal timing in the macaque superior colliculus during reflexive visually guided reaching”, Neural Control of Movement, Victoria, Canada, 2023.